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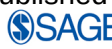

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Quantitative Model of the Relationship Between Dipeptidyl Peptidase-4 (DPP-4) Inhibition and Response: Meta-Analysis of Alogliptin, Saxagliptin, Sitagliptin, and Vildagliptin Efficacy Results

John P. Gibbs, PhD, Jill Fredrickson, PhD, Todd Barbee, PharmD, Itzela Correa, MS, Brian Smith, PhD, Shao-Lee Lin, MD, PhD, and Megan A. Gibbs, PhD

Dipeptidyl peptidase-4 (DPP-4) inhibition is a well-characterized treatment for type 2 diabetes mellitus (T2DM). The objective of this model-based meta-analysis was to describe the time course of HbA1c response after dosing with alogliptin (ALOG), saxagliptin (SAXA), sitagliptin (SITA), or vildagliptin (VILD). Publicly available data involving late-stage or marketed DPP-4 inhibitors were leveraged for the analysis. Nonlinear mixed-effects modeling was performed to describe the relationship between DPP-4 inhibition and mean response over time. Plots of the relationship between metrics of DPP-4 inhibition (ie, weighted average inhibition [WAI], time above 80% inhibition, and trough inhibition) and response after 12 weeks of daily dosing were evaluated. The WAI was most closely related to outcome, although other metrics performed well. A model was constructed that included fixed effects for placebo and drug and random effects for intertrial variability and residual error. The relationship between WAI and outcome was nonlinear, with an increasing response up to 98% WAI. Response to DPP-4 inhibitors could be described with a single drug effect. The WAI appears to be a useful index of DPP-4 inhibition related to HbA1c. Biomarker to response relationships informed by model-based meta-analysis can be leveraged to support study designs including optimization of dose, duration of therapy, and patient population.

Keywords: *Pharmacokinetics; pharmacodynamics; PK/PD; diabetes; DPP-4; drug development; meta-analysis*

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Type 2 diabetes mellitus (T2DM) is characterized by the progressive loss of pancreatic β-cell function and insulin resistance, leading to increased risk of cardiovascular disease and microvascular disorders such as retinopathy and nephropathy.[1,2] An increase in the understanding of the role of intestinal incretin hormones has provided additional therapeutic options in the treatment of T2DM.[3] Several recent articles provide a review of the efficacy profile of dipeptidyl peptidase-4 (DPP-4) inhibitors based on emerging results from randomized clinical trials.[1,4-6] Recently, sitagliptin (SITA) and saxagliptin (SAXA) were approved for use by the US Food and Drug Administration (FDA), and vildagliptin (VILD) has been approved for use by the European Medicines Agency (EMEA). Data to support the registration of alogliptin (ALOG) were submitted to the FDA in 2008. In general, these selective DPP-4 inhibitors have similar characteristics with respect to pharmacokinetics

From Pharmacokinetics and Drug Metabolism (Dr J. P. Gibbs, Dr M. A. Gibbs), Biostatistics–Medical Science (Dr Smith), and Global Development (Dr Lin), Amgen Inc, Seattle, Washington and Thousand Oaks, California; and Pharsight–A Cetara Company, St Louis, Missouri (Dr Fredrickson, Dr Barbee, Ms Correa). Supplementary data for this article are available at http://jcp.sagepub.com/supplemental/. Submitted for publication August 13, 2010; revised version accepted April 15, 2011. Address for correspondence: John P. Gibbs, PhD, Amgen Inc, 1201 Amgen Court West, AW2/D2262, Seattle, WA 98119; e-mail: gibbsj@amgen.com.
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and potency. Their pharmacokinetic properties support oral administration with a dosing frequency of once- or twice-daily administration in a fed or fasted state.[7-12] Nanomolar concentrations produce significant DPP-4 enzyme inhibition in vitro.[13]

Translational research involves the bidirectional flow of knowledge from basic science and clinical investigation to improve the application of medicines in the treatment of human disease. The development of biomarkers serves to drive more efficient selection of appropriate dose regimens by defining the cascade of biochemical and/or physiological events occurring after drug administration. Target, mechanism, and outcome biomarkers have been defined and are selected based on knowledge of the pharmacological mechanism, physiology, and disease.[14,15] For drug mechanisms such as DPP-4 with several late-stage and marketed drugs using similar biomarkers (target and outcome), there is an opportunity to investigate the biomarker to outcome relationship across the class of compounds. Pharmacokinetic/pharmacodynamic (PK/PD) models integrate information involving dose, drug concentration, biomarker, and outcome responses. These mathematical models can be used to simulate future studies and inform trial design, taking into account variability arising from interindividual differences. Additional information derived from disease and trial models are elements of model-based drug development.[16]

Meta-analysis entails the pooling of data across studies to define the mean and variance associated with a measured characteristic across studies. In a drug development setting, model-based meta-analysis techniques have been used to characterize the dose-response relationship for statins, antimigraine treatments including sumatriptan and eletriptan, neutropenic effects of trabectedin, and the PD effects of latanoprost on intraocular pressure.[17-20] In addition, an analysis of the relationship between tumor size and survival in patients with non–small cell lung cancer has been performed to improve oncology drug development.[21] Quantitative models support rational dose selection, maximizing the probability of success, and informing trial variable decisions, as recently demonstrated in the treatment of diabetes with rivoglitazone.[22]

The objectives of this PK/PD meta-analysis were to (1) determine the DPP-4 inhibition metrics; (2) characterize the relationship between DPP-4 inhibition and glycosylated hemoglobin (HbA1c) response using metadata from randomized clinical trials; and (3) evaluate the effect of covariates on HbA1c response. Because there is an approximate 3-month time delay to achieve a steady-state reduction in HbA1c, the model could be useful for designing a proof-of-concept study (ie, 3-month duration) on the basis of results from a shorter study (ie, 1-month duration).

