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The efficacy of placebo-adjusted taspoglutide on body weight reduction in clinical trials

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Received July 23, 2014, accepted September 5, 2014

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Pharmazie 70: 110–116 (2015) *doi: 10.1691/ph.2015.4716*

Taspoglutide has elicited a long-lasting glycemic control effect with favorable body weight loss. The objective of this study was to develop a quantitative model to delineate the net efficacy of taspoglutide on body weight (WT) loss from the response of placebo in type 2 diabetes patients, and further find pharmacodynamic potency of taspoglutide for half of maximum reduction response of WT. Several PD data about taspoglutide treatments for type 2 diabetes patients were digitalized from the published papers. The model based meta-analysis (MBMA) study for WT loss was performed with Monolix 4.3 software. The MBMA successfully described the effects of placebo and taspoglutide on the pharmacological index of WT loss in clinical trials. The pharmacodynamic potency (41.7 pmol/l) produced 50% of maximum response of WT (−1.85 kg) from the responses of placebo (−1.33 kg). The longitudinal MBMA could be utilized to quantitatively describe the efficacy of taspoglutide on body weight loss and may lead to a clinical guideline for treatment of type 2 diabetes patients in the future.

1. Introduction

Between 2010 and 2030, there will be a 69% increase in the numbers of adults (aged 20-79 years) with diabetes in developing countries and a 20% increase in developed countries (Shaw et al. 2010), and the number of people with diabetes is expected to rise from 382 to 592 million (Guariguata et al. 2014) between 2013 and 2035. Furthermore, the majority of newly diagnosed cases of diabetes can be directly attributed to obesity which is closely associated with high risk for cardiovascular disease (Biggs et al. 2010; Hollander et al. 2013). Therefore, lowering body weight is imperative in controlling glycemic levels of obesity patients.

Patients with type 2 diabetes mellitus are characterized by dysfunction of β cell which leads itself to unregular secretion of enough insulin to overcome insulin resistance (Gastaldelli et al. 2014), and the release of glucagon-like peptide-1 (GLP-1) in response to a glucose load is reduced in patients. GLP-1 receptor agonists are a novel class of drugs against type 2 diabetes due to their ability to stimulate insulin secretion and reduce blood glucose with fevorable weight loss (Drucker 2007; Sebokova et al. 2010). Taspoglutide is a long-acting GLP-1 receptor agonist that has undergone phase 3 clinical development for the treatment of type 2 diabetes (Gastaldelli et al. 2013), and is considered to have equivalent potency to natural GLP-1(Nauck et al. 2009), it has been shown to elicit a long-lasting glycemic control effect (Raz et al. 2012). Several clinical trials have shown that taspoglutide 10 or 20 mg controlled glycemic levels in patients with type 2 diabetes and reduced glucagon levels with favorable weight loss (Nauck et al. 2009; Bergenstal et al. 2012; Henry et al. 2012; Raz et al. 2012).

The MBMA approach can 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 clinical results from a large number of trials to develop a PK/PD model (Kimko et al. 2012). The model can be used to predict the clinical outcomes following administration of a drug with different dosing regimens (Gibbs et al. 2012). We present here a quantitative model to describe time course of WT loss, and this model provides a linkage between drug and responses. Such model based analysis (MBMA) can leverage prior knowledge from clinical studies, and may conduct comparison of competing drugs (Gross et al. 2013) in the future.

Therefore, the present study was performed to delineate the net effects of taspoglutide on WT loss from the responses of placebo in type 2 diabetes patients, and further find pharmacodynamic potency (IC_{50}) for half of maximum reduction response of WT. The retrospectively integrated prior knowledge from clinical studies will give prospective information of taspoglutide in the field of controlling body weight of patients with type 2 diabetes mellitus.

2. Investigations and results

2.1. PD Data

The computer searches yielded 9 publications (Nauck et al. 2009; Ratner et al. 2010; Bergenstal et al. 2012; Henry et al.

