

**MEDICAL OFFICER REVIEW**  
**Division of Metabolic and Endocrine Drug Products (HFD-510)**

21-332

APPLICATION #: \_\_\_\_\_ APPLICATION TYPE: NDA Review Advisory Committee Briefing Document .....

SPONSOR: Amylin..... Pharmaceuticals PROPRIETARY NAME: Symlin

CATEGORY OF DRUG: Antidiabetic USAN / Established Name: Pramlintide

ROUTE: Subcutaneous injection

MEDICAL REVIEWER: Robert I Misbin MD REVIEW DATE: 6/21/01

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

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**Overview of Application/Review:**

Pramlintide reduces postprandial hyperglycemia during the first few weeks of treatment, but the long-term reduction in HbA1c is trivial and is completely overshadowed by the risk of severe hypoglycemia. Particularly alarming is the number of patients that had life-altering events on pramlintide related to hypoglycemia. The trials deviated so much from good medical practice that they provide little insight into which patients would benefit from pramlintide or how pramlintide should be used.

**Recommended Regulatory Action: Not Approvable**

Signed: Medical Reviewer: Robert I Misbin MD \_\_\_\_\_ Date: June 21, 2001

Medical Team Leader: Saul Malozowski MD \_\_\_\_\_ Date: June 18, 2001

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## **Executive Summary:**

### **I. Recommendations:**

#### **A. Approvability:**

Pramlintide reduces postprandial hyperglycemia levels during the first few weeks of treatment, but the long-term reduction in HbA1c is trivial and is completely overshadowed by the risk of severe hypoglycemia. Particularly alarming is the number of patients on pramlintide that had life-altering events due to hypoglycemia. The design and/or conduct of the studies deviated so much from good medical practice that it is not possible to determine what role, if any, pramlintide may have in the treatment of patients with diabetes.

#### **B. Additional Studies:**

The Sponsor should perform a trial to determine if pramlintide improves glycemic control under conditions in which patients receive treatment with insulin and life-style management in accordance with the recommendations of the American Diabetes Association. One possibility would be a 12-month placebo-controlled trial in patients with hemoglobin A1c levels of 7.5% or less. Reduction in HbA1c without an increase in hypoglycemia should be criteria for a successful trial.

Review of the results from clinical pharmacology studies raises concern about the possibility that a five-day exposure to pramlintide could cause hypoglycemia unawareness. But the studies were too small to be definitive. Prior to undertaking the 12-month trial described above, the Sponsor should investigate the possibility that pramlintide causes hypoglycemia unawareness in study with adequate power.

### **II. Summary of Clinical Findings**

#### **A. Brief overview of Clinical Program**

There were six phase three trials, three in patients with type 1 diabetes, and three in patients with type 2. All the trials were comparisons of pramlintide vs. placebo as adjuncts to insulin in patients who had been on stable doses of insulin for at least two months, and had inadequate glycemic control. In the two earliest trials, patients/physicians were allowed to adjust their insulin regimen “consistent with good medical practice.” In the other four trials, patients were asked to maintain a constant regimen of insulin, diet and exercise.

Shortcomings in the clinical development program were brought to the Sponsor's attention at a meeting that took place at FDA on October 28, 1997. The minutes of that meeting state:

*“Since keeping a constant insulin dose is not how diabetes is treated, the Agency stated that it will have difficulty in evaluating data from study designs that are inconsistent with clinical practice.”*

*“The Agency recommended [an insulin titration study with] endpoints that should be either reduction in HbA1c or [reduction in episodes of] hypoglycemia.”*

*“The Agency stated that the current study data is not considered pivotal data for an NDA.”*

### **B. Efficacy:**

Pramlintide treatment resulted in a small (mean reduction about 0.30 % units) but statistically significant reduction in HbA1c in patients whose mean baseline was about 9%, and whose insulin regimen remained constant, or nearly so, over the course of the study. This is a very small response, particularly when one considers that the patients were required to take multiple injections (2-4) of pramlintide. Since routine adjustment in patients' insulin regimen would be expected to improve glycemic control more than injections of pramlintide, it is not clear from these studies which patients, if any, would benefit from pramlintide or how pramlintide should be used.

Weight loss was a consistent feature of pramlintide treatment. Whereas patients on insulin alone tended to gain weight, patients on pramlintide generally lost weight. The mean weight loss in pramlintide-treated patients was about 1-2 kg in 26 weeks.

### **C. Safety:**

Pramlintide treatment caused nausea. Severe hypoglycemia was much more of a problem in patients on pramlintide than in patients on insulin alone and appeared to be associated with major trauma, motor vehicle accidents and death. Driving-related events associated with hypoglycemia were reported four times more frequently in pramlintide-treated patients than in patients on insulin alone. The frequency and severity of hypoglycemia in pramlintide-treated patients seems out of proportion to the small reduction in HbA1c.

Random inspections of 44 patient records by the Division of Scientific Investigation (DSI) disclosed one hypoglycemic event that did not appear in the database and one motor vehicle accident that did not appear in the database. Based on the results of these inspections, I fear that the safety database submitted in the NDA is not reliable.

#### **D. Dosing:**

The clinical trials do not provide enough information to determine the dose-response relationships of pramlintide. In type 1 diabetes, the lowest effective dose appears to be 30 ug injected four times per day before meals. In type 2 diabetes, the lowest effective dose was 120 ug injected twice per day before breakfast and dinner.

Over and above the question of pramlintide dosing is the issue of who should be treated with pramlintide and how those patients should adjust their insulin. The trials were done in patients whose diabetes treatment regimen had been inadequate and that inadequacy was perpetuated by the design and/or conduct of the trials. The trials provide little, or no, insight into how pramlintide should be used in patients who are being treated as recommended by the American Diabetes Association (ADA).

#### **E. Special Populations:**

Not reviewed

## *Clinical Review*

### **I. Introduction and Background**

Amylin is a 37 amino acid peptide that is secreted by the pancreatic beta cell in response to meals. The plasma concentration of amylin is low in most, if not all, patients with type 1 diabetes, and may also be low in patients with type 2 diabetes. Short term studies showed that injections of pramlintide given before a meal greatly reduced glucagon secretion and post-prandial hyperglycemia. These findings led to the speculation that amylin deficiency was a characteristic of the diabetic state and that amylin “replacement” would lead to improved glycemic control. The clinical development program included three phase 3 trials in patients with type 1 diabetes and three trials in patients with type 2 diabetes who were also being treated with insulin. All six trials had double blind placebo control designs in which pramlintide was given before meals by injection. Insulin injections were given separately because pramlintide and insulin cannot be mixed in the same syringe.

### **II. Consultant Reviews**

For clinically relevant findings from biostatistics, chemistry, toxicology, microbiology and biopharmaceutics reviews, refer to the biostatistics, chemistry, toxicology, microbiology and biopharmaceutics reviews.

### **III. Biopharmaceutics**

The bioavailability of pramlintide is substantially less in patients with type 2 diabetes than in patients with type 1 diabetes. Pramlintide cannot be mixed with insulin in the same syringe. Mixing of pramlintide with insulin in the same syringe changes the absorption characteristics of both. Refer to biopharmaceutics review for details and for other issues relating to human pharmacokinetics and pharmacodynamics

### **IV. Description of clinical data and sources**

There were three phase three clinical trials in type 1 diabetes and three in type 2 diabetes. All were double-blind placebo controlled trials in patients who were taking insulin. The clinical pharmacology studies were not reviewed in detail.

Type 1 diabetes: Study 117 (26 weeks)  
Study 121 (52 weeks)  
Study 112 (52 weeks)

Type 2 diabetes: Study 122 (52 weeks)  
Study 123 (26 weeks)  
Study 111 (52 weeks)

This drug has not been approved elsewhere, therefore there are no post-marketing data available.

## **V. Clinical Review Methods**

### **A. Conduct of the Review**

The review was conducted from paper copies of the study reports.

### **B. Evaluation of Data Quality and Integrity**

The Division of Scientific Investigation (DSI) inspected four sites, all from trials of type 1 diabetes. At one of these sites, 16 records were reviewed of the 35 patients randomized. An episode of hypoglycemia (glucose of 18 mg/dl), in a patient on placebo, that required paramedic intervention was not properly reported. At a second site, seven study records were examined. They were incomplete for two patients. At a third site, 21 records were examined. There was one case of a patient on pramlintide who had been involved in a motor vehicle accident associated with hypoglycemia. This MVA had not been entered into the database submitted to the FDA. Results from the fourth site are not available yet. The results of these inspections raise doubts about the reliability of the safety database. Of a total of 44 patients records examined, there was one episode of severe hypoglycemia and one motor vehicle accident that had not been entered into the database.

### **C. Ethical standards**

The model consent form for study 117 adequately described the nature of the experimental procedures. The risks of hypoglycemia were described, as are the gastrointestinal side effects of pramlintide. The nature of the placebo group was adequately described. The form clearly stated that patients would not necessarily benefit personally from having participated in the study. In the section about alternative treatments, the following statement occurs “If you do not want to participate in this study, alternative medications are currently available on the market for the treatment of your diabetes”. I do not understand what this statement means. No treatments are currently available for type 1 diabetes other than insulin and all these patients were already taking insulin. Omitted from the form is that patients were not allowed to titrate their insulin doses in order to reduce HbA1c levels. It is standard practice for patients with type 1 diabetes to adjust their insulin dose. Maintaining elevated HbA1c levels long-term would be expected to increase the risk of microvascular complications. This issue was not addressed.

