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Modeling Sitagliptin Effect on Dipeptidyl Peptidase 4 (DPP4) Activity in Adults with Hematological Malignancies After Umbilical Cord Blood (UCB) Hematopoietic Cell Transplant (HCT)

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Abstract

Background and Objectives—Dipeptidyl peptidase-4 (DPP4) inhibition is a potential strategy to increase the engraftment rate of hematopoietic stem/progenitor cells. A recent clinical trial using sitagliptin, a DPP4 inhibitor approved for type 2 diabetes mellitus, has shown to be a promising approach in adults with hematological malignancies after umbilical cord blood (UCB) hematopoietic cell transplant (HCT). Based on data from this clinical trial, a semi-mechanistic model was developed to simultaneously describe DPP4 activity after multiple doses of sitagliptin in subjects with hematological malignancies after a single-unit UCB HCT.

Methods—The clinical study included 24 patients that received myeloablative conditioning followed by 4 oral sitagliptin 600mg with single-unit UCB HCT. Using a nonlinear mixed effects approach, a semi-mechanistic pharmacokinetic/pharmacodynamic model was developed to describe DPP4 activity from this trial data using NONMEM 7.2. The model was used to drive Monte-Carlo simulations to probe various dosage schedules and the attendant DPP4 response.

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Conflicts of interest

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Results—The disposition of sitagliptin in plasma was best described by a 2-compartment model. The relationship between sitagliptin concentration and DPP4 activity was best described by an indirect response model with a negative feedback loop. Simulations showed that twice a day or three times a day dosage schedules were superior to once daily schedule for maximal DPP4 inhibition at the lowest sitagliptin exposure.

Conclusion—This study provides the first pharmacokinetic/pharmacodynamic model of sitagliptin in the context of HCT, and provides a valuable tool for exploration of optimal dosing regimens, critical for improving time to engraftment in patients after UCB HCT.

1 Introduction

Sitagliptin is a dipeptidylpeptidase-4 (DPP4) inhibitor approved for use in type 2 diabetes mellitus. DPP4 inhibition leads to decreased cleavage of endogenous incretins, indirectly improving glucose homeostasis [1]. However, DPP4, also known as CD26, truncates other endogenous proteins, including the cytokine stromal-derived factor-1 α (SDF-1 α), which in combination with its receptor CXCR4 plays a critical role in chemotaxis and engraftment of hematopoietic stem/progenitor cells [2–4] as well as for colony stimulating factors, which are growth factors for hematopoiesis [5].

The use of Umbilical Cord Blood (UCB) in Hematopoietic Cell Transplant (HCT) has been limited due to delayed engraftment resulting in increased morbidity and mortality [6–8]. Pre-clinical studies in mice have shown inhibition of DPP4 enhances stem cell engraftment [5]. A recent trial investigated the feasibility, safety, and potential efficacy of systemic inhibition of DPP4 using sitagliptin to enhance engraftment of single unit UCB transplants in adults with hematological malignancies (clinical trial NCT00862719) [9]. While prior studies, summarized in Table 1 [9–17], have extensively explored the pharmacokinetics of sitagliptin and DPP4 inhibition, this had not been done in a population of recipients undergoing a HCT [10, 11, 14–17]. Surprisingly, this trial [9] did not achieve the reported sustained inhibition of plasma DPP4 activity, greater than 90% plasma DPP4 inhibition for 24 hours in healthy volunteers [10, 15]. In the HCT population sitagliptin exposure, as measured by C_{max} and $AUC_{0-\infty}$, was approximately half that previously observed in non-HCT populations. These differences highlight the need for a quantitative description of sitagliptin pharmacokinetics and DPP4 inhibition during HCT.

Population pharmacokinetic-pharmacodynamic models can facilitate the clinical development of DPP4 inhibition for the acceleration of engraftment. Based on data from a pilot UCB HCT study in adult patients with leukemia and lymphoma [9], we have developed a semi-mechanistic model simultaneously describing sitagliptin pharmacokinetics and DPP4 activity after multiple doses of sitagliptin. The model-based approach to understanding sitagliptin concentration and DPP4 activity provides opportunity to explore and optimize dose and schedule for this novel approach to enhance engraftment of UCB cells from a single UCB unit in adult patients.

2 Methods

2.1 Study design

The full details of the clinical trial are presented in Farag *et al.* [9] but salient design issues to the trial are as follows. The trial was approved by the Indiana University Institutional Review Board and was registered at ClinicalTrials.gov (NCT00862719). All patients gave written informed consent. Twenty four adult patients with advanced hematologic malignancies, Karnofsky performance status ≥ 70 , with adequate end-organ function, but lacking HLA-identical or well-matched unrelated donors were enrolled in the clinical trial. The preparative regimen consisted of 13.2 Gy total body irradiation in 8 fractions days -7 to -4 , cyclophosphamide 60 mg/kg days -3 to -2 , and rabbit antithymocyte globulin (ATG) 2.5 mg/kg days -4 to -2 . After 11 patients were recruited, ATG was replaced with fludarabine 30 mg/m² days -4 to -2 . Single units of UCB were infused on day 0. Prophylaxis of graft-versus-host disease was with sirolimus and tacrolimus. Filgrastim 5 g/kg/day was administered subcutaneously day +5 until neutrophil recovery. Sitagliptin, 600 mg once daily (OD), was administered days -1 to $+2$.

Sampling for blood to measure sitagliptin plasma concentrations and plasma DPP4 activity were taken at baseline, 0.5, 1, 2, 4, 8, 12, 16, and 24 hours after the first dose, and at 2, 4, 8, 16 and 24 hours after the second, third and fourth dose. Sitagliptin concentrations were assayed by high-turbulence liquid chromatography online extraction method and detected by mass spectroscopy (API 4000, Applied Biosystems, Toronto, Canada) using selected reaction monitoring with turbo-ionspray interface in positive ion mode. Plasma DPP4 activity was assayed using the DPPIV-Glo Protease Assay (Promega, Madison, WI, USA), according to manufacturer's instructions. More details regarding the bioanalytical assay are presented in the electronic supplementary material.

2.2 Data analysis

Population modeling of sitagliptin concentrations and DPP4 inhibition was performed in NONMEM version 7.2 (Icon Development Solutions, Hanover, Maryland, USA) using the First Order Conditional Estimation method with the INTERACTION option implemented. Pharmacokinetic and pharmacodynamic analyses were performed simultaneously. Between subject variability (BSV) was modeled using exponential functions. Statistical significance was set at $p < 0.01$.

