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Monograph

Imeglimin in type 2 diabetes

Jessica Huston[1], Hannah Schaffner[2], Logan Langley[1,2], Blake Skrable[2], Andrea Ashchi[2], Jason Berner[3], Ashwini Gore[4], Mae Sheikh-Ali[5], David Sutton[5] and Rebecca Goldfaden[2]

[1]University of Florida, College of Pharmacy, Jacksonville, Florida, USA; [2]East Coast Institute for Research, Jacksonville, Florida, USA; [3]Georgia Mountain Endocrinology, Canton, Georgia, USA; [4]The Jones Center, Macon, Georgia, USA; [5]Northeast Florida Endocrine & Diabetes Associates, Jacksonville, Florida, USA

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Summary

Type 2 diabetes mellitus is a chronic disease most often characterized by increased glucose levels. When blood glucose levels are inadequately controlled or left untreated, the result is a variety of microvascular and macrovascular complications. To prevent these outcomes, many medications are available to manage type 2 diabetes mellitus and prevent disease progression. However, most of the medications available to date only target a few of the physiological defects caused by diabetes and may come with side effects that make adherence to the medication improbable. Imeglimin, a medication currently under investigation in the United States and approved in Japan, is a novel, first-in-its-class medication with a mechanism that is currently understood to target multiple pathways to provide glycemic control. This review aims to present and discuss the current clinical and scientific evidence pertaining to imeglimin.

Correspondence: Rebecca F. Goldfaden, PharmD, East Coast Institute for Research, Jacksonville, FL, USA. E-mail: rg@eastcoastresearch.net.

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Background

Over nine classes of medications exist and are approved for the treatment of type 2 diabetes mellitus (T2DM), yet the disease state remains one of the leading causes of death in the United States. An astounding 11.3% of the United States population has diabetes and another 38.0% or 96 million people aged 18 years or older in the United States have prediabetes according to the Centers for Disease Control and Prevention (1). With increasing prevalence and healthcare costs associated with T2DM, novel mechanisms and pathways are continuously under review to address the needs of patients in achieving their glycemic goals.

Researchers have identified several pathways successful in achieving significant reductions in blood glucose levels, with the newest medications in the sodium/glucose cotransporter 2 inhibitor (SGLT2-I) and glucagon-like peptide 1 receptor agonist (GLP-1RA) classes (2). However, these medications often come with a variety of adverse effects such as gastrointestinal (GI) symptoms and genital yeast infections. While these medications are recommended by the American Diabetes Association (ADA) due to their safety and efficacy profiles, some patients are still unable to attain their individualized blood glucose levels. Recently, medications using pathways with multiple targets have been the focus of research.

There are three main physiological defects associated with T2DM: increased glycogenesis in the liver, impaired insulin secretion from the pancreas and insulin resistance in muscles (3). A multifactorial approach which aims to correct the major flaws associated with T2DM while minimizing adverse side effect profiles can be expected to have a substantial impact on patients who are struggling to achieve or maintain glycemic control. Imeglimin, a novel medication and first in its class, is suggested to appropriate several of these barriers and is currently in clinical studies to determine its safety and efficacy in patients with T2DM (4).

Imeglimin Molecule and Properties

Imeglimin hydrochloride (PXL-008, Twymeeg; Poxel/Sumitomo) (Fig. 1) is the first agent in a new class of oral tetrahydrotriazine-containing drugs, with many promising effects for treating T2DM (5). Its chemical name, (6*R*)-(+)-4-dimethylamino-2-imino-6-methyl-1, 2,5,6-tetrahydro-1,3,5-triazine hydrochloride, places it in the "glimins" class, which carries out its antidiabetic effects by targeting multiple organ systems that are affected by T2DM (3, 6).

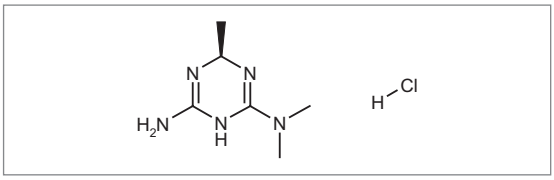

Figure 1. Chemical structure of imeglimin hydrochloride.

Mechanism of Action

Imeglimin's mechanism of action is complex and still relatively unknown; however, there are several recognized pathways that are known to treat induced abnormalities of T2DM where imeglimin plays a role (7). Imeglimin's unique abilities include focuses on increased hepatic glucose production, decreased glucose uptake by tissues, abnormally low levels of insulin secretion, and increased β-cell apoptosis (8, 9).

First, imeglimin has shown an ability to reduce hepatic gluconeogenesis (9). In 2014, a study led by Guillaume Vial investigated the underlying mechanism by which imeglimin affects hepatic gluconeogenesis in rat hepatocytes compared to metformin (8). It was found that both metformin and imeglimin inhibited glucose production, but imeglimin, unlike metformin, did not affect the level of mitochondrial respiration (8). Instead, imeglimin triggered a competitive mitochondrial complex I inhibition, which is enabled by an increase in redox potential and a decrease in mitochondrial membrane potential (8). The ATP/ADP ratio is therefore decreased, independently of inorganic phosphate levels, resulting in

less energy per ATP available (8). The gluconeogenesis pathway, which is dependent on the availability of ATP for glucose production, is therefore inhibited (8). Since this pathway avoids affecting mitochondrial respiration, there is no risk of lactic acidosis, resulting in a safer risk profile of imeglimin than that of metformin (8).