METHODS

Studies Included

A literature search focused on studies lasting between 4 and 26 weeks was carried out using PubMed/MEDLINE (1998 to January 2008), FDA regulatory documents, EMEA regulatory documents, published abstracts, meeting presentations, symposia, and various clinical trial registries. Searches employed medical subject heading terms and text words related to diabetes mellitus and glucose, HbA1c, DPP-4 activity, glucagon-like peptide-1, and PK and PD for the following drugs: ALOG (SY-322), SAXA (BMS 477118, Onglyza, Bristol-Myers Squibb, Princeton, New Jersey), SITA (MK-0431, Januvia, Merck & Co Inc, Whitehouse Station, New Jersey), and VILD (LAF 237, Galvus, Novartis Europharm, Horsham, United Kingdom). Additional DPP-4 inhibitors, such as linagliptin, dutogliptin, and gemigliptin, were omitted from the search because less clinical data were available at the time of the search. A search was also conducted for combinations of ALOG, SAXA, SITA, and VILD added to metformin or rosiglitazone (Avandia, GlaxoSmithKline, London, United Kingdom) and sulfonylureas including glyburide, glimepiride, and glipizide. While SITA has been approved for use in combination with insulin, insulin was not included as a cotherapy for this analysis because we focused on noninsulin-dependent diabetes.

These searches resulted in a list of over 150 clinical trials of potential interest. Trials were selected for inclusion in the database based on the following criteria: patients with diabetes mellitus or T2DM, randomized trials, double-blind clinical trials, clinical trials of competitors of interest, and clinical trials of competitors of interest with endpoints of interest. Crossover and open-label design studies were also included if other criteria were met. Following the selection process, there were 31 trials of primary interest (see list of sources in Supplementary Table SI).[39-63] A review of the references within the 31 trials of primary interest was also performed, and no additional sources were identified.

Mean HbA1c results were collected from tables and figures. Additional trial information was collected

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Table I Overview of Pharmacokinetic and Pharmacodynamic Studies Included in the DPP-4 Inhibition Metric Evaluation

DPP-4 Inhibitor	Dose (mg)	Regimen	No. of Patients	Reference
Sitagliptin	12.5, 25, 50, 100, 200, 400, and 600	Single dose	42	Herman et al[64]
Vildagliptin	10, 25, 50, 100, and 200	Single dose	79	He et al[65]
	10, 25, and 100	BID for 28 days	36	He et al[66]
Saxagliptin	2.5, 5, 15, 30, 40, 50, 100, 150, 200, 300, and 400	QD for 14 days	70	Boulton[67]
Alogliptin	25, 50, 100, 200, 400, and 800	Single dose	30	Christopher et al[68]
	25, 100, and 400	QD for 14 days	42	Covington et al[10]

BID, twice daily; QD, once daily.

including baseline HbA1c, washout period, percentage of patients naïve to oral hypoglycemic agents, and use of DPP-4 inhibitors in combination with oral hypoglycemic agents (add-on) therapy. Studies that characterized the PK and PD of DPP-4 inhibition for SITA, VILD, SAXA, and ALOG were selected (Table I). Data extraction from figures was performed using Didger software (Golden Software Inc, Golden, Colorado). Although an exact quantification of the precision of data extraction is not available, data extraction was performed consistently across referenced data.

Data Analysis

PK/DPP-4 relationship. The PD endpoints were used to summarize the mean inhibition of DPP-4 observed after chronic dosing regimens. Three inhibition metrics were selected for characterization including trough DPP-4 inhibition, percentage of time above 80% inhibition, and WAI of DPP-4, which was defined by the area under the effect-time curve (AUEC) for DPP-4 inhibition divided by 24 hours. DPP-4 inhibition metrics were obtained according to the following steps. First, the available PK/PD data were digitized from available references included in Table I. Next, the pooled data were fit to a 1-compartment model with a direct effect on DPP-4 inhibition using WinNonlin Professional software (version 5.1e, Pharsight Corporation, Mountain View, California). Steady-state PK and DPP-4 inhibition profiles were simulated for clinical dosing regimens using PK/PD model parameters. Finally, predicted DPP-4 inhibition metrics were calculated from the steady-state DPP-4 inhibition profiles to serve as common measures across DPP-4 inhibitors. A summary table of PK and PK/PD parameters for each drug (Supplementary Table SII) is included in the supplementary materials.

