

MEDICAL OFFICER REVIEW			
Division of Metabolic and Endocrine Drug Products (HFD-510)			
APPLICATION #:	21-332	APPLICATION TYPE:	Commercial NDA
SPONSOR:	Amylin Pharmaceuticals INC	PROPRIETARY NAME:	Symlin
CATEGORY OF DRUG:	Amylinomimetic	GENERIC NAME:	Pramlintide Acetate
		ROUTE:	Injectable (subcutaneous)
MEDICAL REVIEWER:	Dragos Roman, MD	REVIEW DATE:	06-14-2001
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Document Date:	CDER Stamp Date:	Submission Type:	Comments:
12/07/2000	12/08/2000	Original NDA	
RELATED APPLICATIONS (if applicable) IND 39,897			
Document Date:	APPLICATION Type:	Comments:	
<p>Overview of Application/Review: Pramlintide is a synthetic analogue of the human neuroendocrine peptide amylin. It slows down the rate of nutrient delivery to the small intestine via an effect on gastric emptying, and inhibits prandial glucagon secretion. It exerts its effects through direct binding to central nervous system receptors and subsequently through the vagus nerve efferent pathways rather than by direct action on the stomach.</p> <p>The following safety concerns are raised by this review:</p> <ol style="list-style-type: none"> 1) When used in addition to insulin, pramlintide results in an increased incidence of severe hypoglycemia particularly during, but not limited to, the first month of treatment. 2) Increased incidence of severe hypoglycemia may explain an increased number of serious adverse events associated with hypoglycemia, including driving-related events and falls. 3) Some information obtained during the clinical pharmacology studies suggests that pramlintide may interfere with the subjects' ability to recognize hypoglycemia. 4) Nausea, decreased appetite and other gastrointestinal adverse events occur with high incidence during pramlintide treatment. 			
<p>Recommended Regulatory Action: Additional clinical studies:</p> <ol style="list-style-type: none"> 1) A clinical pharmacology study (randomized, double-blind, placebo controlled) in type 1 diabetes subjects powered enough to reach statistically significant conclusions concerning hypoglycemia awareness during pramlintide treatment. 2) A placebo-controlled, randomized, double-blind, trial of pramlintide in insulin-receiving diabetics which, not only meets efficacy endpoints, but also reduces the risk of severe hypoglycemia during the first month of treatment. Such a study will likely involve some form of insulin titration. 			

Signed:	Medical Reviewer: _____	Date: _____
	Medical Team Leader: _____	Date: _____

Executive Summary (Safety Review)

I. Recommendations:

A. Recommendations on Approvability

Two major safety issues stand out from the current review of NDA 21-332 (it should be noted that some areas such as ECG, clinical laboratory tests have not raised any outstanding safety issues so far but are not yet fully reviewed):

- 1) The use of pramlintide in addition to insulin in the treatment of type 1 diabetes is associated with an increase in **serious adverse events** (SAEs) associated with hypoglycemia. A subgroup of hypoglycemic SAEs consists in driving-related events and falls which are four times more frequent in the pramlintide treatment group when compared to the placebo group.

Clinical pharmacology studies have not been able to establish that pramlintide does not interfere with the ability to recognize hypoglycemia. On the contrary, two five-day studies suggest a loss of hypoglycemia awareness in the pramlintide treated subjects.

Given the life-threatening nature of these events an appropriately powered, double-blind, placebo controlled study in type 1 diabetes subjects that will investigate the integrity of hypoglycemia awareness mechanisms in subjects receiving pramlintide in addition to insulin is recommended prior to the approval of the drug.

- 2) Based on the studies conducted so far, the first month of pramlintide treatment is a time of increased hypoglycemia-related morbidity. Twice as many subjects experience **severe hypoglycemia** in the pramlintide treated groups in both type 1 and type 2 diabetics. 40% of the driving-related events occur during the first month of treatment. This reviewer cannot identify any definitive feature that predicts the risk of **severe hypoglycemia** and SAEs associated with hypoglycemia during the first month of pramlintide treatment.

A recommendation is being made to complete an additional double blind, randomized, placebo-controlled trial of pramlintide in insulin-receiving diabetics in which efficacy endpoints are met while avoiding at the same time the occurrence of severe hypoglycemia (particularly during the first month of treatment). Several possible designs can be envisioned most likely involving some form of insulin titration. Such a study should be carried out in a patient population with

characteristics that are similar to those of the subjects enrolled in the previous phase 3 trials. It should be done at least in type 1 diabetes subjects.

B. Recommendations on Phase 4 Studies: none at this point of the review process.

II. Summary of Clinical Findings As They Relate to Safety:

1) Adequacy of Safety Testing:

Overall, 4415 subjects have been exposed to pramlintide and 1504 subjects received placebo in 48 completed clinical trials. The mean pramlintide exposure time per subject is 0.62 years and the total exposure time is 2726 subject-years.

Six long-term controlled trials have been completed, three in type 1 diabetes subjects (1179 pramlintide- and 538 placebo-treated patients) and three in type 2 diabetes subjects (1273 pramlintide- and 420-placebo treated patients). The long-term trials range from six months in duration (two) to one full year (four). Several hundred subjects have been evaluated in extension studies for up to and over two years.

During this review type 1 and type 2 diabetes trials mean long-term controlled type 1 and type 2 diabetes trials unless otherwise specified. Pramlintide treatment means pramlintide plus insulin, and placebo treatment means placebo plus insulin. Severe hypoglycemia is defined by the sponsor as “assisted hypoglycemia” (i.e. any hypoglycemic event that requires the assistance of another individual with the ingestion of oral carbohydrates, glucagon injection, or intravenous glucose administration).

2) Serious Adverse Events:

There are seventeen **deaths** recorded during the pramlintide clinical trials. The distribution of deaths in various trials does not allow definitive mortality rate comparisons among treatment and placebo groups. Two deaths may have been related to hypoglycemia (one being a motor vehicle crash). Both deaths occurred in type 1 diabetes patients receiving pramlintide.

