Drugs of the Future 2011, 36(11): 813-818

CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.11.1722071

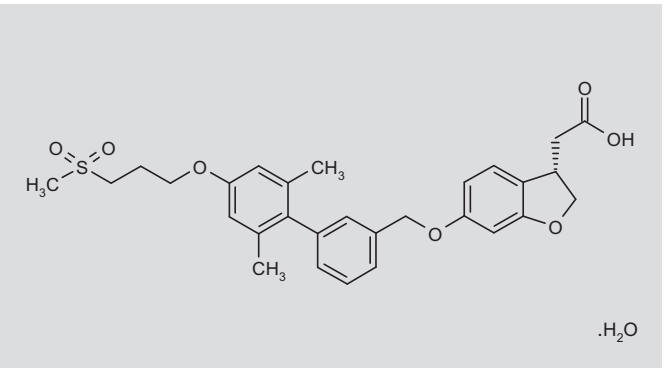
MONOGRAPH

TAK-875

Free Fatty Acid Receptor FFA1 Agonist
Insulin Secretagogue
Treatment of Type 2 Diabetes

2-[6-[2',6'-Dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-ylmethoxy]-2,3-dihydro-1-benzofuran-3(*S*)-yl]acetic acid hydrate

InChI: 1S/C29H32O7S.H2O/c1-19-12-25(34-10-5-11-37(3,32)33)13-20(2)29(19)22-7-4-6-21(14-22)17-35-24-8-9-26-23(15-28(30)31)18-36-27(26)16-24;/h4,6-9,12-14,16,23H,5,10-11,15,17-18H2,1-3H3,(H,30,31);1H2/t23-;/m1./s1



$C_{29}H_{34}O_8S$
Mol wt: 542.64
EN: 642642

SUMMARY

TAK-875 is a free fatty acid receptor 1 (FFA1R/GPR40) agonist, the first in this novel class of antidiabetic agents to enter clinical development. It is a glucose-dependent insulinotropic agent, with a mechanism of action that is novel among insulinotropic drugs, including sulfonylureas, incretins and meglitinides. Single oral doses of TAK-875 stimulate enhanced glucose-dependent insulin secretion and improve postprandial and fasting hyperglycemia, with a low risk of hypoglycemia and no evidence of beta cell toxicity, in preclinical testing. It is well tolerated and has demonstrated efficacy in phase I and II clinical trials, with rapid and effective improvements in postprandial and fasting hyperglycemia, glycosylated hemoglobin-lowering activity, and a low risk of hypoglycemia in patients with type 2 diabetes. TAK-875 is currently undergoing phase III testing in Japan and phase II testing in the U.S. and Europe.

J. de Lartigue, PhD. 16 Maultway Crescent, Camberley, Surrey GU15 1PN, UK. E-mail: jdelartigue@gmail.com.
*Synthesis prepared by R. Castañer, C. Estivill, J. Bolòs. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

SYNTHESIS*

Suzuki coupling of 4-bromo-3,5-dimethylphenol (I) with 3-formylphenylboronic acid (II) in the presence of $Pd(PPh)_3$ and Na_2CO_3 in EtOH/toluene at 80 °C affords 4'-hydroxy-2',6'-dimethylbiphenyl-3-carbaldehyde (III), which is then condensed with 3-(methylsulfonyl)propyl tosylate (IV) by means of K_2CO_3 at 90 °C in DMF to give 2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-carbaldehyde (V). Reduction of aldehyde (V) with $NaBH_4$ in MeOH/THF at 0 °C produces the corresponding alcohol (VI), which upon Mitsunobu condensation with methyl [6-hydroxy-2,3-dihydro-1-benzofuran-3(*S*)-yl]acetate (VII) in the presence of Bu_3P and ADDP in toluene yields the corresponding ether (VIII). Finally, ester (VIII) is hydrolyzed with NaOH in MeOH/THF/H_2O at 50 °C (1, 2). Scheme 1.

3-(Methylsulfonyl)propyl tosylate (IV) is prepared by sulfonylation of 3-(methylsulfanyl)-1-propanol (IX) using TsCl in the presence of TMHDA and Et_3N in toluene to produce the corresponding tosylate (X), which is finally oxidized with oxone in MeOH/H_2O (1, 2). Scheme 1.

