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ORIGINAL ARTICLE

Pharmacometric Approaches to Guide Dose Selection of the Novel GPR40 Agonist TAK-875 in Subjects With Type 2 Diabetes Mellitus

H Naik[1], J Lu[2], C Cao[1], M Pfister[2], M Vakilynejad[1] and E Leifke[1]

The G-protein-coupled receptor 40 agonist (GPR40) TAK-875 is being developed as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Pharmacometric approaches such as model-based exposure-response and meta-analyses were applied to (i) characterize exposure/dose–efficacy responses of TAK-875, (ii) characterize the time course of glycosylated hemoglobin A1c (HbA1c) response with TAK-875 6.25 to 200 mg q.d. doses for 12 weeks, (iii) project and compare HbA1c response with dipeptidyl peptidase 4 (DPP-4) inhibitors and TAK-875 up to 24 weeks, and (iv) provide a quantitative rationale for dose selection in phase 3. On the basis of phase 2 data, relationships between TAK-875 concentrations and HbA1c were well characterized by exposure–response models. EC_{50} and E_{max} of TAK-875 were estimated to be 3.16 µg/ml and 0.366, respectively. Model-based simulations over 24 weeks indicated that the 25- and 50-mg q.d. doses of TAK-875 achieve efficacy as comparable with or better than that of commonly used antidiabetic agents.
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Type 2 diabetes mellitus (T2DM) accounts for 90–95% of all diabetes cases; its global incidence is expected to increase from 171 million to 366 million by the year 2030.[1,2] Despite new classes of antidiabetic medications, the National Health and Nutrition Examination Survey has concluded that the proportion of patients who achieve a glycosylated hemoglobin A1c (HbA1c) level of <7% (the American Diabetes Association goal) remains relatively unchanged at about 37%.[3,4]

TAK-875 (**Supplementary Figure S1** online) though being developed as an adjunct to diet and exercise to improve glycemic control in patients with T2DM, differs from sulfonylurea-receptor activators and other secretagogues in its effects on β cells. Sulfonylureas and glinides stimulate insulin secretion even at low blood glucose concentrations; nonclinical data suggest that TAK-875 stimulates insulin secretion only at elevated blood glucose levels.[5] TAK-875 is an agonist of free fatty acid receptor 1 (or G-protein-coupled receptor 40 agonist, GPR40) and is expressed in pancreatic islets cells. Binding of free fatty acids to the GPR40 receptor leads to glucose-stimulated insulin secretion.[5,6] This novel mechanism of action may allow safe and effective T2DM treatment by selectively improving glucose-dependent insulin secretion with a low probability of hypoglycemia.

TAK-875 pharmacokinetics (PK) appear similar between healthy individuals[7,8] and patients with T2DM.[9] After single and multiple doses (25–800 mg) in healthy subjects and patients with T2DM, TAK-875 was absorbed from the gastrointestinal tract with a median time to maximum concentration of ~3–4 h, and was slowly eliminated from the systemic circulation, with a terminal half-life of ~28–51 h. A dose-proportional increase in exposure (maximum concentration and area under the curve) without induction of hypoglycemia was observed in placebo-controlled ascending single- or multiple-dose studies.[7–9] TAK-875 is primarily eliminated by hepatic metabolism via formation of glucuronide conjugates, with minimal renal clearance (CLr ≤ 0.003 l/h).[7]

This study presents two pharmacometric approaches. First, utilizing phase 2 data, population exposure-response models were developed to (i) characterize the time course of TAK-875 plasma concentrations and fasting plasma glucose (FPG) and HbA1c levels in patients with T2DM receiving 6.25–200 mg oral q.d. doses of TAK-875, (ii) characterize the exposure-efficacy response of TAK-875, (iii) identify the sources of variability associated with PK and efficacy parameters of TAK-875, and (iv) project HbA1c response with TAK-875 up to 24 weeks. Second, using publicly available clinical efficacy data, model-based meta-analyses were performed to (i) characterize dose–efficacy responses of dipeptidyl peptidase 4 (DPP-4) inhibitors and TAK-875, and (ii) project and compare HbA1c response with glimepiride, DPP-4 inhibitors (drug class), and TAK-875 up to 24 weeks. Model-based simulations provided a quantitative rationale for dose selection in phase 3.

RESULTS

Demographics and disposition

This population PK analysis used 1,211 TAK-875 plasma samples collected from 286 patients with T2DM. Population PK-efficacy models were developed based on the data collected from all patients. Patients who received placebos were

[1]Takeda Global Research & Development Center, Inc., Chicago, Illinois, USA; [2]Quantitative Solutions, Inc., Bridgewater, New Jersey, USA. Correspondence: M Vakilynejad (majid.vakily@takeda.com)
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Table 1 Summary statistics of baseline subject demographics and clinical laboratory measures

