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Imeglimin: A new antidiabetic agent that provides added benefit to DPP-4 inhibitor therapy

Pascale Fouqueray, MD[1], Valdis Pirags, MD[2], Michaela Diamant, MD[3], Guntram Schernthaner, MD[4], Harold E. Lebovitz, MD[5], Silvio E. Inzucchi, MD[6], Clifford J. Bailey, PhD[7]

[1]Poxel SA; [2]Paul Stradins Clinical University Hospital, Riga, Latvia; [3]VU University Medical Center, Amsterdam, The Netherlands; [4]Rudolfstiftung Hospital, Vienna, Austria; [5]State University of New York, Health Sciences Center, Brooklyn, NY, USA [6]Yale School of Medicine, New Haven, CT, USA; [7]Aston University, Birmingham, United Kingdom

Abstract

This 12-week study assessed the efficacy and tolerability of imeglimin as add-on therapy to sitagliptin in type 2 diabetes patients (T2D) inadequately controlled with sitagliptin monotherapy.

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study of imeglimin (1,500 mg BID) or placebo added to sitagliptin (100 mg QD) in 170 patients with type 2 diabetes (mean age, 56.8 years; 52.9% male; BMI, 32.2 kg/m2) who were inadequately controlled with sitagliptin alone (A1C ≥ 7.5%) during a 12-week run-in period. The primary efficacy endpoint was change in A1C from baseline vs. placebo; secondary endpoints included corresponding changes in fasting plasma glucose (FPG), % A1C responders, and certain non-glycemic parameters.

Imeglimin-sitagliptin reduced A1C (LS mean) from baseline (8.5%) by 0.60% compared with an increase of 0.12% with placebo (P <0.001), for a placebo-adjusted decrease of 0.72% with imeglimin. The corresponding changes in FPG were a decrease of 0.93 mmol/L with imeglimin vs. a decrease of 0.11 mmol/L with placebo (P =0.014). 54.3% of subjects achieved a decrease in A1C ≥ 0.5% with imeglimin vs. 21.6% with placebo (P <0.001), and 19.8% of subjects receiving imeglimin achieved an A1C ≤ 7% compared with placebo (1.1%), (P =0.004). Sitagliptin-imeglimin was generally well tolerated with a comparable safety profile to the sitagliptin-placebo group and no related treatment-emergent adverse events.

Imeglimin demonstrated incremental efficacy as an add-on therapy to sitagliptin, with comparable tolerability to sitagliptin-placebo, highlighting the potential for imeglimin to complement the efficacy of oral anti-hyperglycemic treatments.

Background

- Imeglimin is the first in a new Tetrahydrotriazine-containing class of oral anti-diabetic agents, the glimins.
- In preclinical studies, imeglimin has been shown to reduce excessive hepatic glucose production, increase glucose uptake in skeletal muscle and improve insulin secretion in response to glucose[1].
- Imeglimin was effective as a monotherapy in achieving glycemic control and has exhibited a favorable tolerability profile in two Phase IIa studies compared with metformin[2].
- Imeglimin has also been shown to improve glycemic control in people with type 2 diabetes inadequately controlled on maximal doses of metformin[3].
- Imeglimin is being developed as an alternative treatment with a mechanism of action that complements those of drugs that act on insulin-resistant organs or on insulin secretion and ß-cell protection.

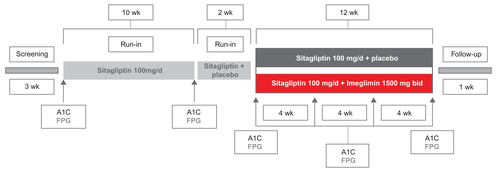
Objective

This Phase II study examined the efficacy, safety and tolerability of imeglimin when combined with sitagliptin in patients with T2D inadequately controlled with sitagliptin alone.

Research Design and Methods

- This 12-week, multi-center, randomized, double-blind, placebo controlled, parallel-group study included subjects with T2D inadequately controlled by 100 mg once-a-day sitagliptin.
- Following a maximum 3-week screening period, eligible subjects, naïve of treatment or on metformin or sulfonylurea monotherapy, were switched to receive 100 mg QD sitagliptin for a 12-week run-in period, before 1:1 randomization to receive 1,500 mg BID imeglimin or placebo (Figure 1).