Methyl [6-hydroxy-2,3-dihydro-1-benzofuran-3(*S*)-yl]acetate (VII) is synthesized as follows:

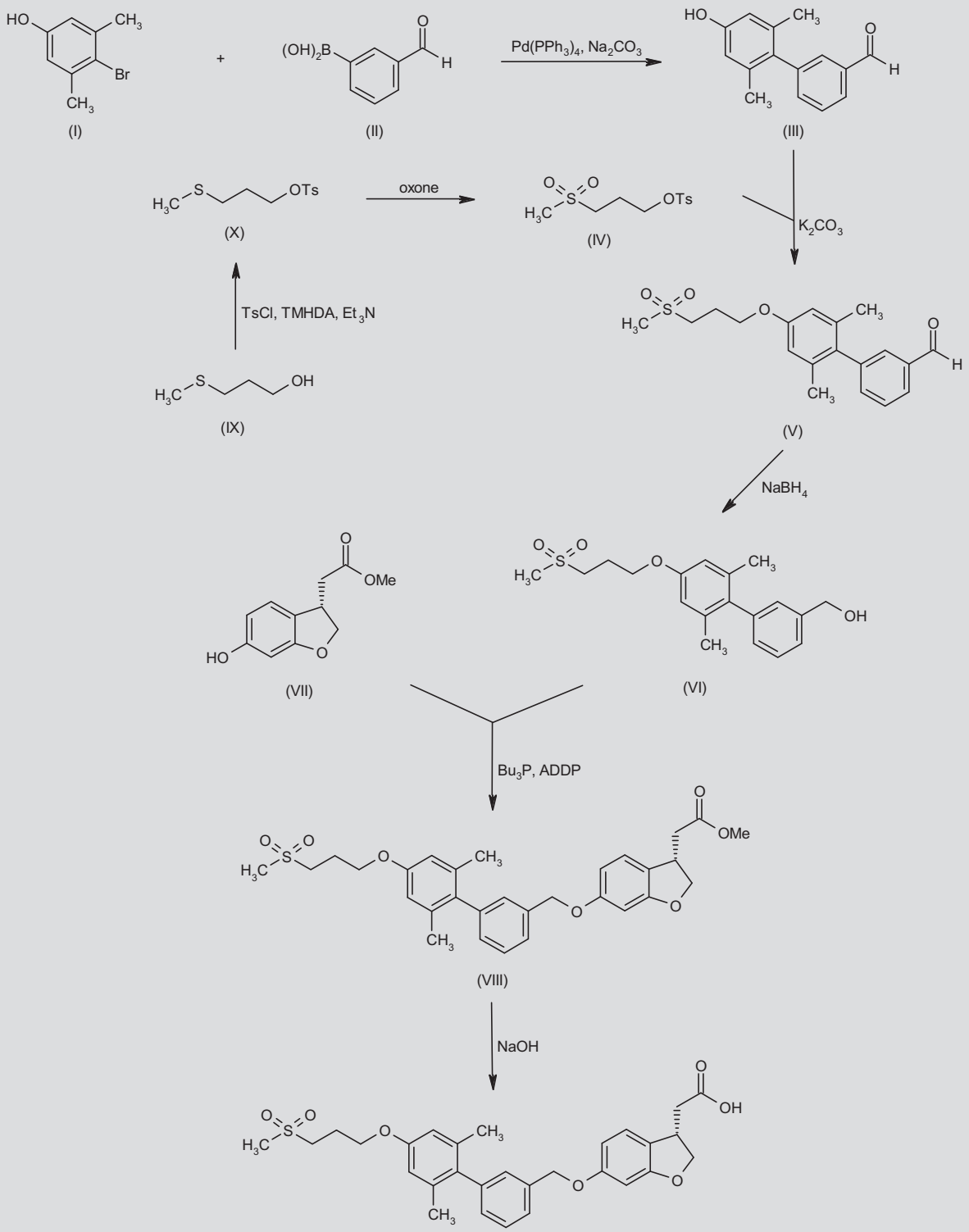
Cyclization of resorcinol (XI) with ethyl 4-chloroacetoacetate (XII) by means of H_2SO_4 gives 4-(chloromethyl)-7-hydroxychromen-2-one (XIII), which by treatment with NaOH at reflux affords (6-hydroxybenzofuran-3-yl)acetic acid (XIV). Esterification of carboxylic acid (XIV) with MeOH in the presence of H_2SO_4 at reflux yields the corresponding methyl ester (XV), which is hydrogenated over Pd/C in MeOH to provide (±)-methyl (6-hydroxy-2,3-dihydro-1-benzofuran-3-yl)acetate (XVI) (1, 2). Finally, the (*S*)-enantiomer (VII) is isolated by preparative HPLC (1). Scheme 2.

