0062. World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease, 19th–21st November 2015, Los Angeles, California, USA

Imeglimin, a New Oral Anti-Hyperglycemic Agent Controls Fasting and Post-Prandial Glucose through an Improvement in both Insulin Secretion and Insulin Sensitivity

Pascale Fouqueray, MD PhD,[1] Sebastien Bolze, PhD,[1] Valdis Pirags, MD,[2] Clifford J. Bailey, PhD,[3] Giovanni Pacini, DSc,[4] Silvio E. Inzucchi, MD,[5] John E. Gerich, MD,[6] Michael Roden, MD,[7–9] Harold E. Lebovitz, MD,[10]

[1]Poxel SA; [2]Paul Stradins Clinical University Hospital, Riga, Latvia; [3]Aston University, Birmingham, UK; [4]Metabolic (Modeling) Unit, Institute of Biomedical Engineering (ISIB-CNR), Padova, Italy; [5]Yale University School of Medicine, New Haven, CT, USA; [6]University of Rochester School of Medicine, Rochester, NY, USA; [7]Department of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [8]Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [9]German Centre for Diabetes Research, Partner Düsseldorf, Germany; [10]State University of New York, Health Sciences Center, Brooklyn, NY, USA

Abstract

Imeglimin is a novel glucose-lowering agent that targets mitochondrial bioenergetics and improves both insulin secretion and sensitivity. This trial assessed the effect of Imeglimin on fasting (FPG) and post-prandial glucose (PPG) control in patients with type 2 diabetes, washed-out of their previous metformin monotherapy.

During this multi-center, double-blind, placebo-controlled, parallel-group, 18-week Phase 2 study and after a 4-week wash-out period, fifty-nine patients (52.5% female; mean age, 56.4 years; HbA_{1c}, 8.13%; BMI, 32.9 kg/m²) were randomized to either Imeglimin 1500 mg BID or placebo. The primary efficacy endpoint was placebo-adjusted reduction of AUC glucose from baseline during a 3-hour OGTT; secondary endpoints included changes in FPG, HbA_{1c}, insulin, C-peptide, AUC insulin and C-peptide to glucose ratio, insulin secretion (insulinogenic index) and insulin sensitivity (Stumvoll) derived indexes.

Imeglimin versus placebo significantly reduced AUC glucose from baseline (–439.2 mmol/L; –17%, p=0.001), the FPG (–1.22 mmol/L; –16%, p=0.022) and the HbA_{1c} by –0.62% (p=0.013). Imeglimin increased both (1) *insulin secretion*, as evidenced by (a) an increase in the incremental AUC insulin and C-peptide to glucose ratio (p=0.025 and 0.004, respectively) and (b) the insulinogenic index (p=0.025) and (2) *insulin sensitivity*, as evidenced by an increase in the Stumvoll index (p=0.001). One patient (3.3%) on Imeglimin required glycemic rescue treatment compared to 10 patients (34.5%) on placebo. Body weight remained stable in both groups. Imeglimin was also generally well tolerated with no reported serious treatment-related adverse events.

In conclusion, Imeglimin appears to have a unique antihyperglycemic profile, enabling control of FPG and PPG by improving both insulin secretion and insulin sensitivity, with a good safety profile.

Background

- Imeglimin is the first in a new tetrahydrotriazine-containing class of oral anti-diabetic agents, the Glimins
- Imeglimin targets mitochondrial bioenergetics and improves the mitochondrial dysfunction observed in high-fat, high-sucrose diet (HFHSD) mice models[1]
- Imeglimin has been shown to induce glucose-stimulated insulin secretion by improving β-cell glucose sensitivity in patients with type 2 diabetes (T2D)[2] and to normalize glucose tolerance and insulin sensitivity in models of diabetes[1]
- The efficacy of Imeglimin has been demonstrated in T2D patients, both as mono and add-on (metformin and sitagliptin) therapies with no safety signals to date (800 subjects)[3–5]
- Imeglimin is being developed as an alternative treatment option with a complementary mode of action to drugs that target insulin-resistant organs or insulin secretion and β-cell protection

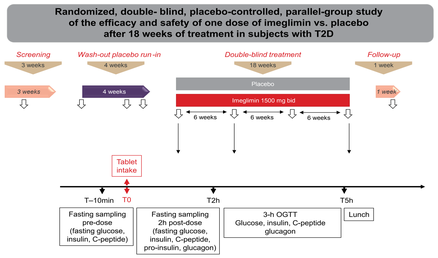
Objectives

This Phase 2 study assessed the effect of 18 weeks of treatment with Imeglimin versus placebo on glucose tolerance with AUC glucose during a 3-hour 75 g oral glucose tolerance test (OGTT) as the primary evaluation criterion in T2D subjects

Research Design and Methods

- This was a multicenter, double-blind, placebo-controlled, randomized study in subjects with T2D treated for 18 weeks with Imeglimin 1500 mg bid (Figure 1)
- Subjects were previously managed using monotherapy with metformin and entered a single-blind placebo-controlled run-in period of 4 weeks before a 1:1 randomization to either Imeglimin or placebo

Figure 1: Study design



bid, twice daily; OGTT, oral glucose tolerance test; T2D, type 2 diabetes

The primary efficacy endpoint of the study was the placebo-adjusted reduction in AUC glucose during a 3-hour OGTT from baseline to week 18. Key secondary endpoints included change from baseline to week 18 in FPG and HbA_{1c}.

