CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-332

Medical Review(s)

Memorandum

Date: February 28, 2005

From: Dragos Roman M.D., Medical Officer, HFD-510

Through: David Orloff, M.D., Acting Team Leader and Division Director, DMEDP

Subject: Retinopathy study of pramlintide in patients with type 1 or type 2 diabetes

To: File (NDA 21-332)

I. Background

Symlin (pramlintide acetate) is an amylinomimetic and antidiabetic agent, currently under review in the Division of Metabolic and Endocrine Drug Products (DMEDP). A potential association between pramlintide treatment and an acceleration of retinopathy progression was previously considered.[1] In subsequent communications between DMEDP and Amylin Pharmaceuticals (the pramlintide manufacturer) it was agreed, in principle, that a Phase IV retinopathy study will address this potential safety concern.

Recently the need for a retinopathy study was questioned within DMEDP since the pramlintide dose at which the potential signal of retinopathy was observed (150 μg) is in excess of the to-be-marketed pramlintide doses of 30 μg, 60 μg, and 120 μg. In this review I am summarizing the findings and conclusions formulated in the initial safety review.[2]

II. Reviewer's comments

It is the opinion of this reviewer (expressed in the initial NDA review dated September 6, 2001) that the data are not supportive of a pramlintide-induced risk of retinopathy progression. The original observations are illustrated in Table 24 of my 2001 review, reproduced below; they indicate an increased incidence of adverse events of "retinal disorders" relative to placebo in only one of nine pramlintide treatment arms (the "150 μg TID" arm of study 137-111). In two additional arms of study 137-111 and in two additional studies (137-122 and 137-123, three pramlintide arms each) the incidence of "retinal disorders" was comparable to placebo.[3] It is also important to recognize, as mentioned above, that the 150 μg pramlintide dose is not a to-be-

[1] See Approvable Letter dated October 10, 2001, in DFS.

[2] See "Original NDA Review" dated September 6, 2001 in DFS.

[3] The sponsor pointed out that the duration of disease in study 137-111 was longer in the 150 μg TID treatment group (mean, 13.3 years) compared to the other treatment groups (means of 11.3 and 11.9 years). Thus, patients in this arm may have had more time to develop this complication.

marketed dose.[4] In addition, if one compares the incidence of retinal adverse events in the 120 μg pramlintide arms of trials 137-122 and 137-123 (120 μg being the highest to-be-marketed dose and a dose closest to that of 150 μg) it is lower or the same as that of placebo in the same trials.[5] Finally and importantly, an analysis of "retinal disorder" adverse events in type 1 diabetes patients, does not indicate any difference relative to placebo.[6] This observation is important since the pathogenesis of retinopathy progression is the same in type 1 and type 2 diabetes.

Table 24 Incidence of Adverse Events Coding to Retinal Disorder in Type 2 Diabetes Long-Term Pramlintide Studies

Study Number Adverse Event	Number (%) of Patients			
137-111	**Placebo** (n=136)	**Pramlintide** **30 μg TID** (n=122)	**Pramlintide** **75 μg TID** (n=136)	**Pramlintide** **150 μg TID** (n=144)
Retinal Disorders	7 (5.1%)*	7 (5.7%)	8 (5.9%)**	15 (10.4 %)***
137-122	**Placebo** (n=161)	**Pramlintide** **90 μg BID** (n=171)	**Pramlintide** **60 μg TID** (n=158)	**Pramlintide** **120 μg BID** (n=166)
Retinal Disorders	10 (6.2%)	10 (5.8%)	6 (3.8 %)	7 (4.2 %)
137-123	**Placebo** (n=123)	**Pramlintide** **90 μg BID** (n=121)	**Pramlintide** **90 μg TID** (n=129)	**Pramlintide** **120 μg BID** (n=126)
Retinal Disorders	3 (2.4 %)	2 (1.7 %)	1 (0.8 %)	3 (2.4 %)

* Does not include one patient with an event coded as retinal hemorrhage.
** Does not include two patients with events coded as retinal hemorrhage.
*** Does not include two patients with events coded as retinal hemorrhage.
Source: ISS and Amylin AC Briefing Document Table 22.

III. Conclusion and recommended regulatory action

There is no clear evidence to suggest an increased risk of diabetic retinopathy in association with pramlintide treatment. Therefore, a Phase 4 retinopathy clinical study is not warranted at this time.

Dragos Roman M.D.
Medical Officer, HFD-510

[4] See labeling section of the February 18, 2005 pramlintide review in DFS.
[5] 4.2 % Symlin vs. 6.2 % placebo in trial 137-122; 2.4 % for both Symlin and placebo in trial 137-123.
[6] In patients with type 1 diabetes the incidence of "retinal disorder" adverse events was the same in pramlintide-treated patients and in placebo-treated patients (2 %). Similarly, for patients with type 2 diabetes the overall (i.e. across all doses) incidence of the retinal adverse events was 5 % irrespective of treatment (placebo or pramlintide).

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/s/

Dragos Roman
2/28/05 10:33:50 AM
MEDICAL OFFICER

David Orloff
2/28/05 06:04:40 PM
MEDICAL OFFICER
Concur that there is no convincing clinical signal for a risk of Symlin regarding retinal disease. No phase 4 required.

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

APPLICATION #:	21-332	**APPLICATION TYPE:**	NDA resubmission
SPONSOR:	Amylin Pharmaceuticals	PROPRIETARY NAME:	Symlin
CATEGORY OF DRUG:	Amylin analog	GENERIC NAME:	Pramlintide acetate
		ROUTE:	Injectable (subcutaneous)
MEDICAL REVIEWER:	Dragos Roman, MD	REVIEW DATE	02-18-2005
		PDUFA DATE:	03-26-2005

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
09/17/2004	09/17/2004	NDA resubmission	
	12/17/2004		
	03/01/2005		
	02/02/2005		
	02/03/2005		
	02/09/2005		
	02/11/2005		

RELATED APPLICATIONS

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review: Symlin (pramlintide acetate) is an injectable synthetic analog of human amylin. Pramlintide acetate was developed as a glucose lowering drug to be used in combination with insulin in patients with type 1 and type 2 diabetes. A New Drug Application for Symlin was originally submitted to the Agency on December 08, 2000. This is the third cycle of review for Symlin. Previous submissions were deemed deficient in that pramlintide/insulin co-administration has been associated with an increased incidence of severe hypoglycemia relative to insulin treatment alone.

In response to the requirements formulated in a second approvable letter dated December 17, 2003, the applicant identifies a patient population and a method of use that support a favorable risk-benefit ratio for Symlin in type 2 and type 1 diabetes. Specifically, when this method of use was applied to the proposed target population in an open-label clinical trial conducted in the setting of clinical diabetology practice, it was associated with a reduction in severe hypoglycemia incidence in both type 1 and type 2 diabetes patients to levels comparable to those

of insulin treatment alone. Symlin, however, carries mechanistically an intrinsic risk of severe hypoglycemia when used in combination with insulin; such risk (particularly in type 1 diabetes) should be clearly communicated in the label (Boxed Warning). Finally, although type 1 and type 2 diabetes are amylin-deficient states, Symlin is pharmacological treatment and should not be labeled as physiological replacement.

Recommended Regulatory Action: Approval

Signed: **Medical Reviewer: Dragos Roman M.D.**
Date: 12/17/2004

Medical Team Leader: _____ **Date:** _____

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EXECUTIVE SUMMARY

Pramlintide acetate (proposed commercial name: Symlin) is a synthetic 37- amino acid analog of the human hormone amylin. An injectable drug product, pramlintide has been developed as a glucose lowering agent for both type 1 and type 2 diabetes patients on insulin. Pramlintide is administered subcutaneously prior to major meals at the same time as the short/rapid acting insulin (but in a different syringe and at a different injection site than insulin). As an antidiabetic agent, pramlintide has a novel and complex mechanism of action which consists in a retardation of gastric emptying (with subsequent delay in glucose absorption and reduction in postprandial glucose elevations), reduction of glucagon secretion (limited to the postprandial period), and suppression of appetite (with subsequent weight loss).

