LIRAGLU TIDE ACHIEVES A1C TARGETS MORE OFTEN THAN SIT AGLIPTIN OR EXENATIDE WHEN ADDED TO METFORMIN IN PATIENTS WITH TYPE 2 DIABETES AND A BASELINE A1C <8.0%

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ABSTRACT

Objective: Compare the safety and efficacy of liraglutide to that of sitagliptin or exenatide as add-on to metformin in patients with type 2 diabetes (T2D) and glycated hemoglobin (A1C) <8.0%.

Methods: Post hoc analysis of 26-week data from liraglutide 1.8 mg once daily (OD) versus exenatide 10 µg twice daily (LEAD-6) and liraglutide 1.8 mg OD versus sitagliptin 100 mg OD (LIRA–DPP-4); only patients treated as add-on to metformin with baseline A1C <8.0% were included. Efficacy analysis was performed on the intention-to-treat population with missing values imputed by last observation carried forward.

Results: More patients achieved A1C targets (<7.0% and ≤6.5%) with liraglutide versus exenatide or sitagliptin; the difference was greatest for A1C ≤6.5% (LEAD-6: 65% versus 35%; odds ratio [OR]=3.37, 95% confidence interval [CI]: 1.31-8.63; \textit{P} = .01 or LIRA–DPP-4: 53% versus 19%; OR = 4.78, 95% CI 2.10 to 10.87; \textit{P} = .0002). Significantly more patients achieved a composite endpoint of A1C <7.0% with no weight gain or hypoglycemia with liraglutide compared with exenatide (78% versus 42%; OR = 4.99, 95% CI: 1.77 to 14.04; \textit{P} = .0023) or sitagliptin (61% versus 21%; OR = 5.95, 95% CI: 2.66 to 13.29; \textit{P}<.0001). All treatments were well tolerated, there was no major hypoglycemia and few patients (8 to 10%) experienced minor hypoglycemia.

Conclusion: When added to metformin in patients with an A1C <8.0%, more patients using liraglutide 1.8 mg reached A1C targets than with exenatide or sitagliptin. Sitagliptin had particularly low efficacy in this analysis. These data support the use of liraglutide 1.8 mg as a safe and effective alternative to sitagliptin or exenatide following metformin failure in patients with an A1C <8.0%.

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INTRODUCTION

Unless contraindicated, metformin is widely accepted as first-line therapy for type 2 diabetes (T2D) due to its more favorable risk-benefit profile than comparator...
therapies (1-3). However, due to the progressive nature of T2D, treatment intensification with additional agent(s) is required to maintain adequate glycemic control (4,5). For most patients, the American Diabetes Association (ADA) recommends targeting a glycated hemoglobin (A1C) level of <7.0%, whereas the American Association of Clinical Endocrinologists (AACE) recommends a more stringent target of ≤6.5%, if it can be achieved safely (6,7). Both organizations emphasize the importance of individualizing glycemic goals based on factors including life expectancy, existence of complications, risk of developing hypoglycemia, and potential adverse events (6,7). Choosing an add-on to metformin monotherapy among the many classes of antihyperglycemic therapies is a complex decision which requires balancing efficacy, safety, and patient preferences (8). This task is made even more difficult by the effect that low baseline A1C can have on the efficacy of T2D therapies (9).

Traditionally, a sulfonylurea (SU) has been the add-on agent of choice following failure of metformin to achieve target glycemia, but this approach has been challenged of late. While SUs have a high glucose-lowering efficacy and are less costly in the short term than most other alternatives, their use is often associated with an increased risk of hypoglycemia and modest weight gain (3). The addition of a SU to metformin increases a patient’s likelihood of experiencing symptomatic hypoglycemia fivefold and can result in up to 2.5 kg weight gain (10). Recently, AACE/American College of Endocrinologists (ACE) have highlighted the desirability of limiting hypoglycemia and weight gain when intensifying antihyperglycemia therapy (1,6). Therefore, incretin-based therapies, which are recommended as an addition to metformin by both the AACE/ACE consensus algorithm and the ADA/European Association for the Study of Diabetes (EASD) position statements, have emerged as increasingly important, efficacious, and safe options when intensifying metformin (1,3).