Another one of these pathways is imeglimin's ability to preserve overall β-cell life and promote its function (10). A study completed in 2018, led by Sandrine Lablanche, investigated imeglimin's role in potentially preventing glucose-induced β-cell death (10). Normally, high levels of glucose in INS-1 cells and human islets results in the opening of a mitochondrial channel called PTP (permeability transition pore), which is an action linked to self-administered cell death (10). In this study, this same pathway was replicated with and without the presence of imeglimin, with PTP status verified through the monitoring of mitochondrial membrane potential and overall cell status verified through monitoring of flow cytometry (10). In cells without imeglimin, cell viability decreased, which was a consequence of increased rates of PTP openings throughout the cell colony (10). However, cells incubated with imeglimin saw no significant change in cell viability nor PTP channel openings. This demonstrates that one of imeglimin's effects is PTP inhibition, resulting in prevention of β-cell mass loss due to high levels of glucose (10).

Another study completed in 2016 analyzed the mechanism of action of imeglimin's effect on promoting glucose-stimulated insulin secretion (GSIS) in rat islets (11). Upon treatment with glucose and imeglimin, islets experienced increased levels of nicotinamide adenine dinucleotide (NAD), through NAD synthesis (11). CD38, a catalytic glycoprotein, is then able to convert NAD into agents responsible for insulin secretion (11). This effect was observed through the 51% increase in GSIS in the rat islets, highlighting increased β-cell activity through imeglimin (11).

Imeglimin is also responsible for improving insulin sensitivity through increased mitochondrial activity as a result of lower oxidative stress. A study completed in 2014 that tested the effect of imeglimin in liver mitochondria of high-fat, high-sucrose diet (HFHSD) mice demonstrated this effect (8). HFHSD mice, without imeglimin, experienced an increased composition of triglycerides, DAG (diacylglycerol), and cholesterol within liver cells (8). Increased lipids in the liver lead to a condition known as liver steatosis. This disease state is associated with inhibited insulin signaling through changes affecting normal mitochondrial processes. However, when HFHSD mice were treated with imeglimin, there were several effects. Primarily, all lipids (triglycerides, DAG, cholesterol) in the liver were reduced, reversing the onset of liver steatosis (8). In addition, imeglimin also affected the oxidative phosphorylation pathway: there was inhibition of complex I activity and reactive oxygen species (ROS) production as well as re-establishment of complex III activity. The alterations made in this pathway enabled higher oxidation of complex II, suggesting higher levels of lipid oxidation. Combined, these processes enable lower oxidative stress and improved insulin signaling through preserved mitochondrial function (8).

Preclinical Pharmacology

The pharmacology of imeglimin is extensively explored and analyzed via in vitro and in vivo studies in the works of Clemence et al. (12). In vitro, paracellular permeation was explored in modified Caco-2 cell cultures using cimetidine, a well-known compound that exhibits cellular uptake, as a control. It was found that imeglimin is absorbed via a saturable active transport process. Upon further investigation, OCT proteins were determined to carry about 30% of imeglimin uptake. Protein binding was examined within rat, canine and human cell cultures and was determined to be independent of imeglimin concentration and was evident in ranges of 4.8-8.3%, 5.7-6.8% and 5.3-6.4% for rats, canines and humans, respectively. Furthermore, using HEK-293 cell cultures, Clemence et al. found via intracellular concentration analysis that imeglimin was a substrate of OCT1, OCT2, MATE1 and MATE2-K, which was confirmed using specific inhibitors and substrates of these transporters as controls (12). In vivo studies were carried out by Clemence et al. on rat (Wistar), canine (beagle) and human subjects to further determine pharmacokinetic (PK) parameters of imeglimin in more clinically applicable settings (12). Rats and canines were both administered intravenous doses of 5 mg/kg radiolabeled imeglimin for

intravenous PK analysis. The animal subjects were then given 5 mg/kg oral doses or 100 mg/kg oral doses of radiolabeled imeglimin for oral PK analysis which demonstrated a bioavailability of 30% in rats and 75.2% in canines. Additionally, a study by Falcoz et al. in 2013 discovered that increasing oral dosage (in a range from 500 to 2000 mg) leads to a decrease in relative bioavailability from 100% reference at 500 mg to 71% at 2000-mg doses (13). This suggests dose-dependent (slow) absorption of imeglimin.

In intravenous doses, the elimination was rapid, producing half-life times of 2.9 and 5.7 hours in rats and canines, respectively, and renal clearance rates of 1.2 L/kg/h in rats and 0.65 L/kg/h in canines (12). Excretion percentages were measured at 48 hours after dosing in rats and 120 hours after dosing in canines. Urinary excretion of intravenous doses was found to be 85% and 95% in rats and canines, respectively, and fecal excretion of intravenous doses was determined to be 3% in rats and 1% in canines. Contrarily, in 5 mg/kg oral doses, urinary excretion was found to be 38% in rats and 77% in canines, while, at 100 mg/kg doses, canine urinary excretion dropped to 55%, suggesting that GI absorption is a rate-limiting process in elimination of imeglimin (12). Overall, imeglimin was found to be primarily excreted in urine, while its presence in feces was determined to be a result of a limitation in GI absorption. Excretion also occurred faster in intravenous doses than in oral doses, suggesting that imeglimin displays 'flip-flop' kinetics or that the rate of excretion is dependent upon the rate of absorption (12). In humans, urinary imeglimin excretion was found to be between 32% and 55%, while fecal excretion was between 44% and 66%. A large percentage of imeglimin found through fecal excretion was determined to be a result of the unabsorbed compound that was administered orally (12).

