BREAKING NEWS on INCRETIN-BASED THERAPIES

Summary Conference Report

In conjunction with the 2008 American Diabetes Association's 68th Annual Scientific Sessions · June 6-10, 2008 · San Francisco, CA

CME/CNE INFORMATION AND CONFLICT OF INTEREST DISCLOSURES CAN BE FOUND ON PAGES 3-4 OF THIS PUBLICATION

Selected Oral Presentations from Saturday, June 7, 2008

β-Cell Function and Glycemic Control Following 1-Year Exenatide Therapy, and After 12-Week Washout, in Patients With Type 2 Diabetes

Presented by Michaela Diamant, on behalf of Mathijs Bunck

β-Cell function continues to decline in patients with type 2 diabetes mellitus (T2DM), and current therapies have little effect altering this process. Exenatide (EXEN) has demonstrated clinical effects such as improving glycemic control and promoting weight reduction; however, the ability of EXEN to modulate β-cell function has not been extensively studied. This randomized trial evaluated the β-cell C-peptide secretion following 1 year of EXEN treatment (n = 36) compared to 1 year of insulin glargine (GLAR) (n = 33) in patients with T2DM taking metformin (baseline age = 58 years, BMI = 30 kg/m^2, A1C = 7.5%, and disease duration = 5 years; **104-OR**). During a hyperglycemic clamp (15 mM), the arginine-stimulated C-peptide secretion was 146% greater with EXEN compared with that of GLAR, $P < .0001$. Despite improved β-cell secretion during treatment, response was not maintained after EXEN discontinuation; after a 4-week washout, all functional parameters returned to pretreatment values. Consistent with previous findings, EXEN reduced A1C similar to GLAR, – 0.8% and – 0.7%, respectively. EXEN reduced body weight to a greater extent at 52 weeks: – 3.6 kg and + 1 kg, $P < .0001$. Again, positive benefits of EXEN or glargine on glycemic control and EXEN on weight reduction were lost with treatment discontinuation. The study investigators conclude that EXEN improves β-cell secretory function; however, ongoing treatment may be necessary.

Efficacy of Exenatide Therapy Over 2 Years in a "Real World" Setting

Presented by Jennifer Loh

In this oral presentation, a retrospective review of patient charts was undertaken to determine the 2-year clinical practice experience in patients using exenatide (EXEN) therapy (**105-OR**). EXEN was initiated in 30 patients (age = 58 years, BW = 103 kg, BMI = 35 kg/m^2, A1C = 7.6%) who were already receiving oral medication, basal insulin, or a combination of both as part of their regular diabetes care. At the end of Year 1, 15 patients remained on EXEN, and at Year 2, 12 patients remained on EXEN. At 6 months, patients lost an average of 3.5 kg. At 1 year, weight loss was 2.05 kg, and at 2 years, weight loss was 1.53 kg, not statistically significant from baseline ($P = .786$), and there was no change in A1C from baseline to 2 years. Sixty-three percent of patients discontinued EXEN after 2 years. In the subgroup of patients receiving EXEN for 2 years (n = 12), A1C and body weight (BW) decreased significantly ($P < .05$). A trend toward greater reductions in A1C and BW were found for those patients receiving oral medications plus EXEN (1.07% and 4.9 kg) compared with those receiving basal insulin plus EXEN (0.22% and 0.36 kg). Investigators conclude that EXEN efficacy may only extend to a subgroup of patients in the "real world" and that future studies are needed to identify factors that predict favorable clinical response.

Exenatide Once Weekly Results in Significantly Greater Improvements in Glycemic Control Compared to Exenatide Twice Daily in Patients With Type 2 Diabetes

Presented by Daniel J. Drucker

This study compared the effects of once-weekly, long-acting-release exenatide (LAR) (2 mg sc) to twice-daily exenatide (EXEN) (10 mcg sc) in an open-label, randomized, 30-week trial in 295 patients with type 2 diabetes (A1C = 8.3%; BMI = 35 kg/m^2; diabetes duration = 6.7 years) who were being treated with diet and exercise (15%), 1 oral agent (45%), or 2 oral agents (40%) (**107-OR**). The least-squares mean changes from baseline in A1C were 1.9% in the LAR group and 1.5% in the EXEN group ($P = .002$). The percent of patients achieving an A1C < 7% was 77% and 61% in the LAR and EXEN groups, respectively. There was an approximate 3.7-kg weight loss in both groups, with a 10% drop-out rate in the LAR group. The rate of nausea (35% EXEN and 26% LAR) and injection site reactions (1% EXEN and 18% LAR) differed between the 2 groups ($P < .05$). Hypoglycemia was not observed in either group, and weight loss was not linked to nausea. More LAR patients developed exenatide antibodies compared with EXEN patients, and patients with positive antibodies had less A1C reduction compared with antibody-negative patients.