2.2.1 Model selection/evaluation—Selection between models was based on visual inspection of goodness of fit plots, including conditional weighted residuals, CWRES [18] and predictive checks, the objective function value and the precision of the parameter estimates. The minimum value of the objective function provided by NONMEM, which is approximately equal to $-2 \log$ likelihood ($-2LL$), served as a guide during model design. A decrease in $-2LL$ of 6.63 points for one additional model parameter, was regarded as a significant model improvement corresponding to p -value of 0.01 for nested models. For non-nested models the Akaike information criteria (AIC), calculated as $AIC = -2LL + 2 \times NP$, where NP is the number of parameter in the model, was used [19]. Precision of parameter estimates expressed as 5th to 95th percentiles were computed from

the analysis of 200 bootstrap data sets (sampling with replacement). The bootstrap analysis was performed using Perl-speaks-NONMEM [20]. Model parameter estimates were presented together with the corresponding relative standard error [RSE(%)], as a measure of parameter imprecision, which were computed from the results obtained from bootstrap analysis. The quantified BSV was expressed as coefficient of variation [CV(%)]. Model performance was evaluated with visual predictive checks (VPC) and numerical predictive checks (NPC). Predictive checks were performed using MATLAB environment (The Mathworks, Natick, MA, USA).

The VPC was performed as follows. Two hundred simulated studies were simulated with the same design characteristics as the original study. At each time observation point the 2.5, 50 and 97.5th percentiles of sitagliptin plasma concentration (C_p) and DPP4 activity were calculated for every simulated study. Then, the 95% predicted interval for the three percentiles (2.5, 50 and 97.5th) was calculated and represented over time together with the raw data.

The NPC was performed as follows. Two hundred simulated studies were simulated with the same design characteristics as the original study. The median and 2.5 and 97.5th percentiles were calculated for the following pharmacokinetic- pharmacodynamic descriptors: (i) pharmacokinetics descriptors: $C_{max(0-24h)}$, $C_{max(24-48h)}$, $C_{max(48-72h)}$, $C_{max(72-96h)}$ (ng/mL), sitagliptin $AUC_{<24h}$, $AUC_{<48h}$, $AUC_{<72h}$ and $AUC_{<96h}$ (ng h/mL); (ii) pharmacodynamics descriptors: the minimum DPP4 activity level $Nadir_{0-24h}$, $Nadir_{24-48h}$, $Nadir_{48-72h}$, $Nadir_{72-96h}$ (relative light units - RLU), DPP4 $AUC_{<24h}$, $AUC_{<48h}$, $AUC_{<72h}$ and $AUC_{<96h}$ (RLU h). Then, the results were compared with the corresponding percentiles obtained from the raw data. Mismatching of these numerical descriptors (predicted and observed values) might help to identify possible model misspecifications.

2.2.2 Pharmacokinetic/pharmacodynamic modelling—Disposition of sitagliptin in plasma was described with compartmental models parameterized in apparent volumes of distribution, inter-compartmental clearances, and total elimination clearance. Selection was made between one-, two-, and three-compartment models.

The following two steps were followed to establish the pharmacokinetic/pharmacodynamic model: baseline model and drug effect model.

Step 1: Baseline model. DPP4 activity (unbound) was best described by one ordinary differential equation (eq.1):

$$\frac{dDPP4}{dt} = k_{syn} - DPP4(t) \times k_{deg} \quad (1)$$

where k_{syn} (zero order) and k_{deg} (first order) are the synthesis and degradation rates, respectively. During homeostasis this system remains in equilibrium, thus:

$$k_{syn} = DPP4_0 \times k_{deg} \quad (2)$$

where $DPP4_0$ is the baseline value for DPP4 (homeostatic value).

Step 2: Drug effect. Sitagliptin is a competitive, reversible and potent inhibitor of DPP4. Initially, simple pharmacodynamic models were evaluated including a direct response model, linear effect-concentration-response model, log-linear effect-concentration model and E_{max} models (with and without sigmoidicity - hill exponent different from 1). Since DPP4 is a factor that is endogenously produced and eliminated, the indirect response model structures were also assessed. More specifically, three strategies were evaluated using this class of models to reflect the observed decrease in DPP4 activity with drug administration. These strategies were to: (i) inhibit the input [k_{syn}], (ii) stimulate the output [$k_{deg} DPP4(t)$] or (iii) both effects simultaneously. The three of them were explored and evaluated using changes in the OFV. In the selected model, binding between sitagliptin and DPP4 affects the output rate (eq.3).

$$\frac{dDPP4}{dt} = k_{syn} - DPP4(t) \times (k_{deg} + E_{drug}) \quad (3)$$

where E_{drug} is increasing hill function (eq. 4) of the sitagliptin C_P :

$$E_{drug} = E_{max} \times \frac{C_P^h}{C_P^h + EC_{50}^h} \quad (4)$$

where E_{max} is the maximum effect; EC_{50} is the drug concentration necessary to achieve 50% of the E_{max} , and h hill exponent (the sigmoid degree).

In order to describe an observed rebound of DPP4 activity following recovery from sitagliptin-mediated inhibition a delayed negative feedback loop (eq. 6) had to be included:

$$\frac{dDPP4}{dt} = k_{syn} \times FB(t) - DPP4(t) \times k_{deg} + E_{drug} \quad (5)$$

$$\frac{dFB}{dt} = k_f \times \left(\frac{DPP4_0}{DPP4(t)} \right)^\gamma - k_f \times FB(t) \quad (6)$$

where k_f regulates the delay of the feedback loop and γ the effect in it after changes in the DPP4 activity. Fig. 1 shows the schematic representation of the semi-mechanistic population pharmacokinetic/pharmacodynamic model of sitagliptin effect on DPP4 for patients who underwent umbilical cord blood transplantation.

2.3 Dose regimen exploration: Methods

Dose exploration was based on the simulation of one thousand patients at each of the following doses: 50, 100, 200, 400, 600, 800, 1000 and 1200mg once daily (OD). Regimen exploration was based on the simulation of one thousand patients dosed at 600 mg at each of the following schedules: OD, twice daily (BID), three times daily (TID) and four times daily (QID).

2.4 Dose regimen optimization: Methods

Mathematical optimization is the selection of the conditions (in this instance, dosing regimen) to maximize achieving a set of criterion. Sitagliptin DPP4 inhibition can be maximized by increased frequency of administration and/or bigger doses. However, this produces an incrementally increased risk of side effects and toxicity. Therefore, the criterion defined were the minimum bi-dimensional space of DPP4 AUC_{0-24h} and sitagliptin AUC_{0-24h}. Using different simulated dosing schemes, both descriptors were calculated and faced in a scatter plot. The optimal dose was defined as the dose whose Euclidean distance to the origin ([0, 0]) is minimized. Population simulations were generated using different doses from 100 mg to 1200mg in increments of 100 mg for OD, BID, TID and QID regimens. Sitagliptin C_{max}, AUC_{0-24h} and DPP4 AUC_{0-24h} were calculated for every dose/scheme.