Alternatively, intermediate (XV) can be reduced by H_2 in the presence of bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate and (*S,S*)-Et-ferrotane in the presence of NaOMe in MeOH (2). Scheme 2.

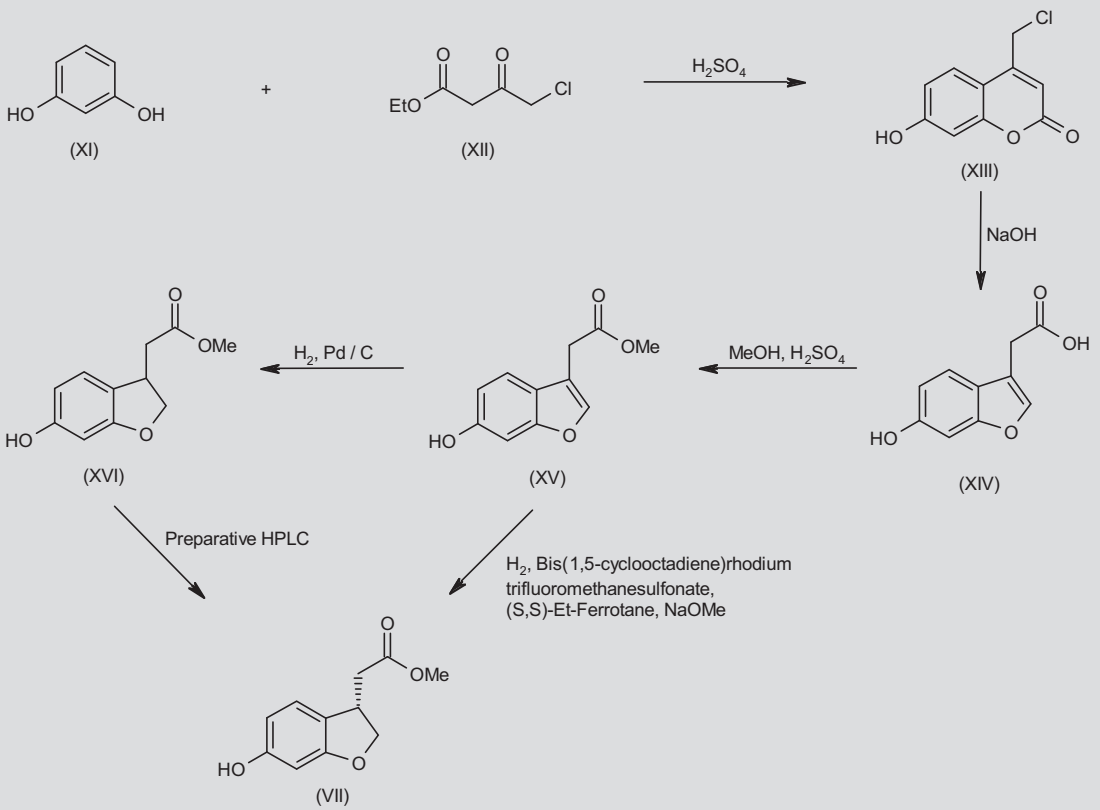
BACKGROUND

Type 2 diabetes (T2D) is a progressively debilitating disorder of increasing worldwide prevalence that is characterized by insulin resistance or reduced insulin sensitivity, combined with reduced

Scheme 1. Synthesis of TAK-875



Scheme 2. Synthesis of Compound (VII)



insulin secretion from pancreatic beta cells. Achieving optimal glycemic control is a priority for the effective management of T2D in order to minimize the risk of long-term macro- and microvascular complications, which are associated with serious morbidity and mortality. Current treatment regimens, including insulin secretagogues such as sulfonylureas, carry an inherent risk of hypoglycemia, which may accelerate loss of pancreatic beta cell function (3), and cardiovascular side effects (4-6). There is therefore a need for new therapies with novel mechanisms of action that offer effective glycemic control with minimal adverse events (AEs) and also allow the potential for optimal combination therapy with existing treatments.

