EMERGING TECHNOLOGIES AND THERAPEUTICS

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

Diabetes Care 2014;37:1924–1930 | DOI: 10.2337/dc13-2349

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

OBJECTIVE

This 12-week study assessed the efficacy and tolerability of imeglimin as add-on therapy to the dipeptidyl peptidase-4 inhibitor sitagliptin in patients with type 2 diabetes inadequately controlled with sitagliptin monotherapy.

RESEARCH DESIGN AND METHODS

In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, imeglimin (1,500 mg b.i.d.) or placebo was added to sitagliptin (100 mg q.d.) over 12 weeks in 170 patients with type 2 diabetes (mean age 56.8 years; BMI 32.2 kg/m^2) that was inadequately controlled with sitagliptin alone (A1C ≥7.5%) during a 12-week run-in period. The primary efficacy end point was the change in A1C from baseline versus placebo; secondary end points included corresponding changes in fasting plasma glucose (FPG) levels, stratification by baseline A1C, and percentage of A1C responders.

RESULTS

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

CONCLUSIONS

Imeglimin demonstrated incremental efficacy benefits as add-on therapy to sitagliptin, with comparable tolerability to placebo, highlighting the potential for imeglimin to complement other oral antihyperglycemic therapies.

Numerous pharmacological agents for the treatment of type 2 diabetes are available, but many of these agents are associated with side effects and contraindications that limit their use (1,2). Furthermore, the progressive nature of the disease will require the use of combination therapy in many patients over time to attain or

[1]Poxel SA, Lyon, France
[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
[6]Yale School of Medicine, New Haven, CT
[7]Aston University, Birmingham, U.K.

Corresponding author: Pascale Fouqueray, pascale.fouqueray@poxelpharma.com.

Received 10 October 2013 and accepted 5 March 2014.

Clinical trial reg. no. EudraCT 2010-023915-33, www.clinicaltrialsregister.eu.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-2349/-/DC1.

maintain their A1C treatment goals (3). Therefore, as type 2 diabetes remains a challenge to control, there is a need for new and better tolerated combination therapies with complementary mechanisms of action (4).

Imeglimin ((6R)-(+)-4-dimethylamino-2-imino-6methyl-1,2,5,6-tetrahydro-1,3,5, triazine hydrochloride) is the first in a new tetrahydrotriazine-containing class of oral antidiabetic 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 (5). Imeglimin offers a unique mechanism of action that targets the mitochondria and is compatible with drugs that counter insulin resistance or enhance insulin secretion and β-cell protection.

Imeglimin is effective as monotherapy in achieving glycemic control, and has exhibited a favorable tolerability profile in two phase IIa studies compared with metformin, with no serious adverse events reported (6). As preclinical data have shown that imeglimin acts on both insulin-resistant organs and β-cells, the effects of imeglimin have been investigated as an add-on to therapies targeting the liver (metformin) and β-cell (dipeptidyl peptidase-4 [DPP-4] inhibitor). In a recently published add-on trial (7), imeglimin was shown to improve glycemic control in people with type 2 diabetes that was inadequately controlled by metformin monotherapy. The current study examined the efficacy, safety, and tolerability of imeglimin when added to sitagliptin, a DPP-4 inhibitor known to increase glucose-stimulated insulin secretion (8,9), in patients with type 2 diabetes that was inadequately controlled with sitagliptin therapy alone.

RESEARCH DESIGN AND METHODS

This was a 12-week, multicenter (29 centers in three countries), randomized, double-blind, placebo-controlled, parallel-group study in subjects with type 2 diabetes that was inadequately controlled by 100 mg q.d. sitagliptin monotherapy (Fig. 1). Because sitagliptin is used mainly as second-line therapy, very few individuals failing sitagliptin monotherapy are available. Therefore, after a 3-week screening period, eligible subjects were switched from previous treatment (10% were treatment-naive, and 90% were receiving other antihyperglycemic treatments, mainly metformin, although some were receiving sulfonylurea and/or a combination of agents) to 100 mg q.d. sitagliptin for a 12-week run-in period prior to randomization. Any subject who had received thiazolidinediones or insulin within 12 weeks prior to randomization was excluded from the study. To ensure subject compliance, there was a single-blind placebo run-in period 2 weeks before randomization, in which subjects received placebo twice daily in addition to the sitagliptin run-in dose. Subjects were then randomized 1:1 to receive 1,500 mg b.i.d. imeglimin or placebo, while continuing sitagliptin therapy for 12 weeks, followed by a 1-week follow-up period with placebo.