3 Results

3.1 Pharmacokinetic model

Disposition of sitagliptin in plasma was best described by a 2-compartment model, with drug absorption as a first order rate constant. Lag in absorption was not supported by the data. BSV was significant for the apparent total plasma clearance (CL/F), apparent volume of distribution in the central compartment (V_C/F), apparent volume of distribution in the peripheral compartment (V_p/F), and relative bioavailability (F), which typical value was fixed to 1 (p<0.01). No pharmacokinetic parameters were time or dose dependent. Covariance between random effects associated to the pharmacokinetics was not significant. Covariate effects were not explored. Table 2 lists the parameter estimates corresponding to the selected pharmacokinetic model, together with the corresponding 90% confidence interval obtained from the nonparametric bootstrap analysis. None of the confidence intervals included zero. -shrinkage (%) was 24.3 (CL/F), 18.41 (V_C/F), 14.27 (V_p/F), and 4.67 (F); -shrinkage was 4.38%. Individual model predictions with the corresponding patient observations of sitagliptin plasma concentrations are plotted in Fig. S1 (electronic supplementary material). Fig. 2 (top) shows the goodness of fit plots, which indicate the selected model properly describes the sitagliptin observations. Similar results were obtained from the numeric predictive check (NPC) (see Table 3). The calculated percentiles of all pharmacokinetic descriptors (C_{max(0-24h)}, C_{max(24-48h)}, C_{max(48-72h)}, C_{max(72-96h)}, sitagliptin AUC_{<24h}, AUC_{<48h}, AUC_{<72h} and AUC_{<96h}) from the simulated data were very similar to the corresponding percentiles calculated from the raw data (Table 3). Fig. 3A, the visual predictive check (VPC) corresponding to the four days treatment, shows that both typical profiles and data dispersion were captured well by the model.

3.2 Pharmacokinetic/pharmacodynamic model

Fig. 1 shows the schematic representation of the selected semi-mechanistic population pharmacokinetic/pharmacodynamic model of sitagliptin effect on DPP4 for patients who underwent umbilical cord blood transplantation. While other drug effect models were explored (see methods), a binding process between sitagliptin and DPP4 affecting the output rate best described the observations. The inclusion of a negative feedback loop was strongly

supported by the observed data, although not previously reported in the literature ($p < 0.01$). BSV was identified for DPP4₀, k_{syn} and EC₅₀.

Table 2 also list the parameter estimates corresponding to the pharmacodynamic model and the corresponding 90% confidence interval obtained from the nonparametric bootstrap analysis. None of the confidence intervals included zero. -shrinkage (%) was 20.31 (DPP4₀), 12.53 (k_{syn}), and 4.27 (EC₅₀); -shrinkage was 5.07 %. Inclusion of covariance (positive correlation) between the random effect associated to EC₅₀ and the bioavailability (F) parameter significantly improved the objective function value (-2LL). Individual model predictions and observed DPP4 levels for every patient are plotted in Fig. S2 (electronic supplementary material). Fig. 2 (*bottom*) shows the goodness of fit plots for the selected model. Results from the NPC are shown in table 4. The calculated percentiles of all pharmacodynamic descriptors (Nadir_{0-24h}, Nadir_{24-48h}, Nadir_{48-72h}, Nadir_{72-96h}, DPP4 AUC_{<24h}, AUC_{<48h}, AUC_{<72h} and AUC_{<96h}) from the simulated data were very similar to the corresponding percentiles calculated from the raw data (Table 4). Fig. 3B, the VPC corresponding to DPP4 values during the period of treatment, show that typical profiles and data dispersion were accurately captured by the model.

Inter occasion variability was evaluated but no tendency or differences were found in any of the model parameters including no change in the objective function value. Data exploration showed no variability or tendency within the four days of DPP4 inhibitor administration (Table 3 and Table 4).

3.3 Dose regimen exploration

Fig. 4 shows the relationship described by the model (eq. 4) between sitagliptin plasma concentration and drug effect in percentage. At the dose of 600mg (dose utilized in the first phase of the clinical trial), the predicted maximum concentration after one single dose produced almost 80% of the maximum possible drug effect. Simulated maximum concentrations reached by other doses (50, 100, 200, 400, 800, 1000 and 1200 mg) were also indicated in Fig. 4.

Four different pharmacokinetic/pharmacodynamic descriptors were calculated from model simulations changing the dose amount and schedule of drug administration: (i) pharmacokinetics: $C_{\text{max}(0-24h)}$ (ng/mL) and sitagliptin AUC_{0-24h} (ng h/mL); (ii) pharmacodynamics: Nadir_{0-24h} (relative light units - RLU) and DPP4 AUC_{0-24h} (RLU h).

Fig. 5 shows dose-dependent changes in these descriptors from one thousand simulated individuals at each of the following doses: 50, 100, 200, 400, 600, 800, 1000 and 1200mg OD. Increasing the dose up to 1200mg OD, sitagliptin $C_{\text{max}(0-24h)}$ increased by 84.34% and AUC_{0-24h} increased by 81.01%, with respect to the reference dose of 600mg OD; DPP4 activity minimum value, Nadir_{0-24h}, decreased 17.08%; and DPP4 area under the curve, AUC_{0-24h}, diminished by 18.77%. Fig. 6 shows the schedule-dependent changes in the same descriptors based on one thousand simulated individuals dosed at 600 mg at each of the following schedules: OD, BID, TID and QID (x-axis). With BID dosing (1200mg total daily dose) sitagliptin $C_{\text{max}(0-24h)}$ increased by 17.86%, and sitagliptin AUC_{0-24h} increased by 90.10%, maximum DPP4 suppression (Nadir_{0-24h}) remained similar (increased by 4.24%)

and the DPP4 AUC_{0-24h} decreased by 41.34%, compared to a reference schedule of 600mg OD. Fig. S3 (electronic supplementary material) shows this same analysis for a 200mg dose. Due to the linearity of pharmacokinetics, the increments for C_{max(0-24h)} and sitagliptin AUC_{0-24h} were similar to the 600mg dose. However, DPP4 AUC_{0-24h} diminished only by 41.34%.

