Name Of Finished Product: SYMLIN® (pramlintide acetate) injection

Name Of Active Ingredient(s): pramlintide acetate

Name Of Sponsor/Company: Amylin Pharmaceuticals, Inc.

Protocol No.: 137-151

Title of Study: A Randomized, Single-Blind, Placebo-Controlled, Crossover Study to Examine the Effect of Pramlintide Dose Timing on Postprandial Plasma Glucose Profiles in Subjects With Type 1 Diabetes Mellitus and Subjects With Type 2 Diabetes Mellitus Using Insulin

Investigators and Study Centers: Two centers in the United States

Studied Period (Years): January 2002 - March 2002

Phase of Development: 3B

Objective: Primary Objective: To determine the effect of the timing of pramlintide injection relative to meal ingestion on postprandial plasma glucose profiles in subjects with type 1 diabetes and subjects with type 2 diabetes using insulin. Secondary Objective: To assess safety and tolerability of pramlintide injection, including adverse events, as a function of the timing of the injection relative to meal ingestion in subjects with type 1 diabetes and subjects with type 2 diabetes using insulin.

Methodology: This was a randomized, two-center, domiciled, single-blind, placebo-controlled, five-way crossover study designed to examine the effect of the timing of pramlintide injection relative to meal ingestion on postprandial plasma glucose profiles in subjects with type 1 diabetes and subjects with type 2 diabetes using insulin. Three study groups were defined by diabetes type and type of mealtime insulin used in their treatment regimen. On 5 study days, subjects received a single dose of one of five treatments (A, B, C, D, or E) in random order:

Treatment	Study Medication	Timing Relative to a Standardized Breakfast
A	Placebo	- 15 min
B	Pramlintide	- 15 min
C	Pramlintide	0 min
D	Pramlintide	+ 15 min
E	Pramlintide	+ 30 min

Each treatment (pramlintide or placebo) was administered subcutaneously (SC) within specified times relative to a standardized breakfast after an overnight fast. Subjects were randomly assigned to one of four treatment sequences according to a randomization schedule generated for each study group. Subjects with type 1 diabetes received pramlintide 60 mg or placebo (equivalent volume). Subjects with type 2 diabetes using insulin received pramlintide 120 mg or placebo (equivalent volume).

Subjects maintained their usual insulin regimen during the study; if necessary, insulin dose adjustments were made in consultation with study personnel to facilitate achievement of fasting fingerstick glucose values in the range of ≥80 mg/dL and ≤250 mg/dL while avoiding hypoglycemia. The timing of the short-acting insulin dose relative to the standardized breakfast was based on recommendations in the respective package inserts for the insulin (0 min for insulin lispro and -30 min for regular insulin).

Number of Subjects: The study population consisted of three study groups, defined by diabetes type and type of mealtime insulin used in their treatment regimen.

Study Group 1: Subjects with type 1 diabetes using insulin lispro,
Study Group 2: Subjects with type 1 diabetes using regular insulin,
Study Group 3: Subjects with type 2 diabetes using insulin lispro.

Fifty-nine subjects (21 type 1 subjects using insulin lispro; 19 type 1 subjects using regular insulin; and 19 type 2 subjects using insulin lispro) were enrolled in this study.

Key Demographics:

Type 1 Subjects Using Insulin Lispro: Of the 21 randomized subjects, 8 (38.1%) were female and 13 (61.9%) were male. The majority of subjects were Caucasian (61.9%), and the mean age of the subject population was 40.8 years. The overall mean duration of diabetes was 20.3 years with a range of 1.6 years to 41.0 years; the overall mean HbA_{1c} was 8.3% with a range of 6.4% to 11.0%; and the overall mean BMI was 25.7 kg/m^2 with a range of 19.6 kg/m^2 to 36.0 kg/m^2. Baseline characteristics appeared to be similar across treatment sequences.

Type 1 Subjects Using Regular Insulin: Of the 19 randomized subjects, 5 (26.3%) were female and 14 (73.7%) were male. The majority of subjects were Caucasian (57.9%), and the mean age of the subject population was 37.3 years. The overall mean duration of diabetes was 21.7 years with a range of 6.1 years to 52.1 years; the overall mean HbA_{1c} was 9.3% with a range from 7.3% to 14.0%; and the overall mean BMI was 26.8 kg/m^2 with a range of 20.1 kg/m^2 to 34.8 kg/m^2. With the exception of the mean duration of diabetes, baseline characteristics appeared similar across treatment sequences.