Figure 1: Imeglimin add-on to sitagliptin study design



- The primary efficacy endpoint of the study was change in A1C from baseline to week 12 versus placebo; secondary end points included changes from baseline in FPG, % of A1C responders, and non-glycemic parameters.
- The safety and tolerability of 12-week treatment with imeglimin versus placebo was assessed, and adverse events were categorized by relation to treatment and severity.

Results

Patients

- Baseline demographic characteristics were similar between the two treatment arms (Table 1).
- A total of 170 subjects were randomized to receive treatment; in the ITT population, 81 subjects received imeglimin and 88 subjects received placebo, in addition to their run-in dose of 100 mg QD sitagliptin.
- Although there was a large variation in A1C responses during the sitagliptin run-in period, the average A1C values in the ITT population changed by -0.01% and 0.04% for imeglimin and placebo treatment groups respectively.

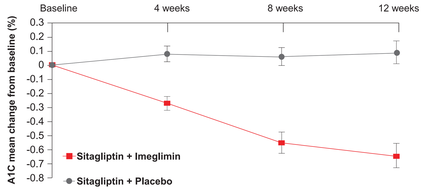
Table 1: Demographics and baseline characteristics (safety population)

Population Characteristic	Sitagliptin + Imeglimin N=82	Sitagliptin + Placebo N=88
Age (years) (SD)	57.5 (8.1)	56.1 (7.9)
Gender		
Male (%)	41 (50)	59 (55.7)
Female (%)	41 (50)	39 (44.3)
Race		
Caucasian (%)	82 (100)	88 (100)
Duration of diabetes (years)	4.95	5.24
BMI (kg/m2) (SD)	32.04 (4.51)	32.34 (4.47)
A1C (%) (SD)	8.47 (0.72)	8.53 (0.66)
FPG (mmol/L) (SD)	10.53 (2.09)	10.91 (2.31)

Efficacy

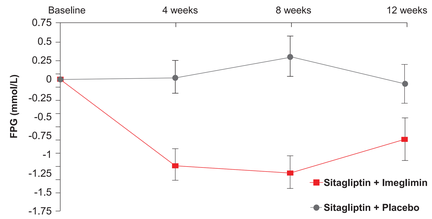
- The addition of imeglimin to sitagliptin demonstrated incremental efficacy in reducing A1C from baseline (-0.60%) compared with no significant change (0.12%) with placebo (Figure 2). The difference in LS mean change (95% CI) from baseline versus sitagliptin-placebo in the ITT population was -0.72% (-0.95 to -0.49), (P<0.001).

Figure 2: Effect of sitagliptin-imeglimin versus sitagliptin-placebo: A1C reductions over the 12-week double-blind treatment period



- Sitagliptin-imeglimin has shown imeglimin to provide incremental efficacy for all A1C baseline subgroups; placebo-subtracted reductions in mean A1C from baseline to week 12 with sitagliptin-imeglimin were 0.78%, 0.62%, and 0.95% for A1C baseline subgroups <8.0%, 8.0–9.0%, and >9.0%, respectively.
- The addition of imeglimin to sitagliptin was associated with a statistically significant greater proportion of responders achieving an A1C ≤7% (19.8%) compared with sitagliptin-placebo (1.1%) (P =0.004).
- Sitagliptin-imeglimin significantly decreased mean FPG levels from baseline to week 12 by -0.93 mmol/L, compared with -0.11 mmol/L in the sitagliptin-placebo treatment arm (P <0.014) (Figure 3).

Figure 3: Effect of sitagliptin-imeglimin versus sitagliptin-placebo: change in FPG (mmol/L) from baseline to week 12



- Positive trends for improvements in non-glycemic parameters, HOMA-IR triglyceride and hs-CRP were observed with sitagliptin-imeglimin compared with sitagliptin-placebo (Table 2).

