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A physiologically-based pharmacokinetic modeling approach to predict drug-drug interactions of sonidegib (LDE225) with perpetrators of CYP3A in cancer patients

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Running Title: PBPK Predictions of Sonidegib Interactions with CYP3A Perpetrators

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Abbreviations:

4ßHC, 4β-hydroxycholesterol

6ßCR, 6β-hydroxycortisol to cortisol ratio

ADME, absorption, distribution, metabolism, and excretion

AE, adverse events

AUC, area under the concentration-time curve

BCC, basal cell carcinoma

B/P, blood to plasma ratio

CI, confidence interval

CL_{int}, intrinsic clearance

C_{max}, maximal concentration

CL_R, renal clearance

CYP, cytochrome P450

DDI, drug-drug interactions

ECG, electrocardiogram

EFV, efavirenz

EMA, European Medicines Agency

E_{max}, maximum fold increase over vehicle control

ERY, erythromycin

FDA, Food and Drug Administration

f_a, fraction of dose absorbed

fu_{gut}, unbound fraction in the gut

fu_{mic}, unbound fraction in microsomes

fu_{plasma}, unbound fraction in plasma

GM, geometric mean

HLM, human liver microsomes

HPLC, high-performance liquid chromatography

Ind_{max}, maximum induction

k_a, absorption rate constant

K_i, inhibition constant

K_m, Michaelis-Menten constant

KTZ, Ketoconazole

PBPK, physiologically-based pharmacokinetics

PE, prediction error

$P_{eff,man}$, effective permeability in man

PK, pharmacokinetics

q.d., once a day dosing

q.o.d. once every other day dosing

Q_{gut}, nominal flow through the gut

R, ratio

RIF, rifampin

SAE, serious adverse events

SD, standard deviation

$t_{1/2}$, half-life

T_{max}, time to reach maximum concentration

V_{max}, maximum velocity

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V_{ss}, volume of distribution at steady-state

Abstract

Sonidegib (Odomzo®) is an orally available Smoothened inhibitor for the treatment of advanced basal cell carcinoma. Sonidegib was found to be metabolized primarily by cytochrome P450 (CYP)3A *in vitro*. The effect of multiple doses of the strong CYP3A perpetrators, ketoconazole (KTZ) and rifampin (RIF), on sonidegib pharmacokinetics (PK) after a single 800 mg dose in healthy subjects was therefore assessed. This data was used to verify a physiologically-based pharmacokinetic (PBPK) model developed to: 1) bridge the clinical drug-drug interaction (DDI) study of sonidegib with KTZ and RIF in healthy subjects to the marketed dose (200 mg) in patients, 2) predict acute (14 days) versus long-term dosing of the perpetrators with sonidegib at steady-state, and 3) predict the effect of moderate CYP3A perpetrators on sonidegib exposure in patients. Treatment of healthy subjects with KTZ resulted in an increased sonidegib exposure of 2.25- and 1.49-fold ($AUC_{0\text{-}240h}$ and C_{max}, respectively) and RIF decreased exposure by 72 and 54%, respectively. The model simulated the single and/or multiple-dose PK of sonidegib (healthy subjects and patients) within ~50% of observed values. The effect of KTZ and RIF on sonidegib in healthy subjects was also simulated well and the predicted DDI in patients was slightly less and independent of sonidegib dose. At steady-state, sonidegib was predicted to have a higher DDI magnitude with strong or moderate CYP3A perpetrators compared to a single dose. Different dosing regimens of sondigeb with the perpetrators were also simulated and provided guidance to the current dosing recommendations incorporated in the product label.

Introduction

Sonidegib (marketed as Odomzo®) is a potent, selective, and orally bioavailable inhibitor of Smoothened, a transmembrane protein involved in Hedgehog signal transduction (Pan et al., 2010, Dreier et al., 2014, Pramanik 2014). Sonidegib is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy or metastatic BCC. The approved indications varies depending on the country/region. With longer follow-up (12 months), sonidegib (200 mg once a day dosing, q.d.) demonstrated sustained tumor responses in patients with advanced BCC (Dummer et al., 2016). The molecular structure of sonidegib is shown in Supplemental Figure 1.

The pharmacokinetic (PK) properties of sonidegib have been characterized extensively. The absorption is low (<10%) but the exposure increases by 7.4- to 7.8-fold (area under the curve, $AUC_{0\text{-}inf}$, and maximal concentration, C_{max}, respectively) in presence of a high-fat meal (Odomzo® Prescribing Information, 2016) after a single dose. Co-administration with esomeprazole resulted in a modest reduction in the AUC and C_{max} concentrations of 32-38% indicating that pH alteration does not have significant effect (Zhou et al., 2016). Sonidegib was extensively distributed and slowly metabolized. Elimination of absorbed sonidegib occurred largely by oxidative (75%) as well as by hydrolytic metabolism (Zollinger et al., 2014). Following the administration of a single dose (100 mg to 3000 mg) under fasted conditions in patients with cancer, the median time to peak concentration was 2 to 4 hours (Rodon et al., 2014). Sonidegib exhibited dose-proportional increases in AUC and C_{max} over the dose range of 100 mg to 400 mg, but less than dose-proportional increases at doses greater than 400 mg.

Steady-state was reached approximately 4 months after starting sonidegib and the estimated accumulation at steady-state was 19-fold with a terminal half-life of 29 days (Goel et al., 2016).

The objective of this study was to first identify the enzyme(s) involved in the clearance of sonidegib in human liver *in vitro*. Based upon these *in vitro* results, as well as results of the radiolabeled human absorption, distribution, metabolism, and excretion (ADME) study (Zollinger et al., 2014), a physiologically-based pharmacokinetic (PBPK) model was constructed using sonidegib physiochemical and absorption properties optimized from modelling clinical PK data, model-predicted distribution, and clinically observed clearance values. The contribution of cytochrome P450 (CYP)3A4 to the clearance of sonidegib in the PBPK model was verified by results from a clinical drug-drug interaction (DDI) study in healthy subjects given sonidegib (800 mg single dose) and the potent inducer, rifampin (RIF) or inhibitor ketoconazole, (KTZ). Refinements were made in the sonidegib intrinsic clearance parameter (CL_{int}) to predict the PK of single and multiple once daily doses of sonidegib (200 and 800 mg) in the target cancer patient population. The qualified PBPK model was then applied to predict the DDI of sonidegib with strong and moderate CYP3A inhibitors and inducers in cancer patients, including exploring different dosing regimen scenarios. We describe herein how these *in vitro* and *in vivo* DDI studies, including PBPK modelling and simulations, helped to develop the product label language regarding the expected CYP3A drug interactions and dosing recommendations for Odomzo®.

Materials and Methods

Materials

[^{14}C]Sonidegib was synthesized in-house (Novartis, East Hanover, NJ). The specific activity was 57.4 mCi/mmol with 99% radiochemical purity. Pooled human liver microsomes (HLM, n = 50, 20 female and 30 male), recombinant human CYP enzymes, ketoconazole, and azamulin were purchased from Corning Gentest (Tewksbury, MA). The following chemicals were obtained from Sigma-Aldrich (St. Louis, MO): NADPH, UDPGA, alamethicin, dimethyl sulfoxide, ammonium formate, potassium phosphate (mono- and di-basic), $MgCl_2$, quinidine, ticlopidine, sulfaphenazole, furafylline. Montelukast was purchased from Sequoia Research Products, Ltd., (Oxford, UK). Acetonitrile and formic acid were purchased from Fisher Scientific Co. (Pittsburgh, PA). IN FLOW 2:1 was purchased from LabLogic Systems, Inc. (Brandon, FL).

In Vitro CYP Reaction Phenotyping

The metabolism of [^{14}C]sonidegib was examined in pooled HLM in the presence of NADPH and/or UDPGA. HLM (1 mg microsomal protein/ml) in 100 mM potassium phosphate buffer (pH 7.4) were pre-incubated with alamethicin (60 µg alamethicin/mg protein, final concentration) for 15 min on ice. $MgCl_2$ (5 mM, final concentration) and [^{14}C]sonidegib (46 µM, 0.5% dimethyl sulfoxide, final concentrations) were then added and the samples and thermally equilibrated at 37ºC for 3 min. The singlet reactions were initiated with 4 mM UDPGA and/or 1 mM NADPH (final concentrations) and the samples were incubated for 30 min at 37°C. The reactions were terminated by the addition of an equal volume of cold acetonitrile and the precipitated protein was removed by centrifugation at 39,000 x *g* for 10 min at ~4°C in

an Avante 30 high speed microcentrifuge (Beckman Coulter, Fullerton, CA). Aliquots of the supernatants were analyzed by reversed-phase high-performance liquid chromatography (HPLC). The HPLC chromatographic equipment consisted of a Waters 2695 Separations module, equipped with an autosampler and quaternary pump system (Waters Corporation, Milford, MA). The chromatographic separation was performed on a Waters Xbridge C18 column (150 x 4.6 mm, 5 µm) at a temperature of 30°C. Gradient elution consisted of solvent A (5 mM ammonium formate with 0.1% formic acid, pH ~3.0) and solvent B (acetonitrile with 0.1% formic acid) at a flow rate of 1 ml/min. The gradient elution program (% B) was 0→30 min (10-50%), 30→45 min (50-90%), 45→55 min (90%), 55→56 min (90-10%). Radioactivity was measured in-line with a β-RAM radioactivity detector (LabLogic Systems, Inc.), with addition of 1.5 ml liquid scintillant/ml (IN FLOW 2:1) to the HPLC eluate prior to flow through a liquid flow cell (250 µL). Chromatograms were evaluated using Winflow (Version 1.4a, LabLogic Systems, Inc.) or Laura (Version 4, LabLogic Systems, Inc.) HPLC application software and plotted using SigmaPlot (Version 9.0, Jandel Corporation, USA).

Kinetic analysis of [^{14}C]sonidegib metabolism was performed in pooled HLM (0.25 mg microsomal protein/ml). Duplicate reactions were prepared (as described above without alamethicin) with varying concentrations of [^{14}C]sonidegib, the reaction was thermally equilibrated, initiated with NADPH, and incubated at 37°C for 20 min. Control samples at each concentration of sonidegib did not contain co-factor. Sonidegib metabolism activity was previously found to be approximately linear with respect to time, however the activity dropped with increasing protein concentration (data not shown), likely due to extensive microsomal protein binding. The time and protein concentration in this study was chosen to maximize the quantification of metabolites. The unbound fraction of sonidegib in microsomes (fu_{mic})

determined by ultracentrifugation (data not shown) was used in the calculation of unbound Michaelis-Menten constant (K_m) values (Supplemental, Table 1). The samples were quenched by the addition of equal volume of cold acetonitrile and the precipitated protein was removed by centrifugation as described above. An aliquot of each sample was analyzed by HPLC with off-line radioactivity counting. The HPLC eluate was collected with a fraction collector (FC204 Gilson Inc., Middleton, WI) at 0.13 min per fraction into Deepwell LumaPlate-96 plates (PerkinElmer Life and Analytical Sciences, Shelton, CT). The fractions were dried with a stream of nitrogen and radioactivity was counted with a TopCount NXT Microplate Scintillation and Luminescence Counter (PerkinElmer Life and Analytical Sciences) with a counting time of 10 min per well. Chromatograms from the TopCount were evaluated using Laura HPLC application software. Sonidegib metabolism activity was plotted against substrate concentration and the kinetic parameters, K_m and maximum velocity (V_{max}), were determined by non-linear regression using GraphPad PRISM software (Version 4.02, San Diego, CA). Total sonidegib metabolism remained below 17% for the reactions.

To identify the CYP enzyme(s) involved in the metabolism of sonidegib in humans, [^{14}C]sonidegib (46 µM, 0.5% dimethyl sulfoxide v/v, final concentrations) was incubated with the recombinant human CYP enzymes: CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP4F2, CYP4F12 (100 pmol CYP/ml), or control microsomes in the same buffer components as described above. The singlet reactions were thermally equilibrated, initiated, and incubated for 30 min at 37°C. Samples were processed and analyzed by HPLC with in-line radioactivity detection, as described above.

