ORIGINAL ARTICLE

Utilization of model-based meta-analysis to delineate the net efficacy of taspoglutide from the response of placebo in clinical trials

Han Qing Li [a,*], **Jia Yin Xu** [b], **Liang Jin** [a], **Ji Le Xin** [a]

[a] State Clinical Trial Institution of New Drugs, International Mongolian Hospital of Inner Mongolia, Hohhot 010065, Inner Mongolia, China
[b] Mongolian Pharmaceutical Preparation Center, International Mongolian Hospital of Inner Mongolia, Hohhot 010065, Inner Mongolia, China

Abstract The objective of this study was to develop quantitative models to delineate the net efficacy of taspoglutide on fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) from the response of placebo in type 2 diabetes patients, and further find pharmacodynamic potency of taspoglutide and FPG for half of maximum reduction responses of FPG and HbA1c, respectively. Several PD data about taspoglutide treatments for type 2 diabetes patients were digitalized from the published papers related with the clinical development of taspoglutide. The model based meta-analysis (MBMA) studies for FPG and HbA1c were performed with Monolix 4.2 software. The MBMA successfully described the effects of placebo and taspoglutide on pharmacological indexes of FPG and HbA1c through mono and multiple combination therapies in clinical trials. The pharmacodynamic potency (25.3 pmol/l) produced 50% of maximum responses of FPG (−2.39 mmol/l) from the responses of placebo for FPG (−0.371 mmol/l); the response change of FPG (−1.81 mmol/l) affected 50% of maximum response change (−1.74%) for HbA1c from the response of placebo (−0.253%). The leveraging prior knowledge from the longitudinal MBMA will be utilized to guide clinical development of taspoglutide and further support study designs including optimization of dose and duration of therapy.

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* Corresponding author at: State Clinical Trial Institution of New Drugs, International Mongolian Hospital of Inner Mongolia, No. 83, Da Xue East Road, Sai Han District, Hohhot 010065, China. Tel.: +86 0471 5182293.
E-mail address: hqltcm@163.com (H.Q. Li).
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1. Introduction

With a steady increase in the prevalence of diabetes from 1980 to 2011, it is estimated that by the year 2030, 552 million people will have diabetes (Whiting et al., 2011), thus the great burden will be brought worldwide by the huge increase in type 1 and 2 diabetes population, of which type 2 diabetes people account for about 90–95% of all diagnosed cases of diabetes

(Gavin et al., 2010; Nyenwe et al., 2011). Although current therapies for type 2 diabetes include lifestyle modification of diet and exercise as first-line therapy, pharmacotherapy is considered an essential component for effective glycemic control (Nathan, 2009). Glucagon-like peptide-1 (GLP-1) receptor agonists are a novel class of pharmacotherapies that provide effective glycemic control with low risk of hypoglycemia and weight loss (Drucker, 2007; Sebokova et al., 2010a). Taspoglutide is a long-acting human GLP-1 analogue and considered to have equivalent potency to natural GLP-1 (Nauck et al., 2009). This GLP-1 analogue has been shown to elicit a long-lasting incretin effect, and sustained glycemic control (Raz et al., 2012).

Taspoglutide contains aminoisobutyric acid which is covalently attached to the GLP-1 sequence at positions 8 and 35 of the native GLP-1 peptide (Dong et al., 2011). These structure modifications prolong the half-life of the circulating complex without otherwise changing its biological activity. Also, apparently, the aminoisobutyric acid molecule sterically inhibits DPP-4 enzyme from degrading taspoglutide (Sebokova et al., 2010b). Taspoglutide shows high binding affinity to the human GLP-1 receptor (Pratley et al., 2013) and its biological activity is not affected through assessment of its relative activity on cyclic adenosine monophosphate stimulation (Sebokova et al., 2010b). Its resistance to DPP-4 enzyme degradation and a zinc-based sustained release formulation confer an extended half-life and allow for QW subcutaneous administration (Ratner et al., 2010). Several multiple dosing regimens in clinical trials have showed that taspoglutide 10 or 20 mg compared with placebo to patients with type 2 diabetes reduced FPG levels, stimulated insulin secretion and reduced glucagon levels with weight loss (Nauck et al., 2009; Bergenstal et al., 2012; Henry et al., 2012; Raz et al., 2012).

We present here quantitative models to describe time courses of FPG and HbA1c, and these models provide linkage between drug and responses. Such models can leverage prior knowledge from clinical studies, and conduct comparison of competing drugs (Gross et al., 2013), and make prediction of unobserved clinical outcomes (Gibbs et al., 2012).

The present study was performed to delineate the net effects of taspoglutide on FPG and HbA1c from the responses of placebo in type 2 diabetes patients, and further find pharmacodynamic potency (IC_{50_F} and IC_{50_H}) for half of maximum reduction responses of FPG and HbA1c, respectively. The retrospectively integrated prior knowledge from clinical studies will be utilized to guide clinical development and application of taspoglutide in future.