Table 1: Summary of clinical efficacy data about body weight loss in clinical trials

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 with metformin or/and a thiazolidinedione	Randomized, open-label, active-comparator, parallel-group

2012; Raz et al. 2012; Hollander et al. 2013; Nauck et al. 2013; Pratley et al. 2013; Rosenstock et al. 2013) which were deemed appropriate for inclusion and used to process quantitative assessment of WT loss. In this literature study, 9 clinical trial data were chosen to be included for model development, and a total of 3702 patients participated in clinical trials of placebo, 10 and 20 mg doses of taspoglutide over weeks 8 to 52. The therapeutic regimens mainly included taspoglutide monotharapy 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 WT loss in randomized clinical trials.

2.2. Metrics for PD modeling

The metrics available to use for WT loss data modeling are summarized in Table 2. The metrics for WT loss data were directly derived from the digitalized taspoglutide concentrations between 2^{th} and 4^{th} 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 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 WT loss was conducted lasting from 8 to 52 weeks of placebo, taspoglutide 10 and 20 mg. Overall, WT loss over time was fitted well by quantitative model, as seen in Fig. 1.

2.3. Weight loss

The time courses of placebo and drug responses for WT loss are shown in Fig. 1 and structure parameter estimates and individual trial variability are presented in Table 3. In the placebo group, the population prediction (Pmax) of WT change from baseline was −1.33 kg (Fig. 1A), which reflected the overall trend of WT loss when the placebo was given to the patients. In the drug group, the population prediction (Dmax) of WT change from baseline was −1.85 kg (Fig. 1B), which reflected the trend of WT reduction when the multiple 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 WT reduction (Figs. 1A *vs.* 1B). Overall, prediction distribution of WT reductions for the placebo and the drug group demonstrated that the 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

Table 2: Metrics used for WT data modeling

Dose (S.C)	Metrics for WT	Conc (pmol/l)
Placebo	0	0
10 mg	Cavg. (2w-4w) /2[b]	59.85
20 mg	Cavg. (2w-4w)[a]	119.7

[a] Average taspoglutide concentration between 2^{th} and 4^{th} week. The mean concentrations were digitalized from the paper published by Ratner et al. (2010)

[b] The average concentration of taspoglutide 10 mg dose was concentration from simple arithmetic calculation of 20 mg dose, as the exposure of taspoglutide appeared dose proportional once weekly (Ratner et al. 2010).

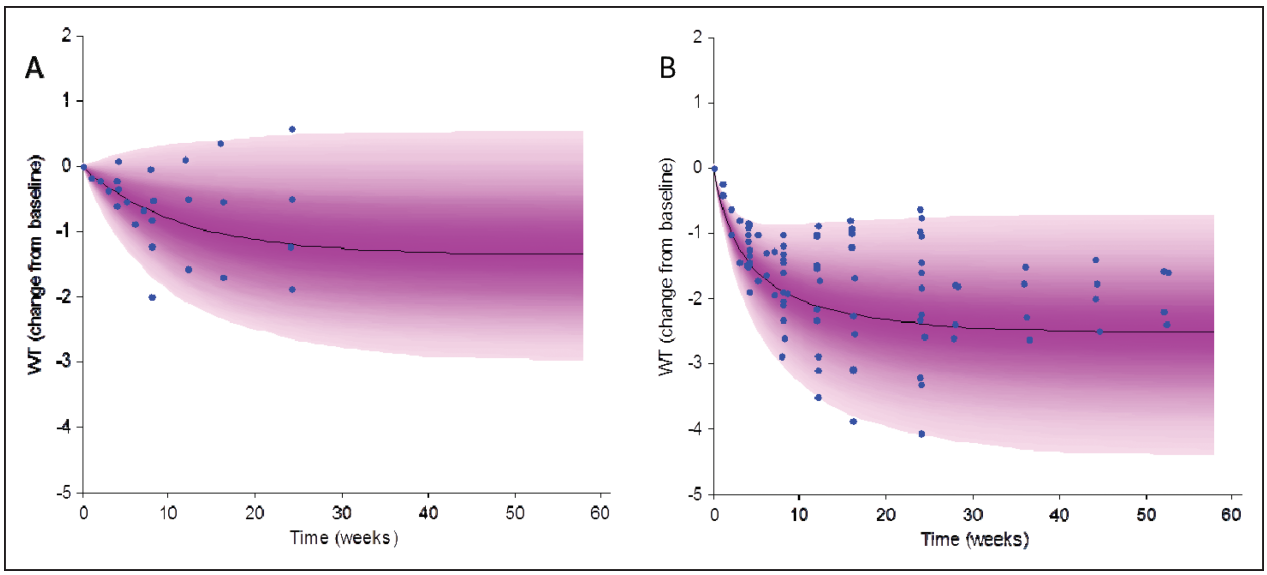

Fig. 1: Observed and prediction distribution of WT response over time in A (placebo response, change from baseline) and B (drug response, change from baseline). The color areas represented the 95% confidence interval of the prediction, the solid dots were mean WT values from the literatures and the solid line represented the median prediction.