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To evaluate the contributions of specific CYP enzymes to the metabolism of sonidegib in human liver, inhibition of total [^{14}C]sonidegib metabolism in HLM was examined using selective inhibitors of CYP enzymes. The experimental concentration ranges used were selected to encompass reported apparent inhibition constant (K_i) values (median) for inhibition of a specific CYP as described in Bohnert et al., 2016. [^{14}C]Sonidegib, at a concentration approximately at its total K_m value in HLM (4.5 µM), in combination with varying concentrations of CYP inhibitors [KTZ (CYP3A4, 0-2 µM), azamulin (CYP3A4, 0-2 µM), ticlopidine (CYP2B6/CYP2C19, 0-10 µM), montelukast (CYP2C8, 0-2 µM), furafylline (CYP1A2, 0-10 µM), quinidine (CYP2D6, 0-2 µM), or sulfaphenazole (CYP2C9, 0-5 µM)] were incubated with HLM (0.25 mg microsomal protein/ml) as described above. Reactions with the time-dependent inhibitors, azamulin, ticlopidine, or furafylline were pre-incubated with NADPH for 15 min at 37°C and the reactions were initiated by the addition of [^{14}C]sonidegib. Control incubations did not contain the inhibitor. Inhibition of [^{14}C]sonidegib total metabolism was expressed as a percent of the control activity (no inhibitor). The data was plotted as a percent of the control activity versus the inhibitor concentration and IC_{50} values were determined by visual inspection.

Clinical DDI Study with KTZ or RIF in Healthy Subjects

The study was conducted according to the ethical principles of the Declaration of Helsinki. The study protocol and amendment were reviewed by the Independent Ethics Committee for the study center (at Quintiles Phase I Services, LLC, Overland Park, KS). Informed consent was obtained from each subject in writing before any screening procedures were performed as per the clinic's standard operating procedures.

Study population. Subjects eligible for inclusion in the study included healthy males or healthy sterile or postmenopausal females between 18-55 years of age with a body mass index within the range of 18–30 kg/m^2, who were in good health as determined by past medical history, physical examination, vital signs, electrocardiogram (ECG), and laboratory tests at screening were eligible for the study. Sexually active males had to use a condom during intercourse while participating in the study and for 6 months after stopping study drug and agree not to father a child in this period. Smoking, use of any prescription drugs, and alcohol use was prohibited during the study.

Study design. This was a single center, parallel group, open label, randomized, study to assess the effects of 200 mg twice daily (b.i.d.) oral dose of KTZ and the effect of 600 mg once daily (q.d.) oral dose of RIF on the PK of a single 800 mg oral dose of sonidegib in healthy subjects. The secondary objectives were to assess the safety and tolerability of a single oral dose of 800 mg sonidegib in healthy volunteers when administered concomitantly with KTZ or with RIF, and to determine the ratio of 6β-hydroxycortisol to cortisol in urine (6ßCR) and plasma 4β-hydroxycholesterol (4ßHC) as *in vivo* markers of CYP3A4 activity.

Approximately 45 healthy subjects were enrolled into the study to ensure at least 12 evaluable subjects for each arm (Arm 1: sonidegib, Arm 2: sonidegib + KTZ, Arm 3: sonidegib + RIF). Subjects who met all inclusion/exclusion criteria were admitted to the study center on Day -2 and remained there until discharge after Day 11 assessments (Arm 1) or Day 15 assessments (Arms 2 and 3) were performed. PK and safety assessments were conducted during the next 30 days post last dose. After discharge, subjects had three additional visits to the study center, including the end of study visit. All subjects fasted overnight for a minimum of 10 hours prior to sonidegib administration, and remained fasted for 4 hours after dosing. Standardized

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meals with regard to caloric and fat content were provided. Each subject participated in a screening period (Days -28 to -3), a baseline period (Day -2 to Day -1), followed by randomization into one of the three parallel arms.

Safety assessments during the study included physical examinations, ECG, vital signs, standard clinical laboratory evaluations (blood chemistry, urinalysis, hematology, and coagulation), adverse events (AE) and serious adverse events (SAE) monitoring.

Pharmacokinetic and biomarker assessments. All blood samples for sonidegib and 4βHC were taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. For Arm 1, PK blood samples for sonidegib were collected from Day 1 to Day 15 (0, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 288, 336 hours). For Arm 2 and Arm 3, the PK blood samples for sonidegib were collected from Day 5 to Day 19 (same time points). At each specified time point, approximately 3 ml of blood was collected in a K3-EDTA tube. All samples were processed immediately and plasma was frozen at -70°C. Plasma 4βHC concentration was assessed on the morning of Days -1 (Baseline), 4, 8, 11, 13 and 15 (for Arm 1) or at baseline on Days -1, 5, 8, 12, 15, 17 and 19 (for Arm 2) or at baseline on Days -1, 4, 5, 8, 12, 15, 17 and 19 (for Arm 3). At each time point, 2 ml of whole blood was taken into a vacutainer tube containing Li-heparin. Urine samples were collected for 6ßCR assessment following the same schedule as outlined above for 4βHC. Urine was collected in the morning on the scheduled day over a 4 h interval (from approximately 8:00 a.m. to noon). Each subject was to void his/her bladder at 8:00 a.m. and at the end of each urine sampling period. During each 4 hr sampling interval, the urine portions were pooled. Upon completion of the collection interval, the urine specimen was thoroughly mixed and the total volume of urine was determined and recorded along with the exact time for start and end of collection. A 30 ml aliquot of the urine

portion was kept frozen at ≤-20°C until shipped to the analytical site for samples analysis. Plasma concentration versus time profiles were used to determine AUC, C_{max}, time to reach maximal concentration (T_{max}) and half-life ($t_{1/2}$) in all subjects for sonidegib using non-compartmental methods (Phoenix WinNonlin, v6.2, Pharsight Corporation). Concentrations below the limit of quantification were treated as zero.

Analytical methods. Plasma concentrations of sonidegib (Zhou et al., 2016), 4βHC (Dutreix et al., 2013) and urinary 6βCR (Dutreix et al., 2013) were measured using a validated liquid chromatography-tandem mass spectrometry assay for each analyte. Experimental details are provided in previously published studies.

Safety assessments. Subjects underwent a routine panel of safety testing (physical examination, routine hematology, biochemistry, and urinalysis, viral serology screening, urine drug, alcohol, and cotinine screening, standard 12-lead ECG, and vital signs assessments) before and during each treatment period, and at the end of study. In addition to the routine safety assessments done at specified time points during the study, subjects were also monitored for adverse events throughout the study. Any AEs/SAEs occurring during this time were evaluated by the investigator to determine their severity and whether they were related to study drug. In addition, concomitant medications or significant non-drug therapies were also monitored.

Statistical analysis. A sample size of minimum 12 complete subjects was deemed to provide the study with at least 80% power to detect a geometric mean ratio ranging from 0.2 (Test 1/Reference) to 5.00 (Test 2/Reference) for $AUC_{0\text{-}240h}$ and C_{max} of sonidegib at a significance level of 10%. Test 1 (KTZ + sonidegib) or Test 2 (RIF + sonidegib) were the test treatments and sonidegib alone was the Reference treatment. A formal statistical analysis was

performed for the primary PK parameters of sonidegib ($AUC_{0\text{-}240h}$ and C_{max}). A linear model including all treatment arms was fit to the log transformed PK parameters ($AUC_{0\text{-}240h}$ and C_{max}) for sonidegib to assess the effect of KTZ and RIF on sonidegib. Included in the model was treatment as a fixed effect. Descriptive statistics (n, geometric mean (GM) and coefficient of variation (CV%), mean, standard deviation (SD), and CV%) were presented for all PK parameters and biomarkers (plasma 4βHC and urinary 6βCR). Only median values and ranges were given for T_{max}.

Sonidegib PBPK Model Input Parameters.

The platform used for the PBPK modeling was the Simcyp® Simulator [Certara Inc., Version 13, release 2 or Version 14, release 1 (for modeling with EFV)]. Physicochemical and PK parameters of sonidegib used for the PBPK model are summarized in Table 1. The first-order absorption model was used and the fraction of dose absorbed (f_a) was user defined as 0.3 or 0.15 for a 200 mg or 800 mg sonidegib dose, respectively. These values were determined by fitting the observed clinical PK data of the two doses in the healthy or patient subjects. Absorption of sonidegib in humans is low, particularly in the fasted state. In the human ADME study, absorption was estimated to be 6-7% of the dose (Study A2110, Zollinger et al., 2014) from a capsule formulation made from dry blending method as opposed to the wet granulation method for capsules used in other clinical studies. It was noted in the publication that the plasma levels of sonidegib were higher in other clinical trials than that in the human ADME study, likely due to the difference in the capsule formulations. Therefore, the f_a values used in the model appeared to describe the majority of the clinical trials used in the model development and qualification. The absorption rate constant (k_a) was also user defined as 0.57/ h and a lag time of 1 h was used to fit the observed clinical data. The effective permeability in man ($P_{eff,man}$) was

predicted as 2.0 x 10^{-4} cm/s based upon Caco-2 permeability data (data not shown). The nominal flow through the gut (Q_{gut}) was predicted in Simcyp (9.086 L/h) and the unbound fraction in the gut (fu_{gut}) was set at 1 (default). The fu_{gut} value was set to 1 in order to minimize the sonidegib F_g value and be conservative with respect to CYP3A-mediated DDI in the intestine (*i.e.* not to under-predict the DDI). Parameter sensitivity analysis of the sonidegib fu_{gut} value and the predicted F_g and DDI magnitude in the presence of KTZ are shown in Supplemental Figure 2. The Advanced Dissolution, Absorption, and Metabolism (ADAM) absorption model was also evaluated to compare with the 1st order absorption model that was used for the modeling and simulation in this manuscript. The input parameters used in that model evaluation can be found in Supplemental Table 2.

The full PBPK model was used with a Simcyp predicted volume of distribution at steady-state (V_{ss}) of 22.6 L/kg. The K_p scalar was set to 1. Sonidegib is primarily metabolized in humans with no urinary excretion of intact sonidegib (Zollinger et al., 2014). Renal clearance (CL_R) was therefore set at 0 l/h. In the Simcyp model, the enzyme kinetics retrograde model was used with an assumed CYP3A4 contribution (oxidative metabolism) of ~75% with the remainder of sonidegib clearance representing ~25%, based upon the human ADME study and results of the *in vitro* CYP reaction phenotyping study, *vide infra*. Specifically, metabolites that were structurally identified and quantified (mean % of dose normalized for total dose recovery) in the urine and feces of the radiolabeled human ADME study were categorized as oxidative or non-oxidative in nature. As shown in Supplemental Table 3, the different metabolic pathways were quantified as 74.3% oxidation on the morpholine moiety, pyridine moiety, and biphenyl moiety plus uncharacterized components (to be conservative for CYP3A-mediated DDI) and 25.7% by amide hydrolysis and *N*-dearylation (Study A2110, Zollinger et al., 2014). Based upon the *in*

vitro enzyme phenotyping study, it was assumed that all oxidative metabolites eliminated from humans *in vivo* arose from primary CYP3A-mediated reactions. The Simcyp predicted intrinsic clearance values for CYP3A4 and the additional clearance pathway in HLM for healthy subjects are shown in Table 1. The resultant output fm_{CYP3A4} (%) values in the model were (mean, median, geometric mean) of 73.3, 75.0, 72.5. To note, the intrinsic clearance in the model was not scaled from the *in vitro* HLM CL_{int} determined in this study (*i.e.* 'bottom-up'), but rather 'top-down' since clinical data was already available. The HLM predicted CL value in the model, however, did not differ greatly from the 'top down' simulated CL value (which was ~20% lower than the HLM CL predicted CL value), see Supplemental Table 4.