3.4 Dose regimen optimization

Population simulations of different dose and schedules were performed to maximize DPP4 inhibition (DPP4 AUC_{0-24h}) while minimizing drug exposure (sitagliptin AUC_{0-24h}), based on the assumption that sitagliptin C_{max0-24h} serves as the main indirect biomarker for adverse effects and DPP4 inhibition AUC_{0-24h} for desired effects. Fig. 7 shows the dose-effect evaluation based on population simulations; different doses from 100 mg to 1200mg in increments of 100 mg for OD, BID, TID and QID schedules. Sitagliptin C_{max(0-24h)} versus sitagliptin AUC_{0-24h} (Fig. 7A) and DPP4 AUC_{0-24h} versus sitagliptin AUC_{0-24h} (Fig. 7B) were compared for the OD, BID, TID and QID schedules with the different doses. Due to the linearity of the pharmacokinetics, the relationship between sitagliptin AUC_{0-24h} and C_{max(0-24h)} for different doses of sitagliptin (doses from 100mg to 1200mg in increments of 100 mg OD, BID, TID and QID) is described by straight lines. Depending on the number of doses per day (OD, BID, TID and QID) their slopes change. That is, as the number of doses per day increases, the lines have higher slopes (Fig. 7A). There is a significant difference between the OD slope and the rest of the dosage frequencies. In other words, similar drug exposures - sitagliptin AUC_{0-24h} - are achieved with significantly lower maximum plasma concentrations - C_{max(0-24h)} - when the same amount of drug is administered as divided doses 2, 3 or 4 times per day. Comparing OD, BID, TID and QID regimes with same daily dose, the 1200mg daily doses for BID, TID and QID regimes produce the same C_{max(0-24h)} as the OD 600mg daily dose, but the sitagliptin AUC_{0-24h} (Fig. 7A) is doubled compared to OD dosing. Interestingly daily doses of 600mg using BID, TID and QID regimes produce similar sitagliptin AUC_{0-24h} to the OD 600mg dose but the DPP4 AUC_{0-24h} decreases by approximately by 33% using BID, TID or QID (Fig. 7B).

Mathematically, the optimal dosages (as defined by the Euclidean distances, please see methods) were 500mg TID –1500mg daily dose, and 400mg QID –1600mg daily dose. If we assume the number of doses per day as a third variable to be minimized, then the optimal dosage is 500mg TID –1500mg daily dose. It can be observed that the resulting DPP4 AUC is close to the mathematically optimal dosages.

4 Discussion

DPP4 cleaves a variety of endogenous proteins, regulating their activity [8, 21, 22]. Relevant to HCT, SDF-1 α and several colony stimulating factors (eg. GM-CSF, G-CSF, IL-3, EPO) are regulated through DPP4 [2, 5, 23]. All play key roles in the production and engraftment of hematopoietic cells in the bone marrow. Therefore, inhibition of DPP4 activity is an appealing strategy to increase engraftment efficiency in patients undergoing HCT. This is particularly relevant when stem cell dose is limited, as is the case with UCB, where low cell dose has been shown to increase transplant related mortality and survival [24–26] and reviewed in [8, 27]. Based on preclinical data showing treatment of mice with sitagliptin

enhanced hematopoietic stem cell and hematopoietic progenitor cell recovery in a comparable manner to DPP4-null mice [5], a clinical trial was initiated using oral sitagliptin in adult subjects undergoing single unit UCB HCT [9]. Clinical trial participants whose data informed this pharmacokinetic/pharmacodynamic model had a median time to engraftment of 21 days, shorter than the majority of single unit UCB HCT reported in the literature [9]. The results showed that sitagliptin can be successfully repurposed for a new clinical indication, e.g. that DPP4 inhibition may be a viable strategy to increase engraftment efficiency.

Sitagliptin is an FDA-approved selective DPP4 inhibitor with minimal toxicity [28]. The trial dose was based on data from healthy volunteers showing greater than 90% DPP4 activity inhibition at 24 hours following a single 600 mg dose [10]. However, in the HCT trial the observed DPP4 inhibition was less than anticipated with DPP4 activity returning to 80% or more of baseline activity by 16 hours. This emphasizes that in a different clinical context, clinical pharmacology of therapeutics can change. Therefore, we developed a population pharmacokinetic/pharmacodynamic model that described the relationship between sitagliptin plasma concentrations and DPP4 activity in patients with hematological malignancies after single unit UCB HCT in adult patients with leukemia and lymphoma.

The kinetics of sitagliptin have been studied extensively – a summary of pharmacokinetic parameters are presented in Table 1. Exposure, described by AUC_{0-24} , and C_{max} , in the non-HCT populations are approximately twice those observed in the HCT population. Similarly, clearance (dose/ $AUC_{0-\infty}$) of sitagliptin in non-HCT populations is 50% lower than those found by Farag *et al.* [9]. Unlike prior populations, HCT patients are exposed to total body irradiation, high doses of chemotherapy, and a variety of other therapeutics to condition the patients for HCT, manage symptoms, mitigate risks, and prevent adverse consequences related to the transplant process, all of which may alter the way drugs behave in vivo [29–32]. This may be particularly important in relation to sitagliptin activity, given that large scale cell death following conditioning regimen cytotoxic therapy is associated with large increases in DPP4 release from dying cells. Similarly, it is likely that the physiologic and pathophysiologic processes and exposure to a number of concomitant medications can impact the absorption, distribution, metabolism, and elimination of sitagliptin. In healthy volunteers, sitagliptin has high bioavailability (87%), with absorption through both passive diffusion and active transport [17, 33, 34]. It has been previously shown that other oral drugs have significant changes in pharmacokinetics as a result of changes such as mucositis, alterations in albumin and other proteins, or alternation in drug metabolism or transport [35]. Once absorbed, there may be differences in protein binding. Sitagliptin has been previously shown to be 34–46% protein-bound [36], and in HCT, albumin frequently declines over the course of transplant – the total serum albumin levels in our study population were below normal (median=2.7 g/dL, normal range=3.2–5 g/dL). However, the effect of albumin (as a covariate) on the sitagliptin pharmacokinetics was not studied due to the design of the clinical trial. While metabolism plays a minor role in healthy volunteers and patients with type 2 diabetes mellitus sitagliptin disposition, with only 16% of administered dose being metabolized via CYP3A and 2C8 [35], it cannot be assumed that this remains the same in the HCT context. Elimination of sitagliptin is largely renal (87%), via both glomerular

filtration and active secretion, both p-glycoprotein (MDR1/Pgp) and hOAT3 have been shown to transport sitagliptin [12, 33, 34]. Beyond the potential for more rapid filtration due to a higher free drug fraction, there are also large fluid shifts in HCT, as well as extensive use of diuretics, which may impact sitagliptin clearance.

