

Twelve- and 52-Week Efficacy of the Dipeptidyl Peptidase IV Inhibitor LAF237 in Metformin-Treated Patients With Type 2 Diabetes

BO AHRÉN, MD¹
RAMON GOMIS, MD²
EBERHARD STANDL, MD³

DAVID MILLS, MSC⁴
ANJA SCHWEIZER, PHD⁴

OBJECTIVE — To assess the 12- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 versus placebo in patients with type 2 diabetes continuing metformin treatment.

RESEARCH DESIGN AND METHODS — We conducted a 12-week, randomized, double-blind, placebo-controlled trial in 107 patients with type 2 diabetes with a 40-week extension in those completing the core study and agreeing, together with the investigator, to extend treatment to 1 year. Placebo ($n = 51$) or LAF237 (50 mg once daily, $n = 56$) was added to ongoing metformin treatment (1,500–3,000 mg/day). HbA_{1c} and fasting plasma glucose (FPG) were measured periodically, and standardized meal tests were performed at baseline, week 12, and week 52.

RESULTS — In patients randomized to LAF237, baseline HbA_{1c} averaged $7.7 \pm 0.1\%$ and decreased at week 12 ($\Delta = -0.6 \pm 0.1\%$), whereas HbA_{1c} did not change from a baseline of $7.9 \pm 0.1\%$ in patients given placebo (between-group difference in $\Delta\text{HbA}_{1c} = -0.7 \pm 0.1\%$, $P < 0.0001$). Mean prandial glucose and FPG were significantly reduced in patients receiving LAF237 versus placebo by 2.2 ± 0.4 mmol/l ($P < 0.0001$) and 1.2 ± 0.4 mmol/l ($P = 0.0057$), respectively, but plasma insulin levels were not affected. At end point of the extension, the between-group differences in change in mean prandial glucose, insulin, and FPG were -2.4 ± 0.6 mmol/l ($P = 0.0001$), 40 ± 16 pmol/l ($P = 0.0153$), and -1.1 ± 0.5 mmol/l ($P = 0.0312$), respectively. HbA_{1c} did not change from week 12 to week 52 in LAF237-treated patients ($n = 42$) but increased in participants given placebo ($n = 29$). The between-group difference in ΔHbA_{1c} after 1 year was $-1.1 \pm 0.2\%$ ($P < 0.0001$).

CONCLUSIONS — Data from this study demonstrate that LAF237 effectively prevents deterioration of glycemic control when added to metformin monotherapy in type 2 diabetes.

Diabetes Care 27:2874–2880, 2004

The compound LAF237 is an agent that potentiates the effects of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) by inhibiting the enzyme responsible for their degrada-

tion (dipeptidyl peptidase IV [DPP-4]). In short-term studies, LAF237 inhibited plasma DPP-4 activity, increased circulating levels of intact GLP-1, and improved glucose tolerance in animal models of type 2 diabetes (1,2) and in diabetic pa-

tients (3). Similar findings were reported for a related compound NVP DPP728 (4), suggesting that DPP-4 inhibitors will be effective as monotherapy.

Given the documented therapeutic effects of GLP-1 agonists, both alone (5) and in combination with metformin (6,7), we hypothesized that LAF237 would also be effective in metformin-treated patients. In view of the potential disease-modifying effects of the incretins (8,9), we further hypothesized that the efficacy of LAF237 would be maintained with long-term treatment. The present study tested these hypotheses by assessing the effects of LAF237 added to an ongoing stable dosage of metformin in patients with type 2 diabetes. In addition to providing “proof of concept” regarding the efficacy of a DPP-4 inhibitor combined with metformin, this study offers the first 52-week data on the efficacy and tolerability of a DPP-4 inhibitor.

RESEARCH DESIGN AND METHODS

This was a multicenter, randomized, double-blind, placebo-controlled trial comparing the effects of 12-week treatment with LAF237 (50 mg once daily, $n = 56$) and placebo ($n = 51$) in patients with type 2 diabetes continuing a stable dosage of metformin (1,500–3,000 mg/day). The 12-week core study was followed by a 40-week extension in those patients completing the core study and agreeing, together with the investigator, to participate ($n = 42$ for the LAF237/metformin group and $n = 29$ for the placebo/metformin group). Male or infertile female patients aged ≥ 30 years diagnosed with type 2 diabetes at least 6 months before enrollment and treated with a stable dosage of metformin for ≥ 3 months were included. Prerandomization HbA_{1c} while on metformin monotherapy was required to be between 7.0 and 9.5% (inclusive), and baseline BMI was required to be between 20 and 35 kg/m² (inclusive).