drug responses over time with a k_p of 0.0987 weeks^{-1} and a k_{drug} of 0.422 weeks^{-1}, and the drug concentration of taspoglutide (IC_{50}) was about 41.7 pmol/l which could produce 50% of maximum efficacy (Dmax = −1.85 kg) in clinical trials. The estimated kdrug was 0.422 weeks^{-1}, which corresponds to a half-life of 11.5 days. Using the estimated k_{drug} value, the steady-state reduction in WT was predicted to be achieved after approximately 57.5 days or 8.2 weeks (Fig. 1B).

The final model provided reasonably precise estimates (≤ 20% RSE) of fixed effect parameters with the exception of the P_{max} and k_p for placebo data (43% and 36% RSE, respectively). Probably, the placebo group for WT loss does not have enough data for one independent clinical trial, and several clinical trials only have endpoint data. The results of the predictive distribution check showed good agreement between the simulated and observed data after 8 to 52 weeks (Figs. 1A and 1B) of taspoglutide therapy for studies involving mono-therapy and combination therapy.

2.4. Model validation

Goodness of fit (GOF) plots suggested that the model adequately fitted WT loss data. The plots of NPDE vs. TIME and NPDE vs. IPRED showed a symmetric distribution around zero (Figs. 2A and 2B). The plots of DV vs. PRED and DV vs. IPRED indicated that the model adequately described the observations (Figs. 2C and 2D).

Table 3: Parameter estimates from quantitative model for WT

Parameter	Estimate	R.S.E (%)	ITV[d] (%)
P_{max} (kg)[e]	−1.33	43	110
K_p (1/week)[e]	0.0987	36	33
D_{max} (kg)	−1.85	15	9.76
IC_{50} (pmol/l)	41.7	5	104
K_{drug} (1/week)	0.422	20	14.6
b	0.189	7	

d ITV represents inter trial viability
e Parameter estimates for WT in placebo were fixed in finally combined PD model
R.S.E represented relative standard error; IC_{50} represents pharmacodynamic potency of drug on the response of WT when the drug was administrated to patients

2.5. Example for one individual mean PD data prediction

Example of individual mean data fits taken from one study (Henry et al. 2012) with placebo plus two doses of taspoglutide is shown in Fig. 3. The model fitted the data well and described the observed values of WT loss data for placebo and drug groups.

3. Discussion

In this study, we had access to the intensely sampled longitudinal PD data from patients in clinical trials that substantially evaluated the efficacy in WT loss of taspoglutide; those data were utilized to a develop quantitative model with specific focus on leveraging information of taspoglutide in clinical drug development. Large samples and clinical trials of taspoglutide for WT loss can further provide insight into drug efficacy, and may lead to clinical guidelines for the treatment of type 2 diabetes patients in the future.

The MBMA has provided novel information on the quantitative characterization of taspoglutide efficacy on WT loss in clinical trials. In PD data modeling, one metric was used for model-based analysis including average drug concentration for WT data. 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, respectively) between 2th and 4th weeks were chosen as metrics to build an empirical relationship between exposure and response in MBMA. MBMA has demonstrated that this approach with empirical metrics adequately described the profiles of WT loss over time for placebo and drug groups, as seen in Figs. 1A and 1B.

