

The Efficacy and Safety of Imeglimin as Add-on Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy

PASCALE FOUQUERAY, MD¹
 VALDIS PIRAGS, MD²
 SILVIO E. INZUCCHI, MD³
 CLIFFORD J. BAILEY, PhD⁴

GUNTRAM SCHERNTHANER, MD⁵
 MICHAELA DIAMANT, MD⁶
 HAROLD E. LEBOVITZ, MD⁷

OBJECTIVE—A 12-week study assessed the efficacy and safety of a new oral antidiabetic agent, imeglimin, as add-on therapy in type 2 diabetes patients inadequately controlled with metformin alone.

RESEARCH DESIGN AND METHODS—A total of 156 patients were randomized 1:1 to receive imeglimin (1,500 mg twice a day) or placebo added to a stable dose of metformin (1,500–2,000 mg/day). Change in A1C from baseline was the primary efficacy outcome; secondary outcomes included fasting plasma glucose (FPG) and proinsulin/insulin ratio.

RESULTS—After 12 weeks, the placebo-subtracted decrease in A1C with metformin-imeglimin was -0.44% ($P < 0.001$). Metformin-imeglimin also significantly improved FPG and the proinsulin/insulin ratio from baseline (-0.91 mg/dL and -7.5 , respectively) compared with metformin-placebo (0.36 mg/dL and 11.81). Metformin-imeglimin therapy was generally well-tolerated with a comparable safety profile to metformin-placebo.

CONCLUSIONS—Addition of imeglimin to metformin improved glycemic control and offers potential as a new treatment for type 2 diabetes.

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Imeglimin is the first in a new tetrahydrotriazine-containing class of oral antidiabetic agents, the glimins. Imeglimin decreases hepatic glucose production, increases muscle glucose uptake, and improves pancreatic glucose-dependent insulin secretion (1).

Previous studies have demonstrated imeglimin to be as effective as metformin in improving glycemia (2). Since metformin is the preferred first-line therapy for type 2 diabetes, the current study examined the efficacy, safety, and tolerability of imeglimin in combination with metformin in patients with type 2 diabetes

inadequately controlled with metformin alone.

RESEARCH DESIGN AND METHODS

This was a 12-week, multicenter (20 centers in three countries), randomized, double-blind, placebo-controlled, parallel-group study in subjects with type 2 diabetes inadequately controlled with the maximum tolerated dose of metformin. The average metformin doses at baseline remained the same throughout the study: 1,901 mg in the metformin-imeglimin group and 1,914 mg in the metformin-placebo group.

After screening, eligible subjects were enrolled into a single-blind, placebo, 2-week run-in period under previous metformin treatment and placebo-imeglimin twice a day (BID). Subjects were then randomized 1:1 to receive 1,500 mg BID imeglimin or placebo-imeglimin BID in addition to their lead-in dose of metformin for 12 weeks, followed by a 1-week period with placebo-imeglimin.

Male and female subjects with type 2 diabetes ($N = 156$), aged ≥ 18 to ≤ 70 years, inadequately controlled ($A1C \geq 7.5\%$) by metformin alone (1,500–2,000 mg/day, both inclusive) were included. Enrolled subjects had received a stable dose of metformin for at least 10 weeks before randomization and had received no other glucose-lowering medication within 3 months prior to randomization. Most other therapeutic classes of concomitant medication were permitted. Exclusion criteria included impaired hepatic or renal function, inadequately controlled hypertension, and clinically significant microvascular or macrovascular complications.

The study protocol was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (3). All participants provided written informed consent before any study-related activities.

The primary efficacy outcome was change in A1C from baseline to week 12. Secondary end points included changes from baseline in fasting plasma glucose (FPG; mg/dL) and proinsulin (pmol/L)/insulin (μ U/mL) ratio. The percentage of patients achieving an A1C $< 7\%$ or a decrease from baseline $\geq 0.5\%$ at week 12 were calculated, and subgroup analyses were performed to determine the effect of baseline A1C and BMI on the change in A1C from baseline to week 12.

Adverse events were specifically assessed into treatment-related and severity.

Statistical analysis

Intention-to-treat efficacy analysis included all randomized subjects who received

From ¹Poxel SA, Lyon, France; the ²Department of Internal Medicine, Paul Stradins Clinical University Hospital, Riga, Latvia; the ³Section of Endocrinology, Yale School of Medicine, New Haven, Connecticut; ⁴School of Life and Health Sciences, Aston University, Birmingham, United Kingdom; the ⁵Department of Internal Medicine, Rudolfstiftung Hospital, Vienna, Austria; the ⁶Diabetes Center/Department of Internal Medicine, VU University Medical Center, Amsterdam, the Netherlands; and the ⁷Department of Medicine, State University of New York, Health Sciences Center, Brooklyn, New York.

Corresponding author: Pascale Fouquieray, pascal.fouquieray@poxelpharma.com.

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at least one dose of imeglimin or placebo and provided a baseline and at least one postbaseline A1C value. Data are presented as last observation carried forward (LOCF). Change of A1C from baseline to week 12 or LOCF was assessed with an ANCOVA model. Statistical significance was assessed at the 5% level.

RESULTS—Demographic and baseline characteristics were similar between the two treatment arms. A1C decreased from baseline to week 12 by -0.65% with metformin-imeglimin and -0.21% with metformin-placebo groups ($P = 0.001$), resulting in a mean treatment difference of -0.44% (95% CI -0.71 to -0.17).

Statistically significant reductions in FPG ($P < 0.001$) and the proinsulin/insulin ratio ($P = 0.007$) from baseline compared with metformin-placebo were also observed (Table 1).

