Chapter 5

A Model-Based Approach to Analyze the Influence of UGT2B15 Polymorphism Driven Pharmacokinetic Differences on the Pharmacodynamic Response of the PPAR Agonist Sipoglitazar

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Abstract

The pharmacokinetics of sipoglitazar, a peroxisome proliferator activated receptor agonist, are subject to high inter-individual variability resulting from a polymorphism of the UGT2B15 genotype. The aim of the current analysis was to apply a PK-PD model-based approach to evaluate the influence of UGT2B15 driven pharmacokinetic differences on the clinical response. Efficacy and safety of sipoglitazar compared to placebo were assessed in Type 2 Diabetes Mellitus patients in two Phase II randomized, double-blind studies (sipoglitazar QD: 8, 16, 32 or 64 mg; sipoglitazar BID: 16 or 32 mg; rosiglitazone 8mg QD and placebo for 13 weeks) (n=780). Changes in fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) levels over time were described as a function of individual drug exposure using a simultaneous, cascading indirect response model structure. The effects on FPG and HbA1c could successfully be described for placebo, rosiglitazone and sipoglitazar treated groups in all three UGT2B15 genotypes. Differences in drug effects between genotypes were fully explained by differences in drug exposure. The current PK-PD analysis confirms that UGT2B15 genotype is a major determinant for differences in FPG and HbA1c response to sipoglitazar treatment between Type 2 Diabetes mellitus patients, due to related differences in drug exposure.

Introduction

Sipoglitazar, a novel orally available peroxisome proliferator activated receptor (PPAR) agonist with activities for PPAR α, δ and γ, was targeted for Type 2 Diabetes Mellitus (T2DM) as a next generation insulin sensitizer. The compound undergoes Phase II biotransformation by conjugation through UDP-glucuronosyltransferase (UGT) [1]. Following a population pharmacokinetic analysis, UGT2B15 genotype was found to be a covariate for the clearance (CL) of sipoglitazar both in healthy subjects and T2DM patients [2]. Higher plasma exposure of sipoglitazar was observed in the UGT2B15*2/*2 genotype than subjects homozygous for the wild-type allele UGT2B15*1/*1 (3.3-fold higher) or heterozygous allele UGT2B15*1/*2 (2.2-fold higher) [3].

T2DM is a complex multi-factorial disease and current therapies target a range of disease pathways, promoting insulin secretion or improving insulin sensitivity [4]. Many of these drugs involve upward titration to effect, based on glycemic targets and/or the addition of combination therapy [5]. Titration based approaches are also applied to limit adverse events such as hypoglycemia or weight gain [6]. Individualized dosing is widely applied and responder rates to treatment may depend on factors such as the duration of the disease or prior anti-diabetic medication, although response rates can be variable and difficult to predict [7]. Consideration should be given not only to factors directly affecting the pathology of the disease but also to those which influence the plasma exposure of these drugs such as genetic polymorphisms which may be additional covariates for clinical response [8]. Genetic polymorphisms in the enzyme responsible for the metabolism of several glucose lowering drugs including rosiglitazone (CYP-2C8) and glimepiride (CYP-2C9) have been identified [9]. For rosiglitzone, 1.5 fold higher clearance was observed in the CYP2C8*3/*3 subjects compared with wild-type (CYP2C8*1/*1) carriers [10]. Whilst in healthy Korean subjects clearance of glimepiride was 1.6 fold higher in CYP2C9*1/*1 subjects than in CYP2C9*1/*3 subjects [11]. However the clinical relevance of these differences in pharmacokinetics has not resulted in specific genotype based dosing recommendations [12].

The implementation of a PK-PD model-based approach to evaluate the influence of genotype provides a more comprehensive link between changes in the pharmacokinetics and its

influence on the magnitude of response [13,14]. *In vitro–in vivo* extrapolation may also be useful when considering the impact of any potential polymorphism and to help define the exposure response relationships [15]. Currently the application of a model-based approach to evaluate the influence of different genotypes, by linking pharmacokinetic changes with response seems limited to only a few drugs. Warfarin has been extensively studied due to its wide use, narrow therapeutic range and large inter patient variability, all making response unpredictable [16]. However genetic data are now an integral part of the drug development program and a model-based approach can aid in addressing the complex nature of the relationship not only between genotype and PK but also including clinical response.

The present population PK-PD analysis was performed to evaluate the role of UGT (UGT2B15*1/*1, UGT2B15*1/*2, and UGT2B15*2/*2) driven exposure differences on the pharmacodynamic response for sipoglitazar in both fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c).

Methods

Subjects and Data Collection

Data from 2 Phase II trials conducted over 13 weeks in T2DM patients were included in this analysis. The baseline patient characteristics are summarised in Table S1. Patients were treated with sipoglitazar, rosiglitazone or placebo: sipoglitazar 8mg QD, 16mg QD, 16mg BID, 32mg QD, 32mg BID and 64mg QD, placebo or rosiglitazone 8mg QD. Serial blood samples for FPG and HbA1c were collected throughout the study (-1, 0, 2, 4, 6, 8, 10 and 12 weeks). The disposition of subjects was as follows: Sipoglitazar n=572, rosiglitazone n=72 and placebo n=136 (total = 780). All subjects were provided with dietary advice for the entire duration of the trial. The three main inclusion criteria were drug naïve patients with a diagnosis of type 2 diabetes, an HbA1c of >7.0% and <10.0% at Screening and age >35 years and <75 years.

An accredited central laboratory (Medical Research Laboratories International, Brussels, Belgium) was responsible for the analysis of samples for FPG and HbA1c. All studies were conducted in accordance with the Declaration of Helsinki (Edinburgh 2000). Written

approval was obtained from the relevant local institutional ethics committee before the start of each study and for the amendments made to the protocols.

Population Data Analysis

Changes in FPG and HbA1c levels over time were described as a function of individual drug exposure using a simultaneous, cascading indirect response model structure. The model was parameterised in terms of a zero order rate constant for the production of FPG (KinG) and a first-order rate constant for the removal of FPG (KoutG). Changes in HbA1c were modelled as secondary changes to FPG, with a first order rate constant (KinH) and a first order HbA1c degradation rate constant, KoutH. As reported by Hamren et al, the relationship between FPG and HbA1c was found to be non-linear, and HbA1c was described as a function of FPG using a power function (FPG^{γ}) [17].

A lower FPG baseline value was observed in the 32mg BID sipoglitazar group compared to all other treatment groups. The addition of a separate FPG baseline for this group was included in the model.

The drug effect (DEF) was incorporated using an Emax model driven by AUC, where Emax is the maximal effect and AUC50 is the AUC0-24h at steady state achieving half the maximal response, implemented with the following equation:

$$DEF = Emax \cdot AUC/AUC50 + AUC \qquad EQ(1)$$

The individual PK parameters derived from a previous analysis were used to calculate individual exposure, AUC (AUC=dose/CL) over the dose interval at steady state [2]. The drug effect was evaluated for FPG on both KinG and KoutG.