DPP-4 to HbA1c relationship. The population PK/PD analysis was conducted using nonlinear mixed-effects modeling with the NONMEM software system (version VI, level 2.0, GloboMax LLC, Hanover, Maryland).[23] A simultaneous approach to the PK/PD analysis was undertaken, whereby the placebo and drug responses over time were estimated simultaneously. The first-order conditional estimation method with η-ε interaction was employed. Modeling proceeded in 3 general steps. First, an adequate structural PK/PD model was determined. Then, various combinations of pharmacostatistical models were investigated, and the most appropriate was selected for use in development of a final model. Finally, the impact of study covariates was investigated.

The time course of HbA1c was predicted according to equation 1:

$$HbA1c(t) = Placebo(t) + Drug(t) + \varepsilon, \quad (1)$$

where Placebo(t) represented the placebo response over time, Drug(t) was the drug response over time, and ε was the random residual error.

The time course of placebo response was predicted according to equation 2:

$$Placebo(t) = P_{max} \times (1 - e^{-k_{placebo} \cdot t}), \quad (2)$$

where P_{max} was the maximal effect of placebo.

Modeling of the time course of drug response was conducted with each of 3 summary DPP-4 inhibition metrics. Overall, each of the DPP-4 inhibition metrics provided a reasonable fit to the data; however, WAI was selected as the best predictor variable on a theoretical basis. The WAI provides a summary of the time course of DPP-4 inhibition over the dosing interval. In contrast, it was difficult to rationalize the cutoff (ie, 80% inhibition) for a time above threshold model, and trough inhibition consisted of a single time point measurement ignoring the effects of DPP-4 inhibition earlier in time. The time course of drug response was predicted according to equation 3:

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$$Drug(t) = \left(\frac{D_{max} . WAI}{DI_{50} + WAI} \right) \times (1 - e^{-k_{drug} . t}), \quad (3)$$

where D_{max} was the maximal drug effect, and DI_{50} was the WAI associated with half-maximal response. P_{max} and D_{max} were scaled by the observed mean baseline HbA1c and the typical mean HbA1c value of 8% at baseline according to equation 4:

$$HbA1c(t) = P_{max} \text{ or } D_{max} \left(\frac{HbA1c_{observed}}{8} \right). \quad (4)$$

The WAI values were transformed to normalize the distribution and to reduce constraints in model estimation as shown in equation 5:

$$T_{WAI} = \frac{WAI}{100 - WAI}. \quad (5)$$

Placebo intertrial random effects were modeled as normally distributed using the structure as shown in equation 6:

$$\theta_i = \hat{\theta} + \eta_{\theta_i}, \quad (6)$$

where θ_i is the estimated parameter value for individual *i* (eg, $P_{max,i}$), $\hat{\theta}$ is the typical population value of the parameter, and $\eta\theta_i$ is individual-specific intersubject random effect for individual *i* and parameter $\hat{\theta}$ and is assumed to be distributed $\sim N(0, \omega^2)$ with covariance defined by the intersubject covariance matrix Ω.

Intertrial variability in drug response D_{max} was modeled as log-normally distributed using an exponential structure as shown in equation 7:

$$\theta_i = \hat{\theta} \cdot \exp(\eta_{\theta_i}). \quad (7)$$

The residual error model for HbA1c response was described by an additive error model as shown in equation 8:

$$R_{ij} = \hat{R}_{ij} + \left(\frac{1}{W}\right) \varepsilon_{ij}, \quad (8)$$

where R_{ij} is the *j*th measured observation in individual *i*, $\hat{R}_{ij}$ is the *j*th model predicted value in individual *i*, and ε_{ij} is the residual random error of response data for study *i* and measurement *j* and was assumed to be distributed $\varepsilon \sim N(0, \sigma^2)$. The residual error was weighted according to the square root of the number of patients included in the study.

The assessment of model adequacy and decisions about increasing model complexity were driven by the data and guided by goodness-of-fit criteria including (1) visual inspection of diagnostic scatter plots (predicted vs observed response, residual/weighted residual vs predicted response or time, histograms of individual random effects); (2) successful convergence of the minimization routine with at least 3 significant digits in parameter estimates; (3) physiological responsibility of parameter estimates; and (4) precision of parameter estimates. All parameter estimates are reported with the relative standard error of the estimates (%RSE).

A predictive check was performed to provide a visual evaluation of model accuracy.[24] A simulation was performed that included 1000 trials under the original trial design. Plots of observed and predicted data (median and 95th percentile) were inspected for evidence of bias. Statistical inferences were based on the likelihood ratio test for a nested model, where a reduction in the minimum objective function value (MOFV) of 10.8 points, which corresponds to $P < .001$, was used as the criteria for the addition of a parameter.[23] The influence of intertrial differences in patient populations was explored graphically. Covariates investigated included baseline HbA1c, washout period, percentage of patients naïve to oral hypoglycemic agents, and use of DPP-4 inhibitors in combination with oral hypoglycemic agents (add-on therapy).