Variable (continuous)	Pharmacokinetics		Pharmacokinetics-efficacy	
	N	Mean ± SD	*N*	Mean ± SD
Age (years)	286	51.2 ± 10.5	346	51.5 ± 10.6
BMI (kg/m^2)	286	31.8 ± 5.1	346	31.7 ± 5.1
Weight (kg)	286	86.3 ± 19.9	346	86.0 ± 20.0
ALB, g/l	286	41.7 ± 3.2	346	41.8 ± 3.3
ALP, U/l	286	84.8 ± 22.5	346	84.8 ± 24.4
ALT, U/l	286	29.2 ± 16.7	346	29.4 ± 16.8
AST, U/l	286	23.7 ± 11.4	346	24.0 ± 11.9
CrCL, ml/min	286	130.9 ± 43.3	346	129.7 ± 44.0
TBIL, µmol/l	286	8.3 ± 4.2	346	8.4 ± 4.2
DD, years	285	5.7 ± 4.9	344	5.7 ± 4.9
GGT, U/l	286	40.7 ± 33.3	346	41.4 ± 33.4
Metformin dose (mg)	221	1,696.2 ± 444.9	273	1,696.3 ± 441.9
BFPG (mg/dl)	286		346	170.3 ± 51.1
Baseline HbA1c (%)	286		346	8.4 ± 0.93
Variable (categorical)	**Category**	**Percentage (%)**	**Category**	**Percentage (%)**
Gender	Male	47.2	Male	46.5
	Female	52.8	Female	53.5
Race	African American	9.4	African American	10.1
	Caucasian	83.6	Caucasian	82.4
	Asian	2.8	Asian	3.2
	Others	4.2	Others	4.3
Ethnicity	Non-Hispanics	30.8	Non-Hispanics	33.2
	Hispanics	69.2	Hispanics	66.8
Smokers	Yes	16.1	Yes	15.6
	No	83.9	No	84.4
Metformin	Yes	77.3	Yes	76.3
	No	22.7	No	23.7
Aspirin	Yes	11.9	Yes	13.0
	No	88.1	No	87.0
Angiotensin-converting enzyme Inhibitors	Yes	25.9	Yes	24.6
	No	74.1	No	75.4
Statins	Yes	15.0	Yes	16.5
	No	85.0	No	83.5

ALB, albumin; ALP, alkaline phosphate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCL, creatinine clearance; DD, disease duration; GGT, γ-glutamyl transpepdidase; TBIL, total bilirubin.

also included for PK-efficacy analysis. This population PK-efficacy analysis used 2,710 FPG and 1,381 HbA1c samples collected from 346 patients with T2DM. The overall population was predominantly Caucasian (82.4%), with mean age 52 years (range 21–79) and mean body weight 86.0 kg (range 49.5–172.7). Subject demographics and covariates are summarized in **Table 1**.

PK analysis

A two-compartment model (**Supplementary Data** online, control stream 3) with first-order absorption and elimination well described the exposure data (**Figure 1**). Interindividual variability (IIV) was estimated only for oral clearance (CL/*F*). Following covariate analysis, sex was identified as a statistically significant covariate for TAK-875 CL/*F* as described in the following equation.

$$\mathrm{CL}/F = 0.752 + 0.308 \times \mathrm{sex} \quad (\mathrm{sex} = 1 \text{ for male and } 0 \text{ for female}) \tag{1}$$

Males appear to have higher clearance as compared with females (**Figure 2**). Inclusion of sex as a covariate for CL/*F* of TAK-875 reduced the objective function value and IIV for CL/*F* in the final model by 14.52 and 7.6% coefficient of variation units, respectively. The parameter estimates along with their associated precisions (% relative standard error for the final PK model for TAK-875) are presented in **Table 2**.

Exposure-efficacy response analysis

The effect of TAK-875 on FPG was well characterized by an indirect response model (**Supplementary Data** online, control stream 2) with stimulation of K_{out} (first-order rate constant for elimination of glucose). IIV was estimated for the model predicted baseline (BL) and E_{max}. The parameter estimates and their associated precision for the final FPG model for TAK-875 are presented in **Table 2**. Estimated E_{max} of TAK-875 increased exponentially with observed baseline FPG (BFPG) whereas it increased linearly with increasing

aspartate aminotransferase (AST) levels as described in the following equation:

$$E_{max} = 0.366 \times \mathrm{EXP}\,(0.00746 \times (\mathrm{BFPG} - 163.5)) + 0.00731 \times (\mathrm{AST} - 21) \quad (2)$$

The identified covariates (BFPG and AST) reduced the objective function value and IIV for E_{max} in the final model by 49.3 and 18.5% coefficient of variation units, respectively.

The relationship between FPG and HbA1c was implemented in the HbA1c model (**Supplementary Data** online, control stream 1) to describe the time course of HbA1c (**Supplementary Figure S2** online). An exponential placebo model with factor for maximum placebo response (MPL) was included in the model to empirically account for the effect of placebo on HbA1c levels observed in this short-term (12 weeks) trial. Due to the short trial duration, the half-life of MPL was fixed to the value (720 h) observed based upon the graphical analysis of data. IIV was estimated for the BL for HbA1c (BLA1), K_{A1C}, and MPL with a covariance term between MPL and K_{A1C}. The parameter estimates and their associated precision for the final HbA1c model for TAK-875 are presented in **Table 2**.

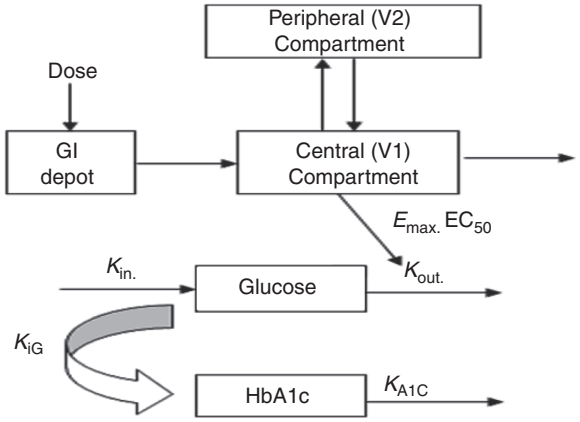

Figure 1 Population pharmacokinetics-efficacy model for TAK-875. GI, gastrointestinal; HbA1c, glycosylated hemoglobin A1c.

The identified covariates (BFPG, sex, and disease duration in years (DD)) reduced the IIV for BLA1, K_{A1C}, and MPL in the final model by 3.2, 29.8, and 7.9% coefficient of variation units as compared with the base model without any covariates. BFPG was added as a covariate for the predicted HbA1c baseline during model refinement step. The relationship between identified covariates and efficacy parameters is presented in the equations below.

$$\mathrm{BLA1} = (8.32 + 0.0133 \times (\mathrm{DD} - 4.61)) \times \mathrm{EXP}\,(0.00181 \times (\mathrm{BFPG} - 163.5)) \quad (3)$$

$$\mathrm{MPL} = 0.0590 + 0.0363 \times (\mathrm{sex}) \quad (4)$$

The magnitude of the covariate effect on PK and efficacy parameters of TAK-875 are presented in **Figure 2**. Standard diagnostic plots for the developed population PK and efficacy models are shown in **Supplementary Figure S3** online. Results of bootstrap evaluations and visual predictive check supported the robustness and predictive ability of the PK and efficacy models (**Figure 3a,b**, **Table 2**).