2. Methods

2.1. Selection of studies

All studies that investigated the efficacy of taspoglutide in clinical trials about pharmacological indexes of FPG and HbA1c were considered in these quantitative models. Data were searched in PubMed/MEDLINE, Google scholar search and clinical trial registries lasting between inception and February 2014, and the medical subject heading terms and text words from electric databases included efficacy, pharmacokinetics, pharmacodynamics, type 2 diabetes, clinical trial, FPG and HbA1c for taspoglutide. Data in each article must be composed of FPG and HbA1c, and the multiple dosing regimens should include placebo, 10 and 20 mg doses and the PD data were only from efficacy of placebo, 10 and 20 mg doses on patients through chronic treatments.

Mean FPG and HbA1c results were collected from the figures, tables and values reported in article content. Data from the articles were transformed to change values from baselines if the actual measurements were used to depict the efficacy in clinical studies, and the each PD group data must have the same units and homogeneous properties. All references cited in this study were carefully reviewed to identify the PD data for final model development. Two investigators independently extracted data from eligible studies, and finally reached an agreement on inclusion criteria for final data entry.

Two PD endpoints were used to summarize the mean efficacy results of taspoglutide after multiple dosing regimens in clinical trials. For all studies, the study protocols were approved by the local ethics and research committees, and written informed consents were obtained from all subjects enrolled in clinical studies.

2.2. Metrics for PD modeling

The average plasma concentration between 2nd and 4th week (Cavg.(2 w–4 w) value) of taspoglutide (20 mg dose per dosing regimen group), which was obtained from the published paper (Ratner et al., 2010), was directly used as metric to characterize the efficacy results (FPG) when taspoglutide 20 mg was subcutaneously administrated to patients with type 2 diabetes. The maximum reduction responses (Dmax_F) in FPG for taspoglutide 10 and 20 mg doses were used as metrics for HbA1c data model development in the taspoglutide group. The metrics (placebo, 10 and 20 mg doses) finally used for FPG and HbA1c data model development are shown in Supplementary Table 1.

2.3. Software

Two quantitative models for taspoglutide PD indexes were developed and estimated on the available digitalized measures, using Monolix 4.3 software (http://software.monolix.org) (Bouazza et al., 2012; Laouenan et al., 2013). Parameters of PD models were estimated by computing the maximum likelihood estimator using the stochastic approximation expectation maximization (SAME) algorithm method. The model building processes were guided by visual inspection of goodness-of-fit (GOF) and change of −2 times the log likelihood (OFV), Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) obtained from Monolix. Prediction distribution graphics were obtained using the Monolix 4.3 software, and other graphics were obtained from R 2.15 (http://www.R-project.org) and RStudio 0.97 (http://www.rstudio.com) program.

2.4. Modeling strategy

The utilization of quantitative model (Gibbs et al., 2012) was extended to delineate the net efficacy of placebo-adjusted taspoglutide in clinical trials. The placebo and taspoglutide responses over time were estimated and processed in 3 general steps. Firstly, the placebo responses over time for FPG and HbA1c were independently estimated and the parameter

estimates were fixed as initial values to model placebo and drug responses simultaneously. Secondly, the Emax equations and metrics were used to develop finally combined response models including changes of FPG and HbA1c for placebo and taspoglutide. Finally various statistical models were investigated, and the most appropriate was selected for use in finally combined model development.

2.5. PD modeling

The drug and placebo directly acted on FPG and indirectly regulated HbA1c changes from the baselines.

The time courses of placebo response were predicted according to Eq. (1):

$$\text{Placebo\_response}_{s,i}(t) = P_{\max\_s,i} \times (1 - e^{-K_{\text{p}\_s,i} \times t}) \quad (1)$$

The time courses of drug response were predicted according to Eq. (2):

$$
\begin{aligned}
\text{Drug\_response}_{s,i}(t) &= \text{placebo\_response}_{s,i}(t) \\
&+ \tfrac{D_{\max\_s,i} \times metric\_s,i}{DI_{50}\_s,i + metric\_s,i} \times (1 - e^{-k_{drug}\_s,i \times t}) + \varepsilon_{s,i}
\end{aligned} \quad (2)
$$

where s is the identification for PD: 1 and 2 for FPG and HbA1c, respectively, and i represents individual PD index. Placebo_response (t) and drug_response (t) represent the placebo and drug responses over time, respectively; Pmax and Dmax are the maximum effects of placebo and drug, respectively; Kp and Kdrug represent the first order rate constants in the reduction of FPG and HbA1c for placebo and taspoglutide; The *metric* variables in Eq. (2) are the metrics associated with half-maximal responses of FPG and HbA1c, ε is the random residual error. Two DI_{50} estimates represent pharmacodynamic potency of drug and FPG on the responses of FPG and HbA1c, respectively, when the drug was administrated to patients.