Hypoglycemia is the leading cause of serious adverse events in both type 1 diabetes trials (incidence: 9% pramlintide vs 4% placebo) and type 2 diabetes trials (incidence: 2% pramlintide; 1% placebo). It occurred predominantly during the first month of treatment in the pramlintide-receiving patients and less frequently thereafter. *Early occurrence of SAEs due to hypoglycemia is a major safety issue associated with the use of pramlintide.*

Overall, serious adverse events are more frequent in the type 1 diabetes trials in the pramlintide groups (14%) when compared to the placebo groups (10%). In contrast, type 2 diabetes trials have similar incidence of SAEs in both groups (14% pramlintide vs 15% placebo).

3) Withdrawals Due to Adverse Events:

Adverse events are the major reason for patient withdrawal in all trials and particularly in the type 1 diabetes trials (18% in the pramlintide group and 6% in the placebo group). Only 66% of the subjects randomized to pramlintide completed the type 1 diabetes trials (vs 75% in the placebo group). Completion rates are equal in type 2 diabetes trials between drug and placebo arms (75%).

Gastrointestinal (GI) adverse events (in particular **nausea**, but also anorexia and vomiting) are the main cause of patient withdrawal. The incidence of GI withdrawals in pramlintide vs placebo treatment groups is 13% vs 2% in type 1 diabetics and 4% vs 2% in type 2 diabetics.

Hypoglycemia was the second most common reason for subject withdrawal but only in the type 1 diabetes trials.

4) Common Adverse Events:

The most common adverse events in the type 1 diabetes trials are: **nausea** (51% pramlintide, 17% placebo), **anorexia** (18% pramlintide, 2% placebo), **hypoglycemia** (27% pramlintide, 19% placebo), **vomiting**, and **fatigue**.

The most common adverse events in the type 2 diabetes trials are: **nausea** (24% pramlintide, 14% placebo), and **anorexia** (8% pramlintide, 3% placebo).

Nausea is an extremely frequent event with a high recurrence rate. Most subjects develop nausea early in the treatment (within the first four weeks). It has a high rate of recurrence (70% in type 1 diabetics and 60% in type 2 diabetics during the next two months). Toward the end of a full year of treatment it still recurs in 49% of type 1 diabetes subjects and 36% of type 2 diabetes subjects. *Nausea is the main reason of subject withdrawal for both type 1 and type 2 diabetes subjects in the long-term controlled trials.*

Severe hypoglycemia has a higher incidence in the pramlintide group in both type 1 diabetes subjects (25% vs 18% placebo) and type 2 diabetes subjects (9% vs 6%). It occurs at least two to three times more often in the pramlintide group at the beginning of the treatment (i.e. during the first month). Thereafter it continues to have a slightly higher incidence in pramlintide-receiving subjects until the end of the study.

5) Serious Adverse Events Associated With Hypoglycemia:

The nature of severe adverse events due to hypoglycemia was explored. A search by keywords in the patient narrative data base identified an increased number of driving-related events and falls associated with hypoglycemia in the pramlintide group. This observation was made primarily in the type 1 diabetes trials. Fifteen driving-related events occurred in the pramlintide group and two in the placebo group. This gives an

event rate per year of exposure of 4:1 pramlintide to placebo. *The occurrence of trauma and driving-related episodes in association with pramlintide use is a major safety concern identified by this review.*

6) Unsolved Safety Issues:

The following safety issues need to be addressed:

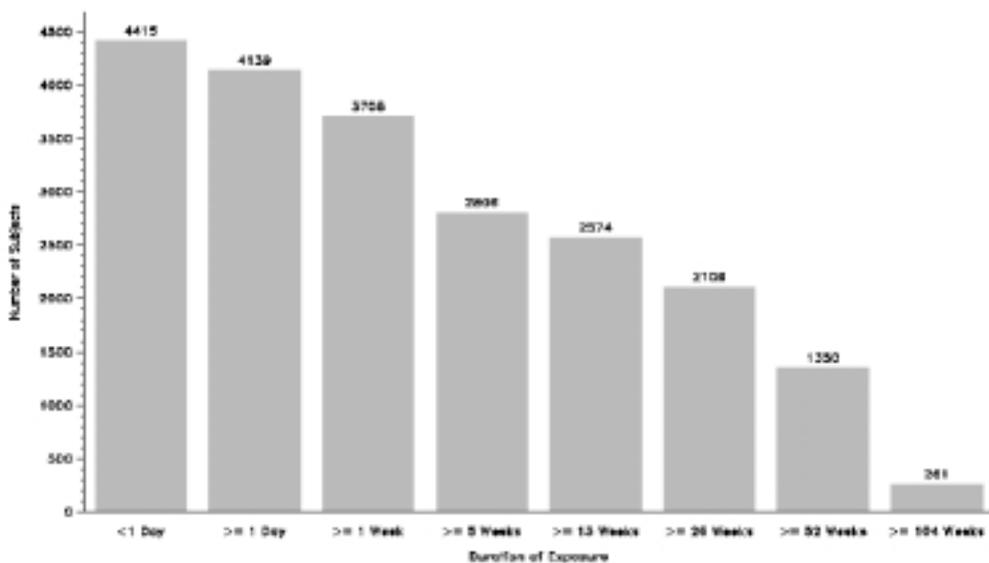
- The increased incidence of **severe hypoglycemia** when pramlintide is used in the treatment of type 1 and type 2 diabetics in addition to insulin, in particular during the first month of treatment.
- The increased number of **serious adverse events** associated with hypoglycemia (in particular driving-related events and falls in type 1 diabetes subjects).
- Does pramlintide administration result in impaired hypoglycemia recognition mechanisms (“hypoglycemia unawareness”) or does it have hypoglycemia-independent central nervous system inhibitory effects?
- Are the **severe hypoglycemia** and the **serious adverse events** associated with hypoglycemia due to an occasionally unpredictable interplay between the effects of two injected medications and a variable meal content?

Clinical review (Safety Review Section):

1) Overview of the pramlintide clinical program, extent of patient exposure and source of information for the safety analysis.