In the rosiglitazone group, no plasma concentration data were collected during the treatment period and as such the treatment effect for rosiglitazone (ROTE) was included using a stimulatory step function on KoutG. The FPG data in the placebo group on average showed no change over time. However at the individual level a lifestyle effect in both placebo and actively treated subjects for FPG (LEFPG) was observed. This effect was described by an additive random effect, capturing both the positive effects of intervention due to diet or

exercise and the negative effects in subjects who showed a loss of glycemic control. HbA1c in the placebo group however, showed on average a gradual decease in HbA1c over time. This reduction in HbA1c was found to be independent of the lifestyle effect identified on FPG and a step function directly inhibiting KinH could be identified for this direct lifestyle effect on HbA1c (LEHB). A difference was also found in LEHB between active and placebo arms. For the active groups this was described relative to the placebo group as shown in EQ(2).

$$LEHBactive = LEHBplacebo - LEHBfactor \quad \text{EQ(2)}$$

The overall model structure for FPG and HbA1c is shown in EQ(3) and EQ(4) respectively.

$$\frac{dFPG}{dt} = KinG \cdot (1 \pm LEFPG) - KoutG \cdot (1 + DEF + STEF) \cdot FPG \quad \text{EQ(3)}$$

$$\frac{dHbA1c}{dt} = KinH \cdot (1 - LEHB) \cdot FPG^{\lambda} - KoutH \cdot HbA1c \quad \text{EQ(4)}$$

In EQ(3) LEFPG is included as a additive random effect with the structural parameter fixed at zero.

To explore any potential differences between daily dosing regimens a different AUC50 value was tested between the BID and QD groups.

Intra-individual Variability and Residual Error

Intra-individual variability (IIV) on FPG baseline was explored assuming a log normal distribution of the individual parameter estimates. However IIV on the baseline for HbA1c was evaluated using a Box-Cox transformation model, which was applied to account for the skewness observed in the individual data [18]. Residual variability was included using a proportional model. The correlation between IIV on baselines was included using the OMEGA BLOCK option. Genotype information was not collected in 10% of the population however these subjects were included in the analysis using an average clearance value for the population.

Covariate Analysis

Potential covariates (Age, sex, weight and duration of disease) were evaluated in the model using a forward inclusion and backward elimination procedure [19].

Data Analysis

All population analyses were performed using nonlinear mixed effects modeling on pharmacodynamic data in the NONMEM software package (version 7, release 1; Icon Development Solutions, Ellicott City, Maryland) and analyzed using the statistical software package S-Plus for Windows (version 6.2 Professional, Insightful Corp, Seattle, Washington). The first-order conditional estimation method with interaction was used with ADVAN6 (general nonlinear model). Berkeley Madonna version 8.3.13 (Macey & Oster, University of California, Berkeley) was used to perform simulations of the time profile for FPG and HbA1c.

Model Qualification

The visual predictive check (VPC) was used to evaluate the ability of the model to predict both the central tendency and the variability of FPG and HbA1c (median and 90th prediction interval) [20]. The VPC for the sipoglitazar treatment groups was performed using the overall proportion of subjects in each genotype (UGT2B15*1/*1=21%, UGT2B15*1/*2=51%, and UGT2B15*2/*2=28%). The clearance values used for each genotype are shown in Table 1.

The stability of the model was tested by using 500 bootstrap replicates of the original dataset. To further inform model validation ETA shrinkage was estimated for all the random effects [21].

Model Selection

No further improvement in the model was considered by a change in objective function of less than 10.8 ($P \leq 0.001$) [19]. In addition to this graphical analysis enabled assessment of bias and the biologically plausibility of the parameter estimates was evaluated.

Evaluation of the Influence of Genotype on FPG and HbA1c Treatment Effects

Simulation of FPG and HbA1c Time Course

To evaluate the influence of genotype on the time profiles for both FPG and HbA1c these data were simulated over a one year time period. Using this data the change from baseline in FPG and HbA1c at 6 months was determined since this could be the primary endpoint for a Phase III trial. Rosiglitazone 8mg QD and sipoglitazar 64mg for all three genotypes were simulated.

Simulation of Clinical Response at 6 months

The model was used for clinical trial simulation to evaluate the impact of genotype on glycemic responder rates, an additional endpoint to allow further appreciation of response to treatment. Two approaches were compared using either pre-selection of dose based on genotype or a single dose level for all subjects. For genotype driven dose selection, three dosing approaches were compared. The doses were selected to target comparable drug exposure levels in each genotype group. Dose assignment was based on the population estimated CL values for each genotype. The dose levels and CL values are shown in Table 1. Clinical response was defined as the % of subjects achieving a HbA1c reduction >0.7% at 6 months [22]. 100 subjects were simulated for each genotype and 300 subjects for the single treatment. For reference, rosiglitazone 8mg QD (n=300 subjects) response was simulated.

Evaluation of genotyped-based and titration-based dosing approaches

The potential differences between genotyped-based dosing, in which subjects already begin their treatment at the optimal dose and titration-based dosing, in which subjects start at a fixed dose and are subsequently titrated to effect was evaluated through simulation. For genotyped-based dosing, Design C (UGT2B15*1/*1=96mg, UGT2B15*1/*2=64mg and UGT2B15*2/*2=32mg) was used and subjects would begin treatment at each of the dose levels depending on their UGT2B15 genotype.

For titration based dosing, all subjects would receive the same 32mg dose level at the start of treatment. Subjects could be titrated up to a maximum of 96mg using 32mg and 64mg tablets. The FPG value was assessed every two months. For those subjects in the UGT2B15*2/*2

genotype, 32mg already represents the optimal dose for this group based on the low drug clearance. Therefore simulations using only the UGT2B15*1/*1 and UGT2B15*1/*2 genotype were performed

Results

PK-PD model

The developed indirect response model adequately described the change in FPG and HbA1c over time for all treatment groups (Figure 1a and Figure 1b). The model parameters are shown in Table 2 along with the bootstrap estimate. During conduct of the bootstrap, 92.6 % of runs minimized successfully. The parameter estimates from the model were consistent with those estimated from the bootstrap and all of the parameters from the final model were within the 95% confidence interval of the bootstrap estimate supporting the robustness and stability of the model. No substantial ETA shrinkage was observed (<12%), and all CV% for each parameter was less than 35%.

Figure 1. (a) Visual predictive check for observed and predicted FPG data.