2.6. Statistical model

The between variability of selected PD parameters was described by the exponential and addictive models. The below exponential and addictive models are used to describe the between variability of selected PD parameters:

$$P_i = P_{pop} \cdot \exp(\eta_{p_i}) \quad (3)$$

$$P_i = P_{pop} + \eta_{p_i} \quad (4)$$

where individual parameters for exponential model mainly include Kp and Kdrug, while individual parameters for addictive model mainly include Pmax, Dmax and IC_{50}; P_i is the individual parameter value, P_{pop} is its typical population value, and η_{Pi} is an independent random variable normally distributed with the mean of zero and standard deviation ω_{pi}.

The combined error models of the residual error were applied to FPG (Eq. (5)) and HbA1c (Eq. (6)) data:

$$Y = F + b \cdot F^c \cdot \varepsilon \quad (5)$$

$$Y = F + (a + b \cdot F^c) \cdot \varepsilon \quad (6)$$

where Y is the observation; F is the corresponding model prediction; a, b and c represent residual error parameters; ε is

assumed to be an independent and normally distributed random variable with the mean of zero and standard deviation σ.

The assessments of model adequacy and decision about increasing model complexity were driven by the data and guided by GOF. All parameter estimates were reported with the relative standard error of estimates (R.S.E %).

2.7. Model validation

The final models were internally examined by GOF, which included plots of normalized prediction distribution error (NPDE) (Brendel et al., 2006) *vs.* time and IPRED, and plots of population prediction (PRED) and IPRED *vs.* observation (DV). Other diagnostics included the OFV and the precision of the parameter estimates.

The finally established models were also externally validated. Additional PD data (Rosenstock et al., 2013) were retrospectively collected from a group of 797 patients with type 2 diabetes who met the same inclusion criteria as the final model building group. FPG and HbA1c data were predicted by fixing the parameters in the structural and statistical model to the parameter estimates in the final model using *post hoc* Bayesian forecasting with Monolix software. The predictive power was determined by comparing the predicted values with the corresponding observed values. Bias (mean prediction error [MPE]) and precision (mean absolute prediction error [MAPE]) were calculated (Han et al., 2011), using Eqs. (7) and (8):

$$MPE = \frac{\sum (PD_{ipred} - PD_{obs})}{N} \times 100\% \quad (7)$$

$$MAPE = \frac{\sum |PD_{ipred} - PD_{obs}|}{N} \times 100\% \quad (8)$$

where N denotes the number of observations, PD_{ipred} and PD_{obs} are individual prediction and observation values of PD data, respectively.

3. Results

3.1. PD Data

The computer searches yielded 9 publications (Nauck et al., 2009, 2013; Ratner et al., 2010; Bergenstal et al., 2012; Henry et al., 2012; Raz et al., 2012; Hollander et al., 2013; Pratley et al., 2013; Rosenstock et al., 2013) which were deemed appropriate for inclusion and used to process pharmacometric assessments based multiple PD indexes. In this literature search study, 8 clinical trial data were chosen to include for model development and 1 clinical trial data (Rosenstock et al., 2013) were used for external model validation, and a total of 3702 patients participated in clinical trials of placebo, 10 and 20 mg doses of taspoglutide over weeks 8–52. The therapeutic regimens mainly included taspoglutide monotherapy with diet control and exercise, or taspoglutide in combination with metformin, metformin or/and sulphonylurea, metformin or/and TZD, and metformin plus TZD in clinical trials. Table 1 provides a summary of available clinical data involving the effects of taspoglutide on the FPG and HbA1c in randomized clinical trials.

Table 1 Summary of clinical efficacy data from computer searches.

Studies	Duration (weeks)	Concomitant medications	Taspoglutide dose (QW)	Patients	Treatment background	Study design
1. Raz et al. (2012)	24	Monotherapy	Placebo,10, 20 mg	373	Drug-naive T2D inadequately controlled	Randomized, double-blind, placebo-controlled study
2. Ratner et al. (2010)	8	Met	Placebo, 20 mg	64	Inadequately controlled on metformin alone	Randomized double-blind placebo-controlled study
3. Nauck et al. (2009)	8	Met	Placebo, 10, 20 mg	148	Inadequately controlled with metformin	Double-blind placebo-controlled study
4. Nauck et al. (2013)	24	Met	10, 20 mg	709	Failing metformin and sulphonylurea combination therapy	Randomized, open-label, parallel-group trial
5. Hollander et al. (2013)	24	Met	Placebo, 10/20 mg	305	Inadequately controlled with metformin monotherapy	Randomized, double-blind, placebo-controlled study
6. Bergenstal et al. (2012)	24	Met	Placebo, 10, 20 mg	481	Inadequately controlled with metformin	Randomized, double-blind, double-dummy, parallel-group trial
7. Henry et al. (2012)	24	Met + TZD	Placebo, 10, 20 mg	326	Inadequately controlled with metformin plus pioglitazone	Randomized, double-blind, parallel-group, placebo-controlled trial
8. Pratley et al. (2013)	24	SU or/and Met	10, 20 mg	499	Inadequately controlled with sulphonylurea or/and metformin	Randomized, double-blind, double-dummy, active-controlled trial
9. Rosenstock et al. (2013)	52	Met or/and SU	10, 20 mg	797	Inadequately controlled type 2 diabetes on metformin ± a thiazolidinedione	Randomized, open-label, active-comparator, parallel-group