Simulations outcome

Simulation performed based on the developed population PK-efficacy model predicted mean reductions in HbA1c

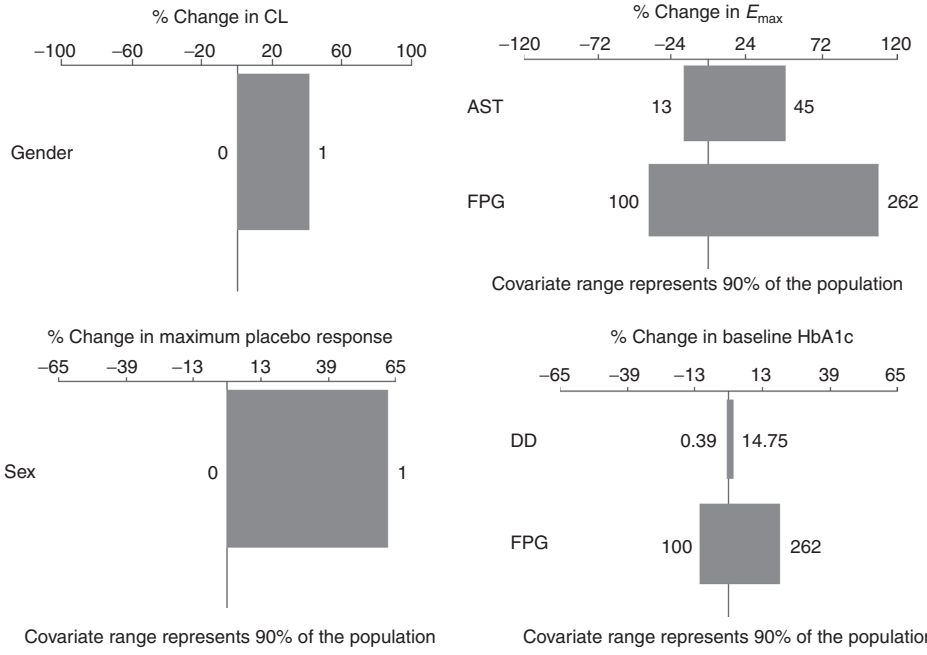

Figure 2 Tornado Plot of covariate effects on pharmacokinetics and efficacy parameters of TAK-875. The reference line represents the typical subject in this population: a 52-year-old female subject with AST level of 21U/L, BFPG of 163.5 mg/dl and having diabetes for 4.61 years. Extreme values represent 5th and 95th percentile value observed for a covariate in this phase 2 study. AST, aspartate aminotransferase; BFPG, baseline fasting plasma glucose; DD, disease duration.

Table 2 Model and bootstrap parameter estimates with 95% bootstrap CI for the final TAK-875 PK, PK-FPG, and PK-efficacy model

Parameter	Model estimate (% RSE)	Bootstrap estimate	Bootstrap 95% CI[a]
Pharmacokinetic analysis			
CL/*F* (l/h)	0.75 (7.46)	0.76	0.67–0.98
V1/*F* (l)	5.86 (11.2)	5.59	3.858–72.2
Q/*F* (l/h)	0.833	0.833	NA
V2/*F* (l)	23.7	23.7	NA
K_a (1/h)	0.075	0.075	NA
Gender on CL/*F* (l/h)	0.31 (27.2)	0.30	0.14–0.55
ω^2 on CL/*F*	0.488 (7.45)	0.479	0.276–1.22
σ^2 (exponential error)	0.152 (3.67)	0.149	0.123–0.177
Pharmacokinetic-FPG analysis			
BL (mg/dl)	164 (1.5)	164	159–168
K_{out} (1/h)	0.00542 (12.5)	0.00543	0.00419–0.0067
E_{max}	0.366 (16.2)	0.366	0.259–0.5006
EC_{50} (μg/ml)	3.16 (32.3)	3.15	1.2–6.7
BFPG on E_{max} (mg/dl)	0.00746 (13.1)	0.00753	0.00454–0.00971
AST on E_{max} (U/l)	0.00731 (44.2)	0.00723	0.00319–0.0122
ω^2 on BL	0.0610 (9.3)	0.0612	0.0518–0.0721
ω^2 on E_{max}	0.0854 (53.9)	0.0754	0.00733–0.182
σ^2 (additive error)[b]	0.0187 (1.39)	0.0186	0.0163–0.0213
Pharmacokinetic-efficacy analysis			
BLA1 (%)	8.25 (0.5)	8.26	8.18–8.33
K_{A1C} (1/h)	0.00052 (11.3)	0.00053	0.00042–0.00064
HL (h)	720 (fixed)	NA	NA
MPL (NA)	0.0590 (21.7)	0.0579	0.0377–0.0794
Gender on MPL	0.0363 (32.1)	0.0394	0.0203–0.0631
DD on BLA1 (%/year)	0.0133 (55.6)	0.0141	0.0023–0.030
BFPG on BLA1 (%/mg/dl)	0.00181 (5.1)	0.0018	0.0016–0.0021
ω^2 on BLA1	0.0057 (9.4)	0.0057	0.0047–0.0068
ω^2 on K_{A1C}	0.95 (17.6)	1.00	0.658–1.55
$COV_{MPL-KA1C}$	0.506 (35.0)	0.486	0.289–0.656
ω^2 on MPL	0.305 (44.9)	0.307	0.168–0.540
σ^2 (additive error)[b]	0.00164 (3.3)	0.00156	0.00131–0.00189

Bootstrap convergence for PK, PK-PD, and PK-PD-efficacy were 99.9, 93.2, and 78%, respectively.
AST, aspartate aminotransferase; BFPG, baseline FPG; BL, model predicted baseline; BLA1, BL for HbA1c; CI, confidence interval; DD, disease duration; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; HL, half-life of MPL; MPL, maximum placebo response; NA, not applicable; PD, pharmacodynamic; PK, pharmacokinetics; RSE, relative standard error.
[a]CI calculated based on median values. [b]Additive error was used on log-transformed scale.

levels from baseline following administration of 25 mg q.d. dosing as –0.94% (observed value = –0.84%) and –1.24% at the end of 3 and 6 months, respectively. Predicted reductions from baseline HbA1c following 50 mg q.d. dosing were –1.16% (observed mean value = –1.05%) and –1.51% at the end of 3 and 6 months, respectively.