RESULTS

Supplementary Table SI provides a summary of the available clinical data involving the effect of DPP-4 inhibitors on HbA1c in randomized clinical studies. The PK/PD studies available to summarize DPP-4 inhibition metrics are listed in Table I. Table II compares the predicted DPP-4 inhibition metrics for SITA, VILD, SAXA, and ALOG at approved or selected phase 3 doses. Differences in PK and/or potency for DPP-4 gives rise to distinct DPP-4 inhibition profiles. For example, at the selected doses for each DPP-4 inhibitor, the percentage of time above 80% inhibition was variable and ranged from 40% for SAXA up to 100% for SITA, while trough DPP-4 inhibition values were more consistent with a range of 66% to 80%. The WAI associated with effective DPP-4 doses ranged from 77% to 95%. An exploratory analysis of the relationship between DPP-4 inhibition metrics and HbA1c response expressed as percentage of change from baseline was conducted after 12 weeks of dosing (Supplementary Figure S1). Overall, a similar trend was observed across the inhibition metrics, where increasing inhibition produced

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Table II Model-Based Predictions of DPP-4 Inhibition Metrics at Approved Doses of Sitagliptin, Vildagliptin, and Saxagliptin and Phase 3 Dose of Alogliptin

			DPP-4 Inhibition Metrics		
Drug	**Dose (mg)**	**Regimen**	**Percentage of Time >80%**	**Trough**	**Weighted Average Inhibition**
Sitagliptin	100	QD	100	80	91
Vildagliptin	50	BID	96	74	95
Saxagliptin	5	QD	40	66	77
Alogliptin	25	QD	99	80	88

BID, twice daily; percentage of time >80%, percentage of time where >80% inhibition of DPP-4 was observed over 24 hours; QD, once daily; trough, percentage of inhibition of DPP-4 observed at the trough; weighted average inhibition, area under the effect-time curve divided by 24 hours.

a greater reduction in HbA1c, although the shape of the trend was variable. The WAI was selected to characterize the relationship between DPP-4 inhibition and HbA1c response using a model-based meta-analysis approach.

An empirical model that linked WAI of DPP-4 to HbA1c response over time was constructed in 3 steps. In the first step, the time course of placebo response was modeled. In the second step, estimates obtained from fitting the placebo response were used as starting values for the combined model, which included placebo and drug responses. In the last step, effects of covariates such as baseline HbA1c, washout time, naïve monotherapy, nonnaïve monotherapy, and add-on therapy were investigated.

The time course of placebo response is shown in Figure 1. Differences in the placebo response were noted for trials involving patients who were naïve to oral hypoglycemic agents (naïve monotherapy), underwent washout from current oral hypoglycemic agents for 2 to 12 weeks (nonnaïve monotherapy), or were given a DPP-4 inhibitor in combination with another oral hypoglycemic agent (add-on therapy). The mean baseline HbA1c for each of the 3 groups was similar (8.19 for add-on therapy, 8.14 for naïve monotherapy, and 8.04 for nonnaïve monotherapy, respectively). Structural parameter estimates and intertrial variability for the model are presented in Table III. The estimated P_{max} values in HbA1c for naïve monotherapy, nonnaïve monotherapy, and add-on therapy were –0.449%, 0.212%, and –0.119% change from baseline, respectively. An exponential function adequately described the change in placebo response over time with a $k_{placebo}$ of 0.141 $weeks^{-1}$ or a half-life of 4.91 weeks (Figure 1). Intertrial variability in the P_{max} value was 0.159 expressed as the standard deviation in HbA1c (percentage of change from baseline).

Figure 2 displays the observed and population predicted time course of drug response after 100-mg oral SITA once-daily (QD) administration for nonnaïve monotherapy and add-on therapy as a representative example. The median of the model prediction fit the time course of HbA1c response well in add-on therapy, and some bias was observed in the prediction of results in nonnaïve patients. It should be emphasized that the model is based on all the data for DPP-4 inhibitors (ie, across dose and time). The inclusion of additional model parameters was examined, and the results are described below. The estimated k_{drug} was 0.207 $weeks^{-1}$, which corresponds to a half-life of 3.35 weeks. Using the estimated k_{drug} value, the steady-state reduction in HbA1c was predicted to be achieved after approximately 17 weeks or 4.3 months. The estimated D_{max} and DI_{50} were –0.716 and 53.8, respectively. The final model provided reasonably precise estimates (≤17% RSE) of fixed effect parameters with the exception of the P_{max} for add-on therapy (46% RSE). The intertrial variability (%CV) estimated for D_{max} was 23%. The results of the predictive check showed good agreement between the simulated and observed data after 4 weeks (Figure 3) and 12 weeks (Figure 4) of DPP-4 inhibitor therapy for studies involving naïve monotherapy, nonnaïve monotherapy, and add-on therapy.

Additional analysis was conducted to determine the value of drug-specific estimates of DI_{50} and D_{max}. For the 4 DPP-4 inhibitors included in this analysis, unique values of DI_{50} did not trigger the $P < .001$ criteria (ΔMOFV = –9.215 with the addition of 3 parameters [$P = .027$]). In addition, when the D_{max} for ALOG was fit separately from the other DPP-4 inhibitors, the estimates were –0.569 and –0.744, respectively; however, the $P < .001$ criteria were not triggered (ΔMOFV = –4.088 with the addition of 1 parameter [$P = .043$]). Thus, a model with common