### **D. Financial disclosure**

Documents have not been reviewed yet.

## **VI. Review of Efficacy**

### **A. Brief statement of conclusions:**

Pramlintide treatment resulted in a small mean reduction of about 0.30 % units in HbA1c in patients whose baseline was about 9%, and whose insulin regimen remained constant, or nearly so, over the course of the studies. Although statistically significant, this is a very small response, particularly when one considers that patients were required to take multiple (2-4) injections of pramlintide. We have little, if any, data on the efficacy of pramlintide in patients whose HbA1c is 8% or less.

Weight loss was a consistent feature of pramlintide treatment. Whereas patients on insulin alone tended to gain weight, patients on pramlintide generally lost weight. The mean weight loss in pramlintide-treated patients was about 1-2 kg in 26 weeks.

Pramlintide treatment caused nausea and vomiting. Severe hypoglycemia was much more of a problem in patients on pramlintide than in patients on insulin alone and appeared to be associated with major trauma, motor vehicle accidents and death. The severity of hypoglycemia in pramlintide-treated patients seems out of proportion to the small reduction in HbA1c. Since routine adjustment in patients' insulin regimen would be expected to improve glycemic control more than injections of pramlintide, it is not clear from these studies which patients, if any, would benefit from pramlintide or how pramlintide should be used.

### **B. Phase 3 Trials in Type 1 Diabetes**

#### **Study 117**

This study was conducted from Dec 11, 1996 through August 27, 1998.

This was a 26 week four arm blinded study of pramlintide vs. placebo. Inclusion criteria were type 1 diabetes with two months of "stable insulin dose" defined as no change in dose of greater than 10% and no change in type of insulin or number of injections. Patients were to have a stable weight (+/- 2.5kg) for at least 2 months before study and HbA1c of at least 8% at screening. The blinded study was preceded by a four-week placebo run-in. Patients on Lispro or oral antidiabetic agents alone were excluded, as were patients on cholestyramine, Colestid and dexfenfluramine.

Treatments were given as 0.1 ml sc injection within 15 minutes before each of three daily meals. Three doses of pramlintide were used: 90 ug bid, 60 ug tid and 90 ug tid. Patients in the 90 ug bid arm got a placebo injection before lunch. Patients measured glucose at bedtime and before each meal using a One Touch Profile memory glucose meter. Patients were instructed to measure glucose during symptoms of hypoglycemia and to maintain a record of hypoglycemic episodes, including if assistance was needed and if glucagon or iv glucose were given.

The ITT population comprises 586 patients equally distributed among the four arms (144-148). Withdrawals were 11.7% of placebo patients and 33.3, 18.2, and 32% of pramlintide 90 ug bid, 60 ug tid and 90 ug tid respectively.

Baseline and demographic data are as follows:

- male 49.7%,
- mean age 38 years,
- mean duration of diabetes 15.9 years,
- race 99.5% white,
- mean weight 73 kg,
- mean height 170 cm,
- mean BMI 25.2,
- mean HbA1c 9.0%.

The mean total daily insulin dose was 50.2 units with 58.3% as short acting insulin.

### **Efficacy**

The primary measure of efficacy is change in HbA1c for the ITT population at 26 weeks. This is shown in the table below.

Change in HbA1c for the ITT population at 26 weeks

	Placebo	90 ug bid	60 ug tid	90 ug tid
Mean HbA1c:				
Baseline	9.07	9.02	9.00	9.03
26 weeks	9.11	8.92	8.79	8.92
Change	0.09	-0.15	-0.23	-0.10
LSM		-0.23	-0.32	-0.19
P value		0.053	0.007	0.123

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Although two of the active-treatment arms fail to achieve statistical significance, the overall comparison of all pramlintide groups vs. placebo is  $p=0.011$ . Thus when taken as a group, pramlintide treatment appears to be associated with a net reduction in HbA1c of about 0.25% units. This net reduction in HbA1c was associated with small net reductions of insulin dose, and body weight.

Placebo patients had a mean increase in insulin dose of about 0.5 units. Patients on pramlintide 90 bid and 60 tid had mean insulin reductions of about 1 unit. There was no mean change in patients on 90 tid.

Placebo patients experienced a mean increase in body weight of about 0.3 kg at 26 weeks compared to mean significant ( $p < 0.01$ ) reductions of 0.7 – 1.6 kg in each of the three pramlintide arms. There were no significant changes in HDL or LDL cholesterol or triglyceride either from baseline to endpoint or between placebo and active treatment.

As shown in the table below, a drug effect was seen at week four of treatment. At this early time point, a net reduction of about 0.32% units is highly significant in all groups. This contrasts to the results shown at 26 weeks shown in the earlier table in which only the 60 ug tid arm was clearly different from placebo.

Change in HbA1c for the ITT population at 4 weeks

	Placebo	90 ug bid	60 ug tid	90 ug tid
Mean HbA1c:				
Baseline	9.07	9.02	9.00	9.03
4 weeks	8.91	8.61	8.55	8.53
Change	-0.13	-0.44	-0.45	-0.48
LSM		-0.32	-0.32	-0.33
P value		0.000	0.000	0.000

Volume 157, table 9

The Sponsor has defined “early glyceemic responders” to be patients whose HbA1c dropped by at least 0.5% units at four weeks. The overall efficacy in “Early Glyceemic responder” subgroup is shown in the table below.  
(vol 157 table 14 and May 2001)

Overall Efficacy in "Early Glycemic Responder" Subgroup – Observed Cases (Type 1 Diabetes Study 137-117)				
	Placebo (N=36)	Pram 60 µg TID (N=64)	Pram 90 µg BID (N=58)	Pram 90 µg TID (N=64)
% of ITT	25%	44%	41%	44%
Baseline HbA <sub>1c</sub>	9.78	9.27	9.25	9.14
HbA <sub>1c</sub> Mean Change at 26 Weeks	-0.48	-0.55	-0.42	-0.49
Insulin Mean % Change at 26 Weeks	+1.9%	-4.1%	-2.0%	+0.6%
Weight (kg) Mean Change at 26 Weeks	+1.0	-2.0	-0.4	-1.6
Severe Hypoglycemia 0-26 Weeks*	0.2	1.0	1.6	1.7
HbA <sub>1c</sub> Mean Change at 4 Weeks	-0.83	-0.86	-0.79	-0.93
Insulin Mean % Change at 4 Weeks	+1.8%	-3.2%	-2.3%	-1.7%
Weight (kg) Mean Change at 4 Weeks	+0.5	-0.7	-0.3	-1.0
Severe Hypoglycemia 0-4 Weeks*	0.4	1.5	4.9	3.6
*Event Rate per Patient Year of Observation.				
Cross-reference: 137-117 CSR Supporting Data Summaries 2.2.5, 2.2.20, 2.3.2, 2.4.2, 2.6.2, 2.6.6				

There were more early responders among pramlintide patients (about 43%) than among placebo patients (25%), but the mean reductions in HbA<sub>1c</sub> were similar in all groups. This provides a way of isolating the effects of pramlintide from those of insulin alone in patients who experience similar reductions HbA<sub>1c</sub>. The mean reduction of HbA<sub>1c</sub> was 0.83% at 4 weeks in placebo patients is about the same as the mean reduction of about 0.86 in pramlintide patients (average of all groups). There were small increases in weight and insulin dose in placebo patients compared to pramlintide patients. **The major difference was a 4-12 fold increases in severe hypoglycemia in patients on pramlintide.** Much of the effect on HbA<sub>1c</sub> and the rate of severe hypoglycemia were lost by 26 weeks. But pramlintide-treated patients still had a much higher rate of severe hypoglycemia than did placebo-treated patients.

**Summary:** Pramlintide treatment results in small reductions in HbA<sub>1c</sub> and body weight when compared to insulin alone, and appeared to increase the risk of severe hypoglycemia. A dose–response relationship for efficacy was not established.

### Study 121

This study was conducted from February 19,1996 through August 20, 1999.

This was a 52-week trial of three doses of pramlintide (60 ug tid, 60 ug qid, and 90 ug tid) vs. placebo in patients with type 1 diabetes, preceded by a four-week placebo run-in. “Patients were to have been on a stable insulin regimen for at least two months prior to starting placebo run-in period, and once screened were instructed to remain on the usual diet, type of insulin, insulin regimen, and exercise regimen throughout the study.....”

The stable insulin regimen was defined as a change of 10% or less except for brief adjustment during acute illness. Patients were to have HbA1c of 8% or greater at screening. Drugs excluded were the same as in trial 117. Based on results of trial 117, the Sponsor decided to exclude results of 90 ug tid from all formal efficacy analyses. Subjects used a One Touch Profile glucose meter with memory, and maintained a hypoglycemia record including a record of episodes that required assistance.