Male and female subjects (*N* = 170), 18–75 years of age, with a BMI of 20–40 kg/m^2 and type 2 diabetes that was inadequately controlled by sitagliptin monotherapy at randomization (A1C ≥7.5%) were included in the double-blind add-on to sitagliptin treatment period with imeglimin or placebo. No other antihyperglycemic agents were allowed to be used during the course of the study. However, most other therapeutic classes of concomitant medication for comorbidities were permitted. Further exclusion criteria included uncontrolled hypertension and impaired hepatic or renal function.

The study protocol was approved by the institutional review board, and conducted in accordance with the Declaration of Helsinki good clinical practice guidelines (10). All participants provided written informed consent before any study-related activities.

The primary efficacy outcome was the change in A1C level from baseline to week 12 versus placebo. Secondary end points included changes from baseline versus placebo at week 12, in fasting plasma glucose (FPG), fasting plasma insulin, C-peptide concentration, homeostasis model assessment-insulin resistance (HOMA-IR), proinsulin/insulin ratio, triglycerides, high-sensitivity C-reactive protein (hs-CRP), blood pressure, and proportion of subjects requiring rescue therapy. Subgroup analyses were also conducted to determine the effect of baseline A1C level and BMI on the change in A1C from baseline to week 12. Safety monitoring included assessments of reported adverse events and changes in vital signs and laboratory variables. Body weight and waist circumference changes were recorded.

Statistical Analysis

All primary and secondary efficacy variables were analyzed using the intention-to-treat (ITT) population. The primary end point was also analyzed in the per-protocol population to confirm the findings in the ITT population. Change-of-efficacy variables from baseline to week 12 or the last observation carried forward (LOCF) was assessed using an ANCOVA model, with country and treatment effect as factors, and baseline values as covariates. The proportion of subjects who achieved an A1C response at week 12 or LOCF (A1C ≤7%, 53 mmol/mol, or a decrease in A1C of ≥0.5%) was assessed using logistic regression analysis, taking into account country and treatment, and baseline values as covariates. Safety and tolerability were analyzed using the safety population. All statistical tests were assessed at the 5% level, and all quoted CIs were two-sided 95% CIs. Unless stated otherwise, values are expressed as least-squares (LS) means ± SEM.

RESULTS

Patient disposition is shown in Supplementary Fig. 1. Baseline demographic and clinical characteristics were similar between treatment groups (Fig. 1). A total of 170 subjects were randomized to receive treatment. In the ITT population, 81 subjects received 1,500 mg b.i.d. imeglimin, and 88 subjects received placebo, in addition to their run-in dose of 100 mg q.d. sitagliptin. There were two discontinuations in the imeglimin group (withdrawal by subject for personal reasons) and four discontinuations in the placebo group (two withdrawals by subjects for personal reasons, and two subjects were rescued for hyperglycemia). These last two subjects were withdrawn from the study in order to receive an appropriate glucose-lowering medication at the discretion of the investigator.

During the 12-week double-blind add-on treatment period, the addition of imeglimin to sitagliptin therapy demonstrated incremental efficacy benefits