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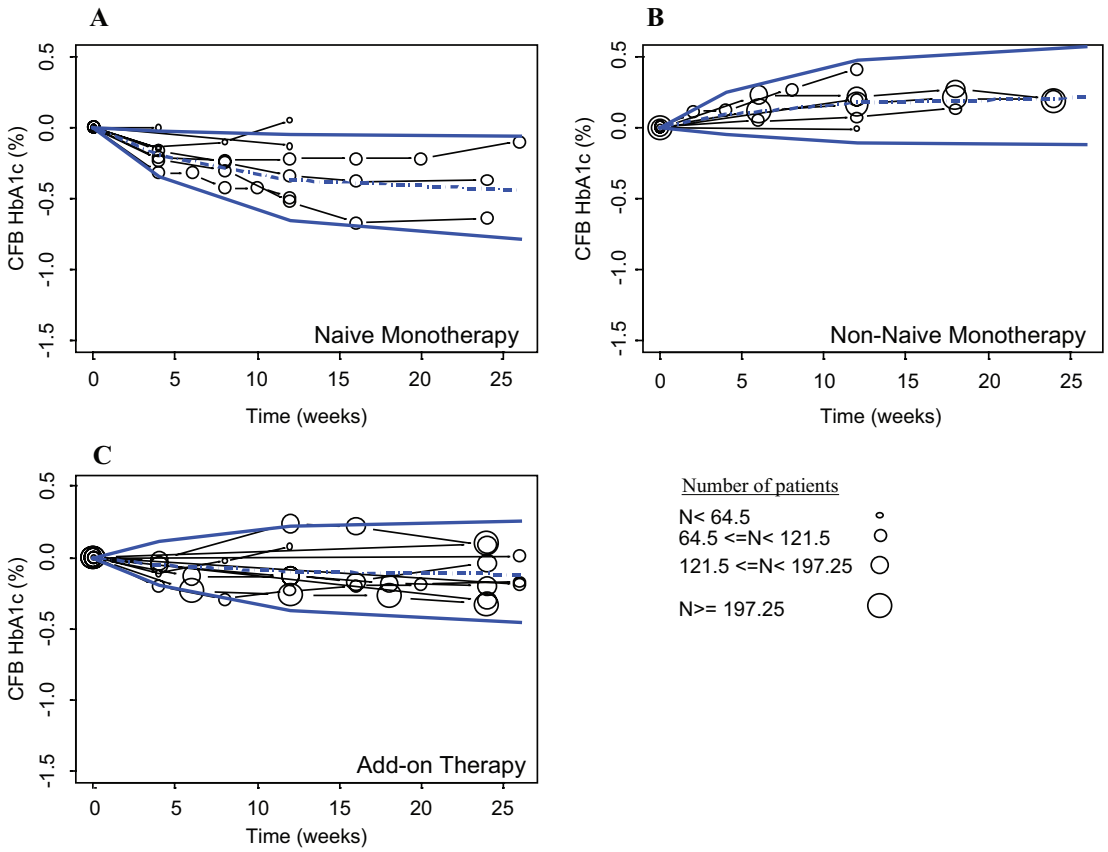

Figure 1. Predicted and observed placebo HbA1c response (percentage of change from baseline) over time in (A) naïve monotherapy, (B) nonnaïve monotherapy, and (C) add-on therapy patients. Open circles represent the observed mean placebo response with the size indicating the number of patients. The dashed line represents the median model prediction and the solid lines represent the 95% confidence interval of the prediction.

Table III Population Parameter Estimates for HbA1c (Percentage of Change From Baseline) Based on the Weighted Average Inhibition (WAI) of DPP-4 Over 24 Hours

		Fixed Effects: Population Mean Parameter		Random Effects: Intertrial/ Residual Variance	
Parameter	**Units**	**Estimate**	**%RSE**	**Estimate**	**%RSE**
$k_{placebo}$	$Weeks^{-1}$	0.141	6	0.00[a]	—
P_{max}	—	—	—	0.0254	24
Naïve monotherapy	HbA1c (%)	−0.449	17	0.00[a]	—
Nonnaïve monotherapy	HbA1c (%)	0.212	13	0.00[a]	—
Add-on therapy	HbA1c (%)	−0.119	46	0.00[a]	—
k_{drug}	$Weeks^{-1}$	0.207	3	0.00[a]	—
D_{max}	HbA1c (%)	−0.716	6	0.0514	29
DI_{50}	WAI (%)	53.8	13	0.00[a]	—
σ^2 (residual error)	—	—	—	0.567	12

%RSE, relative standard error of the estimate calculated as (*SE/Estimate*)· 100; SE, standard error of the estimate.
a. Interstudy random variance was fixed at 0 in the model.