In addition, plasma levels decreased in a biphasic manner in humans. This pattern saw the first phase at 0-24 hours after dosing and a second slower phase from 24-72 hours after dosing. The renal clearance of imeglimin in human studies was found to be 35.4 L/h, which is higher than CrCl, indicating that imeglimin undergoes active tubular secretion (12). The main metabolites of imeglimin were found using 1000-mg oral doses in humans. The first, EMD-601811, is generated by oxidative aromatization together with N-demethylation and was found in 5% of blood samples obtained at 8 hours after dosing. The second metabolite, EMD-647302, is produced through N-demethylation of imeglimin alone and was found in 2% of blood samples at 8 hours after dosing. Additionally, in humans, EMD-647302 was found in 0.7% of urine samples and EMD-27355 was found in 0.3% of urine samples at 48 hours after dosing. Human fecal samples did not contain measurable metabolites of imeglimin (12). In all study subjects, the main found constituent was unchanged imeglimin. In blood, unchanged imeglimin was found to be 93% in humans. In urine samples, unchanged imeglimin was found to make up 43% of imeglimin-derived compounds in both canines and humans. In feces, imeglimin was found to be 40% and 55% in the samples of canines and humans, respectively. Finally, distribution was measured via two parameters, including time to C_{max} and V_{ss}. C_{max} was found to occur at 3.5 hours in humans and V_{ss} was reportedly 1422 L (12).

In conclusion, it was determined that imeglimin undergoes flip-flop kinetics, is dependent on GI absorption as the rate-limiting process in elimination, and it undergoes active tubular secretion in renal clearance studies.

Clinical Evaluation of Imeglimin

Phase II clinical studies

Eight randomized, multicenter, phase II studies conducted in European countries, the United States and Japan assessed the efficacy and safety of imeglimin as monotherapy or as adjunct therapy to a single oral antidiabetic agent in adults with T2DM (5, 14-19). Population characteristics were similar among each study, as participant mean baseline age ranged from 55 to 61 years, participants were predominantly Caucasian or Asian, and approximately 40% to 60% of individuals were male. Participants had a mean 5-year history of diabetes, a mean baseline hemoglobin A_{1c} (HbA_{1c}) of 7% to 8.5% and fasting plasma glucose (FPG) values ranging from approximately 150 to 190 mg/dL.

Two double-blind phase II studies evaluated the effects of imeglimin monotherapy on insulin sensitivity and secretion and glycemic control following

4 and 8 weeks of treatment (5). Both study designs incorporated a period of glucose ingestion, either through an oral glucose tolerance test (OGTT) or a prolonged meal, followed by incremental plasma glucose (PG) and insulin measurements along with other glycemic assessments. Primary outcomes measured were change from baseline to week 4 in the area under the curve for plasma glucose concentration over 3 hours (PG $AUC_{0\text{-}3h}$) and change from baseline to week 8 in the area under the curve for plasma glucose concentration over 6 hours (PG $AUC_{0\text{-}6h}$). Participants in the 4-week study were randomized (1:1:1) to receive twice-daily imeglimin 1000 mg, once-daily imeglimin 2000 mg or twice-daily metformin 850 mg. In the 8-week study, participants were randomized (1:1:1:1) to receive twice-daily imeglimin 500 mg or 1500 mg, twice-daily metformin or placebo.

Significant reductions from baseline in PG $AUC_{0\text{-}3h}$ were observed in each treatment group of the 4-week study, with changes of −10% ($P = 0.0305$), −33% ($P < 0.0001$) and −30% ($P < 0.0004$) seen in the imeglimin 2000-mg once-daily, imeglimin 1000-mg twice-daily and metformin groups, respectively. However, reductions in PG $AUC_{0\text{-}6h}$ were seen only in the imeglimin 1500-mg (−10.7%) and metformin (−15.9%) groups of the 8-week study, where imeglimin 1500 mg demonstrated a significant difference from baseline versus placebo yet no significant difference when compared to metformin. In the 4-week study, each treatment group demonstrated marginal reductions in insulin $AUC_{0\text{-}3h}$, whereas insulin $AUC_{0\text{-}6h}$ slightly increased in each of the 8-week study groups, although neither study exhibited significant between-group differences in these results. Improvements in the insulinogenic index were seen in the imeglimin 1000-mg and metformin groups of the 4-week study, while insulin AUC/PG AUC ratios at 3 and 6 hours increased in the imeglimin 1000-mg, imeglimin 1500-mg and both metformin groups of both studies. In the 8-week study, FPG increased from baseline by 3.6% in the imeglimin 500-mg group and 14.6% in the placebo group, while reductions of −10.7% and −14.6% occurred in the imeglimin 1500-mg and metformin groups, respectively. Similarly, respective changes in HbA_{1c} from baseline of +5.3%, −2.4%, −2.1% and +4.3% were observed in the imeglimin 500-mg, imeglimin 1500-mg, metformin and placebo groups (5).

Drug-related treatment-emergent adverse effects (TEAEs) occurred in 6 (30%), 7 (35%) and 13 (68%) patients following 4-week treatments with once-daily imeglimin 2000 mg, twice-daily imeglimin 1000 mg and metformin, respectively, and in 3 (10%), 7 (21%) and 3 (9%) patients following 8-week treatments with imeglimin 500 mg, metformin and placebo. Of note, there were no TEAEs reported in participants who received imeglimin 1500 mg in the 8-week study and GI disorders were most prevalent in the metformin groups of both studies (5).