The addition of an incretin-based therapy to metformin—such as the glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide or exenatide, or the dipeptidyl peptidase-4 (DPP-4) inhibitors sitagliptin, saxagliptin and linagliptin—has been shown to reduce A1C with a low risk of weight gain (or lead to weight loss with GLP-1 receptor agonists) or hypoglycemia (11-16). Head-to-head studies of up to 12 months’ duration (baseline A1C 7.0 to 11.0%) suggest that liraglutide once daily (OD) has greater glycemic and weight reduction efficacy compared with sitagliptin OD (LIRA–DPP-4 study) and greater A1C-lowering efficacy compared with exenatide twice daily (BID) (LEAD-6 study) (15,17-19). However, there are few data available on the comparative safety and efficacy of incretin-based therapies in patients with an A1C <8.0%.

Baseline A1C should be an important consideration when selecting a therapy for patients with T2D, as a lower baseline A1C value is associated with a smaller reduction in absolute A1C, regardless of which class of antihyperglycemic agent is used (9,20-22). The A1C-lowering efficacy of liraglutide 1.8 mg, exenatide BID and sitagliptin, can vary by 1.1% (–0.7 to –1.8%), 0.9% (–0.4 to –1.3%) and 1.1% (0.0 to –1.1%), respectively, dependent on baseline A1C (21). The AACE/ACE treatment algorithm recommends three different treatment pathways based on a patients baseline A1C category (6,5 to 7.5%, 7.6 to 9.0%, or >9.0%) (1). However, change in A1C data from clinical trials is rarely stratified by baseline A1C, making therapeutic decision-making within these pathways complex.

With these issues in mind, using data from the LEAD-6 and LIRA–DPP-4 studies, we compared the safety and efficacy of the maximal approved dose of liraglutide OD (1.8 mg) with that of sitagliptin OD (100 mg) and exenatide BID (10 µg) when used as add-on therapy to metformin in patients with T2D and an A1C <8.0%.

METHODS

Participants and Study Design

We performed a post hoc analysis of 26-week data from the LEAD-6 and LIRA–DPP-4 studies. The 26-week study designs and inclusion/exclusion criteria for LEAD-6 and LIRA–DPP-4 have been reported previously (15,17). Briefly, participants were aged 18 to 80 years, had a body mass index (BMI) ≤45 kg/m² and were diagnosed with T2D. In LEAD-6, patients uncontrolled (baseline A1C: 7.0 to 11.0%) on metformin and/or a SU were randomized to receive either liraglutide 1.8 mg OD or exenatide 10 µg BID. In LIRA–DPP-4, patients inadequately controlled (A1C: 7.5 to 10.0%) on metformin ≥1500 mg/day after ≥3 months were randomized to receive additional liraglutide 1.2 mg, liraglutide 1.8 mg, or sitagliptin 100 mg (all once daily).

In this post hoc analysis, only patients treated as a true add-on to metformin monotherapy (not switched from prior therapy) and having a baseline A1C of <8.0% were included. Metformin therapy was continued at prestudy dose. As the aim of this analysis was to compare the maximal approved dose of liraglutide with that of exenatide BID and sitagliptin OD, only patients receiving the liraglutide 1.8 mg OD dose were included: LEAD-6, liraglutide 1.8 mg OD (n = 44) versus exenatide 10 µg BID (n = 41) and LIRA–DPP-4, liraglutide 1.8 mg OD (n = 72) versus sitagliptin 100 mg OD (n = 61). Participants randomized to liraglutide or exenatide BID underwent dose-escalation as previously reported (15,17).