This is the third cycle of review for Symlin. The current submission is a complete response to the December 17, 2003 approvable letter issued by the Division of Metabolic and Endocrine Drug Products, which stated that the applicant "must identify, through clinical trials, a patient population and a method of use for pramlintide where there is an acceptable risk-benefit profile (i.e. either without an increased risk of significant hypoglycemia or where there is an added benefit that clearly counterbalances any potential for increases in episodes of hypoglycemia)." In previous clinical trials pramlintide has been associated with an increased risk of severe hypoglycemia relative to insulin alone (approximately twofold). Throughout the pramlintide development program severe hypoglycemia has been the only major and consistent safety signal. [1]

In response to the requirements formulated in the December 17, 2003 approvable letter, the applicant identifies a patient population and a method of use that support a favorable risk-benefit ratio for Symlin. Specifically, the applicant has restricted the target population to patients who, despite appropriate insulin therapy, have not been able to reach optimal glycemic control and who, in addition, are treated with pramlintide under the care of health care professionals with expertise in treating diabetes.[2] The method of use is that of pramlintide titration to tolerability combined with an initial reduction of insulin (particularly bolus/short acting insulin); this method has been initially characterized in a "blinded" setting (Study 137-150, previously reviewed); when applied in an open-label fashion in the setting of clinical diabetology practice, it has been associated with a reduction in severe hypoglycemia incidence in both type 1 or type 2 diabetes to levels comparable to those of insulin alone (Study 137-155, current submission).[3] However, it is important to recognize that, when used in combination with

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[1] Pramlintide is not a hypoglycemic agent by itself; however, when used in combination with rapid/short acting insulin, by lowering the postprandial glucose levels, it favors the occurrence of insulin-induced hypoglycemia.

[2] The latter is a very important requirement for a safe treatment due to the complexity of the combined pramlintide/insulin regimen.

[3] The current submission includes interim efficacy and safety data collected from three ongoing open-label clinical trials (two extension trials and a new uncontrolled clinical trial) and a new analysis of the incidence of severe hypoglycemia across the pramlintide development program in type 1 and type 2 diabetes patients.

insulin, pramlintide carries an intrinsic risk of severe hypoglycemia; this risk, highlighted by the Agency in previous reviews and communications, is currently fully acknowledged by the applicant and is central to the proposed Boxed Warning (see the pramlintide label) and to the Risk Management Plan.[4]

A substantial body of knowledge and evidence, comprised of several clinical and mechanistic studies, has accumulated since the original Symlin NDA submission on December 8, 2000.[5] In final analysis, these data indicate a favorable risk/benefit balance for pramlintide in type 2 diabetes. In this condition, pramlintide use is associated with a mean absolute reduction in HbA1c at 6 months of approximately 0.4 % relative to placebo[6] and 0.6 % relative to baseline.[7] As obesity is a significant co-morbidity in type 2 diabetes, the weight reduction induced by pramlintide, which was observed consistently in multiple clinical trials, is highly desirable. Importantly, the risk of severe hypoglycemia during pramlintide treatment in type 2 diabetes is comparable to that of insulin alone.[8]

It is clear that the risk/benefit ratio is more favorable in type 2 diabetes than in type 1 diabetes. In type 1 diabetes the mean absolute HbA1c reduction at 6-months is lower (0.38 % relative to placebo in study 137-112[9], 0.2 % relative to baseline in study 137-155, and equivalent to insulin alone in study 137-150), obesity is less prevalent (although

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This new analysis compares the incidence of severe hypoglycemia in the clinical practice setting with that observed in the blinded clinical trials.

[4] In previous reviews the risk of severe hypoglycemia has been captured under a variety of manifestations including: serious adverse events associated with hypoglycemia, severe hypoglycemia (requiring third-party intervention), trauma/motor vehicle accidents (MVAs). It is important to recognize that unlike during previous review cycles when we did not have a clear mechanistic explanation of this adverse event, now we can point out with a large degree of comfort to the causes of severe hypoglycemia, its timing with respect to pramlintide administration, and how the risk of hypoglycemia relates to the duration of pramlintide treatment. Briefly, hypoglycemia is to be expected within the first 2-3 hours after pramlintide administration ("mealtime hypoglycemia") and the risk of hypoglycemia is higher during the first 3 months of treatment and declines subsequently (but it does not fully resolve). Consequently, particularly during the first 2-3 hours after pramlintide treatment (and particularly in type 1 diabetes), patients should not engage in activities that place themselves or others at risk such as driving a motor vehicle, operating heavy machinery, mountain climbing, etc. Simply put, if one does not perform any of these activities during 2-3 hours after a pramlintide injection the impact of severe hypoglycemia will be practically eliminated. From the standpoint of integrating pramlintide in an antidiabetic regimen, it contributes another layer of variability that works against the attempt to match the carbohydrate intake with the optimal dose of insulin, not unlike commonly known factors such as exercise, alcohol ingestion, inappropriate (excessive) insulin dosing, variations in appetite.

[5] Clinical studies: study 137-150 (see previous review in DFS), the open-label clinical trials 137-155, 137-150E, and 137-140 (this submission), and six safety updates. Mechanistic and PK/PD studies: 137-151 and 137-153 (provided important information on the effects of the anatomical injection site and timing of pramlintide administration on postprandial glucose profiles); 137-149 (studied the effects of pramlintide on food intake); 137-152 (evaluated the effect of pramlintide on the recognition of symptoms of hypoglycemia); and 137-156 (assessed pramlintide's effect on postprandial glucose fluctuations).

[6] In the phase III clinical trial 137-111 (see Dr. Robert Misbin's efficacy review of the first pramlintide submission in DFS).

[7] In the clinical practice trial 137-155, current submission.

[8] See the results of the open-label study 137-155.

[9] See Dr. Robert Misbin's efficacy review of the first pramlintide submission in DFS.

it is recognized that weight gain is an undesirable consequence of insulin treatment), and the risk of severe hypoglycemia is higher. It should be recognized that, although the mean treatment effects may not be impressive in type 1 diabetes, some patients had better individual responses than the mean responses of the cohort studied (for instance, absolute HbA1c reductions of –2.1 and weight reductions of –17.7 kg at 6 months were noted in trial 137-155). It should also be recognized that pramlintide treatment, especially in type 1 diabetes, is not simply an add-on treatment to insulin but in some patients may be an alternative regimen which achieves the same efficacy as insulin with associated weight loss and improvement in quality of life for patients who remain on trial despite initial tolerability issues and who do not see additional injections as a burden of (see study 137-150 treatment satisfaction questionnaire data).

Therefore, in that pramlintide reduces HbA1c (while having also a desirable weight loss effect in obese type 2 diabetes patients) without increasing significantly the risk of severe hypoglycemia, this reviewer recommends approval of pramlintide as an adjunct to insulin in patients with type 2 diabetes for the proposed target population (patients who fail to achieve adequate glycemic control despite optimal insulin management).

Given that pramlintide reduces HbA1c levels (albeit only moderately), reduces postprandial glucose excursions, may improve quality of life in some patients, prevents insulin-induced weight gain, and thus, offers patients with type 1 diabetes an alternative treatment regimen to insulin alone, it should be approved in patients with type 1 diabetes who fail to achieve adequate glycemic control despite optimal insulin management. This recommendation is made only in conjunction with a strong labeling indicating the potential risk of severe hypoglycemia (boxed warning included) and a robust Risk Management Plan.

Finally, it is clear that pramlintide is not replacement therapy but pharmacological treatment and this fact should be adequately reflected in the label (see labeling recommendations).

CLINICAL REVIEW

I. Background

Pramlintide acetate (proposed commercial name: Symlin) is a synthetic 37- amino acid analog of the human hormone amylin. Pramlintide, an injectable drug product, has been developed as a glucose lowering agent for both type 1 and type 2 diabetes patients on insulin. Amylin Pharmaceuticals Inc., the maker of Symlin, submitted a New Drug Application for Symlin on December 08, 2000. Following a multidisciplinary review and an evaluation of the drug's efficacy and safety profile at the July 26, 2001 Endocrinologic and Metabolic Drugs Advisory Committee Meeting, the Division issued an approvable letter on October 10, 2001. The applicant re-submitted the pramlintide NDA on June 16, 2003 and addressed satisfactorily three of the four clinical deficiencies listed in the initial action letter. From a clinical perspective, the only remaining issue was that of an increased risk of severe hypoglycemia in pramlintide/insulin treated patients, relative to patients treated with insulin alone. As a result a second approvable letter was issued on December 17, 2003. The letter stated that

"To be approved, you must identify, through clinical trials, a patient population and a method of use for pramlintide where there is an acceptable risk-benefit profile (i.e. either without an increased risk of significant hypoglycemia or where there is an added benefit that clearly counterbalances any potential for increases in episodes of hypoglycemia)."

Following several meetings, teleconferences, and discussions between the applicant and the Division, the applicant submitted on September 17, 2004 a complete response to the second approvable letter. In the complete response, which is the subject of this review, the applicant claims to have identified a patient population and a method of use that support a favorable risk-benefit ratio for Symlin. Specifically, the applicant has restricted the target population to patients who, despite appropriate insulin therapy, have not been able to reach optimal glycemic control (and who, in addition, are treated with pramlintide under the care of health care professionals with expertise in treating diabetes). The method of use is that already defined in clinical trial 137-150 (previously reviewed by the Agency); this method of use was associated with less severe hypoglycemia when pramlintide was used in an open-label fashion in the clinical practice setting (Study 137-155, reviewed in this resubmission).