The effects of imeglimin monotherapy on glucose response and glycemic control were studied in a double-blind phase II study following 18 weeks of treatment (15). In this study, patients underwent OGTTs during which incremental glucose, insulin and C-peptide were measured aside other glycemic parameters assessed during the treatment period. The primary outcome measured change in PG $AUC_{0\text{-}3h}$ from baseline to week 18, while key secondary endpoints included change from baseline to week 18 in the following: HbA_{1c}, FPG, insulinogenic index, incremental insulin, PG and C-peptide AUCs, glucagon, β-cell glucose sensitivity, rate sensitivity and Stumvoll insulin sensitivity index. A total of 59 participants were randomized (1:1) to receive twice-daily imeglimin 1500 mg or placebo.

At week 18, reductions of PG $AUC_{0\text{-}3h}$ (−17%, $P = 0.001$), FPG (−16%, $P = 0.022$) and HbA_{1c} (−0.62%, $P = 0.013$) observed in the imeglimin group were statistically significant when compared with placebo. Imeglimin also demonstrated significant improvements in β-cell glucose sensitivity, rate sensitivity, insulinogenic index, Stumvoll insulin sensitivity index and incremental C-peptide AUC/PG AUC ratio. Significant improvements in fasting and peak-glucose insulin AUCs were observed in the imeglimin group versus placebo, while total insulin secretion rate (ISR) with imeglimin was also significantly higher. However, imeglimin did not appear to influence glucagon secretion comparatively. TEAEs occurred in 8 (26.7%) and 17 (58.6%) participants of the imeglimin and placebo groups, respectively, with 1 (3.3%) participant in the imeglimin group and 4 (13.8%) in the placebo group experiencing TEAEs

related to the study drug. No serious drug-related TEAEs were reported in either group (15).

An additional randomized, 24-week, double-blind, placebo-controlled, dose-ranging study assessed the efficacy and safety of imeglimin at multiple doses in Japanese adults with T2DM (16-18). The primary outcome measured change in HbA_{1c} from baseline to week 24. Secondary endpoints included the proportion of patients with $HbA_{1c} < 7.0\%$ at study completion, proportion of patients who received rescue therapy, and change from baseline to week 24 in the following: FPG, glycated albumin, fasting insulin, fasting proinsulin, fasting C-peptide, proinsulin/C-peptide ratio, homeostatic model assessment of β-cell function (HOMA-β), homeostatic model assessment of insulin resistance (HOMA-IR), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides. Following a 6- to 10-week washout/run-in period, a total of 299 participants were randomized (1:1:1:1) to receive placebo or twice-daily imeglimin at 500-, 1000- or 1500-mg doses. Recent treatment histories included oral glucose-lowering agents only, as individuals treated with insulin or injectable glucose-lowering agents within 3 months of screening were excluded from the study.

At week 24, reductions in mean HbA_{1c} from baseline of −0.09%, −0.51% and −0.57% in the imeglimin 500-, 1000- and 1500-mg groups, respectively, were significant when compared with a mean increase of 0.43% seen in the placebo group ($P < 0.0001$ for all). Each imeglimin group also demonstrated significant reductions in glycated albumin versus placebo, and significant reductions in FPG versus placebo were observed in the imeglimin 1000- and 1500-mg groups. Of the 268 participants who completed the double-blind treatment period, 11 (15.7%), 22 (33.3%), 23 (32.9%) and 6 (8.2%) participants achieved target $HbA_{1c} \leq 7.0\%$ at week 24 in the imeglimin 500-mg, 1000-mg, 1500-mg and placebo groups, respectively (17).

Throughout the study, 2 (2.7%) participants in the imeglimin 500-mg group, 2 (2.7%) in the imeglimin 1000-mg group and 7 (9.3%) in the placebo group required rescue therapy. Glycated albumin decreased significantly compared with placebo by −0.35%, −2.13 % and −2.25% in the imeglimin 500-, 1000- and 1500-mg groups, respectively, versus an increase of 1.98% in the placebo group. Increases in fasting insulin were observed in all treatment groups, although the change compared with placebo was only significant with imeglimin 1500 mg. Fasting proinsulin was reduced in each imeglimin group, while fasting C-peptide was reduced in the 500- and 1000-mg groups and increased in the 1500-mg group. Reductions in fasting proinsulin/C-peptide ratio were seen in the 1000- and 1500-mg groups, with only the 1500-mg group demonstrating a significant difference versus placebo. Significant, dose-dependent increases in HOMA-β values compared with placebo were observed in all imeglimin groups. HOMA-IR decreased in the 500- and 1000-mg groups yet increased in the 1500-mg group. No significant differences in LDL-C, HDL-C or triglycerides were observed in any group at week 24 (17).

TEAEs were comparable between imeglimin and placebo, occurring in approximately 50% of participants in each. Of these participants, only 4 (5.3%), 4 (5.4%), 18 (24.0%) and 6 (8.0%) in the imeglimin 500-mg, 1000-mg, 1500-mg and placebo groups, respectively, experienced TEAEs determined to be related to the study drug. Among the most common adverse events (AEs) were GI disorders, which appeared to be dose-dependent with prevalence ranging from 14.7% in the placebo group to 32.0% in the imeglimin 1500-mg group. All reported hypoglycemic events were asymptomatic and occurred in 5 (6.7%), 2 (2.7%), 4 (5.3%) and 1 (1.3%) participants of the imeglimin 500-mg, 1000-mg, 1500-mg and placebo groups, respectively (17).