Model-based meta-analysis

With the model-based meta-analysis, time-response curves for DPP-4 inhibitors (therapeutic doses), glimepiride (therapeutic dose of 4 mg), and TAK-875 (selected therapeutic dose of 50 mg) were projected up to 24 weeks (**Figure 4a**); and dose–efficacy response curves for DPP-4 inhibitors and TAK-875 were characterized. Results indicated that therapeutic doses of DPP-4 inhibitors are associated with ~80–90% of maximum effect on HbA1c, whereas 50 mg of TAK-875 is expected to produce ~85% of maximum effect on HbA1c (**Figure 4b**).

DISCUSSION

One purpose of our analysis was to develop a population PK-efficacy model to describe the time course of TAK-875 plasma concentrations and FPG and HbA1c levels following oral 6.25–200 mg q.d. doses in patients with T2DM for 12 weeks. Furthermore, the main objective of the present analysis was to provide a quantitative rationale for selection of doses for phase 3 trial using two pharmacometric approaches.

The disposition kinetics of TAK-875 in patients with T2DM was best described using a PK model with first-order absorption and elimination processes. One- and two-compartment models were evaluated, with the latter PK model resulting in lower objective function value and Akaike Information Criterion values with substantially improved diagnostic plots. However, the two-compartment base PK model showed signs of instability during the bootstrap evaluation, which could indicate model over-parameterization. The model parameters describing the absorption and distribution of TAK-875 could not be precisely estimated because of the sparse sampling in this phase 2 study.[10] It was also determined that the model was not sensitive to the particular values of intercompartmental clearance (*Q*/*F*), peripheral volume of distribution (V3/*F*), and first-order absorption rate constant (K_a). Therefore, these parameters were fixed to values estimated in an earlier population PK analysis performed using frequently collected PK samples in a multiple rising dose study in patients with T2DM.[9] Although potential for nonlinearities in the PK model (e.g., Michaelis–Menten elimination) was not tested, the lack of bias in the diagnostic plots suggested that a linear PK model adequately described the data and that TAK-875 exhibited linear PK over the evaluated dose range. Furthermore, approximate dose proportionality was previously demonstrated for TAK-875 following oral administration of 25–800 mg single doses in healthy subjects[7] and 25–400 mg once-daily oral doses for 14 days in patients with T2DM.[9] PK parameters of TAK-875 were also constant over time after multiple administrations of 200 and 400 mg doses in healthy subjects.[8] These data together further support the appropriateness of considering a linear PK model for TAK-875.

Among baseline characteristics, only sex was identified as a statistically significant covariate on the CL/*F* of TAK-875, with ~41% higher clearance in males (1.1 l/h) than in females (0.75 l/h). The estimated CL/*F* value for males in this study is consistent with the CL/*F* of 0.9–1.7 l/h previously observed in healthy subjects.[7] TAK-875 primarily undergoes phase 2 metabolism via glucuronide conjugation. The results of this covariate analysis for PK of TAK-875 are not unexpected, given that higher glucuronidation activity in males