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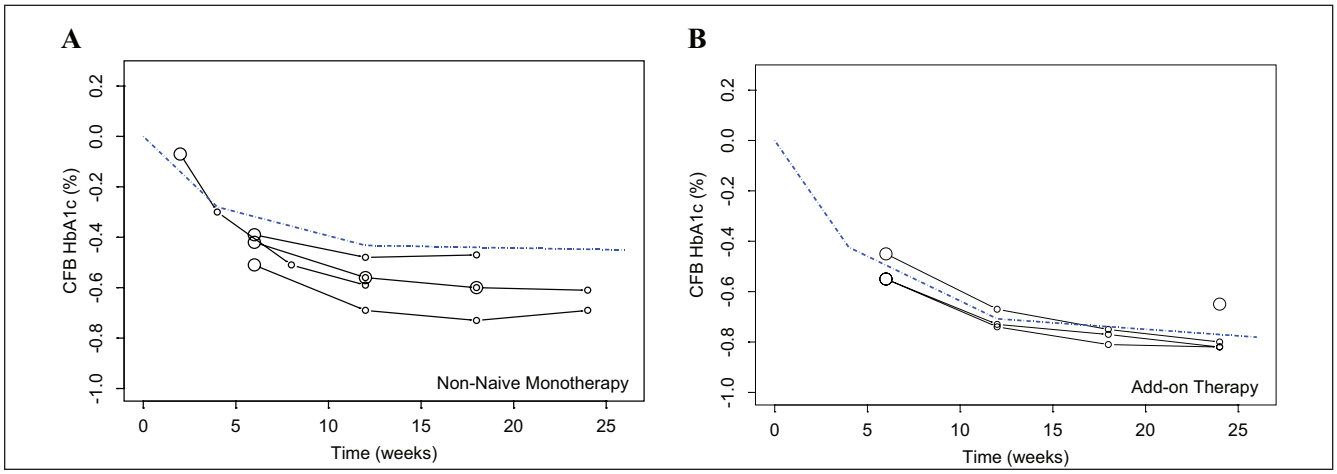

Figure 2. Predicted and observed HbA1c response (percentage of change from baseline) over time for 100-mg once-daily oral sitagliptin in (A) nonnaïve monotherapy and (B) add-on therapy. Open circles represent the observed HbA1c response, and the dashed line represents the mean population prediction.