This latter point touches on another set of salient differences between non-HCT and HCT populations in regards to sitagliptin disposition – the potential for drug-drug interactions. Clinically significant drug-drug interactions are a known concern in HCT. In addition to the chemotherapeutics of the preparative conditioning regimens, HCT patients are on a cocktail of antibiotics, antifungals, immunosuppressants, and other supportive care medications. In the pilot study by Farag *et al.* trial [9], such medications included cyclophosphamide, tacrolimus, sirolimus, fluconazole, acyclovir, and dexamethasone. Several of these drugs are known to have the potential for pharmacokinetic interactions at the level of metabolic enzymes and transporters. While it remains unclear if there are clinically significant interactions between these drugs and sitagliptin, there are studies showing some potential for drug interactions [33, 34]. Our pharmacokinetic/pharmacodynamic model does not mechanistically describe all these potential interactions, but accurately describe the profiles allowing for refinement and optimization of dose and schedule of sitagliptin in HCT. Fludarabine replaced ATG following the first 11 patients to reduce the risk of infection. As the data available were limited and the identity of those patients in the dataset not available to us, it was not possible to evaluate the effect of the replacement. In principle this should not impact the pharmacokinetics of sitagliptin, nor are any pharmacodynamic interactions between DPP4 and either fludarabine or ATG are reported in the literature.

Simulation based on this model was then used to explore optimal dosing strategies for sitagliptin in HCT to maximize both the extent and longevity of DPP4 inhibition. In mathematics, optimization is the selection of a best element with regard to some criterion from some set of available alternatives. Since sitagliptin is a DPP4 inhibitor, larger doses as well as more frequent administration of the drug during the day will produce higher DPP4 inhibition. Increments in the dose and the number of administrations also produce higher drug exposure which may increase the probability of an adverse drug reaction. In this study, we defined just one criterion for optimizing this trade-off. We developed a scatter plot comparing sitagliptin AUC and DPP4 AUC with different dosing schemes and identified the dosage regimen that resulted in responses closest to the origin [0,0]. Among the alternatives simulated with regard to latest criterion, we found two optimal dosages: (i) 500mg TID –1500mg daily dose, and (ii) 400mg QID –1600mg daily dose. It is notable that the selected dose for the multicenter phase II trial (600 mg BID), based on additional, unpublished, dosing cohorts defining maximal tolerated dose (MTD) clinically, is very close to the optimal solutions (Fig. 7). The trial dose going forward defined by the MTD is only 15% less than the mathematically predicted optimal predicted dose in terms of DPP4 inhibition.

Interestingly, beyond the intended clinical application of this model, some questions of basic biology were raised. While DPP4 is known to be expressed on the surface of hematopoietic cells as CD26, and as an active soluble form in plasma, the regulation of DPP4 expression is not fully characterized [21, 22, 37]. In order to capture the observed DPP4 activity in this trial, a feedback loop had to be incorporated to capture a rebound in DPP4 activity above

baseline activity in the inter-dose intervals. While not previously reported in the literature, this feedback might represent a biological process in response to the rapid decline in DPP4 activity.

There are some limitations to the study conclusions that are secondary to the data characteristics used to build the models. There were a small number of patients and therefore BSV may not be as well defined, given the possibility that these individuals did not represent the full random distribution of disposition or response across individuals. Another limitation was the use of a single dosing cohort. The use of different doses provides very informative data for the model development, usually reducing the level of uncertainty and improving the precision of the parameter. Finally, a wide variety of disease subtypes were incorporated and given the small total number of individuals, it was impossible to adequately assess if there was a potential interaction between the disease kind/state, the pharmacokinetics of sitagliptin and the DPP4 response. Despite these limitations, sample size and limited dosing cohorts are not uncommon in dense pharmacokinetic trials, and we do not expect a systematic disease-pharmacokinetics or disease-pharmacodynamics interaction. In addition to these data and experiment driven limitations, there are some limitations arising from the modeling approach. The modeling approach is potentially limited by being only semi-mechanistic. For instance, while we have observed a feedback loop in DPP4 activity, to-date a mechanistic explanation of this loop has not been described, therefore this component of the model remains an empirical finding discovered during the model building process.

5 Conclusions

Sitagliptin pharmacokinetics in the HCT population are significantly lower (~50%) with respect to profiles already published in the literature. This difference, probably due to the clinical context, highlights the need for such quantitative analysis, a valuable tool for the exploration of more optimal doses. Therefore, the data of Farag et al. [9] and the reported model based analysis fills in critical clinical pharmacology information relevant to the repurposing of DPP4 inhibitors for this new indication. Further, based on model simulations, we explored dose regimes including OD, BID, TID and QID with 100 up to 1200mg, looking for an optimal dose and schedule to minimize DPP4 activity with minimal drug exposure (AUC). Our results indicate that the starting dose in the safety and tolerability clinical trial [9], i.e. 600mg OD, was an inefficient dose regimes. Indeed, any amount of dose administered once per day is inferior in terms of maximizing DPP4 inhibition at the same total daily number of milligrams. This highlights the necessity of increment the frequency of the administration at least to a BID schedule.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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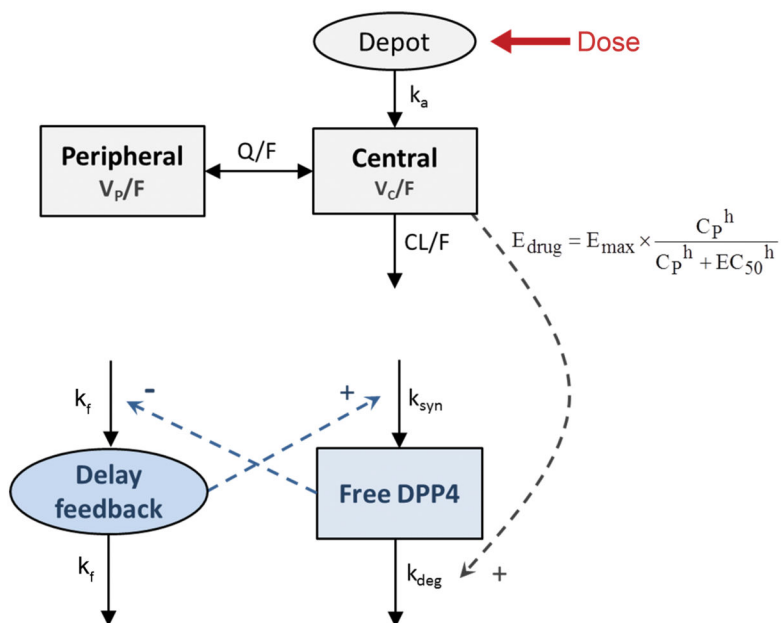
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**Fig. 1.**

Schematic representation of the selected pharmacokinetic/pharmacodynamic model. Pharmacokinetics: k_a , first order rate constant of absorption; V_C/F , and V_P/F , apparent volumes of distribution of the central and the peripheral compartments, respectively; CL/F apparent plasma clearance (oral); Q/F , inter-compartmental distribution clearance. pharmacodynamics: DPP4 activity (free receptor) can be synthesized at a zero-order rate (k_{syn}) and degraded at a first-order (k_{deg}). E_{drug} induces activity loss by the receptor binding. C_p , predicted sitagliptin plasma concentration; E_{max} is the maximum effect; EC_{50} is the drug concentration need to achieve the 50% of the E_{max} ; h is the hill exponent. $1/k_f$ represents the expected time delay for the feedback.

