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REVIEW ON IMEGLIMIN A NOVEL THERAPEUTIC AGENT FOR TYPE 2 DIABETES

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ABSTRACT

Imeglimin is an investigational first-in-class novel oral agent for the treatment of type 2 diabetes (T2D). Several pivotal phase III trials have been completed with evidence of statistically significant glucose lowering and a generally favorable safety and tolerability profile, including the lack of severe hypoglycemia. Imeglimin is unique and different in action compared to other hypoglycemic drugs. meglimin's mechanism of action involves dual effects: (1) amplification of glucose-stimulated insulin secretion (GSIS) and preservation of β-cell mass; and (2) enhanced insulin action, including the potential for inhibition of hepatic glucose output and improvement in insulin signalling in both liver and skeletal muscle. Imeglimin has been shown to have a beneficial effect on 3 key pathogenetic elements of Type 2 diabetes mellitus, i.e., 1. increased gluconeogenesis, 2. inadequate glucose-induced insulin secretion by beta cells, and 3. peripheral insulin resistance. Subjects receiving Imeglimin at 1000- and 1500-mg doses twice daily also achieved significantly greater reductions in fasting plasma glucose (FPG) levels at week 24 compared to the placebo group. This review can be helpful for further study of Imeglimin hydrochloride.

KEYWORD: Imeglimin, Type 2 diabetes, Hypoglycaemic agent, Glimins, Insuline increasing agent.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major worldwide health problem. The prevalence of T2DM is estimated to be over 500 million cases, and it is the fourth leading cause of death worldwide.[1,2] According to the latest International Diabetes Federation (IDF) 2019 estimates, the number of people with diabetes worldwide will increase from 463 to 700 million by 2045. T2DM is characterized by a relative insulin deficiency mainly due to beta cells dysfunction and peripheral insulin resistance resulting in glucotoxicity, which induces microvascular and macrovascular complications.[3-4] T2DM is more common in older adults. But the increase in the number of children with obesity has led to more cases of type 2 diabetes in younger people. There is no cure for type 2 diabetes. Losing weight, eating well and exercising can help manage the disease. If diet and exercise aren't enough to control blood sugar, diabetes medications or insulin therapy may be recommended.[5]

Imeglimin is the first drug in a new tetrahydrotriazine containing class of oral antidiabetic agents referred to as ‘glimins’. Imeglimin is under investigation, with three pivotal phase III clinical trials having been recently completed in Japan.[6] As described in this review, the mode of action of Imeglimin is unique and distinct compared with other major classes of therapeutic agents. It involves dual effects, both to enhance insulin action and to reverse pancreatic β-cell dysfunction. The mode of action of Imeglimin is generally well aligned with our current understanding of the pathophysiology of T2D. A genetic predisposition plus key environmental factors, principally overnutrition and reduced energy expenditure, are drivers of disease. Consequently, defects in insulin action plus pancreatic islet β-cell dysfunction develop and conspire to yield glucose intolerance and, subsequently, the onset of overt diabetes.[7]

Chemical Properties

Imeglimin possesses a cyclic 1,3,5-triazine structure. Containing a biguanide substructure, it bears a similarity with metformin (Figure 1). At least three possible prototropic tautomers can be proposed for derivatives with the biguanide moiety. These isomers are a consequence of amino–imino tautomeric conversions.