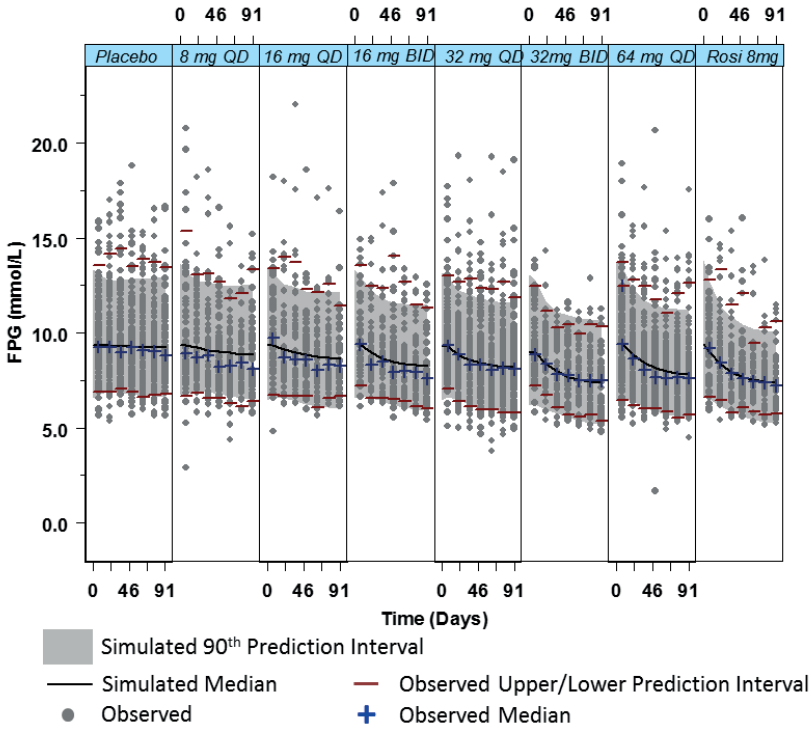
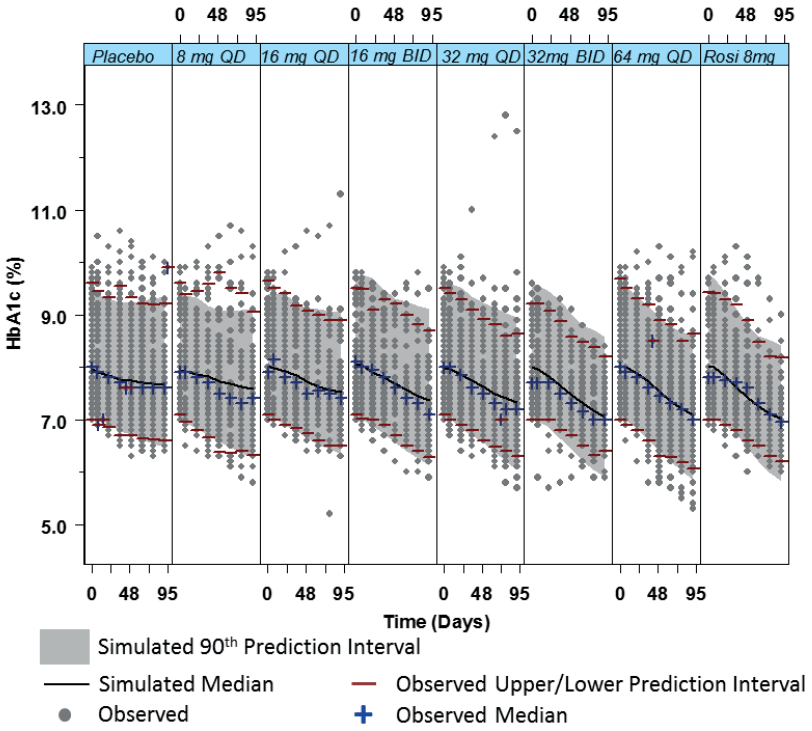


Figure 1. (b) Visual predictive check for observed and predicted HbA1c data.



The inclusion of the Box-Cox transformation on IIV for the baseline on HbA1c (BSLH) resulted in a significant ($P \leq 0.001$) change in the objective function. The inclusion of the Box-Cox transformation on the baseline for FPG (BSLG) did not result in a significant improvement in the model; this is likely a result of the screening criteria (HbA1c>7%) being based solely on HbA1c levels.

Histogram plot for FPG and HbA1c showing the model fitted baseline distributions are presented in supplemental Figures S1 and S2, respectively.

No bias was observed in the diagnostic plots by genotype for HbA1c or FPG. These are shown in supplemental Figures S4-S6 and S7-S9, respectively.

Drug effect model

The effect of sipoglitazar was included as a stimulatory effect acting on KoutG. The Emax of this effect was estimated at 49% and AUC50 was 1.2 mg.day/L. This Emax is similar to that reported from other PPAR agonists, 41% and 43% [17,23]. Treatment effect (ROTE) for rosiglitazone was also included as a stimulatory effect on KoutG with a population mean value of 28% at the studied dose level. The relationship between FPG and HbA1c could be described using a power function with an estimated slope of 0.7. The estimated Kout value for both FPG and HbA1c was 0.027 days-1 and 0.031 days-1 respectively, this is consistent with the values reported by other studies [24].

Using the model, the overall effect of sipoglitazar treatment (Drug + placebo) at 3 months was derived and is shown in comparison to the rosiglitazone group in Figure S3. The median value and associated 25th and 75th percentiles for the 8mg QD rosiglitazone treatment effect relative to the sipoglitazar groups shows that a total daily dose of at least 64mg for sipoglitazar (for all genotypes) would be needed to achieve comparable treatment response. For the different genotype groups the treatment effect was found to increase in the order UGT2B15*2/*2 > UGT2B15*1/*2 > UGT2B15*1/*1.

Lifestyle effect model

The lifestyle effect for FPG (LEFPG) was zero for the mean population but individual effects were observed and implemented in the model using an additive random effect. A lifestyle effect on HbA1c (LEHB) was best described by an effect on KinH during the course of the study. This effect was independent of the drug treatment effects which were carried over from changes in FPG to HbA1c. The lifestyle effect was found to be lower in actively treated groups compared to the placebo group. Specifically, a population mean decrease of 3.7% was identified for the lifestyle effect in the placebo group, whilst in the actively treated groups the reduction was slightly lower, 2%. No significant ‘lifestyle’ effect on HbA1c could be identified on the rosiglitazone group.

Covariate Analysis

Potential covariates on IIV were evaluated, during forward inclusion for BSLG, BSLH, LEFPG and LEHB. However neither sex, weight, duration of disease or age had a significant effect on any of these parameters and no covariates were retained in the final model.

Evaluation of the Influence of Genotype on FPG and HbA1c Treatment Effects

Simulation of FPG and HbA1c Time Course

Based on the simulated time profiles for sipoglitazar by genotype and for rosiglitazone over a one year period, 90% of steady state for FPG and HbA1c is expected to be reached at approximately 2.3 months and 3.7 months, respectively (Figure 2a and 2b).

Figure 2. (a) Simulated FPG over time for sipoglitazar 64 mg by genotype and rosiglitazone (8mg QD).