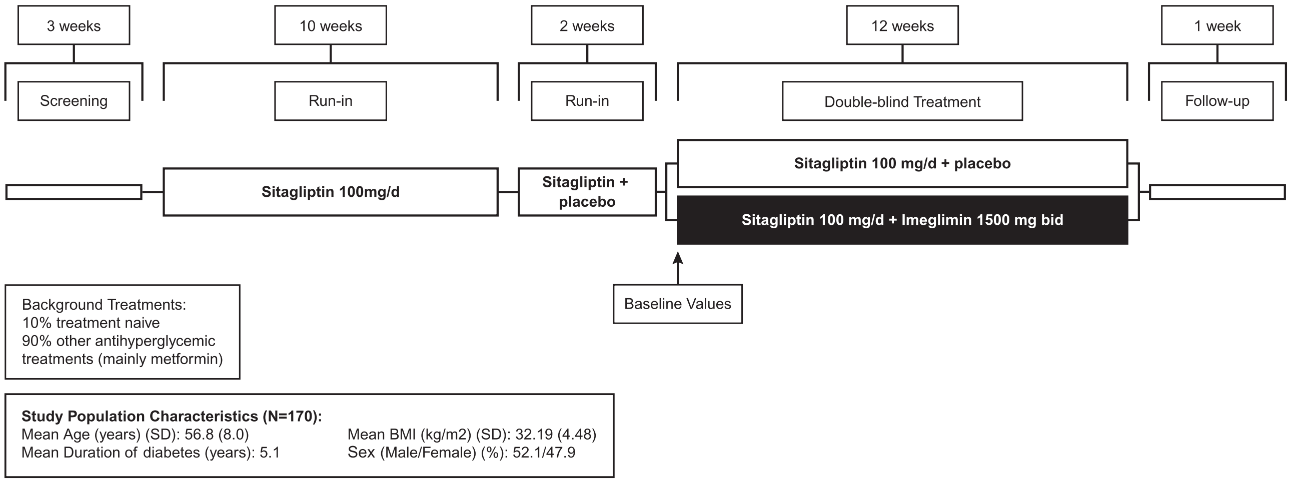

Figure 1—Imeglimin add-on to sitagliptin study design.

in the primary end point, A1C level from baseline, in all subjects (−0.60%), compared with no significant change (0.12%) with placebo. The difference in the LS mean change from baseline versus placebo in the ITT population was −0.72% ($P < 0.001$) (Fig. 2*A*).

Approximately 90% of subjects in the ITT population at screening were previously treated with metformin monotherapy, and 10% were naive to treatment. The mean A1C value for the ITT population at screening was 8.5% (69 mmol/mol). After the 12-week sitagliptin monotherapy run-in period, the overall mean A1C value at baseline remained at 8.5% (69 mmol/mol); however, changes in A1C level varied among subjects. Indeed, stratification by A1C value at screening showed that 32% of subjects had an A1C level of <8.0% (<64 mmol/mol); 46% of subjects had an A1C level ranging from 8.0 to 9.0% (64–75 mmol/mol); and 22% of subjects had an A1C level of >9.0% (>75 mmol/mol). After switching from their previous therapy to sitagliptin monotherapy in the 12-week sitagliptin run-in period, A1C values changed by 0.67%, 0.03%, and −0.88% in the A1C screening groups <8.0% (<64 mmol/mol), 8.0–9.0% (64–75 mmol/mol), and >9.0% (>75 mmol/mol), respectively.

After the 12-week double-blind treatment period, imeglimin therapy was shown to be more effective than placebo in reducing A1C levels from baseline to week 12 for all prespecified baseline A1C subgroup measurements. Placebo-subtracted reductions in mean A1C level from baseline to week 12 with imeglimin were −0.78%, −0.62%, and −0.95% for A1C baseline subgroups <8.0% (<64 mmol/mol), 8.0–9.0% (64–75 mmol/mol), and >9.0% (>75 mmol/mol), respectively (Fig. 2*B*).

There was a statistically significant difference in the proportion of subjects (19.8%) achieving an A1C level of ≤7% (53 mmol/mol), and the proportion of those (54.3%) experiencing a decrease