Liraglutide, a Once-Daily Human GLP-1 Analog, Reduces Fat Percentage, Visceral and Subcutaneous Adipose Tissue, and Hepatic Steatosis Compared With Glimepiride When Added to Metformin in Subjects With Type 2 Diabetes

Presented by Johan Jendle

This LEAD 2 study is a placebo-controlled, double-blind, randomized 26-week study of the efficacy of the human GLP-1 analog liraglutide when added to metformin (MET) (**106-OR**). This subanalysis (N = 160) of the LEAD 2 study was designed to evaluate the effect of body composition in patients with type 2 diabetes mellitus (T2DM). Patients taking MET (1 g twice a day) were randomized to one of the following groups: liraglutide (LIRA; 0.6, 1.2, or 1.8 mg sc daily), glimepiride (GLIM, 4 mg daily), or placebo (PBO). Body composition was studied using dual energy x-ray absorptiometry (DEXA) and CT. Results are presented in Table 1. Body weight reduction that occurred with LIRA was dose dependent and was distributed between fat and lean tissue in a ratio of approximately 2:1, as compared with an approximate 1:1 ratio in the weight loss seen with PBO and the weight gain seen with GLIM. There was a significant reduction in the percentage of fat in the 1.2- and 1.8-mg LIRA groups compared with GLIM ($P < .05$). A significant change in liver:spleen attenuation ratio was seen for the highest dose of LIRA demonstrating a reduction in hepatic steatosis ($P < .05$).

Table 1. Effect of liraglutide on body composition and hepatic steatosis

Parameter, unit	LIRA 0.6 + MET	LIRA 1.2 + MET	LIRA 1.8 + MET	PBO + MET	GLIM + MET
ΔFat mass, kg	-0.74*	-1.64*	-2.40*	-1.13	+1.13
ΔLean body mass, kg	-0.26*	-0.84*	-1.54*	-1.33	+1.28
ΔFat, %	-0.5	-1.1*	-1.2*	-0.2	+0.4
ΔVisceral fat, %	-12.9	-17.1	-16.4	-7.7	-4.8
ΔSubcutaneous fat, %	-5.2*	-7.8*	-8.5*	-4.2	+3.4
ΔLiver/spleen attenuation	-0.02	+0.02	+0.10*	-0.00	-0.00

Mean least-squares changes from baseline. *$P < .05$ vs GLIM + MET.

Eight Weeks of Treatment With the Long-Acting Human GLP-1 Analog Taspoglutide (R1583) Improves Glycemic Control and Lowers Body Weight in Subjects With Type 2 Diabetes Treated With Metformin: A Double-Blind, Placebo-Controlled Phase 2 Study

Presented by Michael Nauck

The results of a randomized, placebo-controlled, 8-week trial to study the efficacy of taspoglutide (R1583), a long-acting human GLP-1 analog given either once weekly (QW) or every 2 weeks (Q2W) in 360 patients with T2DM (age 55 years; BMI = 32.7 kg/m^2; A1C = 7.9%; duration of type 2 diabetes = 5 years) were presented (**108-OR**). A1C was significantly decreased relative to placebo at all doses tested ($P < .0001$), and was most markedly decreased relative to baseline in taspoglutide QW at a dose of 10 or 20 mg (– 1.2%), with smaller decreases seen in the 5-mg QW and 10-mg and 20-mg Q2W groups (– 1%). Significant weight loss from baseline ($P < .05$) was seen in the 10-mg QW group (2 kg), 20-mg QW group (2.8 kg), and in the 20-mg Q2W group (1.9 kg).

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Selected Liraglutide (LIRA) Poster Presentations

07-LB *(Garber);* **504-P** *(Nauck);* **505-P** *(Matthews);* **536-P** *(Russell-Jones);* **554-P** *(Colagiuri);* **555-P** *(Flint);* **556-P** *(Flint);* **1573-P** *(Prazak)*

A number of posters were presented on liraglutide (LIRA), a human GLP-1 analog with 97% homology to human GLP-1. In terms of randomized clinical trials, LIRA posters presented data on LIRA monotherapy (**07-LB**), combination therapy with metformin (MET) (**504-P**), and combination therapy with MET and sulfonylurea (**536-P**). Results of the monotherapy study (07-LB), which was a 52-week randomized trial (N = 746), showed significant improvements in glycemic control (A1C, FPG, and PPG) compared with glimepiride (GLIM). LIRA was also associated with weight loss and a reduction in hypoglycemic events relative to GLIM (**Table 1**).

Table 1. Efficacy and safety of LIRA monotherapy compared with glimepiride

	LIRA 1.2 mg	LIRA 1.8 mg	GLIM
ΔA1C, %	-0.84*	-1.14*†	-0.51
ΔWeight, kg	-2.05*	-2.45*	1.12
ΔFPG, mg/dL	-14*	-26*†	-5.4
ΔPPG, mg/dL	-31	-38*	-25
% reporting minor hypo Hypo events/subject/year	12 0.30*	8 0.25*	24 1.96
% reporting nausea	27.5	29.3	8.5

*P < .05 vs GLIM; †P < .05 1.8 mg vs 1.2 mg.

The results of the Liraglutide Effects and Action in Diabetes 2 (LEAD 2) study, a placebo (PBO)-controlled, double-blind, randomized 26-week trial (N = 1091 randomized, N = 880 completed) examined the safety and efficacy of 3 doses of LIRA as add-on therapy to MET. The findings showed that LIRA + MET improved glycemic control compared with PBO + MET (**504-P**). More patients also achieved A1C < 7% and ≤ 6.5% with LIRA + MET than with PBO + MET. A significant reduction in weight was also demonstrated, and hypoglycemia appeared to be lower in the LIRA groups, although no statistical analyses were done (**Table 2**). Initial rates of nausea were low (6%-12% of subjects in the LIRA + MET groups) and declined to 2% (about the same as PBO + MET) between 8 and 16 weeks.