This submission includes interim efficacy and safety data collected from three ongoing open-label clinical trials (studies 137-155, 137-140, and 137-150E), a new analysis of the incidence of severe hypoglycemia across the pramlintide development program in type 1 and type 2 diabetes patients, as well as the results of a mechanistic study on pramlintide-induced weight loss (Study 137-149). In addition, and importantly, the applicant submitted a revised label (which includes a boxed warning that highlights the risk of severe hypoglycemia) and updated a comprehensive Risk Minimization Plan (which includes a post-marketing observational study). The proposed indication currently reads as follows:

This review will summarize and analyze the new clinical data submitted, bring to date our understanding of the mechanism of action of pramlintide, and update the risk-benefit analysis of pramlintide in light of the substantial body of mechanistic and clinical information accumulated since the time of the previous reviews.

II. Summary of new clinical data presented in this submission

A. Open-label clinical practice Study 137-155

Study 137-155 was an open-label, clinical trial in which pramlintide was administered in the setting of clinical diabetology practice. In effect, it was an uncontrolled clinical observational study of the safety and efficacy of pramlintide, a drug whose pharmacological activity in diabetes had already been established, and whose primary risk (insulin-mediated hypoglycemia) has been identified and addressed (though not fully eradicated) by changes in the prescribed method of use. The objective of the study was to evaluate the efficacy and safety of pramlintide/insulin regimen in a "real life" clinical setting. The trial enrolled both patients with type 1 and type 2 diabetes. The administration of pramlintide and insulin followed an already established regimen in which pramlintide was titrated to tolerability while the insulin dose (primarily the bolus/short acting insulin) was initially and temporarily reduced to avoid the risk of hypoglycemia; subsequently, pramlintide was given as a fixed dose and insulin was adjusted to glycemic goal.[10] The patients enrolled in the trial were selected by their providers on the basis of their inability to achieve glycemic control[11] despite "sustained best efforts at intensive insulin therapy maintained with appropriate educational support." The investigators and the health care providers participating in the trial were described as particularly familiar and skilled in the use of insulin therapy. This trial is ongoing and the cutoff for the data presented in this submission is June 30, 2004. The trial is reviewed in detail in the Appendix.

In patients with type 1 diabetes (N=265), open-label use of pramlintide for up to 6-12 months resulted in a small mean absolute reduction in HbA1c relative to baseline (approximately - 0.2) and a mean weight reduction of approximately 2-4 kg. These efficacy results were achieved with a mean reduction in total daily insulin use of approximately 12% and a mean reduction in daily bolus/short-acting insulin use of approximately 22% at 6 months; there was almost no change in the mean daily

[10] This regimen has been successfully used in clinical trial 137-150 where, under "blinded" conditions, it reduced significantly the initial impact of pramlintide-induced nausea and decreased the incidence of pramlintide-associated severe hypoglycemia relative to the phase III clinical trials (but not relative to insulin alone).

[11] Mean baseline HbA1c was 8.0 for patients with type 1 diabetes and 8.3 for patients with type 2 diabetes.

basal/long-acting insulin use. Individual changes for all efficacy measures (HbA1c, weight) and for insulin use varied widely (range of absolute HbA1c changes at 6 months: -2.1 to +3.4; range of weight reduction at six months: -17.7 kg to +3.6 kg).[12] The safety profile associated with pramlintide in the clinical trial was comparable to that previously described.[13] The applicant does not report any motor vehicle accidents (MVAs) associated with hypoglycemia.[14]

In patients with type 2 diabetes (N=176), open-label use of pramlintide resulted in a mean absolute reduction in HbA1c at 6-months of approximately 0.6 % relative to baseline; this reduction was larger than that observed in type 1 diabetes. The weight reduction was on average 2-3 kg at 6-9 months of treatment. Individual responses for all efficacy measures (i.e. HbA1c, weight) also varied (range for absolute HbA1c changes at 6 months: -3.9 to +2.2; range of weight reduction at six months: -18.1 kg to +4.5 kg). These efficacy results were achieved with a mean reduction in total daily insulin use of approximately 7%, a mean reduction in daily bolus/short-acting insulin use of approximately 10%, and a small reduction in daily basal/long-acting insulin use (approx. 4 %) at 6 months.[15] The overall safety profile was consistent with that observed in previous clinical trials.[16] Importantly, there were no SAEs associated with hypoglycemia and only one patient withdrawal (0.6%) which listed hypoglycemia as an adverse event. The applicant does not report any MVAs for patients with type 2 diabetes enrolled in this study.

B. Study 137-150E

This study is a multicenter, open-label extension of clinical study 137-150, and includes exclusively patients with type 1 diabetes.[17] The patients enrolled in this extension study were those who completed the parent study and were compliant with the treatment regimen. They were in good glycemic control (baseline mean HbA1c of 7.6 %). The objective of the extension study was to evaluate the long-term safety profile of

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[12] Specifically, the range of insulin adjustments (in units) at 6-moths were as follows: -77.9 to + 46.3 for total daily insulin, -94.2 to +300 for daily short acting/bolus insulin, and –52.5 to + 125 for daily long acting/basal insulin.

[13] Gastrointestinal adverse events (nausea (2.6%) and vomiting (2.8%)) and hypoglycemia (1.1%) were the most frequent group of adverse events leading to patient withdrawal. The most frequent TEAEs were nausea (37%) followed by hypoglycemia (32%). Only two patients experienced hypoglycemia as a serious adverse event (0.8%).

[14] The only MVA was, reportedly, alcohol-related. Another patient (33002) had a loss of consciousness episode which occurred in the car in the parking lot without an associated accident; the patient subsequently discontinued the trial.

[15] Specifically, the range of insulin adjustments (in units) at 6-moths were as follows:-82.9 to +100 for total daily insulin, -92.7 to 233.3 for daily short acting/bolus insulin, and –61.3 to 100 for daily long acting/basal insulin.

[16] Nausea was the most frequent reason for trial discontinuation (5 patients or 2.8%).

[17] Study 137-150 has been presented to the Agency (see review in DFS). It is a randomized, placebo controlled, non-inferiority clinical study in type 1 diabetes patients that compares descriptively the safety (primarily as it relates to hypoglycemia) of a pramlintide plus insulin regimen to that of an insulin plus placebo regimen.

pramlintide and to collect data on HbA1c and weight changes in this patient population. The clinical protocol of study 137-150E was very similar to that of studies 137-150 (the parent study) and study 137-155 (summarized above). Taking into consideration background treatment regimens in the core study (i.e. pramlintide vs. placebo in trial 137-150), trial 137-150E included two groups of patients: pramlintide-naïve and pramlintide-experienced. The data cutoff for this submission is June 30, 2004. The study is summarized in detail in the Appendix.

Pramlintide-naïve patients (N=108) who were switched from an insulin plus placebo regimen to a pramlintide/insulin regimen administered in an open-label fashion, showed a minimal change in glycemic control,[18] along with a mean weight reduction at 6-12 months that was consistent with that observed in previous clinical trials (approx. 2.7 kg). These changes in efficacy variables were associated with a mean reduction in daily bolus/short-acting insulin use (22 to 26%), a small mean reduction in basal/long-acting insulin use (approximately 2-5%), and a mean reduction of total daily insulin use (14%). Pramlintide-experienced patients (N=97) who were maintained on a pramlintide/insulin regimen had a small loss of glycemic control (mean HbA1c increased by 0.2 and 0.3 at 6 and 12 months, respectively), lost some additional weight (-0.1 to -0.3 kg) and had no changes in the pattern of daily insulin use. There were no new safety signals identified in this clinical trial.[19] The applicant reported eight subjects who were involved in motor vehicle accidents for the whole study; of these, five accidents were associated with hypoglycemia, one of which was associated with bodily injury (fractured tibia; patient 23701).[20]

C. Study 137-140

This study is an ongoing open-label study of pramlintide use in subjects with type 1 or 2 diabetes mellitus using insulin. The study includes subjects who were originally enrolled in the initial phase III clinical trials. The data cutoff for this safety analysis is April 30, 2004. This submission includes only a safety update. An analysis of the 87 patients with type 1 diabetes and 52 patients with type 2 diabetes did not reveal any new safety signals.[21] No MVAs were reported in either patient population.

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[18] Absolute mean HbA1c increased by approximately 0.1 % at 6-12 months.