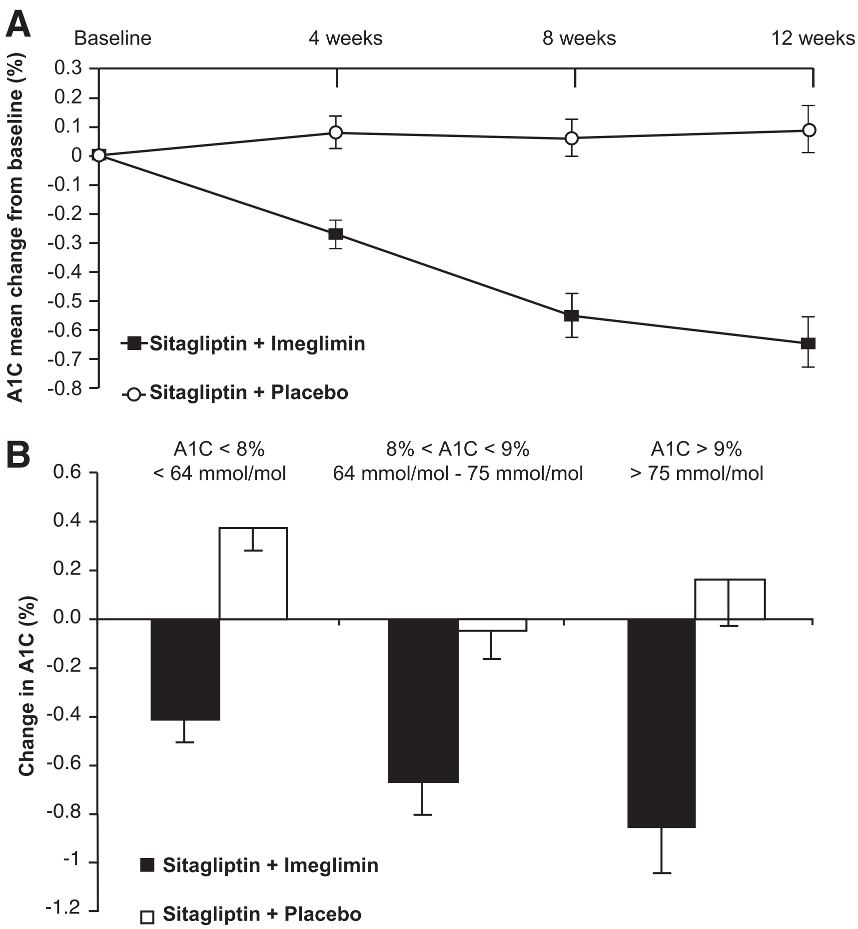

Figure 2—*A*: Effect of sitagliptin-imeglimin vs. sitagliptin-placebo: A1C reductions over the 12-week double-blind treatment period. *B*: Effect of sitagliptin-imeglimin vs. sitagliptin-placebo: change in A1C depending on baseline A1C value.

in A1C of at least 0.5% with imeglimin versus placebo (1.1% [P = 0.004] and 21.6% [$P < 0.001$], respectively).

Reductions in A1C levels from baseline were similar for imeglimin treatment when subjects were stratified by baseline BMI ≤30 kg/m^2 (−0.66%) and >30 kg/m^2 (−0.62%). No reduction in A1C was observed with placebo treatment for either BMI baseline subgroup.

Imeglimin treatment also decreased mean FPG levels from baseline after 12 weeks by −0.93 mmol/L, and by −0.11 mmol/L in the placebo group, resulting in an LS mean treatment difference of −0.81 mmol/L (95% CI −1.46 to −0.17, $P < 0.014$).

There were no significant differences in the mean changes from baseline to week 12 between treatment groups for parameters of β-cell function (fasting insulin concentration, C-peptide concentration, HOMA-IR, proinsulin/insulin ratio) and for other parameters (triglyceride and hs-CRP levels, and systolic blood pressure) (Table 1).

Imeglimin as an add-on to sitagliptin therapy was generally well-tolerated during the double-blind run-in period (Table 2). A higher incidence of treatment-emergent adverse events (TEAEs) considered to be related to study medication was reported during the double-blind treatment period in the placebo group (seven events in three subjects), compared with the imeglimin group, in which no related TEAEs were reported. One subject in the placebo group required rescue therapy, whereas none was necessary in the imeglimin group. One subject in the imeglimin group experienced a serious adverse event not related to treatment during the double-blind treatment period (surgery for appendicitis).

CONCLUSIONS

The current study demonstrates that imeglimin 1,500 mg b.i.d. added to ongoing sitagliptin therapy for 12 weeks is well-tolerated and demonstrates incremental efficacy benefits in reducing levels of A1C versus placebo in patients with type 2 diabetes that was inadequately controlled with sitagliptin alone.

In order to investigate the effect of imeglimin when added to sitagliptin monotherapy, the study was designed to treat a study population with type 2 diabetes that was inadequately controlled with sitagliptin monotherapy. The A1C value of 8.5% (69 mmol/mol) at screening demonstrates that subjects with type 2 diabetes that was inadequately controlled with their current treatment regimen (subjects were predominately receiving metformin) and were therefore switched to sitagliptin monotherapy. In this 12-week period, and after a switch from their previous monotherapy to sitagliptin, 25% of subjects demonstrated improvements in A1C level; 25% of subjects saw their A1C levels deteriorate and levels in 50% of subjects remained stable. However, for the entire study population, the baseline A1C value remained unchanged at the end of this run-in period compared with the A1C value at screening (8.5% [69 mmol/mol]). Only those subjects with type 2 diabetes that remained uncontrolled (A1C level ≥7.5% [58 mmol/mol]) were randomized to receive imeglimin or placebo.