From ¹Lund University, Lund, Sweden; ²Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain; the ³Diabetes Research Institute, Munich, Germany; and ⁴Novartis Pharma, Basel, Switzerland.

Address correspondence and reprint requests to Dr. Bo Ahrén, Department of Medicine, Lund University B11 BMC, SE-221 84 Lund, Sweden. E-mail: bo.ahren@med.lu.se.

Received for publication 28 May 2004 and accepted in revised form 7 September 2004.

Abbreviations: Δ , adjusted mean change; CIR_{Glucose}, corrected insulin response at peak glucose; DPP-4, dipeptidyl peptidase IV; ECG, electrocardiogram; FPG, fasting plasma glucose; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; I/G, insulinogenic index at peak glucose; ITT, intent to treat; SAE, serious adverse event; SMBG, self-monitoring of blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

© 2004 by the American Diabetes Association

Patients were excluded if they had a history of type 1 or secondary forms of diabetes, significant diabetes complications, clinically significant cardiovascular abnormalities, liver disease, acromegaly, asthma, major skin allergies, or major gastrointestinal surgery. Patients with fasting triglyceride levels >5.1 mmol/l or fasting plasma glucose (FPG) <6.1 or ≥ 13.3 mmol/l were excluded, as were those treated with any drugs considered possibly able to affect results or their interpretation.

Preceding randomization, there was a 4-week run-in period in which patients received placebo while maintaining their previous metformin regimen. During this period, baseline assessments (HbA_{1c}, FPG, lipids, standard biochemistry, hematology and urinalysis, physical exam, and electrocardiogram [ECG]) were made to verify eligibility, and patients underwent a baseline standard meal test. Patients were then randomized to LAF237 plus metformin or placebo plus metformin for 12 weeks of double-blind treatment. Fasting plasma levels of insulin and lipids and FPG were measured at weeks 1, 2, 4, 8, and 12. HbA_{1c} was measured at weeks 4, 8, and 12, and the standard meal test was repeated at week 12 (or at end point). Forty-two and 29 patients receiving LAF237 plus metformin or placebo plus metformin, respectively, participated in the extension, during which double-blind treatment continued; HbA_{1c} and FPG were measured at weeks 16, 24, 36, and 52. The standard meal test was repeated at week 52 (or at end point) of the extension.

For standard meal tests, patients fasted overnight and study drug was administered 30 min before consumption of a standardized 465-kcal breakfast meal. The meal was consumed within 15 min, and samples for determination of glucose and insulin were obtained 35 and 5 min before and 5, 10, 15, 30, 60, 90, 120, 180, and 240 min after the start of the meal (time 0).

All samples were analyzed at a central laboratory (Medical Research Laboratories International, Zaventem, Belgium) using standardized procedures. Insulin was measured by radioimmunoassay (Boehringer Mannheim, Mannheim, Germany), glucose was measured with a glucose oxidase technique, and HbA_{1c} was measured using Tosoh ion-exchange high-performance liquid chromatography (normal range 4.0–6.0%).

All adverse events were recorded and assessed as to their severity and possible relationship to study medication. Vital signs were measured and safety laboratory assessments made at every visit. Patients were provided with glucose monitoring devices and supplies and instructed on their use. An episode of hypoglycemia was defined as symptoms suggestive of hypoglycemia accompanied by a self-monitoring of blood glucose (SMBG) measurement of <3.1 mmol/l plasma glucose equivalents.

Data handling and statistical analysis

The primary efficacy variable was the change from baseline (mean of week -2 and week 0) to the end point in HbA_{1c} in the intent-to-treat (ITT) population, with the last observation carried forward in both the core study and the extension. The areas under the curve (AUCs) for glucose and insulin were calculated with the trapezoidal method. The insulinogenic index at peak glucose [$I/G = \Delta$ insulin (μ U/ml) at peak glucose/ Δ glucose (mg/dl) at peak] and the corrected insulin response at peak glucose $\{CIR_{GluPeak} = \text{insulin at peak glucose } (\mu\text{U/ml}) \times 100 / [\text{peak glucose (mg/dl)} \times \text{peak glucose (mg/dl)} - 70]\}$ (10,11) were calculated as measures of β -cell function. Secondary end points were change from baseline in FPG, lipids and body weight, the 4-h mean (AUC/time) prandial glucose, and insulin levels during standardized meal test, I/G and $CIR_{GluPeak}$.