Table 2. Efficacy and safety of LIRA as add-on therapy to metformin

	LIRA 0.6 + MET	LIRA 1.2 + MET	LIRA 1.8 + MET	PBO + MET	GLIM + MET
ΔA1C, %	-0.7*	-1.0*	-1.0 *	+0.1	-1.0
ΔFPG, mg/dL	-20*	-29*	-30*	+7	-23
ΔWeight, kg	-1.8^	-2.6*^	-2.8*^	-1.5	+0.9
% reporting minor hypo events[a]	3.7	0.8	2.5	2.5	16.9

*P < .05 compared with PBO + MET; ^P < .05 compared with GLIM + MET; [a]No statistical analysis.

The LEAD 5 study was a 26-week, randomized trial (N = 581 randomized, 522 completed) examining the efficacy and safety of LIRA (1.8 mg), PBO, and open-label glargine (GLAR), all as add-on therapy to MET and GLIM (**536-P**). When LIRA 1.8 + MET + GLIM was compared with PBO + MET + GLIM, results again demonstrated a significant improvement in A1C among patients receiving LIRA. Additionally, LIRA 1.8 mg + MET + GLIM was also associated with a significant reduction in A1C compared with GLAR + MET + GLIM. LIRA combination therapy was associated with weight loss, low incidence of hypoglycemia, and transient nausea (**Table 3**). Approximately 10% of LIRA patients developed antibodies, but this finding did not appear to have clinical relevance.

Table 3. Efficacy and safety of LIRA as add-on therapy to MET and GLIM

	LIRA 1.8 + MET + GLIM	PBO + MET + GLIM	GLAR + MET + GLIM
ΔA1C, %	-1.33*^	-0.24	-1.09
A1C ≤ 6.5%, % of patients	37.1*^	10.9	23.6
ΔWeight, kg	-1.81*^	-0.42	1.62
ΔFPG, mg/dL	-27.92*	9.56	-32.16
% reporting minor hypo events	27.4	16.7	28.9
% reporting nausea	13.9	3.5	1.3

*Statistically significant in comparison to PBO + MET + GLIM; ^statistically significant in comparison to GLAR + MET + GLIM.

In addition to the beneficial effects of LIRA on A1C and weight, LIRA was also shown to decrease PPG level (**556-P**), and postprandial hunger and energy intake (**555-P**). Pooled analyses of 3 of the LEAD studies showed beneficial effects of LIRA on systolic, but not diastolic, blood pressure (**554-P**). The LEAD 1, 2, and 5 studies also showed that relative to comparator agents, LIRA significantly increased HOMA-β-cell function and decreased the proinsulin/insulin ratio (**505-P**). LIRA was also shown to prevent β-cell apoptosis in human islet cell cultures (**1573-P**).

Selected Saxagliptin (SAXA) Poster Presentations

517-P *(Rosenstock)*

The effect of saxagliptin (SAXA) on various parameters of glycemic control and body weight were studied in a 24-week, randomized, placebo (PBO)-controlled, parallel-group, multicenter clinical trial of 467 treatment-naïve patients with type 2 diabetes mellitus (T2DM) (**517-P**). After a 2-week run-in with PBO, the main treatment cohort (n = 401) was randomized to PBO, SAXA 2.5 mg, SAXA 5 mg, or SAXA 10 mg daily (baseline A1C = 7%-10%). An open-label treatment cohort (n = 66) was treated with SAXA 10 mg daily without PBO run-in (baseline A1C > 10% but ≤ 12%). Statistically significant differences in A1C, FPG, and 2-hour PPG relative to baseline and to PBO were observed in the main treatment cohort for all SAXA doses. Less weight loss was observed in patients treated with 5- or 10-mg SAXA (– 0.1 to + 0.1 kg) than in the PBO and 2.5-mg SAXA groups. Hypoglycemia incidence was similar in the SAXA (5.2%) and PBO (6.3%) groups, and no confirmed hypoglycemic episodes with blood glucose < 50 mg/dL (2.8 mmol/L) were observed in any cohort or subgroup.

Selected Exenatide (EXEN) Poster Presentations

05-LB *(Maggs);* **454-P** *(Brixner);* **482-P** *(Yoon);* **485-P** *(Brodows);* **494-P** *(Kim);* **513-P** *(Kendall);* **1198-P** *(Nielsen);* **1213-P** *(Fabunmi);* **1873-P** *(Best);* **1885-P** *(Martin)*

A large retrospective trial (N = 1784) found 6-month exenatide (EXEN) efficacy in clinical practice to be similar to controlled trials, and glycemic control improved independent of weight change (**454-P**). Although most studies of EXEN describe efficacy in the context of background medications, a recent trial found that 24-week EXEN monotherapy in drug-naïve patients with type 2 diabetes improves glycemic control and reduces body weight with limited incidence of hypoglycemia (**485-P**). EXEN also improves LDL and HDL cholesterol independent of weight reduction, but improvement in triglycerides was related to weight loss (**513-P**). Compared with insulin, more patients achieve tighter glycemic control with EXEN, which translates to greater reductions in total cholesterol and LDL-C. Both EXEN and insulin significantly improve HDL-C and triglyceride levels (**05-LB**). Furthermore, better adherence to therapy and lower incidence of hypoglycemic events was shown for EXEN compared with insulin glargine (GLAR; **1213-P**, **1198-P**). When EXEN is combined with insulin, glycemic control and weight reduction is still achieved (**482-P**). Once-weekly EXEN (LAR) or BID EXEN therapies equally improve glycemic control and reduce weight (**494-P**, **1873-P**). Both groups reported overall treatment satisfaction and improved weight-related quality of life (**494-P)**. More patients receiving LAR reported injection and injection preparation as the most problematic aspects of treatment compared with BID EXEN, 43% vs 29%. However, when specifically asked about any injection difficulties, 77% LAR and 89% BID reported no problems.