Although sitagliptin has been extensively studied, both as a monotherapy and in combination with other antihyperglycemic treatments (11–14), the current study represents an original design intended to investigate the incremental efficacy benefits in patients with type 2 diabetes that was suboptimally controlled with sitagliptin monotherapy. One study (15) implementing a similar design demonstrated that the sodium-glucose cotransporter 2 inhibitor dapagliflozin, when added to sitagliptin therapy, reduced A1C level by −0.56% versus placebo, similar to the −0.72% difference achieved in our study. Moreover, since the mean A1C value in the sitagliptin-imeglimin treatment group was not yet plateauing, further incremental effects on improvements in A1C level beyond 12 weeks might be anticipated; this will be investigated in an ongoing 24-week phase IIb dose-ranging study.

The current study also demonstrates that, regardless of baseline A1C level, a greater and significant reduction in A1C level was observed in the group receiving treatment with imeglimin compare with placebo, even for those patients with a baseline A1C level of <8.0% (64 mmol/mol). Although the full effect of DPP-4 inhibitors can be obtained in 10–12 weeks, a varying A1C response was observed across different subgroups receiving placebo in the double-blind treatment period (0.31%, −0.05%, and 0.16% for baseline A1C values of <8.0% [64 mmol/mol], 8.0–9.0% [64–75 mmol/mol], and >9.0% [75 mmol/mol], respectively). This may be attributed to baseline values being recorded at the end of the run-in period, with individual subject factors, such as previous metformin dose and treatment compliance, influencing A1C level during the double-blind treatment period.

The study also examined the effect on A1C values during the sitagliptin run-in period. For the subgroup of subjects exhibiting an A1C level of >9.0% (75 mmol/mol) at screening, the switch from previous treatment to sitagliptin for 12 weeks resulted in a decrease in A1C of 0.87%, with the addition of imeglimin for a further 12 weeks contributing to an incremental decrease in A1C of 0.74%, resulting in a total A1C reduction of 1.61% over the 24-week treatment period. Considering that in this subpopulation the A1C value at screening was 8.5% (69 mmol/mol) and remained stable during the run-in period with sitagliptin, this current study demonstrates the potential of imeglimin to complement the efficacy of DPP-4 inhibitors.

No statistically significant effects on fasting insulin concentration, C-peptide concentration, or HOMA-IR were observed with sitagliptin-imeglimin treatment compared with sitagliptin-placebo as demonstrated by the insulin/glucose and C-peptide/glucose ratios. The glucose-lowering effects of imeglimin in combination with sitagliptin demonstrated in the current study, and the previous observations in combination with metformin (7), suggest that the mechanism of action of imeglimin is complementary to and therefore additive to both DPP-4 inhibition and metformin action. Additional mechanistic studies will be necessary to confirm the precise contributions of imeglimin to correcting some of the many pathophysiological defects encountered in patients with type 2 diabetes.

Imeglimin add-on to sitagliptin appeared to be well tolerated, with no serious treatment-related adverse events reported. The greater incidence of adverse events in the placebo group compared with the imeglimin group during the double-blind treatment period

Table 1—Efficacy end points, week 12 (LOCF) (ITT population)