3.2. Metrics for PD modeling

The metrics available to use for FPG and HbA1c data modeling are summarized in Supplementary Table 1. The metrics for FPG data were directly derived from the digitalized taspoglutide concentrations between 2nd and 4th week (Ratner et al., 2010). The three individual concentrations for 20 mg doses were averaged and the average value was directly used as metric for PD modeling of subsequent taspoglutide 20 mg dose. The metric for 10 mg dose of taspoglutide was directly calculated from simple arithmetic of the average concentration value of 20 mg dose, as the exposure of taspoglutide appeared dose proportional once weekly (Ratner et al., 2010). The metric for placebo was set to zero, as no drug concentrations were involved in the pharmacokinetics in clinical trials. An exploratory analysis of the relationship between the metric and FPG was conducted lasting from 8 to 52 weeks of placebo, taspoglutide 10 and 20 mg. Overall, FPG over time was fitted well by quantitative models, as seen in Figs. 1 and 2.

The metrics for HbA1c modeling were derived from the population prediction values for taspoglutide 10 and 20 mg in FPG modeling. However, the metric for placebo HbA1c data modeling were set to zero, as the drug concentration was not involved in treatment response. The exploratory analysis approach for taspoglutide concentration-FPG was also used to characterize relationship between FPG and HbA1c, which was also adequately described by quantitative model, as seen in Fig. 2.

3.3. FPG

The time courses of placebo and drug responses for FPG are shown in Fig. 1 and structure parameter estimates and individual trial variability are presented in Table 2. In the placebo group, the population prediction (Pmax_F) of FPG change from baseline was −0.371 mmol/l (Fig. 1A), which reflected the overall trend of FPG when the placebo was given to the patients. While in the drug group, the population prediction (Dmax_F) of FPG change from baseline was −2.39 mmol/l (Fig. 1B), which reflected the trends of FPG reduction when the doses (10 and 20 mg) were given to the patients. Compared with placebo responses, the drug responses of two doses were much more significant in FPG reduction (Fig. 1A *vs.* Fig. 1B). Overall, prediction distribution of FPG reductions for the drug group demonstrated that quantitative model could adequately fit the observed mean values from published papers.

An exponential function for combined placebo and drug responses adequately described the changes of placebo and drug responses over time with a Kp_F of 0.781 weeks^{-1} and a Kdrug_F of 2.0 weeks^{-1}, and the drug concentration of taspoglutide (IC$_{50\_F}$) was about 25.3 pmol/l which could produce 50% of maximum efficacy (Dmax_F = −2.39 mmol/l) in clinical trials. The estimated kdrug_F was 2.0 weeks^{-1}, which corresponds to a half-life of 2.4 days. Using the estimated kdrug_F value, the steady-state reduction in FPG was predicted to be achieved after approximately 12 days or 1.7 weeks (Fig. 1B).