Assessments and Endpoints

Endpoints included change in A1C and body weight from baseline to week 26 and the proportion of patients achieving A1C targets (<7.0 and ≤6.5%), and a composite endpoint (A1C <7.0%, no weight gain, no hypoglycemia) at week 26. Treatment satisfaction was assessed by the
eight-item Diabetes Treatment Satisfaction Questionnaire (DTSQ) in a subgroup of 183 patients (LEAD-6: liraglutide 1.8 mg [n = 34] versus exenatide 10 µg [n = 38]; LIRA–DPP-4: liraglutide 1.8 mg [n = 63] versus sitagliptin 100 mg [n = 48]), although the number of patients for whom data was available within each treatment arm varied slightly for each DTSQ endpoint analyzed. Overall treatment satisfaction was the sum of 6 of the 8 DTSQ scores (23).

Safety variables included treatment-emergent gastrointestinal adverse events and patient-reported hypoglycemia; major hypoglycemia was defined as requiring third-party assistance and minor hypoglycemia as self-treated plasma glucose concentration of <3.1 mmol/L (<55.8 mg/dL).

**Statistical Analysis**

Efficacy analysis was performed on the intention-to-treat (ITT) population, using last observation carried forward (LOCF). Changes in A1C, body weight and treatment satisfaction from baseline were assessed by analysis of covariance (ANCOVA) with country and treatment as fixed effects and baseline value as a covariate. The proportion of patients achieving glycemic targets (≤6.5 and <7.0%) and the composite endpoint were analyzed by logistic regression analysis with randomized treatment as a fixed effect and baseline A1C (all endpoints) and body weight (composite endpoint only) as covariates. All data are least squares (LS) mean unless stated otherwise. Safety analyses were performed on all patients exposed to at least 1 dose of trial drug.

**RESULTS**

**Baseline Demographics**

Patient baseline data were generally well balanced across the treatment groups in each study (Table 1). Mean baseline A1C was similar for liraglutide and exenatide BID in LEAD-6 and liraglutide and sitagliptin in LIRA–DPP-4. However, in LEAD-6, patients treated with exenatide BID had a shorter mean disease duration compared to liraglutide (3.9 versus 6.9 years).

**LEAD-6: Addition of Liraglutide 1.8 mg OD or Exenatide 10 µg BID to Metformin When A1C <8.0%**

Following 26- weeks of treatment, substantially more patients achieved the A1C targets of <7.0 and ≤6.5% with liraglutide compared with exenatide ($P = .03$ and $P = .01$, respectively) (Fig. 1); the more stringent AACE target was achieved by 65% of liraglutide-treated patients compared with 35% of those treated with exenatide. The mean reduction in A1C and weight tended to be greater with liraglutide than exenatide but the differences were not statistically significant (estimated treatment difference [ETD] = –0.27% [95% CI: –0.55 to 0.00]; $P = .05$ and ETD = -1.06 kg [95% CI: –2.54 to 0.42]; $P = .16$) (Fig. 2 and 3). Almost twice as many participants reached the composite endpoint of A1C <7.0%, with no weight gain and no confirmed major or minor hypoglycemia with liraglutide compared to exenatide ($P = .0023$) (Fig. 4).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline Characteristics*</th>
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<tbody>
<tr>
<td></td>
<td>LEAD-6</td>
</tr>
<tr>
<td><strong>Factor</strong></td>
<td><strong>Liraglutide 1.8 mg OD</strong></td>
</tr>
<tr>
<td></td>
<td>(n = 44)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>54.3 (9.3)</td>
</tr>
<tr>
<td>Diabetes duration (y)</td>
<td>6.9 (5.2)</td>
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<tr>
<td>A1C (%)</td>
<td>7.4 (0.3)</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>8.5 (2.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.0 (5.2)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>94.8 (18.7)</td>
</tr>
</tbody>
</table>

Abbreviations: A1C = glycated hemoglobin; BID = twice daily; BMI = body mass index; FPG = fasting plasma glucose; ITT = intention to treat; OD = once daily; SD = standard deviation.

* Data are mean (SD) from ITT analysis set.
Intensifying Metformin When A1C <8%, *Endocr Pract.* 2013;19(No. 1) 67

Treatment satisfaction scores improved in 7 of the 8 DTSQ categories for both liraglutide and exenatide after 26 weeks’ treatment (Fig. 5). Patients reported greater improvements in “current treatment” (P = .04), “convenience” (P = .03), “continue treatment” (P = .02), and overall treatment satisfaction (P = .03) with liraglutide compared with exenatide.