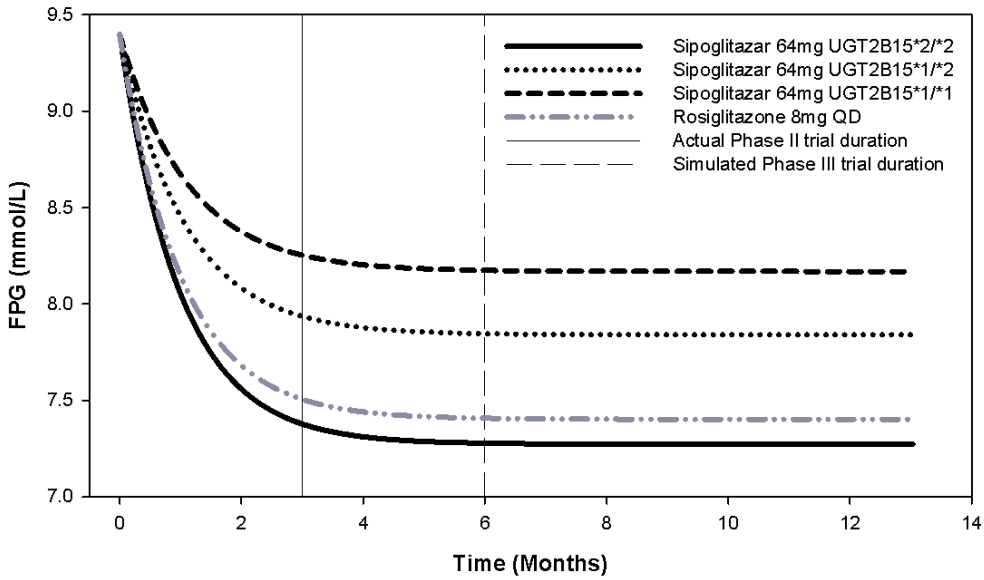
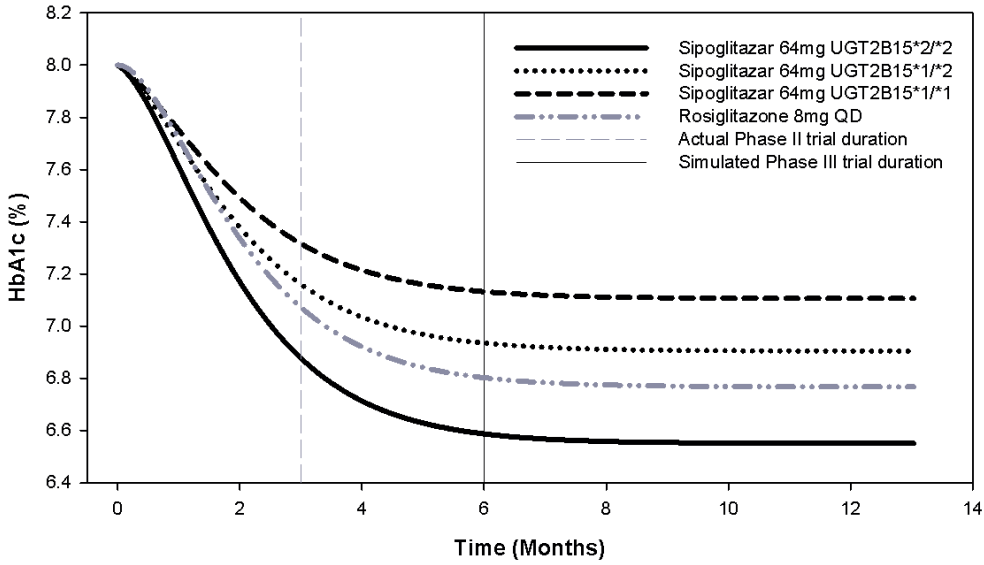


Figure 2. (b) Simulated HbA1c over time for sipoglitazar at 64 mg by genotype and rosiglitazone (8mg QD)

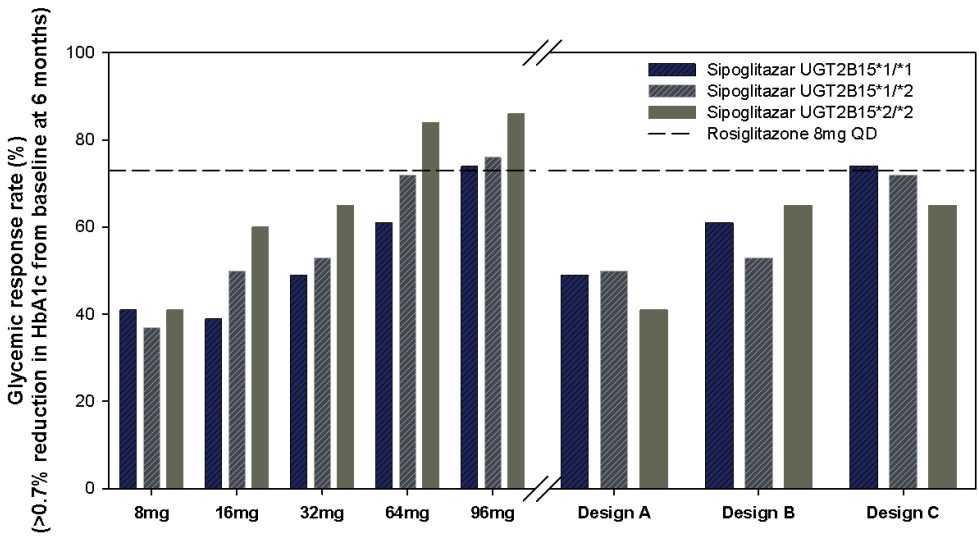


The simulated median change from baseline in FPG for a total daily dose of 64mg sipoglitazar at 6 months was -1.2 mmol/L, -1.6 mmol/L and -2.1 mmol/L for UGT2B15*1/*1, UGT2B15*1/*2 and UGT2B15*2/*2 genotypes respectively. The same trend is observed for HbA1c, the median change from baseline by genotype was -0.9%, -1.1% and -1.4% for the UGT2B15*1/*1, UGT2B15*1/*2 and UGT2B15*2/*2 genotypes, respectively. For the reference treatment rosiglitazone 8mg QD, predicted changes in FPG and HbA1c at 6 months were -2.0 mmol/L and -1.2%, respectively.

Simulation of Clinical Response at 6 Months

The percentage of patients achieving a reduction in HbA1c > 0.7% at 6 months for doses of 8, 16, 32, 64 and 96 mg by genotype were simulated and are shown in Figure 3.

Figure 3. Bar graph for the % of responders (>0.7% reduction in HbA1c at 6 months) by dose and genotype. Design A (UGT2B15*1/*1=32mg, UGT2B15*1/*2=16mg and UGT2B15*2/*2=8mg) Design B (UGT2B15*1/*1=64mg, UGT2B15*1/*2=32mg and UGT2B15*2/*2=16mg) Design C (UGT2B15*1/*1=96mg, UGT2B15*1/*2=64mg and UGT2B15*2/*2=32mg)



A comparable result to the 8mg rosiglitazone treatment was obtained for all genotypes at a dose level of 96 mg sipoglitazar (single dose approach). For genotyped-based dose assignment this was achieved in all three genotypes using Design C (UGT2B15*1/*1=96mg, UGT2B15*1/*2=64mg and UGT2B15*2/*2=32mg) with lower doses being administered to the UGT2B15*1/*2 and UGT2B15*2/*2 groups than with the single dose approach. Within Design C the percentage of subjects achieving a target reduction in HbA1c were 74, 72 and 65% for the UGT2B15*1/*1, UGT2B15*1/*2 and UGT2B15*2/*2 groups respectively, as compared to 73% for rosiglitazone.

Evaluation of genotyped-based dosing and titration-based dosing approaches

Figures 4a and 4b show the response for FPG and HbA1c over a 12 month period for genotyped and titration-based dosing approaches for the UGT2B15*1/*1 and

UGT2B15*1/*2 genotypes respectively. For the UGT2B15*1/*1 genotype, FPG at 2 months was 8.8 mmol/L and 8.1 mmol/L for the titration and genotyped based dosing respectively. At 2 months in the titration-based approach the dose was increased from 32mg to 64mg. At 4 months the median value for FPG was 8.3 mmol/L in the titration-based group and a further titration step up to 96mg was included.

Figure 4. (a) Simulated FPG and HbA1c profiles for genotyped and titration-based dosing approaches for UGT2B15*1/*1.