Despite the MBMA approach has been used 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. In quantitative analysis, the drug or placebo directly regulated the changes of WT and controlled the WT loss in type 2 diabetic patients. Therefore, through quantitative model, the net effects of drug treatment (Shang et al. 2009) delineated from

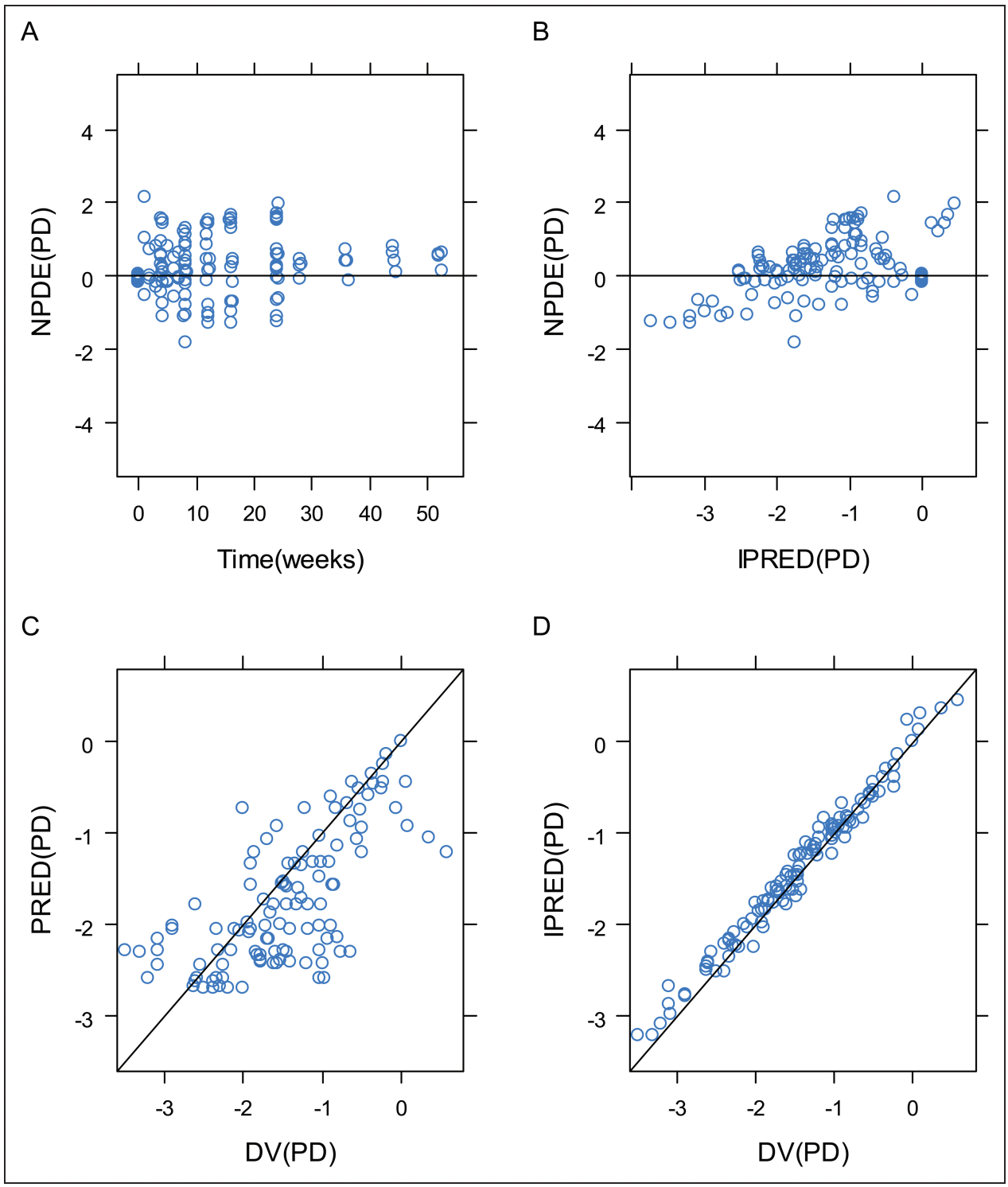

Fig. 2: Diagnostic plots: normalized prediction distribution error (NPDE) vs. time and individual prediction (IPRED) (A and B); population prediction and individual prediction (PRED) vs. observation (DV) (C and D).

placebo responses can be conveniently assessed, and more information about WT loss control for patients with type 2 diabetes can be obtained. An Emax model for the change in WT loss showed that 50% of maximal reduction in WT adjusted from placebo response was achieved at a drug plasma concentration of 41.7 pmol/l (IC_{50}), which was already reached and maintained when taspogutide 10 and 20 mg doses were administrated to type 2 diabetes patients once weekly (Ratner et al. 2010). Thus it can be seen that taspogutide 10 mg seems to be an effective dose for type 2 diabetes patients in clinical trials. The first-order rate constant ($k_{drug} = 0.422$ weeks^{-1}), which describes the effect of taspoglutide, suggested that steady state in WT loss would be achieved after 2 months.