Table 2: Change in non-glycemic efficacy parameters

Efficacy endpoint		Sitagliptin + Imeglimin 1,500mg BID (N=81)	Sitagliptin + Placebo (N=88)
HOMA-IR	Baseline (SD)	5.14 (4.8)	5.22 (4.98)
	Week 12/end of treatment (SD)	4.46 (3.59)	5.52 (7.02)
	LS mean change (SE)	–0.184 (0.68)	0.098 (0.64)
	P-value compared to placebo	P =0.572	
Triglycerides (mmol/L)	Baseline (SD)	2.35 (1.36)	2.36 (1.45)
	Week 12/end of treatment (SD)	2.26 (1.50)	2.55 (2.17)
	LS mean change (SE)	–0.167 (0.19)	0.161 (0.18)
	P-value compared to placebo	P =0.106	
hs-CRP (mg/L)	Baseline (SD)	4.04 (5.58)	4.64 (4.87)
	Week 12/end of treatment (SD)	3.42 (4.94)	4.75 (4.82)
	LS mean change (SE)	–1.16 (0.64)	0.009 (0.59)
	P-value compared to placebo	P =0.082	

Safety

- Imeglimin as an add-on treatment to sitagliptin was generally well tolerated with a comparable safety profile to the sitagliptin monotherapy run-in period (Table 3).
- No treatment-related TEAEs were reported in the sitagliptin-imeglimin group, compared with 7 events from 3 subjects (3.4%) in the sitagliptin-placebo group.
- There was no incidence of hypoglycemia reported in the sitagliptin-imeglimin treatment group.
- One subject in the sitagliptin-imeglimin group experienced a serious adverse event during the double-blind treatment period (surgery for appendicitis) not related to treatment.

Table 3: Summary of Adverse Events (Safety Population)

	Sitagliptin + Imeglimin 1,500 mg BID N=82				Sitagliptin + Placebo N=88			
	Sitagliptin Run-In		Double-blind Treatment Period		Sitagliptin Run-In		Double-blind Treatment Period	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAEs	12 (14.6)	18	12 (14.6)	15	12 (13.6)	13	20 (22.7)	28
Any Related TEAEs	2 (2.4)	5	0 (0.0)	0	0 (0.0)	0	3 (3.4)	7
Gastrointestinal	1 (1.2)	1	0 (0.0)	0	0 (0.0)	0	1 (1.1)	3
Abdominal Pain Upper	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.1)	1
Constipation	1 (1.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Vomiting	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.1)	2
Investigations	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.1)	1
Weight increased	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.1)	1
Metabolism	1 (1.2)	4	0 (0.0)	0	0 (0.0)	0	2 (2.3)	2
Hyperglycemia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.1)	1
Hypoglycemia	1 (1.2)	4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Increased Appetite	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.1)	1
CNS	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.1)	1
Headache	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.1)	1
Any EAC adjudicated cardiovascular events	0 (0.0)	0	1 (1.2)	1	0 (0.0)	0	0 (0.0)	0
TEAE leading to withdrawal	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

E = number of events; N = number of subjects exposed; n = number of subjects with AEs;
SAE = serious adverse event; TEAE = treatment-emergent AE

Discussion

- The study intended to investigate the incremental effects of imeglimin in patients uncontrolled on sitagliptin.
- The average A1C during the sitagliptin run-in period remained unchanged thereby providing subjects who were considered to be uncontrolled on sitagliptin monotherapy at randomization.
- The mean A1C value in the sitagliptin-imeglimin treatment group was continuing to fall at 12 weeks, therefore further incremental effects on A1C improvements beyond 12 weeks might be anticipated.
- Regardless of baseline A1C, a greater and significant reduction in A1C was observed with sitagliptin-imeglimin treatment compared with sitagliptin-placebo, even for those patients with a baseline A1C <8.0%.
- The glucose lowering effects of imeglimin in combination with sitagliptin, and the previous observations in combination with metformin[3] suggest that the mechanism of action of imeglimin is complementary to, and in part additive to both the DPP-IV inhibitory effect and metformin action on hepatic resistance.

Conclusions

- Twice-daily imeglimin combined with sitagliptin for 12 weeks resulted in statistically significant improvements in A1C and FPG.
- Addition of imeglimin to sitagliptin was generally well tolerated; no treatment-related TEAEs were observed in the sitagliptin-imeglimin treatment group.
- This Phase II study demonstrates that imeglimin may represent a new treatment option for patients with T2D, particularly in combination with other anti-hyperglycemic treatments.

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PAULA STRADIŅA KLĪNISKĀ UNIVERSITĀTES SLIMNĪCA

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Pascale Fouqueray, 200 avenue Jean Jaurès F-69007 Lyon,
pascale.fouqueray@poxelpharma.com