Findings from this study indicate that imeglimin significantly improved glycemic control at each of the 500-, 1000- and 1500-mg doses. While HbA_{1c} reduction was slightly higher in the 1500-mg than the 1000-mg group, investigators considered this between-group difference to be of minimal clinical importance. Moreover, dose-dependent occurrences of GI events were observed across the treatment arms, suggesting the efficacy/safety profile of twice-daily imeglimin 1000 mg was best suited for late-phase studies (16-18).

Two 12-week, double-blind, placebo-controlled studies assessed the efficacy and safety of imeglimin in combination with either metformin or sitagliptin (19, 20). The primary outcome of both the metformin add-on and sitagliptin add-on studies measured

change in HbA_{1c} from baseline to week 12. The studies also shared secondary endpoints of change in FPG and proinsulin/insulin ratio from baseline to week 12. Additional secondary outcomes of the study with sitagliptin included measurements of β-cell function and non-glycemic parameters. Participants were randomized (1:1) to twice-daily imeglimin 1500 mg plus metformin 1500-2000 mg/day or placebo plus metformin 1500-2000 mg/day for the metformin add-on study, and imeglimin 1500 mg plus once-daily sitagliptin 100 mg or placebo plus once-daily sitagliptin 100 mg in the sitagliptin add-on study.

HbA_{1c} reductions from baseline were observed in both the imeglimin-metformin (−0.65%) and imeglimin-sitagliptin (−0.60%) groups, with significant placebo-adjusted changes of −0.44% ($P = 0.001$) and −0.72% ($P < 0.001$), respectively. Also, a higher proportion of individuals achieved an $HbA_{1c} \leq 7\%$ in both the imeglimin-metformin (14.3%) and imeglimin-sitagliptin (19.8%) groups versus respective placebo (3.8%, 1.1%). Imeglimin also demonstrated placebo-adjusted FPG reductions of −16.4 mg/dL ($P < 0.001$) when combined with metformin and −14.6 mg/dL ($P < 0.014$) when combined with sitagliptin. Improvement in the proinsulin/insulin ratio was seen in the treatment groups of both studies, although only the imeglimin-metformin group demonstrated a significant change in comparison to placebo ($P = 0.007$). Moreover, between-group differences in change for other β-cell function parameters of the sitagliptin study were not significant (19, 20).

Safety profiles were similar between the imeglimin and placebo combination groups of both studies. Throughout the double-blind treatment periods, drug-related TEAEs occurred in 8 (10.3%), 1 (1.3%), 0 (0%) and 3 (3.4%) participants of the imeglimin-metformin, placebo-metformin, imeglimin-sitagliptin and placebo-sitagliptin groups, respectively. Drug-related TEAEs in the imeglimin-metformin group were predominantly GI-related, although none of them were serious (19, 20).

A 7-day double-blind, placebo-controlled study examined the effect of imeglimin on GSIS (21). Study outcomes addressed data collected during a hyperglycemic clamp conducted immediately following the final dose of a 7-day treatment course with imeglimin or placebo. The primary outcome measured incremental insulin $AUC_{0\text{-}45min}$, while key secondary endpoints included total ISR, first-phase and second-phase ISR, incremental glucagon $AUC_{0\text{-}45min}$, proinsulin $AUC_{0\text{-}45min}$/insulin AUC ratio and glucose sensitivity. Following a 2-week washout/run-in period, 30 participants were randomized 1:1 to receive twice-daily imeglimin 1500 mg or matching placebo. Participants were either treatment-naive or treated with metformin monotherapy for 12 weeks prior to screening.

Hyperglycemic clamp values revealed an incremental insulin $AUC_{0\text{-}45min}$ in the imeglimin group +112% higher than that in the placebo group ($P < 0.05$). Significant improvements were also seen in total ISR, first-phase ISR and second-phase ISR of the imeglimin group, as values were +31%, +110% and +29% higher than for placebo, respectively ($P < 0.05$ for all). Additionally, glucose sensitivity measured 36% higher in the imeglimin group than in the placebo group ($P = 0.034$). No significant differences between the imeglimin and placebo groups were observed in incremental glucagon $AUC_{0\text{-}45min}$ or proinsulin $AUC_{0\text{-}45min}$/insulin AUC ratio. Comparison of hyperglycemic clamp results between the imeglimin and placebo group implies the effects of imeglimin on β-cell function to be direct rather than secondary to its effects on blood glucose. Also, the utility of imeglimin in sustaining glycemic control is supported by the significantly enhanced biphasic insulin secretion observed within the imeglimin treatment group (21).

A 24-week double-blind, placebo-controlled, dose-ranging study assessed the efficacy and safety of imeglimin at multiple doses (16). The primary outcome measured placebo-adjusted change in HbA_{1c} from baseline to week 24. Key secondary endpoints included change in FPG from baseline to week 24, proportion of participants achieving $HbA_{1c} \leq 7\%$, and proportion of patients requiring rescue therapy. Following a 3- to 6-week washout/run-in period, 382 participants were randomized (1:1:1:1:1) to receive placebo or twice-daily imeglimin at 500-, 1000-, 1500- or 2000-mg doses.