Data were analyzed with an ANCOVA model including terms for treatment, baseline value, pooled center (or country for extension study), and treatment-by-baseline interaction. Analyses were conducted using two-sided tests and a significance level of 0.05. The Cochran Mantel-Haenszel test was used to assess comparability of baseline characteristics for qualitative variables and the *t* test for quantitative variables. Unless otherwise specified, data are presented as means \pm SEM.

Ethics and good clinical practice

Written informed consent was obtained from all patients and renewed before participation in the extension. The institutional review boards and independent ethics committees at each site approved the protocol. The study was conducted

with good clinical practice in accordance with the Declaration of Helsinki.

RESULTS

Patient disposition and baseline characteristics

In the core study, 56 and 51 patients were randomized to receive LAF237 plus metformin or placebo plus metformin, respectively. Fifty (89%) of the LAF237 plus metformin-treated patients and 47 (92%) of the placebo plus metformin-treated patients completed the core study and were eligible to participate in the extension. Participation in the 40-week extension required agreement by patient and investigator: 42 and 29 LAF237 plus metformin- and placebo plus metformin-treated patients, respectively, were included in the extension. Thirty-two (76%) and 26 (90%) of LAF237 plus metformin- and placebo plus metformin-treated extension study participants, respectively, completed the 1-year treatment.

Table 1 reports the baseline characteristics of the ITT populations in the core study and extension and reasons for discontinuations. The patients were predominantly overweight, male, and Caucasian, with a mean age of ~ 57 years. Approximately 50% were hypertensive. There were no significant differences among the groups in any baseline characteristic.

Efficacy

Figure 1 depicts HbA_{1c} levels during the 12-week core study and during the 52-week treatment in extension study participants. During the 12-week core study, in patients randomized to placebo plus metformin, HbA_{1c} did not change from a mean baseline of $7.9 \pm 0.1\%$ (adjusted mean change [AM Δ] $0.1 \pm 0.1\%$). In patients receiving LAF237 plus metformin, HbA_{1c} decreased from a mean baseline of $7.7 \pm 0.1\%$ (AM Δ $-0.6 \pm 0.1\%$). The between-group difference in the AM Δ HbA_{1c} was $-0.7 \pm 0.1\%$ ($P < 0.0001$). Baseline HbA_{1c} averaged 7.6 ± 0.1 and $7.8 \pm 0.1\%$ in the extension study participants receiving LAF237 plus metformin and placebo plus metformin, respectively. In the placebo plus metformin-treated patients, HbA_{1c} increased from week 12 to week 52 at a rate of 0.0656% per month, whereas the rate of Δ HbA_{1c} in patients taking LAF237 plus metformin was less (0.0128% per month) than that in patients taking placebo plus metformin

Table 1—Baseline characteristics and patient disposition of the ITT populations for the 12-week core and extension studies*

	Randomized for 12-week study		Extension population	
	LAF/MET	PBO/MET	LAF/MET	PBO/MET
n	56	51	42	29
Age (years)	57.9 ± 10.0	55.7 ± 11.0	58.4 ± 9.2	54.3 ± 12.2
Sex (male)	39 (69.6)	34 (66.7)	26 (61.9)	22 (75.9)
BMI (kg/m ²)	29.4 ± 3.6	30.2 ± 3.6	29.6 ± 3.7	29.9 ± 3.6
Duration of diabetes (years)	5.6 ± 4.2	5.5 ± 3.7	5.8 ± 4.2	4.6 ± 3.6
Duration of previous MET treatment (months)	28.2 ± 25.6	29.8 ± 36.1	28.7 ± 24.0	23.7 ± 25.1
HbA _{1c} (%)	7.7 ± 0.6	7.8 ± 0.7	7.6 ± 0.6	7.8 ± 0.6
FPG (mmol/l)	9.9 ± 2.0	10.3 ± 2.0	9.6 ± 1.6	10.1 ± 1.8
Hypertension	28 (50.0)	27 (52.9)	25 (59.5)	13 (44.8)
Discontinued	6 (10.7)	4 (7.8)	10 (23.8)	3 (10.3)
Adverse event	0	0	3 (7.1)†	0
Abnormal laboratory value	1 (1.8)	0	1 (2.4)	0
Unsatisfactory therapeutic effect‡	1 (1.8)	1 (2.0)	3 (7.1)	2 (6.9)
Protocol violation	1 (1.8)	1 (2.0)	2 (4.8)	1 (3.4)
Withdrew consent	1 (1.8)	1 (2.0)	0	0
Lost to follow-up	1 (1.8)	0	0	0
Administrative problems	1 (1.8)	0	1 (2.4)	0
Abnormal test procedure results	0	1 (2.0)	0	0