The predicted intrinsic clearance (CL_{int}) values for the cancer patient population are also included in parentheses in Table 1. These values reflect a reduced clearance of sonidegib in this population based upon 'top-down' fitting and was the only parameter modified for modeling the patient population in Simcyp. Based upon population PK modeling, clinically relevant covariate effects between healthy volunteers and cancer patients included a 3-fold lower CL/F in patients (Goel et al., 2016). The mechanism of the difference in CL/F between healthy volunteers and patients still remains unknown. It may be a difference in metabolic clearance of the two populations or effects on the bioavailability, such as absorption differences (*e.g.* potential compliance issues with respect to food intake in patient versus healthy volunteer studies). However, the mean elimination half-life ($t_{1/2}$) in healthy volunteers is reported to be 319 h (~13) days (Zollinger et al., 2014) and 265 h (~11) days in study A2114 (*internal data*). In patients, the $t_{1/2}$ was reported to be ~29.6 days (Goel et al., 2016). This suggests that clearance, as opposed to absorption differences in the populations could be the reason for the difference in CL/F, although one or both factors cannot be ruled out. The magnitude of reduction in CL_{int} in

this population in the Simcyp model was based upon fitting of the observed data from one patient trial (X2101) and three healthy volunteer trials (A2114, A2110, and control arm of A2108), of which there was full PK profile data after single and multiple 200 and/or 800 mg doses for model qualification. The resultant change in CL_{po} reported from the modeling in Simcyp was a 1.87-fold reduction in the patient PBPK model, slightly less (~40%) of a change than that reported from population PK model (Goel et al., 2016). A graph of the predicted concentration-time profiles of sonidegib in healthy volunteers compared to cancer patients with overlaid observed data is presented in Supplemental Figure 3. The contribution of CYP3A4 to sonidegib total clearance in the patient model was maintained the same as the healthy volunteer model. Since it remains unknown why there is a reduction in CL/F in patients, the fm_{CYP3A4} was not modified in order to be conservative with respect to DDI mediated through CYP3A4 inhibition or induction, *i.e*. the reduction in clearance was not due to reduction in contribution of CYP3A4. Sonidegib was not found to be an *in vitro* CYP inducer nor an inhibitor or time-dependent inactivator of CYP3A4 (internal data) therefore no CYP3A perpetrator parameters for sonidegib were entered in the model.

PBPK Modeling of Sonidegib PK and DDI.

The Simcyp Simulator was used for these simulations with the Simcyp "Healthy Volunteer" population. The proportion of females in the model was set as 0.5. Ten trials of 10 subjects were simulated for each dosing regimen. The input parameters for sonidegib are described in Table 1. The input parameters for KTZ, ERY, and RIF were the library values provided in the Simcyp Simulator (Version 13, release 2 with an Ind_{max} of 16 for RIF). The maximum induction, Ind_{max} (*i.e.* E_{max} + 1) of 16 for RIF is used in current Simcyp versions of the software and has been found to be more predictive of RIF clinical DDI with CYP3A substrates

(Almond et al, 2016; Wagner et al., 2016). The EFV model was recently published (Ke et al., 2016). The input parameters for the perpetrators used are tabulated in the Supplemental Data (Supplemental Tables 5-8). Two different sonidegib Simcyp models (healthy subject and patient models) were developed to predict single or multiple q.d. dosing regimens in healthy subjects and in cancer patients. The contribution of CYP3A4 to the clearance of sonidegib was verified using the DDI results from the clinical trial of sonidegib in combination with KTZ or RIF. The clinical trials used to develop and verify the model for sonidegib can be found in Table 2. This model was then applied to predict the DDI of KTZ and RIF with sonidegib in cancer patients using the same clinical study trial design for healthy subjects and also using the currently marketed sonidegib dose of 200 mg (Table 2, Trials 1a and 2a). The model was also applied to predict the DDI of sonidegib at steady-state with either KTZ or RIF dosed concomitantly (Table 2, Trials 1b and 2b) or after an acute dose (14 days) of the perpetrator (Table 2, Trials 1c and 2c). In addition, these modeling scenarios were applied to predict the DDI of sonidegib with the moderate CYP3A inhibitor and inducer, ERY (Table 2, Trials 3a-c) and EFV (Table 2, Trials 4a-c), respectively.

Several other scenarios were modeled to assess the magnitude of the sonidegib DDI with KTZ or RIF interaction with an adjusted sonidegib dose during co-administration. In one scenario, the DDI of sonidegib was assessed after every other day (q.o.d.) dosing with concomitant dosing of KTZ (200 mg b.i.d.) to steady-state (Table 2, Trial 1d). In another simulation, sonidegib was given as a 200 mg q.d. dose from day 1-28, then given as a 200 mg q.o.d. dose in the presence of KTZ (200 mg b.i.d.) days 29-42 (14 days) and, after discontinuation of KTZ, the 200 mg q.d. sonidegib dose was resumed (Table 2, Trial 1e). Lastly, sonidegib was modeled as a 200 mg q.d. dose from day 1-28, then given as a 800 mg q.d. dose in

the presence of RIF (600 mg q.d.) days 29-42 (14 days) and, after discontinuation of RIF, the 200 mg q.d. sonidegib dose was resumed (Table 2, Trial 2d).

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Results

In Vitro CYP Reaction Phenotyping.

[^{14}C]Sonidegib was metabolized in HLM in the presence of NADPH to form several oxidative metabolites which had been previously structurally characterized in the human ADME study (Zollinger et al., 2014). No direct glucuronidation or secondary glucuronidation reactions were observed by radiochemical detection when [^{14}C]sonidegib was incubated in HLM in the presence of UDPGA alone or in the presence of both UDPGA and NADPH, respectively (data not shown). Kinetic parameters (K_m, V_{max}) of [^{14}C]sonidegib metabolism in pooled HLM were determined by the analysis of [^{14}C] sonidegib concentration dependence on the rate of metabolite formation and non-linear regression of the steady-state data. The HPLC chromatogram of the metabolism of sonidegib in HLM and kinetic analysis of the data can be found in the Supplemental Fig. 4. The calculated kinetic parameters of sonidegib metabolism can be found in the Supplemental Table 1.

To examine the roles of specific CYP enzymes to metabolize sonidegib, several recombinant CYP enzymes were tested for [^{14}C]sonidegib metabolizing activity. Metabolism of [^{14}C]sonidegib by CYP enzymes above the control levels was only detectable in incubations with CYP3A4 and CYP3A5 (data not shown). The metabolites observed by radiochemical detection in incubations with CYP3A4 were the same as formed in HLM (as shown in Supplemental Fig. 1A). Minor metabolism by CYP3A5 was found.

To further elucidate the contributions of different CYP enzymes to the metabolism of sonidegib in human liver, the ability of selective inhibitors of specific CYP enzymes to inhibit total oxidative metabolism of [^{14}C]sonidegib (at a concentration approximately at its total K_m

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value) in HLM was examined. IC_{50} values were estimated by the concentration of compound which inhibited 50% of total metabolism. The inhibitors of CYP3A4, KTZ and azamulin, inhibited total [^{14}C]sonidegib metabolism with approximate IC_{50} values of 0.04 and 0.01 □M, respectively. These IC_{50} values were in the range of the expected IC_{50} values for the inhibition of CYP3A substrates by these inhibitors (Bohnert et al., 2016). The maximal percent of inhibition achieved by KTZ and azamulin at the concentrations examined were 89 and 96%, respectively. The remaining examined inhibitors did not inhibit [^{14}C]sonidegib metabolism to the reported K_i or IC_{50} values for that specific CYP inhibition. Maximal inhibition of total [^{14}C]sonidegib metabolism by these inhibitors was 0-28%. These data, as well as the data from the recombinant CYP enzyme incubations indicated that sonidegib hepatic oxidative microsomal metabolism is mainly mediated by CYP3A4.

Clinical DDI study of sonidegib with KTZ and RIF.

Effect of KTZ and RIF on the PK of sonidegib. A 1.49-fold increase of C_{max} (90% CI of 1.11-1.99) and 2.25-fold increase of $AUC_{0\text{-}240h}$ (90% CI of 1.78-2.86) was observed when sonidegib was concomitantly administered with KTZ (Table 3, observed data columns). A 54% decrease (ratio 0.46 with 90% CI of 0.35-0.61) of C_{max} and 72% decrease (ratio 0.28, 90% CI 0.22-0.35) of $AUC_{0\text{-}240h}$ was observed when sonidegib was concomitantly administered with RIF. Median T_{max} (2 h) did not change in either sonidegib + KTZ or in sonidegib + RIF arms compared with sonidegib arm alone. $T_{1/2}$ was 124 h for sonidegib alone arm. Due to the even slower terminal phase in sonidegib + KTZ, $T_{1/2}$ of sonidegib could not be estimated for majority of the subjects. Due to the faster elimination/terminal phase for sonidegib in the sonidegib + RIF arm compared with sonidegib arm and sonidegib + KTZ arm, the $T_{1/2}$ in the sonidegib + RIF arm was estimated for all 16 subjects, and the geometric mean was 82.9 hours.

Plasma 4βHC. In the sonidegib alone arm, the mean 4βHC level appeared stable with time from baseline Day -1 to Day 15 (Supplemental Fig. 5A). In the sonidegib + KTZ arm, by Day 19, the mean 4βHC level was approximately 15% lower than the baseline mean. Maximal decrease by KTZ was 25% on Day 8. In the sonidegib + RIF arm, 4βHC level continued to increase until Day 15 where the mean value was maximum (about 3.6-fold) compared to the baseline mean. The elevated level started to return to baseline from Day 15 to Day 19 and remained about 2.9-fold on Day 19 when compared to the baseline mean.

Urinary 6βCR. In the sonidegib alone arm, the 6βCR appeared relatively stable with time from baseline Day -1 to Day 15 (Supplemental Fig. 5B). In the sonidegib + KTZ arm, the 6βCR decreased with time from baseline until Day 15, with the greatest reduction (97%) observed on Day 5. By Day 19, the mean 6βCR was only approximately 7% lower than the baseline mean. Compared with the 4βHC, the 6βCR decreased more promptly and to a greater extent by CYP3A4 inhibition. As a reflection of CYP3A4 induction, 6βCR continued to increase until Day 15 where the mean value was maximum (~4.9-fold) compared with the baseline mean. The level started to come down from Day 15 to Day 19 and remained about 2.6-fold on Day 19 when compared to the baseline mean.

PBPK Modeling of Sonidegib PK and DDI with CYP3A Perpetrators.

In vitro phenotyping studies with sonidegib found CYP3A4 primarily responsible for the oxidative metabolism of sonidegib in HLM, *vide supra*. Based upon the metabolites excreted in the human ADME study, the PBPK model was developed to incorporate ~75% of the metabolic clearance by CYP3A4 and to predict the PK of at 200 and 800 mg doses in healthy subjects (single dose) and in cancer patients (single and multiple doses) from several clinical trials. The observed and simulated PK parameters are shown in Table 4. The simulated concentration-time

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profiles and observed concentrations of sonidegib in these two modeled populations can be found in Fig. 1 (healthy subjects) and Fig. 2 (cancer patients). The healthy subject PBPK model predicted the $AUC_{0\text{-}240}$ and C_{max} values within 38 and 14% of the observed value for the 200 mg dose and within 24 and 55% for the 800 mg dose, respectively, in this population. The C_{max} for the 800 mg single dose that was predicted within 55% was for the human ADME study (A2110, Zollinger et al., 2014). For the other trials listed in Table 2 (Studies A2114 and A2108, control arm of the KTZ and RIF DDI trial) the C_{max} value was predicted within 3-8% of the observed value. The patient PBPK model predicted the $AUC_{0\text{-}last}$ and C_{max} values for the two doses within 24 and 35% of the observed value for the single doses and 9 and 24% for the multiple doses, respectively, in the patient population (Study X2101, Rodon et al., 2014).

The contribution of CYP3A4 to sonidegib clearance in the PBPK model was then verified by the prediction of the interaction of sonidegib (800 mg dose) with the CYP3A strong perpetrators, KTZ and RIF. The simulated and observed PK parameters can be found in Table 3 and concentration-time profiles in Fig. 3. The predicted geometric mean (GM) AUC ratio $(R)_{0\text{-}240h}$ and GM $C_{max}R$ of sonidegib in the presence of KTZ were 2.37 and 1.48, respectively. For comparison, the observed values were 2.25 and 1.49, respectively (as mentioned above). The GM $AUCR_{0\text{-}240h}$ and $C_{max}R$ values for sonidegib DDI with KTZ were predicted within 5 and 1% of the observed values, respectively. The predicted GM $AUCR_{0\text{-}240h}$ and $C_{max}R$ of sonidegib in the presence of RIF were 0.157 and 0.346, respectively. These values were within 43 and 25% of the observed GM $AUCR_{0\text{-}240h}$ and $C_{max}R$ values (0.276 and 0.461, respectively).