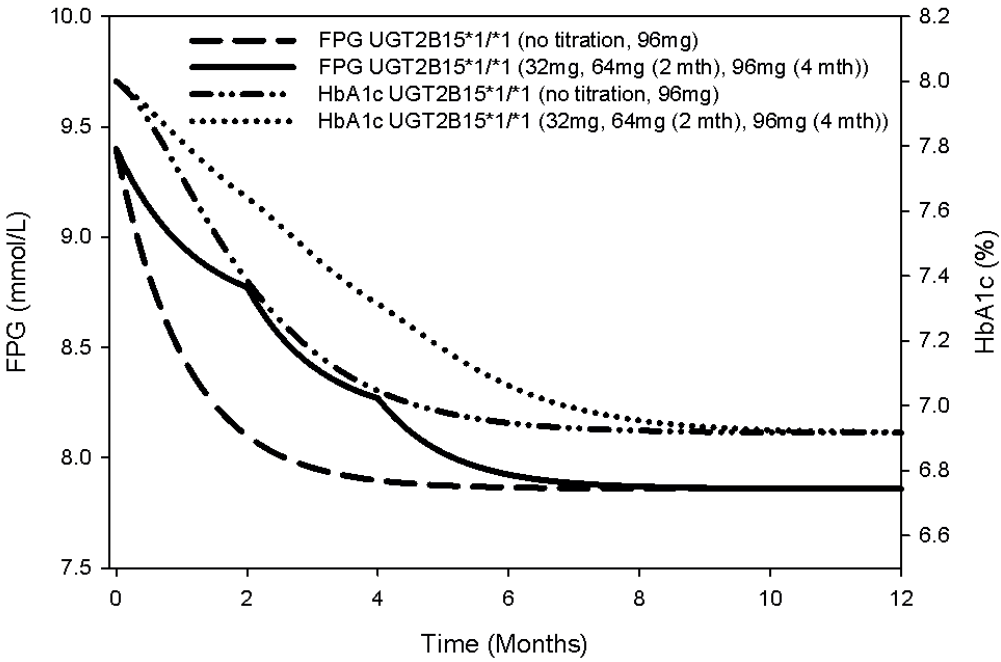
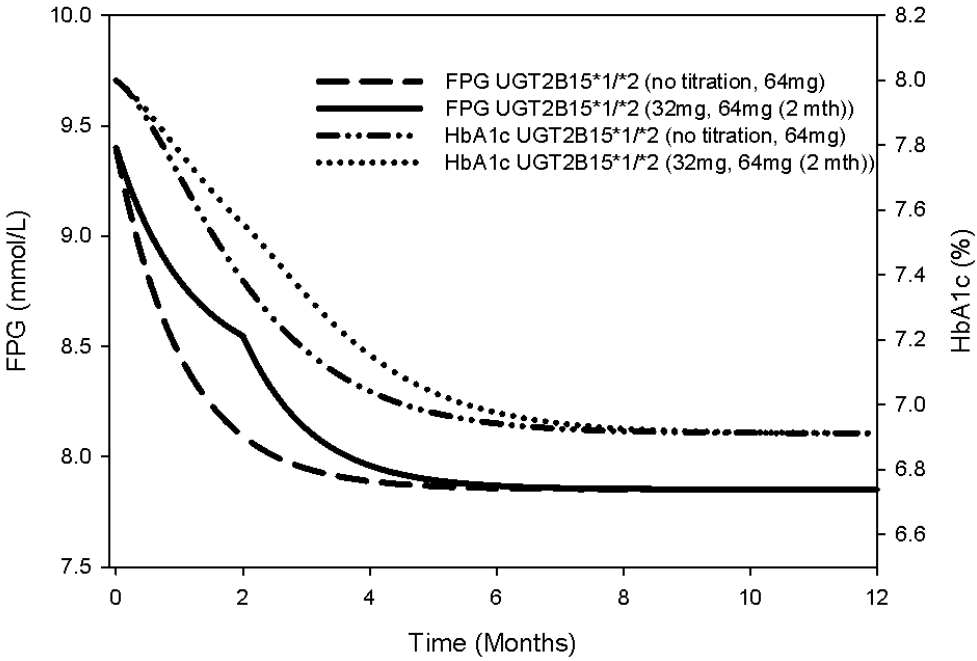


Figure 4. (b) Simulated FPG and HbA1c profiles for genotyped and titration-based dosing approaches for UGT2B15*1/*2.



For genotyped based dosing, where this subject receives 96mg from the start a stronger reduction in FPG was observed over the first 6 months of treatment. The difference in FPG between the two approaches at 2 months and 4 months was -0.7 mmol/L and -0.4 mmol/L. The time to achieve 90% of FPG steady state was approximately 2.4 months and 4.6 months for genotype and titration-based dosing respectively

For the UGT2B15*1/*2 genotype, only one titration step was included at 2 months from 32mg to 64mg. The value for FPG at 2 months was 8.6 mmol/L and 8.1 mmol/L for the

titration and genotype designs respectively. For FPG, 90% of steady state for the two approaches was reached at approximately 1.7 and 2.7 months.

Discussion

A PK-PD model-based approach was applied to simultaneously evaluate changes in FPG and HbA1c in type 2 diabetic patients with no prior exposure to anti-diabetic medication. The aim of our analysis was to characterize the relationship between differences in exposure due to genotype and the clinical response using FPG and HbA1c data as biomarkers. After accounting for genotype-related differences in exposure, a single unique PK-PD relationship was found to apply to the entire patient population. We found that genotype driven differences in exposure resulted in differences in clinical response for both FPG and HbA1c. The application of genotype-based dosing was found to normalize the differences in HbA1c response whilst minimizing the potential for over exposure of the drug in the UGT2B15*1/*2 and UGT2B15*2/*2 genotypes.

The mean influence of genotype on FPG and HbA1c response was simulated over a one year time period. Based on these simulations, greater reductions in both FPG and HbA1c were observed in the UGT2B15*2/*2 genotype as compared to the other groups. At a dose of 64mg for sipoglitazar, the values of the HbA1c decrease at 6 months were -0.9% versus -1.4% for the UGT2B15*1/*1 and UGT2B15*2/*2 genotype respectively. This may translate into clinically meaningful differences, since reducing hyperglycemia improves morbidity and mortality in T2DM patients [25]. Long term studies (10 years in duration) showed that a 1% reduction in HbA1c was associated with a reduction in risk of 21% for any end point related to diabetes, of 21% for deaths related to diabetes, of 14% for myocardial infarction, and of 37% for microvascular complications [26]. Furthermore a 0.5% decrease in HbA1c could avert 10% of cardiovascular complications over the course of 5 years [27]. Subjects with the UGT2B15*1/*1 genotype, would have the potential to gain clinical benefit from individualized dosing in order to achieve further reductions in HbA1c.

A simulation study was performed to evaluate the utility of genotype based dosing to account for the differences in exposure due to genotype. The number of subjects achieving a HbA1c

reduction >0.7% at 6 months was used for evaluation. Based on these results to achieve equivalence to the reference PPAR agonist rosiglitazone, for all subjects irrespective of genotype, a dose of 96mg of sipoglitazar would be required. However using genotype based dosing uniform response rates could be achieved with lower doses for the UGT2B15*2/*2 and UGT2B15*1/*2 groups. The responder rates of genotype design C (UGT2B15*1/*1=96mg, UGT2B15*1/*2=64mg and UGT2B15*2/*2=32mg) were comparable to that of 8mg rosiglitazone. As previously described some outlying subjects had considerably higher exposure than expected based on their genotype [3]. For these outlying subjects for whom there is disconnect between genotype and exposure a therapeutic drug monitoring approach or further safety evaluation at higher exposures would probably still be needed even though genotype based dose selection is a valid approach to improve HbA1c reduction.