Other secondary endpoints included change from baseline to week 18 in fasting and AUC insulin, C-peptide and glucagon, incremental AUCs for glucose, insulin and C-peptide, AUC insulin or C-peptide/glucose ratio, parameters of insulin secretion and β-cell function, and insulin sensitivity (Stumvoll index) derived index.

Pancreatic β-cell function was assessed using a previously characterized model that describes the relationship between insulin secretion and glucose concentration.[6–8] The model expressed insulin secretion (in pmol/min per m² of body surface area). The following parameters were calculated from the model:

- The sensitivity of the β cell to changes in plasma glucose levels, called glucose sensitivity
- The insulin response to the rate of change in glucose concentration, called rate sensitivity and related to early insulin release
- The safety and tolerability of 18 weeks of treatment with Imeglimin versus placebo were assessed, with adverse events categorized by relationship and severity

Results

Patients

- In total, 59 subjects were randomized for the study (Table 1a)
- Baseline characteristics were balanced between all treatment groups (Table 1b)

Table 1a and b: Subject disposition and baseline characteristics

a)

	Placebo	Imeglimin 1500 mg bid	Total
Randomized	**29**	**30**	**59**
ITT	**28**	**29**	**57**
Drop-out	**11 (37.9%)**	**5 (16.7%)**	**16 (27.1%)**
• Withdrawal of consent	0	4 (13.3%)	4 (6.8%)
• Rescue therapy	10 (34.5%)	1 (3.3%)	11 (18.6%)
• Protocol deviation	1 (3.4%)	0	1 (1.7%)
• Adverse events	0	0	0

bid, twice daily; ITT; intention to treat

b)

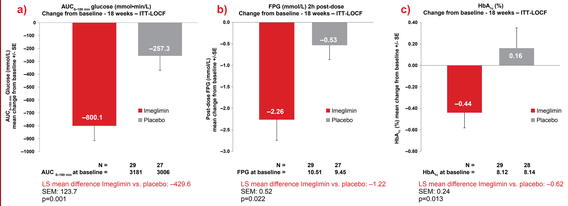
	Placebo	Imeglimin 1500 mg bid
Mean duration of diabetes (year)	4.99	5.86
Age (year) (SD)	54.3 (8.9)	58.4 (8.0)
Male (n) (%)	16 (55.2%)	12 (40%)
BMI (kg/m²) (SD)	32.91 (4.26)	32.83 (4.95)
HbA_{1c} (%) (SD)	8.14% (0.61)	8.12% (0.56)
FPG (mmol/L) (SD)	10.25 (1.92)	11.33 (2.55)

bid, twice daily; BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; SD, standard deviation

Efficacy

- Imeglimin improved glucose control by significantly improving glucose tolerance, FPG and HbA_{1c} in a fairly balanced manner (Figure 2a, b and c):
  - AUC glucose from baseline (–439.2 mmol/L; –17%, p=0.001)
  - FPG (–1.22 mmol/L; –16%, p=0.022)
  - leading to an overall change of –0.62% (p=0.013) in HbA_{1c}

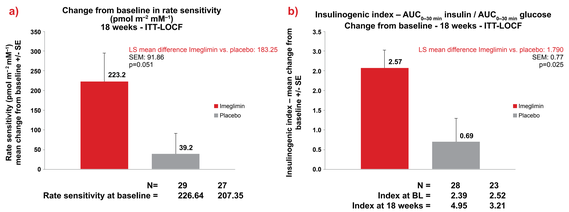
Figure 2a, b and c: Imeglimin significantly improved glucose tolerance (a), reduced FPG (b), and decreased HbA_{1c} (c) compared with placebo



AUC, area under curve; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; ITT, intention to treat; LOCF, last observation carried forward; LS, least squares; SE, standard error; SEM, standard error of the mean

- Imeglimin improved insulin secretion as confirmed by:
  - The doubling of the rate sensitivity and insulinogenic index as measures for early insulin secretion (Figure 3a and b)
  - The beneficial effect of Imeglimin on β-cell function after 18 weeks of treatment was confirmed by a change versus placebo in the ratio of incremental AUC C-peptide over incremental AUC glucose from baseline (0.091; +59%, p=0.003) (data not shown)

Figure 3a and b: Imeglimin improved insulin secretion as demonstrated by rate sensitivity (a) and insulinogenic index (b)

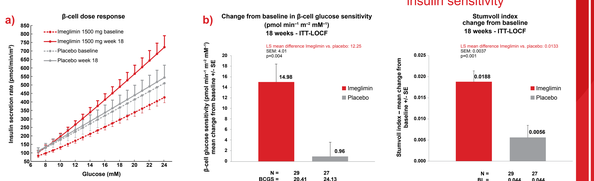


AUC, area under curve; BL, baseline; ITT, intention to treat; LOCF, last observation carried forward; LS, least squares; SE, standard error; SEM, standard error of the mean