Efficacy end point	Sitagliptin + imeglimin 1,500 mg b.i.d. (*N* = 81)		Sitagliptin + placebo (*N* = 88)
A1C % [mmol/mol]			
Baseline	8.47 [69] (0.72)		8.53 [70] (0.66)
Week 12/end of treatment	7.83 [62] (0.9)		8.61 [71] (0.95)
Change from baseline to week 12 (LOCF)*	−0.6 (0.11)		0.12 (0.10)
P value compared with placebo		<0.001	
FPG (mmol/L)			10.91 (2.31)
Baseline	10.53 (2.09)		
Week 12/end of treatment	9.74 (2.39)		10.69 (2.07)
Change from baseline to week 12 (LOCF)*	−0.93 (0.31)		−0.11 (0.29)
P value compared with placebo		0.014	
Insulin (μIU/mL)			
Baseline	9.31 (8.24)		12.5 (32.01)
Week 12/end of treatment	8.95 (7.34)		10.58 (14.36)
Change from baseline to week 12 (LOCF)*	−1.17 (0.78)		−0.81 (0.72)
P value compared with placebo		0.655	
C-peptide (ng/mL)			
Baseline	3.48 (1.43)		3.32 (1.54)
Week 12/end of treatment	3.58 (1.56)		3.47 (1.67)
Change from baseline to week 12 (LOCF)*	0.17 (0.13)		0.23 (0.12)
P value compared with placebo		0.663	
Proinsulin/insulin ratio			
Baseline	534.69 (305.21)		642.52 (553.34)
Week 12/end of treatment	462.6 (308.22)		557.58 (527.8)
Change from baseline to week 12 (LOCF)*	−120.51 (46.98)		−80.98 (43.93)
P value compared with placebo		0.428	
HOMA-IR			
Baseline	5.14 (4.8)		5.22 (4.98)
Week 12/end of treatment	4.46 (3.59)		5.52 (7.02)
Change from baseline to week 12 (LOCF)*	−0.184 (0.68)		0.098 (0.64)
P value compared with placebo		0.572	
Triglycerides (mmol/L)			
Baseline	2.35 (1.36)		2.36 (1.45)
Week 12/end of treatment	2.26 (1.50)		2.55 (2.17)
Change from baseline to week 12 (LOCF)*	−0.167 (0.19)		0.161 (0.18)
P value compared with placebo		0.106	
hs-CRP (mg/L)			
Baseline	4.04 (5.58)		4.64 (4.87)
Week 12/end of treatment	3.42 (4.94)		4.75 (4.82)
Change from baseline to week 12 (LOCF)*	−1.16 (0.64)		0.009 (0.59)
P value compared with placebo		0.082	
Systolic blood pressure (mmHg)			
Baseline	132.0 (10.2)		132.8 (10.3)
Week 12/end of treatment	132.8 (10.3)		135.9 (9.2)
Change from baseline to week 12 (LOCF)*	1.0		2.8
Change compared with placebo		−1.8	
Diastolic blood pressure (mmHg)			
Baseline	79.3 (7.1)		80.7 (6.6)
Week 12/end of treatment	80.2 (6.8)		81.3 (7.2)
Change from baseline to week 12 (LOCF)*	0.9		0.6
Change compared with placebo		0.3	

Data are the mean (SD), unless otherwise stated. *Data are the LS mean (SE) or mean difference.

could be indicative that type 2 diabetes in the subjects receiving placebo was inadequately controlled with sitagliptin monotherapy, as demonstrated by the higher number of subjects presenting with hyperglycemia or having their A1C elevation noticed as adverse events (with two subjects receiving rescue therapy). The absence of reported hypoglycemia in the imeglimin add-on to sitagliptin treatment group is noteworthy, given the significant glucose-lowering effects observed in subjects receiving this combination.

Positive trends for improvements in triglyceride and hs-CRP levels, and systolic blood pressure were observed in the group of patients receiving imeglimin treatment compared with the group receiving placebo. In combination with sitagliptin, imeglimin treatment had a neutral effect on body weight and waist circumference, which contrasts with previous studies where

Table 2—Summary of adverse events (safety population)

	Sitagliptin + imeglimin 1,500 mg b.i.d. (*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
Upper abdominal pain	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 SAE	0 (0.0)	0	1 (1.2)	1	0 (0.0)	0	0 (0.0)	0
Any cardiovascular TEAE	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 adverse events; SAE, serious adverse event.

imeglimin reduced these parameters (6,7). Longer-term studies that include body weight measurements will clarify these effects.

In summary, this original study design demonstrates that the addition of imeglimin to sitagliptin monotherapy provides incremental efficacy benefits in reducing A1C and FPG levels in subjects with type 2 diabetes that was inadequately controlled with sitagliptin monotherapy, particularly in subjects with a high baseline A1C level (>9.0% [75 mmol/mol]) at screening. The current data, along with previous studies (6,7), have shown imeglimin to be a well-tolerated and effective treatment, both as monotherapy and in combination with other antihyperglycemic agents, and therefore may provide a valuable new treatment option for patients with type 2 diabetes. Further longer-duration studies in the phase IIb/III program will help to confirm these primary results.