The low solubility of sonidegib is the likely the primary reason for the low and dose-dependent absorption. To model the different doses, f_a values of 0.3 and 0.15 were used in the 1st order absorption model of Simcyp for the 200 and 800 mg doses, respectively. To evaluate

the assumption for use of these particular f_a values in the 1st order absorption model, the ADAM model in Simcyp was also evaluated to predict the PK and DDI with KTZ and RIF in the healthy volunteer population. Based upon predictions of f_a and k_a values using Caco-2 cell permeability data and an intrinsic solubility in the model of 0.005 mg/ml (a value that best predicted the PK of the 2 doses and a value close to the actual reported solubility in water of 0.007 mg/ml, *internal data*), the simulated PK and DDI with KTZ and RIF for the two sonidegib doses were predicted within 2-fold of the observed values, as did the 1st order absorption model (Supplemental Tables 9 and 10). The resultant f_a values from the ADAM model were 0.25 and 0.10 for the 200 and 800 mg doses, very similar to the values used in the 1st order absorption model. Therefore, the magnitude of change in the f_a values used for the two doses in the 1st order absorption model was deemed appropriate. In general, however, the prediction errors for many of the PK parameters were larger and DDI with the strong CYP3A4 perpetrators more under-predicted using the ADAM model. Particularly, the 1st order absorption model predicted the DDI at C_{max} very well, compared to predictions using the ADAM model, inferring that the 1st order absorption model had adequately predicted the DDI both at the level of the intestine and liver.

Using the PBPK model developed to predict the PK of sonidegib in healthy and cancer patient populations (200 and 800 mg) as well as the clinical DDI (800 mg sonidegib dose in healthy subjects) with strong CYP3A perpetrators, the DDI of sonidegib with KTZ and RIF at the marketed sonidegib dose (200 mg) in healthy subjects was then predicted. The predicted GM AUCR and C_{max}R values for sonidegib at the 200 mg dose in the presence of KTZ or RIF were identical to those simulated at the 800 mg dose (data not shown). The model was then applied to predict the DDI of sonidegib (200 or 800 mg) with these strong CYP3A perpetrators in cancer patients using the same trial design as the actual clinical trial described above. The simulated

results can be found in Table 5 (Trial 1a) and Table 6 (Trial 2a) and the simulated concentration-time profiles (for 200 mg sonidegib dose) can be found in Fig. 4A (KTZ) and Fig. 5A (RIF). Similarly as the KTZ and RIF DDI was predicted in healthy volunteers, there was no difference in the GM AUCR or $C_{max}R$ with the dose of sonidegib in cancer patients. The predicted sonidegib DDI with KTZ and RIF in cancer patients was slightly less than that found in healthy subjects. The GM $AUCR_{0\text{-}240h}$ and $C_{max}R$ for sonidegib (200 or 800 mg dose) in the presence of KTZ was 1.85 and 1.29, respectively, and RIF was 0.21 and 0.45, respectively. The model was also applied to predict the DDI with KTZ and RIF using different dosing regimens: (Trial b) long-term dosing (4 months) of both sonidegib and the strong CYP3A perpetrator and (Trial c) acute dosing of the perpetrator (14 days) with sonidegib after sonidegib had reached steady-state (120 days). The results of these simulations can be found in Table 5 (Trial 1b and 1c) and Table 6 (Trial 2b and 2c). The simulated concentration-time profiles can be found in Fig. 4B and 4C and Fig. 5B and 5C. The DDI increased with the long-term dosing of sonidegib and the strong CYP3A perpetrators. The GM $AUCR_{0\text{-}24h}$ and $C_{max}R$ values were 3.53 and 2.99, respectively, for the interaction with KTZ (Table 5, Trial 1b) and 0.12 and 0.20, respectively, for the interaction with RIF (Table 6, Trial 2b). Acute dosing of the perpetrator (14 days) with sonidegib at steady-state resulted in lower GM $AUCR_{0\text{-}24h}$ and $C_{max}R$ values of 2.01 and 1.81, respectively for the KTZ interaction (Table 5, Trial 1c) and 0.20 and 0.27, respectively, for the RIF interaction (Table 6, Trial 2c). The magnitude of the predicted interaction with sonidegib at steady-state with an acute dose of KTZ was similar to the magnitude of drug interaction found in the healthy subject DDI trial.

Predictions of DDI with a moderate CYP3A inducer or inhibitor. The sonidegib patient PBPK model was applied to predict the interaction of the moderate CYP3A inhibitor, ERY, and

inducer, EFV, on sonidegib PK (200 mg dose) in cancer patients using the different dosing regimens (Trial a: same trial design as an actual clinical DDI trial, Trial b: long-term (4 months) dosing, and Trial c: acute dosing of the perpetrator (14 days) with sonidegib at steady-state). The simulated results and concentration-time profiles can be found in Table 7 and Fig. 6 for the interaction with ERY and Table 8 and Fig. 7 for the interaction with EFV. For the ERY interaction Trial 3a, The PBPK model predicted the GM $AUCR_{0\text{-}240h}$ and $C_{max}R$ of sonidegib to be 1.70 and 1.26, respectively. After long-term dosing for 4 months of both sonidegib and the moderate CYP3A inhibitor, ERY, (Trial 3b) the predicted GM $AUCR_{0\text{-}24h}$ and $C_{max}R$ values of sonidegib were 2.79 and 2.43, respectively. Acute dosing of the moderate inhibitor (Trial 3c) resulted in a predicted GM $AUCR_{0\text{-}24h}$ and $C_{max}R$ of sonidegib of 1.79 and 1.64, respectively (Table 7). The predicted interaction of the moderate CYP3A inducer, EFV, with sonidegib with the clinical DDI trial design (Trial 4a) was 0.53 and 0.81 for GM $AUCR_{0\text{-}240h}$ and $C_{max}R$ (Table 8). Long-term dosing of both sonidegib and moderate CYP3A inducer (Trial 4b) resulted in a predicted DDI (GM $AUCR_{0\text{-}24h}$ and $C_{max}R$) of 0.35 (65% decrease) and 0.46 (54% decrease), respectively. Acute dosing of EFV (14 days) with sonidegib at steady-state (Trial 4c) resulted in a predicted GM $AUCR_{0\text{-}24h}$ and $C_{max}R$ of 0.47 (56% decrease) and 0.56 (44% decrease), respectively.

Simulations of different dosing regimens. Finally, the sonidegib patient PBPK model was used to evaluate the effect of sonidegib dose adjustments during acute co-administration of the strong CYP3A perpetrators, KTZ and RIF (Trial designs described in Table 2, Trial 1d, 1e, and 2d). The tabulated results of simulated Trial 1d (200 mg q.o.d. sonidegib concomitantly with 200 mg b.i.d. KTZ for 133 days) can be found in Table 5. The DDI was less than if sonidegib was dosed once a day GM $AUCR_{0\text{-}48}$ and CmaxR values of 1.93 and 1.62, respectively for

sonidegib q.o.d. dosing (versus 2.01 and 1.81, respectively, for sonidegib q.d. dosing). The simulated concentration-time profiles of sonidegib from the simulated trials 1e and 2d are shown in Fig. 8. In these simulations, sonidegib was dosed for one month (200 mg q.d.) and then co-administered with the perpetrator either increasing the sonidegib dose (to 800 mg q.d.) in combination with RIF or dosing sonidegib 200 mg q.o.d. in the presence of RIF. The PK was then assessed on day 43 (0-24h) after the dose of sonidegib was returned to 200 mg q.d. and dosed without perpetrator. The GM $AUCR_{0-24}$ and CmaxR were calculated by comparison of these PK parameters to those calculated by modeling a 200 mg q.d. dose of sonidegib alone to day 43. For the trial with KTZ, the $AUCR_{0-24}$ and CmaxR values were 1.32 and 1.28, respectively, and for the RIF trial, the values were 0.26 and 0.30, respectively.

Discussion

PBPK modeling and simulation has had an increasing impact on product labels, particularly influencing dosing recommendations, including guidance for specific dose adjustments for drug-drug interactions. The FDA has published several papers emphasizing the importance of modeling and simulations in drug development including specifics on the best practice for use of PBPK modelling in regulatory submissions (Huang et al., 2012, Huang et al., 2013, Zhao et al., 2011, Zhao et al., 2012). The increasing number of submissions including PBPK data has now prompted regulators to provide specific guidance for this type of modeling (EMA Draft PBPK modeling guideline, 2016; FDA Draft PBPK modeling guideline, 2016). In a recent review, Jamei (2016) lists 19 approved drugs where PBPK simulations had informed the drug label, including Odomzo®. Looking into the details of the PBPK modeling used in submissions, there was a notable trend in predictions of DDI for moderate inhibitors and/or inducers of CYP3A and recommendations for dosing according to the magnitude of the predicted interaction. In the case of sonidegib, the modeling and simulation work presented here was influential for the dosing strategy in the product label for patients when co-administered with strong or moderate perpetrators of CYP3A and understanding potential consequences of acute or chronic dosing of them with sonidegib at steady-state (*i.e.* real-world scenarios).

Verification of the contributions of specific enzymes to the total clearance of a drug is an important aspect in the prediction of DDI. Due to the predominant involvement of CYP3A4 in the clearance of sonidegib in humans, based upon the results of the *in vitro* enzyme reaction phenotyping and radiolabeled human ADME study, a clinical DDI trial in healthy subjects with the strong CYP3A perpetrators, KTZ and RIF was conducted to assess the magnitude of exposure change of sonidegib with CYP3A inhibition or induction. The moderate DDI effect of

sonidegib (800 mg) with KTZ observed in the trial (GM $AUCR_{0\text{-}240h}$ of 2.37) and effect the strong inducer, RIF, (72% reduction in the GM $AUCR_{0\text{-}240h}$) confirmed the ~75% contribution of CYP3A4 to the total clearance of sonidegib. In addition, time course change of the *in vivo* CYP3A biomarker data have demonstrated the inhibition and induction effect achieved from KTZ and RIF treatment and correlated with the PK exposure of sonidegib in different arms. The CYP3A activity biomarkers, plasma 4ßHC and urinary 6ßCR, were included as exploratory tools to further our understanding on what changes to expect in the presence of a strong inhibitor/inducer. The 3.6-fold increase in plasma 4ßHC by rifampicin after 14 days of dosing in our study is consistent with the model predicted increases for a strong CYP3A inducer as described in an earlier publication (Mangold et al., 2016). Based on the biomarker measurement, minimal to no effect of single dose of sonidegib on CYP3A4 activity was observed.

In order to extrapolate this clinical DDI study to the currently marketed dose of 200 mg sonidegib in cancer patients, a PBPK model was developed to predict the concentration-time profiles and PK parameters of sonidegib at the 200 and 800 mg doses in both healthy subjects and cancer patients. As mentioned earlier, likely due to the low solubility of sonidegib, there are absorption differences with these two doses and that is reflected in the model. The modeling presented here and also as Supplemental Data, found that the 1^{st} order absorption model performed well with adequate DDI predictions in both the intestine and liver, even compared to the more mechanistic ADAM model in Simcyp. Two PBPK models were created to predict the specific populations with the cancer patient model developed with a lower CL_{int} compared to the healthy subject model. It remains unclear as to the differences in the CL/F of sonidegib in patients and healthy volunteers (Goel et al., 2016); both clearance and absorption may be playing

a role. However, based upon the shorter mean elimination $t_{1/2}$ in healthy volunteers (~11-13 days) compared to patients (~29.6 days) it is suggested that clearance, as opposed to absorption differences in the populations, maybe the important factor for the difference in CL/F. The resultant models predicted the sonidegib PK parameters well at both the 200 and 800 mg single and multiple doses for the different populations compared with observed values. The predicted DDI of sonidegib with KTZ and RIF in healthy subjects was also qualified with the observed interaction.