Type 2 Subjects Using Insulin Lispro: Of the 19 randomized subjects, 10 (52.6%) were female and 9 (47.4%) were male. The majority of subjects were Hispanic (52.6%), and the mean age of the subject population was 49.6 years. The overall mean duration of diabetes was 14.9 years with a range from 2.8 years to 31.7 years; the overall mean HbA_{1c} was 9.3% with a range from 6.7% to 12.6%; and the overall mean BMI was 35.2 kg/m^2 with a range from 23.3 kg/m^2 to 45.3 kg/m^2. With the exception of duration of diabetes, HbA_{1c}, and BMI, baseline characteristics appeared to be similar across treatment sequences.

Subject Disposition: All 21 (100.0%) type 1 subjects using insulin lispro, 19 (100.0%) type 1 subjects using regular insulin, and 19 (100.0%) type 2 subjects using insulin lispro completed all study procedures/visits.

Diagnosis and Main Criteria for Inclusion: Type 1 or type 2 males or females (otherwise healthy); requiring insulin treatment for at least 1 year at screening; aged between 18 and 65 years, inclusive; screening HbA_{1c} of 7.0% to 11.0%, inclusive; free of symptoms of severe hypoglycemia or hyperglycemia for 2 months prior to screening; who met all other protocol defined inclusion and exclusion criteria.

Test Form, Dose and Mode of Administration: Subjects with type 1 diabetes: pramlintide 60 µg (0.1 mL), subjects with type 2 diabetes: pramlintide 120 µg(0.2 mL), syringe-vial administration of SC injection.

Duration of Treatment: Five single-dose periods relative to the timing of a standardized breakfast (0 min) with at least a 24-hour interval between doses.

Reference Therapy, Dose and Mode of Administration: placebo; 0.1 mL per subject with type 1 diabetes, 0.2 mL per subject with type 2 diabetes; syringe-vial administration of SC injection.

Criteria for Evaluation:

Pharmacodynamics: The primary pharmacodynamic measure was area under the plasma glucose incremental concentration-time curve from time zero (meal ingestion) to last time point ($AUC_{(0\text{-}4\ hr)}$). While this assessment was useful, the interpretation was confounded by the variability of pramlintide injection times across treatments, coupled with the variability in baseline (fasting) plasma glucose concentrations. Thus, a more appropriate approach for understanding the clinical implications of the data was to descriptively assess the glucose concentration-time profiles. In particular, this approach clearly reveals the impact of elevations in plasma glucose concentrations occurring at different times relative to the meal, as a result of different pramlintide injection times. While this approach was not outlined in the statistical analysis plan, the conclusions drawn from this descriptive assessment of the data are supported by the formal analysis of the primary endpoint. For these reasons, the pharmacodynamic results section has focused primarily upon the descriptive assessment of the mean incremental plasma glucose concentration-time curves.

Other pharmacodynamic measures included time-weighted mean concentration ($C_{ave(0\text{-}4\ hr)}$), peak concentration (C_{max}), minimum concentration (C_{min}), time to peak concentration (T_{max}), time to minimum concentration (T_{min}) of incremental plasma glucose concentrations; and $AUC_{(0\text{-}4\ hr)}$, $C_{ave(0\text{-}4\ hr)}$, C_{max}, and C_{min} of absolute plasma glucose concentrations. Additionally, the variables $AUC_{(0\text{-}2\ hr)}$, $AUC_{(2\text{-}4\ hr)}$, $C_{ave(0\text{-}2\ hr)}$, and $C_{ave(2\text{-}4\ hr)}$ were calculated for incremental plasma glucose concentrations.

Pharmacokinetics: Pharmacokinetic measures included AUC from time of study medication injection to 4 hours relative to the standardized breakfast ($AUC_{(dosing)}$), time-weighted mean concentration over the sampling period ($C_{ave\ (dosing)}$), C_{max}, C_{min}, T_{max}, T_{min}, and $t_{½}$ (terminal elimination half-life).

Safety: Safety and tolerability were assessed throughout the study period by monitoring adverse events, clinical laboratory measures, vital signs, and physical examinations.