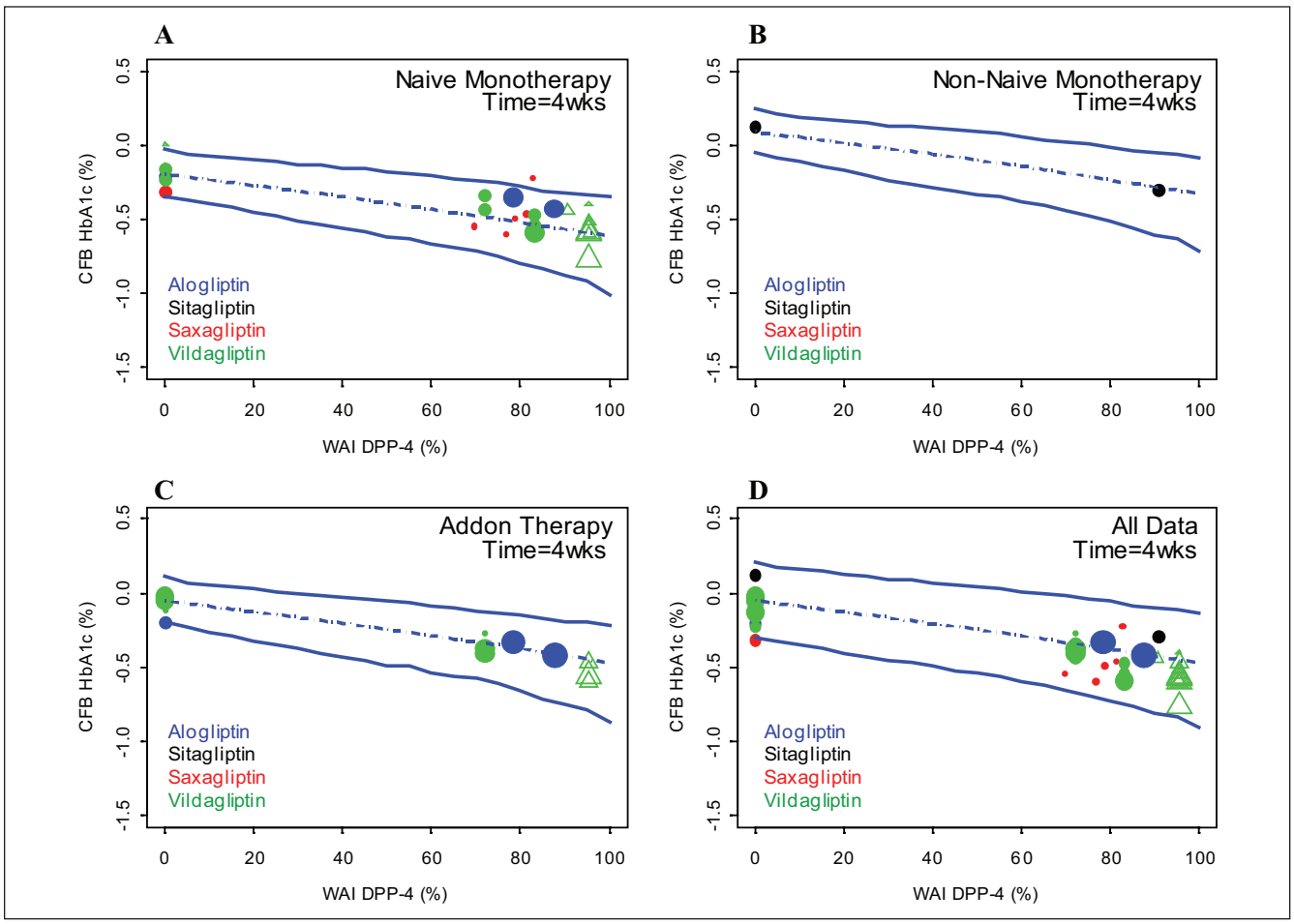

Figure 3. Predicted and observed HbA1c response (percentage of change from baseline) versus weighted average inhibition of DPP-4 over 24 hours after DPP-4 administration or placebo for 4 weeks in (A) naïve monotherapy, (B) nonnaïve monotherapy, (C) add-on therapy patients, and (D) all data. Closed circles and open triangles represent the observed mean treatment response after QD or BID administration, respectively, with the symbol size indicating the number of patients as indicated in Figure 2. The dashed line represents the median model prediction and the solid lines represent the 95% confidence interval of the prediction.

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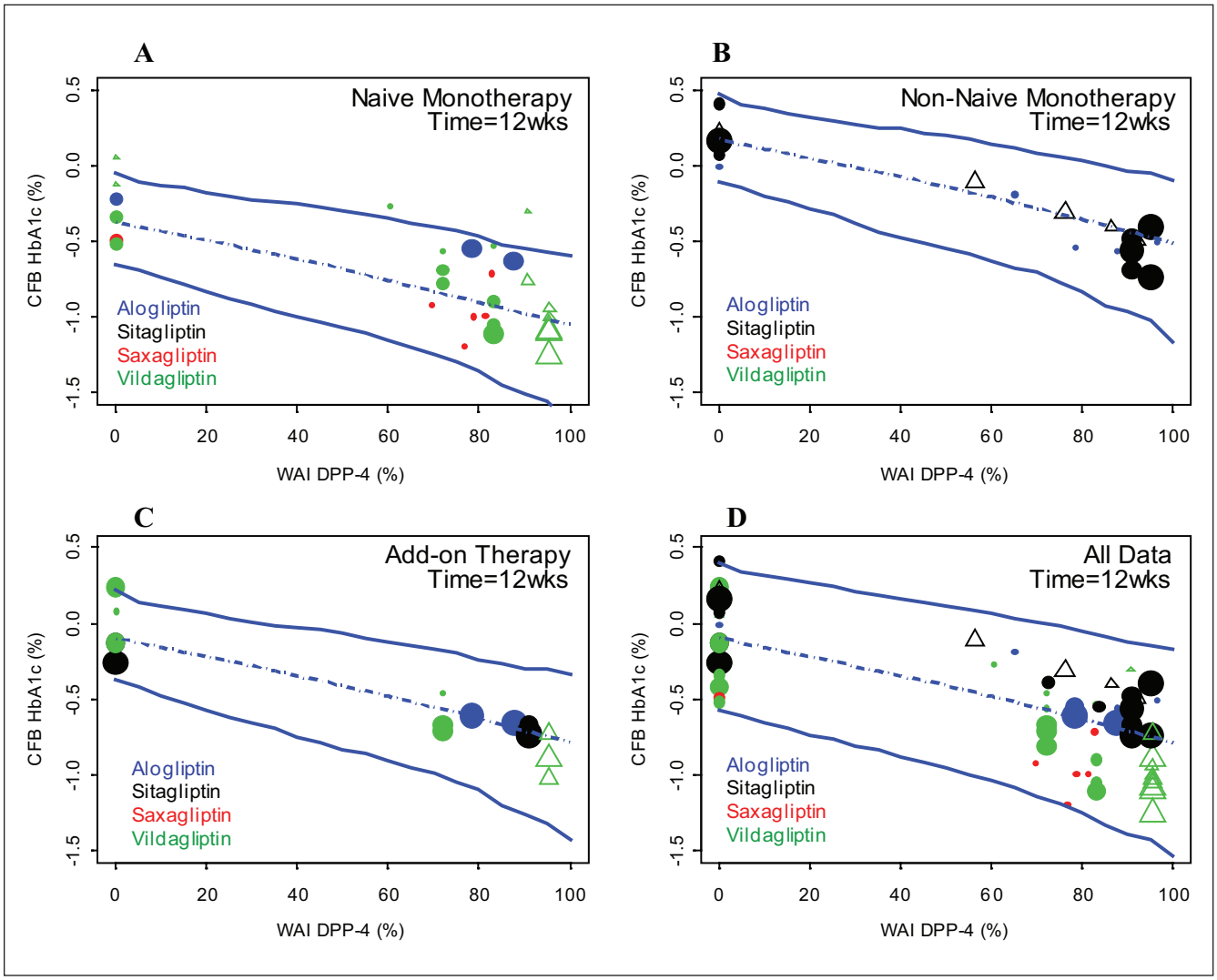

Figure 4. Predicted and observed HbA1c response (percentage of change from baseline) versus weighted average inhibition of DPP-4 over 24 hours after DPP-4 administration or placebo for 12 weeks in (A) naïve monotherapy, (B) nonnaïve monotherapy, (C) add-on therapy patients, and (D) all data. Closed circles and open triangles represent the observed mean treatment response after QD or BID administration, respectively, with the symbol size indicating the number of patients as indicated in Figure 2. The dashed line represents the median model prediction and the solid lines represent the 95% confidence interval of the prediction.