The ITT population consisted of 651 patients, who were distributed as follows:

- 51% male,
- 90% white,
- mean age 41 years,
- mean duration 19 years of diabetes,
- mean BMI 26.5
- mean HbA1c 8.9%.
- mean insulin dose 52 units, 37% short acting.

Mean lipid levels were:

- cholesterol 188 mg/dl,
- LDL 116 mg/dl,
- HDL 55 mg/dl,
- LDL/HDL 2.3,
- triglyceride 93 mg/dl

The primary measure of efficacy was change in HbA1c at 26 weeks. As shown in the table below, there was a small reduction in all groups. The difference between active treatment and placebo was statistically significant.

Efficacy data at 26 weeks

HbA1c	Placebo	60 ug tid	60 ug qid	90 ug tid
Baseline	8.92	8.95	8.93	8.90
Change	-0.18	-0.41	-0.39	-0.38
LSM diff		-0.25	-0.25	ND
P value		0.012	0.013	ND

The effects shown at 26 weeks largely persisted through 52 weeks as shown below.

Efficacy data at 52 weeks:

Change	-0.04	-0.29	-0.34	-0.26
Mean diff		-0.25	-0.30	-0.22

Insulin dose was largely unchanged in the placebo group and fell in the pramlintide treated groups:

Change in Insulin dose, %	Placebo	60 ug tid	60 ug qid	90 ug tid
26 weeks	+3.5%	-0.1%	-4.2%	-8.1%
52 weeks	-0.3%	-2.5%	-6.1%	-12.1%

The percent short-acting insulin was 35-40% at baseline and changed little except for the 90 ug tid group where it fell from 34.6% at baseline to 29.8% and 28.3% at 26 and 52 weeks, respectively.

Body weight tended to rise in placebo patients and fall in pramlintide-treated patients. As shown in the table below, the weight reduction in pramlintide patients appears to plateau at 13 weeks (see table). There were no consistent changes in lipid levels.

Change* in weight, %	Placebo	60 ug tid	60 ug qid	90 ug tid
Week 13	0.6%	-1.2%	-1.0%	-1.8%
Week 26	0.7%	-1.2%	-1.9%	-1.8%
Week 52	0.8%	-0.3%	-0.6%	-1.6%

\* initial mean was 79 kg

“Early responders” were defined as patients who have a drop in HbA1c of 0.5% at 4 weeks. “Durable responders” were patients who have a drop of at least 0.5% at 4 and 26 weeks. The proportions of early and durable responders for each arm are shown below.

	Placebo	60 ug tid	60 ug qid	90 ug tid
Early responders, %	20	38	42	36
Durable responders, %	10	23	22	21

### Adverse Events

Withdrawals due to AE’s occurred in 3.9% of placebo patients and 19.5, 13.0 and 21.5% of patients at 60 ug tid, 60 ug qid and 90 ug tid respectively. Nausea was reported by about 12% of placebo patients and 50% of pramlintide patients. Anorexia, nausea and fatigue were reported more frequently among Pramlintide patients.

As shown in the table below, severe hypoglycemia was more of a problem with pramlintide-treated patients than with placebo patients. A total of 9/497 (2%) of pramlintide-treated patients withdrew compared to 0/154 placebo-treated patients.

### Severe Hypoglycemia

	Placebo n=154	60 tid n=164	60 qid n=161	90 ug tid n=172
Incidence*, %	22	30	28	29
Events per subject	0.5	0.9	0.9	0.7
Events per subject year	0.7	1.3	1.1	1.2
Withdrawal	0	4	1	4

\*Multiple severe events are counted only once per subject

### Subgroup analysis:

“Early responders” were defined as patients who have a drop in HbA1c of at least 0.5% at 4 weeks. Results from the early responders subgroup is shown in the table below.

<b>Overall Efficacy in "Early Glycemic Responder" Subgroup – Observed Cases (Type 1 Diabetes Study 137-121)</b>				
	Placebo (N=31)	Pram 60 µg TID (N=61)	Pram 60 µg QID (N=67)	Pram 90 µg TID (N=61)
% of ITT	20%	38%	42%	36%
Baseline HbA <sub>1c</sub>	9.39	9.22	8.93	9.11
HbA <sub>1c</sub> Mean Change at 26 Weeks	-0.65	-0.98	-0.63	-0.74
Insulin Mean % Change at 26 Weeks	-3.5%	-3.3%	-5.4%	-6.3%
Weight (kg) Mean Change at 26 Weeks	+1.4	-1.6	-0.6	-2.2
Severe Hypoglycemia 0-26 Weeks*	0.8	1.2	1.1	1.3
HbA <sub>1c</sub> Mean Change at 4 Weeks	-0.75	-0.89	-0.84	-0.84
Insulin Mean % Change at 4 Weeks	+2.8%	+1.5%	-2.2%	-2.4%
Weight (kg) Mean Change at 4 Weeks	+0.6	-0.8	-0.3	-0.9
Severe Hypoglycemia 0-4 Weeks*	0.4	2.9	3.6	4.9
*Event Rate per Patient Year of Observation.				
Cross-reference: 137-121 CSR Supporting Data Summaries 2.2.8, 2.2.26, 2.3.2, 2.4.2, 3.3.2, 3.3.4				

There were more early responders among pramlintide patients (about 39%) than among placebo patients (20%), but the mean reductions in HbA1c were about the same in all groups. This provides a way of isolating the effects of pramlintide from those of insulin alone in patients who experience similar reductions HbA1c. The mean reduction of HbA1c was 0.75% at 4 weeks in placebo patients is nearly as great as the mean reduction of about 0.86 in pramlintide patients (average of all groups). There were small increases in weight and insulin dose in placebo patients compared to pramlintide patients. But the major difference was a nearly 10 fold increase in severe hypoglycemia.

**Summary:** Pramlintide treatment results in small reductions in HbA1c and body weight, but increases the risk of severe hypoglycemia

## **Study 112**

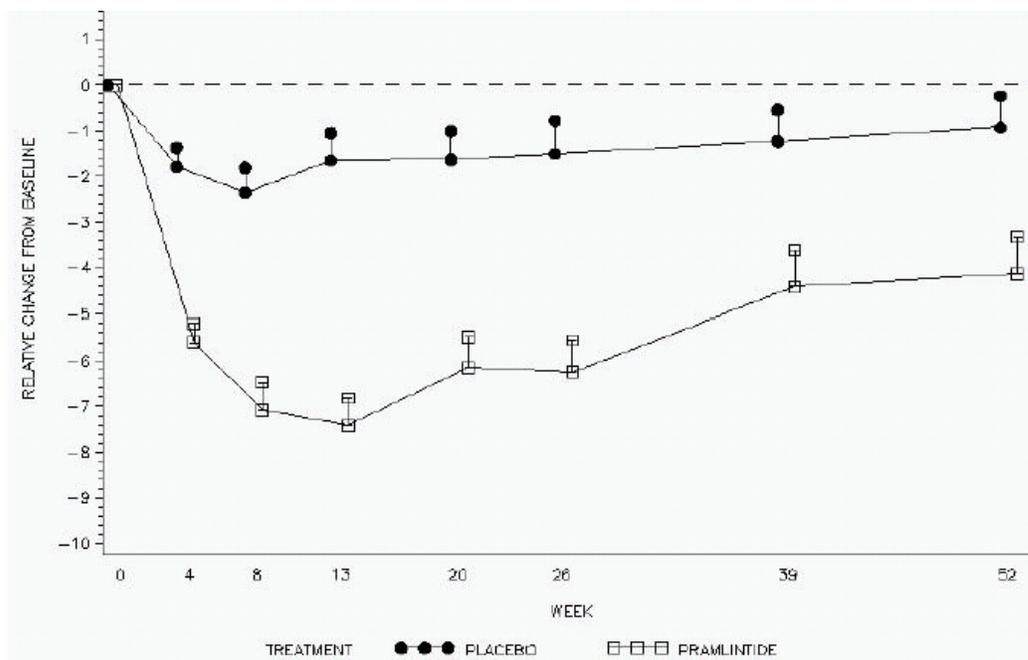
This study was conducted from September 7 1995 through December 27, 1997.

This was a 52-week double blind placebo controlled study in patients with type 1 diabetes. Investigators were allowed to make adjustment in patients' insulin regimen that were "consistent with good medical practice" so that the study was designed to represent a "clinical use situation."

Patients were treated four times per day with pramlintide 30 ug or placebo. At week 20, the pramlintide patients who were found to have had a decrease in HbA1c of less than 1% units from baseline to week 13 were re-randomized to one of two treatment groups: 30 ug or 60 ug qid. All patients were to complete 52 weeks of treatment. To maintain the blind, all patients were given new study medication at week 20. Placebo patients were also "re-randomized" based on their initial response but were continued on placebo. This study also included bone densitometry because of homology between amylin and calcitonin.

Patients were included who had typical type 1 diabetes and were free of symptoms of severe hypo or hyperglycemia for two weeks and had not changed their insulin dose by more than 10% the previous week. HbA1c was 7-13% at screening. The ITT populations were n=237 for placebo and n=243 for pramlintide.