Statistical Methods:

Pharmacodynamics: Within each study group, pharmacodynamic parameters were calculated and summarized for the evaluable population. Absolute and incremental plasma glucose concentrations at each sampling time point were summarized descriptively (mean, standard deviation, median, minimum, and maximum) by treatment. Absolute and incremental mean plasma glucose concentration profiles were plotted by treatment. Absolute and incremental plasma glucose pharmacodynamic parameters were summarized descriptively (mean, standard deviation, median, minimum, and maximum) by treatment and analyzed using mixed effect models. The mixed effect models included treatment, treatment sequence, and period as fixed effects, and subject-within-sequence as a random effect. The 95% confidence intervals were constructed for the differences of the least square (LS) means for the incremental plasma glucose pharmacodynamic parameters between placebo and each of the four pramlintide treatments and between pramlintide treatment B (-15 min) and each of the other three pramlintide treatments (C [0 min], D [+15 min], and E [+30 min]).

Pharmacokinetics: Within each study group, pharmacokinetic parameters were calculated and summarized for the evaluable population. Plasma pramlintide concentrations at each sampling time point were summarized descriptively (mean, standard deviation, median, minimum, and maximum) by treatment. Individual and mean pramlintide concentration profiles were plotted by treatment. Plasma pramlintide pharmacokinetic parameters were summarized descriptively (mean, standard deviation, median, minimum, and maximum) by treatment.

Safety: Within each study group, safety parameters were summarized for the intent-to-treat (ITT) population. Adverse events, clinical laboratory measures, and vital signs were presented using descriptive statistics.

SUMMARY - CONCLUSIONS:

PHARMACODYNAMIC RESULTS:

Incremental Plasma Glucose $AUC_{(0\text{-}4\ hr)}$. Within each study group (type 1 subjects using insulin lispro, type 1 subjects using regular insulin, and type 2 subjects using insulin lispro), the mean incremental plasma glucose $AUC_{(0\text{-}4\ hr)}$ for each of the four pramlintide injection times was lower than the value observed following placebo, with the 0 min injection showing the largest reduction in each of the three study groups.

Mean (SD) Incremental Plasma Glucose $AUC_{(0\text{-}4\ hr)}$ (mg*hr/dL) Following a Standardized Breakfast by Study Group and by Treatment

Evaluable Type 1 Subjects Using Insulin Lispro (N=20)				
Placebo	**Pramlintide 60 μg**			
-15 min	-15 min	0 min	+15 min	+30 min
179.1 (198.9)	114.4 (186.6)	45.1 (169.2)	81.7 (218.4)	109.6 (164.4)
Evaluable Type 1 Subjects Using Regular Insulin (N=18)				
Placebo	**Pramlintide 60 μg**			
-15 min	-15 min	0 min	+15 min	+30 min
198.4 (220.4)	69.0 (189.4)	-10.3 (188.9)	54.0 (184.4)	0.9 (227.2)
Evaluable Type 2 Subjects Using Insulin Lispro (N=19)				
Placebo	**Pramlintide 120 μg**			
-15 min	-15 min	0 min	+15 min	+30 min
187.9 (170.0)	109.9 (148.7)	36.2 (118.0)	51.3 (141.4)	76.8 (171.1)

Incremental Plasma Glucose Concentrations. Within each study group, mean incremental plasma glucose concentrations for all four pramlintide injection times, compared to placebo, were generally lower through at least the initial 120 min following ingestion of the standardized breakfast.

Mean (SD) Incremental Plasma Glucose Concentrations (mg/dL) Following a Standardized Breakfast by Study Group and by Treatment