- Imeglimin improved several makers of β-cell function:
  - β-cell glucose sensitivity (derived from the mean slope of the insulin secretion rate as a function of glucose concentration) is increased by 73% (Figure 4a and b)
  - Insulin secretion at a fixed glucose level of 10 mM (approximately the mean fasting glucose concentration in the groups) and at 18 mM (approximately the mean peak glucose concentration during the OGTT) was significantly improved by 48% and 64%, respectively (data not shown)
  - Total insulin secretion rate during the course of the OGTT was also significantly greater with Imeglimin versus placebo (p=0.035) (data not shown)

Figure 4a, b: Imeglimin improved β-cell dose response (a) and glucose sensitivity (b)

Figure 5: Imeglimin significantly improved insulin sensitivity



BCGS, β-cell glucose sensitivity; BL, baseline; ITT, intention to treat; LOCF, last observation carried forward; LS, least squares; SE, standard error; SEM, standard error of the mean

- Imeglimin improved insulin sensitivity as indicated by an increase in the Stumvoll index (p=0.001) (Figure 5)
- Imeglimin treatment had no effect on fasting or stimulated glucagon levels

Table 2: Imeglimin has a good tolerability and safety profile

	Placebo (n=29) N (%) – E	1500 mg bid (n=30) N (%) – E
Any AE	19 (65.5%) – 40	13 (43.3%) – 53
Any TEAE	**17 (58.6%) – 25**	**8 (26.7%) – 24**
• Mild	8 (27.6%) – 9	7 (23.3%) – 20
• Moderate	11 (37.9%) – 15	2 (6.7%) – 4
• Severe	1 (3.4%) – 1	–
Any related TEAE	**4 (13.8%) – 5**	**1 (3.3%) – 1**
• Hyperglycemia	4 (13.8%) – 5	1 (3.3%) – 1
Any AE leading to discontinuation	10 (34.5%) – 10	1 (3.3%) – 1
• Hyperglycemia		
Any serious TEAE	–	**1 (3.3%) – 3**
• Related	–	–
• Non-related	–	1 (3.3%) – 3
• Meigs' syndrome		1 (3.3%) – 1
• Cerebrovascular accident		1 (3.3%) – 1
• Hypertension		1 (3.3%) – 1
Any MACE	–	**1 (3.3%) – 1**

AE, adverse event; bid, twice daily; MACE, major adjudicable cardiovascular event; TEAE, treatment-emergent adverse event

Safety and tolerability

- Imeglimin was well tolerated with 26.7% of subjects presenting at least one treatment-emergent adverse event (TEAE) versus 58.6% of subjects in the placebo group. Most of the TEAEs were not related, with only one (3.3%) related adverse event (AE) of hyperglycemia in one subject in the Imeglimin group versus five (13.8%) related AEs of hyperglycemia in four subjects in the placebo group. Only one (3.3%) subject in the Imeglimin group discontinued the study for rescue therapy versus 10 (34.5%) subjects in the placebo group (Table 2)
- Three non-related serious AEs occurred in one subject in the Imeglimin group (cerebrovascular accident, worsening of hypertension and Meig's syndrome)
- No episode of hypoglycemia was reported

Discussion

- Imeglimin is the first in new class of oral antihyperglycemic agents with a unique mechanism of action, targeting mitochondrial bioenergetics. This leads to an improvement in both glucose-dependent insulin secretion and insulin sensitivity. This translates into a significantly balanced reduction in the 2-hour post-dose FPG and AUC glucose versus baseline with a consistent effect on HbA_{1c} reduction over the 18 weeks of treatment
- Imeglimin improves several markers of the β-cell function, which may be viewed as positive in light of the progression of the disease
- Imeglimin has no effect on glucagon and a neutral effect on other cardiovascular risk factors (body weight, lipids, blood pressure and CRP)
- The very safe profile of Imeglimin is comparable with previous Phase 2b monotherapy trial and with combination trials with metformin and with sitagliptin
- The unique mode of action of Imeglimin, with its dual effect on glucose-dependent insulin secretion and insulin action in addition to its cell protective capacity, makes it a promising candidate for the future of T2D treatment

References

1. Vial G, et al. *Diabetes* 2015;64:1–11; 2. Pacini G, et al. *Diabetes, Obesity and Metabolism* 2015;17:541–545; 3. Pirags V, et al. *Diabetes, Obesity and Metabolism* 2012;14:852–858; 4. Fouqueray P, et al. *Diabetes Care* 2013;36:565–568; 5. Fouqueray P, et al. *Diabetes Care* 2014;10:1935–5548; 6. Mari A, et al. *American Journal of Physiology, Endocrinology and Metabolism* 2002;283:E1159–E1166; 7. Mari A, et al. *Diabetes* 2002;51(Suppl 1):S221–S226; 8. Mari A & Ferrannini E. *Diabetes, Obesity and Metabolism* 2008;10(Suppl 4):77–87

Presenting author: Dr Pascale Fouqueray
Email: pascale.fouqueray@poxelpharma.com