The safety data analyzed are derived from 48 completed clinical studies that comprise the pramlintide clinical development program. These clinical trials cover a wide range of subjects and purpose (from phase I tolerability, PK/PD studies to large phase III controlled and uncontrolled trials in type 1 and type 2 diabetic subjects). Overall, 4415 subjects have been exposed to pramlintide and 1504 subjects received placebo. The mean pramlintide exposure time per subject was 0.62 years and the total exposure time was 2726 subject-years. The range of distribution of pramlintide exposure is illustrated in Figure 1:

Figure 1: Cumulative Number of Subjects Exposed to Pramlintide at Various Times (All Studies*)



*<day = at least one dose

Although most safety analyses include subjects pooled from all the studies, particular emphasis is placed on the data derived from the six, long-term, controlled studies in both type 1 and type 2 diabetes. These trials represent a substantial segment of the study population (56% for pramlintide and 64% for placebo), include a placebo arm (thus allowing drug-to-placebo comparisons), and have the longest duration of pramlintide exposure (6 months to one year). Table 1 includes the cumulative number of patients randomized to pramlintide and placebo in the long-term type 1 and type 2 diabetes studies. (It should be noted that in the safety review pramlintide treatment means pramlintide plus insulin, while placebo treatment refers to placebo plus insulin).

Table 1: Enumeration of Subjects in The Long-term Type 1 and Type 2 Diabetes Trials

	<i>Type 1 diabetes</i>		<i>Type 2 diabetes</i>	
<i>Treatment</i>	Pramlintide	Placebo	Pramlintide	Placebo
<i>Number of Subjects</i>	1179	538	1273	420

2) Deaths:

There were seventeen deaths recorded during the clinical trials (controlled and uncontrolled) as illustrated in table 2:

Table 2: Number of Deaths and Distribution by Study and Treatment Type:

	<i>Type 1 diabetes</i>					<i>Type 2 diabetes</i>				
	Controlled				Uncntr.	Controlled				Uncntr.
	Short-term		Long-term			Short-term		Long-term		
	Pram	Pbo	Pram	Pbo	Pram	Pram	Pbo	Pram	Pbo	Pram
Deaths	0	0	3	2	2	1	0	3	5	1

Note: Pram=pramlintide; Pbo=placebo; Uncntr.=uncontrolled

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.

Serum glucose levels are not available for any of the above cases.

3) Serious Adverse Events Other Than Deaths:

Serious adverse events are defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongs an

existing hospitalization, is severely or permanently disabling, or results in a congenital anomaly. Cumulative incidence of SAEs during the long-term trials is presented in Table 3.

Table 3: Incidence of Serious Adverse Events in Long-term Controlled Type 1 and Type 2 Diabetes Trials*:

	<i>Type 1 diabetes</i>		<i>Type 2 diabetes</i>	
	Pramlintide (n=1179)	Placebo (n=538)	Pramlintide (n=1273)	Placebo (n=420)
Incidence	14%	10%	14%	15%

*Individuals experiencing multiple SAEs are counted once.
n=total number of subjects

Serious adverse events in the controlled long-term type 1 diabetes trials:

Hypoglycemia was the leading cause of serious adverse events in this category (9% incidence in the treatment group and 4% in the placebo group, Table 4). Indeed, 62% of all SAEs were due to hypoglycemia in the pramlintide group compared to 43% in the placebo group. Hypoglycemia was the only SAE that occurred at a rate in the pramlintide group at least 1% greater than in placebo.

When groups of related signs and symptoms (“body systems”) were considered, only three categories (body as a whole, metabolic/nutritional system, and nervous system) met this criterion. In the metabolic/nutritional category, hypoglycemia was the main contributor. The most frequently reported SAE in the body as a whole system was syncope (12 subjects in the pramlintide group and 1 subject in the placebo group). In the central and peripheral nervous system category all serious adverse events were reported in the pramlintide group and none in the placebo control group (convulsions in four subjects, coma in three subjects, and ataxia, headache, vertigo and migraine, each reported by a single subject).

Of note is the fact that in the inflicted injury category there were eleven SAEs reported in the treatment group and only one in the placebo control group.

Table 4 : Most Frequent Serious Adverse Events (by Individual Symptoms and Body Systems) in the Controlled Long-term Type 1 Diabetes Trials*

		<i>Type 1 diabetes</i>		
		Pramlintide (n=1179)	Placebo (n=538)	% difference
Symptoms	Hypoglycemia	9%	4%	5%
	Metabolic/Nutritional	10%	6%	4%
Body system	Body as a Whole	2%	1%	1%
	Nervous System	1%	0%	1%

*included are only symptoms occurring with a frequency of 1% or greater over placebo; individuals experiencing multiple SAEs within the same category are counted once; n=total number of subjects.

Serious adverse events in the controlled long-term type 2 diabetes trials:

Type 2 diabetes trials include an older population (mean age 57.5 for the drug group and 56.2 for the placebo group). The cumulative effect of age and diabetes appears to translate into a different serious adverse event profile. While in type 1 diabetes studies hypoglycemia is the single dominating serious adverse event, in the type 2 diabetes studies it is present in only 2% of the pramlintide subjects and 1% of the placebo group (it represents 12% and 7%, respectively, of all SAEs). There was not a single SAE, other than hypoglycemia, which occurred at a rate in the pramlintide group at least 1% greater than placebo.

The body systems with the greatest percentage of serious adverse events in the treatment group when compared to control are: gastrointestinal, metabolic/nutritional, and vascular (extracardiac), (Table 5). In each body system mentioned above the signal-to-noise difference is only one percentage point. Within the gastrointestinal and the cardiac/extravascular system there is no single dominant symptom which accounts for the drug-placebo difference. For the metabolic/nutritional system however, hypoglycemia is the main contributor.