Selected Vildagliptin (VILDA) Poster Presentations

511-P *(Woerle),* **560-P** *(Ahrén),* **561-P** *(Iwamoto)*

Vildagliptin (VILDA) is a potent and selective DPP-4 inhibitor that improves glycemic control in patients with type 2 diabetes. In 18 patients with T2DM, VILDA lowered postprandial peak glucose and delayed gastric emptying, with no differences in insulin and C-peptide concentrations compared with placebo. Postprandial glucagon levels were lower with VILDA, as were total rates of glucose appearance and meal rates of glucose appearance. VILDA reduced 2-hour postprandial plasma glucose (PPG) by reducing glucagon release after meals and delaying gastric emptying, although glucagon excretion during hypoglycemia is increased, suggesting that the counterreulatory response is preserved. The effects of VILDA 100 mg daily were compared to the α-glucosidase inhibitor voglibose. At the end of the study, A1C was 1% lower in the VILDA group compared with 0.4% lower in the voglibose group (P < .001). Almost 19% of patients in the VILDA group and 32.8% of patients in the voglibose group reported GI upset (P = .002).

Selected Sitagliptin (SITA) Poster Presentations

495-P *(Williams-Herman);* **496-P** *(Katzeff)*

A pooled analysis of 4 randomized, placebo (PBO)-controlled trials (N = 1691, n_{SITA} = 1036) of sitagliptin (SITA) 100 mg, administered as once-daily monotherapy for 18 or 24 weeks showed that patients treated with SITA had greater reductions in A1C (ΔA1C) than patients treated with PBO (**495-P**). ΔA1C was equivalent whether patients were stratified by age or gender. A1C was reduced in all body mass index (BMI) groups, with a trend toward less reduction with increasing BMI. ΔA1C was – 0.9, – 0.7, and – 0.5 for BMI < 25, 25 to < 30, and ≥ 30, respectively.

β-Cell function (BFX) may be assessed by a number of different measures. Fasting measures of BFX include HOMA-β and the proinsulin:insulin (P:I) ratio (**496-P**). This study found that 100-mg SITA monotherapy produced the largest reductions in A1C for patients in the lowest HOMA-β or highest P:I ratio tertile at baseline. Postprandial measures of BFX include the insulinogenic index and model-based assessments. Patients on SITA + MET had sustained improvements in all fasting and postprandial measures of BFX, insulin sensitivity, and insulinogenic index.

Selected Alogliptin (ALO) Poster Presentations

444-P *(Rosenstock);* **445-P** *(Pratley);* **446** *(DeFronzo);* **477** *(Nauck);* **478** *(Pratley);* **479** *(Fleck);* **521** *(Hirayama);* **538** *(Karim)*

Alogliptin (ALO) is an investigational dipeptidyl peptidase-4 (DPP-4) inhibitor that is primarily renally excreted. ALO has been studied as monotherapy, in combination with glyburide, metformin, pioglitazone ± sulfonylurea/metformin, or insulin ± metformin in patients with type 2 diabetes (age 53-57 years; BMI = 31-33 kg/m^2; A1C = 7.9%-9.3%; duration of type 2 diabetes = 3.3-13 years). The results (Table 1) indicate that ALO is effective at reducing A1C. ALO therapy did not result in clinically significant weight or lipid changes. The incidence of hypoglycemia ranged between 0% and 7% in the ALO groups. Between 0.8% and 4.7% of patients in the ALO groups dropped out secondary to adverse events. The incidence of rash in the ALO-treated patients was less than 1%. It is recommended that the dose of ALO be reduced by ½ in patients with creatinine clearance between 30 and 50 mL/min and reduced to ¼ the standard dose in patients with creatinine clearance less than 30 mL/min.

Table 1. Alogliptin results of randomized, double-blind, controlled 26-week trials: Least-squares mean change from baseline compared with placebo

Therapy			ALO	
	N	PBO	12.5 mg	25 mg
Monotherapy	329			
A1C (%)		-0.02	-0.56*	-0.59*
FPG (mg/dL)		11.3	-10.3*	-16.4*
Glyburide	500			
A1C (%)		+0.01	-0.38*	-0.52*
FPG (mg/dL)		+2.2	-4.7	-8.4
Metformin	527			
A1C (%)		-0.1	-0.6*	-0.6*
FPG (mg/dL)		0	-19*	-17*
Pioglitazone ± metformin/sulfonylurea	493			
A1C (%)		-0.19	-0.66*	-0.8*
FPG (mg/dL)		-5.7	-19.7*	-19.9*
Insulin ± metformin	131			
A1C (%)		-0.13	-0.63*	-0.71*
FPG (mg/dL)		5.8	2.3	-11.7*

*P < .05.

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CME/CNE INFORMATION

Release Date: June 26, 2008

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Program Overview

Type 2 diabetes (T2D) is a complex and heterogeneous disorder associated with numerous pathophysiologic defects. Many conventional therapies address only a single defect, not the constellation of pathophysiologic challenges associated with T2D. Further, most conventional therapies do not offer the potential to correct underlying pathophysiologic defects and, as such, tend to lose efficacy as the disease progresses. Conventional therapies are associated with a number of perceived clinical challenges, including weight gain and hypoglycemia. Incretin-based therapies, however, address numerous pathophysiologic defects in T2D with limited side effects. They offer the potential to alter the course of the disease.