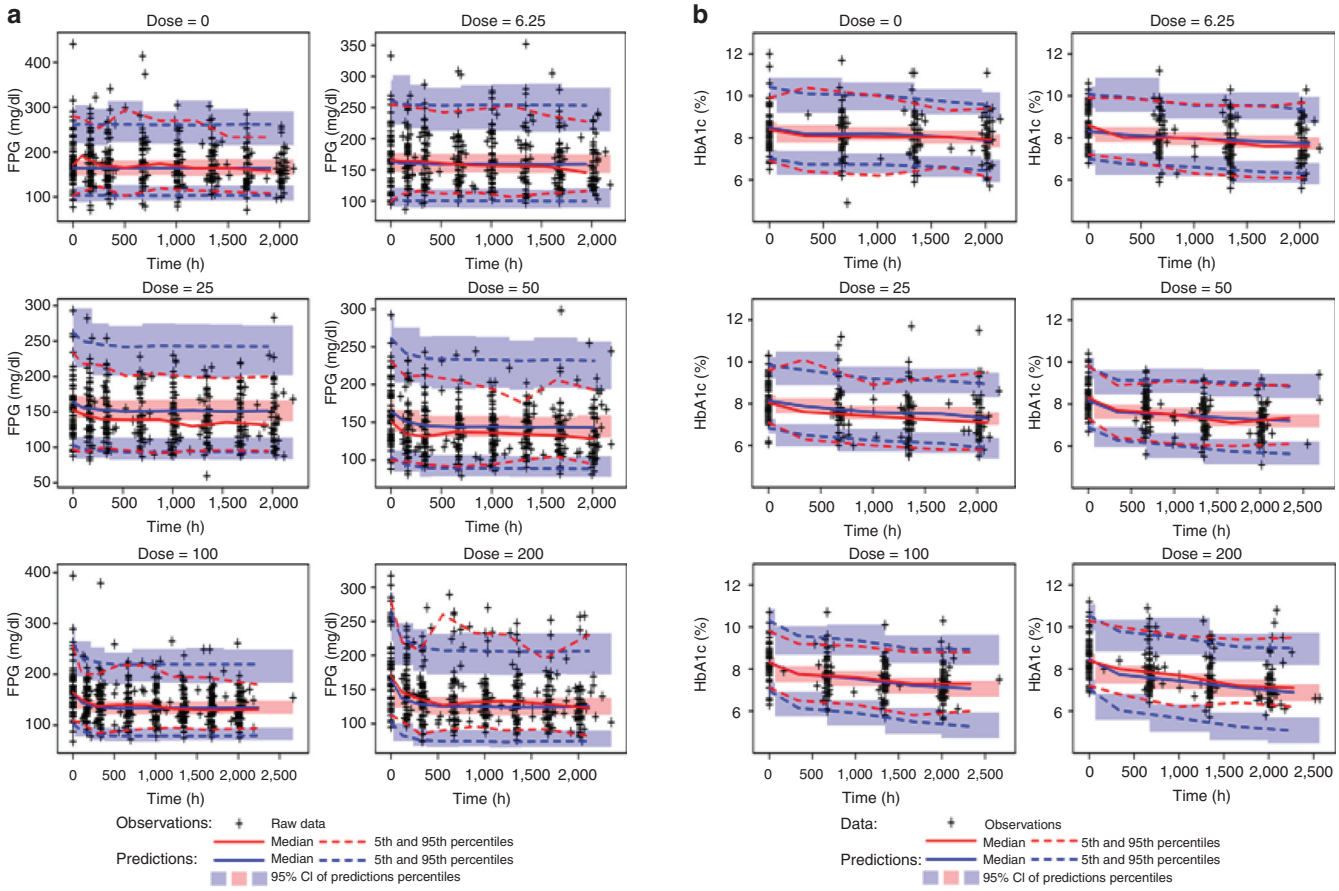

Figure 3 (**a**) Visual predictive check for the fasting plasma glucose using final pharmacokinetics-efficacy model. (**b**) Visual predictive check for the HbA1c using final pharmacokinetics-efficacy model. FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c.

has previously been reported for drugs mainly metabolized by glucuronidation.[11,12] On the basis of the simulations, males are expected to have maximum concentration and area under the curve values at steady state ~25 and 29% lesser than those of females, respectively. This difference is expected to lead to ≤5 mg/dl and ≤0.01% differences in FPG and HbA1c levels between males and females over 12 weeks, and is not expected to have a clinically meaningful impact, given the dose response for efficacy and safety of TAK-875.

Insulin-glucose homeostatic pharmacodynamic (PD) models reported in the literature[13,14] were not evaluated as TAK-875 did not appear to have an apparent effect on fasting serum insulin based on the graphical examination of fasting serum insulin levels vs. time obtained in this phase 2 study. This may be partially attributed to the glucose-dependent action of TAK-875. TAK-875 effects on glucose-stimulated insulin secretion leading to increases in the insulin levels are expected to become more noticeable in the state of elevated and rapidly changing glucose levels as seen postprandially. This will be explored in future studies using more frequent sampling to capture the early rise in insulin levels after intake of a standard meal and by developing a mechanistic model to account for complete insulin-glucose homeostasis. The placebo effect for FPG response was investigated as linear and exponential placebo response terms. However, the inclusion of placebo response did not improve model predictability and resulted in deviation from observed data in the diagnostic plots during PK-FPG analysis, because an inconsistent and highly variable placebo response was observed for FPG. Therefore, no placebo effect was included in the base and final PK-FPG models.

The covariate analysis for TAK-875 PD parameters identified observed BFPG and AST for E_{max} as statistically significant covariates. The effect of BFPG on TAK-875 E_{max} is consistent with the strong correlation between BFPG and E_{max} observed for many antidiabetic drugs[15–17]; the higher the baseline for FPG, the greater was the magnitude of TAK-875 response. On the basis of simulations over 12 weeks, the changes in FPG and HbA1c levels from baseline were –8.5 mg/dl and –0.62%, respectively, for a subject with observed BFPG value of 100 mg/dl (5th percentile). By contrast, the changes in FPG and HbA1c levels from baseline were –62 mg/dl and –1.79%, respectively, with the observed BFPG value of 262 mg/dl (95th percentile). The effect of AST on E_{max} of TAK-875 was mainly driven by seven outliers with AST levels ≥70 U/l at baseline. On removal of these seven patients, baseline AST did not have statistically significant effect on E_{max} of TAK-875 (P value ≥ 0.005).