3.4. HbA1c

The time courses of placebo and drug responses for HbA1c are shown in Fig. 2 and structure parameter estimates and individual
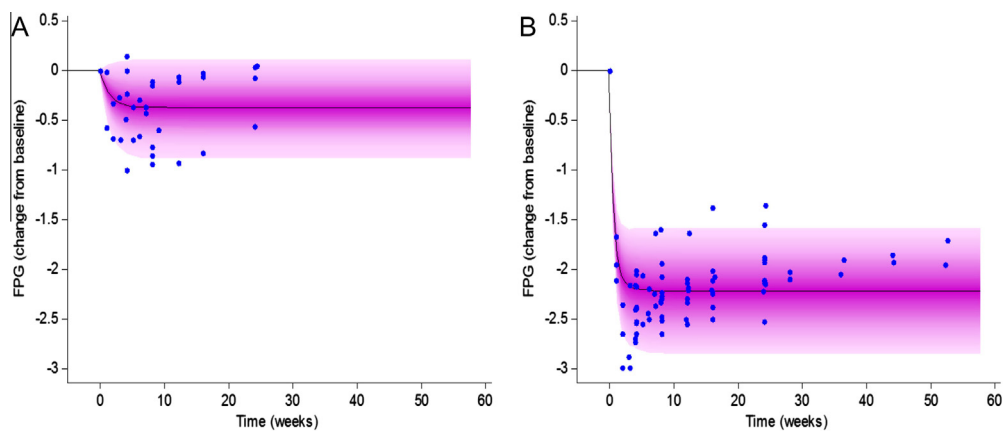
Figure 1 Observed and prediction distribution of FPG response over time in A (placebo response, change from baseline) and B (drug response, change from baseline). The color areas represented the 95% confidence interval of the prediction around the simulated percentiles, the solid dots were mean FPG values from the literatures and the solid line represented the median prediction.
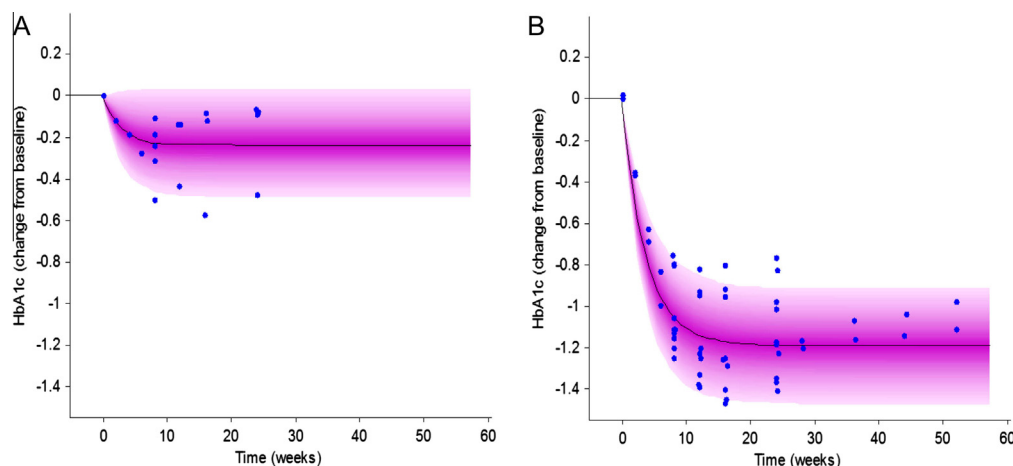

Figure 2 Observed and prediction distribution of HbA1c response over time in A (placebo response, change from baseline) and B (drug response, change from baseline). The color areas represented the 95% confidence interval of the prediction around the simulated percentiles, the solid dots were mean FPG values from the literatures and the solid line represented the median prediction.

Table 2 Parameter estimates from quantitative model for FPG.

Parameter	Estimate	R.S.E (%)	ITV[d] (%)
Pmax_F(mmol/l)[e]	−0.371	35	29.8
Kp_F (1/week)[e]	0.781	43	37.8
Dmax_F (mmol/l)	−2.39	6	24.8
IC$_{50\_F}$ (pmol/l)	25.3	0	5.43
Kdrug_F (1/week)	2.0	2	12.5
b	0.194	8	
c	0.182	37	

R.S.E represented relative standard error; F represents FPG; IC$_{50\_F}$ represents pharmacodynamic potency of drug on the response of FPG when the drug was administrated to patients.
[d] ITV represents inter trial viability.
[e] Parameter estimates for FPG in placebo were fixed in finally combined PD model.

trial variability are presented in Table 3. In the placebo group, the population prediction (Pmax_Hb) of HbA1c change from baseline was −0.253% (Fig. 2A), which reflected the overall trend of HbA1c when the placebo was given to the patients.

While in the drug group, the population prediction (Dmax_Hb) of HbA1c change from placebo response was −1.74% (Fig. 2B). Compared with placebo responses, the drug reduction responses of two doses were much more significant (Fig. 2A vs. Fig. 2B),

Table 3 Parameter estimates from quantitative model for HbA1c.

Parameter	Estimate	R.S.E (%)	ITV[d] (%)
Pmax_Hb (%)[e]	−0.253	26	15.2
Kp_Hb (1/week) [e]	0.382	23	14.7
Dmax_Hb (%)	−1.74	8	8.65
IC$_{50\_H}$ (mmol/l)	−1.81	15	26.8
Kdrug_Hb (1/week)	0.249	13	19.9
a	0.00532	16	
b	0.0717	13	
c	0.239	66	

R.S.E represented relative standard error; Hb represents HbA1c; IC$_{50\_H}$ represents pharmacodynamic potency of FPG on the response of HbA1c when the drug was administrated to patients.

[d] ITV represents inter trial viability.