With a steady increase of prevalence of both obesity and diabetes (Shaw et al. 2010), therapies that lower blood glucose and provide weight loss might offer meaningful benefits for obese patients with type 2 diabetes (Hollander et al. 2013). In clinical trials, taspoglutide significantly led to WT loss for patients receiving 10 and 20 mg doses, in contrast to sulfonylureas and thiazolidinediones which led to weight gain (Chiquette et al. 2004; Kahn et al. 2006). The model population predicted result of maximum reduction of body weight was −1.85 kg compared

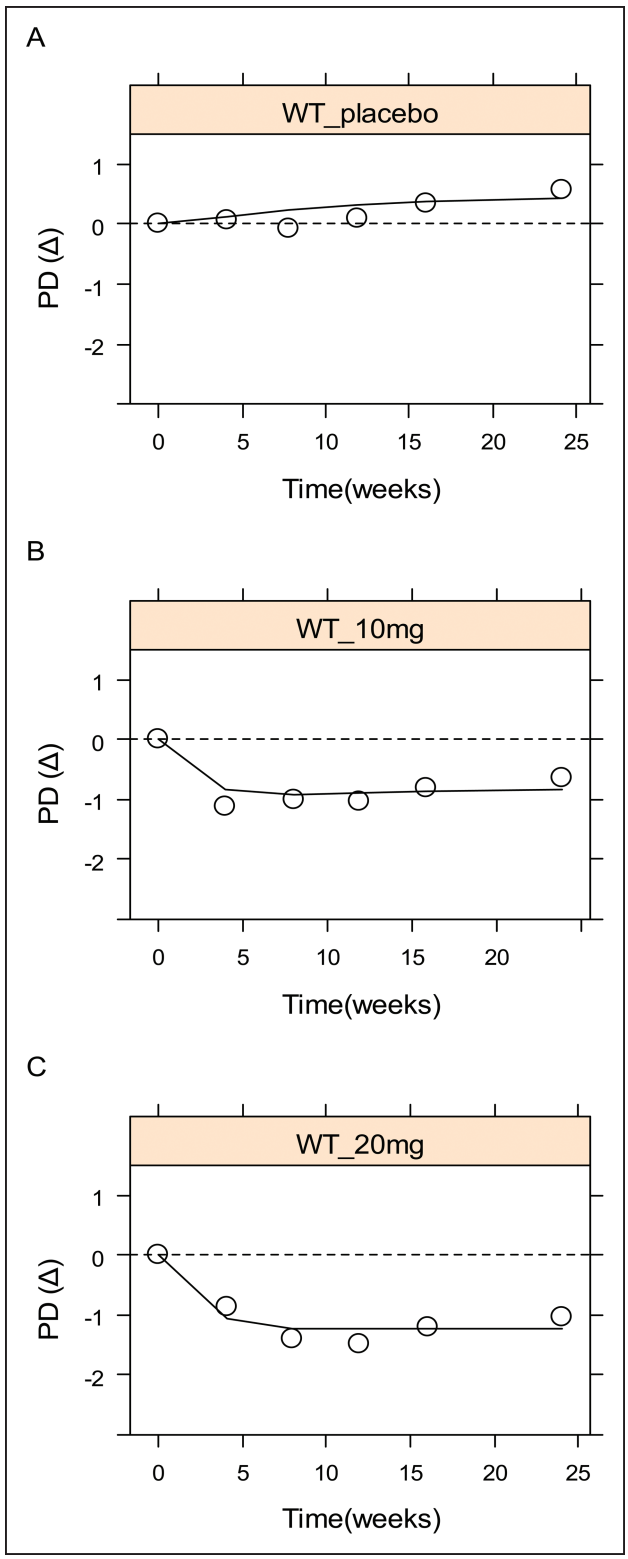

Fig. 3: Individual PD fits for one representative individual mean data. Observed and predicted PD response (change from baseline) over time in A (the placebo action to WT), B (the drug of 10 mg doses action to WT) and C (the drug of 20 mg doses action to WT). The open cycle and solid line symbols represented the mean observed and predicted PD changes, respectively. The mean PD data were digitalized from the paper published (Henry et al. 2012).

with −1.33 kg reduction in the placebo control group. The reported value of body weight loss for taspoglutide 20 mg was 3.16 kg compared to reduction from the baseline in literature (Hollander et al. 2013). Overall, the maximum reduction (-3.28 kg) of body weight from the baseline was close to the reported value (3.16 kg) in clinical trials.