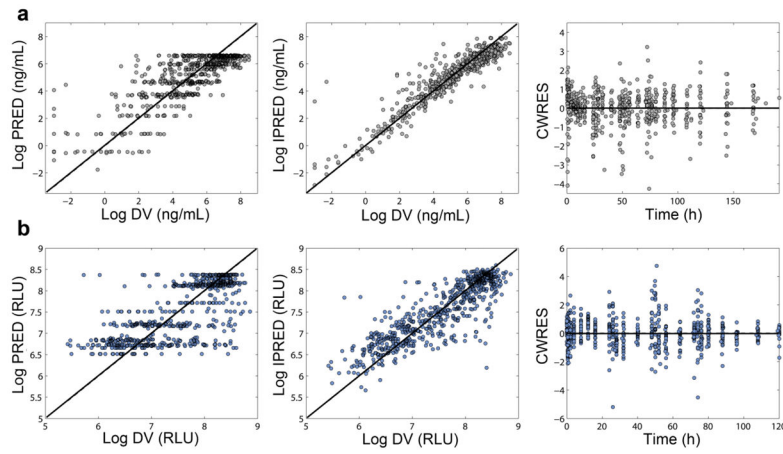
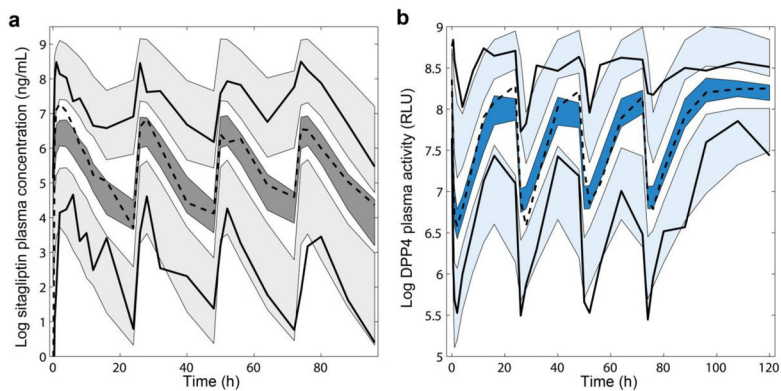


Fig. 2. Goodness-of-fit plots corresponding to the selected population pharmacokinetic/pharmacodynamic model. Sitagliptin plasma concentrations (a) and DPP4 activity (b). IPREDs = individual model predictions; DV = observed concentrations; CWRES = Conditional Weighted Residuals.

**Fig. 3.**

Visual Predictive Checks (VPC). Results from 200 simulated studies. Shaded area corresponds to the 95% prediction interval of the 2.5th, 50th and 97.5th percentiles. Dashed lines represent the mean of the raw data profiles; solid lines the 2.5th and 97.5th percentile. (a) VPC for the pharmacokinetics (grey): sitagliptin plasma concentrations in log scale. (b) VPC for the pharmacodynamics (blue): DPP4 plasma activity (relative light units - RLU) in log scale.

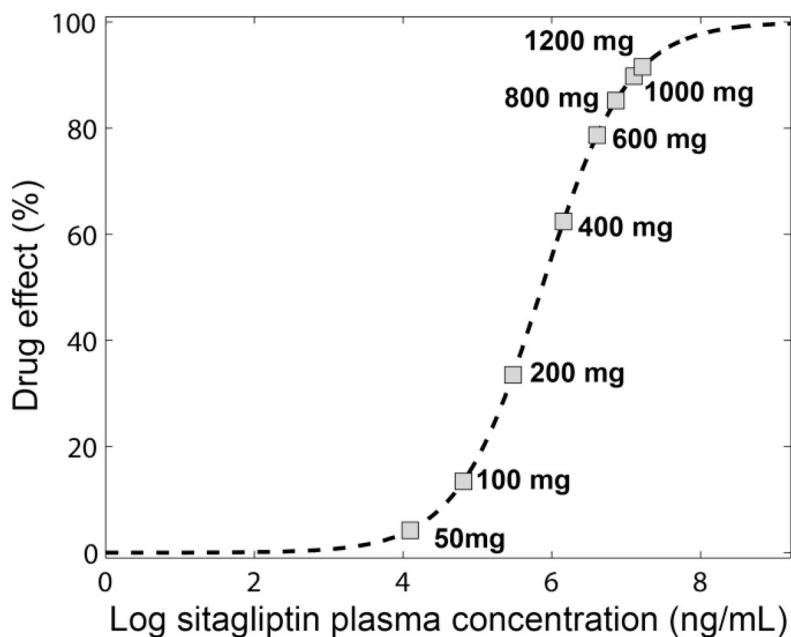


Fig. 4. Drug effect. Relationship between the plasma concentration and the drug effect in percentage defined in the equation 4 (see methods). Squares identify the maximum concentration reached after the 50, 100, 200, 400, 600, 800, 1000 and 1200 mg doses.

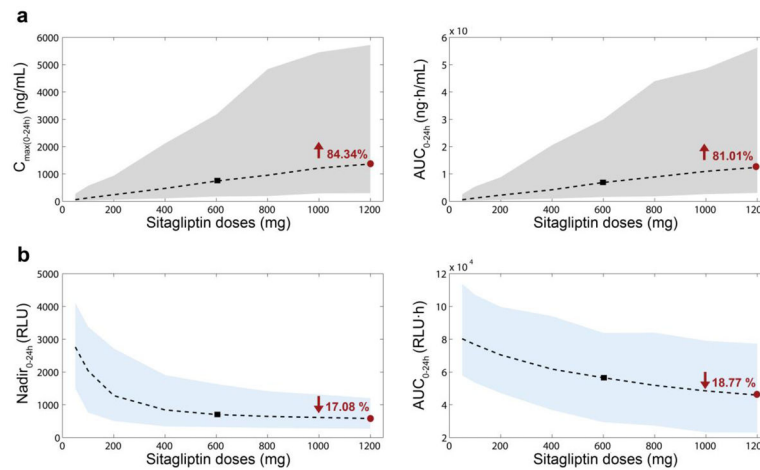


Fig. 5.