The proportion of patients experiencing treatment-emergent gastrointestinal disorders was similar with exenatide and liraglutide (46% versus 48%), although nausea (37% versus 21%) and vomiting (10% versus 2%) appeared to be more common with exenatide, respectively (Table 2). No episodes of major hypoglycemia were reported with either treatment. While minor hypoglycemia was reported by a similar proportion of patients receiving liraglutide and exenatide (9.1 versus 9.8%), the incidence rate was higher with liraglutide (1.53 versus 0.45 events/patient-year), respectively. However, after excluding 1 outlier who experienced 24 episodes of minor hypoglycemia with liraglutide treatment, the incidence rates were very similar (0.39 versus 0.45 events/patient-year, respectively).

**LIRA–DPP-4: Addition of Liraglutide 1.8 mg OD or Sitagliptin 100 mg OD to Metformin When A1C <8.0%**

After 26 weeks of treatment, more than twice as many liraglutide-treated patients achieved the <7.0 and ≤6.5% A1C targets compared to exenatide (OR = 3.29, 95% CI: 1.15 to 9.45, P = .03) (Fig. 1). However, the treatment difference was not statistically significant for achieving A1C ≤6.5% (OR = 1.37, 95% CI: 1.31 to 8.63, P = .01) (Fig. 2).

**Fig. 1.** Proportion of patients achieving glycated hemoglobin (A1C) targets at week 26. Data are least squares (LS) mean. Treatment comparisons were performed by logistic regression for the intention-to-treat (ITT) population, last observation carried forward (LOCF).

**Fig. 2.** Change in glycated hemoglobin (A1C) from baseline to week 26. Data are least squares (LS) mean (2SE). Estimated treatment difference (ETD) was calculated by analysis of covariance (ANCOVA) on intention-to-treat (ITT), last observation carried forward (LOCF).
Intensifying Metformin When A1C <8%, *Endocr Pract.* 2013;19(No. 1)

A1C targets (*P* < .0001 and *P* = .0002, respectively) (Fig. 1); only 19% of sitagliptin-treated patients achieved the AACE-recommended A1C target of ≤6.5%, compared with 53% of liraglutide-treated patients. The mean reduction in A1C and weight from baseline was significantly greater with liraglutide compared with sitagliptin (*P* < .0001 for both) (Fig. 2 and 3) and almost 3 times as many liraglutide-treated patients achieved the composite endpoint (A1C < 7.0% and no weight gain or reported hypoglycemia) compared with sitagliptin (*P* < .0001) (Fig. 4).

Treatment satisfaction scores improved from baseline for all 8 DTSQ items with both liraglutide and sitagliptin (Fig. 5). However, liraglutide treatment resulted in significantly greater improvements in “perceived hyperglycemia” (*P* = .04), “flexibility” (*P* = .005), and “understanding” (*P* = .02) compared with sitagliptin; no difference was recorded in perceived “convenience” between the oral and injectable therapies. Overall treatment satisfaction score improved by 4.5 with liraglutide compared to 2.4 with sitagliptin (*P* = .05).

The overall frequency of gastrointestinal adverse events was greater with liraglutide compared with sitagliptin (43% versus 28%), largely due to more nausea and vomiting with liraglutide (Table 2). No episodes of major hypoglycemia were reported with either agent. The proportion of patients experiencing at least 1 episode of minor hypoglycemia was similar for liraglutide and sitagliptin (8.3% versus 8.2%) but the incidence rate was higher with liraglutide (0.84 versus 0.17 events/patient-year). However, following the exclusion of an outlier, who experienced 21...
Intensifying Metformin When A1C <8%,

**DISCUSSION**

This post hoc analysis suggests that in patients with inadequate glycemic control on metformin and with a baseline A1C <8.0%, the addition of liraglutide, titrated to a maximal dose of 1.8 mg OD, is more likely to bring them to A1C target than exenatide 10 µg BID or sitagliptin 100 mg OD. Despite the relatively lower baseline A1C in these analyses, liraglutide 1.8 mg still reduced A1C by 0.87 and 1.01%, respectively, resulting in the majority of patients (53 and 65%, respectively) achieving the stringent AACE A1C target (≤6.5%). Conversely, the A1C-lowering efficacy of sitagliptin was considerably less in this baseline A1C range, with less than 1 in 5 patients achieving the AACE glycemic target. This may be due to differences in mechanism of action between DPP-4 inhibitors, which are dependent on endogenous GLP-1, and GLP-1 receptor agonists that can be dosed to pharmacological levels.