The PBPK model was applied to various clinical situations that were not tested, however were impactful to the Odomzo® product label (Odomzo® Prescribing Information, 2016): 1) The effect of an acute dose (14 days) of a strong CYP3A inhibitor on steady-state sonidegib in cancer patients and 2) The effect of acute (14 days) and long-term (4 months) doses of moderate CYP3A inhibitors or inducers on steady-state sonidegib in cancer patients. In the former modeling scenario, the PBPK model results were presented in the Pharmacokinetics section (12.3) of the Odomzo® Food and Drug Administration (FDA) product label. The data was presented to indicate that the results of the clinical DDI trial with sonidegib (800 mg single dose) and KTZ in healthy subjects (GM $AUCR_{0\text{-}240h}$ of 2.25) could be bridged to cancer patients dosed at the marketed 200 mg dose to steady-state (predicted GM $AUC_{0\text{-}24h}$ of 2.01). The common strategy behind the dosing recommendations of CYP3A4 inhibitors in combination with sonidegib was to not exceed a 2-fold increase in exposure of the 200 mg sonidegib dose. This was based upon the exposure difference of the 800 mg dose compared to the 200 mg dose in cancer patients. The 800 mg dose was the highest tested dose in the pivotal trials wherein it was well tolerated from a safety perspective and provided ~2.5-fold higher exposure than the 200 mg dose in cancer patients (Goel et al., 2016). To note, there is no/flat exposure-efficacy

relationship for sonidegib. Based upon these criteria, the recommendation in the FDA product label is to avoid the co-administration of strong inhibitors of CYP3A4 (chronically or acutely dosed) with sonidegib. The EMA offers a possibility for a sonidegib dose adjustment to every other day regimen with co-administration of strong CYP3A4 inhibitors. Given the PK linearity at this dose range (*i.e.* below 400 mg), 200 mg every other day dosing in theory would provide half of the exposure from 200 mg every day dosing. The DDI predicted in cancer patients with every other day dosing of sonidegib to steady-state in the presence of KTZ was less than 2-fold (Table 5, Trial 1d). Additionally, as shown in the simulation of sonidegib dosed once a day for one month prior to co-administration of sonidegib every other day with KTZ) for 14 days (Fig. 8B), this type of dosing regimen appears to adequately minimize the exposure to sonidegib in the presence of strong inhibitors. In the latter modeling scenario of the DDI with moderate CYP3A inhibitors or inducers, the PBPK model results were also presented in the Pharmacokinetics section, as well as the Drug Interactions section (7.1) of the Odomzo® FDA product label. Based upon the PBPK modeling results, the product label recommends "avoid(ing) long-term (greater than 14 days) use of moderate CYP3A inhibitors". The PBPK model predicted < 2-fold (1.79-fold) drug interaction of the moderate CYP3A inhibitor, ERY, with steady-state sonidegib when ERY was dosed for only 14 days. However, long-term multiple doses of ERY (4 months) was predicted to increase steady-state sonidegib >2-fold (2.79-fold).

For inducers, strong or moderate, the use of concomitant sonidegib should be avoided. Due to the large magnitude of DDI effect on steady-state sonidegib (>80% reduction in exposure) predicted with strong CYP3A inducers and the >50% reduction in exposure predicted for moderate inducers in cancer patients, regardless of the dosing regimen (acute vs. long-term dosing of the perpetrator) the recommendation is to avoid CYP3A inducers. The EMA

recommends avoiding strong inducers, however, if inducer treatment is necessary, the daily dose of sonidegib may be increased to 400-800 mg during the co-treatment. The modeling of this dosing regimen after one month of sonidegib dosing is shown on Fig. 8A. The modeling suggests that the exposure of sonidegib declines in the presence of a strong CYP3A inducer for 14 days to exposures similar to those after a few days of dosing sonidegib.

In conclusion, a well-built PBPK model fitting both healthy volunteer and patient populations was developed based upon available *in vitro* and clinical data and verified to predict single and multiple dose PK and the CYP3A-mediated DDI of sonidegib after a single dose. The model was then applied to predict dosing scenarios that could not be easily tested in typical clinical pharmacology studies (*i.e.* effect of CYP3A perpetrators on sonidegib with long-term dosing and dose adjustments during perpetrator dosing). Based upon the qualified model, alternative dose regimens were evaluated for the magnitude of the interaction with sonidegib. The magnitude of interaction predicted was important for decisions made regarding dosing recommendations and made an impact on the current FDA and EMA labeling language for Odomzo®.

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Authorship Contributions

Participated in research design: Einolf, Zhou, Won

Conducted experiments: Einolf, Zhou, Won, Wang

Performed data analysis: Einolf, Zhou, Won, Wang

Wrote or contributed to the writing of the manuscript: Einolf, Zhou, Won, Rebello

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Figure Legends

Fig. 1. Observed and simulated concentration-time profiles of a single dose of sonidegib in healthy subjects. Mean concentration of sonidegib dosed as a (A) 200 mg or (B) 800 mg single dose in healthy subjects. The black line is the simulated mean concentration of sonidegib and the grey lines represent the upper 90th and lower 10th confidence intervals. The symbols and error bars are the actual mean concentration data and standard deviation, respectively, from trial A2114 (circles), A2108 (triangles), and A2110 (squares).

Fig. 2. Observed and simulated concentration-time profiles of single or multiple doses of sonidegib in cancer patients. Mean concentration of sonidegib dosed as single or multiple (A) 200 mg or (B) 800 mg doses in cancer patients. The black line is the simulated mean concentration of sonidegib and the grey lines represent the upper 90th and lower 10th confidence intervals. The symbols and error bars are the actual mean concentration data and standard deviation, respectively, from trial X2101.

Fig. 3. Observed and simulated concentration-time profiles of sonidegib (800 mg) in the presence and absence of KTZ or RIF in healthy subjects. (A) Mean concentration of sonidegib (800 mg) dosed as a single dose on day 5 in the absence (simulated: black line; observed, open symbols) or presence (simulated: grey line; observed, grey symbols) of KTZ (200 mg b.i.d.) or (B) RIF (600 mg q.d.) dosed on days 1-14. The standard error bars of the observed data are the standard deviation.

Fig. 4. Simulations of the DDI of sonidegib (200 mg) with the strong CYP3A inhibitor, KTZ, in cancer patients. (A) Mean concentration of sonidegib (200 mg) dosed as a single dose on day 5 in the absence (black line) or presence (grey line) of KTZ (200 mg b.i.d.) dosed on days 1-14, (B) both dosed to steady-state (120 days), or (C) sonidegib dosed for 133 days with KTZ dosed as an acute dose on days 120-133 (14 days).

Fig. 5. Simulations of the DDI of Sonidegib (200 mg) with the strong CYP3A inducer, RIF, in cancer patients. (A) Mean concentration of sonidegib (200 mg) dosed as a single dose on day 5 in the absence (black line) or presence (grey line) of RIF (600 mg q.d.) dosed on days 1-14, (B) both dosed to steady-state (120 days), or (C) sonidegib dosed for 133 days with RIF dosed as an acute dose on days 120-133 (14 days).

Fig. 6. Simulations of the DDI of sonidegib (200 mg) with the moderate CYP3A inhibitor, ERY, in cancer patients. (A) Mean concentration of sonidegib (200 mg) dosed as a single dose on day 5 in the absence (black line) or presence (grey line) of ERY (500 mg q.i.d.) dosed on days 1-14, (B) both dosed to steady-state (120 days), or (C) sonidegib dosed for 133 days with ERY dosed as an acute dose on days 120-133 (14 days).

Fig. 7. Simulations of the DDI of sonidegib (200 mg) with the moderate CYP3A inducer, EFV, in cancer patients. (A) Mean concentration of sonidegib (200 mg) dosed as a single dose on day 5 in the absence (black line) or presence (grey line) of EFV (600 mg q.d.) dosed on days 1-14, (B) both dosed to steady-state (120 days), or (C) sonidegib dosed for 133 days with EFV dosed as an acute dose on days 120-133 (14 days).

Fig. 8. Simulations of sonidegib concentrations over-time in cancer patients when co-administered with RIF 600 mg q.d. (A) or KTZ 200 mg b.i.d. (B) for 14 days using different dosing regimens of sonidegib during the co-treatment period. The line represents the mean concentration of sonidegib (200 mg q.d.) on days 1-28 and 43-112 in the absence of perpetrator and sonidegib dosed (A) 800 mg q.d. with RIF (600 mg q.d.) or (B) 200 mg q.o.d. with KTZ (200 mg b.i.d.) on days 29-42.

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Tables

TABLE 1

PBPK model input parameters for sonidegib

Parameter	Value
Physical Chemistry and blood binding	
Molecular weight (g/mol)	485.5
logP	4.26
pK_a	4.2
B/P	0.55
$f_{u,plasma}$	0.025
Absorption	
Model used	1st order
f_a	0.3 (200 mg); 0.15 (800 mg)
Lag time (h)	1
k_a (per h)	0.57
$P_{eff,man}$ ($x10^{-4}$ cm/s)	2
fu_{gut}	1
Q_{gut} (l/h)	9.086
Distribution	
Model used	Full PBPK
V_{ss} (l/kg)	22.7
Elimination	
Model used	Enzyme Kinetics[a]
CL_{int} CYP3A4 (µl/min/pmol CYP)	0.687 (0.417 cancer patients)
Additional HLM CL_{int} (µl/min/mg protein)	31.38 (19.06 cancer patients)
CL_R (l/h)	0

B/P, blood to plasma ratio
$f_{u,plasma}$, fraction unbound in the plasma
[a]The CL_{int} values were estimated using the Simcyp retrograde model, see Materials and Methods

TABLE 2

Simulated Trials

Type of simulation	Trial and Description	Dose and regimen of sonidegib	Dose and regimen of perpetrator
Model development			
	Study A2114 (Internal data) Relative bioavailability study and effect of food on sonidegib PK in healthy subjects	200 and 800 mg single doses of CSF (clinical service form) capsule formulation (fasted)	NA
	Study A2110 (Zollinger et al., 2014) Human radiolabeled ADME study in healthy subjects	800 mg single dose	NA
	Study X2101 (Rodon et al., 2014) A phase I, multicenter, open-label, first-in-human, dose-escalation study of sonidegib in patients with advanced solid tumors.	200 and 800 mg single and multiple q.d. doses	NA
Model verification			
	Effect of KTZ or RIF on sonidegib PK in healthy subjects (Study A2108)	800 mg single dose on day 5	KTZ (200 mg b.i.d.) or RIF (600 mg q.d.) days 1-14
Model application			
	1. Effect of KTZ on sonidegib PK in cancer patients	a. 200 or 800 mg single dose on day 5	a. KTZ (200 mg b.i.d.) days 1-14
		b. 200 mg q.d. days 1-120	b. KTZ (200 mg b.i.d.) days 1-120
		c. 200 mg q.d. days 1-133	c. KTZ (200 mg b.i.d.) days 120-133 (14 days)
		d. 200 mg q.o.d. days 1-133	d. KTZ (200 mg b.i.d.) days 120-133 (14 days)

	e. 200 mg q.d. days 1-28, 200 mg q.o.d. days 29-42, 200 mg q.d. days 43-112[a]	e. KTZ (200 mg b.i.d.) days 29-42
2. Effect of RIF on sonidegib PK in cancer patients	a. 200 or 800 mg single dose on day 5	a. RIF (600 mg q.d.) days 1-14
	b. 200 mg q.d. days 1-120	b. RIF (600 mg q.d.) days 1-120
	c. 200 mg q.d. days 1-133	c. RIF (600 mg q.d.) days 120-133 (14 days)
	d. 200 mg q.d. days 1-28, 800 mg q.d. days 29-42, 200 mg q.d. days 43-112[a,b]	d. KTZ (200 mg b.i.d.) days 29-42
3. Effect of ERY on sonidegib PK in cancer patients	a. 200 mg single dose on day 5	a. ERY (500 mg q.i.d.) days 1-14
	b. 200 mg q.d. days 1-120	b. ERY (500 mg q.i.d.) days 1-120
	c. 200 mg q.d. days 1-133	c. ERY (500 mg q.i.d.) days 120-133 (14 days)
4. Effect of EFV on sonidegib PK in cancer patients	a. 200 mg single dose on day 5	a. EFV (600 mg q.d.) days 1-14
	b. 200 mg q.d. days 1-120	b. EFV (600 mg q.d.) days 1-120
	c. 200 mg q.d. days 1-133	c. EFV (600 mg q.d.) d120-133 (14 days)

NA, not applicable

[a]PK assessed on day 43 (0-24h)

[b]Due to a technical limitation of Simcyp, to simulate the PK of 800 mg (f_a = 0.15), the compound file for the 200 mg dose was used and the dose was entered as 400 mg (f_a = 0.30) in the custom dosing table. The exposure to 400 mg (with f_a = 0.3) was identical to the exposure to 800 mg (with f_a = 0.15).