Table 5 : Most Frequent Serious Adverse Events (by Individual Symptoms and Body Systems) in the Controlled Long-term Type 2 Diabetes Trials*

		<i>Type 2 diabetes</i>		
		Pramlintide (n=1273)	Placebo (n=420)	% difference
Symptoms	Hypoglycemia	2%	1%	1%
	Gastrointestinal	2%	1%	1%
Body system	Metabolic/Nutritional	2%	1%	1%
	Vascular (extracardiac)	2%	1%	1%

*included are only symptoms occurring with a frequency of 1% or greater over placebo. Individuals experiencing multiple SAEs within the same category are counted once; n= number of subjects.

4) Withdrawals:

Adverse events were the major reason for patient withdrawal in the long-term controlled trials (Table 6).

Table 6: Withdrawal and Trial Completion Rates in the Long-term Type 1 and Type 2 Diabetes Trials*

	<i>Type 1 diabetes</i>		<i>Type 2 diabetes</i>	
	<i>Pramlintide</i>	<i>Placebo</i>	<i>Pramlintide</i>	<i>Placebo</i>
<i>Total Population</i>	1179	538	1273	420
<i>Completed Trial</i>	778(66%)	403(75%)	968(76%)	321(76%)
<i>Withdrew (all reasons)</i>	401(34%)	135(25%)	305(24%)	99(24%)
<i>Withdrew (adverse events)</i>	217(18%)	31(6%)	117(9%)	31(7%)

Withdrawals due to adverse events were three times more frequent in the pramlintide group during the type 1 diabetes trials, while for the type 2 diabetes trials the withdrawal rate was only slightly higher in the treatment group over placebo. Other reasons for withdrawal (such as non-compliance, withdrawal of consent, protocol violation, lost to follow-up, investigator decision, administrative reasons) had equal or very close rates between the treatment and placebo arms. Individually, each accounted for a relatively small percentage of the enrolled patients who withdrew.

It should be also noted that the trial completion rates were almost identical between all treatment groups with the exemption of the type 1 diabetes subjects treated with pramlintide who had the lowest completion rates (66% compared to 75% for the placebo group).

Adverse Events Leading to Withdrawals in the Controlled Type 1 Long-term Diabetes Trials:

Nausea was by far the main reason for patient withdrawal due to an adverse event in these studies (12% of subjects in the pramlintide group and 1% in the placebo arm withdrew due to this adverse event). The next most frequently reported adverse events were hypoglycemia and anorexia.

Gastrointestinal system adverse events (which included symptoms such as nausea, abdominal pain, diarrhea, flatulence, anorexia, dyspepsia) were those principally responsible for subject withdrawal, followed by metabolic/nutritional system adverse events. Table 7 summarizes the main reasons for subject withdrawal by symptoms and body systems.

Table 7: Most Frequent Individual Adverse Events (Symptoms and Body System) Leading to Withdrawal in the Controlled, Long-term Type 1 Diabetes Trials*

		<i>Type 1 diabetes</i>		
		Pramlintide (n=1179)	Placebo (n=538)	% difference
Symptoms	Nausea	12%	1%	11%
	Hypoglycemia	3%	1%	2%
	Anorexia	2%	0%	2%
	Vomiting	2%	1%	1%
	Dyspepsia	1%	0%	1%
	Somnolence	1%	0%	1%
Body systems	Gastrointestinal	13%	2%	11%
	Metabolic/nutritional	4%	1%	3%
	Body as a Whole	2%	1%	1%
	Secondary terms	1%	0%	1%

*included are only symptoms with occur with a frequency of 1% or greater over placebo; individuals experiencing multiple AEs within the same category are counted once.
n=number of subjects.

The individual signs and symptoms which account for the events in the “body as a whole” reported among pramlintide subjects and absent among placebo patients are: asthenia, syncope, back pain, hot flushes, influenza-like symptoms, malaise, and pain. Fatigue was also more frequent in the pramlintide group when compared to placebo (11 pramlintide subjects=1%, and 2 placebo subjects or <1%).

Among the “secondary terms” system, **inflicted injury** was the predominant individual subcategory with five events in the treatment arm and none in the placebo control group.

A similar profile is emerging in the long-term uncontrolled studies where the most common causes of patient dropout are in the gastrointestinal system (13%), metabolic/nutritional system (3%) and body as a whole (1%, with fatigue as a main contributor).

Withdrawals in the Controlled Type 2 Long-term Diabetes Trials:

Similar to the type 1 diabetes trials, gastrointestinal system adverse events were the most frequent causes of subject dropout in the type 2 diabetes studies, albeit not to the same extent (Table 8). Nausea did not stand out to the same degree among all other gastrointestinal symptoms.

Hypoglycemia, the second most common individual reason for withdrawal in type 1 diabetes studies, was not a significant factor in type 2 diabetes trials, accounting for only four dropouts in the pramlintide group (<1%) compared to none in the placebo arm.

Table 8: Most Frequent Individual Adverse Events (Symptoms and Body System) Leading to Withdrawal in the Controlled, Long-term Type2 Diabetes Trials *

		Type 2 diabetes		
		Pramlintide (n=1273)	Placebo (n=420)	% difference
Symptoms	Nausea	3%	2%	1%
	Abdominal pain	1%	0%	1%
	Anorexia	1%	0%	1%
Body system	Gastrointestinal	4%	2%	2%
	Skin and Appendages	1%	0%	1%
	Vascular (extracardiac)	1%	0%	1%

*included are only symptoms with occur with a frequency of 1% or greater over placebo; individuals experiencing multiple AEs within the same category are counted once.
n=number of subjects.

The “skin and appendages” system included the following subcategories with dropouts in the pramlintide group only: cellulitis, rash, skin ulceration, increased sweating, and urticaria.

The vascular (extracardiac) system included cerebrovascular disorder (five subjects), flushing, deep thrombophlebitis and vascular disorder (one subject each), all in the pramlintide group.

The withdrawal profile emerging from the type 2 uncontrolled diabetes studies is similar in that the gastrointestinal symptoms (in particular nausea) were the most prevalent reason for subject withdrawal (2%).

5) Treatment Emergent Adverse Events

The most frequent treatment-emergent adverse events were in the gastrointestinal body system group during the long-term controlled trials of type 1 diabetes (Table 9). Hypoglycemia and fatigue were the third and the fifth most common symptoms, respectively.