Recent advances have heralded the development of new secretagogue drug targets with a unique mechanism of action, including dipeptidyl peptidase 4 (DPP IV) inhibitors and glucagon-like peptide 1 (GLP-1) analogues (7). In theory, these drugs, which amplify glucose-stimulated insulin secretion (GSIS) and thereby have a glucose-lowering activity that is dependent on plasma glucose levels, could overcome some of the side effects associated with current therapies. GSIS from pancreatic beta cells is also prompted by nutrients, including free fatty acids (FFAs), which are both an important energy source and also act as signaling molecules in the cell (8, 9). Aberrant FFA-mediated functions could plausibly lead to increased insulin resistance and beta cell dysfunction.

The human genome encodes for 865 G-protein coupled receptors (GPCRs), which have historically been a prime target for drug discovery. Over 100 of these receptors are "orphan", with as yet unidentified ligands and functions (10, 11). Recently, several GPCRs were deorphanized, including GPR40, which was identified as a receptor for medium- (C6-C12) and long-chain (C14-C24) fatty acids (12).

GPR40 belongs to a family of GPCRs that include GPR40, GPR41, GPR43 and GPR120. It is highly and predominantly expressed in the pancreas, particularly in pancreatic islets, with comparable expression levels to the GLP-1 and sulfonylurea receptors. In pancreatic beta cell lines (MIN-6 and INS-1E), siRNA targeting GPR40 prevented FFA-stimulated insulin secretion, confirming that GPR40 is involved in stimulation of acute GSIS (12, 13). Several studies suggest that GPR40 couples mainly with the G protein alpha subunit of the Gq family ($G\alpha q$), activating $G\alpha q$ signaling, leading to release of calcium from the endoplasmic reticulum, upregulation of calcium influx through L-type calcium channels and, ultimately, enhanced insulin secretion in a glu-

cose-dependent manner (12-14). Potent and selective FFA1 receptor agonists could function as glucose-dependent insulin secretagogues and may prove to be effective antidiabetic drugs with a novel mechanism of action and little or no risk of hypoglycemia.

Several FFA1 receptor agonists have been identified in recent years (15). The most advanced agonist in the R&D pipeline is TAK-875 (Takeda Pharmaceutical Co., Ltd.), which is currently in phase III trials in Japan and phase II trials in the U.S. and Europe. In October 2011, Takeda announced its intention to progress to phase III clinical testing of TAK-875 in the U.S. and Europe.

PRECLINICAL PHARMACOLOGY

Takeda identified a range of potential synthetic FFA1 receptor agonists using ligand-based drug design and an arylalkanoic acid scaffold, and screened for activity using a fluorometric imaging plate reader (FLIPR) assay. Benzyloxyphenylpropanoic acids were selected as a promising lead series. A medicinal chemistry approach was employed to suppress metabolism and reduce lipophilicity. Cyclization of the phenylpropanoic acid moiety of the lead compound produced fused phenylalkanoic acids that had favorable in vitro agonist activity and pharmacokinetic profiles. Further optimization ultimately led to the discovery of TAK-875 (1).

Preclinical studies of TAK-875 have shown that it has high selectivity and binding affinity for the human FFA1 receptor over other closely related GPCRs; the half-maximal effective concentration (EC_{50}) of TAK-875 for the human FFA1 receptor was 0.014 μM, compared to values above 10 μM for the other receptors, while the K_i was 0.038 μM. This specificity was reportedly achieved in the drug design process by moving away from the fatty acid structure and reducing lipophilicity. Several modeling studies verified the interaction between TAK-875 and the FFA1 receptor, in which three groups of interactions were observed through which TAK-875 is thought to exert its FFA1 receptor agonist activity (1).