Time From Breakfast (min)	Placebo	Evaluable Type 1 Subjects Using Insulin Lispro (N=20) Pramlintide 60 μg			
	-15 min	-15 min	0 min	+15 min	+30 min
30	52.6 (34.6)	-8.2 (17.4)	-8.7 (28.8)	41.1 (31.7)	56.3 (32.6)
45	79.9 (38.9)	**-18.3 (29.6)***	-23.0 (35.3)	22.5 (35.0)	70.3 (40.4)
60	87.2 (46.6)	-16.6 (40.7)	**-31.9 (43.0)***	0.9 (45.6)	42.9 (44.3)
90	78.0 (59.3)	0.3 (60.8)	-21.9 (57.9)	**-6.3 (65.1)***	4.0 (48.3)
120	71.9 (66.2)	30.8 (63.7)	7.5 (61.5)	1.4 (76.5)	**0.5 (51.1)***
150	46.8 (67.4)	55.2 (68.0)	28.3 (56.9)	26.9 (80.4)	14.7 (55.1)
180	27.0 (68.2)	63.8 (79.2)	44.2 (66.6)	40.4 (80.6)	34.8 (59.2)
240	-8.4 (67.1)	77.7 (82.3)	47.2 (80.8)	46.7 (95.8)	41.9 (84.3)
	Placebo	**Evaluable Type 1 Subjects Using Regular Insulin (N=18) Pramlintide 60 μg**			
	-15 min	-15 min	0 min	+15 min	+30 min
30	37.1 (31.6)	-3.5 (30.1)	-7.4 (15.9)	31.9 (27.1)	26.1 (32.8)
45	63.1 (36.9)	**-8.4 (37.6)***	**-18.5 (24.6)***	25.0 (33.0)	39.8 (37.4)
60	77.8 (48.3)	-5.9 (44.8)	-14.3 (26.0)	12.2 (38.1)	29.3 (49.9)
90	86.9 (60.1)	5.5 (59.1)	-15.1 (48.9)	**0.7 (51.6)***	-0.9 (65.2)
120	82.9 (69.9)	27.6 (60.6)	-1.7 (63.4)	1.7 (62.0)	-14.4 (65.7)
150	64.0 (71.7)	30.7 (60.9)	4.7 (69.1)	10.5 (63.6)	**-15.1 (71.4)***
180	36.8 (76.1)	39.8 (67.8)	11.2 (71.0)	21.2 (65.0)	0.7 (73.8)

	Placebo	Evaluable Type 2 Subjects Using Insulin Lispro (N=19) Pramlintide 120 μg			
	-15 min	-15 min	0 min	+15 min	+30 min
30	37.9 (20.6)	**1.7 (16.2)***	-1.6 (15.6)	30.7 (21.9)	39.4 (32.7)
45	57.4 (31.6)	3.3 (25.5)	-7.6 (23.1)	17.0 (27.6)	59.2 (39.1)
60	72.9 (34.9)	7.6 (31.1)	**-12.3 (33.3)***	0.7 (33.7)	41.4 (41.1)
90	77.4 (42.8)	23.4 (38.3)	-3.5 (42.5)	**-7.2 (40.6)***	10.4 (42.5)
120	67.7 (54.3)	35.7 (43.0)	12.8 (46.5)	3.0 (54.8)	**5.7 (54.8)***
150	59.1 (61.1)	50.5 (60.9)	21.3 (38.3)	22.5 (47.0)	13.6 (58.5)
180	38.5 (66.0)	49.7 (72.1)	29.8 (43.3)	24.5 (48.2)	17.9 (60.0)
240	6.1 (63.9)	27.7 (58.9)	8.3 (60.8)	24.1 (52.8)	13.1 (61.5)

*Mean incremental plasma glucose C_{min}.

Within each study group, the magnitude of reduction in postprandial glucose excursions was most pronounced for the 0 and -15 min pramlintide injection time points, in which the early postprandial surge in plasma glucose concentrations was effectively prevented. While the profiles observed for the -15 and 0 min dose timings were generally similar, pramlintide administration at 0 min appeared slightly more optimal in terms of the extent and duration in reduction of postprandial glucose excursions during the first 2 hours of the postprandial period. When pramlintide was administered at +15 and +30 minutes mean incremental plasma glucose concentrations increased immediately following ingestion of breakfast, paralleling the early glucose rise observed with the placebo injection. Mean incremental plasma glucose concentrations in these profiles subsequently began to decrease within 30 min of pramlintide injection. For all four pramlintide treatments, plasma glucose concentrations remained suppressed through 45 to 90 min following pramlintide injection, compared to placebo.

Within each study group, glucose concentrations started to increase but remained lower or similar to placebo beyond 150 min following pramlintide injection. The largest increase in plasma glucose concentrations was observed in type 1 subjects using insulin lispro, with the most notable increase associated with the earlier injection times (-15 and 0 min). This is probably attributable to the pharmacokinetic properties of pramlintide combined with the short duration of action of insulin lispro. The latter aspect is supported by the fact that, compared to type 1 subjects using insulin lispro, mean incremental postprandial glucose concentrations were lower at the end of the 4-hour postprandial period in type 1 subjects using regular insulin, which has a longer duration of action.