At week 24, each imeglimin group demonstrated reductions in HbA_{1c}, with significant placebo-adjusted reductions seen in the imeglimin 1500-mg (−0.63%, $P < 0.001$) and 2000-mg (−0.50%, $P = 0.002$) groups. Significant placebo-adjusted reductions in FPG of −22.5 mg/dL ($P = 0.001$) and −14.6 mg/dL ($P = 0.29$)

were also observed in these groups, respectively. The proportion of patients who achieved $HbA_{1c} \leq 7\%$ was significantly greater than in the placebo group in the 1500-mg group only (−33.3%, $P = 0.005$). Also, no participants in the 1500-mg group required rescue therapy, while respective proportions of participants requiring rescue therapy were 5 (6.9%), 6 (7.8%), 4 (5.8%) and 6 (7.5%) in the imeglimin 500-mg, 1000-mg, 2000-mg and placebo groups (16).

TEAEs were comparable between imeglimin and placebo and occurred in approximately 30-40% of participants in each group. TEAEs determined to be related to the study drug occurred in 6 (8.1%), 13 (16.5%), 5 (6.8%), 13 (17.6%) and 6 (7.4%) participants of the imeglimin 500-mg, 1000-mg, 1500-mg, 2000-mg and placebo groups, respectively. GI disorders occurred in 2-10% of participants in each of the imeglimin groups but were not reported in the placebo group (16).

Phase III clinical studies

The imeglimin phase III program, TIMES, consists of three phase III clinical studies investigating the effects of imeglimin in 1,142 Japanese subjects with T2DM.

To further investigate the efficacy and safety of twice-daily oral imeglimin 1000 mg, investigators conducted the TIMES 1 study, a 24-week randomized, double-blind, placebo-controlled clinical study (22, 23). The primary outcome measured change in HbA_{1c} from baseline to week 24 of therapy. Secondary endpoints measured the proportion of participants with $HbA_{1c} < 7.0\%$ and the proportion of participants with a relative decrease of ≥ 7% in HbA_{1c} from baseline at week 24. Following a 4- to 12-week washout/run-in period, a total of 213 participants were randomized (1:1) to receive twice-daily imeglimin 1000 mg or matching placebo. Participants were mostly male (78.4%) with baseline mean age of 62 years, mean HbA_{1c} of 7.96%, and mean 7.5-year history of diabetes. At baseline, 71.8% of participants were treatment-naive, and the remaining were recently treated with oral glucose-lowering agents only.

At week 24, an absolute reduction in HbA_{1c} from baseline of −0.72% was observed in the imeglimin group versus an absolute increase of 0.15% seen in placebo (least square mean [LSM] −0.87, 95% confidence interval [CI] −1.041 to −0.691, $P < 0.0001$). Subgroup analysis of the primary outcome revealed placebo-adjusted HbA_{1c} reductions from baseline were similar between subgroups of treatment-naive participants (−0.87%, 95% CI −1.07 to −0.67, $P < 0.0001$) and those previously treated (LSM −0.84, 95% CI −1.16 to −0.52, $P < 0.0001$). However, absolute reductions from baseline in HbA_{1c} of −0.81% and −0.51% were seen in these groups, respectively. Significant between-group differences were observed for both secondary outcomes, as 38 (15.8%) and 8 (7.5%) participants in the imeglimin and placebo groups, respectively, achieved $HbA_{1c} < 7.0\%$ ($P < 0.0001$) at week 24, and 61 (57.5%) and 12 (11.3%) demonstrated a relative decrease of ≥ 7% in HbA_{1c} from baseline ($P < 0.0001$) (22).

Imeglimin demonstrated a mild safety profile, with 5 (4.7%) and 7 (6.5%) participants in the imeglimin and placebo groups, respectively, experiencing TEAEs related to the study drug. GI disorders occurred in 12 (11.3%) participants of the imeglimin group and 9 (8.4%) participants of the placebo group. Hypoglycemic events were reported in 3 (2.8%) participants within the imeglimin group and 1 (0.9%) participant within the placebo group. Only 2 of the hypoglycemic events that occurred were symptomatic, and both occurred in the same individual (22).

Results of TIMES 1 pertaining to glycemic control were consistent with those of the previous phase II trials, as twice-daily imeglimin 1000 mg demonstrated the ability to significantly lower HbA_{1c} and FPG in Japanese adults with T2DM. Additionally, a subgroup analysis of the primary outcome revealed a potentially greater benefit in treatment-naive patients than in those previously treated, suggesting the efficacy of imeglimin may depend on its capacity to improve GSIS. Favorable changes in proinsulin ratios, QUICKI (quantitative insulin sensitivity check index) and HOMA-β in the treatment group further imply imeglimin may substantially improve human pancreatic β-cell function and insulin sensitivity. Additionally, neither advanced age nor decreased renal function appeared to influence the safety or efficacy of imeglimin (22, 23).

A 52-week randomized, open-label, phase III comparator study was held to evaluate the safety and efficacy of imeglimin as monotherapy or combination therapy with existing antidiabetic agents in

Japanese patients with T2DM (24, 25). The primary objective of the study was to assess the safety of imeglimin as monotherapy and in combination with another glucose-lowering agent. A total of 714 participants were randomized in a 2:2:1:1:1:1:1:1:1 fashion to receive 1000 mg imeglimin twice daily as monotherapy or in single combination with a sulfonylurea, α-glucosidase inhibitor, biguanide, dipeptidyl peptidase 4 inhibitor (DPP4-I), glinide, GLP-1RA, SGLT2-I or thiazolidinedione. Most participants were male (73.7%) with baseline mean age of 58 years, diabetes duration of 8.7 years and HbA_{1c} of 8.43%.