[19] For pramlintide-naïve patients hypoglycemia (2.8%), ketosis (2.8%), coronary artery disorder (1.9%), and inflicted injury (1.9%) were the most frequent SAEs. The most common adverse event leading to withdrawal was nausea (6.5%) and the most common TEAEs were hypoglycemia (85%), nausea (44.4%), URI (28.7%), inflicted injury (13 %) and headache (9.3%). For pramlintide-experienced patients the most common adverse event leading to withdrawal was hypoglycemia (2.1%). The most common TEAEs were hypoglycemia (93.5%), nausea (25.8%), URI (29.9 %), inflicted injury 16.5%) and UTI (10.3 %). The most frequent SAEs were ketosis (3.1%), syncope (3.1%) hypoglycemia (2.1%). The incidence of SAEs was similar between the two cohorts.

[20] See "Analysis of severe hypoglycemia" section for further discussion.

[21] In type 1 diabetes patients, the most common TEAEs were nausea (43%), hypoglycemia (35%), and inflicted injury (14%). As seen in other type 1 diabetes trials several patients had severe hypoglycemia (8 SAEs, 2 patient withdrawals, 14 overall adverse events who met the definition of "assisted" hypoglycemia). Only one of the "inflicted injury" AE was associated with hypoglycemia. No MVAs were reported. In type 2 diabetes patients there were no SAEs, patient withdrawals, injuries, or MVAs associated with hypoglycemia.

D. Study 137-149

This was a single center, randomized, double-blind, placebo-controlled, cross-over study whose primary objective was to evaluate the acute effect of pramlintide on satiety and food intake. The patient population consisted of normal-weight and obese non-diabetic subjects, and insulin-treated subjects with type 1 and type 2 diabetes (15 subjects for each category, 60 subjects overall). The subjects were given pramlintide and underwent a standardized meal test. The pramlintide doses were consistent with the to-be-labeled doses. This was the first clinical study that evaluated and clarified the mechanism(s) underlying pramlintide's weight loss effect. Following a single dose of pramlintide given 1 hour prior to the meal, total energy intake at a buffet meal was reduced by ~23% and ~21%, compared with placebo, in patients with type 2 and type 1 diabetes, respectively. These observations were statistically significant for the 11 patients with type 2 diabetes ($p=0.0088$) and showed a trend toward statistical significance for a group of 6 patients with type 1 diabetes ($p=0.0170$). Based on hunger and fullness ratings collected during the trial, the applicant proposes that the effect of pramlintide on food intake reduction may be attributable to increased sensations of fullness independent of nausea. There were no adverse events of hypoglycemia in this clinical trial.

III. Analysis of severe hypoglycemia across the clinical trials

In this submission the applicant presents a new analysis of severe hypoglycemia; this analysis integrates data for the first 6 months of pramlintide treatment across clinical trials. The choice of this time interval is appropriate in that it allows inclusion of data collected in the original phase III clinical trials (which lasted 6-12 months), trial 137-150 (a 6-month trial) and clinical trials 137-150E and 137-155, which are ongoing and include large cohorts with 6 months safety and efficacy data. This analysis presents the data for two 3-month intervals: the "adjustment" period (Months 0-3) in which both the pramlintide and insulin doses undergo significant changes and the "steady-state" period (Months >3 to 6) when both insulin and pramlintide reach a stable dose regimen.[22]

This new analysis presents the previously reported severe ("assisted") hypoglycemia under the name of " patient-reported hypoglycemia." It focuses, however, on a subgroup of hypoglycemic events within the larger "patient-reported" severe hypoglycemia category named "medically-assisted severe hypoglycemia." This new definition attempts to capture hypoglycemia in an objective way.[23] Specifically, it includes severe hypoglycemic events that were associated with glucagon or IV glucose administration,

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[22] This partition of the time on-trial reflects the observation made during study 137-150 that the sharpest increase in severe hypoglycemia occurred in the first 3 months of pramlintide treatment, in particular at the time when insulin titration to glycemic goal is initiated. Study 137-150 is particularly important since it has established a method of pramlintide treatment initiation that addressed successfully many of the criticisms previously raised by the Division and several members of the 2001 Metabolic Drugs Advisory Committee.

[23] In this new definition the applicant attempts to separate events in which the patient "requested assistance but did not absolutely require assistance in order to adequately treat the event."

hospitalization, paramedic assistance, emergency room visits, loss of consciousness precluding treatment with oral carbohydrate, seizures, motor vehicle accidents, as well as serious adverse events reported by the investigator as severe hypoglycemia. The results of this new analysis will be presented separately for type 1 and type 2 diabetes as the safety profile of pramlintide in these two conditions showed quantitative differences in the original phase III clinical trials.

2.5.1 Type 1 diabetes

The data on patient-reported hypoglycemia for Months 0-3 of treatment are consistent with previous analyses that indicated a twofold increase in risk of severe hypoglycemia for the pramlintide/insulin regimen relative to insulin alone during the original phase III trials and trial 137-150 (Table 1). The results of the open-label, clinical practice study 137-155 indicate a reduction of the incidence and event rate of patient-reported hypoglycemia to a level comparable to that observed with insulin alone in study 137-150 and below that observed in the original phase III clinical trials. For paramlintide-naïve patients started on pramlintide in study 137-150E, the incidence and the event rate of severe hypoglycemia were somewhere between those reported in the clinical practice trial 137-155 and those of clinical trial 137-150 (see Pram/Pbo column in Table 1). It is important to recognize that this 137-150E cohort started pramlintide treatment with a lower HbA1c (7.6% vs. 8.1% in the other trials), and was, thus, at higher risk of hypoglycemia.

The observations made for the medically-reported hypoglycemia are consistent with those made for the patient-reported category in that the open-label use of pramlintide in the clinical practice study 137-155 was associated with a reduction in hypoglycemia risk to a level similar to that of patients treated with insulin alone in study 137-150. Similar to aforementioned observations, open-label pramlintide treatment in a patient cohort with lower baseline HbA1c (pramlintide-naïve patients in study 137-150E) resulted in a higher risk of medically-related hypoglycemia relative to patient cohorts with higher baseline HbA1c in trials 137-150 and 137-155; it was however, below that recorded in pramlintide-treated patients in the original phase III clinical trials.

Table 1: Severe hypoglycemia across the type 1 diabetes clinical trials Months 0-3 (ITT)

Analysis	Blinded Trials				Open-label Trials		
	Phase III Trials		Trial 137-150		137-150 Extension		137-155
	Placebo	Pram.	Placebo	Pram	Pram/Pbo	Pram/Pram	Pram
Patient-Reported Severe Hypoglycemia							
Incidence	10.8 %	16.8 %	6.1 %	13.5 %	10.2 %	5.2 %	5.7 %
Event Rate	1.33	1.55	0.28	0.69	0.60	0.25	0.29
Medically-Assisted Severe Hypoglycemia							
Incidence	3.3	7.3	2.0	3.4	6.5	1.0	2.3
Event Rate	0.19	0.50	0.08	0.14	0.28	0.04	0.10

Source: Figures 21 and 22, current submission.
Event rate = event rate/patient year.
Pram = pramlintide. Pram/Pbo = Pramlintide during extension study and Placebo during the controlled phase of the trial.
Pram/Pram = Pramlintide during both the extension study and during the controlled phase of the trial.

In response to the second approvable letter, the applicant has proposed that pramlintide alters the dynamics of insulin administration in such a fundamental way that blinded studies may not be the best method for investigating pramlintide use.[24] To this end, the applicant proposes that the reduction in incidence of severe hypoglycemia in the clinical practice, uncontrolled, open-label study 137-155 supports this argument. If this were to be the case, one would expect to see a change in the pattern of insulin use in patients treated with pramlintide when the blinded trials and the open-label trials are compared. Such an analysis is presented by this reviewer in Table 2. This descriptive comparison of the pattern of insulin use in the blinded and the open-label clinical trials indicates that, when the investigator and the patient are blinded to therapy, there is a tendency to use more basal/long-acting insulin (see pramlintide and placebo groups in study 137-150); in contrast, when pramlintide is used in an open-label fashion (studies 137-150E and 137-155) the mean basal/long-acting insulin is almost unchanged. This observation is consistent with the current interpretation of the mechanism of action of pramlintide.[25] Table 2 integrates the insulin use data with the efficacy and safety information.

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[24] See also the Agency's Minutes to the July 21, 2004 meeting with the applicant, as well as the September 8, 2004 request by Amylin Pharmaceuticals Inc. to amend the Agency's Minutes. In the complete response the applicant states that "...it is unreasonable and unsafe to study a new insulin in a blinded design, the same can be said of an agent such as pramlintide, which spares insulin dose (functionally a 23% "short-acting insulin equivalent" [...]) and disrupts both the usual food-intake quantities and the underlying dynamics of the insulin regimen. Adding pramlintide in a blinded fashion to the usual intensive insulin therapy regimen is a major disruption of the usual, and thus fraught with untoward consequences such as hypoglycemia resulting from inappropriate insulin dosing (insufficient reduction of dose), less than optimal timing of insulin administration, and the inability to alter insulin regimens (study protocol deviation).