PHARMACOKINETIC RESULTS:

Within each study group, relative to the timing of pramlintide injection, similar mean plasma pramlintide concentration-time profiles were observed following a single SC injection of pramlintide at various times in relation to a standardized breakfast. As shown in the following table, relative to the timing of pramlintide injection, similar plasma pramlintide absorption (C_{max} and T_{max}), bioavailability ($AUC_{(dosing)}$), and elimination ($t_{1/2}$) profiles were observed across treatments.

Mean (SD) Plasma Pramlintide Pharmacokinetic Parameters by Study Group and Treatment

Parameter	Evaluable Type 1 Subjects Using Insulin Lispro (N=20) Pramlintide 60 μg							
	-15 min		0 min		+15 min		+30 min	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
$AUC_{(dosing)}$* (pmol•hr/L)	106.4	(47.6)	103.3	(62.4)	113.2	(56.4)	112.4	(74.1)
C_{ave} (pmol/L)	25.0	(11.2)	25.8	(15.7)	30.2	(15.2)	32.1	(21.2)
C_{max} (pmol/L)	84.7	(33.7)	89.5	(40.5)	98.2	(41.9)	98.5	(49.6)
T_{max} (hr)	0.3	(0.2)	0.3	(0.1)	0.3	(0.2)	0.3	(0.1)
$t_{1/2}$ (hr)	0.8	(0.2)	0.7	(0.2)	0.8	(0.3)	0.8	(0.2)
	Evaluable Type 1 Subjects Using Regular Insulin (N=18) Pramlintide 60 μg							
	-15 min		0 min		+15 min		+30 min	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
$AUC_{(dosing)}$* (pmol•hr/L)	125.3	(55.8)	117.6	(83.0)	109.3	(59.0)	103.9	(47.3)
C_{ave} (pmol/L)	29.5	(13.2)	29.4	(20.7)	29.2	(15.7)	29.7	(13.6)
C_{max} (pmol/L)	86.8	(27.9)	82.5	(41.1)	82.0	(33.4)	78.2	(30.3)
T_{max} (hr)	0.4	(0.3)	0.4	(0.2)	0.3	(0.3)	0.3	(0.2)
$t_{1/2}$ (hr)	0.8	(0.4)	0.9	(0.5)	0.7	(0.3)	0.8	(0.5)
	Evaluable Type 2 Subjects Using Insulin Lispro (N=19) Pramlintide 120 μg							
	-15 min		0 min		+15 min		+30 min	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
$AUC_{(dosing)}$* (pmol•hr/L)	200.7	(123.7)	188.5	(135.1)	180.2	(144.6)	182.8	(133.1)
C_{ave} (pmol/L)	47.2	(29.3)	47.1	(33.8)	48.0	(38.4)	52.5	(37.9)
C_{max} (pmol/L)	147.3	(89.5)	150.8	(105.7)	135.3	(88.6)	150.4	(110.0)
T_{max} (hr)	0.4	(0.2)	0.4	(0.1)	0.4	(0.2)	0.4	(0.1)
$t_{1/2}$ (hr)	1.1	(0.4)	1.0	(0.3)	0.9	(0.3)	0.9	(0.3)

*$AUC_{(dosing)}$ is the AUC from time of pramlintide injection through 4 hours post-breakfast.

A consistent pharmacodynamic-pharmacokinetic relationship was established within each study group. Plasma pramlintide concentration profiles for each pramlintide treatment were consistent with respective 4-hour postprandial plasma glucose concentration profiles.

SAFETY RESULTS:

Adverse Events:

Within each study group, there were no reports of severe (assisted) hypoglycemia. During the 4-hour postprandial period, the majority of hypoglycemic events were of mild intensity in the type 1 and type 2 lispro groups, while *all* hypoglycemic events in the type 1 regular group were of mild intensity. The majority of hypoglycemic events experienced during the 4-hour postprandial period occurred on study days in which fasting glucose concentration values were < 126 mg/dL (the criteria established by the American Diabetes Association to separate normal from elevated fasting plasma glucose concentrations). These values were generally lower compared to the fasting values on the days placebo was administered; yet, the pre-meal insulin dose remained unchanged or increased, compared to placebo treatment.