Breaking News on Incretin-Based Therapies: Summary Conference Report in Conjunction With the 2008 American Diabetes Association's 68th Annual Scientific Sessions is an educational activity designed to increase awareness and understanding of the role of incretin-based therapies in the treatment of patients with T2D. The report provides a practical overview of the most clinically relevant data on incretin-based therapies presented through posters and oral presentations at the 68th Scientific Sessions of the American Diabetes Association in San Francisco, June 6-10, 2008.

Intended Audience

This activity is intended for endocrinologists, diabetologists, diabetes educators, nurses, and other healthcare professionals (HCPs) who treat patients with T2D.

Learning Objectives

After participating in this activity, participants should be able to:

- Summarize current data that describe the clinical efficacy and safety of DPP-4 inhibitors for the treatment of T2D
- Discuss current data that describe the clinical efficacy and safety of incretin mimetics for the treatment of T2D
- Discuss the appropriate clinical application of incretin-based therapies, including proper patient selection based on clinical need and current glycemic control

CME/CNE Accreditation Statements

For Physicians

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Institute for Medical and Nursing Education (IMNE) and International Medical Press (IMP). IMNE is accredited by the ACCME to provide continuing medical education for physicians.

IMNE designates this educational activity for a maximum of 0.75 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Disclosures

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Acknowledgment of Commercial Support

This activity was supported by an educational grant from Novo Nordisk Inc.

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POSTTEST ANSWER RESPONSES (A score of 80% or greater is required to receive credit.)

1. ___ 2. ___ 3. ___ 4. ___ 5. ___ 6. ___ 7. ___ 8. ___ 9. ___ 10. ___

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___ minutes (Not to exceed 45 minutes)

Signature (required for certificate issuance) _____ Date _____

LEARNING OBJECTIVES
Rating Scale: 1 = Poor 2 = Fair 3 = Good 4 = Very Good 5 = Excellent

Please evaluate how well the following learning objectives were met:

- Summarize current data that describe the clinical efficacy and safety of DPP-4 inhibitors for the treatment of type 2 diabetes — 1 2 3 4 5
- Discuss current data that describe the clinical efficacy and safety of incretin mimetics for the treatment of type 2 diabetes — 1 2 3 4 5
- Discuss the appropriate clinical application of incretin-based therapies, including proper patient selection based on clinical need and current glycemic control — 1 2 3 4 5

OVER

BALANCE AND OBJECTIVITY

	Yes	No
• Were all data evidence based and reported in an objective manner?	☐	☐
• Was the overall content of this educational activity presented objectively and free of bias?	☐	☐

If you answered "No" to either of the above questions, please explain:

OVERALL ACTIVITY

	Yes	No
• Was the subject matter relevant to your clinical practice?	☐	☐
• Was the educational format an effective learning method?	☐	☐

If you answered "No" to either of the above questions, please explain:

Cite one new piece of information learned from this activity:

What related topics would you like to have offered as future CME activities?

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☐ Live conferences
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Additional comments:

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To assess impact on clinical behavior, outcomes surveys are conducted at 3 months and 1 year following educational activities. Surveys are issued to a convenience sampling of activity participants. We appreciate your feedback to these surveys, as it assists us in identifying and meeting additional educational needs.

Thank you for participating in this educational activity.

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POSTTEST

1. Generally speaking, which of the following statements about incretin-based therapies is *not* true?
   a. In clinical trials, DPP-4 inhibitors reduced A1C by about 1.5%
   b. DPP-4 inhibitors are associated with less nausea than incretin mimetics
   c. Incretin mimetics and DPP-4 inhibitors are associated with weight loss
   d. Incretin mimetics and DPP-4 inhibitors are associated with a low risk of hypoglycemia

2. GLP-1 analogs and DPP-4 inhibitors reduce ____.
   a. Both fasting plasma glucose (FPG) and postprandial glucose (PPG)
   b. FPG only
   c. PPG only
   d. PPG, but only in lean patients

3. Which of the following is true regarding DPP-4 inhibitors?
   a. Most DPP-4 inhibitors also inhibit DPP-8 and DPP-9
   b. Nausea is the most common side effect
   c. They promote weight loss
   d. They act by enhancing circulating levels of endogenous GLP-1

4. Which of the following statements about exenatide LAR is *not* true?
   a. Weight loss was about the same as for exenatide
   b. Glycemic control was better with LAR than with exenatide
   c. More patients had A1C < 7% on LAR than on exenatide
   d. More patients had nausea on LAR than on exenatide

5. Improvements in measures of β-cell function have been demonstrated in clinical trials for all of the following agents *except* ___.
   a. Exenatide
   b. Liraglutide
   c. Sitagliptin
   d. Taspoglutide

6. Which of the following agents was shown to reduce hepatic steatosis?
   a. Alogliptin
   b. Liraglutide
   c. Saxagliptin
   d. Taspoglutide

7. In phase 3 studies, alogliptin lowered A1C by approximately ___.
   a. 0.5%-0.8%
   b. 0.8%-1.2%
   c. 1.2%-1.5%
   d. 1.5%-2.0%

8. In phase 3 studies, liraglutide 1.8 mg lowered A1C by approximately___ .
   a. 0.5%-0.8%
   b. 0.8%-1.0%
   c. 1.0%-1.3%
   d. 1.4%-1.8%