These findings are consistent with the respective core studies, except the change in A1C was not significantly greater for liraglutide compared with exenatide (P = .05) (15,17). This may be attributable to the small sample size (n = 85), as the estimated treatment differences were similar between data sets (–0.27% versus –0.33% in LEAD-6, respectively), or the difference in disease duration between liraglutide- and exenatide-treated patients (6.9 versus 3.9 years, respectively) in this subset. While liraglutide exhibits significant A1C-lowering throughout the continuum of baseline A1C (21), liraglutide has previously been shown to be somewhat more effective at lowering A1C and achieving a composite endpoint (A1C <7.0%, no weight gain or hypoglycemia) when used earlier in disease (24,25). In line with previous data for all classes of T2D therapies (9,20-22), reductions in A1C were proportionally smaller for liraglutide, exenatide BID, and sitagliptin in these patients with A1C <8.0% compared to the core study data where patients had a higher mean baseline A1C (8.1 to 8.5%) (15,17). The moderate glycemic efficacy of exenatide in this analysis is consistent with the larger EUREXA trial, where 977 patients were randomized to receive exenatide BID or a SU following metformin failure (mean baseline A1C: 7.5 and 7.4%, respectively) (26). After a mean of 2 years treatment, 29% of exenatide-treated patients (change in A1C: –0.36%) and 18% of those randomized to SU therapy (change in A1C: –0.21%) achieved an A1C of ≤6.5%.

Previous stratification of change in A1C data by baseline A1C in sitagliptin (+ metformin) studies demonstrate that its efficacy decreases substantially as baseline A1C falls below 8.0%, which supports its low efficacy in this analysis (19,27). In patients close to target, the higher efficacy of GLP-1 receptor agonists over DPP-4 inhibitors is also supported by a large meta-regression model of patients at A1C target (<7.0%) following treatment with non-insulin classes of antidiabetic therapy (28). More
patients achieved A1C target with GLP-1 receptor agonists than DPP-4 inhibitors at all baseline A1C categories; in the lowest baseline A1C category (7.5%), DPP-4 inhibitors were ranked sixth out of the 7 classes of T2D therapies studied.

The AACE/ACE algorithm recommends the use of GLP-1 receptor agonists over DPP-4 inhibitors as add-on therapy to metformin in patients with T2D with a baseline A1C of 6.5 to 7.5%, based on greater effectiveness in reducing postprandial glucose excursions and inducing weight loss. The present data provide further support to the recommendation, since a significantly greater number of patients achieved a stringent A1C target (A1C ≤6.5%) and a composite endpoint of A1C <7.0% with no weight gain or hypoglycemia when taking liraglutide than those who were taking sitagliptin.

The greater efficacy of liraglutide at bringing patients to target compared with sitagliptin or exenatide BID may be attributable to their different mechanisms of action and pharmacokinetic profiles. Inhibition of the DPP-4 enzyme increases endogenous GLP-1 within physiological levels (by approximately two- to three-fold), while GLP-1 receptor agonists can be dosed to achieve pharmacological stimulation of the GLP-1 receptor (29,30). Additionally, while liraglutide and sitagliptin have similar pharmacokinetic half-lives (13 hours versus 8 to 14 hours, respectively), the increase in endogenous GLP-1 with sitagliptin is primarily observed postprandially, while liraglutide does not reach its maximal concentration for 8 to 12 hours, resulting in a sustained 24-hour response from OD dosing (15,31-33). Exenatide BID reaches its median peak concentration within approximately 2 hours of dosing and has a terminal half-life of 2.4 hours (34). As a result, exenatide BID provides a greater postprandial glucose (PPG) reduction after breakfast and dinner compared with liraglutide 1.8 mg, while liraglutide has a superior fasting plasma glucose (FPG) effect (17).

