

## Converting Patients from Oral Therapy to Intensive Insulin Management

### 12 Glycemia-Optimization Treatment: Glycemic Control and Rate of Severe Hypoglycemia for 5 Different Dosing Algorithms of Insulin Glargine in Patients with Type 2 Diabetes Mellitus

Robert Tanenberg, MD, FACP, The Brody School of Medicine at East Carolina University; John Stewart, sanofi-aventis, Laval Canada; Ariel Zisman, University of Miami Miller School of Medicine

**Objective:** To compare the rate of severe hypoglycemia and proportion of patients achieving glycosylated hemoglobin (A1C) values of <7.0% for 5 insulin glargine (GLAR) dosing algorithms.

**Methods:** Included in this 24-week, randomized, open-label study were 4824 patients with type 2 diabetes mellitus (DM) with A1C level of  $\geq 7.0\%$  and not currently using insulin. Patients continued oral antidiabetic agents (thiazolidinediones were discontinued) and began GLAR 10 U/d titrated weekly to fasting blood glucose (FBG) goal (80, 90, 100, 110, or 120 mg/dL) per algorithm group. Demographic characteristics (median age, 56 years; 48% male; 70% white; mean duration of DM, 8.3 years), baseline characteristics (mean A1C level, 9.3%; body mass index, 34.7 kg/m<sup>2</sup>), and study completion rates (88.4%–90.5%) were similar in all groups.

**Results:** A1C values improved from baseline in all groups (Table). Overall incidence of hypoglycemia was low; severe hypoglycemia was associated with increasing dose titration. Aggressive FBG targets required higher GLAR doses, resulting in greater A1C improvement and higher proportions of patients achieving an A1C value of <7.0%. The number of patients achieving an A1C value of <7.0%, at the expense of severe hypoglycemia, was lower with less aggressive titration. The risk of severe hypoglycemia was not higher among patients who achieved target A1C values of <7.0%.

Table.

Goal FBG (mg/dL)*	GLAR Daily Dose, IU Mean (SD) <sup>†</sup>	A1C, % Mean (SD) <sup>†</sup>	Proportion of Patients with A1C <7.0%, %	Modeled <sup>‡</sup> Rate of Severe Hypoglycemia (SE) <sup>§</sup>	Severe Hypoglycemia Observed Rate <sup>§</sup>	
					A1C <7.0%	A1C $\geq 7.0\%$
120, n = 952	59.2 (36.6)	7.58 (1.1)	31.5	0.02 (0.007) (0.01, 0.04)	0.02	0.02
110, n = 974	62.2 (37.3)	7.52 (1.1)	32.2	0.03 (0.008) (0.02, 0.05)	0.02	0.08 <sup>  </sup>
100, n = 973	69.6 (41.0)	7.41 (1.1)	37.5	0.05 (0.009) (0.04, 0.07)	0.04	0.05
90, n = 950	74.9 (50.3)	7.36 (1.1)	41.1	0.08 (0.012) (0.06, 0.11)	0.08	0.12
80, n = 975	78.1 (42.9)	7.32 (1.2)	44.3	0.13 (0.023) (0.09, 0.18)	0.11	0.19

FBG = fasting blood glucose; GLAR = insulin glargine; A1C = glycosylated hemoglobin.

\*Intent-to-treat; <sup>†</sup>endpoint; <sup>‡</sup>means using unadjusted data (Poisson regression); <sup>§</sup>rate = events/patient-year; <sup>||</sup>P < 0.05, between patients with an A1C level of <7.0% and  $\geq 7.0\%$ .

**Conclusion:** Targeting a FBG value of 100 to 110 mg/dL yielded the best balance between A1C levels and hypoglycemia risk. Targeting this goal should allow more patients to achieve target (ie, A1C value of <7.0%) without experiencing severe hypoglycemia.

### 13 Biphasic Insulin Aspart 30 Added to Metformin Plus Pioglitazone Therapy Enables 50% of Patients with Type 2 Diabetes Mellitus to Reduce Their Glycosylated Hemoglobin Level from >8.0% to <6.5%

Philip Raskin, MD, Department of Internal Medicine, University of Texas; Louis Chaykin, Medical Research Unlimited; Rogelio Braceras, Novo Nordisk Inc.; Sherwyn L. Schwartz, Diabetes & Glandular Disease Research Associates, PA

**Background:** Patients with inadequately controlled type 2 diabetes mellitus (DM) are often treated with oral antidiabetic drugs (OADs) long after insulin therapy is required to achieve target levels of glycemic control.

**Objective:** To determine if adding biphasic insulin aspart 30 (BIAsp30) (30% soluble and 70% protaminated insulin aspart) to optimized metformin and pioglitazone (met + pio) treatment would enable more subjects with poorly controlled type 2 DM to reach glycosylated hemoglobin (A1C) treatment goals established by the American Diabetes Association (ADA) and the International Diabetes Federation/American College of Endocrinology (IDF/ACE).