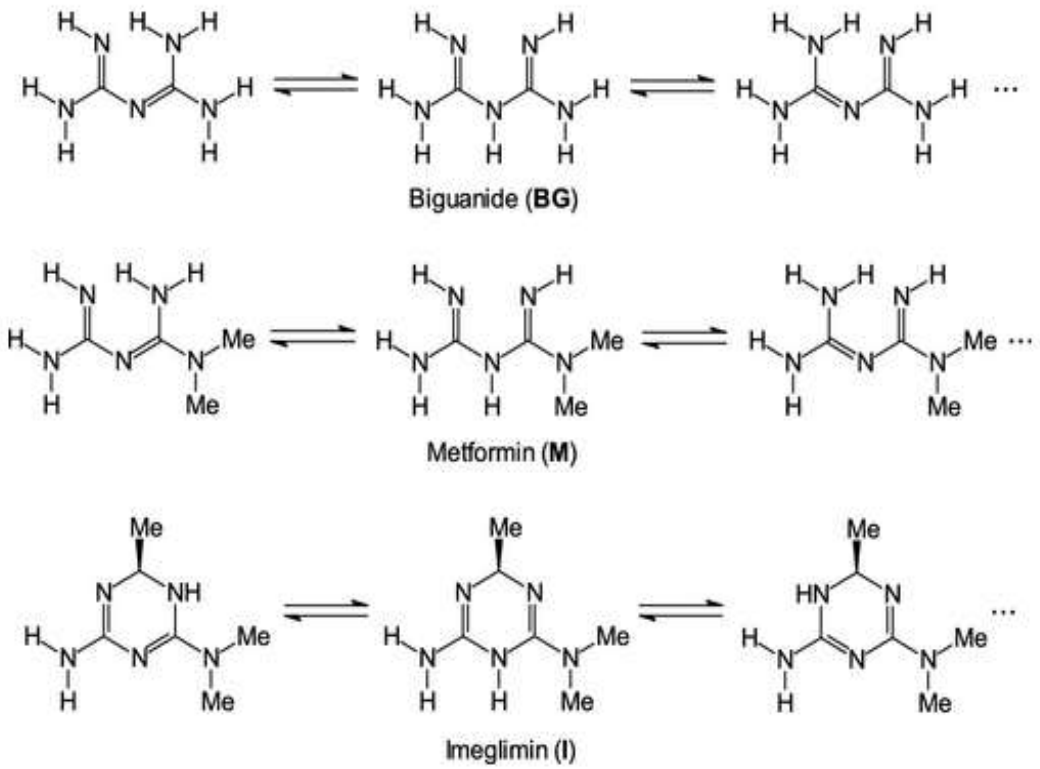

Figure 1: Selected tuotomer of Biguanide (BG), Metformin (M), and Imeglimin (I).[8]

The molecular weight of Imeglimin have 155.20 g/mol and the molecular formula is $C_6H_{13}N_5$. IUPAC name of Imeglimin is (4R)-6-N,6-N,4-trimethyl-1,4-dihydro-1,3,5-triazine-2,6-diamine(figure 2).

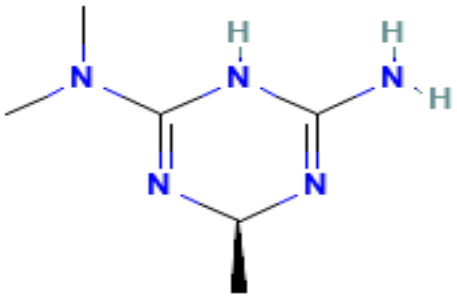

Figure 2: (4R)-6-N,6-N,4-trimethyl-1,4-dihydro-1,3,5-triazine-2,6-diamine.

Mechanism of Action

In this study, the effect of Imeglimin administration on lowering blood glucose in type 2 diabetic patients with inadequate glycemic control will be measured using HbA1c, GA and 1,5-AG as indices. The divergence between HbA1c and the rate of blood glucose-lowering with GA and 1,5-AG will be evaluated whether HbA1c is an appropriate index for Imeglimin

administration. The effect of Imeglimin on erythrocytes will also be examined as a cause of the divergence. If Imeglimin lengthens erythrocyte lifespan, HbA1c is not an appropriate measure of the hypoglycemic effect of Imeglimin in the early stages of administration, but GA and 1,5-AG are appropriate measures to evaluate instead. If Imeglimin improves erythrocyte deformability, Imeglimin may be a new treatment strategy for peripheral arterial occlusive disease, a chronic complication of T2D.

In the TIMES 1–3 studies, Imeglimin, both as monotherapy and in combination with other antidiabetic drugs, slowly decreases HbA1c, reaching a plateau around 24 weeks after administration. Furthermore, the fasting blood glucose trend in the TIMES 1 (monotherapy) study (106 subjects) showed a large decline at week 4 and plateaued from weeks 8 to 24. This observation differed from the slowly declining trend of HbA1c, which was measured simultaneously. We also reported in a retrospective observational study that, under routine medical care, Imeglimin treatment of type 2 diabetic patients resulted in a slower decrease in HbA1c than GA, with a divergence in the rate of change between the two. These results suggest that HbA1c may appear to be high. To assess whether HbA1c is an appropriate measure, this study will ensure reliability by comparing HbA1c with the rate of decrease in blood glucose over time for GA or 1.5-AG and by measuring sustained blood glucose variability with FGM and its association with changes in these measures.