TABLE 3

Observed and simulated clinical PK parameters of sonidegib in the presence and absence of the strong CYP3A perpetrators, KTZ and RIF, in healthy subjects

Treatment	Statistics	$AUC_{0\text{-}240}$ (ng·h/ml)		C_{max} (ng/ml)	
		Observed	*Simulated*[a]	Observed	*Simulated*
800 mg sonidegib single dose on day 5	n	16	*100*	16	*100*
	Mean (SD)	6080 (2530)	*6431 (2993)*	246 (158)	*238 (73.4)*
			PE = +6%		*PE = -3%*
	CV% mean	41.6	*46.5*	64.4	*30.9*
	GM	5620	*5816*	212	*227*
			PE = +3%		*PE = +7%*
	CV% GM	42.0	-[b]	56.3	-
800 mg sonidegib single dose on day 5 + KTZ (200 mg b.i.d.) days 1-14	n	15	*100*	15	*100*
	Mean (SD)	13400 (4430)	*15043 (6638)*	330 (102)	*351 (102)*
			PE = +12%		*PE = +6%*
	CV% mean	33.0	*44.1*	30.8	*29.0*
	GM	12700	*13778*	316	*337*
			PE = +8%		*PE = +7%*
	CV% GM	38.2	-	31.9	-
	GM ratio (CI)	2.25 (1.78, 2.86)	*2.37 (2.25, 2.49)*	1.49 (1.11, 1.99)	*1.48 (1.44, 1.52)*
			PE = +5%		*PE = -1%*
800 mg sonidegib single dose on day 5 + RIF (600 mg q.d.) days 1-14	n	16	*100*	16	*100*
	Mean (SD)	1660 (579)	*1172 (851)*	111 (54.5)	*90.8 (49.2)*
			PE = -29%		*PE = -18%*
	CV% mean	34.8	*72.6*	49.0	*54.2*
	GM	1550	*912*	97.7	*78.4*

		PE = -41%		*PE = -20%*
CV% GM	41.6	-	60.5	-
GM ratio (CI)	0.276	*0.157*	0.461	*0.346*
	(0.219, 0.349)	*(0.141, 0.175)*	(0.346, 0.613)	*(0.319, 0.375)*
		PE = -43%		*PE = -25%*

n, number of subjects with non-missing values
GM, geometric mean
CI, confidence interval (90%)
PE, prediction error % = [(predicted value – observed value)/observed value]*100
[a]simulated data for control arm is reported from the sonidegib and KTZ simulation. There was little difference in the PK parameters observed in the control arm of the sonidegib and RIF simulation compared to the control arm of the sonidegib and KTZ simulation.
[b]not available

TABLE 4

Observed and simulated clinical PK parameters of sonidegib in healthy subjects and cancer patients

Treatment	Population (Study)		$AUC_{0\text{-}last}$[a] (ng·h/ml)		C_{max} (ng/ml)	
		Statistics	Observed	*Simulated*	Observed	*Simulated*
200 mg sonidegib single dose	Healthy Subjects (A2114)	n	10	*100*	12	*100*
		Mean (SD)	3327 (1822)	*4596 (2178)* *PE = +38%*	104 (45)	*119 (36.8)* *PE = +14%*
		GM	2481	*4104*	87.0	*113*
	Cancer Patients (X2101)	n	6	*100*	6	*100*
		Mean (SD)	3673 (2133)	*4026 (1759)* *PE = +10%*	160 (115)	*140 (41.6)* *PE = -13%*
		GM	-[b]	*3695*	-	*134*
800 mg Sonidegib single dose	Healthy subjects (A2114)	n	11	*100*	13	*100*
		Mean (SD)	12087 (7888)	*9192 (4355)* *PE = -24%*	258 (155)	*238 (73.6)* *PE = -8%*
		GM	10348	*8208*	216	*227*
	Healthy subjects (A2110)	n	6	*100*	6	*100*
		Mean (SD)	8680 (2510)	*9192 (4355)* *PE = +6%*	154 (33)	*238 (73.6)* *PE = +55%*
		GM	8370	*8208*	151	*227*
	Healthy subjects (A2108, control arm)	n	16	*100*	16	*100*
		Mean (SD)	6080 (2530)	*6431 (2993)* *PE = +6%*	246 (158)	*238 (73.4)* *PE = -3%*
		GM	5620	*5816*	212	*227*

	Cancer patients (X2101)	n	25	*100*	25	*100*
		Mean (SD)	7867 (6950)	*8052 (3517)* *PE = +2%*	429 (381)	*280 (83.2)* *PE = -35%*
		GM	-	*7390*	-	*268*
200 mg sonidegib multiple dose	Cancer patients (X2101)	n	5	*100*	5	*100*
		Mean (SD)	5916 (3886)	*5788 (2690)* *PE = -2%*	269 (163)	*333 (130)* *PE = +24%*
		GM	-	*5243*	-	*310*
800 mg sonidegib multiple dose	Cancer patients (X2101)	n	20	*100*	20	*100*
		Mean (SD)	12781 (6351)	*11575 (5380)* *PE = -9%*	840	*666 (259)* *PE = -21%*
		GM	-	*10485*	-	*621*

n, number of subjects with non-missing values
GM, geometric mean
PE, prediction error % = [(predicted value – observed value)/observed value]*100
[a]AUClast for A2114 = 0-2016h; X2101 = 0-168h for the single dose and 0-24h for the multiple dose; A2110 = 0-2016h; A2108 = 0-240h
[b]not determined

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TABLE 5

Simulated clinical PK parameters of sonidegib in the presence and absence of the strong CYP3A inhibitor, KTZ, in cancer patients

Trial	Treatment	**AUC** (ng·h/ml) mean (SD) 0-24 h	0-240 h	**C_{max}** (ng/ml) mean (SD)
1a	800 mg sonidegib single dose on day 5	2855 (879)	9504 (4324)	280 (83)
	800 mg sonidegib single dose on day 5 + KTZ (200 mg b.i.d.) days 1-14	4036 (1186)	17526 (7819)	361 (105)
	GM ratio (CI)	1.42 (1.39, 1.45)	1.85 (1.78, 1.93)	1.29 (1.27, 1.32)
	200 mg sonidegib single dose on day 5	1428 (440)	4754 (2163)	140 (41.5)
	200 mg sonidegib single dose on day 5 + KTZ (200 mg b.i.d.) days 1-14	2018 (593)	8763 (3910)	181 (52.4)
	GM ratio (CI)	1.42 (1.39, 1.45)	1.85 (1.78, 1.93)	1.29 (1.27, 1.32)
1b	200 mg sonidegib q.d. days 1-120	8285 (3857)	-[a]	439 (176)
	200 mg sonidegib q.d. days 1-120 + KTZ (200 mg b.i.d.) days 1-120	28836 (12772`)	-	1318 (547)
	GM ratio (CI)	3.53 (3.31, 3.76)	-	2.99 (2.83, 3.16)
1c	200 mg sonidegib q.d. days 1-133	8301 (3871)	-	440 (177)
	200 mg sonidegib q.d. days 1-133 + KTZ (200 mg b.i.d.) days 120-133 (14 days)	16189 (6628)	-	786 (293)
	GM ratio (CI)	2.01 (1.92, 2.11)	-	1.81 (1.74, 1.88)
1d	200 mg sonidegib q.o.d. days 1-133	8293 (3867)[b]	-	280 (101)
	200 mg sonidegib q.o.d. days 1-133 + KTZ (200 mg b.i.d.) days 120-133 (14 days)	15522 (6310)[b]	-	450 (153)
	GM ratio (CI)	1.93 (1.84, 2.02)		1.62 (1.57, 1.67)

SD, standard deviation
GM, geometric mean
CI, confidence interval (90%)
[a]not simulated
[b]$AUC_{0\text{-}48h}$

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TABLE 6

Simulated clinical PK parameters of sonidegib in the presence and absence of the strong CYP3A inducer, RIF, in cancer patients

Trial	Treatment	**AUC** (ng·h/ml) mean (SD) 0-24 h	0-240 h	**C_{max}** (ng/ml) mean (SD)
2a	800 mg sonidegib single dose on day 5	2856 (879)	9510 (4328)	280 (83.1)
	800 mg sonidegib single dose on day 5 + RIF (600 mg q.d.) days 1-14	1054 (528)	2246 (1481)	136 (62.6)
	GM ratio (CI)	0.34 (0.31, 0.37)	0.21 (0.19, 0.23)	0.45 (0.43, 0.49)
	200 mg sonidegib single dose on day 5	1428 (440)	4755 (2164)	140 (41.5)
	200 mg sonidegib single dose on day 5 + RIF (600 mg q.d.) days 1-14	532 (285)	1133 (795)	68.7 (34.0)
	GM ratio (CI)	0.34 (0.32, 0.37)	0.21 (0.19, 0.23)	0.46 (0.43, 0.49)
2b	200 mg sonidegib q.d. days 1-120	8288 (3859)	-[a]	439 (176)
	200 mg sonidegib q.d. days 1-120 + RIF (600 mg q.d.) days 1-120	1124 (886)	-	94.4 (59.0)
	GM ratio (CI)	0.12 (0.11, 0.13)	-	0.20 (0.18, 0.22)
2c	200 mg sonidegib q.d. days 1-133	8303 (3872)	-	440 (177)
	200 mg sonidegib q.d. days 1-133 + RIF (600 mg q.d.) days 120-133 (14 days)	1858 (1364)	-	126 (73.6)
	GM ratio (CI)	0.20 (0.18, 0.22)	-	0.27 (0.24, 0.29)

SD, standard deviation
GM, geometric mean
CI, confidence interval (90%)
[a]not simulated

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TABLE 7

Simulated clinical PK parameters of sonidegib in the presence and absence of the moderate CYP3A inhibitor, ERY, in cancer patients

Trial	Treatment	**AUC** (ng·h/ml) mean (SD) 0-24 h	0-240 h	$\mathbf{C_{max}}$ (ng/ml) mean (SD)
3a	200 mg sonidegib single dose on day 5	1427 (439)	4752 (2162)	140 (41.5)
	200 mg sonidegib single dose on day 5 + ERY (500 mg q.i.d.) days 1-14	1940 (587)	8087 (3737)	176 (51.1)
	GM ratio (CI)	1.36 (1.33, 1.39)	1.70 (1.31, 2.32)	1.26 (1.23, 1.28)
3b	200 mg sonidegib q.d. days 1-120	8279 (3855)	-[a]	439 (176)
	200 mg sonidegib q.d. days 1-120 + ERY (500 mg q.i.d.) days 1-120	23457 (11611)	-	1091 (497)
	GM ratio (CI)	2.79 (1.76, 4.61)	-	2.43 (1.63, 3.94)
3c	200 mg sonidegib q.d. days 1-133	8297 (3869)	-	440 (177)
	200 mg sonidegib q.d. days 1-133 + ERY (500 mg q.i.d.) days 120-133 (14 days)	14600 (6329)	-	718 (280)
	GM ratio (CI)	1.79 (1.71, 1.86)	-	1.64 (1.58, 1.70)

SD, standard deviation
GM, geometric mean
CI, confidence interval (90%)
[a]not simulated

TABLE 8

Simulated clinical PK parameters of sonidegib in the presence and absence of the moderate CYP3A inducer, EFV, in cancer patients