MBMA also has several limitations like traditional meta-analysis, it adopts available information from public reports or literature 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 of taspoglutide and may decrease the prediction ability of the quantitative model. 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 flexible application of mathematical equations for leveraging prior clinical information without consideration of time delay effects between PK and PD.

In summary, a quantitative model was developed to delineate the net efficacy of taspoglutide from the response of placebo in large clinical trials. Exposure to WT relationship informed by MBMA can be leveraged to give novel information about taspoglutide development in clinical trials.

4. Experimental

4.1. Selection of studies

In this quantitative model, all studies that investigated the efficacy of taspoglutide in clinical trials about WT loss were considered. Efficacy 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, WT loss for taspoglutide. The data in each article must be composed of WT, and the multiple dosing regimens should include placebo, 10 and 20 mg doses and PD data were only from efficacy of placebo, 10 and 20 mg doses on patients.

Mean WT loss results were collected from the figures, tables and values reported in article content. The 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.

WT loss was used to summarize the mean efficacy result of taspolutide 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.

4.2. Metrics for PD modeling

The average plasma concentration between 2^{th} and 4^{th} week (Cavg.(2w-4w) value) of taspoglutide (20 mg dose per dosing regimen group), which was obtained from a published paper (Ratner et al. 2010), was directly used as metric to characterize WT loss when taspoglutide 20 mg was subcutaneously administered to patients with type 2 diabetes.

4.3. Software

A quantitative model for taspoglutide PD index was developed and estimated on the digitalized measures available, 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.

4.4. 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 response over time were estimated and

processed in three general steps. Firstly, the placebo response over time for WT loss was independently estimated and the parameter estimates were fixed as initial values to model placebo and drug responses simultaneously. Secondly, metrics were used to develop combined response models including changes of WT loss for placebo and taspoglutide. Finally various statistical models were investigated, and the most appropriate was selected for use in finally combined model development.

4.5. PD modeling

The drug and placebo directly acted on WT loss from the baseline. The time course of placebo response was predicted according to equation 1:

$$Placebo\_response_i(t) = P_{\max,i} \times (1 - e^{-K_{p,i} \times t}) \quad (1)$$

The time courses of drug response were predicted according to equation 2:

$$Drug\_response_i(t) = placebo\_respounse_i(t) + \frac{D_{\max,i} \times metric_i}{DI_{50,i} + metric_i} \times (1 - e^{-k_{drug,i} \times t}) + \varepsilon_i \quad (2)$$

where i represents individual PD index. Placebo_response (t) and drug_response (t) represent the placebo and drug responses over time, respectively; P_{max} and D_{max} are the maximum effects of placebo and drug, respectively; k_p and k_{drug} represent the first order rate constants in reduction of WT for placebo and taspoglutide; The *metric* variables in Eq. (2) are the metrics associated with half-maximal responses of WT loss, ε is the random residual error. IC_{50} represents pharmacodynamic potency of drug on the response of WT loss, when the drug was administered to patients.

4.6. Statistical model

The between variability of selected PD parameters was described by the exponential and addictive models. The exponential and addictive models below 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 k_p and k_{drug}, while individual parameters for addictive model mainly include P_{max}, D_{max} 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 mean of zero and standard deviation ω_{pi}.
The proportional error model of the residual error was applied to WT loss (Eq. 5) data:

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

where Y is the observation; F is the corresponding model prediction; b represents residual error parameter; ε is assumed to be an independent and normally distributed random variable with the mean of zero and standard deviation σ.
All parameter estimates were reported with the relative standard error of estimates (R.S.E %).

4.7. Model validation

The final model was 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.
Conflicts of interest: The authors have indicated that they have no conflicts of interest regarding the content of this article.

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