Data are means ± SD and n (%). *One patient in the randomized LAF/MET group was Asian, all other participants were Caucasian. †Adverse events leading to discontinuation were worsening of hypertension, moderate, not suspected to be related to study medication; first-degree atrioventricular block, mild, suspected to be related to study medication; and moderate peripheral edema suspected to be related to study medication. ‡As judged by the investigator. LAF/MET, LAF237 plus metformin group; PBO/MET, placebo plus metformin group.

($P = 0.0243$) and not significantly different from zero. In the extension population, the between-group difference in the Δ HbA_{1c} was $-1.1 \pm 0.2\%$ ($P < 0.0001$). An end point HbA_{1c} of $<7.0\%$ was achieved by 41.7% of patients taking LAF237 plus metformin and by 10.7% of those taking placebo plus metformin.

During the core study, in patients receiving placebo plus metformin, mean baseline FPG was 10.2 ± 0.3 mmol/l and increased slightly at the end point (Δ FPG 0.2 ± 0.3 mmol/l). In patients receiving LAF237 plus metformin, FPG decreased from a mean baseline of 9.8 ± 0.3 mmol/l (Δ FPG -1.0 ± 0.3 mmol/l). Thus, the between-group difference in Δ FPG was -1.2 ± 0.4 mmol/l ($P = 0.0057$). In the extension, in patients receiving LAF237 plus metformin, FPG decreased from an average baseline of 9.6 ± 0.2 mmol/l to the end point (Δ FPG -0.6 ± 0.3 mmol/l), whereas in placebo plus metformin-treated patients, FPG increased from a baseline of 10.2 ± 0.3 mmol/l (Δ FPG 0.5 ± 0.4 mmol/l). The between-group difference was -1.1 ± 0.5 mmol/l ($P = 0.0312$).

Figure 2 depicts plasma glucose and insulin profiles during standard meal tests performed at baseline and at the end point