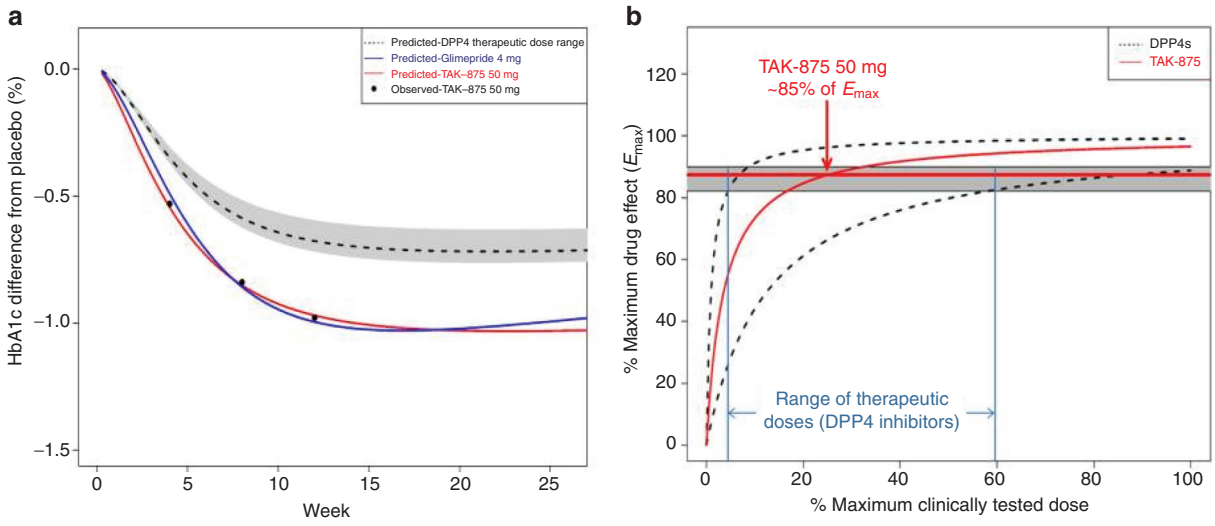

Figure 4 (**a**) Predicted mean changes in placebo adjusted HbA1c up to 24 weeks for the 50 mg dose of TAK-875, the 4 mg dose of glimiperide and the therapeutic doses of DPP-4 inhibitors (linagliptin 5 mg, saxagliptin 2.5 mg, sitagliptin 100 mg, and vildagliptin 100 mg). Shaded area shows the range of mean HbA1c responses for the four DPP-4 inhibitors. (**b)** Dose–response curves for TAK-875 and DPP-4 inhibitors (reference drug class). Doses are shown as % of maximum clinically tested dose (i.e., highest clinically tested dose is 100%). Drug effect is shown as % of maximum drug effect on HbA1c (% E_{max}) at week 24. Shaded area shows range of % E_{max} associated with therapeutic doses. Vertical lines delimit range of therapeutic doses. Dashed lines delimit range of dose response curves for DPP-4 inhibitors. DPP-4, dipeptidyl peptidase 4; HbA1c, glycosylated hemoglobin A1c.

Disease duration had no significant effect as a covariate on PK or efficacy parameters if controlled for BLA1. However, this may be due in part to the limited range of disease duration in the study population (0.39–14.75 years from diagnosis).[18] No differences in efficacy parameters were observed for sex. This supports our interpretation that the difference found for PK between males and females is minor and not relevant to the PD effect of TAK-875.

Of note, none of the comedications evaluated (metformin, statins, aspirin, and angiotensin-converting enzyme inhibitors) had a statistically or clinically significant effect on PK and efficacy parameters of TAK-875. This further indicates the limited potential for drug–drug interactions between TAK-875 and these drugs based on various TAK-875 interaction studies (data not shown). The lack of effect of metformin on the PD profile of TAK-875 can be attributed to the fact that patients were already on metformin treatment before entering this study.

On the basis of the simulation of HbA1c levels for 24 weeks, the predicted placebo-adjusted mean reductions in HbA1c levels from baseline to the end of 6 months were −0.80 and −1.06% for 25- and 50-mg doses of TAK-875, respectively (**Supplementary Figure S4** online). Therefore, TAK-875 50-mg q.d. dosing is expected to cause a decrease in HbA1c level from baseline as comparable with that of sulfonylureas (0.9–2%)[10,19–23] and potentially greater than that of DPP-4 inhibitors.[24–28] On the basis of the simulations and observed data over 12 weeks, only minimal therapeutic gain (reduction in HbA1c levels from baseline) can be expected at TAK-875 doses >50 mg.[10] Doses <25 mg may exhibit adequate pharmacological response; however, it is not expected to provide efficacy as comparable with the currently approved T2DM therapies (DPP-4 inhibitors, sulfonylureas, and glucagon like peptide-1 analogs).[19–22]

The following limitations should be considered for the empirical model presented. (i) The effect of TAK-875 on HbA1c levels did not reach plateau by month 3 in the present phase 2 study; therefore, the projection beyond 12 weeks may be slightly over or under estimated; (ii) a substantial proportion of subjects on placebo needed rescue medication for glycemic control and were excluded from this analysis after the start of the rescue medications. As a result, the placebo response was not implemented in the PK-FPG model; (iii) the developed model assumes that BFPG and HbA1c are at steady state at the time of randomization which may not be true slightly biasing overall simulated response; and (iv) a caution should be exercised for the projection on durability of TAK-875 response and extrapolation of placebo response beyond 12 weeks due to the short duration of current phase 2 trial. The model will be further optimized, if necessary, once long-term data are available from phase 3 trial to evaluate the accuracy of the prediction using the current model and assumptions considered during the development of the model.

Applying a model-based meta-analysis approach, projected HbA1c response with TAK-875 at the selected therapeutic dose of 50 mg was consistent with that based on the exposure-efficacy response analysis. Results indicated that 50 mg of TAK-875 is expected to produce a potentially greater HbA1c response than DPP-4 inhibitors and a response similar to that of sulfonylureas after 24 weeks of treatment. Furthermore, characterized dose–response curves indicated that 50 mg of TAK-875 is expected to produce ~85% of maximum effect on HbA1c, which is consistent with values associated with therapeutic doses of DPP-4 inhibitors (~80–90% of maximum effect on HbA1c).

In conclusion, findings from pharmacometric analyses provided a quantitative rationale for dose selection of 25 and 50

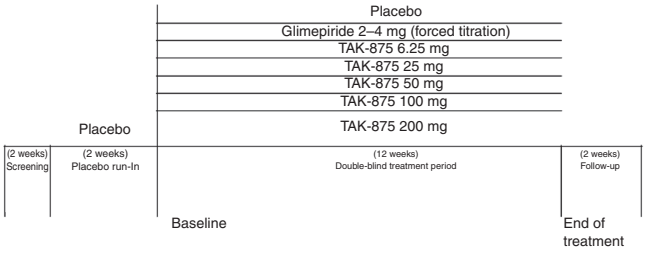

Figure 5 Schematics of study design.

mg q.d. TAK-875. Both doses will be evaluated in the future clinical phase 3 program.