A number of studies using both primary cells and pancreatic cell lines have examined the in vitro pharmacological effects of TAK-875 on insulin secretion and beta cell function. Acute stimulation with TAK-875 was compared to the sulfonylurea glibenclamide in primary rat islets and an INS-1 833/15 insulinoma cell line (a model of pancreatic beta cells). Both TAK-875 and glibenclamide caused an increase in insulin secretion; however, unlike glibenclamide, the insulinotropic action of TAK-875 was found to be dependent on the glucose concentration. Examination of the EC_{50} for inositol monophosphate (IP) production in Chinese hamster ovary (CHO) cells expressing human FFA1 demonstrated that stimulation with TAK-875 leads to an increase in intracellular IP and calcium concentrations. This is consistent with activation of the Gαq signaling pathway, the proposed mechanism of action of FFA stimulation of GSIS. The agonist action of TAK-875 was 400-fold more potent than the endogenous FFA ligand, oleic acid, requiring much lower concentrations to activate the receptor. This was reflected in the respective EC_{50} for IP, which was 0.072 μM for TAK-875 and 29.2 μM for oleic acid (16, 17).

The in vivo pharmacological effects of TAK-875 on glucose tolerance and insulin secretion have been examined in a variety of animal models. An oral glucose tolerance test (OGTT) in a diabetic rat model (Wistar fatty rats, which develop obesity and obesity-related features such as impaired glucose tolerance, hyperinsulinemia and hyperlipidemia) demonstrated that administration of a single oral dose of TAK-875 prior to oral glucose challenge decreased blood glucose excursions and increased insulin secretion, with a minimum effective dose of 1 mg/kg (1). In type 2 diabetic N-STZ-1.5 rats with impaired postprandial glucose tolerance, there was a dose-dependent improvement in glucose tolerance and increase in insulin secretion upon administration of a single oral dose of TAK-875 (1-10 mg/kg) (17).

The glucose-dependent insulinotropic effects of TAK-875 demonstrated in vitro were confirmed in in vivo studies using male Zucker diabetic fatty (ZDF) rats as a model of hyperglycemia and normal Sprague–Dawley rats as a model of fasting normoglycemia. While TAK-875 (10 mg/kg) increased plasma insulin levels and decreased fasting plasma glucose levels in the ZDF rats, it did not alter fasting glucose levels in the normal Sprague–Dawley rats, even at concentrations as high as 30 mg/kg, demonstrating that TAK-875 exerts its effects on insulin secretion only when blood glucose levels are increased. In contrast, the sulfonylurea glibenclamide, although leading to a significant increase in plasma insulin levels, also caused a decrease in plasma glucose levels to below normal fasting levels. Furthermore, single oral administration of TAK-875 in ZDF rats resulted in more potent improvement of fasting hyperglycemia than glibenclamide and the meglitinide nateglinide (17).

FFAs have pleiotropic effects on beta cells, with evidence suggesting that while acute exposure promotes GSIS, chronic exposure leads to lipotoxicity and impairs beta cell function and secretory capacity. It is unclear whether the chronic effects of FFAs are mediated by GPR40, but it raises concerns as to whether prolonged treatment with agonists, such as TAK-875, may lead to lipotoxicity. Thus, the effects of chronic stimulation, over a 72-hour period, of TAK-875 on beta cell function and apoptosis were also examined in preclinical studies. At pharmacologically active concentrations in the cytokine-sensitive INS-1 823/13 insulinoma cell line, TAK-875 had no prolonged effect on insulin secretion or insulin content and did not affect caspase-3/7 activity, demonstrating that chronic exposure does not cause beta cell dysfunction or apoptosis. Similar exposure to the FFA palmitic acid, on the other hand, did cause increased insulin secretion, insulin content and caspase-3/7 activity (16). The metabolic effects of chronic administration (72 hours) of TAK-875 were also examined in vivo in female Wistar fatty rats. A dose-dependent decrease in glycosylated hemoglobin (HbA1c) levels was observed, with no effects on body weight or pancreatic insulin content.

These preclinical studies suggested that TAK-875 acts directly on pancreatic beta cells to increase GSIS when blood glucose levels are elevated, improving both postprandial and fasting hyperglycemia, with no evidence of prolonged effects on beta cell function. The binding of TAK-875 to the human FFA1 receptor was shown to be stronger than for the rat receptor (K_i = 0.038 μM vs. 0.14 μM), suggesting that these promising preclinical findings in rat models may translate into a potential treatment for T2D, with a novel mechanism of action that could be added to existing treatment regimens to allow optimal combination therapy. Indeed, one study examined the effects of a combination of TAK-875 with the oral antidiabetic agent metformin in ZDF rats. A combination of TAK-875 (3 mg/kg) and

metformin (50 mg/kg) additively decreased fasting plasma glucose compared to either monotherapy. In a subsequent multiple-dose study a combination of twice-daily TAK-875 and once-daily metformin additively decreased HbA1c levels and fasting plasma insulin compared to monotherapy with either TAK-875 or metformin, while pancreatic insulin remained the same as in control rats, suggesting that a combination of TAK-875 and metformin has the potential to effectively treat diabetes and improve beta cell function (18).