In general, HbA1c levels depend not only on blood glucose but also on erythrocyte lifespan. Therefore, shortening or lengthening erythrocyte lifespan results in falsely low or high HbA1c levels, respectively. If HbA1c is falsely elevated by Imeglimin, lengthening of erythrocyte lifespan is suggested, but erythrocyte lifespan has not been studied in routine practice. Thus, this study will examine hemoglobin concentration, erythrocyte lifespan, and erythrocyte deformability to determine the effects on erythrocytes. Furthermore, if Imeglimin improves erythrocyte deformability, it is expected to have the potential to be effective in treating peripheral arterial occlusive disease, so an index of arteriosclerosis will also be measured.

Erythrocytes can deform and pass through capillaries flexibly (erythrocyte deformability), which improves blood flow through good blood circulation and oxygen transportation. Erythrocyte deformability is mainly dictated by three factors: geometric cell factors (surface area to volume ratio, morphological changes), internal cell viscosity, and cell membrane viscoelasticity. MCV is related to the surface area to volume ratio, and increased MCV

improves erythrocyte deformability. In addition, internal erythrocyte viscosity is dependent on hemoglobin concentration; viscosity increases non-linearly with increasing MCHC. and erythrocyte deformability decreases markedly. In our retrospective observational study, Imeglimin increased MCV and decreased MCHC. These results suggest that Imeglimin may improve erythrocyte deformability. Various blood rheology abnormalities have been reported in diabetes mellitus, and there are reports of decreased erythrocyte deformability. Therefore, the ability of Imeglimin to improve erythrocyte deformability would greatly benefit patients with T2D.

Imeglimin is a drug with a novel mechanism of mitochondrial function improvement. It has been suggested that Imeglimin converts nicotinamide (NAM) to NAM mononucleotide (NMN) via increased gene expression of NAM phosphoribosyltransferase (NAMPT) in the salvage pathway utilizing NAM in islet beta cells. Then, NAM adenine dinucleotide (NAD+) is synthesized from NMN by NMN adenylyltransferase (NMNAT), which may enhance insulin secretion as well as mitochondrial function. However, NMNAT is also expressed in the cytoplasm of human erythrocytes. Mice lacking the NMNAT gene show a marked decrease in erythrocyte NAD+ levels and a shorter erythrocyte lifespan of about 10 days compared to that of normal mice (about 60 days), with most of them having deformed and abnormal morphology. Therefore, if Imeglimin can increase erythrocyte NAD+ levels, it would affect erythrocyte lifespan and deformability (Figure 3).

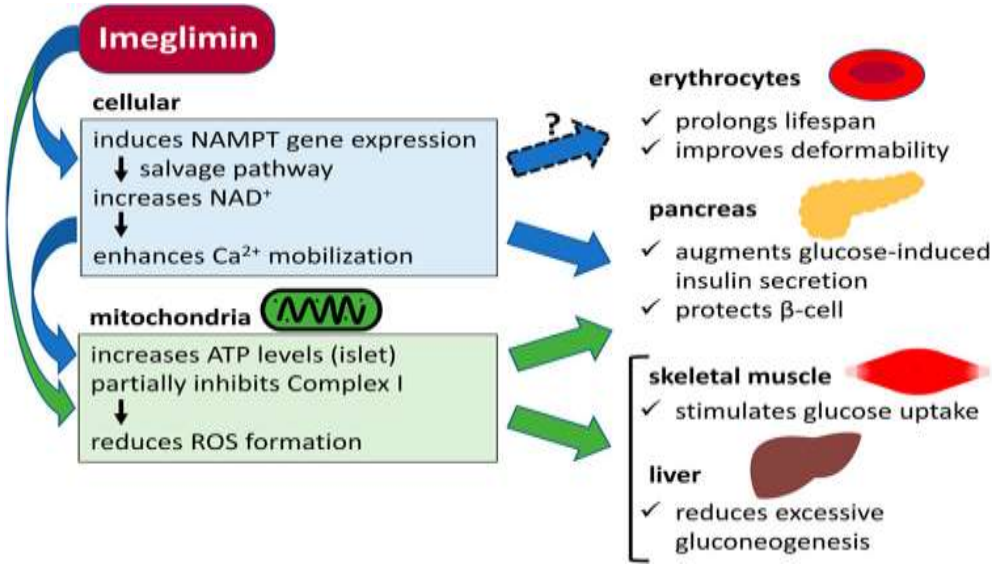

Figure 3: Mechanism of action of Imeglimin.