Table 9: Treatment Emergent Adverse Events With a Difference in Incidence Between Pramlintide and Placebo higher than 1% (Long-term Controlled Type 1 Diabetes Trials)*

<i>Type 1 diabetes</i>			
	Pramlintide (n=1179)	Placebo (n=538)	% difference
<i>Nausea</i>	51%	17%	34%
<i>Anorexia</i>	18%	2%	16%
<i>Hypoglycemia</i>	27%	19%	8%
<i>Vomiting</i>	13%	7%	6%
<i>Fatigue</i>	7%	4%	3%

*individuals experiencing multiple AEs within the same category are counted once.
n=number of subjects.

In the type 2 diabetes studies the most common individual symptoms responsible for treatment-emergent adverse events were also gastrointestinal in nature (Table 10). However two differences are apparent: hypoglycemia is not a major factor, occurring with a frequency slightly higher (1%) over placebo control, while small differences in the incidence of central nervous system and psychiatric symptoms (e.g. headache, fatigue, dizziness, anxiety, etc.) emerge.

Table 10: Treatment Emergent Adverse Events With a Difference in Incidence Between Pramlintide and Placebo higher than 1% (Long-term Controlled Type 2 Diabetes Trials)*

<i>Type 2 diabetes</i>			
	Pramlintide (n=1273)	Placebo (n=420)	% difference
<i>Nausea</i>	24%	14%	10%
<i>Anorexia</i>	8%	3%	5%
<i>Headache</i>	12%	9%	3%
<i>Fatigue</i>	7%	4%	3%
<i>Dyspepsia</i>	6%	3%	3%
<i>Abdominal pain</i>	8%	6%	2%
<i>Vomiting</i>	7%	5%	2%
<i>Dizziness</i>	6%	4%	2%
<i>Gastroenteritis</i>	4%	2%	2%
<i>Anxiety</i>	4%	2%	2%
<i>Neuropathy</i>	3%	1%	2%
<i>Cellulitis</i>	3%	1%	2%

*individuals experiencing multiple AEs within the same category are counted once.
n=number of subjects.

A summary of the individual symptoms with an incidence 5% higher in the treatment group over background in either type 1 and type 2 diabetes is presented in Table 11:

Table 11: Treatment Emergent Adverse Events With a Difference in Incidence Between Pramlintide and Placebo of at Least 5% (Long-term Controlled Type 1 and Type 2 Diabetes Trials)*

	Type 1 diabetes			Type 2 diabetes		
	Pram	Pbo	% diff.	Pram	Pbo	% diff.
<i>Nausea</i>	51%	17%	34%	24%	14%	10%
<i>Anorexia</i>	18%	2%	16%	8%	3%	5%
<i>Hypoglycemia</i>	27%	19%	8%	28%	27%	1%
<i>Vomiting</i>	13%	7%	6%	7%	5%	2%

* individuals experiencing multiple SAEs within the same category are counted once. Pram=pramlintide. Pbo=placebo. % diff.= percent difference between pramlintide and placebo.

6) Specific Treatment Emergent Adverse Events:

Nausea:

Nausea is a central adverse event in the pramlintide trials due to the extent with which it occurs. It is the most common cause of treatment-emergent adverse events and, most importantly, the most common cause of subject withdrawal in both type 1 and type 2 diabetes studies.

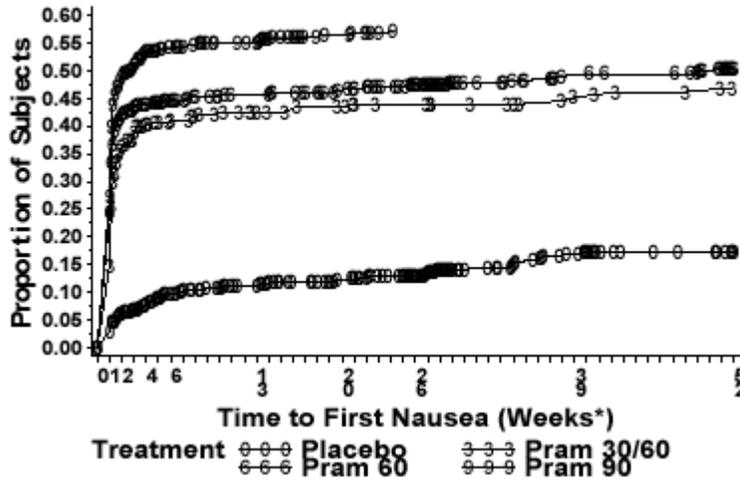
Time of occurrence and dose relationship for nausea:

In the type 1 diabetes long-term controlled trials, 601 pramlintide-treated subjects (51%) reported nausea. Of these, 552 (92%) had their first occurrence during the first four weeks of treatment. Recurrence of nausea occurred in 70% of subjects during week >4-13, 54% between weeks 13-20, 53% between weeks 26 and 39, and 49% between weeks 39 and 52.

A similar pattern of early occurrence and high recurrence was observed during the type 2 diabetes trials. 308 (24%) of all pramlintide-treated subjects reported nausea in this group. Of these, 224 (73%), had their first occurrence of nausea in the first four weeks of treatment. Recurrence rates of nausea was high among this group (60.5% during weeks >4-13, 44% during weeks >13-20, 40% during weeks >26-29, and 36% during weeks 39-52, respectively).

When the occurrence of nausea is explored as a function of time and dose for the type 1 diabetes trials (Figure 2), it becomes clear that nausea occurs early in the course of the treatment (most subjects report it within the first four weeks) and reporting incidence increases with increasing dose.