9. Which of the following antidiabetic agents was *not* used as a comparator in the LEAD studies?
   a. Glimepiride
   b. Glyburide
   c. Insulin glargine
   d. Rosiglitazone

10. Which of the following dosing schedules are being examined for taspoglutide?
    a. Once daily and twice daily
    b. Once daily and once weekly
    c. Once weekly and once every 2 weeks
    d. Once weekly and once monthly

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Liraglutide and Others

Speaker: David D'Alessio

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that has been shown to have a wide range of actions that promote glucose homeostasis. However, endogenous GLP-1 in the human body is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). Thus, a central challenge in using GLP-1-based agents is to develop incretin mimetic compounds that are resistant to this degradation (exenatide [EXEN] or liraglutide [LIRA]) or to extend the half-life of endogenous GLP-1 by inhibiting the enzymatic breakdown of endogenous GLP-1 by DPP-4 (incretin enhancers, such as sitagliptin, saxagliptin, vildagliptin, alogliptin).

LIRA is a human GLP-1 analog with modifications designed to extend its half-life, including an amino acid substitution and an attachment of a C16 acyl chain. These modifications promote albumin binding and result in a plasma half-life that makes it suitable for once-daily dosing. Research has demonstrated that once-daily LIRA injection reduced A1C, FPG, and PPG; increased β-cell sensitivity, and reduced postprandial glucagon secretion. In a 14-week study of LIRA monotherapy, patients treated with LIRA had a more normal insulin secretory response, a lower A1C and FPG, with a dose-dependant weight loss. At the higher tested doses of LIRA, the A1C change was approximately – 1.5%.

EXEN long-acting release (LAR), another incretin mimetic in development, has been shown to have a plasma half-life of 2 weeks. LAR has been injected weekly in clinical trials in patients with type 2 diabetes and has been shown to produce a reduction in A1C by – 1.7%. EXEN and LIRA have been compared with other antidiabetic treatments in a number of clinical trials.

Other incretin mimetics in development include R1583 (taspoglutide), AVE-0010, CJC1134-PC, and albiglutide. The profile of action for incretin mimetics currently available and/or in clinical studies suggests that incretin mimetics represent a promising class of compounds to treat type 2 diabetes. These agents use a variety of physiological strategies to improve glucose homeostasis and decrease appetite and promote weight reduction.

Dipeptidyl Peptidases – Physiological Functions and Overlapping Activities

Presented by Carolyn F. Deacon

In this oral presentation, the role of inhibiting the ubiquitous enzyme dipeptidyl peptidase 4 (DPP-4) to sustain endogenous glucagon-like peptide 1 (GLP-1) activity was discussed. Circulating GLP-1 has a half-life of less than 2 minutes due to rapid degradation by DPP-4, and selective inhibition of this enzyme by the inhibition of DPP-4 prolongs the half-life of active GLP-1. It is well known that GLP-1 is secreted by the intestinal L cells in response to food intake, which in turn improves insulin secretion and inhibits glucagon release to lower blood glucose concentrations.

For patients with type 2 diabetes, it has been shown that blood concentrations of GLP-1 are considerably lower compared with normal controls. Thus, increasing circulating GLP-1 levels in patients with type 2 diabetes has become an important therapeutic goal. Two classes of drugs address this need: (1) GLP-1 analogs (incretin mimetics) that are resistant to DPP-4 degradation and have long circulating half-lives, and, as discussed in this presentation, (2) DPP-4 inhibitors (incretin enhancers), which sustain circulating levels of endogenous GLP-1.

Table 1: DPP-4 inhibitors

DPP-4 inhibitor	Half-life (hours)	% Inhibition
Sitagliptin	8-24	80
Vildagliptin	1.5-4.5	>60
Alogliptin	12-21	80
Saxagliptin	2-4	80
BI 1356	10-40	80

DPP-4 is an ubiquitously expressed serine dipeptide transmembrane protein that is also soluble in circulation. DPP-4 not only has a major role in glucose metabolism but also immune regulation, as it is part of the T-cell surface antigen CD26. Because of DPP-4's many roles, selectivity for the glucose modulating pathway is an important concern. The catalytic site of DPP-4 is located in the center of the molecule, such that small molecule inhibitors of DPP-4 do not disrupt the external structure of the enzyme. However, DPP-4 has many substrates and is part of a larger family of proteins. The clinical effects on this vast number of substrates that DPP-4 inhibitors have the potential to affect are still unknown. In vitro studies demonstrate that all of the small molecule DPP-4 inhibitors listed in Table 1 have high selectivity for DPP-4. Compared with other inhibitors, vildagliptin has lower selectivity for DPP-4, yet at doses that inhibit DPP-8 and DPP-9, no toxicity was found. So far clinical studies show good safety profiles with the DPP-4 inhibitors sitagliptin and vildagliptin. Urinary tract infections and headaches were noted as the most common adverse events; however, more long-term studies are needed.

Like GLP-1 analogs, DPP-4 inhibitors reduce fasting and postprandial plasma glucose to control hyperglycemia. However, unlike GLP-1 analogs, DPP-4 inhibitors are weight neutral, do not slow gastric emptying, and have minimal gastrointestinal side effects. The modest enhancement of circulating levels of endogenous GLP-1 with DPP-4 inhibitors is more physiologic, compared to a pharmacologic increase in GLP-1 with the injection of a GLP-1 analog. Other benefits of DPP-4 inhibitors include oral and once daily dosing as well as low incidence of hypoglycemia.