[e] Parameter estimates for HbA1c in placebo were fixed in finally combined PD model.

but the responses between dose 10 and 20 mg did not show significant differences in the reduction of HbA1c. Overall, prediction distribution of HbA1c changes for the drug group demonstrated that quantitative model could adequately fit the observed mean values from published papers.

An exponential function for combined placebo and drug responses adequately described the changes of placebo and drug response over time with an Kp_Hb of 0.382 weeks^{-1}

and an Kd_Hb of 0.249 weeks^{-1}, and the reduction of FPG (IC$_{50\_H}$) in plasma concentration was about −1.81 mmol/l which could produce 50% of maximum efficacy (Dmax_Hb = −1.74%) in clinical trials. The estimated kdrug_Hb was 0.249 weeks^{-1}, which corresponds to a half-life of 2.8 weeks. Using the estimated kdrug_Hb value, the steady-state reduction in HbA1c was predicted to be achieved after approximately 14 weeks or 3.5 months (Fig. 2B).

3.5. Model validation

For internal evaluation, the combined diagnostic plots for quantitative models of FPG and HbA1c are shown in Fig. 3. GOF plots suggested that the models adequately fitted FPG and HbA1c data. The plots of NPDE vs. TIME and NPDE vs. IPRED, showed a symmetric distribution around zero (Fig. 3A and B). The plots of DV vs. PRED and DV vs. IPRED indicated that the model adequately described the observations (Fig. 3C and D).

In the external validation as shown in Fig. 4, the individual predictions of FPG for 10 and 20 mg doses were in agreement with observed values with slight bias, with an MPE of −40.5% and −36.1%, respectively, and a precision of 40.5% and 38.1%, respectively. The individual predictions of HbA1c for dose 10 and 20 mg were not biased, with an MPE of 16.6% and 0.81%, respectively, and a precision of 16.6% and 11.1%, respectively. Overall, the individual predictions of HbA1c for 10 and 20 mg doses were much more consistent
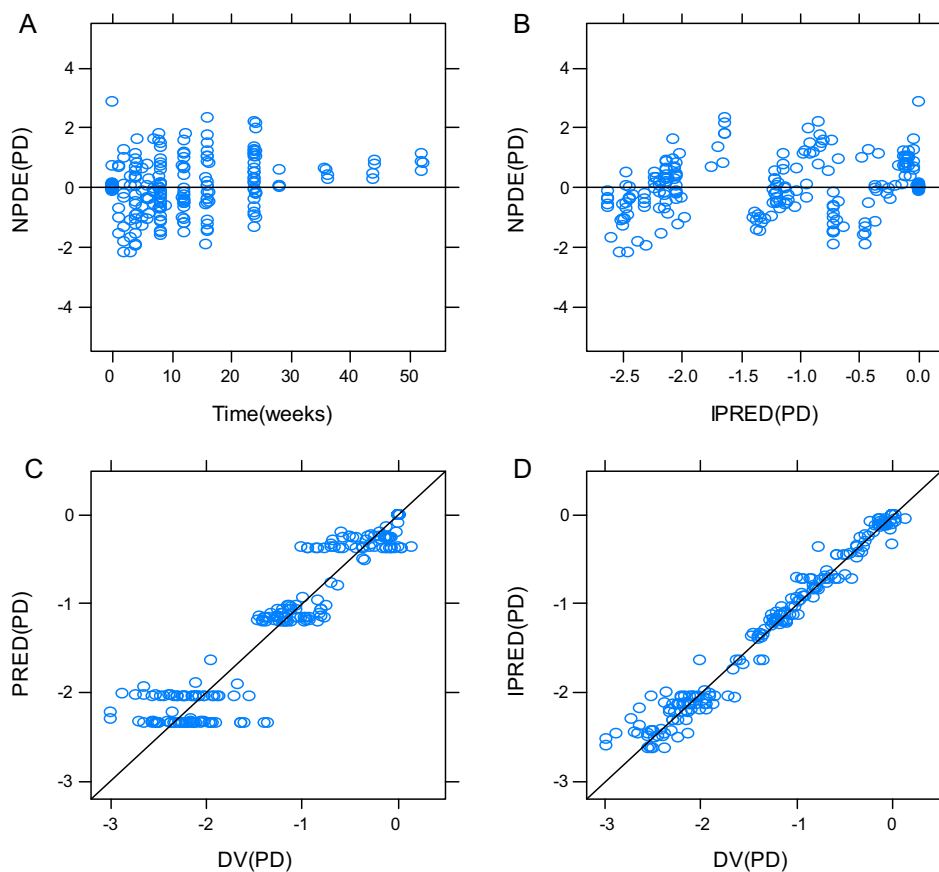