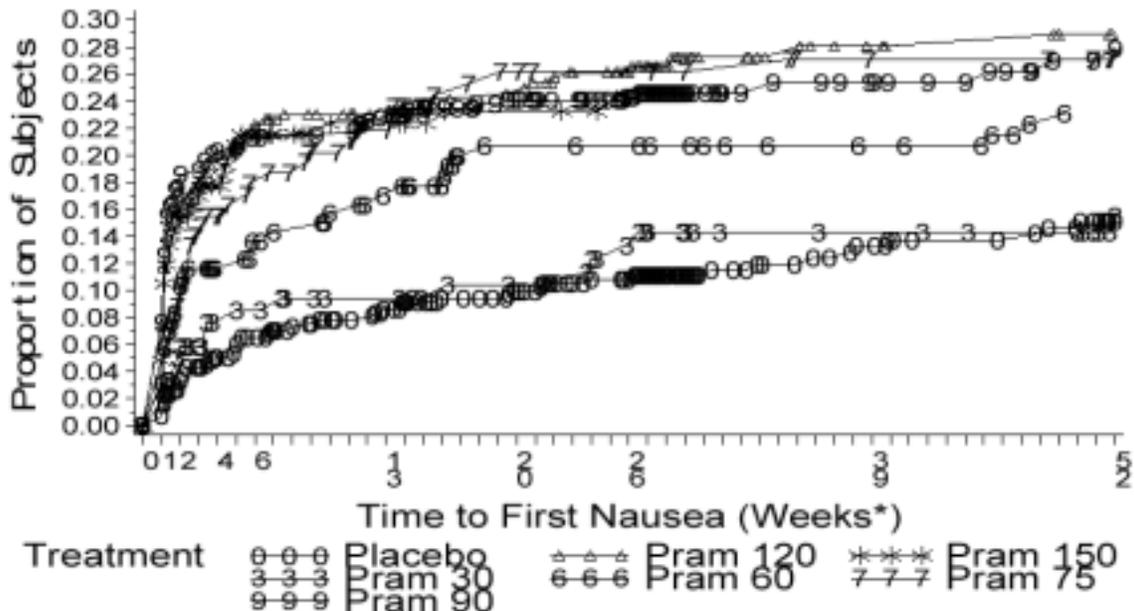
Figure 2: Cumulative Frequency Distribution of Time to First Onset of Nausea by Dose (Long-term Controlled Studies in Subjects With Type 1 Diabetes)



A similar conclusion can be drawn from the type 2 diabetes trials, i.e. nausea occurs early in the course of the treatment and reporting incidence increases with increasing dose (Figure 3).

Quantitative differences, however, are present between type 1 and type 2 diabetes subjects. While a similar proportion of subjects experience nausea in the placebo group in both type 1 and type 2 diabetes subjects, the pramlintide subjects in the type 1 trials are more sensitive to the drug (e.g. roughly twice the percentage of subjects experience it among the type 1 diabetics when compared to type 2 diabetes subjects exposed to comparable doses).

Figure 3: Cumulative Frequency Distribution of Time to First Onset of Nausea by Dose (Long-term Controlled Studies in Subjects With Type 2 Diabetes)



Since nausea is the most common reason for subject withdrawal in both type 1 and type 2 diabetes long-term trials, it is important to understand when nausea-related withdrawals occur. In all three type 1 diabetes trials the withdrawals occurred early (mostly during the first 4-6 weeks of treatment). In one of the trials (137-112) the withdrawals took place almost exclusively during the first two months, while in the other two, withdrawals occurred early (first 4-6 weeks of the trial) and were followed by a small number of withdrawals during subsequent months. A similar pattern was noted for the long-term type 2 diabetes trials except that the absolute number of dropouts was much smaller.

Hypoglycemia

Accurate analysis of incidence of severe hypoglycemia is dependent on consistent collection of data and on a uniform definition of the event. The sponsor used a definition of severe hypoglycemia that approximates the DCCT definition. It is described in the submission as “**any hypoglycemic episode which requires the assistance of another individual with the ingestion of oral carbohydrate, glucagon injection, or intravenous glucose administration**”. This definition has been applied consistently only during the long-term controlled studies in subjects with type 1 and type 2 diabetes. Therefore the hypoglycemia analysis focuses primarily on these trials: 137-121, 137-117, 137-112 (type 1 diabetes) and 137-122 and 137-123 (type 2 diabetes). The long-term study 137-111 (type 2 diabetes) was excluded by the sponsor due to inconsistent methodology in data collection.

Table 12 provides information about the overall incidence of severe hypoglycemia in the long-term controlled type 1 and type 2 diabetes trials. It can be noted that the number of subjects who experienced at least one episode of severe hypoglycemia was higher in the type 1 diabetes trials (compared to the type 2 diabetes trials) and that it was consistently higher than placebo for both types of diabetes subjects.

Table 12: Number and (%) of Subjects With at Least One Episode of Severe Hypoglycemia in Type 1 and Type 2* Long-term Diabetes Studies:

	<i>Type 1 Diabetes</i>		<i>Type 2 Diabetes</i>	
	<i>Pramlintide</i>	<i>Placebo</i>	<i>Pramlintide</i>	<i>Placebo</i>
<i>Total number of subjects</i>	1179	538	871	284
<i>Number and (%) subjects with hypoglycemia</i>	295 (25%)	96 (18%)	76 (9%)	17 (6%)

* Only studies 137-122 and 137-123 are included (study 137-111 did not capture severe hypoglycemia in a way consistent with the rest of the long-term studies). Individuals experiencing multiple AEs are counted once.

Individual subjects experienced a variable number of severe hypoglycemic events. While most of them had only a few events, some subjects had a considerable number of events (up to 128 in a placebo subject). The distribution of these events per subject is displayed in Table 13:

Table 13: Distribution of Number of Severe Hypoglycemic Events per Subjects With Events (Type 1 and Type 2 Diabetes Long-Term Trials*):

NO.EVENTS PER SUBJECT	NUMBER OF SUBJECTS WITH EVENTS- TYPE 1 DIABETES		NUMBER OF SUBJECTS WITH EVENTS- TYPE 2 DIABETES	
	Pramlintide (n=1179)	Placebo (n=538)	Pramlintide (n=871)	Placebo (n=284)
1	126	45	47	11
2	66	26	15	1
3	40	5	7	4
4	18	6	4	0
5	18	3	1	0
6	8	1	1	0
7	3	2	0	0
8	5	2	0	0
9	1	0	0	0
≥10-19	8	3	1	1
≥20	2 ⁽¹⁾	3 ⁽²⁾	0	0

* For type 1 diabetes all three long-term trials are included; for type 2 diabetes only trials 137-122 and 137-123 are included (study 137-111 did not collect severe hypoglycemia in a way consistent with the other studies).