FIGURE 3. Potential cellular and mitochondrial mechanisms of the action of Imeglimin in erythrocytes, pancreas, skeletal muscle, and liver. NAMPT, nicotinamide phosphoribosyl transferase; NAD^+, nicotinamide adenine dinucleotide; Ca^{2+}, calcium ion; ATP, adenosine triphosphate; Complex I, mitochondrial respiratory chain complex I; ROS, reactive oxygen species.[9]

Pharmacokinetics

The peak effect on glycated haemoglobin (HbA1c) levels of Imeglimin appears to be reached after 16 weeks of treatment.[10] Subjects receiving Imeglimin at doses of 1000 and 1500 mg twice daily (BID) also achieved significantly greater reductions in fasting plasma glucose (FPG) levels at week 24 compared with the placebo group (–24.6 ± 4.45; –24.6 ± 4.46 vs. –8.6 ± 4.4 mg/dL, $p < 0.0001$).[11] Fouquieria published the results of a study evaluating the pharmacokinetics of Imeglimin in monotherapy and as supplementation to treatment with metformin (MET) or sitagliptin (SITA). T2DM patients received MET 850 mg BID with placebo (n = 16) or SITA 100 mg once a day (OD) with placebo (n = 16) on days 1-6 followed by MET 850 mg BID with Imeglimin 1500 mg BID or SITA 100 mg OD with Imeglimin 1500 mg BID on days 7–12. The authors demonstrated that concomitant administration of SITA with Imeglimin did not result in clinically significant changes in systemic availability for SITA. The slight reduction in MET bioavailability after concomitant Imeglimin administration was not clinically significant. The use of Imeglimin with MET or SITA was safe and well tolerated.[12]

Studies suggest that Imeglimin prevents human endothelial cell death by inhibiting mitochondrial permeability without concomitant inhibition of mitochondrial respiration, which may reduce the risk of cardiovascular complications in T2DM.[13]

Clinical Studies

Metformin is the first-line agent in the treatment of type 2 diabetes, mainly due to its safety, efficacy and low cost. It does not cause hypoglycaemia, and offers an effective reduction in HbA1c as a monotherapy or in combination with other oral glucose-lowering agents. However, in some patients, the use of metformin is limited, mostly due to its gastrointestinal side effects. There are several phase II and phase III studies that demonstrate the effectiveness of Imeglimin as an alternative option.

In a 4-week phase IIa, three-arm parallel group trial in 59 patients with type 2 diabetes by Pirags et al., Imeglimin was compared with metformin and placebo based on safety profile and efficacy to reduce the plasma glucose concentration AUC (AUCPG). The patients (HbA1c: 6.5–8.5%) either did not receive any treatment at all, or were treated with monotherapy sulfonylurea or metformin before the initiation of the study, and were randomized to Imeglimin 2,000 mg once daily, Imeglimin 1,000 mg twice daily (BID), metformin 850 mg BID (mean baseline HbA1c levels of 7.41, 7.07 and 7.27%, respectively), or placebo. Imeglimin BID presented the greatest reduction in AUCPG from baseline, followed by metformin and Imeglimin once daily dosing (-33%, -30% and -10%, respectively). The results of this trial indicated that Imeglimin presented a similar efficacy to metformin.

In a second 8-week phase IIa, four-arm, controlled multicentre study by Pirags et al. in 128 patients with type 2 diabetes, patients who were treatment naïve or received a sulfonylurea or metformin as a monotherapy were randomized to Imeglimin 500 mg BID, Imeglimin 1,500 mg BID, metformin 850 mg BID or placebo (mean baseline HbA1c levels of 7.20%, 7.35%, 7.12% and 7.21%, respectively). Imeglimin 1,500 mg BID and metformin BID were superior to placebo in the assessment of the AUC up to 6 hours (AUC0-6h) for glucose during a prolonged meal, and both led to the reduction of FPG and HbA1c from baseline; Imeglimin 500 mg BID was the least effective dosing, and led to an increase of FPG and HbA1c from the baseline across all Imeglimin groups. Concerning the safety profile of Imeglimin, only 16 patients experienced headache compared with 20 patients in the metformin group, and gastrointestinal side effects were mainly observed in the metformin group.11 Although these studies highlight the efficacy of Imeglimin based on specific glycaemic parameters, they cannot reliably examine the true effect of Imeglimin on HbA1c, which represents a 3-month blood glucose average.