Through simulation, genotype and titration based-dosing approaches were compared. As shown in Figures 4a and 4b the advantage for genotype dosing is that glycemic control can be achieved in a shorter time duration. The difference in the time to 90% of steady state between genotyped and titration-based dosing was approximately 1 and 2 months for the UGT2B15*1/*2 and UGT2B15*1/*1 genotypes. However, ultimately the magnitude of FPG reduction achieved for the two approaches would be expected to be the same. The biggest impact of genotyped-based dosing seems to be observed for those subjects with UGT2B15*1/*1. In the Caucasian population the frequency for UGT2B15*1/*1 is reported between 19-22% which is consistent with our own studies [28]. However in Asian American and Japanese American subjects the frequency was reported as 47% and 100% respectively [28]. Therefore in the Asian population the impact of this polymorphism would be greater on a larger percentage of the population and may have the potential to impact on any future clinical trial results if genotype frequency information was not collected or considered. Those subjects with UGT2B15*1/*1 would have a lower clinical response if only a fixed dose approach was used or a longer time to maximum effect if titration based dosing was applied. Newly approved therapies such as dipeptidyl peptidase 4 inhibitors have no requirement for dose titration to effect included in the label, which is in contrast to older drugs such as

rosiglitazone [29]. Therefore the impact of genotyping and dose titration for this drug would have to be considered in relation to new and upcoming therapies that do not require titration to effect.

There are several limitations of our model. During the trial no PK data were collected for rosiglitazone. In addition the 6 month simulation is based only on trial data up to 3 months both of which may increase the uncertainly in our extrapolations. However, simulated changes in FPG and HbA1c at 6 months for rosiglitazone 8mg total daily dose, based on the currently developed model, were fairly comparable to those previously reported in T2DM patients over the same time period. The mean change from baseline for rosiglitazone 4mg twice daily for FPG and HbA1c was reported as -3.0 mmol/L and -1.5%, respectively [30]. Simulated responder rates were slightly higher than those reported using the same criteria, 54% (actual) vs. 73% (simulated) [31]. However a direct comparison may be confounded by differences in the patient baseline characteristics and enrolment criteria.

A non-linear relationship between FPG and HbA1c was observed. This is consistent with other reports, and was best described with the use of a power function with a value of 0.7. This value is comparable to a previous PK-PD analysis with tesaglitazar, where this value was reported as 0.7 [17]. In addition a reduction in HbA1c that was visibly observed in the placebo group could also be identified in active treatment. This effect was found to be independent of changes in FPG. It is hypothesized that this disconnect between FPG and HbA1c may result from the contribution of post-prandial glucose (PPG) since the value of HbA1c is the result of both fasting and postprandial hyperglycemia [32]. Ozmen et al also showed that mean plasma glucose (the arithmetic mean of FPG and PPG) may better correlate with HbA1c [33]. This relationship between average glucose and HbA1c was explored using a semi-mechanistic model-based approach by Garcia et al. However, a model-based approach incorporating both post-prandial and fasting plasma glucose simultaneously with HbA1c may offer further insight into the complex relationship between HbA1c and glycemia.

In conclusion, we show how the genotype effect on the PK does translate to differences in FPG and HbA1c response and this could be addressed with a genotype-based dosing

approach. A model-based analysis should be performed to elucidate these genotype differences while considering the other components affecting clinical response.

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Supplemental Appendix

Table S1. Baseline characteristics

Characteristics	Median and range (or count)
Age (years)	56 (34 – 75)
Sex (male:female)	388:392
Body weight (kg)	88.8 (55 – 160)
Duration of disease (years)	1.0 (0 – 30.9)
FPG baseline (mmol/L)	9.3 (2.9 – 20.8)
HbA1c baseline (%)	7.9 (6.9 – 9.9)
UGT2B15 genotype* (*1/*1:*1/*2:*2/*2)	149:357:194

*genotype information not collected in 80 subjects

FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin

Figure S1. Histogram plot for baseline FPG for all subjects included in the analysis

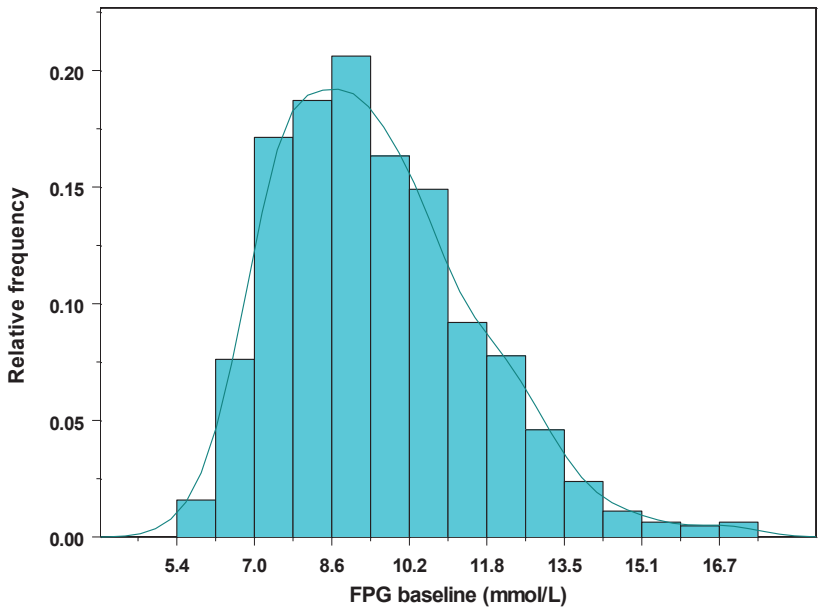


Figure S2. Histogram plot for baseline HbA1c for all subjects included in the analysis

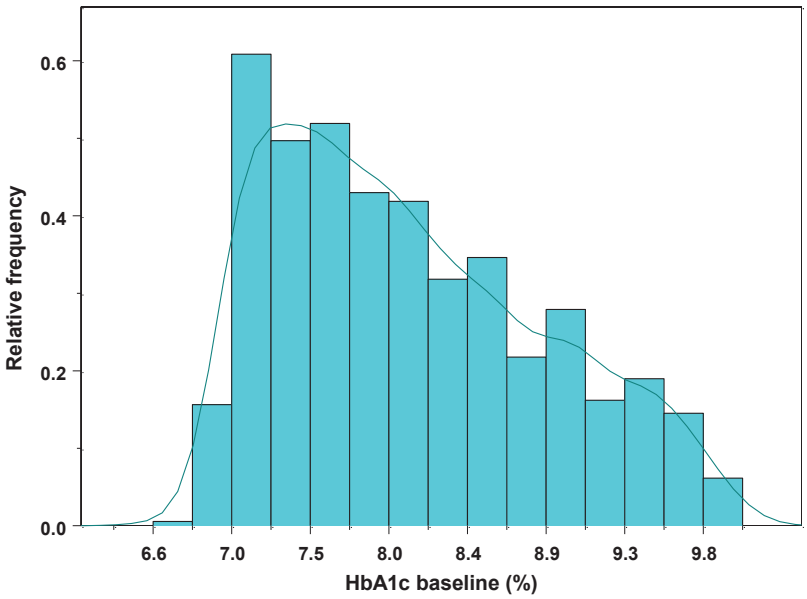


Figure S3. Box plots (median, 25th, and 75th percentiles) for the effect (Drug + placebo) by genotype and treatment group for placebo and sipoglitazar. (solid grey line = median rosiglitazone, dashed greyline=rosiglitazone 25th, and 75th percentiles). (1= UGT2B15*1/*1, 2= UGT2B15*1/*2, 3=UGT2B15*2/*2)