In fact, one can argue that the proper control arm for a blinded study with pramlintide added to intensive insulin therapy would not be placebo added to pre-existing intensive insulin therapy, but rather an equally disruptive blinded add-on therapy (active control) such as a replacement of the usual preprandial insulin with an equivalent dose of a novel insulin exhibiting different pharmacokinetics, in addition to being an appetite suppressant. This trial would be impossible and unethical to conduct. The blinded study approach for pramlintide is a major factor that has made the regulatory development of pramlintide, as neither an insulin nor an oral agent, both difficult and trail-blazing. Like novel insulins or insulin pumps, the safe and efficacious use of a novel control variable like pramlintide, when added to insulin, can best be gleaned in a clinical practice setting when neither the patient nor physician is blind."

[25] See in Appendix an updated summary of pramlintide's mechanisms of action. Also note that, although Table 2 presents efficacy and insulin use data at 6 months, while the safety data is for the Month 0-3 interval, the pattern of insulin changes at 3 months was similar to that at six months. For blinded study 137-150, at 3 months, in pramlintide-treated patients the bolus/short acting insulin was reduced by -21.5 ± 41.8 and the basal/long acting insulin was increased by 8.2 ± 43.6. For study 137-155, in pramlintide-treated patients with type 1 diabetes, at 3 months, the bolus/short acting insulin was reduced by -25.71 ± 30.96 % and the basal/long acting insulin was minimally changed at -3.34 ± 17.36 %. For study 137-150E, in pramlintide naive patients, at 3 months, the bolus/short acting insulin was reduced by -24.5 ± 31.7, while the basal/long acting insulin was minimally reduced by -2.8 ± 19.4.

Table 2: Integrated efficacy data for the 6 month timepoint and severe hypoglycemia for Months 0-3 across blinded and open-label safety trials

Variable	Blinded-study 137-150		Open label studies	
			137-150E	137-155
	Placebo* N=147	Pramlintide N=148	Pramlintide# N=108	Pramlintide N=265
Demographics				
Baseline HbA1c	8.1 (0.8)	8.1 (0.8)	7.6 (0.8)	8.0 (1.07)
Baseline total daily insulin use (units)	56.6 (28.9)	56.0 (28.1)	58.4 (33.0)	46.8 (24.31)
Baseline weight (kg)	80.9 (17.0)	81.4 (16.9)	83.5 (18.2)	81.7 (17.48)
Baseline BMI (kg/m^2)	27.8 (4.8)	27.7 (4.6)	28.4 (5.0)	28.6 (5.28)
Efficacy				
HbA1c change	-0.5 (0.9)	-0.4 (0.9)	0.1 (0.8)	-0.18 (0.86)
Weight change (kg)	1.25 (0.24)	-1.33 (0.31)	-2.8 (3.3)	-3.02 (3.68)
Total daily insulin: % change from baseline	1.3 %	-11.7%	-13.9 (15.4)	-12.02 (18.39)
Short-acting insulin: % change from baseline	-2.3 (35.8)	-22.8 (39.1)	-26.1 (34.7)	-21.68 (38.14)
Long-acting insulin: % change from baseline	19.7 (71.3)	12.2 (58.3)	- 2.1 (21.2)	- 0.35 (21.38)
Safety				
Patient-reported severe hypoglycemia (incidence)	6.1%	13.5%	10.2%	5.7%
Patient-reported severe hypoglycemia (events)	0.28	0.69	0.60	0.29
Medically-assisted severe hypoglycemia (incidence)	2.0%	3.4%	6.5%	2.3%
Medically-assisted severe hypoglycemia (events)	0.08	0.14	0.28	0.10

* Placebo means insulin plus placebo injections

Placebo in blinded study 137-150 followed by pramlintide in the extension phase.

Table 3 summarizes the information on severe hypoglycemia for months > 3-6 of treatment. This represents a period when the major pramlintide/ insulin adjustments have already been made. The incidence and event rate of severe hypoglycemia in the clinical practice trial 137-155 are lower than those observed with placebo (i.e. insulin plus placebo) under "blinded" conditions in study 137-150 and during the initial phase 3 trials. Observations made in trial 137-150E are consistent with prior observations in that that the risk of severe hypoglycemia is reduced after the "adjustment" period (see the "Pram/Pbo" column in Table 3 and the Pram/Pram column in Table 1) but not completely eliminated (see the "Pram/Pram" column in Table 3).

Table 3: Severe hypoglycemia across the type 1 diabetes clinical trials Months >3-6 (ITT)

Analysis	Blinded Trials				Open-label Trials		
	Phase III Trials		Trial 137-150		137-150 Extension		137-155
	Placebo	Pram.	Placebo	Pram	Pram/Pbo	Pram/Pram	Pram
Patient-Reported Severe Hypoglycemia							
Incidence	8.7 %	11.1 %	5.8 %	10.5 %	5.7 %	6.5 %	3.8 %
Event Rate	1.06	0.82	0.3	0.49	0.24	0.31	0.16
Medically-Assisted Severe Hypoglycemia							
Incidence	4.3 %	5.2 %	2.9 %	4.5 %	2.3 %	4.3 %	0.9 %
Event Rate	0.24	0.27	0.15	0.20	0.09	0.22	0.04

Source: Figures 21 and 22, current submission.

Event rate = event rate/patient year.

Pram = pramlintide. Pram/Pbo = Pramlintide during extension study and Placebo during the controlled phase of the trial.

Pram/Pram = Pramlintide during both the extension study and during the controlled phase of the trial.

2.5.2 Type 2 diabetes

The phase III clinical trials showed a lower incidence of severe hypoglycemia in patients with type 2 diabetes relative to type 1 diabetes patients during both the "adjustment" and "steady-state" periods.[26] In addition, as illustrated in Table 4, a historical comparison between trial 135-155 (open-label pramlintide use) and the original phase III trials (blinded pramlintide use) shows a reduction in both the incidence and event rate of severe hypoglycemia below that noticed with insulin alone. This observation applies to both periods analyzed (Months 0-3 and Months>3-6).

Table 4: Severe hypoglycemia across the type 2 diabetes clinical trials Months 0-3 and Month>3-6 (ITT)

Analysis	0-3 Months			>3-6 Months		
	Phase III Blinded Trials		Open-label (137-155)	Phase III Blinded Trials		Open-label (137-155)
	Placebo	Pram	Pram	Placebo	Pram	Pram
Patient-Reported Severe Hypoglycemia						
Incidence	2.1 %	8.2 %	0.6 %	2.4 %	4.7 %	0.7 %
Event Rate	0.24	0.45	0.05	0.13	0.39	0.03
Medically-Assisted Severe Hypoglycemia						
Incidence	0.7 %	1.7 %	0.6 %	1.2 %	0.4 %	0.7 %
Event Rate	0.06	0.09	0.05	0.07	0.02	0.03

Source: Figures 15 and 16, current submission.
Event rate = event rate/patient year.
Pram = pramlintide.

IV. Updated risk-benefit analysis of pramlintide use in type 2 and type 1 diabetes

The pramlintide development program has spanned several "generations" of clinical studies beginning with the original phase III clinical studies in patients with type 1 and type 2 diabetes,[27] the titration study 137-150,[28] and the open-label clinical trials (137-155, 137-150E, and 137-140). In addition, several studies have provided important information on the effects of the anatomical site and timing of pramlintide administration on its PK/PD characteristics (studies 137-151 and 137-153), on the effects of pramlintide on food intake (study 137-149), on the recognition of symptoms of hypoglycemia during pramlintide use (study 137-152), and on pramlintide's effect on postprandial glucose fluctuations (study 137-156). All these studies have expanded our understanding of the mechanisms of action of pramlintide, have defined a safer method of treatment initiation

[26] During the initial phase III clinical trials the incidence of patient-reported hypoglycemia for months 0-3 was 8.2 % (type 2 diabetes) vs. 16.8 % (type 1 diabetes); medically-assisted severe hypoglycemia for months 0-3 was 1.7 % (type 2 diabetes) vs. 7.3 % (type 1 diabetes). For month >3-6 the incidence of patient-reported severe hypoglycemia was 4.7 % (type 2 diabetes) vs. 11.1 % (type 1 diabetes); medically-assisted severe hypoglycemia for months >3-6 was 0.4 % (type 2) vs. 5.2 % (type 1).
[27] See previous reviews in DFS.
[28] See previous review in DFS.