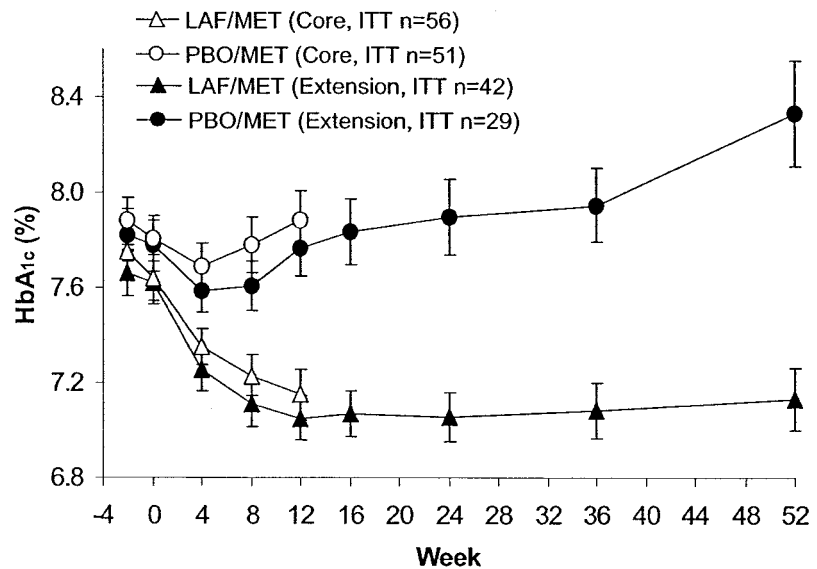


Figure 1—Time course of HbA_{1c} in core study (open symbols) and extension (closed symbols). In the core study, the ITT populations consisted of 56 patients in the LAF237 plus metformin group (LAF/MET, Δ) (50 mg once daily) and 51 patients in the placebo plus metformin group (PBO/MET, \circ). Forty-two patients receiving LAF237 plus metformin (LAF/MET) participated in the extension (\blacktriangle) and 29 patients receiving placebo plus metformin (PBO/MET) participated in the extension (\bullet). Data are means ± SEM. Due to discontinuations or missing values, the number of measurements depicted for LAF237 plus metformin in the core study was 51 at weeks 4, 8, and 12 and for placebo plus metformin in the core study was 50 at weeks 4 and 8 and 48 at week 12. Due to discontinuations or missing values, the number of determinations depicted for LAF237 plus metformin in the extension was 40 at week 24, 36 at week 36, and 33 at week 52 and for placebo plus metformin in the extension was 28 at weeks 16 and 36 and 26 at week 52.

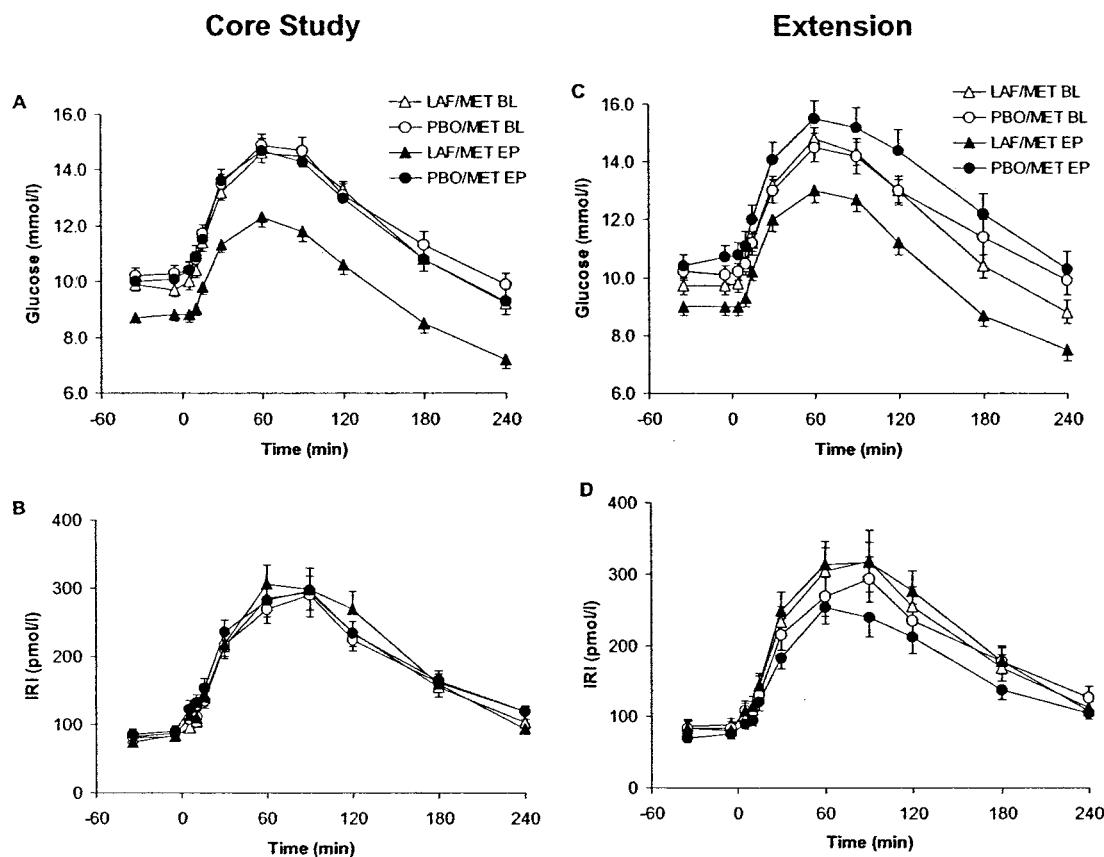


Figure 2—Glucose (A and C) and immunoreactive insulin (IRI) (B and D) profiles during standardized meal tests performed at baseline (BL) (open symbols) and end point (EP) (closed symbols) of the 12-week core study (A and B) and the extension (C and D) in patients randomized to LAF237 plus metformin (LAF/MET) (50 mg once daily, triangles) or placebo plus metformin (PBO/MET, circles). Data are means \pm SEM of ITT populations. In the core study, $n = 56$ for LAF237 plus metformin and $n = 51$ for placebo plus metformin. In the extension, $n = 42$ for LAF237 plus metformin and $n = 29$ for placebo plus metformin.