A time course of the change in HbA1c is shown in the figure below (Study 112 - figure 2 p 54 vol 155). When interpreting these results it must be borne in mind that the first 20 weeks represent a simple comparison of pramlintide 30 ug qid vs. placebo. 32% of pramlintide patients and 13% of placebo patients achieved HbA1c reduction of at least 1% units at 13 weeks and were therefore not re-randomized. Also, it must be noted that the data in the figure are "relative change from baseline". The mean baseline HbA1c values were 8.69% and 8.72% for pramlintide and placebo groups respectively. At 52 weeks, the mean HbA1c levels were 8.29 and 8.57 for pramlintide and placebo groups respectively. The placebo- subtracted change in HbA1c was -0.5 at 13 week, -0.38 at 20 weeks, -0.39 at 26 weeks and -0.25 at 52 weeks. All these differences were statistically significant. But the treatment effect waned with time despite the step up in the dose of pramlintide. Looking specifically at HbA1c levels in patients who were re-randomized, it is clear that 60 ug qid was no more effective than 30 ug qid. In patients re-randomized to 60 ug qid, HbA1c levels were 8.35% and 8.28% at baseline and 52 weeks respectively. In patients re-randomized to continue 30 ug qid, mean HbA1c values were 8.31% and 8.1% at baseline and 52 weeks, respectively.



[1] Relative Change =  $\frac{[HbA_{1c} \text{ (post-baseline)} - HbA_{1c} \text{ (baseline)}]}{HbA_{1c} \text{ (baseline)}} * 100$

Note: 55 of the 174 evaluable subjects receiving 30 µg pramlintide were re-randomized at Week 20 to receive 60 µg pramlintide.

Mean body weight at baseline was 76 kg in both groups. At 13, 26 and 52 weeks, the mean changes in the pramlintide group were -0.99, -0.80 and -0.47 kg. The mean changes in the placebo group were 0.17, 0.75, and 1.01 kg. The differences between treatments were highly significant at all time points. It is worth noting that the maximal fall in body weight in patients on pramlintide was achieved at 13 weeks and that body weight rose thereafter even despite dose titration.

The Sponsor did a categorical analysis of change in insulin dose. Increasing the insulin dose > 10% from baseline at weeks 13, 26, and 52 occurred in 11% of pramlintide patients and 14% of placebo patients. Decreasing the insulin dose > 10% from baseline at weeks 13, 26, and 52 occurred in 13% of pramlintide patients and 3% of placebo patients. A change of within 10% at weeks 13, 26, and 52 occurred in 32% of pramlintide patients and 28% of placebo patients.

Mean LDL levels were about 120 mg/dl at baseline. There was little change in placebo group but a mean fall of about 6 mg/dl at 52 weeks in pramlintide patients ( p<0.01). LDL/HDL fell from 2.36 at baseline to 2.07 at 52 in pramlintide patients and from 2.26 to 2.13 in placebo patients ( p<0.01). There were no notable changes in triglyceride or total cholesterol.

Severe hypoglycemia was reported in 26% of patients on pramlintide and 19% of patients on placebo. This was taken from patients' records and was defined as requiring assistance or requiring glucagon or iv glucose. A Kaplan Meier plot of the proportion of patients with severe hypoglycemia vs. the time to the first event shows the trend that pramlintide patients had the first event earlier than placebo patients (p=0.07) (plot not shown). This difference was most evident at day 30, where 13% of pramlintide vs.. 4% of placebo patients had had their first event. The total number of hypoglycemic events was 130 in the pramlintide group (n=174) and 126 in the placebo group (n=167). The event rate per

subject year was 0.74 in both groups. The apparent difference between event rate and proportion of patients with severe hypoglycemia is the result of multiple events in the same patient.

Early responders were defined as having a fall in HbA1c of at least -0.5% at four weeks. There were 44% pramlintide patients who were early responders compared to 24% placebo patients. The mean HbA1c at baseline for pramlintide patients was 9.22% with mean changes of -0.90 and -0.67 at 26 and 52 weeks respectively. The mean HbA1c at baseline for placebo patients was 9.72% with mean changes of -0.61 and -0.46 at 26 and 52 weeks respectively. In considering the potential significance of these “early responder” data, it should be noted that the mean HbA1c levels at baseline were higher in the “early responders” than in the groups as a whole. Mean HbA1c at baseline was 8.69 for the pramlintide groups as a whole and 9.22 in the “early responders”.

<b>1: Overall Efficacy in "Early Glycemic Responder" Subgroup – Observed Cases (Type 1 Diabetes Study 137-112)</b>		
	Placebo (N=56)	Pram 30/60 µg QID (N=105)
% of ITT	24%	44%
Baseline Mean HbA <sub>1c</sub>	9.72	9.22
BA <sub>1c</sub> Mean Change at 26 Weeks	-0.61	-0.90
Insulin Mean % Change at 26 Weeks	+8.4%	-1.7%
Weight (kg) Mean Change at 26 Weeks	+1.4	-0.8
Severe Hypoglycemia 0-26 Weeks*	0.9	0.9
HbA <sub>1c</sub> Mean Change at 4 Weeks	-0.89	-0.91
Insulin Mean % Change at 4 Weeks†		
Weight (kg) Mean Change at 4 Weeks	+0.7	-0.6
Severe Hypoglycemia 0-4 Weeks*	0.9	1.6
*Event Rate per Patient Year of Observation.		
† Change in insulin at Week 4 not calculable in this study.		
Cross-reference: 137-112 CSR Supporting Data Summary 2.2.2.3; Severe Hypoglycemia data have not been previously submitted.		

**Summary:** Pramlintide treatment results in small reductions in HbA1c, body weight and insulin dose. The risk of severe hypoglycemia during the first four weeks of treatment is increased by pramlintide.

## Type 2 diabetes

### Study 122

This study was conducted from Nov 26, 1996 through June 24, 1999

This was a 52-week placebo-controlled study in patients with type 2 diabetes on insulin. There was a 9-day stabilization period and a 4-day placebo lead-in. Thereafter patients were randomized to one of four arms: Pramlintide 120 ug bid, 90 ug bid, 60 ug tid and placebo. Patients were to be on a stable insulin dose for two months before the run-in. Excluded drugs were drugs that effect GI motility, bile acid sequestrants, precose, insulin-lispro, dexfenfluramine and troglitazone. The primary measure of efficacy was change in HbA1c at 26 weeks. Patients were instructed to use a Glucometer with memory before each of three meals and to record glucose during symptoms of hypoglycemia.

There were 656 subjects from 77 centers in USA and 1 in Canada. Approximately 70% completed 52 weeks of study, 70.2% on placebo and 68.1% on 120 bid. Demographic characteristics are:

- 51% male,
- mean age 57 years,
- mean duration of diabetes 12 years,
- 76% white,
- mean weight 90 kg ,
- mean BMI 34,
- 70 units of insulin per day, 26% short acting.
- 16% had HbA1c under 8%.

#### Change in HbA1c at 26 weeks

	Placebo	90 bid	60 tid	120 bid`
Baseline	9.28	9.07	9.01	9.04
26 weeks	8.96	8.54	8.40	8.36
Change	-0.32	-0.54	-0.62	-0.68
LSM		-0.21	Nd	-0.34
P value		0.053	Nd	0.002

At 52 weeks, the LSM treatment effect of -0.33 ( p=0.004) persisted for 120 ug bid. There was no treatment effect for 90 ug bid (-0.09, p=0.44). The 60 ug tid was eliminated by the sponsor from the formal statistical analysis.

There were no consistent changes in insulin dose (vol 86 fig 14). However, there was a difference in change in body weight. At 52 weeks, there was a mean weight gain of 0.7 kg in placebo patients and mean losses of 0.5, 0.2, and 1.4 kg in pramlintide 90 bid, 60 tid and 120 bid. There were no consistent changes in lipid levels.

As shown in the following table, there was more severe hypoglycemia in the 60 ug tid and 120 bid arms than in the other arms. Part of this difference was attributable to two outliers who dropped out of the study after a brief period. Even eliminating these two outliers, however, the event rate per subject per year of exposure was still 2.5x higher at 120 ug bid than placebo. This difference is described as being statistically significant (vol 68 p 126).

#### Severe Hypoglycemia

	Placebo	90 ug bid	60 ug tid	120 ug bid
% of patients	9.3	5.3	12	15.7
Rate*	0.2	0.1	2.6	1.6
Rate, w/o outlier	0.2	0.1	0.3	0.5

**Summary** – Pramlintide was effective in lowering HbA1c at a dose of 120 ug bid. The placebo subtracted change was -0.34 and -0.33 at 26 and 52 weeks respectively. This was associated with weight loss and more reports of severe hypoglycemia.

#### Study 123 –

This study was conducted between Dec 12, 1996 – July 28, 1998.