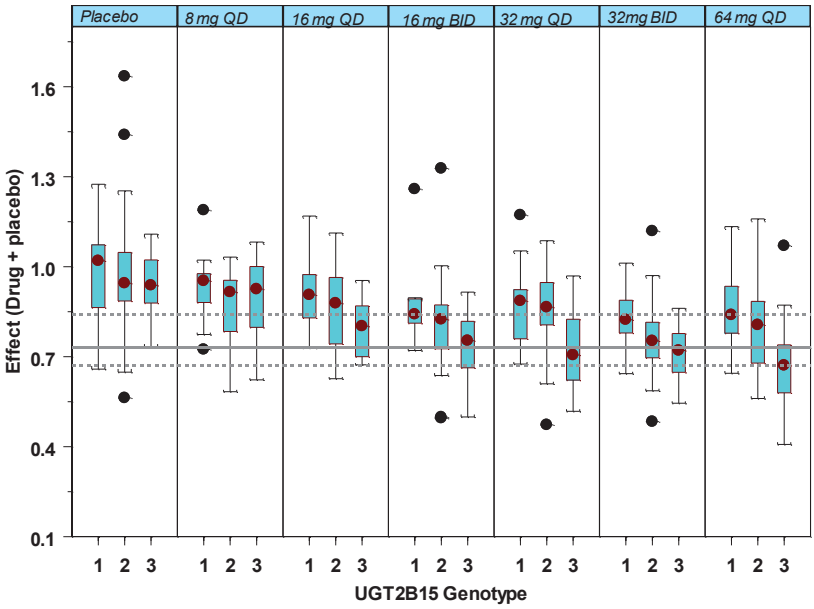
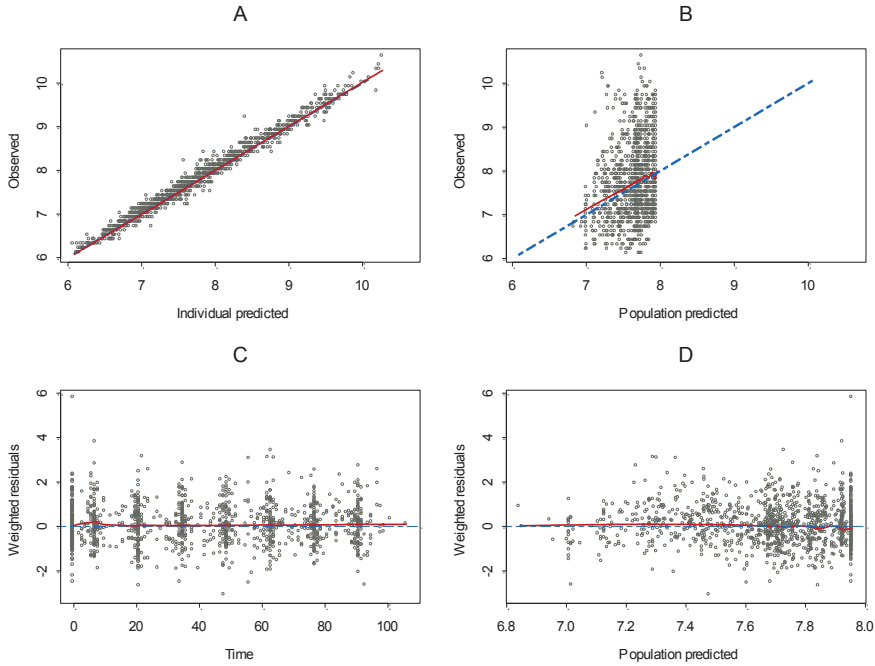


Figure S4. Diagnostic plots of HbA1c for all treatment groups of sipoglitazar UGT2B15*1/*1



A: Observations vs. individual fitted values

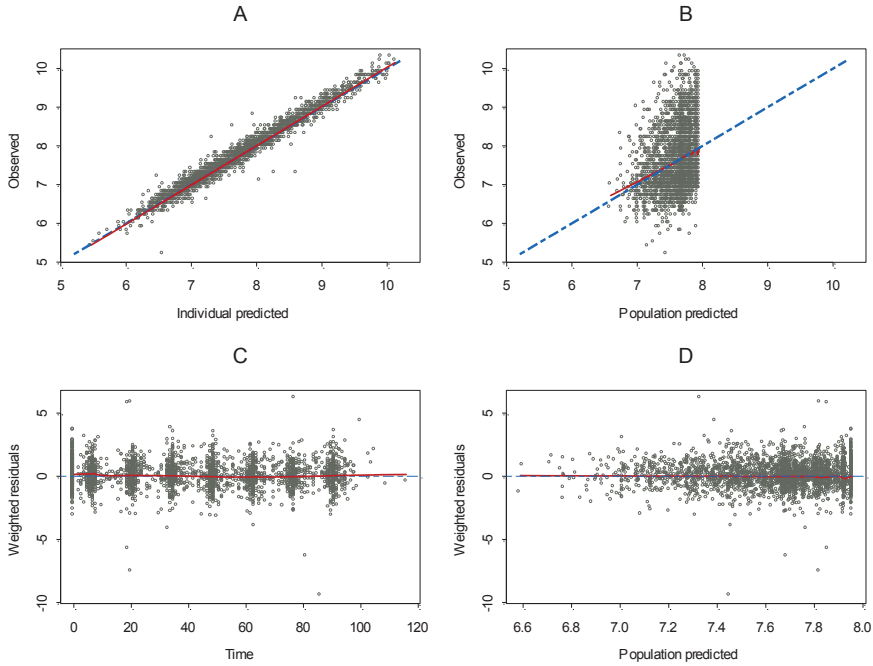
B: Observations vs. population fitted values

C: Conditional weighted vs. time

D: Conditional weighted vs. population fitted values

Dashed line: line of identity (A and B) or line indicating 0 (C and D)

Figure S5. Diagnostic plots of HbA1c for all treatment groups of sipoglitazar UGT2B15*1/*2



A: Observations vs. individual fitted values

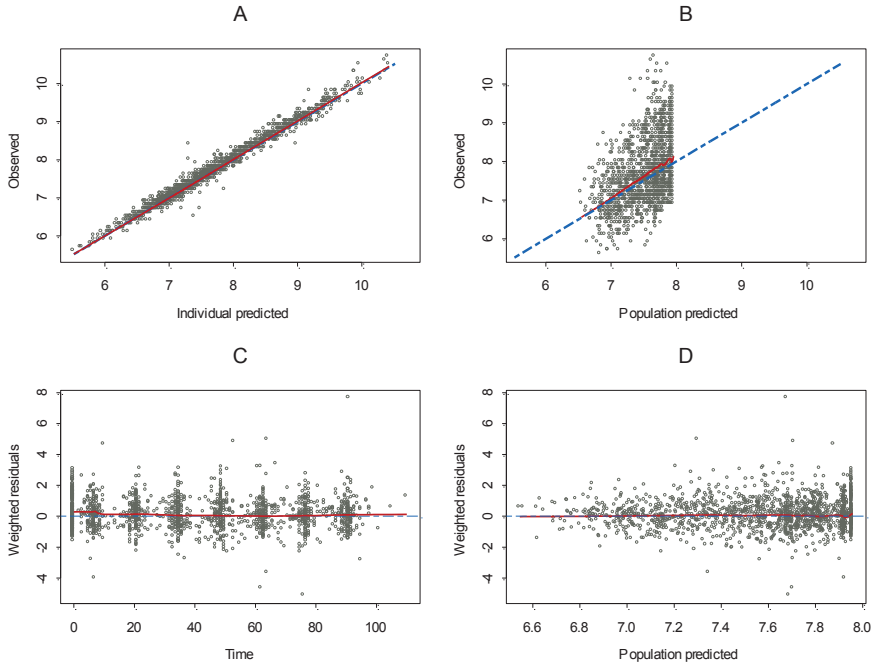
B: Observations vs. population fitted values