METHODS

Study design. Data used here were obtained from a phase 2, randomized, double-blind, placebo- and active comparator-controlled, parallel-group, multicenter study.[10] The study was conducted to evaluate the efficacy, safety, and tolerability of TAK-875 q.d. treatment in patients with T2DM who were inadequately controlled on a stable dose of metformin as monotherapy for at least 8 weeks before screening, or who had been without chronic antidiabetic therapy within 8 weeks before screening with an 8-week documented diet and exercise plan. Eligible patients were randomized to seven treatment groups (**Figure 5**). The study was conducted in accordance with the guidelines on Good Clinical Practice and with the Ethical Standard for Human Experimentation established by the Declaration of Helsinki. The protocol and amendments were reviewed and approved by the Institutional Review Board.

Sample collection. Four blood samples (two trough and two nontrough, 4 ml each) were collected from each subject at two separate occasions at visit 7 (week 4) and visit 8 or 9 (week 6 or 8) for quantitation of TAK-875 steady-state plasma concentrations. TAK-875 plasma concentrations were measured using a validated ultraperformance liquid chromatography coupled with tandem mass spectrometry analysis.[7] FPG and HbA1c samples were collected from all patients at screening, baseline, day 7 (only FPG), day 14 (only FPG), and weeks 4, 6 (only FPG), 8, 10 (only FPG), and 12. FPG and HbA1c levels were measured using a standard laboratory method in a Clinical Laboratory Improvement Act (CLIA) certified central laboratory. Plasma pharmacokinetic, FPG, and HbA1c data collected from subjects on glimiperide were not included in the analysis.

Pharmacokinetic software. NONMEM software version VII, level 1.0 (ICON Development Solutions, Ellicott City, MD) was used for nonlinear mixed–effect population PK-efficacy modeling.[29] NONMEM output was accessed through KIWI graphical interface (Cognigen Corporation, Buffalo, NY). Xpose version 4.0 (Uppsala University, Uppsala, Sweden) was used for generalized additive modeling analysis. Model-based meta-analyses and graphical plots were generated using S-PLUS version 8.0 (Tibco Software, Palo Alto, CA), Microsoft Excel 2007, and R version 2.12.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Exposure-efficacy models. Population PK and efficacy analyses for TAK-875 were conducted using ADVAN4 TRANS4 (PK) or ADVAN6 TRANS1 (PK-efficacy) subroutines and first-order conditional estimation with η-ε interaction method as implemented in NONMEM VII.[29] Selection of base and final models was guided by the minimum objective function value, Akaike Information Criterion, visual inspection of diagnostic plots, and the precision of parameter estimates.

One- and two-compartment models with first-order absorption and linear elimination were evaluated as base structural PK models. Efficacy models were developed to characterize the time course of FPG and HbA1c levels. A semimechanistic indirect response model.[30,31] with stimulation of K_{out} (first-order rate constant for removal of fasting glucose) as depicted in **Figure 1** and described in differential equations below was used to describe changes in FPG following administration of TAK-875.

$$\frac{\mathrm{dFPG}}{\mathrm{d}t} = K_{in} - K_{out} \times (1+S) \times \mathrm{FPG}$$
$$S = \frac{E_{max} \times \mathrm{Cp}}{\mathrm{EC}_{50} + \mathrm{Cp}} \quad \mathrm{BL} = \frac{K_{in}}{K_{out}} \tag{5}$$

where K_{in} is the zero order rate constant for the production of FPG, E_{max} is the maximum effect of TAK-875 on the removal of FPG, EC_{50} is TAK-875 concentration resulting in the 50% of maximum reduction in FPG levels from baseline, BL is model predicted baseline for FPG, and Cp is the concentration of TAK-875 following administration of different doses of TAK-875. Changes in HbA1c were modeled secondary to changes in FPG and the relationship between FPG and HbA1c was implemented in the PK-efficacy model[15] as depicted in **Figure 1** and described in the equation below:

$$\frac{\mathrm{dHbA1c}}{\mathrm{d}t} = K_{iG} \times \mathrm{FPG} - \mathrm{HbA1c} \times K_{A1C}$$
$$\mathrm{BLA1} = \frac{K_{iG} \times \mathrm{BL}}{K_{A1C}} \tag{6}$$

K_{iG} is the first-order rate constant for the production of HbA1c, BLA1 is model predicted baseline for HbA1c, and K_{A1C} is the first-order rate constant for removal of HbA1c. On the basis of the graphical analysis, a consistent reduction in HbA1c levels was observed in patients who were on placebo. As a result, a placebo factor (PLAC), as defined by the equation below, was included in the differential equation to account for the effect of lifestyle intervention or placebo on HbA1c levels.

$$\mathrm{PLAC} = 1 - \mathrm{MPL} \times \left(1 - e^{\left((-Ln(2)/HL) \times \mathrm{time}\right)}\right) \tag{7}$$

$$\frac{\mathrm{dHbA1c}}{\mathrm{d}t} = K_{iG} \times (\mathrm{PLAC}) \times \mathrm{FPG} - \mathrm{HbA1c} \times K_{A1C} \tag{8}$$

HL is the half-life of MPL, the maximum placebo response, and PLAC refers to overall placebo effect. IIV associated

with PK and efficacy parameters of TAK-875 was modeled assuming a log-normal distribution.

$$P_i = P_{pop} \times \exp(\eta_i) \quad (9)$$

where P_i is the estimated parameter value for individual i, P_{pop} represents the typical population estimate for the parameter, and η_i is the deviation of P_i from P_{pop}. A diagonal covariance matrix was implemented for PK and PK-FPG analyses whereas a block matrix was implemented for the HbA1c analysis.