PHARMACOKINETICS AND METABOLISM

Preclinical studies of the pharmacokinetics (PK) and metabolism of TAK-875 demonstrated an excellent PK profile in rats and dogs. It exhibited a low plasma clearance (CL) of 34.16 mL/h/kg in rats and 29.79 mL/h/kg in dogs, and a low volume of distribution of 208.49 and 224.67 mL/kg, respectively, resulting in a sustained half-life ($t_{1/2}$ = 4.7 and 5.9 hours, respectively). Oral administration exhibited rapid absorption, with a t_{max} of 1 and 2 hours, respectively, high C_{max} and plasma exposure, and high bioavailability (29.45%) (1).

Several clinical studies in healthy human subjects have examined the PK characteristics of TAK-875 following single oral ascending doses and multiple daily dosing. A randomized, double-blind phase I trial of single ascending oral doses of TAK-875 (25, 50, 100, 200, 400 or 800 mg) compared to placebo in 60 healthy male and female volunteers demonstrated that TAK-875 is eliminated slowly, with a $t_{1/2}$ for TAK-875 and its principal metabolite, M-I, of 28-37 hours (19, 20), suggesting that TAK-875 is suitable for once-daily dosing. Mean oral clearance ranged from 0.88 to 1.70 L/h, with only a fraction of the dose excreted as TAK-875 (≤ 0.32%). Systemic exposure exhibited a dose-proportional increase up to doses of 200 mg, with a slight deviation from dose-proportional increases at higher doses. However, this deviation is unlikely to be clinically relevant given that these doses are outside the therapeutic range. Only a fraction of TAK-875 and the M-I metabolite were excreted into the urine intact, suggesting that nonrenal clearance, including hepatic metabolism, is the predominant route of clearance. This could offer a potential advantage for T2D patients with renal insufficiency, although further investigation is required to confirm this. Using a double-blind, randomized, crossover design, a preliminary food effect assessment was conducted on a 200-mg dose following a 7-day washout. There was no substantial change in systemic exposure to TAK-875 in response to a high-fat meal, suggesting that TAK-875 could be administered with or without a meal.

Two randomized, double-blind, placebo-controlled phase I trials assessed single oral ascending doses of TAK-875 (25, 50, 100, 200, 400 or 800 mg; n = 9/group) under fasting conditions, and multiple dosing of 200 and 400 mg of TAK-875 administered once daily over a 14-day period in healthy male Japanese subjects. In the single-dose study there was an approximately dose-proportional increase in AUC and C_{max}, with a t_{max} of 3-4 hours and a $t_{1/2}$ of 21-28 hours. The multiple-dose study demonstrated a 1.7-fold increase in AUC and C_{max} to almost steady-state levels, suggesting no time-dependent PK for TAK-875 (21). These studies also confirmed that there was no change in systemic exposure upon feeding and negligible renal excretion of TAK-875.

SAFETY

The safety and tolerability of TAK-875 were also reported in clinical testing and it was generally found to be well tolerated, with an excellent safety profile. Of particular note was the low incidence of hypoglycemic events, which adds further support to the hypothesis that the novel glucose-dependent mechanism of TAK-875 may help to mitigate the hypoglycemic risks observed with other T2D treatments.

In phase I trials no serious AEs were reported and AEs were generally mild and transient, exhibiting no dose-dependent pattern (19). Both single and multiple doses of TAK-875 were well tolerated, with no hypoglycemic events reported (21).

A phase II trial of once-daily dosing of TAK-875 (200 or 400 mg) over a 2-week period also reported no serious AEs and mild AEs that were not dose-dependent. In the larger, dose-ranging phase II study of TAK-875 (6.25-200 mg) over 12 weeks, there were few discontinuations as a result of AEs related to TAK-875. Furthermore, treatment-related AEs were lower compared to glimepiride. Importantly, the number of hypoglycemic episodes was significantly less in the TAK-875-treated group compared to the glimepiride-treated group, and was comparable to placebo (2.3 vs. 16 vs. 3.3) (22).