(study 137-150), and more recently have provided evidence indicating a different "behavior" of the drug under "blinded" investigational conditions and open-label conditions of clinical practice use. Most importantly, the collective knowledge derived from the above-mentioned mechanistic and clinical studies has impacted our understanding of the safety signals identified in the original phase III clinical trials, primarily severe hypoglycemia.[29] We can point out with a large degree of comfort to the causes of severe hypoglycemia, its timing with respect to pramlintide administration, and how the risk of hypoglycemia relates to the duration of pramlintide treatment. In this submission, the applicant has provided two pieces of information that impact favorably the risk-benefit balance for pramlintide.

Firstly, information accumulated in the open-label, uncontrolled, clinical practice study 137-155 supports the applicant's claim that open-label use of pramlintide may indeed reduce the incidence of severe hypoglycemia relative to its use under "blinded" conditions. This observation is supported by the fact that the patterns of basal/long acting insulin use were different when pramlintide was given under "blinded' and open-label circumstances.

Secondly, the applicant has limited the target population to patients who cannot achieve glycemic control with insulin alone. This is in recognition of the fact that pramlintide treatment is not appropriate for all patients with diabetes (in particular not for all patients with type 1 diabetes) due to its complex interactions with insulin dosing and its risk of severe hyperglycemia discussed above. In recognition of these facts the applicant has identified a restricted patient population (in essence the patient population of trials 137-155 and 137-150).

It is also to be recognized that an intrinsic risk of severe hypoglycemia remains when pramlintide is given together with insulin. In simple terms, when administered in addition to insulin (in particular to patients with type 1 diabetes), pramlintide adds another layer of variability that works against the attempt to match the carbohydrate intake with the optimal dose of insulin, not unlike commonly known factors such as exercise, alcohol ingestion, inappropriate (excessive) insulin dosing, variations in appetite. However, this risk can be reduced (and the risk-benefit balance can be improved) with the following measures:

- placing pramlintide management in the hands of experienced diabetes teams with appropriate patient support as proposed in the applicant's Risk Management Plan[30]
- warning clearly about the potential risk of hypoglycemia; this should be accomplished, as proposed, by a boxed warning (among others) that should state clearly the safety information that we have gleaned in the clinical trials [31]

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[29] Pramlintide is not itself a hypoglycemic agent. Hypoglycemia occurs when pramlintide is used in a combination regimen with insulin.

[30] The revised RMP includes, among others, limited promotion, a health care provider education program, a patient education program, a postmarketing surveillance study, a nationwide Call Center functioning around the clock.

[31] The boxed warning should make clear that hypoglycemia is to be expected within the first 2-3 hours after pramlintide administration ("mealtime hypoglycemia"), particularly in type 1 diabetes, and that patients should not engage in activities that place themselves or others at risk (driving a motor vehicle, operating

- restricting the indication to patients who cannot achieve desired glycemic goals despite optimal insulin therapy
- recognizing the need to individualize the treatment (as indicated by the range of responses in study 137-155 some patients may respond substantially with respect to HbA1c and weight reductions while others do not now show any benefit).

It is clear that the risk/benefit ratio is more favorable in type 2 relative to type 1 diabetes. In type 2 diabetes there is a larger mean absolute reduction of HbA1c (0.4 % relative to placebo in the phase III clinical trial 137-111[32] and 0.6 % relative to baseline in clinical practice trial 137-155), obesity is a significant co-morbidity as is the need for weight reduction, and there is a lower risk of severe hypoglycemia (which in the open-label study 137-155 is comparable to that of insulin alone). In contrast, in type 1 diabetes the absolute Hb A1c reduction is lower (0.38 % relative to placebo in study 137-112[33] and 0.2 % relative to baseline in study 137-155), the need for weight reduction is less than in type 2 diabetes (although it is recognized that weight gain is an undesirable consequence of insulin treatment), and the risk of severe hypoglycemia is higher. It should be recognized that, although the mean treatment effects may not be impressive in type 1 diabetes, some individual patients had better responses than the mean responses (for instance, absolute HbA1c reductions of –2.1 and weight reductions of –17.7 kg at 6 months were noted in trial 137-155). It should also be recognized that pramlintide treatment, especially in type 1 diabetes, is not simply an add-on treatment to insulin but in some patients may be an alternative regimen which achieves the same efficacy as insulin with associated weight loss and improvement in quality of life for patients who remain on trial and are not affected by the additional injections (see study 137-150 results).[34]

Additionally, and importantly, it is also to be expected that sole approval of pramlintide in type 2 diabetes (a desirable course of action based on the above-mentioned risk/benefit profile in this patient population) will likely be associated with off-label use of the drug in type 1 diabetes patients. There is a significant body of literature published on the efficacy of the drug in type 1 diabetes which mentions little of the complexity of a pramlintide/insulin regimen, as we understand it today.[35] There is, as well, a sense of

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heavy machinery, mountain climbing, etc). Simply put, if one does not perform any of these activities during 2-3 hours after a pramlintide injection the impact of severe hypoglycemia will be practically eliminated.

[32] See Dr. Robert Misbin's efficacy review of the first pramlintide submission in DFS.

[33] See Dr. Robert Misbin's efficacy review of the first pramlintide submission in DFS.

[34] Treatment satisfaction was evaluated prospectively in study 137-150 (and also in studies 137-150E and 137-155) in a non-validated 14-item satisfaction questionnaire. In study 137-150 (placebo-controlled) pramlintide-treated patients perceived greater improvements in glucose, weight, and appetite control, compared with placebo-treated patients ($p<0.001$). Pramlintide-treated patients also reported improvements in their ability to function at home, work or school, how they felt overall, confidence in self-management (all $p\leq0.001$), and reduction in "some worries" about having diabetes ($p = 0.003$). In addition, pramlintide-treated patients indicated that the benefits of pramlintide outweighed the need for additional injections ($p<0.001$). Pramlintide-treated patients were also aware of more side effects ($p=0.002$).

[35] R.E. Ratner et al.: "Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial." Diab. Med. 21, 1204-1212 (2004).

anticipation in the diabetes community as pramlintide would be the only drug, other than insulin, that could be used in patients with type 1 diabetes since the introduction of insulin itself. There is the risk that patients will see pramlintide therapy as pure replacement therapy and will not understand that it is in fact pharmacological treatment and, to a large extent, as mentioned above, not a simple add-on treatment to insulin but rather a component of novel combination drug therapeutic regimen. As the dose in type 2 diabetes is substantially higher than in type 1 diabetes and the tolerability to the drug is worse in type 1 patients, off label pramlintide use could endanger patients; such a risk is likely to be reduced by appropriate labeling.

V. Recommendations

4.1 Type 2 diabetes

In that pramlintide reduces HbA1c (while having also a desirable weight loss effect in obese type 2 diabetes patients) without increasing significantly the risk of severe hypoglycemia, this reviewer recommends approval of pramlintide as an adjunct to insulin in patients with type 2 diabetes for the proposed target population (patients who fail to achieve adequate glycemic control despite optimal insulin management).

4.2 Type 1 diabetes

Given that pramlintide reduces HbA1c levels (albeit to a modest degree), reduces postprandial glucose excursions, may improve quality of life in patients who remain on treatment, prevents insulin-induced weight gain, and thus, offers patients with type 1 diabetes an alternative treatment regimen to insulin alone, it should be approved in patients with type 1 diabetes who fail to achieve adequate glycemic control despite optimal insulin management. This recommendation is made only in conjunction with a strong labeling of the potential risk of severe hypoglycemia (boxed warning included, as previously discussed) and a robust Risk Management Plan.

Hollander PA et al.: "Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes. A 1-year randomized controlled trial." Diabetes Care 26: 784-790, 2003.

APPENDIX

VI. Study 137-155

A. Study design and objectives

This open-label multicenter clinical trial evaluated the "clinical utility" and the safety of pramlintide treatment in subjects with type 1 and type 2 diabetes who are failed to achieve glycemic control with insulin alone[36]. Clinical utility was defined as changes in HbA1c, seven-point glucose profile, body weight, and insulin use. During study 137-155 pramlintide was administered under conditions of actual clinical practice. The investigators and the health care providers participating in the trial were particularly familiar and skilled in the use of insulin therapy. The patients were selected by these providers on the basis of failing to achieve glycemic control (baseline HbA1c was 7 to 11%, inclusive) despite "sustained best efforts at intensive insulin therapy maintained with appropriate educational support." This trial is ongoing and the cutoff for this analysis is June 30, 2004.