Trial	Treatment	**AUC** (ng·h/ml) mean (SD) 0-24 h	0-240 h	$\mathbf{C_{max}}$ (ng/ml) mean (SD)
4a	200 mg sonidegib single dose on day 5	1470 (510)	4970 (2142)	151 (53.5)
	200 mg sonidegib single dose on day 5 + EFV (600 mg q.d.) days 1-14	1058 (398)	2738(1361)	124 (46.2)
	GM ratio (CI)	0.71 (0.69,0.74)	0.53 (0.50, 0.57)	0.81 (0.79, 0.83)
4b	200 mg sonidegib q.d. days 1-120	9238 (5229)	-[a]	487 (243)
	200 mg sonidegib q.d. days 1-120 + EFV (600 mg q.d.) days 1-120	3380 (2126)	-	227 (114)
	GM ratio (CI)	0.35 (0.33,0.38)	-	0.46 (0.44,0.49)
4c	200 mg sonidegib q.d. days 1-133	9256 (5251)	-	488 (244)
	200 mg sonidegib q.d. days 1-133 + EFV (600 mg q.d.)) days 120-133 (14 days)	4585 (3107)	-	279 (155)
	GM ratio (CI)	0.47 (0.44, 0.50)	-	0.56 (0.53,0.59)

SD, standard deviation
GM, geometric mean
CI, confidence interval (90%)
[a]not simulated

Figures

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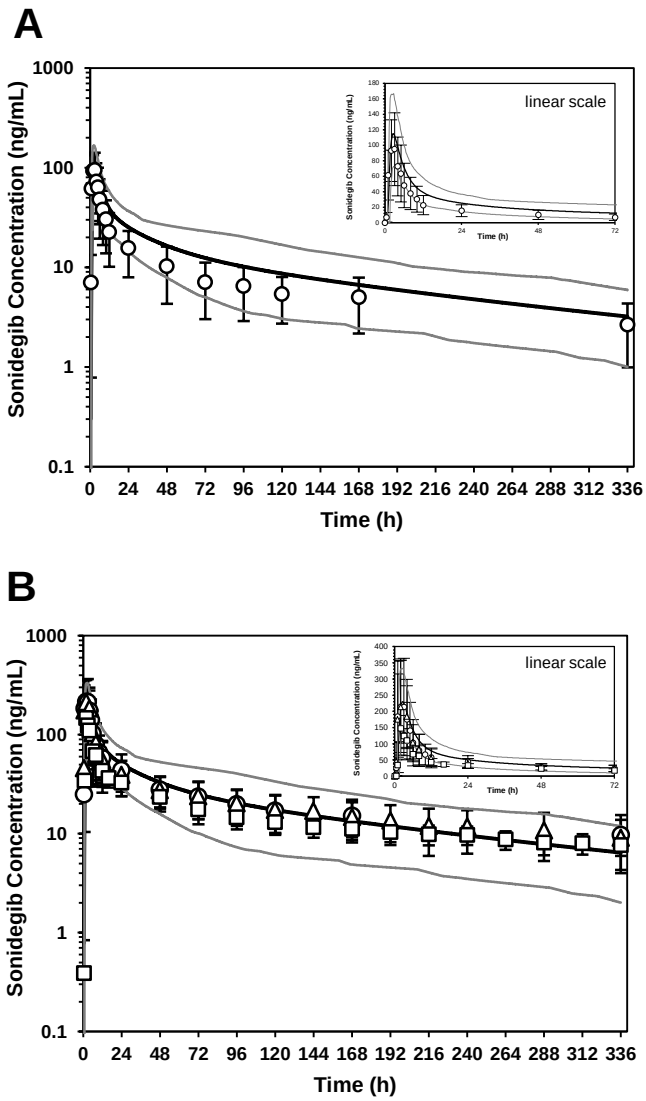

Figure 1

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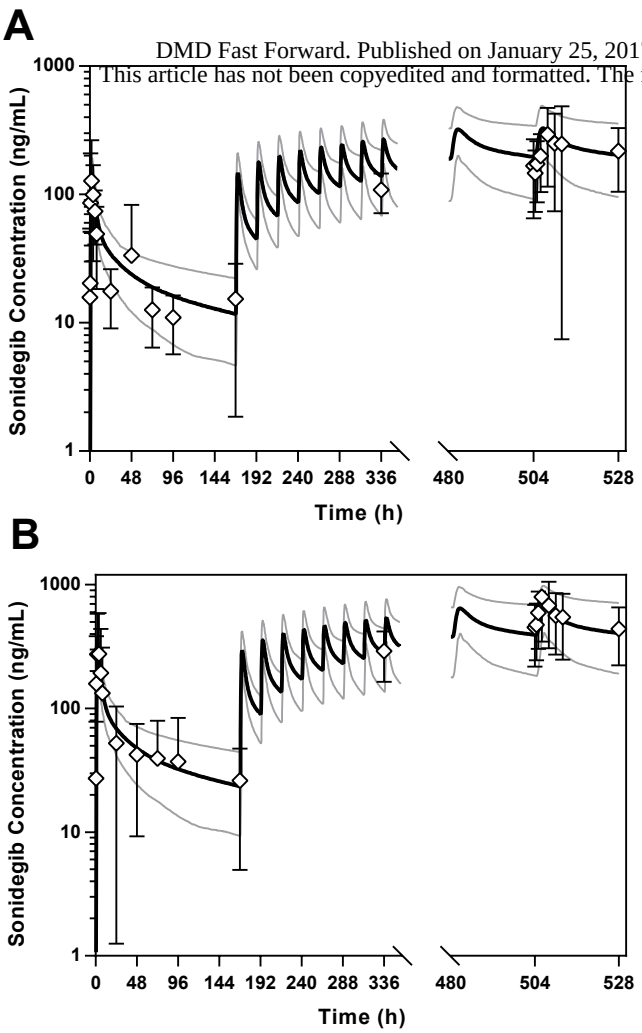

Figure 2

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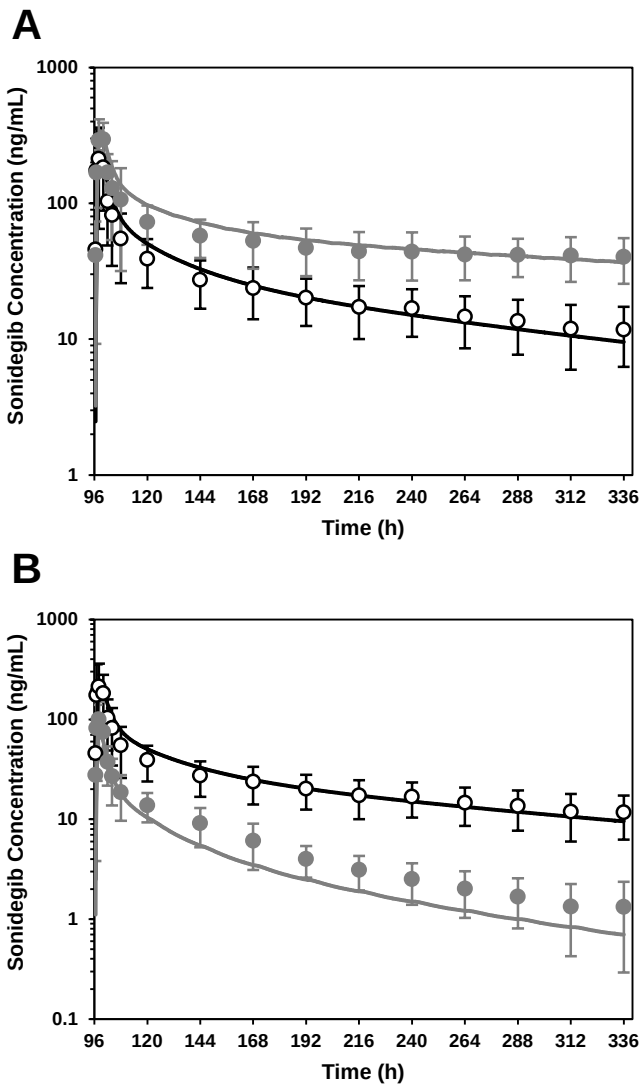

Figure 3

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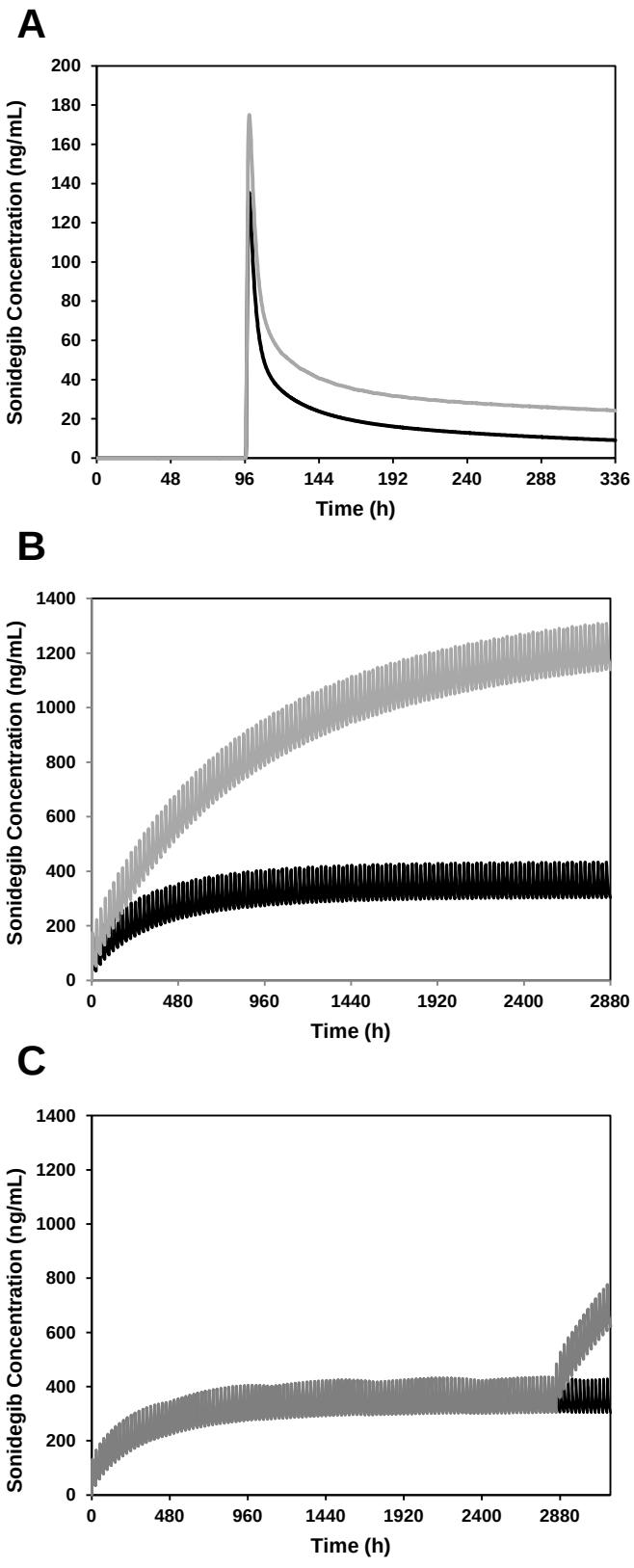