Changes in pharmacokinetic/pharmacodynamic descriptors depending on the dose amount. One thousand individuals were simulated per dose. Doses simulated were 50, 100, 200, 400, 600, 800, 1000 and 1200mg (X axis). Two pharmacokinetic descriptors were calculated (a): $C_{max(0-24h)}$ (ng/mL) (left) and AUC_{0-24h} (ng·h/mL) (right). Two pharmacodynamic descriptors were calculated (b): Nadir_{0-24h} (RLU) (left) and AUC_{0-24h} (RLU·h) (right). Shaded areas correspond to the 90% prediction interval for the pharmacokinetics (grey) and the pharmacodynamics (blue) descriptors. Dashed lines represent the medians. Black squares indicate the median values for the reference dose –600mg (OD). Red circles correspond to twice the reference dose –1200mg (OD); values in red are the corresponding increment/decrement (%) with respect to the reference dose (black square). AUC_{0-24} area under the concentration time curve from 0 to 24 h, $C_{max(0-24h)}$ maximum concentration from 0 to 24 hours, OD once daily, RLU relative light units

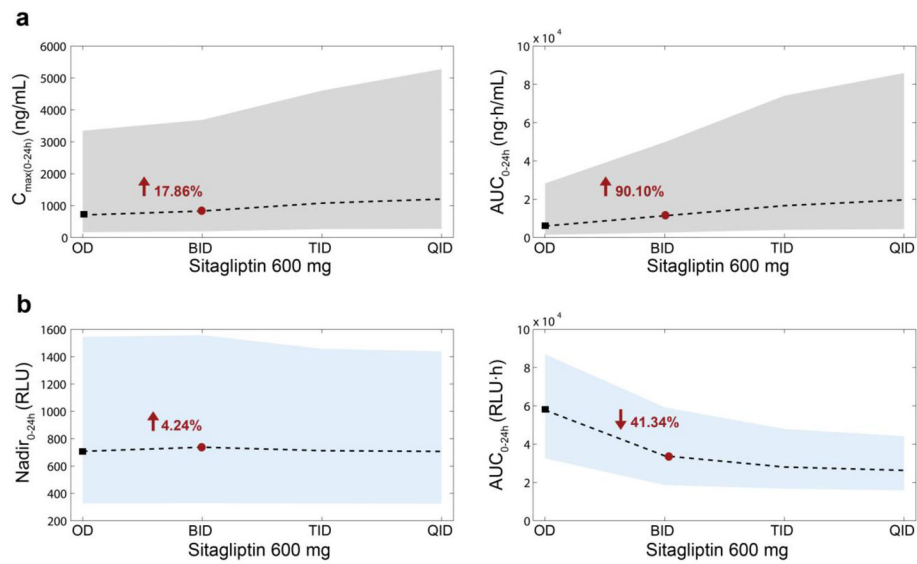
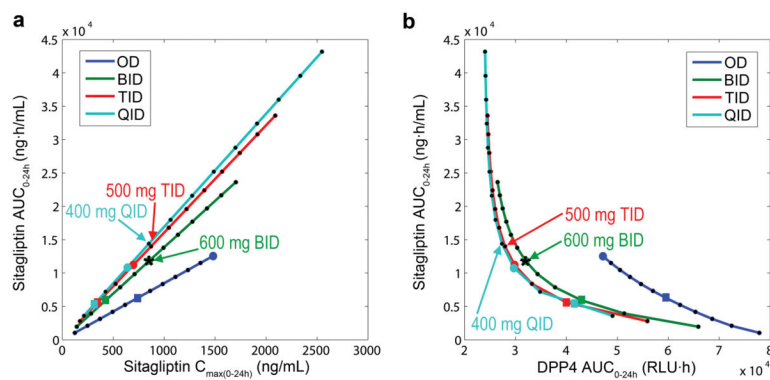


Fig. 6. Changes in pharmacokinetic/pharmacodynamic descriptors depending on the number of doses per day. One thousand individuals were simulated per schedule. Doses simulated were 600 mg OD, BID, TID and QID. Two pharmacokinetic descriptors were calculated (**a**): $C_{max(0-24h)}$ (ng/mL) (*left*) and AUC_{0-24h} (ng·h/mL) (*right*). Two pharmacodynamic descriptors were calculated (**b**): Nadir_{0-24h} (RLU) (*left*) and AUC_{0-24h} (RLU·h) (*right*). Shaded areas correspond to the 90% prediction interval for the pharmacokinetics (grey) and the pharmacodynamics (blue) descriptors. Dashed lines represent the medians. Black squares indicate the median values for the reference dose –600mg OD. Red circles correspond to twice the reference dose –600mg BID; values in red are the corresponding increment/decrement (%) with respect to the reference dose. AUC_{0-24} area under the concentration time curve from 0 to 24 h, BID twice daily, $C_{max(0-24h)}$ maximum concentration from 0 to 24 hours, OD once daily, QID four times daily, RLU relative light units, TID three times daily

**Fig. 7.**

Evaluation of dose effect. Population simulations were performed for different doses from 100 mg to 1200mg, in increments of 100 mg, administered one (OD, blue), two (BID, green), three (TID, red) and four (QID, light blue) times daily. The non-simulated intermediate doses were calculated by means of a linear interpolation process. Squares represent daily doses of 600mg; big circles correspond to daily doses of 1200mg. (a) Sitagliptin $C_{\max(0-24h)}$ (ng/mL) concentration *versus* sitagliptin AUC_{0-24h} (ng·h/mL). (b) DPP4 AUC_{0-24h} (RLU·h) *versus* sitagliptin AUC_{0-24h} (ng·h/mL). Optimal dosages are (i) 500mg TID –1500mg daily dose, and (ii) 400mg QID –1600mg daily dose (indicated by arrows). The selected dose for the multicenter phase II trial, 600 mg BID, is marked with an asterisk. AUC_{0-24} area under the concentration time curve from 0 to 24 h, BID twice daily, $C_{\max(0-24h)}$ maximum concentration from 0 to 24 hours, DPP4 dipeptidylpeptidase-4, OD once daily, QID four times daily, RLU relative light units, TID three times daily

Table 1

Sitagliptin pharmacokinetic parameters already published in the literature.