**Methods:** A subanalysis of subjects with A1C values of >8.0% and >9.0% was performed from a recently conducted clinical trial. Insulin-naïve patients with A1C levels between 7.5% and 12.0% who were taking 2 OADs were enrolled in this treat-to-target, 34-week study of BIAsp30. During an 8-week run-in period, treatment was changed to met + pio and doses were adjusted to 2500 mg/day and 30 or 45 mg/day, respectively. Subjects were randomized to continue with optimized met + pio therapy or to have BIAsp30 added to met + pio. BIAsp30 was initiated at 6 U BID (prebreakfast and presupper) and titrated to target blood glucose level (80–110 mg/dL).

**Results:** In the BIAsp30 + met + pio group, 50% (21/42) of subjects with an A1C level of >8.0% reached their target A1C value of <6.5%, compared with 8% (3/39) of subjects who took met + pio. The A1C target of <7.0% was reached by 67% (28/42) of subjects taking BIAsp30 + met + pio and by 15% (6/39) of subjects taking met + pio. No subjects with a baseline A1C level of >9.0% achieved target A1C values af-

ter met + pio treatment, compared with 33% and 60% who achieved values of <6.5% and <7.0%, respectively, after BIAsp30 + met + pio treatment.

**Conclusion:** Adding BIAsp30 to optimized met + pio treatment enabled more subjects with poorly controlled type 2 DM to reach A1C treatment goals established by the ADA and IDF/ACE.

#### 14 Adding Biphasic Insulin Aspart 30 to Metformin Plus Pioglitazone Therapy Reduced Glycosylated Hemoglobin Levels to <7.0% in 75% of Patients with Type 2 Diabetes Mellitus

*Philip Raskin, MD, Department of Internal Medicine, University of Texas; Rogelio Braceras, Novo Nordisk Inc.; Sherwyn L. Schwartz, Diabetes & Glandular Disease Research Associates, PA; Louis Chaykin, Medical Research Unlimited; Pei-Ling Chu; Alan Wynne*

**Objective:** To compare a metformin plus pioglitazone (met + pio) regimen with treatment with biphasic insulin aspart 30 (BIAsp30) plus met + pio in insulin-naïve patients with type 2 diabetes mellitus (DM).

**Methods:** This 34-week, treat-to-target study of BIAsp30 (30% soluble and 70% protaminated insulin aspart) enrolled 181 patients with a glycosylated hemoglobin (A1C) level between 7.5% and 12.0% being treated with 2 oral antidiabetic drugs (OADs). During an 8-week run-in period, treatment was optimized to 2500 mg/day (met) and 30 or 45 mg/day (pio). At randomization, BIAsp30 was initiated at 6 U BID (prebreakfast and presupper) and titrated to plasma glucose level (80–110 mg/dL).

**Results:** At week 34, patients in the BIAsp30 + met + pio group (n = 93) reduced their A1C level by 1.5% compared with 0.2% for patients in the met + pio group (n = 88) ( $P < 0.0001$ ). More patients treated with BIAsp30 + met + pio reached A1C targets of <6.5% and <7.0% than patients taking only met + pio. Final A1C and fasting plasma glucose values were significantly lower for patients in the BIAsp30 group (**Table**). The rate of minor hypoglycemia (blood glucose level of <56 mg/dL) was greater in the BIAsp30 + met + pio group than in the met + pio group (8.3 vs 0.1 events/year,  $P < 0.001$ ). Both groups gained weight during treatment (BIAsp30 + met + pio,  $4.6 \pm 4.3$  kg; met + pio,  $0.8 \pm 3.2$  kg,  $P < 0.05$ ).

**Conclusion:** The majority of patients with type 2 DM whose A1C level is poorly controlled by 2 OADs can achieve the A1C target values recommended by the American Diabetes Association and the International Diabetes Federation/American College of Endocrinology by adding BIAsp30 to their OAD regimen.

**Table.**

	Baseline	BIAsp30 + Met + Pio	Met + Pio
A1C, % (mean $\pm$ SD)	EOS	$8.1 \pm 1.0$	$7.9 \pm 0.9$
	EOS	$6.5 \pm 1.0$	$7.8 \pm 1.2$
Percentage of Patients with A1C			
<7.0	EOS	76.3	24.1
$\leq 6.5$	EOS	59.1	11.5
$\leq 6.0$	EOS	33.3	2.3
$\leq 5.5$	EOS	14.0	0
FPG, mg/dL	EOS	$130 \pm 50$	$162 \pm 41$

A1C = glycosylated hemoglobin; FPG = fasting plasma glucose; EOS = end of study.