C: Conditional weighted vs. time

D: Conditional weighted vs. population fitted values

Dashed line: line of identity (A and B) or line indicating 0 (C and D)

Figure S6. Diagnostic plots of HbA1c for all treatment groups of sipoglitazar UGT2B15*2/*2



A: Observations vs. individual fitted values

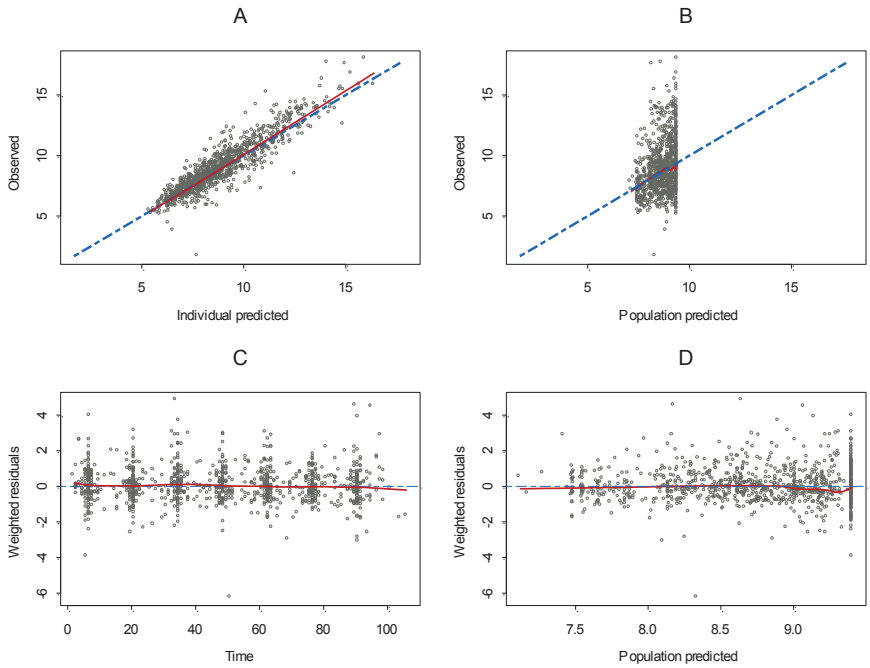
B: Observations vs. population fitted values

C: Conditional weighted vs. time

D: Conditional weighted vs. population fitted values

Dashed line: line of identity (A and B) or line indicating 0 (C and D)

Figure S7. Diagnostic plots of FPG for all treatment groups of sipoglitazar UGT2B15*1/*1



A: Observations vs. individual fitted values

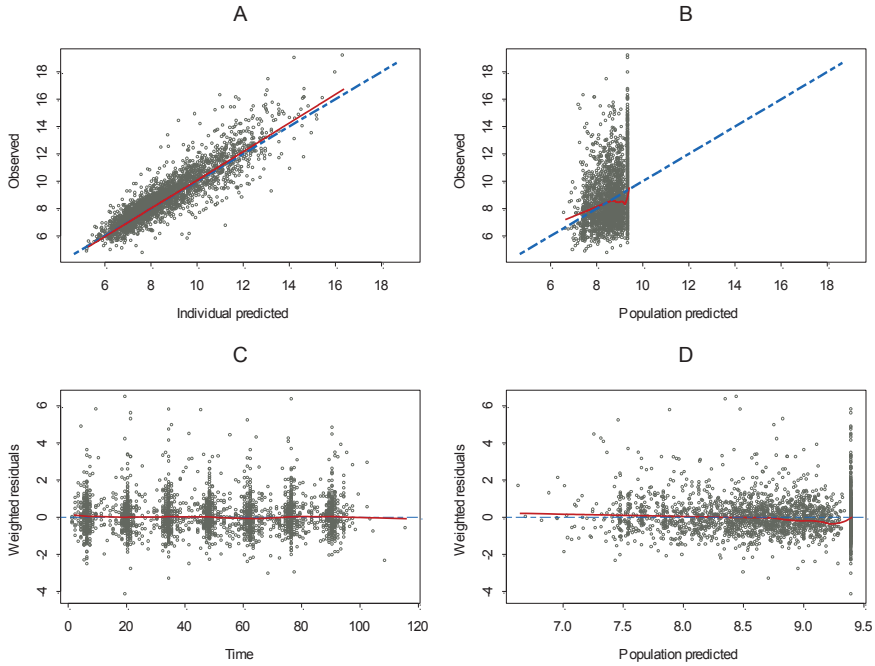
B: Observations vs. population fitted values

C: Conditional weighted vs. time

D: Conditional weighted vs. population fitted values

Dashed line: line of identity (A and B) or line indicating 0 (C and D)

Figure S8. Diagnostic plots of FPG for all treatment groups of sipoglitazar UGT2B15*1/*2



A: Observations vs. individual fitted values

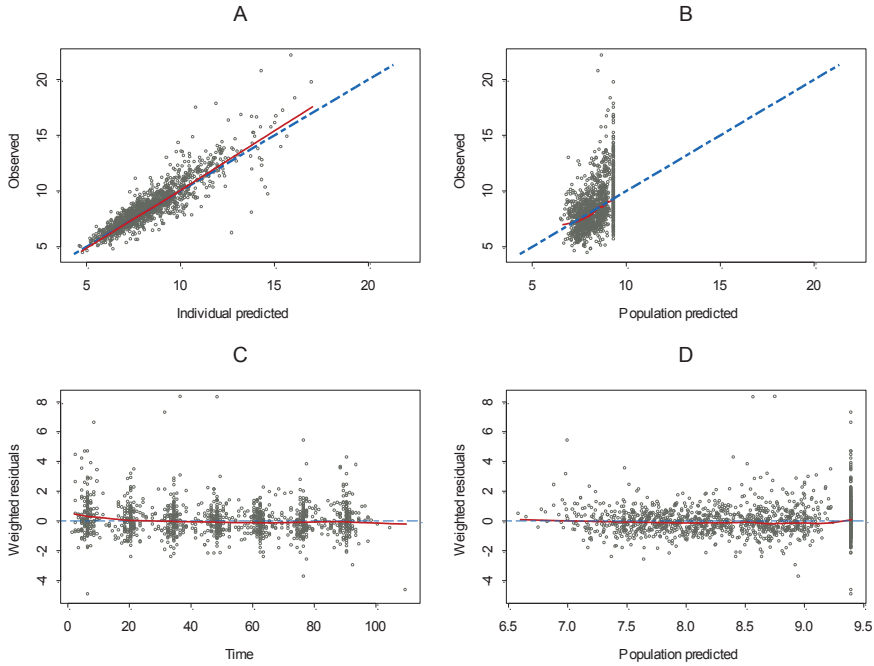
B: Observations vs. population fitted values

C: Conditional weighted vs. time

D: Conditional weighted vs. population fitted values

Dashed line: line of identity (A and B) or line indicating 0 (C and D)

Figure S9. Diagnostic plots of FPG for all treatment groups of sipoglitazar UGT2B15*2/*2



A: Observations vs. individual fitted values

B: Observations vs. population fitted values

C: Conditional weighted residuals vs. time

D: Conditional weighted vs. population fitted values

Dashed line: line of identity (A and B) or line indicating 0 (C and D)