Duality of Interest. IMC Healthcare Communication helped in the preparation of this manuscript, and this service was funded by Poxel SA. P.F. is an employee of Poxel SA. V.P. was the Principal Investigator of the current study, and has received a speaker honorarium from Glenmark Pharmaceuticals Ltd. M.D. is a consultant for Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb/AstraZeneca, Eli Lilly & Co, Merck, Novo Nordisk, Poxel SA, and Sanofi; and a speaker for Bristol-Myers Squibb/AstraZeneca, Eli Lilly & Co, Novo Nordisk, and Sanofi. Through M.D., the VU University Amsterdam Medical Center has received research grants from Boehringer Ingelheim, Bristol-Myers Squibb/AstraZeneca, Eli Lilly & Co, MSD, Novo Nordisk, and Sanofi. M.D. receives no personal payments in connection with the above-mentioned activities, but all payments are directly transferred to the Institutional Research Foundation. G.S. has received lecture fees and honoraria for serving on for advisory boards from Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, GSK, Merck, Novartis, Novo Nordisk, Poxel SA, Roche, Sanofi, Servier, and Takeda. H.E.L. is a member of the scientific advisory boards of Amylin Pharmaceuticals, Biocon Pharma, Intarcia Pharma, Merck, Metacure, and Poxel SA. He serves as a consultant for AstraZeneca, Bristol-Myers Squibb, and Sanofi. He owns stock in Merck. He is on the Board of Directors of the American Association of Clinical Endocrinologists and Metacure. S.E.I. has served as a consultant to Merck, Novo Nordisk, Janssen, Boehringer Ingelheim and Poxel SA. C.J.B. has attended advisory board meetings of Bristol-Myers Squibb and AstraZeneca; undertaken ad hoc consultancy for Bristol-Myers Squibb, AstraZeneca, Merck, Novo Nordisk, GlaxoSmithKline, Boehringer Ingelheim, Eli Lilly, Poxel SA, and Takeda; received research grants from AstraZeneca and Sanofi; delivered continuing medical educational programs sponsored by Bristol-Myers Squibb, AstraZeneca, GlaxoSmithKline, Merck Serono, Boehringer Ingelheim, Eli Lilly, and Merck; and received travel/accommodation reimbursement from GlaxoSmithKline and Bristol-Myers Squibb. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.F. contributed to the design of the study, researched and interpreted the data, and reviewed and edited the manuscript. V.P. was the Principal Investigator of the study, researched and interpreted the data, and reviewed and edited the manuscript. M.D., G.S., H.E.L., S.E.I., and C.J.B. researched and interpreted the data, and reviewed and edited the manuscript. P.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014;37(Suppl. 1):S14–S80
2. Tahrani AA, Piya MK, Kennedy A, Barnett AH. Glycaemic control in type 2 diabetes: targets and new therapies. Pharmacol Ther 2010;125: 328–361
3. Nathan DM, Buse JB, Davidson MB, et al.; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203
4. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379
5. Fouqueray P, Leverve X, Fontaine E, et al. Imeglimin—a new oral anti-diabetic that targets the three key defects of type 2 diabetes. J Diabetes Metab 2011;2:126.
6. Pirags V, Lebovitz H, Fouqueray P. Imeglimin, a novel glimin oral antidiabetic, exhibits a good

efficacy and safety profile in type 2 diabetic patients. Diabetes Obes Metab 2012;14:852–858
7. Fouqueray P, Pirags V, Inzucchi SE, et al. The efficacy and safety of imeglimin as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy. Diabetes Care 2013;36:565–568
8. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE; Sitagliptin Study 021 Group. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 2006;29:2632–2637
9. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care 2006;29:2638–2643
10. World Medical Association. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997;277:925–926
11. Dhillon S. Sitagliptin: a review of its use in the management of type 2 diabetes mellitus. Drugs 2010;70:489–512
12. Buse JB, Rosenstock J, Sesti G, et al.; LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39–47
13. Diamant M, Van Gaal L, Stranks S, et al. Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. Diabetes Care 2012;35:683–689
14. Frederich R, McNeill R, Berglind N, Fleming D, Chen R. The efficacy and safety of dipeptidyl peptidase-4 inhibitor saxagliptin in treatment-naïve patients with type 2 diabetes mellitus: a randomized controlled trial. Diabetol Metab Syndr 2012;4:36
15. Jabbour SA, Hardy E, Sugg J, Parikh S. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care 2013;37:740–750