More subjects achieved a decrease in $A1C \geq 0.5\%$ with metformin-imeglimin (63.6%) than metformin-placebo (36.4%)

Table 1—Efficacy and safety results of the imeglimin add-on to metformin phase II study

Statistic/category	Characteristic	Metformin + imeglimin 1,500 mg BID	Metformin + placebo
Baseline	A1C (%)		
N		77	78
Mean (SD)		8.5 (0.72)	8.6 (0.73)
Minimum–maximum		7.1–10.2	7.3–10.2
Week 12 (end of treatment)			
N		68	69
Mean (SD)		7.84 (1.03)	8.31 (0.94)
Minimum–maximum		5.5–11.0	6.6–11.3
Change from baseline to week 12 (LOCF)			
LS mean (SE)		-0.65 (0.1)	-0.21 (0.1)
P value compared with placebo		$P = 0.001$	
Baseline	FPG (mg/dL)		
N		77	78
Mean (SD)		10.4 (2.47)	10.28 (2.32)
Minimum–maximum		6.4–18.9	6.4–17.1
Week 12 (end of treatment)			
N		67	71
Mean (SD)		9.53 (2.57)	10.59 (2.62)
Minimum–maximum		5.5–18.5	4.0–18.7
Change from baseline to week 12 (LOCF)			
LS mean (SE)		-0.91 (0.24)	0.36 (0.24)
P value compared with placebo		$P < 0.001$	
Baseline	Proinsulin/insulin ratio		
N		61	64
Mean (SD)		64.12 (36.18)	62.62 (37.03)
Minimum–maximum		2.3–168.7	9.6–211.9
Week 12 (end of treatment)			
N		53	56
Mean (SD)		58.15 (29.54)	74.32 (52.03)
Minimum–maximum		10.5–176.5	19.7–288.3
Change from baseline to week 12 (LOCF)			
LS mean (SE)		-7.5 (5.12)	11.81 (4.83)
P value compared with placebo		$P = 0.007$	
Any TEAE	Adverse events		
Number of events		43	28
Number of subjects with AEs (%)		18 (23.1)	15 (19.2)
SAE			
Number of events		0	3
Number of subjects with AEs (%)		0 (0.0)	3 (3.8)
TEAE leading to withdrawal			
Number of events		2	1
Number of subjects with AEs (%)		2 (2.6)	1 (1.3)
EAC adjudicated CV event			
Number of events		0	4
Number of subjects with AEs (%)		0 (0.0)	2 (2.6)

AE, adverse events; CV, cardiovascular; EAC, Event Adjudication Committee; N = number of subjects exposed; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

($P = 0.001$). Furthermore, 14.3% of subjects receiving metformin-imeglimin achieved an A1C $<7\%$ compared with 3.8% of subjects receiving metformin-placebo ($P = 0.04$).

Metformin-imeglimin was more effective than placebo in reducing mean A1C from baseline after 12 weeks of treatment in all subgroup analyses. For prespecified baseline A1C subgroup measurements $<8.0\%$, $8.0\text{--}9.0\%$, and $>9.0\%$, reductions in mean (SD) A1C (%) from baseline to week 12 for metformin-imeglimin were -0.41% (0.44), -0.68% (0.86), and -0.78% (0.98), respectively, as compared with -0.09% (0.59), -0.15% (0.96), and -0.43% (0.89) for metformin-placebo. Reductions in A1C based on baseline BMI were similar for subjects with baseline BMI (kg/m^2) ≤ 30 and for subjects with baseline BMI (kg/m^2) > 30 for both treatment arms of the study.

Metformin-imeglimin therapy was well-tolerated with a safety profile comparable to metformin-placebo. No serious adverse events or cardiovascular events were reported with metformin-imeglimin. Although not statistically significant, a slight decrease in mean values for body weight ($P = 0.08$) and waist circumference ($P = 0.053$) was observed for metformin-imeglimin compared with metformin-placebo.

CONCLUSIONS—Current guidelines recommend metformin as the first-line pharmacological treatment for type 2 diabetes (4). However, metformin alone is frequently insufficient to obtain or maintain glycemic goals; therefore, many patients require multiple pharmacotherapies for optimal disease management (5).

The current study shows that imeglimin appeared to complement the actions of metformin by producing modest, but clinically and statistically significant improvements in A1C, FPG, and proinsulin/insulin ratio. Metformin-imeglimin progressively reduced the mean A1C value throughout the 12-week treatment period, implying that further improvements might be expected beyond 12 weeks. This reduction in A1C is comparable to other recently approved antihyperglycemic treatments (6–8). Furthermore, the effect on A1C is related to beneficial effects of imeglimin on both FPG and glucose tolerance, as previously demonstrated (9).

Metformin-imeglimin was effective in reducing the proinsulin/insulin ratio, indicating a potential beneficial effect of

imeglimin on β -cell function. Further studies are necessary to determine if this translates to β -cell protection over time, as suggested in previous preclinical studies in which imeglimin reduced β -cell apoptosis induced by cytokine stress and high glucose conditions (2).

Drug–drug interaction studies in healthy subjects have shown that multiple dosing of imeglimin did not affect metformin exposure (unpublished data, Poxel). The novel mechanism of action of imeglimin provides additional benefits to metformin monotherapy in patients with type 2 diabetes.

Metformin-imeglimin was generally well-tolerated compared with metformin-placebo with no serious adverse events or cardiovascular events reported. This phase II study demonstrated that first-in-class imeglimin was well-tolerated and effective when combined with metformin as a potential new treatment for type 2 diabetes.

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