The treatment regimen in type 1 diabetes patients followed the same general lines established in the clinical study 137-150.[37] Specifically, pramlintide was titrated based on tolerability (mostly gastrointestinal adverse events) up to a predefined maintenance dose of 30 μg or 60 μg in type 1 diabetes patients.[38] Once a maintenance dose was reached and tolerated, it was continued for the duration of the clinical trial. The background insulin dose (primarily the preprandial short-acting insulin dose) was reduced temporarily during the pramlintide titration phase by ~30% to 50% in order to reduce the risk of hypoglycemia and was adjusted at the discretion of the investigator once a pramlintide maintenance dose was reached. Insulin was titrated to glycemic goal (target HbA_{1c}<7.0%). The guidance provided was flexibly followed from site to site. Subjects had frequent access to clinical trial pharmacists and to certified diabetes educators for guidance on how to implement the new pramlintide/insulin regimen. The study design for patients with type 1 diabetes is summarized in applicant's table, bellow:

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[36] The formal title of this study is: "A Phase 3B, Multicenter, Open-Label Study Investigating the Clinical Utility and Safety of Pramlintide in Subjects With Type 1 and Type 2 Diabetes Mellitus Who Have Not Achieved Glycemic Targets With Insulin Therapy."

[37] This study has been reviewed by this reviewer in detail (see DFS review).

[38] For type 1 subjects, pramlintide was administered subcutaneously immediately prior to meals, TID or QID, depending on whether the subject's typical meal pattern included a snack containing ≥30 grams of carbohydrate.

Study Design for Subjects With Type 1 Diabetes

Pramlintide Initiation Period				Pramlintide Maintenance Period
Progressive Pramlintide Dose Escalation Insulin Dose Reduction				Pramlintide Dose Maintenance Ongoing Insulin Dose Adjustment
Level 1	Level 2	Level 3	Level 4	
			60 µg	60 µg
		45 µg		
	30 µg	30 µg[3]	30 µg	30 µg[4]
15 µg	15 µg[2]			

[2]Subjects who experience repeated (occurring on 3 consecutive days) CSN should remain on the initial dose of pramlintide (15 µg) until CSN symptoms abate. When CSN symptoms have abated, these subjects should increase to pramlintide 30 µg and remain at this dose level for the remainder of the study.
[3]Subjects who experience repeated CSN symptoms during Level 2 (30 µg) should remain on pramlintide 30 µg for the remainder of the study. Subjects experiencing repeated CSN symptoms during Level 3 (45 µg) or Level 4 (60 µg) should decrease to pramlintide 30 µg for the remainder of the study.
[4]Subjects who experience repeated CSN symptoms during the pramlintide maintenance period, which are deemed clinically significant by the investigator and likely related to study medication, should decrease to pramlintide 30 µg. If CSN subsides after decreasing to pramlintide 30 µg, the decision to escalate back to 60 µg should be based on investigator discretion.
Note: If CSN symptoms persist for >2 weeks at any dose level, the sponsor should be contacted to evaluate the subject's continued participation in the study.

In patients with type 2 diabetes the pramlintide dose was constant during the whole trial (i.e. there was no pramlintide titration period)[39]. Insulin doses (primarily preprandial doses of short-acting insulin) were reduced during the initiation of pramlintide treatment in order to reduce the risk of hypoglycemia. Subjects using oral antidiabetes agents in addition to insulin had to maintain a constant dose of their oral agent(s) throughout the study. Subjects were allowed to adjust the insulin dose during the pramlintide initiation phase if they did not have gastrointestinal symptoms (nausea, decreased appetite) with the goal of reaching desired glycemic targets (HbA_{1c}<7.0%). If they displayed gastrointestinal adverse events, further insulin adjustments were left at the discretion of the investigator. The study design for patients with type 2 diabetes is summarized in applicant's table below:

Study Design for Subjects With Type 2 Diabetes

Insulin Dose Reduction	Ongoing Insulin Dose Adjustment*
120 µg	120 µg
Initiation of Pramlintide	**Pramlintide Maintenance**

*Subjects who have not experienced repeated (occurring on 3 consecutive days) CSN should subsequently adjust their insulin doses, both mealtime and basal components, based upon self-monitored blood glucose concentrations in the pursuit of recommended glycemic targets. Subjects who do experience repeated CSN should adjust insulin doses when deemed appropriate by the investigator and CDE.

Approximately 1600 adult patients were to be enrolled in the study. Subjects had to be euthyroid, competent to participate in a clinical trial, had to have HbA_{1c} between 7.0% and 11.0% at screening, and, if females of reproductive age, had to agree to an appropriate method of contraception. Patients were excluded for pregnancy, cardiac disease, untreated or unstable hypertension, evidence of hepatic, renal, or malignant disease, use of any antiobesity drug.

The study was planned to last over 6 months or "until pramlintide is commercially available." The primary endpoints of the study are:

- change in HbA_{1c} from baseline to the 12-week visit
- change in body weight from baseline to the 12-week visit

[39] For type 2 subjects, pramlintide was administered SC immediately prior to meals, BID or TID depending on the subject's typical meal pattern.

- "data on the baseline subject profile defined by current insulin regimen and assessment of the clinical management unmet needs"

The secondary endpoints of the study are:

- change in body weight from baseline to all subsequent visits
- percent change in total daily insulin from baseline to all subsequent visits
- questionnaire data on study healthcare professional's and subject's assessments of their experience with pramlintide treatment
- data on the seven-point glucose profiles

The data on all endpoints were to be summarized descriptively. The analysis populations were the intent-to-treat (ITT) population (defined as all subjects enrolled who have received any pramlintide) and the evaluable population (defined as all ITT subjects who have HbA_{1c} measured at baseline and at the 12-week visit). The protocol was amended once (January 29, 2003). This amendment reduced the number of patients enrolled from 1600 to 400 and added one more secondary endpoint: change in HbA1c at visits subsequent to Week 12 (i.e. Month 6 and Month12); because some patients already had the 6 month assessment prior to this amendment, not all patients completing 6 months of pramlintide therapy in Study 137-155 have a HbA1c measurement. The data presented in this submission has a cutoff date of June 30, 2004.

B. Subject disposition

Subject disposition by type of diabetes is presented in Table 5. The most frequent reasons for patient withdrawal were "withdrawal of consent", followed by "adverse events" and "investigator decision."

Table 5: Subject disposition (ITT Population)

Disposition	Type 1 Diabetes (N=265)	Type 2 Diabetes (N=176)
Intent-to-Treat (ITT)*	265 (100.0%)	176 (100.0%)
Withdrew	91 (34.3%)	60 (34.1%)
Withdrawal of consent	56 (21.1%)	20 (11.4%)
Adverse Event	21 (7.9%)	19 (10.8%)
Investigator Decision	7 (2.6%)	14 (8.0%)
Protocol Violation	2 (0.8%)	0 (0.0%)
Lost to Follow-up	5 (1.9%)	7 (4.0%)

*ITT (sponsor's definition): all enrolled subjects who have received at least one dose of pramlintide.
Source: SDS 1.1

Baseline demographics characteristics are listed in Table 6. They are similar to those of other pramlintide phase III clinical trials.

Table 6: Demographics and baseline characteristics (ITT Population)

Variable	Type 1 Diabetes (N=265)	Type 2 Diabetes (N=176)
Age at screening (yr)	42.7 (10.77)	54.1 (10.68)
Weight (kg)	81.7 (17.48)	111.7 (24.92)
BMI (kg/m2)	28.6 (5.28)	38.6 (7.86)
HbA1c (%) (Screening)	8.0 (1.07)	8.3 (1.39)
Duration of diabetes (yrs)	21.20 (10.218)	13.13 (8.549)
Total daily insulin use (Units)	46.8 (24.31)	110.6 (94.54)
Daily short acting/bolus insulin use	20.6 (12.18)	48.4 (65.21)
Daily long acting/basal insulin use	26.2 (17.51)	69.0 (45.43)

*ITT (sponsor's definition): all enrolled subjects who have received at least one dose of pramlintide. Data presented as mean and standard deviation (SD).
** MDI = multiple dose insulin
Source: SDS 1.3.1

The primary and secondary reasons for initiating pramlintide treatment are listed in Table 7. The most common reasons for starting pramlintide treatment were inability to achieve glucose targets, glucose fluctuations, weight concerns (especially for type 2 diabetes patients) and poor postprandial glucose.