CLINICAL STUDIES

The phase I trials previously mentioned also examined the effects of TAK-875 on insulin secretion and blood glucose levels in healthy patients. Consistent with the hypothesis that TAK-875 only exerts its insulinotropic effects when blood glucose levels are elevated, there was no glucose-lowering effect and no increase in insulin or C-peptide secretion in healthy volunteers upon administration of a single oral dose of TAK-875, and the frequency of blood glucose concentrations < 70 mg/dL was comparable between the TAK-875- and placebo-treated groups. This supports the preclinical findings relating to the mechanism of action of TAK-875 and further suggests that TAK-875 would likely pose a low risk of hypoglycemia in T2D patients (19).

A randomized, double-blind, placebo-controlled phase II study examined the effect of once-daily dosing of TAK-875 100 or 400 mg over 2 weeks in Japanese patients with T2D. TAK-875 was observed to rapidly and effectively improve both postprandial and fasting hyperglycemia. Following a 75-g OGTT, there was a significant decrease in plasma glucose, fasting plasma glucose and $AUC_{0\text{-}3h}$ of plasma glucose in the TAK-875-treated groups, with a larger effect in the 400-mg group compared to the 200-mg group. There was also a dose-dependent increase in the $AUC_{0\text{-}3h}$ of insulin in the TAK-875 group (23).

A second randomized, double-blind, placebo- and active-controlled, dose-ranging phase II study examined the effects of TAK-875 (6.25-200 mg) once daily in 426 T2D patients over 12 weeks in comparison to the sulfonylurea glimepiride. All doses of TAK-875 were found to reduce HbA1c levels at week 12 comparable to doses of ≥ 50 mg glimepiride. Compared to placebo, twice as many patients treated with TAK-875 doses of ≥ 25 mg achieved an HbA1c < 7% at week 12, similar to glimepiride (22).

DRUG INTERACTIONS

Interactions of TAK-875 with other antidiabetic agents or other medications have yet to be investigated. This will be an important

future area of study, especially if TAK-875 is to be used in combination with other antidiabetic agents in the effective treatment of patients with T2D.

SOURCE

Takeda Pharmaceutical Co., Ltd. (JP).

DISCLOSURES

The author is a freelance medical writer based in the U.K., affiliated with Jane de Lartigue Scientific Communications, and has no significant financial relationships or conflicts of interest to disclose.