This is a 26-week placebo-controlled study in patients with type 2 diabetes. Patients were to be of stable weight and insulin regimen. The total dose of insulin could not have changed by more than 10% within 2 months of the four-week placebo run-in. HbA1c had to be at least 8% at screening. The protocol stated: “Following randomization, changes in insulin doses were not encouraged in order to limit the impact of alterations in insulin dosing on glycemic control”. Patients were instructed to use a One Touch Profile memory glucose meter three times a day before meals. They were told to record episodes of hypoglycemia in a diary and were advised to obtain glucose readings when symptoms of hypoglycemia occurred and to record action taken, including assistance by another person. Exclusions for concomitant drugs and medical conditions were as in previous studies Following a 28 day placebo-run-in, patients were randomized to one of four arms: pramlintide at 90 ug bid, 120 ug bid, and 90 ug tid and placebo. To maintain blinding, patients randomized to bid injection received a placebo injection at lunchtime.

At baseline patients were:

- 98% white,
- 53% female,
- mean age 58 years,
- mean duration of diabetes 13.5 years,
- mean weight of 85 kg,
- mean BMI 30.6,.

- mean HbA1c 9.4%,
- mean insulin dose of 55.5 units (39.1% short acting).

Mean lipids in molar units were

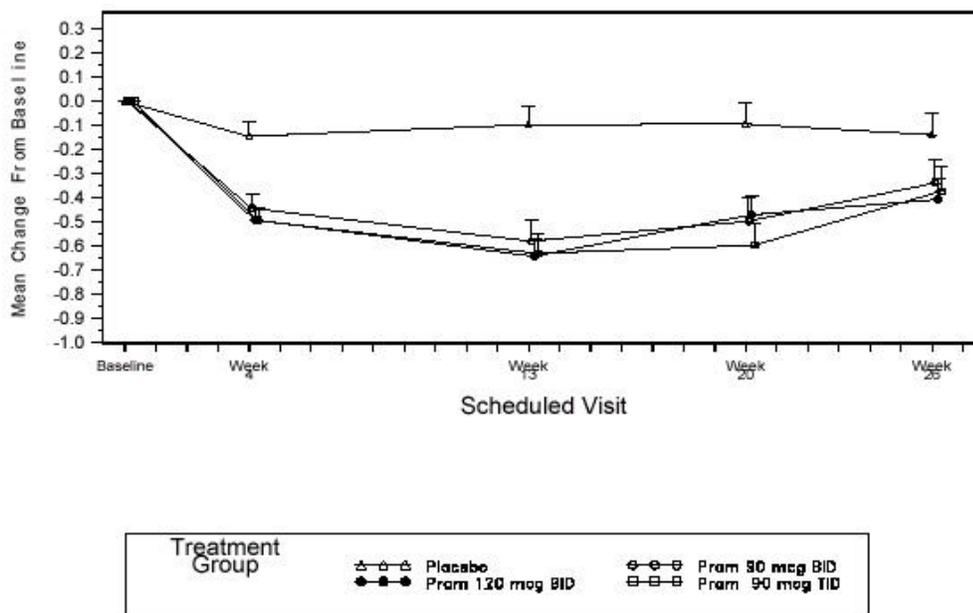
- chol 5.4,
- LDL 3.4,
- HDL 1.3,
- Triglyceride 1.8,
- LDL/HDL 2.8

Mean HbA1c values for the ITT population are shown in the table

HbA1c,%	Placebo n=123	90 bid n=121	120 bid n=126	90 tid n=129
Baseline	9.48	9.27	9.29	9.43
Week 13	9.41	8.69	8.65	8.76
Week 26	9.36	8.93	8.89	9.02

Statistical analysis of each arm vs. placebo showed that the reduction in HbA1c at 120 ug bid of 0.30 % units for the ITT population was statistically significant (p=0.029). There was also significant reduction of 0.29 % units vs.. placebo for the evaluable population (p=0.048) at 120 ug bid. The other doses were not significantly different from placebo unless one used the baseline HbA1c as a covariant. If one made that adjustment, all three doses of pramlintide were statistically different from placebo in the ITT population with net HbA1c reductions of 0.31, 0.36, and 0.26 % units for each of the three doses. Using the evaluable population, the placebo-subtracted changes were -0.23, -0.34, and -0.22 % units for 90 ug bid, 120 ug bid and 90 ug tid respectively. Only the difference between 120 ug bid and placebo was statistically significant ( p=0.011).

As shown in the figure (study 123, fig 1, vol, 173, p.73), the maximal effect of pramlintide on reduction in HbA1c occurred at 13 weeks. Had the change at 13 weeks (instead of 26 weeks) been the primary measure of efficacy, all doses would have been significantly different from placebo.



The early responder population was defined as a reduction of HbA1c of at least 0.5% at weeks. Durable responders had reduction at least 0.5% at 4 and 26 weeks. The proportions of patients who were early and durable responders are shown in the table.

	Placebo	90 bid	120 bid	90 tid
Early responder	31%	56%	62%	65%
Durable resp	17%	27%	32%	39%

Insulin dose rose about 7% in the placebo group at 26 weeks. With pramlintide there was essentially no change in insulin dose. The change was +2%, -1%, 0 at 90 bid, 120 bid, and 90 tid, respectively. The text of the study report does not mention any statistically significant differences in insulin dose or proportion of short-acting insulin.

Mean body weight did not change in the placebo group, but fell by 0.9, 1.7, and 1.4 kg at 90 ug bid, 120 ug bid, and 90 ug tid respectively in the evaluable patients at 26 weeks. All these changes were significantly different from placebo. Other than a fall in LDL at 13 weeks at 90 ug tid, none of the other lipid comparison were significant.

Analysis of severe hypoglycemia (defined as requiring the assistance of another person or administration of glucagon or iv glucose) are shown in the following tables.

#### Severe Hypoglycemia – Weeks 0-26 (vol 173 p 111 table 18)

	Placebo	90 bid	120 bid	90 tid
#of patients (%)	2 (1.6)	7 (5.8)	10 (7.9)	5 (3.9)
# of events	3	9	17	13
Rate/subject	0	0.2	0.3	0.2
Rate/subj-yr	0.1	0.2	0.3	0.2

Incidence counts each patients once despite multiple events

The event rate per subject was lower for placebo than pramlintide by Poisson regression (p=0.009).

The major difference between pramlintide and placebo with respect to severe hypoglycemia occurred during weeks 0-4. As shown in the table below, there were zero events in patients on placebo during the first 4 weeks compared to 4-5 events in each of the pramlintide arms.

Severe hypoglycemia weeks 0-4 ( table 2.6.5 p 331)

	Placebo	90 bid	120 bid	90 tid
# of patients(%)	0	4 (3.3)	3 (3.2)	2 (1.6)
# of events	0	4	4	5
Rate/subject	0	0.4	0.4	0.5
Rate/subj-yr	0	0.4	0.4	0.5

But even for weeks 13-26, the incidence of severe hypoglycemia was higher for pramlintide patients than placebo, although the rates were not very different.

Severe hypoglycemia weeks 13-26 ( table 2.6.5 p 333)

	Placebo	90 bid	120 bid	90 tid
# of patients(%)	2 (1.8)	4 (3.5)	6 (5.3)	2 (1.7)
# of events	2	4	8	4
Rate/subject	0	0.1	0.1	0.1
Rate/subj-yr	0.1	0.1	0.3	0.1

Eight pramlintide-treated patients experienced hypoglycemia episodes described as serious adverse events. There were no such events reported in placebo-treated patients.

**Summary:** Pramlintide treatment resulted in a small reduction in HbA1c but increased the risk of severe hypoglycemia. The efficacy data were statistically significant at 120 ug bid.

## Study 111

This study was conducted from June 6 1995 through July 24, 1997.

This was a 52-week trial of three doses of pramlintide vs. placebo in patients with type 2 diabetes. There was a 3-10 day single blind placebo run-in before randomization. Glucose control was reviewed by the investigators and adjustments to the patients' insulin regimen were made as needed consistent with "good medical practice". Inclusion criteria were type 2 diabetes with HbA1c of 7.5 – 13% at the prescreening visit. Patients were required to have been on insulin for at least six months and to have not had an adjustment of insulin dose by more than 10% in the prior week. Patients with proliferative retinopathy requiring photocoagulation were excluded as were patients with serum creatinine of 2 mg/dl or greater or sustained blood pressure over 150/95. Patients could be on a stable dose of metformin (over three months) but could not be taking Reglan, Propsulsid, Questran, thiazide diuretics or corticosteroids. Patients were randomized by strata: HbA1c 7.5- 9 and 9.1-13%. Antibodies to pramlintide were tested at screening and at weeks 13, 52, and 56. Pramlintide 30 ug, 75 ug, or 150 ug was given by injection fifteen minutes before each of three meals.

Patients characteristics at baseline were as follows:

- 58% male,
- 78% white,
- 12% black
- 9% Hispanic
- mean age 56 years,
- mean 12 years with diabetes,
- mean weight 91 kg,
- mean BMI 30.7,
- mean HbA1c 9.16%

Mean insulin doses at baseline and endpoint in evaluable patients are shown in the table below. There was a small mean rise in insulin dose in all groups, but no differences between groups.