In a multicentre, randomized controlled trial, 156 patients (HbA1c >7.5%) were randomized 1:1 to receive Imeglimin 1,500 mg BID or placebo, added to a stable dose of metformin (1,500–2,000 mg/day). At 12 weeks, patients on combination metformin + Imeglimin therapy had a significant decrease from baseline in both HbA1c (8.5–7.8% versus 8.6–8.3%) and FPG (10.4–9.5% versus 10.3–10.6%) when compared with the metformin + placebo group. Metformin + Imeglimin therapy was well tolerated, with a similar safety profile to metformin + placebo. In a second multicentre, randomized, placebo-controlled study,

conducted by Fouquieria et al., 170 patients (HbA1c >7.5%) on sitagliptin monotherapy were randomized to receive sitagliptin + placebo or sitagliptin + Imeglimin 1,500 mg BID for 12 weeks. In the Imeglimin arm, there was a notable decrease in HbA1c (-0.6%) from baseline (8.5%), compared with an increase of 0.12% in the placebo group (baseline HbA1c: 8.47%). There was also a significant decrease in FPG (-0.93% from baseline (10.53%), compared with a decrease of 0.11% in the placebo group. The reported side effects in the Imeglimin group were similar to those in the placebo group. There were also no significant differences in the mean changes from baseline to week 12 between treatment groups for triglyceride and C-reactive protein levels, as well as systolic blood pressure. Based on these studies, it may be concluded that Imeglimin BID dosing is more effective than once-daily dosing, and can be used efficiently in combination with metformin or sitagliptin without any major side effects compared with placebo.

In a recent larger study that included 299 Japanese adults with diabetes who were treatment naïve or previously treated with only one oral antidiabetic medication, the efficacy and safety profile of Imeglimin as a monotherapy was assessed compared with placebo. In this 24-week, randomized, double-blind, parallel group, dose-ranging, phase IIb clinical trial, the participants were randomized (1:1:1:1) to the following: Imeglimin 500 mg, Imeglimin 1,000 mg, Imeglimin 1,500 mg or placebo BID. At week 24, Imeglimin considerably reduced HbA1c versus placebo (Imeglimin 500 mg versus placebo: -0.52%; Imeglimin 1,000 mg versus placebo: -0.94%; Imeglimin 1,500 mg versus placebo: -1.00%). Adverse events were observed in 68.0%, 62.2%, 73.3% and 68.0% of the patients receiving Imeglimin 500 mg, Imeglimin 1,000 mg, Imeglimin 1,500 mg and placebo, respectively. The most common adverse events were infections and infestations, with a slight increase over placebo in all Imeglimin groups. The second most common adverse events were gastrointestinal disorders. The proportion of patients reporting gastrointestinal events was higher in the Imeglimin 1,500 mg group compared with the placebo and other Imeglimin dosage groups; there was a higher proportion of diarrhoea, abdominal discomfort, nausea and vomiting at the dose of 1,500 mg. Hypoglycaemic events were balanced between the groups. According to this trial, Imeglimin was proven to be well tolerated as a monotherapy, significantly boosting glycaemic control by reducing HbA1c, compared with the placebo.

The approval of Imeglimin in Japan is supported by a phase III clinical programme, which includes three trials: TIMES 1, TIMES 2 and TIMES 3 (Trials of Imeglimin for efficacy and

safety). In TIMES 1, which was a randomized, double-blind, placebo-controlled monotherapy study that included 213 Japanese patients (mean age 62 years) with type 2 diabetes, orally administered Imeglimin (1,000 mg BID) was compared with placebo for 24 weeks. In the Imeglimin group, there was a notably greater reduction in HbA1c compared with the placebo group (placebo group mean HbA1c at baseline 7.93%), with an HbA1c placebo-corrected mean change from the baseline of -0.87%. The decrease in FPG level was also higher among patients who received Imeglimin versus placebo (placebo-adjusted least squares [LS] mean decrease of 19 mg/dL in the Imeglimin group). In TIMES 1, only 44.3% of the patients treated with Imeglimin and 44.9% of those given placebo reported adverse effects, while 2.8% and 5.6%, respectively, experienced side effects resulting in treatment discontinuation.