REFERENCES

1. Negoro, N., Sasaki, S., Mikami, S. et al. *Discovery of TAK-875: A potent, selective, and orally bioavailable GPR40 agonist.* ACS Med Chem Lett 2010, 1: 290-4.
2. Yasuma, T., Negoro, N., Yamashita, M., Itou, M. (Takeda Pharmaeutical Co., Ltd.). *Fused cyclic compounds*. CA 2656003, EP 2041123, EP 2248812, JP 2009280585, JP 2009542580, US 2010004312, US 7732626, WO 2008001931.
3. Maedler, K., Carr, R., Bosco, D., Zuellig, R., Berney, T., Donath, M. *Sulfonylurea induced beta-cell apoptosis in cultured human islets.* J Clin Endocrinol Metab 2005, 90(1): 501-6.
4. Cryer, P. *Hypoglycemia: The limiting factor in the glycaemic management of type I and type II diabetes.* Diabetologia 2002, 45(7): 937-48.
5. Burge, M., Sood, V., Sobhy, T., Rassam, A., Schade, D. *Sulfonylurea-induced hypoglycemia in type 2 diabetes mellitus: A review.* Diabetes Obes Metab 1999, 1(4): 199-206.
6. Tzoulaki, I., Molokhia, M., Curcin, V. et al. *Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: Retrospective cohort study using UK general practice research database.* BMJ 2009, 339: b4731.
7. Drucker, D., Nauck, M. *The incretin system: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes.* Lancet 2006, 368(9548): 1696-705.
8. Prentki, M., Tonkheim, K., Corkey, B. *Signal transduction mechanisms in nutrient-induced insulin secretion.* Diabetologia 1997, 40(Suppl. 2): S32-41.
9. Haber, E., Ximenes, H., J, P., Carvahlo, C., Curi, R., Carpinelli, A. *Pleiotropic effects of fatty acids on pancreatic beta-cells.* J Cell Physiol 2003, 194(1): 1-12.
10. Schyler, S., Horuk, R. *I want a new drug: G-protein-coupled receptors in drug development.* Drug Discov Today 2006, 11(11-12): 481-93.
11. Milligan, G. *G-protein-coupled receptor heterodimers: Pharmacology, function and relevance to drug discovery.* Drug Discov Today 2006, 11(11-12): 541-9.
12. Itoh, Y., Kawamata, Y., Harada, M. et al. *Free fatty acids regulated insulin secretion from pancreatic beta cells through GPR40.* Nature 2003, 422(6928): 173-6.
13. Shapiro, H., Shachar, S., Sekler, I., Hershfinkel, M., Walker, M. *Role of GPR40 in fatty acid action on the beta cell line INS-1E.* Biochem Biophys Res Commun 2005, 335(1): 97-104.
14. Fujiwara, K., Maekawa, F., Yada, T. *Oleic acid interacts with GPR40 to induce Ca^{2+} signaling in rat islet beta-cells: Mediation by PLC and L-type Ca^{2+} channel and link to insulin secretion.* Am J Physiol Endocrinol Metab 2005, 289(4): E670-E7.
15. Bharate, S., Nemmani, K., Vishwakarma, R. *Progress in the discovery and development of small-molecule modulators of G-protein-coupled receptor 40 (GPR40/FFA1/FFA1R): An emerging target for type 2 diabetes.* Expert Opin Ther Pat 2009, 19(2): 237-64.
16. Takeuchi, K., Tsujihata, Y., Ito, R., Suzuki, M., Harada, A. *A selective GPR40 agonist, TAK-875, stimulates glucose-dependent insulin secretion without beta cell toxicity and decreases blood glycosylated haemoglobin levels in diabetic rats.* Diabetologia 2010, 53(Suppl 1): Abst 882.
17. Tsujihata, Y., Ito, R., Suzuki, M. et al. *TAK-875, an orally available GPR40/FFA1 agonist enhances glucose-dependent insulin secretion and improves both postprandial and fasting hyperglycemia in type 2 diabetic rats.* J Pharmacol Exp Ther 2011, 339(1): 228-37.
18. Matsuda-Nagasumi, K., Ito, R., Tsujihata, Y., Takeuchi, K. *Improved glycemic control and beta cell function by treatment with TAK-875, a GPR40 agonist, in combination with metformin in Zucker diabetic fatty rats*. 47th Annu Meet Eur Assoc Study Diabetes (EASD) (Sept 12-16, Lisbon) 2011, Abst 187:
19. Naik, H., Vakilynejad, M., Wu, J., Viswanathan, P., Dote, N., Higuchi, T., Leifke, E. *Safety, tolerability, pharmacokinetics, and pharmacodynamic properties of the GPR40 agonist TAK-875: Results from a double-blind, placebo-controlled single oral dose rising study in healthy volunteers.* J Clin Pharmacol 2011, Epub ahead of print.
20. Vakily, M., Wu, J., Viswanathan, P., Leifke, E. *A safety, tolerability, pharmacokinetics, and pharmacodynamics and preliminary food-effect study of TAK-875 GPR40 agonist, following oral administration of sequential ascending single doses to healthy subjects.* Diabetes 2010, 59(Suppl. 1): Abst 630-P.
21. Matsuno, K., Hirayama, M., Araki, T., Dote, N., Kondo, T. *Pharmacokinetics, safety and tolerability of single and multiple doses of TAK-875, a novel GPR40 agonist, in Japanese healthy male subjects.* Diabetes 2010, 59(Suppl. 1): Abst 707-P.
22. Viswanathan, P., Marcinak, J., Cao, C., Xie, B., Vakilynejad, M., Leifke, E. *A randomized, double blind, placebo- and active-controlled, dose-ranging study to determine the efficacy and safety of the novel GPR40 agonist TAK-875 in patients with type 2 diabetes mellitus*. 47th Annu Meet Eur Assoc Study Diabetes (EASD) (Sept 12-16, Lisbon) 2011, Abst 187.
23. Araki, T., Hirayama, M., Hiroi, S., Kaku, K. *TAK-875, a novel GPR40 agonist, improves both postprandial and fasting hyperglycemia in Japanese patients with type 2 diabetes*. 71st Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 24-28, San Diego) 2011, Abst 0312-OR.