Evaluable population - Insulin dose, units

	Placebo	30 ug tid	75 ug tid	150 ug tid
Baseline	58	55	60	61
52 weeks	65	58	62	64

Mean changes in the evaluable and ITT populations are shown in the table below  
Relative\* change in HbA1c at 52 weeks

		Placebo	35 ug tid	75 ug tid	150 ug tid
Evaluable	Week 52 n=	99	90	102	90
	LS mean change	-1.91	-3.58	-4.31	-6.17
	LSM diff		-1.67	-2.40	-4.26
ITT	Week 52 n=	136	122	136	144
	LS mean change	-1.16	-3.38	-4.42	-5.55
	LSM diff		-2.22	-3.26	-4.39*

\*Note that this table shows the *relative change* in HbA1c from baseline.

Because of the multiple comparisons, a Hochberg adjustment to the Bonferonni procedure was used. The only pair-wise comparison found to be significantly different from placebo was the net change of -4.39% in the ITT population at 150 ug tid. It should also be noted that this table shows the relative change in HbA1c from baseline. The baseline HbA1c was 9.16 in the ITT population at 150 ug tid. Thus, absolute change from baseline in this group is about -0.5% units and the placebo-subtracted change is about -0.4 % units.

Absolute values for HbA1c from baseline to week 52 and changes at week 52 are shown below for the evaluable population. It should be noted that the maximal reduction in HbA1c occurs at week 13 in all groups.

#### Evaluable population

	Placebo n=99	30 tid n=90	75 tid n=102	150 tid n=90
Baseline	9.10	8.96	9.27	9.04
Week 13	8.60	8.24	8.32	8.05
Week 26	8.72	8.42	8.45	8.23
Week 52	8.96	8.64	8.79	8.44
Change from baseline to week 52	-0.14	-0.32	-0.48	-0.60
Difference		-0.18	-0.34	-0.46

As shown in the table below, there was a mean rise in body weight in placebo patients and mean reductions in body weight in all three pramlintide groups. All of the placebo comparisons to pramlintide were statistically significant (p<0.01). It is of interest to note that all the mean reduction in body weight occurred in pramlintide-treated patients at week 13. Therefore there appears to be temporal relationship between weight loss and reduction in HbA1c in pramlintide-treated patients.

Evaluable population – Change in body weight, kg

	Placebo	30 ug tid	75 ug tid	150 ug tid
Week 13	0.79	-0.51	-0.54	-1.59
Week 26	0.96	-0.51	-0.72	-1.56
Week 52	1.04	-0.49	-0.52	-1.49

“Severe hypoglycemia data were obtained from the record of concomitant medications.” Severe hypoglycemia events were defined as those requiring glucagon or iv glucose. Seven subjects (2 placebo and 2,1, and 2 on 30 ug 75ug and 150 ug pramlintide respectively reported eight events). There were no reports of hypoglycemia as serious AE. The incidence of severe hypoglycemia was not formally assessed.

“Retinal disorder” was reported as an AE in 5% of placebo patients, and 6%, 6%, and 10% in the three-pramlintide groups. There were also AE reports of retinal hemorrhage and macular edema. There was one withdrawal at 150 ug tid because of retinal disorder. Although retinal exams were not performed routinely at baseline, the Sponsors interpreted this increased reporting at 150-ug tid to represent “progression of underlying conditions.”

In response to a request for the number of unique patients with diabetic retinopathy as a treatment-emergent event, the Sponsor provided summary data on all patients with reports of “retinal disorder”, “retinal hemorrhage”, “retinopathy”, “vitreous detachment”, and “macular edema”. Some patients were reported with more than one term. The search disclosed 42 unique patients. Information on these patients is shown in the table below.

	Placebo	30 ug tid	75 ug tid	150 ug tid
ALL Patients N=	99 (100%)	90 (100%)	102 (100%)	90 (100%)
HbA1c				
Baseline	9.10	8.96	9.27	9.04
Change	-0.14	-0.32	-0.48	-0.60
With AE of Retinopathy N=	8(8%)	7(8%)	10(10%)	17(19%)
Baseline	8.86	9.94	10.0	8.82
Change	-0.66	-0.57	-0.81	-0.80

These results raise concern about the possibility of a dose-dependent increase in progression of diabetic retinopathy in patients treated with pramlintide. It should be noted that in all treatment categories (placebo and pramlintide) the reduction in HbA1c was greater in patients with treatment-emergent retinopathy than in other patients. This possible significance of this point will be discussed later in the section on the integrated summary of safety.

**Conclusion:** A statistically significant reduction in HbA1c was observed at 150 ug tid of pramlintide. Lower doses were not different from placebo. Patients on 150 ug pramlintide experienced a mean weight reduction of 1.5 kg at 52 weeks compared to a mean weight gain of about 1.0 kg in placebo-treated patients. Patients on lower doses of pramlintide experienced mean weight loss of about 0.5 kg. Diabetic retinopathy was reported as an adverse event in 19% of patients on 150 ug tid of pramlintide compared to 8% of patients on placebo.

## **C. Efficacy Conclusions**

### **1. Trial Design**

There were six phase three trials, three in patients with type 1 diabetes and three in patients with type 2. All the trials were comparisons of pramlintide vs. placebo as adjuncts to insulin in patients who had been on stable doses of insulin for at least two months, and whose hyperglycemia was inadequately controlled. In the two earliest trials, (study 112 in type 1 diabetes and study 111 in type 2 diabetes), patients/physicians were allowed to adjust their insulin regimen “consistent with good medical practice.” In the other four trials (studies 117 and 121 for type 1 diabetes and studies 122 and 123 for type 2 diabetes), patients were asked to maintain a constant regimen of insulin, diet and exercise. Although the study design used in these four trials is a scientifically valid way to isolate the effects of pramlintide, it is difficult to apply the results to ordinary clinical practice in which patients should be encouraged to modify their insulin dose, diet and exercise in ways designed to lower their HbA1c.

Results for these four trials are summarized in the tables that follow. Based on a global assessment of all these data, it appears that pramlintide-treated patients had an average baseline HbA1c of about 9%, which fell roughly 0.3% units to about 8.7% at the end of 26 weeks. This is a very small response, particularly when one considers that they were required to take multiple injections of pramlintide.

### **Type 1 diabetes – Average\* changes at 26 weeks**

<b>Trial 117</b>	<b>Placebo</b>	<b>Pramlintide (all doses)</b>
<b>Baseline HbA1c</b>	9.07	9.02
<b>Mean change</b>	0.09	-0.16
<b>LSM</b>		-0.25

<b>Trial 121</b>	<b>Placebo</b>	<b>Pramlintide (all doses)</b>
<b>Baseline HbA1c</b>	8.92	8.93
<b>Mean change</b>	-0.18	-0.39
<b>LSM</b>		-0.25

### **Type 2 diabetes – Average\* changes at 26 weeks**

<b>Trial 122</b>	<b>Placebo</b>	<b>Pramlintide (all doses)</b>
<b>Baseline HbA1c</b>	9.28	9.04
<b>Mean change</b>	-0.32	-0.61
<b>Difference</b>		-0.28 (approx)

<b>Trial 123</b>	<b>Placebo</b>	<b>Pramlintide (all doses)</b>
<b>Baseline HbA1c</b>	9.48	9.33
<b>Mean change</b>	-0.12	-0.38
<b>Difference</b>		-0.26

\* averages of means for individual studies, not adjusted for the size of each arm.

In study 112, physicians were allowed to make insulin adjustments “consistent with good medical practice” in order to represent a “clinical use situation.”. But even here, the mean HbA1c at endpoint was 8.3% in pramlintide-treated patients. Study 111 was the “good medical practice” trial for type 2 diabetes. Patients on the maximal dose of pramlintide experienced a fall in HbA1c from 9.04 to 8.44% at 52 weeks. In neither of these trials did a majority of pramlintide-treated patients achieve a level of HbA1c that would be considered acceptable by ADA standards (the goal of treatment should HbA1c <7% and “additional action” is suggested for HbA1c >8%).

It is not clear why the Sponsor’s goal in studies 111 and 112 of treating patients in a manner “consistent with good clinical practice” was not achieved. The DCCT trial has shown that groups of patients with type 1 diabetes can maintained with a mean HbA1c of about 7% for many years (N Engl J Med 329: 977-86 1993)). For patients with type 2

diabetes, the data in the table below illustrate that the goal of good glycemic control is achievable in the setting of a clinical trial. The data are from a 24 week placebo-controlled trial published in *Annals of Internal Medicine* 131, 185, 1999. The fall in HbA1c of 1.6% units from the baseline of 9.1% in patients on insulin alone is about as good as one can generally expect. The reduction of 0.9% units attributable to metformin represents value added to what could reasonably be achieved with insulin alone. This is a very different situation from the pramlintide trials.

Metformin as an Adjunct to Insulin in Patients with Type 2 diabetes

	Metformin+insulin (n=21)	Placebo+insulin(n=22)
Baseline HbA1c	9.0	9.1
Change	-2.5	-1.6
Difference	-0.9% units (p=0.04)	
Baseline Insulin dose, U/d	96	97
Change	-5	+23
Difference	-27 units (p=0.002)	
Baseline Weight, kg	103.9	106.6
Change	+0.5	+3.2
Difference	-2.7 kg (p=0.07)	

In conclusion, patients treated with pramlintide showed a small reduction in HbA1c relative to placebo but the design and/or conduct of the studies were so much at variance with good medical practice that it is not possible to say that pramlintide is safe and effective to be used in patients with diabetes. The increase in severe hypoglycemia is particularly worrisome and seems out of proportion to the small reduction in HbA1c. It is reasonable to believe that intensification of their insulin regimen would yield better results than subjecting patients to additional injections with pramlintide.