Dose (mg)	AUC _{0-∞} (ng·h/mL)	C _{max} (ng/mL)	Reference
600 OD	22772.81 ^a	3156.65	Bergman, A.J. et al. [10]
600 OD	22402.05	3437.7	Herman, G.A. et al. [11]
83 OD	2460.15	309.14	Vincent, S.H. et al. [12]
100 OD	2407.23	383.17	Kim, B.H. et al. [13]
100 OD	3523.23	390.61	Herman, G.A. et al. [14]
100 OD	3217.74	332.77	Bergman, A. et al. [17]
200 BID	5987.45 ^b	928.66	Herman, G.A. et al. [16]
100 OD	3470.28	386.94	Bergman, A. et al. [15]
600 OD	11661	1690	Farag, S.S. et al. [9]

AUC_{0-∞}, area under the concentration-time curve to infinite time; C_{max}, maximum concentration; OD, once daily; BID, *bis in die* –twice a day.

^a AUC₀₋₂₄;

^b AUC₀₋₁₂

Table 2

Population pharmacokinetic/pharmacodynamic parameter estimates

Parameters	Estimate (RSE%)	ISV (RSE%)	Bootstrap analysis Median [5 – 95 th percentiles]	
			Estimate	BSV
CL/F (L/h)	84.79 (11.91)	36.55 (51.16)	79.48 [64.33 – 98.44]	36.18 [17.26 – 49.99]
V _C /F (L)	176.43 (16.39)	63.19 (60.85)	169 [125.89 – 223.47]	62.02 [28.11 – 99.19]
k _a (h ⁻¹)	0.22 (7.47)		0.22 [0.20 – 0.25]	
Q/F (L/h)	14.29 (13.25)		13.14 [10.47 – 16.45]	
V _p /F (L)	217.62 (13.19)	41.53 (44.80)	207.51 [160.11 – 249.82]	40.71 [26.14 – 56.78]
F	1 FIXED	85.70 (38.37)		84.56 [46.72 – 107.44]
Residual error [log(ng/mL)] ^a	0.70 (17.66)		0.70 [0.51 – 0.93]	
DPP4 ₀ (RLU)	3573.82 (5.83)	20.12 (60.71)	3608 [3239 – 3932]	19.53 [1.34 – 28.20]
k _{syn} (h ⁻¹)	3924.63 (13.07)	56.60 (43.95)	3788 [2963 – 4481]	54.25 [25.43 – 75.93]
k _f (h ⁻¹)	0.06 (21.43)		0.06 [0.05 – 0.09]	
E _{max} (unitless)	7.64 (17.43)		7.32 [5.78 – 9.93]	
EC ₅₀ (ng/mL)	353.88 (21.56)	102.17 (38.39)	357.57 [296.57 – 530.99]	101.33 [54.53 – 129.86]
h (unitless)	1.76 (9.95)		1.75 [1.48 – 2.05]	
(unitless)	0.80 (16.98)		0.79 [0.63 – 1.06]	
Cov(² _{EC50} , ² _F)		86.08 (44.22)		85.04 [31.65 – 110.50]
Residual error [log(RLU)] ^a	0.20 (11.12)		0.20 [0.16 – 0.24]	

^a Additive error model in log scale

All parameters were simultaneously estimated and listed here twith their corresponding relative standard error (RSE%); BSV, between subject variability expressed as coefficient of variation (%). CL/F, total apparent oral clearance; V_C/F and V_p/F, apparent volumes of distribution of the central, and peripheral compartments, respectively; k_a, first order rate constant of absorption; Q/F inter-compartmental distribution clearances between the central and peripheral compartment; F, oral bioavailability; DPP4₀, baseline value for DPP4 activity; k_{syn}, synthesis rate of DPP4; k_f regulates the delay of the feedback loop; E_{max}, maximum effect; EC₅₀, the drug concentration necessary to achieve 50% of the E_{max}; h, hill exponent; γ, feedback exponent; ², variance.

Table 3

Numerical Predictive Check of sitagliptin pharmacokinetic descriptors

PK descriptor	Observed ^a	Simulated ^a
Log AUC_{<24h} (ng·h/mL)	9.23 (6.56–10.29)	8.79 (7.03–10.58)
Log AUC_{<48h} (ng·h/mL)	9.73 (7.34–10.85)	9.41 (7.53–11.26)
Log AUC_{<72h} (ng·h/mL)	9.86 (7.72–11.32)	9.79 (7.86–11.66)
Log AUC_{<96h} (ng·h/mL)	10.05 (8.09–11.71)	10.05 (8.00–11.96)
Log C_{max(0-24h)} (ng/mL)	7.50 (4.80–8.46)	6.55(4.83–8.32)
Log C_{max(24-48h)} (ng/mL)	6.85 (3.69–8.43)	6.27 (2.56–8.26)
Log C_{max(48-72h)} (ng/mL)	6.72 (3.83–7.92)	6.27 (2.56–8.28)
Log C_{max(72-96h)} (ng/mL)	6.67 (3.25–8.48)	6.34 (2.58–8.30)

^aValues are expressed as median (2.5th–97.5th percentiles)AUC_{<xh}, area under the plasma drug concentration time curve from 0h to xh; C_{max(i-jh)}, maximum plasma concentration from ih to jh.

Table 4

Numerical predictive check of sitagliptin pharmacodynamic (DPP4 activity)

PD descriptor	Observed ^a	Simulated ^a
Log AUC_{<24h} (RLU·h)	11.01 (10.45–11.47)	10.86 (10.04–11.42)
Log AUC_{<48h} (RLU·h)	11.64 (11.28–12.11)	11.57 (10.79–12.11)
Log AUC_{<72h} (RLU·h)	12.09 (11.58–12.52)	11.99 (11.22–12.53)
Log AUC_{<96h} (RLU·h)	12.31 (11.90–12.80)	12.29 (11.53–12.82)
Log Nadir_{0-24h} (RLU)	6.30 (5.51–7.88)	6.57 (5.61–7.48)
Log Nadir_{24-48h} (RLU)	6.47 (5.50–7.11)	6.82 (6.09–7.55)
Log Nadir_{48-72h} (RLU)	6.53 (5.49–7.36)	6.84 (6.12–7.55)
Log Nadir_{72-96h} (RLU)	6.55 (5.47–7.83)	6.85 (6.12–7.56)

^aValues are expressed as median (2.5th–97.5th percentiles)AUC_{<xh}, area under the DPP4 activity time curve from 0h to xh; Nadir_{i-jh}, minimum DPP4 activity level from ih to jh.