The TIMES 2 and TIMES 3 trial results were recently presented at the 56th European Association for the Study of Diabetes annual meeting. 16,17 In TIMES 2, a 52-week, open-label, parallel-group trial, Imeglimin 1,000 mg BID was orally administered to 714 Japanese patients with type 2 diabetes as monotherapy or as an add-on to stable doses of oral or approved, injectable hypoglycaemic therapies. The respective changes in mean HbA1c values from baseline at 52 weeks after co-administration of Imeglimin and the other studied hypoglycaemic agents were as follows: dipeptidyl peptidase-4 inhibitors (-0.92%), thiazolidinediones (-0.88%), alpha-glucosidase inhibitors (-0.85%), glinides (-0.70%), metformin (-0.67%), sodium–glucose transport protein 2 inhibitors (-0.57%), sulphonylureas (-0.56%), glucagon-like peptide 1 receptor agonists (-0.12%), Imeglimin monotherapy (-0.46%).

In the TIMES 3 trial, the combination of Imeglimin and insulin was studied in a 16-week, double-blind, placebo-controlled, randomized trial of 215 Japanese patients with type 2 diabetes who were insufficiently controlled on insulin therapy (mean HbA1c placebo-corrected reduction from baseline at 16 weeks: -0.60%, $p<0.0001$; primary endpoint). Consequently, in a 36-week, open-label extension period that was not placebo-controlled, 208 participants who completed the first 16-week, placebo-controlled phase of the study received Imeglimin 1,000 mg BID orally and insulin. In the group receiving Imeglimin and insulin for 16 weeks and Imeglimin and insulin for the next 36 weeks, a decrease of 0.64% mean HbA1c versus the baseline was observed. Lastly, in the group that received placebo

and insulin for the first 16 weeks, followed by co-administration of Imeglimin and insulin on the extension period, there was a change of -0.54%, compared with the baseline.

In both TIMES 2 and TIMES 3, the adverse events were similar to previous clinical trials; overall, the safety profile of Imeglimin was favourable and the adverse event incidence was similar to that of a placebo. Hypoglycaemic events reported during TIMES 3 were mild, and the number of patients receiving Imeglimin who experienced hypoglycaemia was similar to the placebo group.[14]

Clinical Uses

The main advantage of Imeglimin is its novel mechanism of action. As the first drug of its kind, it allows patients with type 2 diabetes the opportunity to try to optimize their therapy by targeting multiple mechanisms with one medication to ultimately improve insulin secretion and insulin sensitivity and decrease peripheral insulin resistance.

Imeglimin has been shown to lower A1C in adults with type 2 diabetes. In recent phase 2 and phase 3 clinical trials, Imeglimin 1,000 mg twice daily was found to lower A1C by 0.5–1%. Furthermore, Imeglimin 1,500 mg twice daily, when added to the DPP-4 inhibitor sitagliptin or to metformin, resulted in A1C reductions of 0.6 and 0.65%, respectively (8). The safety profile is also promising, with no major adverse events, cardiovascular events, or increased incidence of hypoglycemia in patients treated with Imeglimin.[15-19]

Side effect

Imeglimin is associated with gastrointestinal adverse reactions such as nausea, abdominal pain, and vomiting. The incidence of gastrointestinal disorders increased as the dose increased and was better tolerated at a dose of 1,000 mg twice daily than at a dose of 1,500 mg twice daily. Ongoing and future studies of Imeglimin will continue to evaluate and shed light on the tolerability and safety of this agent. Furthermore, Imeglimin has not been fully studied in patients with hepatic dysfunction and chronic kidney disease.[20-21]

CONCLUSION

Imeglimin is the first member of promising oral antidiabetic agents known as glimins, which are currently is in phase 3 trial. It is an inhibitor of the oxidative-phosphorylation process and thereby can provide potent metabolic effects, including on glucose homeostasis. There is growing evidence that Imeglimin reduces postprandial hyperglycemia, normalizes glycated

hemoglobin, and improves beta-cell function in patients with T2DM. Moreover, other possible molecular pathways may be involved which have not been evaluated yet. For example, modulatory effects of Imeglimin on inflammatory responses, possible effects on adipokines and adiponectins, and the possible effects of Imeglimin on glucagon secretion as well as other molecular pathways by which Imeglimin induces insulin sensitivity could be examined in future studies to recognize all aspects of the pharmacologic potentials of Imeglimin.

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