At week 52, imeglimin monotherapy demonstrated a −0.46% mean reduction in HbA_{1c}, while improvements with combination therapies ranged from −0.12% in the GLP-1RA group to −0.92% in the DPP4-I group. The proportion of participants with a final HbA_{1c} < 7.0% was greatest in the monotherapy (40.3%) and DPP4-I (37.2%) groups and least in the SGLT2-I (8.1%) and GLP1-RA (9.2%) groups. Proportions of participants with a ≥ 7% relative decrease in HbA_{1c} from baseline were comparable among treatments. Changes in FPG from baseline were also similar in most groups and ranged from −15.0 to −23.45 mg/dL, although only a −0.88 mg/dL reduction was observed with thiazolidinedione therapy. A total of 8 (11.4%) participants in the GLP-1RA group required rescue medication, while prevalence was lower (< 5%) within the remaining groups (25).

The proportion of patients with any TEAE was consistent, approximately 75-80%, across most groups, except the α-glucosidase inhibitor group (51.6%). Drug-related TEAEs in the biguanide group were most prevalent, occurring in 24 (37.5%) participants, while those in the α-glucosidase inhibitor and thiazolidinedione groups were least prevalent, occurring in 6 (9.4%) and 6 (9.2%) participants, respectively. Most AEs were mild and similar to those reported in previous imeglimin studies. Hypoglycemia occurred in 14.1% and 16.5% of participants in the glinide and sulfonylurea groups, respectively, and in 2.9-9.4% of those in the remaining groups. Of these participants, 3.9% in the sulfonylurea group and 0.0-3.1% in the remaining groups experienced symptomatic, nonsevere hypoglycemia. Incidence of GI disorders was typically low (< 10%) across treatment groups, although nausea and vomiting occurred in 12.5% and 17.2%, respectively, of participants in the biguanide group (25).

The results of TIMES 2 indicate imeglimin to be both safe and effective not only as monotherapy, but also in combination with the glucose-lowering medications included in the treatment arms. As with previous data for imeglimin monotherapy, neither advanced age nor decreased renal function appeared to influence the safety or efficacy of imeglimin with or without combination therapy (24, 25).

TIMES 3, the third randomized study in the TIMES program, was a placebo-controlled, combination, double-blind and open-label trial to evaluate the long-term safety and efficacy of imeglimin and insulin as dual treatment in Japanese patients with T2DM inadequately controlled by insulin monotherapy (26-28). The primary outcome was placebo-adjusted reduction in HbA_{1c} from baseline at week 16 of therapy, while the secondary outcome measured absolute change in HbA_{1c} at week 52 from baseline. A total of 215 participants were randomized (1:1) to receive twice-daily imeglimin 1000 mg with insulin or matching placebo with insulin during weeks 0-16. Placebo was then replaced with twice-daily imeglimin 1000 mg for the remainder of the study. The baseline mean participant age was 58 years, mean duration of diabetes was 13.3 years, and 80.5% of participants were treated with insulin monotherapy at randomization. A total of 70% of participants were treated with basal therapy, and mean baseline insulin daily dose was 21.3 IU.

At week 16, the imeglimin combination group demonstrated a significant placebo-adjusted mean HbA_{1c} reduction of −0.60% (P < 0.0001). Participants in the initial treatment group showed a similar mean HbA_{1c} reduction of −0.64% at week 52, whereas the initial placebo group demonstrated a mean −0.54% reduction in HbA_{1c} at week 52, following a total 36 weeks of imeglimin combination therapy. Safety outcomes reported for the 16-week double-blind period were similar between the imeglimin and placebo combination groups, with slightly greater incidence of hypoglycemia seen in 23 (21.3%) versus 17 (15.9%) participants in the imeglimin and placebo combination groups, respectively. Findings from TIMES 3 confirm the safety and sustained efficacy of imeglimin added to insulin monotherapy in Japanese patients with T2DM (27).

Table I summarizes the clinical studies for imeglimin.