of the core study and the extension. As illustrated in Fig. 2A, in the core study plasma glucose profiles were superimposable in the two groups at baseline and did not change during the 12-week treatment with placebo plus metformin. However, at week 12 or at the end point, plasma glucose levels were substantially lower in patients receiving LAF237 plus metformin than in those receiving placebo plus metformin at all time points. The between-group difference in the AM Δ 4-h mean glucose level was -2.2 ± 0.4 mmol/l ($P < 0.0001$).

As shown in Fig. 2B, in the core study the plasma insulin profiles were essentially indistinguishable at baseline and at the end point in both groups of patients. The between-group difference in the AM Δ 4-h mean insulin was 2.1 ± 10.2 pmol/l ($P = 0.8415$). However, the CIR_{GluPeak} was significantly increased, and the I/G tended to be improved in patients receiving LAF237 plus metformin

relative to those receiving placebo plus metformin. The between-group difference in the AM Δ CIR_{GluPeak} was 0.05 ± 0.01 ($P = 0.0007$), and the between-group difference in the AM Δ I/G was 0.13 ± 0.07 ($P = 0.0565$).

As illustrated in Fig. 2C, although the glucose profiles in the extension participants randomized to LAF237 plus metformin and placebo plus metformin were very similar at baseline, prandial glucose control worsened in patients taking placebo plus metformin and clearly improved during the 52-week treatment with LAF237 plus metformin. The between-group difference in the AM Δ 4-h mean glucose was -2.4 ± 0.6 mmol/l ($P = 0.0001$).

As depicted in Fig. 2D, during the 52-week treatment in the extension population, prandial insulin levels decreased in patients randomized to placebo plus metformin and increased in those receiving LAF237 plus metformin. The between-

group difference in AM Δ 4-h mean immunoreactive insulin level was 40 ± 16 pmol/l ($P = 0.0153$). The CIR_{GluPeak} and I/G were also significantly increased in patients receiving LAF237 plus metformin relative to those receiving placebo plus metformin. The between-group difference in the AM Δ CIR_{GluPeak} was 0.05 ± 0.01 ($P = 0.0005$), and the between-group difference in the AM Δ I/G was 0.17 ± 0.07 ($P = 0.0160$).

During the core study, there was no significant change in any lipid parameter (fasting triglycerides and total, HDL, and LDL cholesterol) or body weight. In the extension study, there was no significant effect of LAF237 on HDL cholesterol, LDL cholesterol, or triglycerides. However, there was a modest decrease in total cholesterol in LAF237 plus metformin-treated patients relative to those receiving placebo plus metformin (between-group difference in AM Δ -0.30 ± 0.14 mmol/l, $P = 0.034$). Body weight decreased by

Table 2—Adverse events occurring in $\geq 5\%$ of patients in any treatment group

	Safety population			
	12-week study		Extension	
	LAF/MET	PBO/MET	LAF/MET	PBO/MET
n	56	51	42	29
Cough	3 (5.4)	0	1 (2.4)	0
Nasopharyngitis	2 (3.6)	6 (11.8)	6 (14.3)	4 (13.8)
Worsening hypertension	0	0	3 (7.1)	0
Urinary tract infection	1 (1.8)	3 (5.9)	1 (2.4)	2 (6.9)
Gastroenteritis	0	0	0	2 (6.9)
Bursitis	0	0	1 (2.4)	2 (6.9)

Data are n (%). LAF/MET, LAF237 plus metformin group; PBO/MET, placebo plus metformin group.

0.4 \pm 0.2 kg in patients receiving LAF237 plus metformin and by 0.5 \pm 0.2 kg in patients receiving placebo plus metformin during the 12-week core study. In extension study participants, the body weight change from baseline to end point was -0.2 kg in both groups.

Safety and tolerability

During the core study, the overall incidence of any adverse event was similar in patients randomized to LAF237 plus metformin (29 patients, 51.8%) and placebo plus metformin (28 patients, 54.9%). In the extension population, 29 (69.0%) and 17 (58.6%) of LAF237 plus metformin-treated and placebo plus metformin-treated participants, respectively, experienced an adverse event. Table 2 details the incidence of adverse events occurring in $\geq 5\%$ of patients in any group. Three patients in the extension population receiving LAF237 plus metformin were observed to have worsening of hypertension, requiring additional antihypertensive treatment. One of these patients discontinued, but none of these adverse events were suspected to be drug related.