The Clinical Experience With Incretin-Based Therapies

Presented by Carol Wysham

Dr Wysham described the results of a retrospective chart review of the clinical experience with DPP-4 inhibitors and GLP-1 analogs in a multidisciplinary clinic by analyzing data from patients who had been on exenatide or sitagliptin within the last 6 months. Approximately 70% of the patients who were cared for by primary care physicians had A1C < 7%, with most patients using metformin, sulfonylureas, thiazolidinediones, or insulin in various combinations to improve their glucose control. Table 1 contains the characteristics of patients treated with sitagliptin and exenatide. During 6 months of therapy, 31 (21.4%) patients in the sitagliptin group and 38 (13.2%) in the exenatide group stopped treatment. Five percent of the patients stopped exenatide due to nausea, and 13% stopped sitagliptin due to lack of efficacy. Dr Wysham acknowledged that among the limitations of this clinical-experience report are the presence of several confounding variables and non-label product use. The results are presented in Table 1.

Table 1: Selected results of a retrospective chart review of clinical experience with incretin-based therapies

Results	DPP-4 inhibitors	GLP-1 analogs
Δkg	~0	~5
ΔA1C (%)	-0.4	-0.6
% of patients with final A1C < 7%	7	38
If baseline A1C < 9%		
ΔA1C (%)	-0.1	-0.7
If baseline A1C > 9%		
ΔA1C (%)	-0.7	-2
Duration < 7.3 y		
ΔA1C (%)	-0.63	-0.6
Duration > 10 y		
ΔA1C (%)	-0.2	-0.6

From the Triumvirate to the Ominous Octet

Presented by Ralph DeFronzo

Dr DeFronzo acknowledged that we have known the pathophysiologic roles of the *Triumvirate* of type 2 diabetes—the liver, pancreas, and muscle—for a long time. He described the well-known course of β-cell decline in type 2 diabetes. Dr. DeFronzo reviewed data that demonstrate that β-cell failure occurs earlier and is more severe than previously thought. These data show that patients with impaired glucose tolerance (IGT) have lost up to 50% of their β-cell volume and at the time of diagnosis of type 2 diabetes, up to 80% of β-cell function is gone. According to Dr. DeFronzo, the effects of compromised β cells in IGT translate to complications. Available findings show that approximately 10% of patients with IGT have retinopathy. In patients with IGT, increased A1C levels are associated with increased incidence of retinopathy.

He went on to describe how, along with the *Triumvirate*, 5 additional factors—adipose tissue, incretin hormones, alpha cells, kidneys, and the brain—make up the *Ominous Octet* of type 2 diabetes. Elevated lipolysis from the adipose tissue increases insulin resistance. Increased release of glucagon from the α cells and increased renal tubular reabsorption of glucose lead to elevated serum glucose levels. Diminished glucose sensitivity in the hypothalamus reduces appetite suppression. In addition, the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are important regulators of satiety, postprandial glucagon, postprandial insulin, and gastric acid emptying. Dr. DeFronzo, specifically, referred to incretin hormones as the fifth member of *Quintessential Quintet*. He described altered secretion of incretin hormones as a key part of glucose regulation and appetite control.

Dr DeFronzo emphasized that effective management of type 2 diabetes requires early treatment with multiple agents targeting the pathophysiologic abnormalities and raised concern that the 2 most commonly prescribed antidiabetic agents (ie, metformin and sulfonylurea) do not preserve β-cell function. In Dr DeFronzo's opinion, drug classes that have strong evidence of β-cell preservation are thiazolidinediones (TZDs) and GLP-1 analogs, with TZDs also attenuating free fatty acid release from adipose tissue.

> *"When it's new, of course it isn't so. And when it's proven, it isn't any longer new."*

He described that, for clinical practice, the initial ideal therapy for managing patients with type 2 diabetes should be a combination of lifestyle management with pharmacologic agents metformin, TZD, and GLP-1 analog used as well to address early on the pathophysiologic abnormalities that promote β-cell decline and function. He suggested that further clinical studies be developed that measure the effects of this type of initial approach for treating patients with type 2 diabetes, while acknowledging that his recommendation is a major paradigm shift from current clinical practice. Dr DeFronzo closed his speech with the following quotation: "When it's new, of course it isn't so. And when it's proven, it isn't any longer new."

Liraglutide, a Once-daily Human GLP-1 Analog, Added to a Sulfonylurea (SU) Offers Significantly Better Glycemic Control and Favorable Weight Change Compared With Rosiglitazone and SU Combination Therapy in Subjects With Type 2 Diabetes

Presented by Michel Marre

The LEAD 1 clinical trial (13-OR) was a 26-week, prospective, randomized, placebo (PBO)-controlled, double-dummy study that compared the effects of 3 different doses of liraglutide (LIRA) (0.6, 1.2, and 1.8 mg/d) added to SU with SU monotherapy, as well as with the active comparitor rosiglitazone (ROSI) (4.0 mg/d), also added to SU. ROSI 4.0 mg was selected because that dose is approved for use in all the countries where LEAD 1 was conducted. A total of 1041 patients with type 2 diabetes from 21 countries at 116 sites were enrolled in LEAD 1. The LEAD 1 patients were aged 18-80 years (mean 56 years), with BMI = 30 kg/m^2, and mean A1C = 8.4%. Patients were stratified by the number of oral antidiabetic drugs (OADs) they were taking at baseline. A1C and FPG were reduced in all LIRA treatment arms relative to the PBO arm, and higher doses of LIRA also yielded significant improvements in glycemic control relative to ROSI (Table 1). Patients previously treated with 1 OAD had consistently greater changes in A1C from baseline (ΔA1C) than patients previously treated with 2 OADs. A reduction in body weight relative to ROSI was observed in all doses of LIRA. Notably, patients previously treated with metformin who were switched to GLIM for LEAD 1 typically gained weight. Minor hypoglycemic events occurred about 3 times more often at the 2 highest LIRA doses than in the PBO group, and nausea was reported in 5.1%-10.5% in the LIRA treatment arms. Dose-dependent increases in the presence of antibodies were also noted in the LIRA arms, although the rate was relatively low.