Treatment-emergent adverse events for each study group are summarized below:

Type 1 subjects using insulin lispro: Eighteen (85.7%) type 1 subjects using insulin lispro reported a total of 60 treatment-emergent adverse events. The most frequently (≥10%) occurring treatment-emergent adverse events occurring during pramlintide treatments were mild or moderate hypoglycemia (20.0% to 33.3%) and mild nausea (4.8% to 14.3%). The incidence of hypoglycemia during placebo treatment was 28.6%; there were no reports of nausea during placebo treatment.

Type 1 subjects using regular insulin: Eighteen (94.7%) type 1 subjects using regular insulin reported a total of 71 treatment-emergent adverse events. The most frequent (≥10%) treatment-emergent adverse events occurring during pramlintide treatments were hypoglycemia (21.1% to 27.8%), nausea (10.5% to 26.3%), headache (0.0% to 15.8%), dizziness (5.3% to 11.1%), and asthenia (0.0% to 11.1%). The incidence of hypoglycemia and nausea during placebo treatment was 15.8% and 10.5%, respectively. All hypoglycemic events were of mild (all mild during the 4-hour postprandial period) or moderate intensity, and all nausea events were of mild intensity.

Type 2 subjects using insulin lispro: Fifteen (78.9%) type 2 subjects using insulin lispro reported a total of 44 treatment-emergent adverse events. The most frequent (≥10%) treatment-emergent adverse events occurring during pramlintide treatments were hypoglycemia (0.0% to 26.3%), nausea (10.5% to 21.1%), headache (5.3% to 10.5%), and injection site reaction (0.0% to 10.5%). The incidence of hypoglycemia and nausea during placebo treatment was 10.5% and 5.3%, respectively. All hypoglycemic events were of mild or moderate intensity, and all nausea events were of mild intensity.

Vital Signs and Physical Examinations: Within each study group, no clinically meaningful or unexpected changes were reported in vital signs or physical examinations.

CONCLUSIONS:

Postprandial Glucose Lowering Effect. Within each study group, the mean incremental plasma glucose $AUC_{(0\text{-}4\ hr)}$ for each of the four pramlintide injection times was lower than the value observed for placebo.

Optimal Timing of Pramlintide Administration Relative to Meals. In subjects with type 1 diabetes and insulin-using subjects with type 2 diabetes, SC administration of pramlintide immediately prior to meal ingestion (0 min) was optimal in terms of reduction in postprandial glucose excursions. Most notably, pramlintide administration at 0 min, in conjunction with insulin lispro in type 1 subjects, resulted in mean reductions of ~20 to 30 mg/dL at 45 to 90 min following the meal. Dosing at 15 min prior to meal ingestion provided a similar pattern of reductions in postprandial glucose excursions.

Reduction of Short-acting Preprandial Insulin Upon Initiation of Pramlintide Treatment. As the effects of pramlintide to reduce postprandial glucose concentrations are additive to the effects of insulin, it appears prudent that appropriate reductions (~30% to 50%) in preprandial doses of short-acting insulin be implemented upon initiation of pramlintide therapy in order to reduce the risk for hypoglycemia. Following the safe introduction of pramlintide, insulin regimens should be adjusted as indicated in order to optimize glucose control.

Basal Insulin Adjustment in Type 1 Subjects Using Insulin Lispro Upon Initiation of Pramlintide Treatment. In type 1 subjects using insulin lispro, the data indicated that appropriate increases in basal insulin coverage will likely be indicated in order to achieve optimal control following the initiation of pramlintide treatment. This increase in basal coverage may assist with improving glucose control during the interval between 150 min following pramlintide injection and the next meal by preventing the rebound of plasma glucose concentrations as observed in a number of type 1 subjects using insulin lispro in this study.

Safety. In subjects with type 1 diabetes and insulin-using subjects with type 2 diabetes, SC administration of pramlintide was well-tolerated across all pramlintide injection times in relation to a standardized breakfast. There were no reports of severe (assisted) hypoglycemia. The events of hypoglycemia occurring during the 4-hour postprandial period were unlikely a direct consequence of the action of pramlintide alone, but rather the result of the dynamic interaction between pramlintide, insulin, and the pre-meal glucose concentration. In light of the pharmacokinetic profile of pramlintide, the events occurring *after* the 4-hour postprandial period were most likely insulin-induced.

This study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.