D_{max} and DI_{50} terms was selected as the final model. The addition of other covariates such as baseline HbA1c and washout time did not further improve the model (data not shown).

DISCUSSION

It is frequently hypothesized that a consistent level of receptor occupancy or enzyme inhibition will produce similar therapeutic effects across a series of drugs designed to interact with a common pharmacological target in a specific manner. Herein, this hypothesis was examined by evaluating the relationship between DPP-4 inhibition and reduction in HbA1c in a model-based meta-analysis of clinical trials involving SITA, VILD, ALOG, and SAXA. A universal relationship between DPP-4 inhibition and HbA1c response was identified that described the time course of effect on HbA1c for DPP-4 inhibitors included in the analysis. Important covariates that helped to distinguish unique placebo response profiles included naïve monotherapy, nonnaïve

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monotherapy, and add-on therapy. In theory, differences in PK and potency should be minimized by characterizing the biomarker-response relationship rather than dose-response relationship. In addition, the model can be used to facilitate the development of follow-on DPP-4 inhibitors. With knowledge of steady-state DPP-4 inhibition profile, optimal doses can be identified to help guide study design for a given study population.

Biomarkers in conjunction with modeling and simulation support drug development and help to rationalize drug-dosing regimens. It was reported that plasma DPP-4 biomarker data were used to accelerate the development timeline for SITA by building internal conviction for the development program.[25] Several other examples exist where biomarker to outcome relationships have been leveraged. In psychiatry, a consistent level of receptor occupancy has been noted for serotonin reuptake inhibitors[26,27] and antipsychotics targeting D2 receptors.[28-31] Leveraging biomarker to outcome relationships using modeling and simulation can facilitate decision making by providing quantitative predictions of outcomes under different scenarios.

Both empirical and mechanistic models have been developed and successfully applied to characterize response after diabetes treatments.[32] A "fit-for-purpose" empirical model was selected to perform meta-analysis of DPP-4 inhibitor results, which described placebo and drug effects. The model relied on summary metrics of DPP-4 inhibition (ie, WAI) rather than the dynamic time course of DPP-4 inhibition resulting from each dose administration. In addition, mean trial results were included in the model rather than individual subject data often required for physiological/mechanistic PK/PD models. With the empirical approach, a quantitative model of the dynamics of HbA1c was developed, and study covariates were identified.

A covariate analysis of the placebo response revealed that specific patterns in the mean placebo response were associated with study populations. In a monotherapy setting, patients' status as naïve/nonnaïve to oral hypoglycemic agents appeared to influence placebo response. While a modest reduction in HbA1c was observed in a naïve population, a slight increase in HbA1c was observed in nonnaïve patients (–0.449% vs 0.212% change from baseline HbA1c, respectively). In addition, add-on therapy was associated with a slight reduction in HbA1c (–0.119% change from baseline HbA1c).

Because T2DM is a progressive disease with impairment of β-cell secretory function and insulin resistance,[1] changes in placebo response according to patient status may reflect differences in disease progression. The rate of disease progression has been described as an increase of 0.2% HbA1c per year.[33] Patients recently diagnosed with T2DM are more likely to be naïve to drug therapy and therefore subject to a greater benefit from diet and exercise compared to patients who have progressed in their disease.[34] Unfortunately, information on the average disease duration was not available to further evaluate this hypothesis. It is important to delineate placebo response from the net effect of drug treatment to gain an accurate assessment of the magnitude of drug effect.[35]

Using the DPP-4 database, a maximal drug effect of 0.716% reduction in HbA1c was predicted. A term to account for the pharmacological interaction between DPP-4 inhibitors and other oral hypoglycemic agents including metformin, sulfonylureas, and thiazolidinediones was not needed to adequately describe the drug effect. The first-order rate constant, k_{drug}, which described the onset of effect, suggested that steady state would be achieved after 4.3 months. This estimate is in agreement with other reports that indicate approximately 4 months to achieve steady state with respect to HbA1c.[33,36]

Several limitations to the meta-analysis reported herein should be noted. This meta-analysis relies on publicly available information and may be subject to publication bias. The analysis was undertaken in a retrospective manner, combining data from different studies. While the current analysis attempted to control for trial-to-trial differences using covariates, other noninvestigated differences in trial design may have influenced the results. To establish true differences in DPP-4 treatments, head-to-head randomized clinical trials are needed. The current model-based analysis did not account for the influence of correlation within the treatment arm, which may have led to an overestimate of the intertrial variability in drug effect.[37] In addition, differences in the DPP-4 assay applied during the clinical development have been noted concerning the substrate, substrate concentration, and level of assay dilution.[38] Despite these differences in the ex vivo measurement of DPP-4 inhibition, a similar relationship to outcome was observed across the DPP-4 inhibitors investigated.

Steady-state WAI of DPP-4 appears to be a useful biomarker related to HbA1c response after chronic therapy. Similar maximal reductions in HbA1c were predicted for ALOG, SITA, SAXA, and VILD. Biomarker-response relationships informed by model-based meta-analysis can be leveraged to support study designs including optimization of dose, duration of therapy, and patient population.

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