Figure 4

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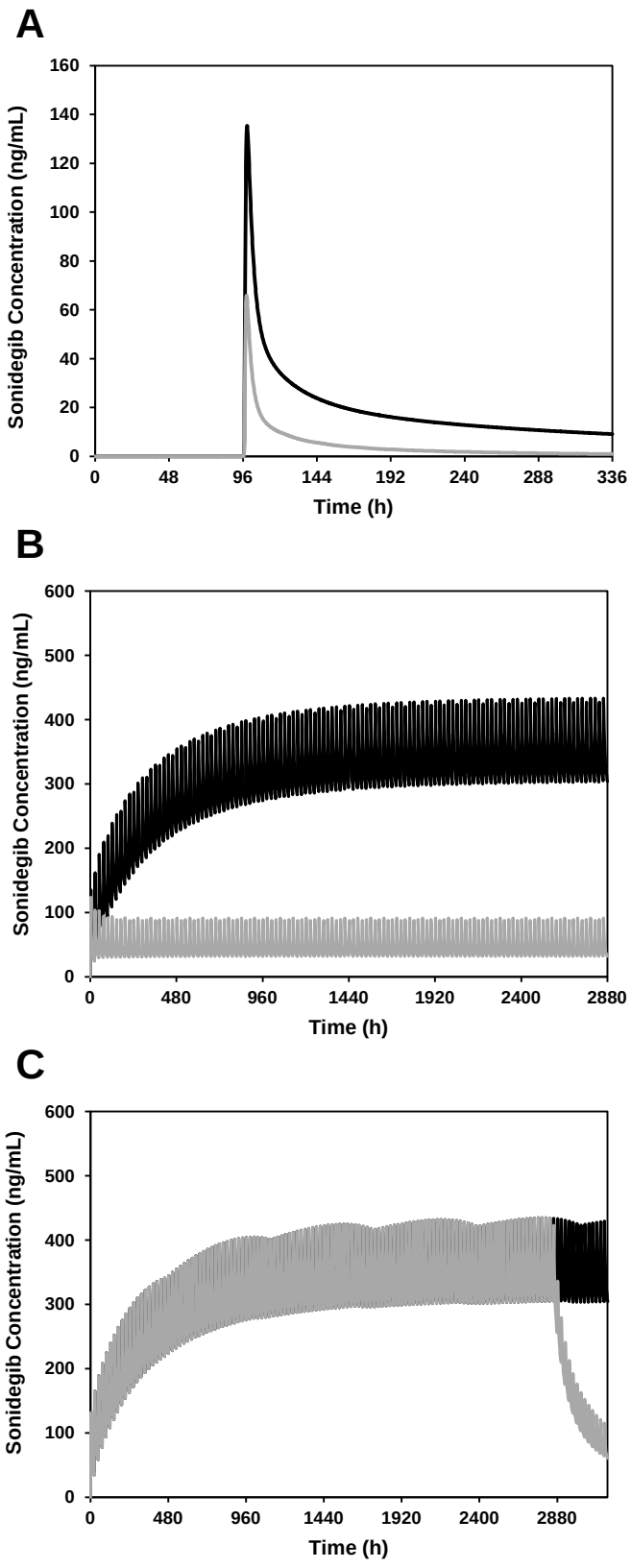

Figure 5

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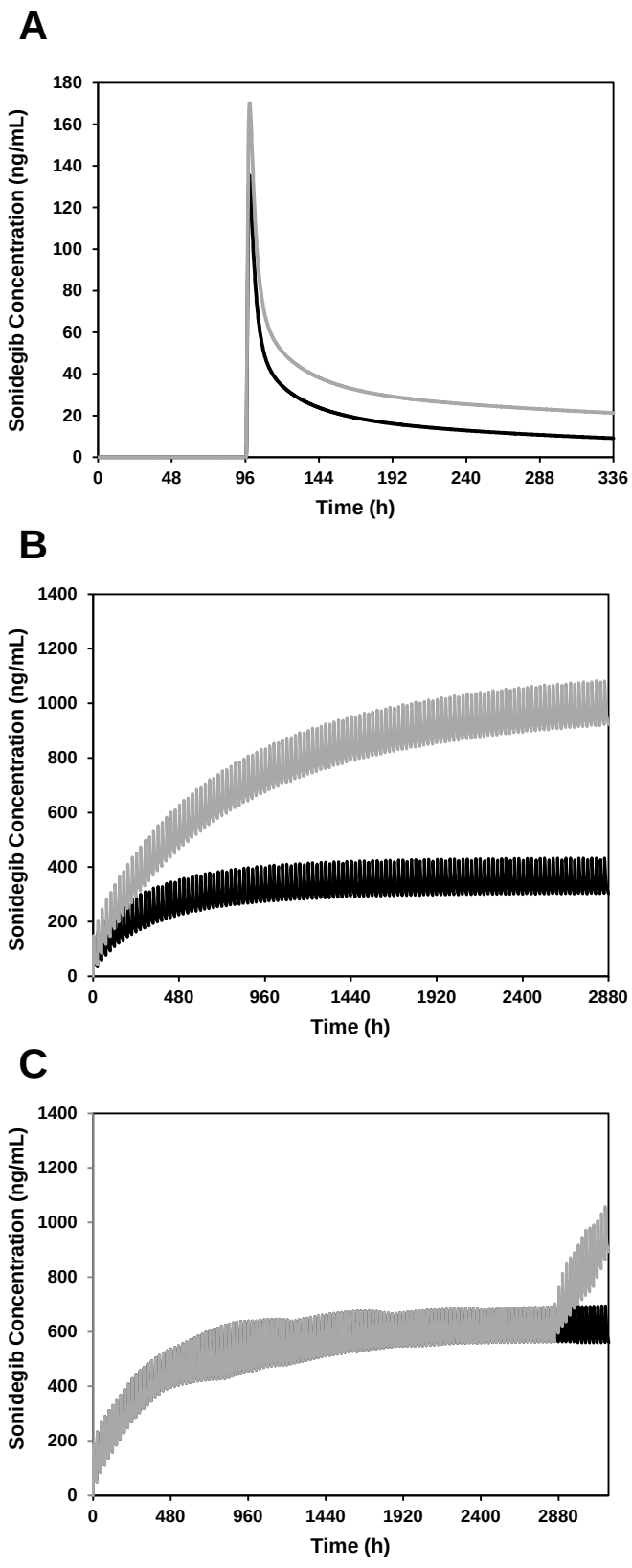

Figure 6

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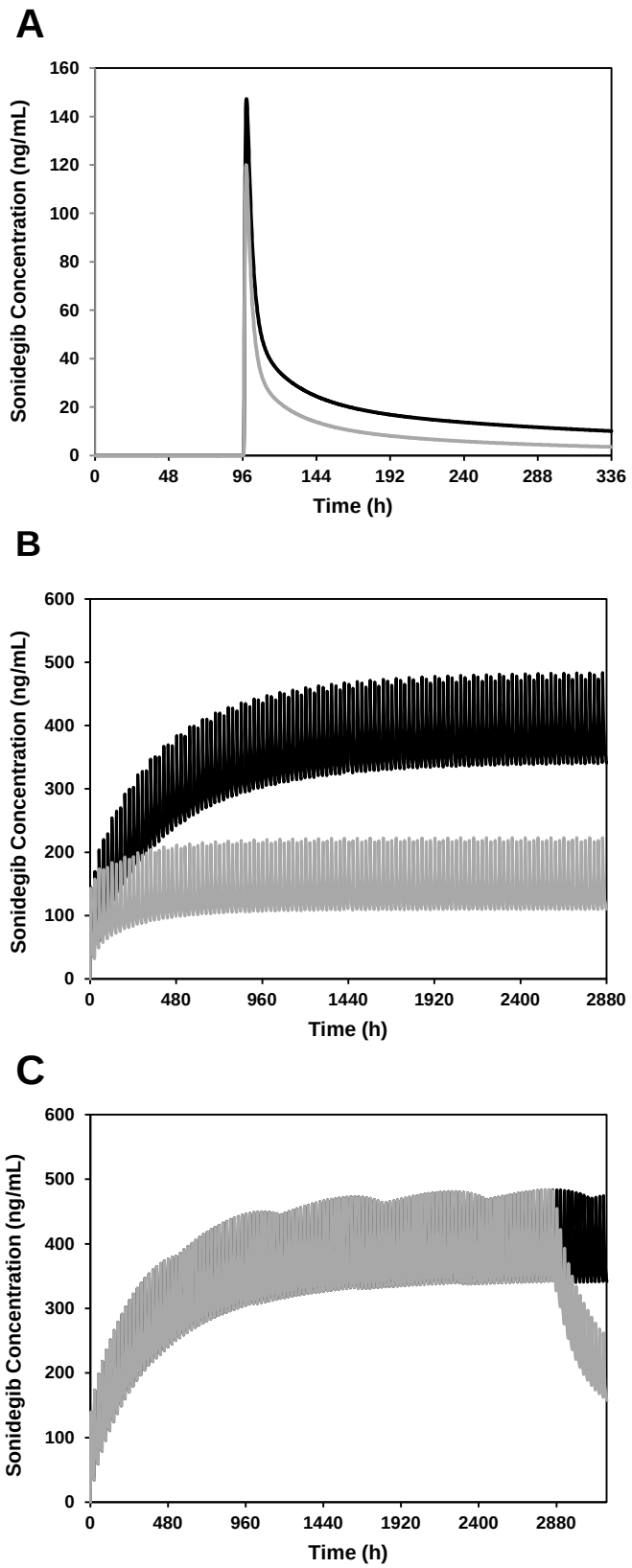

Figure 7

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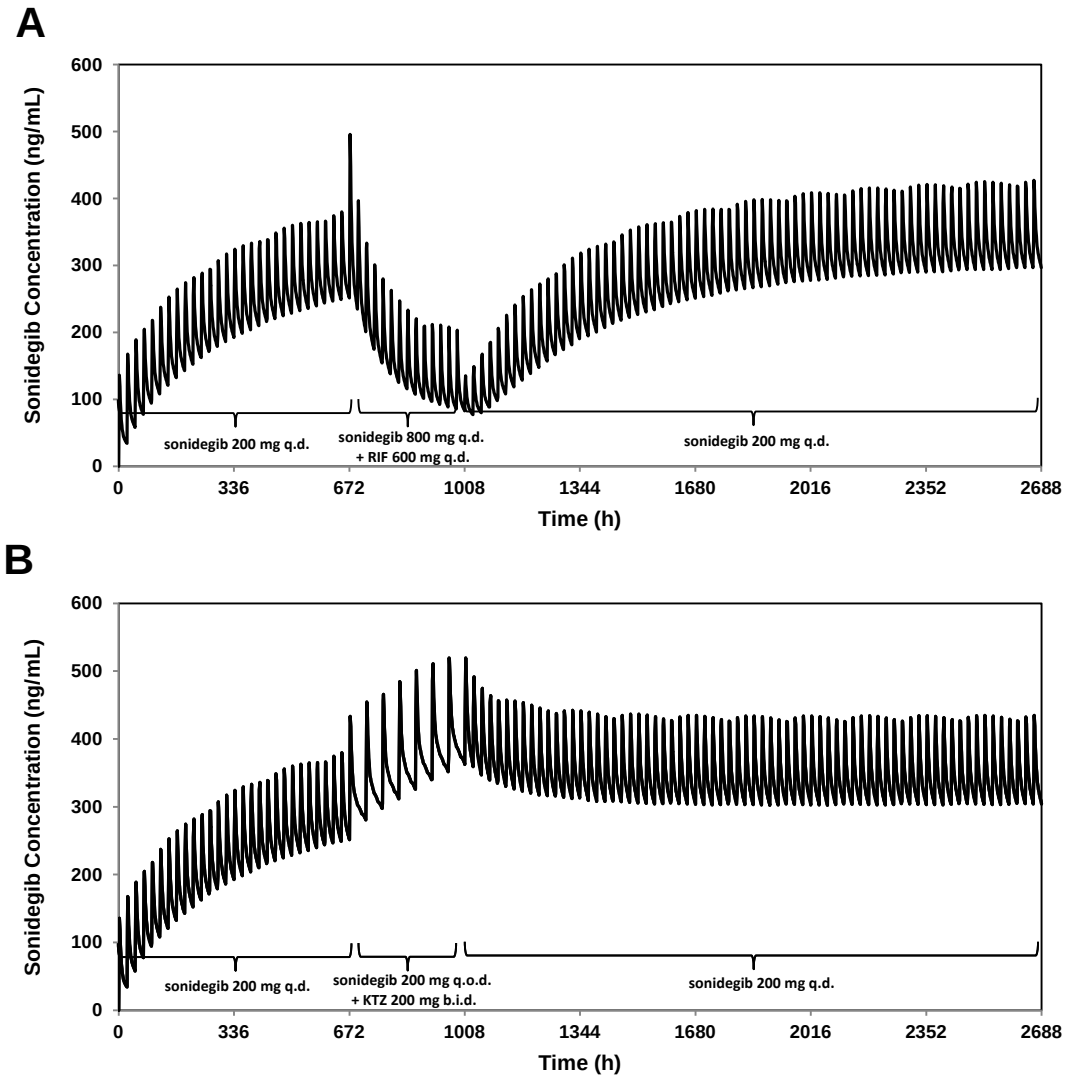

Figure 8