Figure 3 Diagnostic plots: normalized prediction distribution error (NPDE) vs. time and individual prediction (IPRED) (A and B); population prediction and individual prediction (PRED) vs. observation (DV) (C and D).
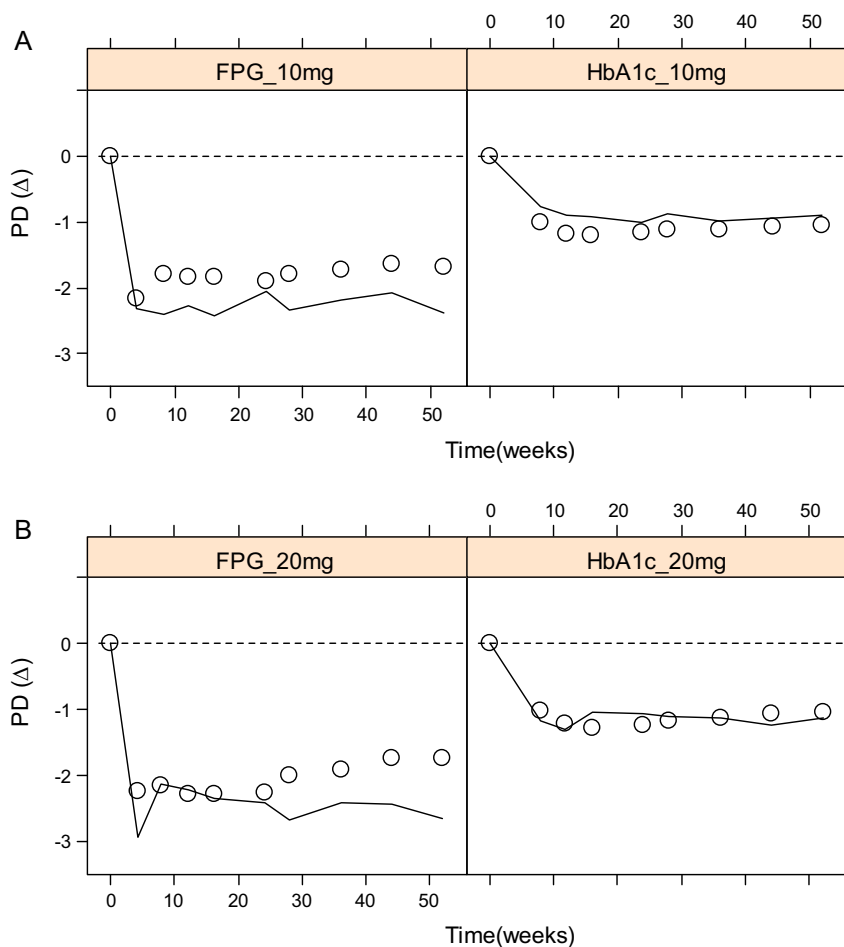
Figure 4 One clinical PD data were used to validate the final model. Observed and predicted PD response (change from baseline) over time in A and B (taspoglutide 10 and 20 mg for FPG and HbA1c), respectively. The open cycle and solid line symbols represented the mean observed and simulated PD changes, respectively. The mean PD data were digitalized from the paper published by Rosenstock et al. (2013).

with observed values without significant biases and with preferable precisions, compared with predictions of FPG for 10 and 20 mg doses.

4. Discussion

The MBMA approach has been developed and used to assess the comparative efficacy of different medications (Gross et al., 2013). This approach can more efficiently incorporate longitudinal and/or dose–response data from trials of different durations and with different sampling time-points, which is distinguished with the methodology of conventional meta-analysis by manner (Ahn and French, 2010; Gross et al., 2013). This analysis method has shown its benefit in summarizing the clinical results from a large number of trials to develop a PK/PD model (Kimko et al., 2012). Developed model can be utilized to predict the clinical outcomes following administration of a drug with different dosing regimens (Gibbs et al., 2012).

In this study, we had access to the intensely sampled longitudinal PD data from patients in clinical trials that substantially evaluated the efficacy with FPG and HbA1c of taspoglutide; these data were utilized to develop quantitative

models with specific focus on leveraging information of taspoglutide in clinical drug development. Large samples and clinical trials of taspoglutide for FPG and HbA1c can further provide insight into the relationship between efficacy and drug, and will give clinical guideline for treatment of type 2 diabetes patients in the future.

The MBMA has provided novel information on the quantitative characterization of taspoglutide efficacy in clinical trials. In PD data modeling, two different kinds of metrics were used for model-based analysis including average drug concentration for FPG data and model population prediction value for HbA1c data. Emax model was commonly used to link PK with PD in which the drug concentrations acted as linkage to efficacy results (Gao and Jusko, 2011). The 8- to 52-week taspoglutide concentrations for different dosing regimens were not directly obtained in publications, so the average concentrations (0, 59.85 and 119.7 pmol/l for placebo, taspoglutide 10 and 20 mg) between 2nd and 4th weeks were chosen as metrics to build the empirical relationships between exposure and responses in MBMA. At the same time, the maximum reduction responses of FPG in the drug group were used as metrics to perform HbA1c data modeling. MBMA has demonstrated that this approach with empirical metrics adequately described

the profiles of FPG and HbA1c over time, as seen in Figs. 1 and 2.