Table I. *Baseline characteristics and results for imeglimin clinical studies.*

Study (Ref.)	Phase	Primary outcomes	Intervention	Baseline characteristics	Results
Insulin sensitivity (5)	IIa	Change from baseline to week 4 in PG $AUC_{0\text{-}3h}$	Twice-daily imeglimin 1000 mg, once-daily imeglimin 2000 mg or twice-daily metformin 850 mg	Age range 55 to 61 years T2DM 5 years	Reduction in PG $AUC_{0\text{-}3h}$ from baseline of −10%, −33% and −30% in the imeglimin 2000-mg, imeglimin 1000-mg and metformin groups, respectively
Insulin sensitivity (5)	IIa	Change from baseline to week 8 in PG $AUC_{0\text{-}6h}$	Twice-daily imeglimin 500 or 1500 mg, twice-daily metformin or placebo	Age range 55 to 61 years T2DM 5 years	Reduction in PG $AUC_{0\text{-}6h}$ from baseline for imeglimin 1500 mg (−10.7%) and metformin (−15.9%)
Glucose response (15)	II	Change in PG $AUC_{0\text{-}3h}$ from baseline to week 18	Twice-daily imeglimin 1500 mg or placebo	Age range 55 to 61 years T2DM 5 years	Reductions of PG $AUC_{0\text{-}3h}$ (−17%, $P = 0.001$), FPG (−16%, $P = 0.022$) and HbA_{1c} (−0.62%, $P = 0.013$) in the imeglimin group were statistically significant vs. placebo
Add-on to metformin (19)	II	Change in HbA_{1c} from baseline to week 12	Twice-daily imeglimin 1500 mg plus metformin or placebo plus metformin	Age range 55 to 61 years T2DM 5 years	HbA_{1c} reduction from baseline for imeglimin-metformin (−0.65%) and placebo-adjusted change of −0.44%
Add-on to sitagliptin (20)	II	Change in HbA_{1c} from baseline to week 12	Imeglimin 1500 mg plus once-daily sitagliptin 100 mg or placebo plus once-daily sitagliptin 100 mg	Age range 55 to 61 years T2DM 5 years	HbA_{1c} reduction from baseline for imeglimin-sitagliptin (−0.60%) and placebo-adjusted change of −0.72%
GSIS (21)	II	Incremental insulin $AUC_{0\text{-}45min}$	Twice-daily imeglimin 1500 mg or placebo	Age 61 years T2DM 5.5 years	Incremental insulin $AUC_{0\text{-}45min}$ in the imeglimin group +112% higher than with placebo
Dose-ranging study (17)	IIb	Change in HbA_{1c} from baseline to week 24	Twice-daily imeglimin at 500, 1000 or 1500 mg vs. placebo	Age 59.1 years T2DM 6.2 years	Mean percent HbA_{1c} reductions of −0.09 (500 mg), −0.51 (1000 mg) and −0.57 (1500 mg) vs. increase of 0.43 with placebo
TIMES 1 (22)	III	Change in HbA_{1c} from baseline to week 24	Twice-daily imeglimin 1000 mg or matching placebo	Age 62 years T2DM 7.5 years	Absolute reduction in HbA_{1c} from baseline of −0.72% in the imeglimin group vs. absolute increase of 0.15% with placebo

(Continued)

Table I. *Baseline characteristics and results for imeglimin clinical studies. (Cont.)*

Study (Ref.)	Phase	Primary outcomes	Intervention	Baseline characteristics	Results
TIMES 2 (25)	III	Safety of imeglimin as monotherapy and in combination with another glucose-lowering agent	Twice-daily imeglimin 1000 mg as monotherapy or in single combination with a sulfonylurea, α-glucosidase inhibitor, biguanide, DPP4-I, glinide, GLP-1RA, SGLT2-I or TZD	Age 58 years T2DM 8.7 years	Mean reduction in HbA_{1c} for imeglimin monotherapy of −0.46% (combination therapies ranged from −0.12% in the GLP-1RA group to −0.92% in the DPP4-I group)
TIMES 3 (27)	III	Long-term safety and efficacy of imeglimin and insulin as dual treatment	Double-blind period: imeglimin 1000 mg twice daily or placebo with insulin Open-label extension: imeglimin 1000 mg twice daily with insulin	Age 58.4 years T2DM 13.3 years	At week 16 HbA_{1c} reduction of 0.63% with imeglimin vs. 0.03% with placebo At week 52 HbA_{1c} decrease of 0.64% in the imeglimin/imeglimin group and 0.54% in the placebo/imeglimin group

DPP4-I, dipeptidyl peptidase 4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; GSIS, glucose-stimulated insulin secretion; HbA_{1c}, hemoglobin A_{1c}; PG $AUC_{0\text{-}3h}$, area under the curve for plasma glucose concentration over 3 hours; PG $AUC_{0\text{-}6h}$, area under the curve for plasma glucose concentration over 6 hours; SGLT2-I, sodium/glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

Efficacy and safety data supported the first approval of imeglimin worldwide in Japan on June 23, 2021, for the treatment of T2DM. Imeglimin is marketed under the trade name Twymeeg, as 500-mg tablets for oral administration (29).

Discussion

Efficacy data provided in the monotherapy studies suggests the effects of imeglimin on glucose response and glycemic control to be dependent on dose strength and frequency. Imeglimin administered twice daily at higher doses may provide benefit comparable to traditional first-line oral therapy, as indicated through between-group comparisons of outcomes in the imeglimin versus metformin treatment groups. In outcomes specific to glucose response, imeglimin appears to improve with extended duration of therapy. Furthermore, twice-daily imeglimin at a dose of 1500 mg appeared to show the greatest improvements on glycemic control without a significant increase in side effects compared to the lower doses. Additionally, the combined safety profile of imeglimin appears tolerable and potentially preferable to that of metformin. Results from the add-on therapy studies suggest imeglimin to be a well-tolerated, effective treatment adjunct to commonly prescribed oral antidiabetic medications. The coadministration of imeglimin with sitagliptin or metformin provides an additive benefit on glycemic control that is well supported by the combined efficacy data, although such additive contributions to β-cell function are less clearly defined.

Conclusions

Imeglimin is the first oral tetrahydrotriazine-containing drug and the first in the class of "glimins", which has a unique multifactorial and novel mechanism of action that affects multiple pathophysiological targets of T2DM. Imeglimin has demonstrated efficacy and safety in the treatment of T2DM in clinical studies to date. Future studies will assist in evaluating the place in patient therapy for imeglimin as monotherapy or adjunct therapy to other antidiabetic medications.

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