(1) Two pramlintide subjects in trial 137-121 had 20 episodes of severe hypoglycemia each.

(2) One placebo subject in study 137-121 had 22 episodes of severe hypoglycemia. **Two placebo subjects in study 137-112 had 49 and 128 episodes of severe hypoglycemia respectively.**
n=number of subjects enrolled in the study.

When the incidence of **subjects with at least one episode of severe hypoglycemia** was analyzed during the two time periods proposed by the sponsor (first four weeks of the study and the interval thereafter to the end of the trial), one can observe a higher incidence of hypoglycemia in the treatment group compared to the placebo group across both time intervals in the type 1 diabetes trials (Table 14). The difference was roughly two fold across all studies for the first month and more modest for the remainder of the trial.

Table 14: Incidence of Severe Hypoglycemia in the Type 1 Diabetes Long-term Controlled Trials (Individual and Combined Studies, Stratified by Time; Population: Intent to Treat)*

Study	Number of Subjects		First 4 weeks Number of subjects, (%) and (%) diff.			4 Weeks to the end of the trial Number of subjects, (%) and (%) diff.		
	Pram	Pbo	Pram	Pbo	% diff	Pram	Pbo	% diff
All Studies	1179	538	154 (13%)	30 (6%)	7%	220 (19%)	85 (16%)	3%
137-121	497	154	71 (14%)	11 (7%)	7%	113 (23%)	31 (20%)	3%
137-117	439	147	61 (14%)	8 (5%)	9%	67 (15%)	18 (12%)	3%
137-112	243	237	22 (9%)	12 (5%)	4%	41 (19%)	36 (17%)	2%

* individuals experiencing multiple AEs are counted once. End of the trial is six to twelve months, depending on the trial. Pram=pramlintide; Pbo=placebo; % diff.=pramlintide-to-placebo-incidence difference.

Severe hypoglycemia had lower overall incidence and smaller treatment-to-placebo differences in the type 2 diabetes trials (Table 15). Similar to the type 1 diabetes trials, a higher incidence was noted during the first month which, to a lower degree, was present for the rest of the trial.

Figure 15: Incidence of Severe Hypoglycemia in the Type 2 Diabetes Long-term Controlled Trials (Individual and Combined Studies, Stratified by Time; Population: Intent to Treat)*

Study	Number of Subjects		First 4 weeks Number of subjects, (%) and (%) diff			4 Weeks to the end of the trial Number of subjects, (%) and (%) diff		
	Pram	Pbo	Pram	Pbo	% diff	Pram	Pbo	% diff
All Studies	871	284	23 (3%)	2 (0.7%)	2.3%	63 (7%)	16 (6%)	1%
137-122	495	161	13 (3%)	2 (1%)	2%	46 (9%)	14 (9%)	0%
137-123	376	123	9 (2%)	0 (0%)	2%	18 (5%)	2 (2%)	3%

* Only studies 137-122 and 137-123 are included (study 137-111 did not capture severe hypoglycemia in a way consistent with the rest of the long-term studies). Individuals experiencing multiple AEs are counted once. End of the trial is six to twelve months, depending on the trial. Pram=pramlintide; Pbo=placebo; %diff.=pramlintide-to-placebo-incidence difference.

When severe hypoglycemic **events** normalized per patient time are stratified by interval of occurrence for the type 1 diabetes trials, it is evident that not only the subject incidence but also the rate of events is high among pramlintide subjects during the first month of treatment (Table 16). Subsequent to the first four weeks of treatment a similar rate of events is recorded across both groups.

Note that study 137-112 was left out from this analysis due to the presence of two outliers. It is remarkable that in this study one placebo subject had no less than 128 events (this alone represents approximately 30% of all placebo-related severe hypoglycemic events reported in all three type 1 diabetes studies). Another subject (also in the placebo group) experienced 49 severe hypoglycemic events. While these two subjects represent fascinating and challenging clinical cases, their inclusion in the

analysis would likely distort the true representation of hypoglycemic events in the type 1 diabetes trials.

Table 16: Number of Severe Hypoglycemic Events per Year of Patient Time in the Long-term Controlled Type 1 Diabetes Trials (Studies 137-121 and 137-117)

Study Number	First 4 Weeks		4 Weeks to the End of Study		Whole Study	
	Pramlintide	Placebo	Pramlintide	Placebo	Pramlintide	Placebo
<i>137-121</i>	3.7	1.0	0.9	0.6	1.2	0.7
<i>137-117</i>	3.2	1.7	1	1	1.4	1.1
Combined	3.45	1.35	0.95	0.8	1.3	0.9

During the long-term type 2 diabetes trials there was a slight increase in the number of events per patient year in the first month of treatment in the pramlintide group; for the remainder of the treatment no differences were noted between drug and placebo (Table 17):

Table 17: Number of Severe Hypoglycemic Events per Year of Patient Time in the Long-term Controlled Type 2 Diabetes Trials*

Study Number	First 4 weeks		4 Weeks to the End of Study		Whole Study	
	Pramlintide	Placebo	Pramlintide	Placebo	Pramlintide	Placebo
<i>137-122</i>	0.4	0.3	0.23	0.3	0.23	0.3
<i>137-123</i>	0.4	0.0	0.2	0.1	0.2	0.1
Combined	0.45	0.2	0.2	0.2	0.24	0.21

* Only studies 137-122 and 137-123 are included (study 137-111 did not capture severe hypoglycemia in a way consistent with the rest of the long-term studies).

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 18). 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 4.3:1 pramlintide to placebo.