**The shortcomings of the clinical development program were brought to the Sponsor’s attention at a meeting that took place at FDA, October 28, 1997. The minutes of the that meeting state:**

“Since keeping a constant insulin dose is not how diabetes is treated, the Agency stated that it will have difficulty in evaluating data from study designs that are inconsistent with clinical practice.”

“The Agency recommended (an insulin titration study with) endpoints that should be either reduction in HbA1c or hypoglycemia.”

“The Agency stated that the current study data is not considered pivotal data for an NDA”

## 2. Clinical significance of the efficacy findings

FDA's acceptance of a statistically significant reduction in HbA1c as the basis for approvability of a new product is based on the findings of DCCT, UKPDS and other studies that a reduction in HbA1c decreases the risk of developing diabetic retinopathy, nephropathy, and neuropathy. There is no convincing evidence for a "threshold" for the benefit of reducing HbA1c. Any reduction in HbA1c might be expected to decrease the risk of diabetic complications regardless of the baseline. Thus, the average reduction in HbA1c of 0.3% units in patients treated with pramlintide might be expected, small as it is, to decrease the risk of developing diabetic complications. But there are several problems with accepting the small reduction in HbA1c observed in pramlintide-treated patients as being clinically meaningful.

- The American Diabetes Association has recommended that the goal of treatment should be to lower HbA1c levels to 7% or less. The reduction from 8.9% to 8.6% typically seen for pramlintide-treated patients in the clinical trials falls far short of this goal. The reduction of HbA1c appears to be transient, peaking at about 13 weeks. At a very minimum, treatment with pramlintide would delay efforts to intensify insulin treatment that would lower and maintain HbA1c at acceptable levels.
- Pramlintide treatment would require three injections per day in addition to insulin. I do not see what argument can be made to start patients on pramlintide in lieu of adjusting their insulin regimen.
- It has not been established that pramlintide lowers HbA1c in patients who are being treated in accordance with ADA standards. Pramlintide treatment results in a small but statistically significant reduction in HbA1c in patients whose baseline is about 9%, provided that their insulin regimen remained constant or nearly so. I do not see how a label could be written based on these results. Since adjustment in patients' insulin regimen would be expected to give better results than addition of pramlintide, it is not clear what instruction patients would be given regarding their insulin treatment. **To refrain from adjusting the insulin dose would be to undermine a very effective treatment for the sake of starting a minimally effective treatment. But adjusting the insulin dose when starting pramlintide would expose patients to an even greater risk of hypoglycemia than what was already seen in the clinical trials.** Furthermore, there would be no way to differentiate the glucose-lowering effects of pramlintide from those of insulin.
- The risk of hypoglycemia appears to be increased in patients taking pramlintide relative to patients on insulin alone.
- Pramlintide and insulin cannot be mixed in the same syringe. Patients will need to take separate injections of each medication before meals. This may lead to confusion with the danger of undermining glycemic control through patient error.

- A draft guidance (March 1998) for new treatments for diabetes discusses the use of HbA1c as a surrogate endpoint but states that “a new treatment could not be approved based on a reduction in HbA1c if there was evidence that it increased the risk of diabetic complications directly.” This statement was directed at curtailing programs to develop IGF-1 as a treatment for diabetes because of our concern that IGF-1 might increase the risk of retinopathy. The same problem may also be relevant to pramlintide, because there appeared to be a possible dose-related progression of diabetic retinopathy in one of the trials (see discussion of retinopathy in the safety section).

The “early responder” subgroup analysis is an attempt to identify patients who may benefit from pramlintide. But even here, it is hard to find a good reason to start patients on pramlintide. The table below is a summary of results for early responders from the three studies in type 1 diabetes. A mean reduction in HbA1c of 0.68 at 26 weeks is not impressive when one considers that the baseline was 9.16%, and that treatment with pramlintide required 2-4 additional injections per day. Even though these patients were not obese (mean BMI about 27), the reduction in weight relative to insulin alone would ordinarily be considered an advantage were it not associated with a substantial increase in severe hypoglycemia. Particularly during the first four weeks there is a six-fold increase in severe hypoglycemia relative to placebo even though the mean reduction in HbA1c is virtually identical (0.84 for placebo and 0.87 for pramlintide).

<b>Overall Efficacy in "Early Glycemic Responder" Subgroup - Observed Cases (Type 1 Diabetes Studies 137-121, 137-112, and 137-117 Combined)</b>			
	All Placebo Combined (N=123)	All Pram Combined (N=480)	
% of ITT	24%	44%	
Baseline HbA <sub>1c</sub>	9.65	9.16	
HbA <sub>1c</sub> Mean Change at 26 Weeks	-0.56	-0.68	
Insulin Mean % Change at 26 Weeks	+3.25%	-3.04%	
Weight (kg) Mean Change at 26 Weeks	+1.25	-1.27	
Severe Hypoglycemia 0-26 Weeks*	0.6	1.4	
HbA <sub>1c</sub> Mean Change at 4 Weeks	-0.84	-0.87	
Insulin Mean % Change at 4 Weeks	+2.26%	-1.75%	
Weight (kg) Mean Change at 4 Weeks	+0.63	-0.64	
Severe Hypoglycemia 0-4 Weeks*	0.5	3.0	
† Includes 30 µg patients in Study 137-112.			
* Event Rate per Patient Year of Observation.			
Cross-reference: Data have not been previously submitted.			

## VII Integrated review of Safety

The integrated review of safety was done by Dr Dragos Roman. His complete review is in a companion document. His description of two pramlintide-related deaths and Section 7, “Serious adverse events associated with hypoglycemia”, is reproduced below. **Not included in the table in this section is the motor vehicle accident that was not in the database but was discovered during a routine DSI inspection** (see V. B – Evaluation of data quality and integrity.)

The concern that treatment with pramlintide might lead to progression of diabetic retinopathy was not included in the integrated review of safety because it stems from a result that was found in only one trial. This issue is discussed later.

Excerpts from Dr Roman’s integrated review of safety:

*The distribution of the deaths does not allow definitive mortality rate comparisons between treatment and placebo groups. Overall, cardiovascular deaths (myocardial infarction, arrhythmias, sudden death, and stroke) predominated, especially in the type 2 diabetes population which included older subjects with multiple co-morbidities. **Two deaths that occurred during the long-term controlled type 1 diabetes studies are noteworthy (both occurred in the pramlintide group):***

*A 48-year-old male with a 12-year history of diabetes had a witnessed, early AM seizure during sleep, followed by cardiac arrest. Resuscitation attempts were unsuccessful. The event occurred 229 days within the study. The subject had a history of seizures due to hypoglycemia.*

*A 35-year-old male with a 6-year history of type 1 diabetes and no other significant medical history was involved in a motor vehicle crash that resulted in his death approximately one day after starting pramlintide.*

### 7) Serious Adverse Events Associated With Hypoglycemia:

*It is worth emphasizing the distinction between severe hypoglycemic events and serious adverse events associated with hypoglycemia. Severe hypoglycemia is in essence assisted hypoglycemia (i.e. any subject who requires the assistance of another individual with the ingestion of oral carbohydrates, glucagon injection, or intravenous glucose administration is experiencing a severe hypoglycemic event). On the other hand, a serious adverse event is an event that results in death, disability, hospitalization, or is perceived as being life threatening and it can have many causes including hypoglycemia.*

*Hypoglycemia is the single most common cause of serious adverse events in the long-term controlled type 1 diabetes trials. It occurs with an incidence of 9% in pramlintide-receiving subjects and 4% in placebo-receiving controls. It is also the most common cause of serious adverse events during the type 2 diabetes trials, albeit with a smaller pramlintide-to-placebo difference (2% vs. 1% incidence). There is a 2.8:1 ratio between pramlintide- and placebo-associated severe hypoglycemic events during the type 1 diabetes trials. This-drug-to placebo discrepancy prompted a search for the specific*

nature of the serious adverse events associated with hypoglycemia. The search was aimed at identifying injuries that may have been associated with hypoglycemia among the type 1 diabetes population during the three long-term controlled type 1 diabetes trials (137-121, 137-112, and 137-117). The narratives of deaths, serious adverse events, and withdrawals were searched for the following keywords: motor vehicle, traffic, motorcycle, driving, road, highway, parking, curb, car, accident, bicycle, trauma, tree, fall, fracture, and skull.