Table 1. Selected study outcomes for LIRA + GLIM combination therapy relative to baseline in the LEAD 1 trial

Parameter	LIRA 0.6 + GLIM	LIRA 1.2 + GLIM	LIRA 1.8 + GLIM	ROSI 4.0 + GLIM	PBO + GLIM
A1C, %	7.9	7.5	7.5	8.0	8.7
ΔA1C, %	-0.6[a]	-1.08[a,b]	-1.13[a,b]	-0.44	+0.23
• *1 OAD subgroup*	*-0.8*	*-1.4*	*-1.5*	*-0.8*	*-0.4*
• *2 OAD subgroup*	*-0.4*	*-0.7*	*-0.8*	*-0.1*	*+0.7*
ΔFPG, mg/dL	-13[a]	-28[a]	-29[a]	-16	+18
ΔWeight, kg	0.7[b]	0.3[b]	-0.2[b]	2.1	-0.1
Minor hypo events/year	0.17	0.51	0.47	0.12	0.17
% reporting nausea	5.1	10.5	6.8	2.5	1.7
% with LIRA antibodies	10.9	12.7	9.3	NR	NR

[a]*P* < .0001 vs PBO + GLIM; [b]*P* < .0001 vs ROSI + GLIM; hypo, hypoglycemic; NR, not reported.

Safety and Tolerability of High Doses of the Long-Acting Human GLP-1 Analog Taspoglutide (R1583) in Diabetic Subjects Treated With Metformin: a Double-Blind, Placebo-Controlled Phase 2 Study

Presented by Robert Ratner

Taspoglutide (TASPO), a long-acting human GLP-1 analog, was tested in subjects with type 2 diabetes (N = 133, aged 57 years, BMI = 32.4 kg/m^2, A1C = 7.9%, duration of diabetes = 7 years; **10-OR**). Patients treated with metformin were randomized to also receive placebo (PBO) or TASPO 20 mg weekly for 4 weeks, followed by either a 4-week continuation of 20 mg (20/20) or a dose escalation to either 30 (20/30) or 40 mg (20/40) of once-weekly TASPO. All 3 TASPO groups had meaningful improvements in both A1C and fasting plasma glucose. Higher TASPO doses were associated with higher rates of withdrawal from the trial: PBO (3%; 1 subject), 20/20 mg (9%; 3 subjects), 20/30 mg (18%; 6 subjects), and 20/40 mg (18%; 6 subjects). Any nausea that occurred usually decreased with continued therapy. Seven withdrawals were due to GI AEs; 3 TASPO-treated patients discontinued the trial because of GI AEs. Therefore, the authors concluded that the maximum effective and safest dose of TASPO was 20 mg.

Effect of Exenatide With or Without Daclizumab on Endogenous Insulin Secretion in Long-Standing Type 1 Diabetes Mellitus

Presented by Kristina I. Rother

Dr Rother presented the results of a small study (N = 20) to determine the efficacy of exenatide (EXEN) on β-cell function in patients with type 1 diabetes mellitus (T1DM). In 2000, a prior study of patients with T1DM found that, contrary to expectation, approximately 38% of screened patients had measurable C-peptide levels (> 0.5 ng/mL), despite more than 20 years of T1DM. Patients rejected from the previous study were then invited back to determine if residual β-cell function could be improved with EXEN therapy.

To overcome the concern that EXEN might stimulate the original autoimmune response in these patients, daclizumab (an IL-2 receptor CD25 antagonist) was added to the treatment regimen. During a 2- to 4-month run-in period, 20 patients (age = 40.6 years, age at onset = 18.1 years, duration of T1DM = 21.5 years, weight = 76.7 kg, BMI = 25.9 kg/m^2, A1C = 7.3%) were managed to achieve stable blood glucose levels. Patients were then randomized to 1 of 4 treatment arms: 1) insulin plus EXEN (2.5 mcg titrated to 10 mcg 4 × daily) plus daclizumab (2 mg/kg IV each month); 2) insulin plus EXEN; 3) insulin plus daclizumab; 4) insulin only. After 6 months of therapy, patients receiving EXEN discontinued therapy, and patients not receiving EXEN in the first 6 months started EXEN therapy for an additional 6 months: all other treatments (daclizumab and insulin) remained unchanged. Following this second treatment period, all patients continued their respective therapies for an additional 3 months. C-peptide secretion was not increased with EXEN treatment when the entire cohort was analyzed. However, 1 patient did show enhanced C-peptide secretion. This particular patient had late-onset T1DM at 42 years of age with a short duration of only 6 years. Interestingly, this patient did not improve glycemic control during the run-in period but did with EXEN therapy. Dr Rother concluded that longer treatment duration may be needed to see an effect on β cells.

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