Overall treatment satisfaction, a potential contributor to treatment adherence and clinical outcomes (35), improved significantly more with liraglutide versus exenatide, as in the core study (36). The different dosing frequencies of liraglutide OD and exenatide BID may explain the significantly greater improvement in treatment convenience with liraglutide. Our results also show that despite injectable versus oral administration, perceived treatment convenience was similar for liraglutide and sitagliptin and perceived treatment flexibility was greater with liraglutide. However, it should be noted that by providing informed consent to participate in the trial, patients were pre-selected as being open to injection therapy. These treatment satisfaction data are largely consistent with the LIRA–DPP-4 26-week study and second extension (weeks 52 through 78 where patients switched from sitagliptin to liraglutide), and may be a reflection of the greater glycemic and weight loss efficacy provided by liraglutide compared with sitagliptin (37,38).

All 3 incretin-based therapies were safe and well-tolerated in these patients. As expected, gastrointestinal adverse events were more frequent with the GLP-1 receptor agonist compared with sitagliptin, but data from the core studies suggest that the GLP-1-associated nausea was largely transient, particularly with liraglutide (15,17). The glucose-dependent mechanism of action of incretin-based therapies limits the increased risk of hypoglycemia often associated with treatment intensification, particularly in comparison to a SU (39).

### Table 2

<table>
<thead>
<tr>
<th>Factor</th>
<th>LEAD-6 Liraglutide 1.8 mg OD (n = 44)</th>
<th>LEAD-6 Exenatide 10 µg BID (n = 41)</th>
<th>LIRA–DPP-4 Liraglutide 1.8 mg OD (n = 72)</th>
<th>LIRA–DPP-4 Sitagliptin 100 mg OD (n = 61)</th>
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<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>21 (47.7)</td>
<td>19 (46.3)</td>
<td>31 (43.1)</td>
<td>17 (27.9)</td>
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<tr>
<td>Nausea</td>
<td>9 (20.5)</td>
<td>15 (36.6)</td>
<td>20 (27.8)</td>
<td>1 (1.6)</td>
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<tr>
<td>Diarrhea</td>
<td>7 (15.9)</td>
<td>5 (12.2)</td>
<td>7 (9.7)</td>
<td>6 (9.8)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4 (9.1)</td>
<td>2 (4.9)</td>
<td>5 (6.9)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (6.8)</td>
<td>2 (4.9)</td>
<td>1 (1.4)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2.3)</td>
<td>4 (9.8)</td>
<td>9 (12.5)</td>
<td>2 (3.3)</td>
</tr>
</tbody>
</table>

Abbreviations: BID = twice daily; OD = once daily.

a Data are number of patients (% of total participants in treatment group) from safety analysis set.
As a post hoc analysis, data were derived from studies that were not initially designed to answer this research question. For example, baseline disease duration was different in the 2 LEAD-6 treatment groups and the inclusion criteria of baseline A1C <8.0% and true add-on to metformin resulted in small treatment groups for comparison. Therefore, further appropriately designed studies will be required to confirm the findings of this analysis.

CONCLUSION

When added to first-line metformin in patients with an A1C <8.0%, liraglutide 1.8 mg was more effective than exenatide BID or sitagliptin at achieving A1C targets, particularly the more stringent AACE goal (A1C ≤6.5%). The efficacy of sitagliptin was particularly low in this patient group, bringing less than 1 in 5 patients to the AACE glycemic target. The proportion of patients achieving A1C <7.0% with no weight gain or hypoglycemia was almost twofold greater with liraglutide 1.8 mg compared to exenatide BID and approximately threefold greater compared with sitagliptin. These data support the use of liraglutide 1.8 mg as a safe and effective alternative to exenatide and sitagliptin as an addition to metformin therapy in patients with A1C <8.0%.

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DISCLOSURE

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