This has led to the identification of fifteen subjects in the pramlintide group and two subjects in the placebo group who were involved in driving-related serious adverse events which were associated with hypoglycemia (Table 16). The nature of the events covered a wide spectrum of severity that ranged from motor vehicle crashes (resulting in trauma and hospital admission) to events in which the subject became “confused” or “disoriented” at the wheel but was apparently able to avoid a collision. Most of them required paramedic intervention, emergency room visits, parenteral glucose administration. The only motor vehicle crash which did not have a clearly documented association with hypoglycemia involved a 35 year old subject who died during the event (no intervention was reported). The driving-related events in the pramlintide group occurred predominantly during the first month (40%) with two of them occurring during the first day of the trial. The remaining events which occurred after the first month did not show any particular time-related distribution. The only two driving-related events associated with hypoglycemia in the placebo group occurred on days 169 and 377 of treatment respectively; both were mild, none reportedly resulted in paramedic intervention or hospital visit. **The event rate per year of exposure was 4:1 pramlintide to placebo.**

Table 16: Driving-related Events Associated with Hypoglycemia (Type 1 and Type 2 Diabetes, All Studies)

	Controlled		Uncontrolled	Controlled		Uncontrolled				
	Long term			Long term						
	Short-term	Long term	Short-term	Long term						
	Pram	Pbo	Pram	Pbo	Pram	Pbo	Pram	Pbo	Pram	
Events	0	0	15	2	3	0	0	1	0	0

Note: Pram=pramlintide; Pbo=placebo

A similar search was done by the sponsor and was presented under two categories: “treatment-emergent motor vehicle accident-related events with a hypoglycemic event within the same day for pramlintide and placebo subjects, all studies in subjects with type 1 diabetes and type 2 diabetes using insulin” and “treatment-emergent automobile related hypoglycemic adverse events not resulting in a motor vehicle accident for both pramlintide and placebo, all studies in subjects with type 1 and with type 2 diabetes using insulin”.

*It should be noted that the results of the two searches are slightly different. Although they share many similarities, numerical and definition differences exist. For instance the sponsor's search identifies three additional subjects with driving-related events associated with hypoglycemia in the non-serious adverse event category (all in the pramlintide group). Subsequently, an additional driving-related event associated with hypoglycemia missing in the original data base was identified, thus raising the total number of type 1 diabetes subjects with driving-related events in open-label studies to seven. In type 2 diabetes trials the sponsor identifies two pramlintide- and one placebo-receiving subjects.*

*In addition to the driving related serious adverse events associated with hypoglycemia mentioned above, two more pramlintide-treated subjects who sustained hypoglycemia-related falls resulting in hospitalization were identified. One subject required hospital admission for surgical repair of a broken elbow, while another was admitted for a skull fracture.*

*The predominance of serious adverse events associated with hypoglycemia in the pramlintide group during the long-term controlled studies in type 1 diabetes trials does not have a clear explanation at this time and needs further exploration and clarification. It is important to keep in mind that amylin is a neuroendocrine hormone with effects mediated through the central nervous system involving specific amylin binding sites. Central nervous symptoms ranging from somnolence, fatigue, syncope, asthenia, dizziness, headache, depression are reported more frequently in the pramlintide group among serious adverse events, albeit in low numbers. Somnolence is the top non-GI and non-nutritional single symptom cause of subject withdrawal. Hypoglycemia unawareness cannot be excluded as potential explanation either. Clinical pharmacology trials which studied the response to an insulin-induced hypoglycemic challenge in pramlintide-receiving patients have not unequivocally established that pramlintide does not interfere with the normal recognition of hypoglycemia (see appendix).*

## **Retinopathy**

The possibility of a dose-related progression of diabetic retinopathy in patients with type 2 diabetes on pramlintide was raised by the results of study 111. It must be stressed that the greater reporting of diabetic retinopathy as an AE occurred only in one arm of one trial and was probably not statistically significant. I would dismiss this observation entirely were it not for the fact that the finding occurred in the high dose arm (150 ug tid) and that this high a dose was not used in any of the other phase three trials. Thus, the possibility of a dose-dependent progression of diabetic retinopathy in pramlintide-treated patients must be taken seriously.

It is well established that intensification of treatment can lead to progression of diabetic retinopathy, at least initially. This issue has been reviewed by Henricsson et al (Diabetes Care 22, 1944, 1999) with particular reference to patients with type 2 diabetes. Two years after initiation of insulin treatment, they found that 19% of patients had progression of

diabetic retinopathy by three or more steps. Duration of diabetes, and the presence at baseline of macular edema or peripheral neuropathy seemed to be the strongest risk factors. Additionally, they found that the reduction in HbA1c appeared to be greater in patients with progression of retinopathy. This finding is summarized in the following table:

	Stable retinopathy*	Progression of retinopathy*
HbA1c, baseline	9.7	10.1
6 months	7.6	7.3
12 months	7.9	7.0

\* Progression of retinopathy is three or more step levels. The stable retinopathy group showed progression by two or less steps. Data taken from figure 3, Henricsson et al Diabetes Care 22, 2948, 1999

That a reduction in HbA1c over 6-12 months can be associated with progression of diabetic retinopathy poses a regulatory dilemma. FDA accepts reduction in HbA1c as a measure of efficacy in trials of new antidiabetic agents. This use of HbA1c as a surrogate endpoint reflects the finding that long-term reduction of HbA1c decreases the risk of diabetic complications, particularly retinopathy. However, the opposite result, progression of retinopathy, can be expected to occur sometimes during the 6-12 months that is typical of a phase 3 trial. An example of how FDA resolved this dilemma comes from the review of the NDA for a new insulin analog. Progression of retinopathy appeared to occur in one of two trials in type 2 diabetes. No progression occurred in the three trials of type 1 diabetes. In consultation with expert ophthalmologists both inside and outside FDA, the strong consensus emerged that this finding probably had no clinical significance and should not delay approval of this new insulin. Still, a condition of approval was that the Sponsor perform a long-term phase 4 trial to make certain that use of their product did not pose a risk.

Not all examples of progression of retinopathy during drug trials are benign. During twelve weeks of treatment with IGF-1, 16 of 169 (10%) drug-treated patients had a three step or greater progression of retinopathy and three (2%) underwent photocoagulation (Diabetes Care 22, 585-1999). This progression seemed greatly in excess of what could reasonably be attributed to intensification of treatment and much more like the rapidly progressive proliferative retinopathy described by Merimee et al. (NEJM 309, 527-1983) in patients with high levels of IGF-1. With respect to pramlintide, there is a report that infusion of amylin causes IGF-1 secretion in lactating goats (J Anim Sci 77:1241-1248), but I do not know if this occurs in humans. I am not aware of any data to suggest that amylin/pramlintide has IGF-1 activity.

In summary, the association between pramlintide treatment and progression of retinopathy is very tenuous.

## **VIII. Dosing**

The lowest recommended dose for a new product is generally the smallest dose that was found to be effective in the clinical trials. Unfortunately, the clinical trials do not provide enough information to determine what is the smallest effective dose of pramlintide. From study 112, we know that 60 ug qid is no more effective than 30 ug qid in patients with type 1 diabetes. But other trials did not employ a 30 ug qid arm, and qid dosing is not generally considered desirable. In study 117 and 121, 60 ug tid was better than placebo but smaller doses were not tested. I think the trial data would support 30 ug qid or 60 ug tid as reasonable estimates of the lowest effective dose in type 1 diabetes. In type 2 diabetes, the lowest dose that was consistently effective is 120 ug bid.

According to the PK review, the bioavailability of pramlintide in patients with type 2 diabetes is lower than in type 1 diabetes. This accounts for the observation that 240 ug is the minimum effective daily dose in type 2 diabetes (120 ug bid) while 120 ug (30 ug qid) is the minimum effective daily dose in type 1 diabetes. The difference in bioavailability between type 1 and type 2 diabetes is presumed to be due to differences in body fat.

Over and above the question of pramlintide dosing is the issue of who should be treated with pramlintide and how those patients should adjust their insulin. The trials were done in patients whose diabetes treatment regimen had been inadequate and that inadequacy was perpetuated by the design and/or conduct of the trials. The trials provide little or no insight into how pramlintide should be used in patients who are being treated in accordance with currently accepted standards.

## **IX. Use in Special Populations**

Section not completed

## **X. Conclusion and Recommendations:**

The plasma concentration of amylin is low in most, if not all, patients with type 1 diabetes, and may also be low in patients with type 2 diabetes. Short term studies showed that injections of pramlintide given before meals greatly reduced glucagon secretion and post-prandial hyperglycemia. These findings led to the speculation that amylin deficiency was a characteristic of the diabetic state and that amylin “replacement” in the form of pramlintide would improve glycemic control.

The results of the long term trials have been a disappointment. **Pramlintide appears to lower glucose levels during the first few weeks of treatment, but the long-term reduction in HbA1c is trivial and is completely overshadowed by the risk of severe hypoglycemia.** Particularly alarming is the number of patients that had life-altering events on pramlintide. The risk of experiencing a hypoglycemia-associated motor vehicle event was increased at least four fold by taking pramlintide. One patient died in a motor vehicle accident the day after starting pramlintide. One patient on pramlintide died during what was probably a hypoglycemic seizure. Two additional pramlintide-treated patients sustained fractures during hypoglycemic events unrelated to motor vehicle accidents.

Random inspections of 44 patient records disclosed one hypoglycemic event that did not appear in the database and one motor vehicle accident that did not appear in the database. Based on the results of these inspections, I fear that the safety database submitted in the NDA is not reliable.

The Sponsor has not demonstrated that pramlintide is safe and effective to be used in patients with diabetes. The NDA is not approvable.

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