Residual variability was modeled using a proportional error term for PK (non log-transformed TAK-875 plasma concentration) and a log-normal error term (additive on log-transformed scale) for PK-FPG and HbA1c analyses. Only clinically relevant and biologically plausible covariate–parameter relationships were explored in the covariate analysis. In addition, comedications taken by more than 10% of the patient population during 80% of the trial period were also evaluated in the covariate analysis. Potential covariates identified by generalized additive modeling and graphical analysis (plot of η_i vs. covariate) were then tested using stepwise forward addition ($P < 0.05$) followed by stepwise backward elimination procedure ($P < 0.005$).[32]

Model qualification was conducted using standard nonparametric bootstrap ($n = 1{,}000$) and visual predictive check to evaluate the precision of model parameter estimates and robustness of the final PK and efficacy models.[33]

Model-based meta-analysis. A model-based meta-analysis used controlled clinical trials from the medical literature, the Food and Drug Administration, and the European Medicines Agency.[34] Clinical outcomes data from 74 prospective randomized clinical trials, with >36,300 patients and 208 different randomized treatment arms, were included in this model-based meta-analysis on efficacy of glimepiride and DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin). For TAK-875, data from a randomized placebo-controlled phase 2 study (excluding glimepiride arm) were evaluated.[10]

Relationships between baseline HbA1c and doses of DPP-4 inhibitors and TAK-875 were analyzed using a nonlinear regression implemented in the Generalized Nonlinear Least Squares routines of R version 2.12.1.[34–36] Changes in HbA1c in a given treatment arm (j) of a trial (i) ($HbA1c_{ij}$) at time T were modeled as a function of the placebo response for HbA1c in that trial ($E_{0,i,T}$), i.e., the intercept, and a dose–response relationship for treatment effects on HbA1c (g(x)). Covariates (X_{ij}) and trial-specific model parameters (θ_i) were included and evaluated according to the following general structure:

$$HbA1c_{ij,T} = E_{0,i,T} + g(Drug_{ij}, Dose_{ij}, X_{ij}, \theta_i, T) \quad (10)$$

where $E_{0,i,T}$ is a nonparametric placebo (i.e., reference) effect, which takes a different value for each study-time combination for each trial.[35–37] Dose–response relationships for randomized treatments were characterized as follows:

$$g(x) = \frac{E_{max,class}(t) \cdot Dose_{ij}}{Dose_{ij} + ED_{50,drug}} \quad (11)$$

where $E_{max,class}$ is the maximal drug effect, reflecting the maximal reduction in placebo-adjusted HbA1c (i.e., difference in response between placebo and active treatment) at a given time (t).[35–37] A different E_{max} was estimated for DPP-4 inhibitors (class effect), glimepiride, and TAK-875. This assumption was tested by allowing for a different E_{max} for each DPP-4 inhibitor. Dose is the total daily dose and ED_{50} is the dose to achieve 50% of E_{max}. A different ED_{50} was estimated for each drug.

Factors such as background treatment and baseline HbA1c were included as covariates on the parameter E_{max} in the model. Additional random between-trial heterogeneity in the relative effect between arms was accounted for by the trial-specific model parameters that were assumed to be normally or log-normally distributed with between-trial variance Ω. Model selection was based on a Log likelihood ratio test and the confidence interval of the parameter estimate at an acceptance P value of 0.01. Confidence intervals of the parameter estimates were derived from the variance matrix of the parameter estimates.[35,36]

For DPP-4 inhibitors, both apparent onset and durability of drug-related effects on HbA1c were estimated. For TAK-875 (due to lack of long-term data), only the onset effect on HbA1c was estimated. To take a conservative approach, the "offset" of TAK-875 related effects (i.e., the durability of TAK-875-related effects) on HbA1c was assumed to be the same as that of DPP-4 inhibitors.[37]

Simulations for projection and comparison of long-term efficacy. The final PK and efficacy models were used to perform simulations to predict TAK-875, FPG, and HbA1c concentrations following administration of 25- and 50-mg q.d. doses of TAK-875 over a period of 6 months (24 weeks). The simulations were used to support dose selection for future studies and also to compare the efficacy of TAK-875 with currently approved pharmacological T2DM therapies. The simulations were performed using a population of 1,000 patients receiving 25- and 50-mg multiple q.d. doses of TAK-875. These sets of simulations assumed durability of efficacy responses beyond 12 weeks, which was the duration of this clinical trial used to generate data utilized to develop PK and efficacy models for TAK-875.

The developed meta-analysis model for HbA1c utilizing publicly available clinical trial outcomes data was also used to project time-response curves for DPP-4 inhibitors (reference drug class) and TAK-875 at the selected therapeutic dose of 50 mg up to 24 weeks. Baseline HbA1c was set to 8.5%, i.e., the baseline value observed in the phase 2 study.[10] A time-response curve for DPP-4 inhibitors (drug class) at therapeutic doses was projected up to 24 weeks (linagliptin 5 mg, saxagliptin 2.5 mg, sitagliptin 100 mg, and vildagliptin 100 mg). In addition, dose–efficacy response curves of DPP-4 inhibitors (reference drug class) and TAK-875 were also characterized.

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Conflict of interest. H.N., E.L., C.C., and M.V. are employees of Takeda Global Research & Development Center, Inc., Deerfield, IL; J.L. and M.P. are employees of Quantitative Solutions, Inc., Bridgewater, NJ.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

GPR40 or free fatty acid receptor 1, expressed in pancreatic β, has become a drug target for treatment of T2DM. GPR40 agonists increase glucose-stimulated insulin secretion and have demonstrated beneficial effects in various preclinical models of T2DM. TAK-875 is a novel and first GPR40 agonist in phase 3 clinical development. TAK-875 produces a similar glucose-lowering effect as sulphonylureas with a considerably lower potential for hypoglycemia.

WHAT QUESTION DID THIS STUDY ADDRESS?

The analysis describes the pharmacometric approaches that guided the selection of TAK-875 dose for phase 3 studies in patients with type 2 diabetes.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

This analysis demonstrates the importance of pharmacometric approaches for rationale therapeutic dose selection for phase 3 trial.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS?

The analysis presented emphasizes the importance of model-based drug development approach for the clinical development of drugs. The pharmacometric approaches implemented in this analysis provided a quantitative rationale for the dose selection and a comparative analysis to compare the efficacy of TAK-875 with marketed product (DPP4i).

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