Table 18: Driving-related Events Associated with Hypoglycemia (Type 1 and Type 2 Diabetes, All Studies)

	Type 1 Diabetes					Type 2 Diabetes				
	Controlled				Uncontrolled	Controlled				Uncontrolled
	Short-term		Long term			Short-term		Long term		
	Pram n=172	Pbo n=43	Pram n=1179	Pbo n=538	Pram n=758	Pram n=153	Pbo n=50	Pram n=1273	Pbo n=420	Pram n=342
Events	0	0	15	2	3	0	0	1	0	0

Note:Pram=pramlintide; Pbo=placebo; n=number of subjects in the trial.

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 uncontrolled studies to seven. In the 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. A third subject who also fell during a hypoglycemic episode sustained a minor cut on the bridge of his nose.

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 coma and seizures to ataxia, vertigo, and headache, 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 a 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).

8) Safety Conclusions:

- The safety profile of pramlintide has significantly different characteristics in type 1 and type 2 diabetes subjects. This may be consistent with the fact that these two conditions have distinct pathogenic mechanisms. While there is considerable overlap in types of adverse events between these two conditions, type 2 diabetes subjects seem less susceptible to many of the adverse events noted in the type 1 diabetes subjects. Therefore one needs to be extremely cautious in extrapolating the safety data obtained from one condition to the other or even interpreting pooled safety data. The most accurate description of the drug’s safety profile for these two conditions can be found in the placebo-controlled, long-term clinical trials.

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- Nausea, albeit a non-life threatening adverse event, is a principal complaint with the use of pramlintide. It has a high rate of occurrence early during the course of the treatment, is the main reason for patient withdrawal, and has a significant recurrence rate. It affects a higher proportion of type 1 diabetes subjects.
- Severe hypoglycemia and serious adverse events associated with hypoglycemia (including driving-related events and falls) are more frequent in the pramlintide treatment groups across all type 1 long-term controlled diabetes studies. This is an issue of particular concern due to its severity and life-threatening nature. Elucidation of the extent and cause of these events needs to take into consideration that these events were not actively ascertained during the study and the actual numbers reported may be an under-representation of their true incidence.

Appendix (contains a summary of clinical pharmacology findings as they relate to the subjective recognition of hypoglycemic symptoms):

The issue of hypoglycemia-related awareness during pramlintide treatment has been explored in three placebo controlled clinical pharmacology trials: AP93-02, AP93-03 (both five day studies) and AP93-08 (fourteen day study). In all these trials the subjects (placebo- and pramlintide-treated alike) underwent an insulin-induced hypoglycemic challenge before initiating the treatment and at the end of the treatment. The pramlintide-treated group was further divided into two groups: “peak” and “trough” (each of these groups underwent the end-of trial hypoglycemic challenge at a predicted peak and trough pramlintide serum level). It should be noted that there were not concomitantly measured serum pramlintide levels (i.e. the timing of the challenge was predicted on prior pharmacokinetic information). The pramlintide dose was not always consistent between subjects within the same study due to the nature of the trial design. It varied from 250 µg to 1000 µg in study AP93-02, while in study AP93-03 it ranged between 100 µg to 800 µg. Study doses in AP93-08 were 30 µg, 100 µg, and 300 µg, respectively.

Subjective symptoms of hypoglycemia were scored at multiple timepoints during the 180 minute hypoglycemic challenge. The reporting of results was slightly different between studies. Table 19 illustrates the results of the insulin-induced hypoglycemic challenge in study AP93-02:

Table 19: Distribution of Subjects With Subjective Symptoms of Hypoglycemia During Hypoglycemic Challenge (AP93-02 Study)

	<i>Pramlintide Peak</i>			<i>Pramlintide trough</i>			<i>Placebo</i>		
	Subjects	Aware	%	Subjects	Aware	%	Subjects	Aware	%
<i>Baseline</i>	12	7	58	12	7	58	8	6	75
<i>End of trial</i>	12	3	25	12	6	50	8	5	62

A lower percentage of subjects were described as being aware of symptoms of hypoglycemia at the end of the study in the pramlintide “peak” group (25%) when compared to the “trough” pramlintide group (50%) or the placebo group (62%). Approximately half of the subjects in the pramlintide ‘peak’ group which were hypoglycemia aware at baseline lost the ability to recognize symptoms of hypoglycemia at the end of the trial.

The results of a similar insulin-induced hypoglycemic challenge done during the study AP93-03 are displayed in table 20:

Table 20: Distribution of Subjects With Subjective Symptoms of Hypoglycemia During Hypoglycemic Challenge (AP93-03 Study)

	<i>Pramlintide Peak</i>			<i>Pramlintide trough</i>			<i>Placebo</i>		
	Subjects	Aware	%	Subjects	Aware	%	Subjects	Aware	%
<i>Baseline</i>	20	19	95	12	9	75	12	10	83
<i>End of trial</i>	20	13	65	12	8	67	12	10	83

Similar to the previous study, there is an apparent decrease in the percentage of subjects who experience subjective symptoms of hypoglycemia in the pramlintide “peak” group (95% to 65%) when compared to both “trough” and placebo groups.

Despite the similarity and relative consistency of findings recorded in these two five day studies, the results did not reach statistical significance.

It should be also noted that these observations were not duplicated in a fourteen-day study (AP93-08). In this trial the assessment of feelings of hypoglycemia was given as a score (higher numbers indicate awareness; implicitly, lower values signify loss of awareness; Table 21).

Table 21: Patient Rating of Hypoglycemic Symptoms (AP93-08 Study)

	<i>Pramlintide</i>			<i>Placebo</i>
	300 µg	100 µg	30 µg	
<i>Baseline Score</i>	1.4±0.5	1.2±0.3	1.1±0.3	1.4±0.4
<i>End of Trial Score</i>	1 ±0.4	0.7±0.2	1.6±0.5	1±0.3

*± SEM values are included.

In conclusion, analysis of hypoglycemia unawareness yielded inconsistent results between the five-day and fourteen-day studies. These studies have not unequivocally established that pramlintide does not interfere with the normal recognition of hypoglycemia.

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