One hypoglycemic episode (symptoms of hypoglycemia confirmed by SMBG < 3.1 mmol/l plasma glucose equivalents) was experienced by each of two patients receiving LAF237 plus metformin during the core study, and there were no hypoglycemic episodes during the extension. Additionally, one patient in the core study and one patient in the extension study receiving LAF237 plus metformin each reported three instances of asymptomatic SMBG ≤ 3.7 mmol/l (3.4, 2.7, and 3.3 mmol/l and 2.1, 3.6, and 3.4 mmol/l, respectively) plasma glucose

equivalents. There were three additional patients receiving LAF237 plus metformin with symptoms suggestive of low glucose: one patient in the core study with an SMBG of 3.5 mmol/l plasma glucose equivalents, one patient in the extension with an SMBG of 3.8 mmol/l plasma glucose equivalents, and one patient in the extension with no glucose measurement obtained.

Notable laboratory abnormalities were uncommon and occurred in a similar percentage of patients in each group. There were no consistent changes in ECG parameters or between-group differences in the change from baseline to end point in ECG parameters.

During the core study, there were five serious adverse events (SAEs), one in the LAF237 plus metformin group and four in the placebo plus metformin group, but none were thought to be drug related. During the extension study there were seven SAEs, five events in four patients in the LAF237 plus metformin group and two events in one patient in the placebo plus metformin group. The only SAE thought to be drug related was an episode of peripheral edema in a patient receiving LAF237 plus metformin. No deaths occurred during this study.

CONCLUSIONS—This study showed that when added to metformin treatment, LAF237 was effective at improving glycemic control for at least 1 year in patients with type 2 diabetes and appeared to be well tolerated. This represents the first data available on combination therapy with a DPP-4 inhibitor and attests to the durability of efficacy of LAF237. Two previous 4-week studies of drug-naïve patients with type 2 diabetes confirmed that

a DPP-4 inhibitor reduces both fasting and postprandial glucose levels and suggested that this approach will be effective as monotherapy (3,4), but questions about longer-term effects of DPP-4 inhibitors and their potential efficacy in combination therapy remained unanswered.

The 12-week treatment with LAF237 produced a placebo-subtracted reduction in HbA_{1c} of 0.7% in patients with baseline HbA_{1c} levels of $\sim 7.7\%$ while on a stable dosage of metformin. After 52 weeks, the between-group difference in HbA_{1c} was -1.1% , reflecting deterioration of glycemic control in placebo plus metformin-treated patients and a stable HbA_{1c} of $\sim 7.1\%$ from week 12 to week 52 in patients treated with LAF237 plus metformin. The magnitude of the effect of LAF237 is notable for at least two reasons. First, HbA_{1c} reductions are invariably found to be proportional to baseline levels, and the patients in this study had only moderately elevated baseline HbA_{1c} while on metformin monotherapy. Second, the essentially flat HbA_{1c} profile seen in LAF237 plus metformin-treated patients from week 12 to week 52 raises the intriguing question of whether LAF237 may influence mechanisms underlying the progression of the disease. This, of course, would need to be addressed in larger and longer studies with a different trial design.

The mechanism by which LAF237 improved glycemic control in these metformin-treated patients was not directly addressed; however, it is likely attributable to inhibition of DPP-4 and resultant increases of circulating levels of the intact, biologically active incretins. Although plasma DPP-4 activity, GLP-1, and GIP were not measured here, earlier studies have shown that LAF237 profoundly suppresses DPP-4 activity and increases plasma levels of intact GLP-1 (3) and GIP (12).

In the core study, addition of LAF237 to ongoing metformin therapy decreased fasting and postmeal glucose levels by 1.2 and 2.2 mmol/l, respectively, but did not significantly affect plasma insulin levels. In light of the consistently reported effects of GLP-1 to augment insulin secretion in the presence of hyperglycemia (13–17), this finding may be initially surprising. However, insulin secretion can improve without changes in circulating insulin levels, and when assessing β -cell function it is appropriate to consider insulin levels in the context of the glucose concentration

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.