Despite MBMA approach being utilized to compare efficacy results of different medications with different durations and dosing regimens, it has been extended to delineate net efficacy results of taspoglutide from placebo effects in large clinical trials. The Emax model acted as linkage to integrate placebo and taspoglutide information from different durations with different concomitant medications during therapeutic process and treatment backgrounds before starting clinical trials. In quantitative analysis process, the drug or placebo directly regulated the changes of FPG and reduced the levels of FPG in type 2 diabetic patients; subsequently the changes of FPG derived from influence of taspoglutide directly influenced the levels of HbA1c. The information on average HbA1c change is available to further evaluate the patient status with type 2 diabetes, as an increase of 0.2% HbA1c per year has reflected the rate of disease progression of patients (de Winter et al., 2006). Therefore through quantitative models, the net effects of drug treatment (Shang et al., 2009) delineated from placebo responses can be conveniently assessed, and more information about glycemic control for patients with type 2 diabetes can be obtained.

Taspoglutide produced clinically meaningful improvements in glycemic control in patients treated with 10 and 20 mg dosing regimens. The reduction in FPG for taspoglutide 20 mg was -2.1 ± 0.2 mmol/l (Pratley et al., 2013) after 24 weeks while the model population predicted value in FPG reduction for drug was -2.39 mmol/l, which indicated that taspoglutide 20 mg already produced the maximum glycemic control in clinical trials. An Emax model for the change in FPG showed that 80% of maximal reduction in FPG adjusted from placebo response was achieved at drug plasma concentration of 101.2 pmol/l (IC_{80_F}), which was already reached and generally maintained above when taspoglutide 20 mg once weekly was given to type 2 diabetes patients (Ratner et al., 2010). Thus it can be seen that taspoglutide 20 mg seems to be an optimal dose for type 2 diabetes patients in clinical trials. However, treatment of taspoglutide 20 mg led to high subsequent rates of discontinuation due to substantial rates of gastrointestinal intolerability and allergic reactions (Rosenstock et al., 2013), therefore the dosage adjustment of taspoglutide should be recommended for type 2 diabetes patients by considering the adverse events in clinical trials.

Likewise, a HbA1c reduction of 1.74% in the drug group compared with 0.253% of the placebo group was estimated in quantitative model and was almost consistent with the published data in clinical trial (Henry et al., 2012), where glycemic control improved to a greater extent in taspoglutide treated patients with robust reduction in HbA1c up to 1.89% from baseline of 8.14% (6.6–10.4%). The first-order rate constant (kdrug_Hb), which described the effect of taspoglutide, suggested that steady state would be achieved after 3.5 months.

MBMA also demonstrated that the level of FPG could be much more quickly controlled than that of HbA1c when taspoglutide was subcutaneously administered to type 2 diabetes patients through multiple dosing regimens in clinical trials. The steady state of FPG could be achieved after 1.7 weeks while that of HbA1c could be achieved 3.5 months, and the time delay between FPG and HbA1c was significantly obvious in controlling type 2 diabetes disease progressions by using taspoglutide. Therefore, the therapeutic duration of taspoglutide could be optimized in clinical treatment of type 2 diabetes disease through half-lives of FPG and HbA1c.

MBMA has several limitations as the same as the traditional meta-analysis. This approach adopts available information from public reports or literatures and may be subject to publication bias. The metrics for characterizing the relationship between exposure and efficacy empirically rely on the average concentrations of 10 and 20 mg doses of taspoglutide and may decrease the prediction ability of quantitative models. In addition, differences in FPG and HbA1c assay applied during the clinical development should be noted concerning the different labs, operators and analytical instruments. Despite these existing differences in the measurement of PD data, a similar relationship to outcome was observed across different clinical trials. Furthermore, covariates were not included in final models and might have impacts on model parameters. However, a major advantage of this MBMA is a flexible application of mathematical equations for leveraging prior clinical information without consideration of time delay effects between PK and PD. This MBMA approach will continue to be used to delineate similar drug efficacy from the placebo response in clinical trials, such as liraglutide and exenatide extended release.

5. Conclusions

In summary, two quantitative models were developed to delineate the net efficacy of taspoglutide from the response of placebo in large clinical trials. The metrics of taspoglutide appear to be useful parameters related to FPG and HbA1c data modeling. Exposure to FPG and FPG to HbA1c relationships informed by MBMA can be leveraged to support study designs including optimization of dose and duration of therapy.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jsps.2014.11.008.

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