Table 7: Primary and Secondary reasons for initiating pramlintide treatment (ITT Population)

Variable	Type 1 Diabetes (N=265)	Type 2 Diabetes (N=176)
Primary Reason		
Poor Postprandial Glucose	40 (15.1%)	24 (13.6%)
Glucose Fluctuation	88 (33.2%)	26 (14.8%)
Hypoglycemia	9 (3.4%)	1 (0.6%)
Weight Concerns	24 (9.1%)	41 (23.3%)
Unable to Achieve Glycemic Target	104 (39.2%)	84 (47.7%)
Secondary Reason		
Poor Postprandial Glucose	83 (31.3%)	42 (23.9%)
Glucose Fluctuation	100 (37.7%)	49 (27.8%)
Hypoglycemia	36 (13.6%)	12 (6.8%)
Weight Concerns	111 (41.9%)	105 (59.7%)
Unable to Achieve Glycemic Target	72 (27.2%)	37 (21.0%)

*ITT (sponsor's definition): all enrolled subjects who have received at least one dose of pramlintide. Data presented as mean and standard deviation (SD).
Source: SDS 1.3.1

A large proportion of subjects had protocol deviations: 126 (47.5%) of type 1 diabetes patients and 79 (44.9%) of type 2 diabetes patients, respectively. Most protocol deviations were in the "inclusion criteria", "exclusion criteria", "other study drug deviation" and "other" categories.[40]

[40] Of the inclusion criteria, HbA1c deviation at screening occurred in 41 (15.5%) of patients with type 1 diabetes and in 38 (21.6%) of type 2 diabetes patients; a deviation from the euthyroid status occurred in 17 (6.4%) of type 1 diabetes patients and in 11 (6.3%) of type 2 diabetes patients. Of the exclusion criteria, enrolling patients with a clinical history of, or an presence of hepatic, renal or malignant diseases requiring chemotherapy occurred in 15 (5.7%) of type 1 diabetics and in 18 (10.2%) of type 2 diabetics. "Other study drug deviation" occurred in 54 (20.4%) of type 1 diabetes patients and in 15 (8.5%) of type 2 diabetes

C. Efficacy

C.1 HbA1c

The efficacy data for the HbA1c reduction in patients with type 1 diabetes are presented descriptively for the ITT and evaluable population in Table 8. The mean absolute reduction in HbA1c relative to baseline was small (approximately – 0.2 on average). The range of HbA1 changes was wide with some patients having vigorous reductions (range of -2.1 to + 3.4 at 6 months).

Table 8: Hb A1c changes in Type 1 diabetes patients (ITT and evaluable populations)

Variable	Baseline	Week 12	Month 6	Month 12
Intent-to-Treat Population				
Baseline Hb A1c				
N	263	208	101	20
Mean(SD)	8.01 (1.066)	7.80 (0.992)	7.88 (1.198)	7.97 (1.123)
Median	7.80	7.70	7.60	7.70
Range	4.9 to 11.8	5.8 to 11.5	6.0 to 11.1	6.3 to 10.2
HbA1c change from baseline				
N		206	99	20
Mean(SD)		-0.25 (0.711)	-0.18 (0.860)	-0.19 (0.782)
Median		-0.30	-0.20	-0.30
Range		-3.2 to 1.9	-2.1 to 3.4	-1.6 to 1.3
Evaluable Population				
Baseline Hb A1c				
N	206	206	96	20
Mean(SD)	8.04 (1.042)	7.80 (0.994)	7.86 (1.214)	7.97 (1.123)
Median	7.90	7.70	7.60	7.70
Range	4.9 to 11.8	5.8 to 11.5	6.0 to 11.1	6.3 to 10.2
HbA1c change from baseline				
N		206	96	20
Mean(SD)		-0.25 (0.711)	-0.17 (0.868)	-0.19 (0.782)
Median		-0.30	-0.15	-0.30
Range		-3.2 to 1.9	-2.1, 3.4	-1.6, 1.3

Source: SDS 2.1.1 and 2.1.2
N = Number of patients

The efficacy data for the major the HbA1c reduction in patients with type 2 diabetes are presented descriptively in Table 9. Consistent with observations made during the phase III, controlled, blinded clinical trials, the mean absolute HbA1c reduction relative to baseline was more pronounced than that noted in type 1 diabetes patients (approximately

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patients. Deviations in the "other" category occurred in 30 (11.3%) of type 1 diabetes subjects and 15 (8.5%) of type 2 diabetes patients.

- 0.6 %). The range of HbA1c changes was wide with some patients having marked reductions (-3.9 at 6 months) while other loosing glycemic control (+ 2.2 at 6 months).

Table 9: Hb A1c changes in Type 2 diabetes patients (ITT and evaluable populations)

Variable	Baseline	Week 12	Month 6	Month 12
Intent-to-Treat Population				
Hemoglobin A1c				
N	176	148	60	10
Mean(SD)	8.28 (1.387)	7.67 (1.328)	7.83 (1.495)	8.42 (1.949)
Median	8.00	7.55	7.50	7.90
Range	4.9 to 12.5	4.7 to 12.0	4.8, 11.8	6.0, 11.9
HbA1c change from baseline				
N		148	60	10
Mean(SD)		-0.68 (1.071)	-0.59 (1.161)	-0.67 (1.406)
Median		-0.60	-0.55	-0.65
Range		-4.6, 3.5	-3.9, 2.2	-2.2, 2.8
Evaluable Population				
Hemoglobin A1c				
N	148	148	59	10
Mean(SD)	8.35 (1.410)	7.67 (1.328)	7.84 (1.507)	8.42 (1.949)
Median	8.05	7.55	7.50	7.90
Range	4.9, 12.5	4.7, 12.0	4.8, 11.8	6.0, 11.9
HbA1c change from baseline				
N		148	59	10
Mean(SD)		-0.68 (1.071)	-0.62 (1.158)	-0.67 (1.406)
Median		-0.60	-0.60	-0.65
Range		-4.6, 3.5	-3.9, 2.2	-2.2, 2.8

Source: SDS 2.1.1 and 2.1.2
N = Number of patients

C.2 Weight loss effect

The efficacy data on weight loss in patients with type 1 diabetes are presented descriptively in Table 10. Weight was reduced on average by approximately 2-4 kg (median values were more consistent at approximately –2.5 kg). Some patients, however lost as much as 20 kg while some actually gained weight.

Table 10: Weight change from baseline in Patients with type 1 diabetes (ITT Population, N=265)

Statistics	Weight change (Kg)				
	Week 4	Week 12	Month 6	Month 9	Month 12
N	245	212	184	97	20
Mean(SD)	-1.34 (1.810)	-2.50 (2.997)	-3.02 (3.680)	-3.14 (4.414)	-4.23 (5.383)
Median	-1.13	-2.22	-2.36	-2.27	-2.63
Range	-14.7 to 2.5	-15.0 to 5.9	-17.7 to 3.6	-20.5 to 5.9	-20.4 to 1.8

Source: SDS 2.2.1

The efficacy data on weight loss in patients with type 2 diabetes are presented descriptively in Table 11. The average weight loss was about 2-3 kg with some patients loosing as much as 20 kg (while others actually gaining some weight).

Table 11: Weight change from baseline in Patients with type 2 diabetes (ITT Population, N=176)

Statistics	Weight change (Kg)				
	Week 4	Week 12	Month 6	Month 9	Month 12
N	158	150	127	68	10
Mean(SD)	-1.60 (1.965)	-2.22 (2.760)	-2.68 (3.776)	-3.29 (4.541)	-0.76 (4.212)
Median	-1.45	-1.93	-2.72	-2.77	-2.09
Range	-7.7 to 4.1	-11.8 to 3.9	-18.1 to 4.5	-20.9 to 5.4	-6.1 to 7.5

Source: SDS 2.2.1

C.3 Insulin use

The data on insulin reduction from baseline in patients with type 1 diabetes are presented descriptively in Table 12. Consistent with previous pramlintide clinical studies, there was a reduction in the daily bolus/short-acting insulin use (median reductions of approximately 25%). There were no changes in the daily basal/long acting insulin use. The total daily insulin use was reduced by approximately 12%.

Table 12: Insulin Percent Change from Baseline in Patients with Type 1 Diabetes (ITT Population, N=265)

Variable	Insulin Percent Change from Baseline				
	Week 4	Week 12	Month 6	Month 9	Month 12
Total daily insulin use (units)					
N	243	212	184	97	20
Mean(SD)	-15.08 (15.30)	-14.37 (16.89)	-12.02 (18.39)	-11.35 (22.35)	-7.11 (29.49)
Median	-15.08	-13.19	-11.07	-10.61	-12.97
Range	-65.4, 38.0	-67.6, 35.3	-77.9, 46.3	-80.3, 57.1	-36.7, 94.0
Daily short acting/bolus insulin use (units)					
N	243	212	184	97	20
Mean(SD)	-29.49 (29.14)	-25.71 (30.96)	-21.68 (38.14)	-19.51 (56.28)	-31.51 (23.37)
Median	-31.25	-25.89	-25.00	-25.93	-31.88
Range	-100, 175.0	-100, 100.0	-94.2, 300.0	-87.1, 433.3	-66.7, 24.4
Daily long acting/basal insulin use (units)					
N	243	212	182	96	20
Mean(SD)	-2.58 (15.89)	-3.34 (17.36)	-0.35 (21.38)	2.24 (25.95)	16.23 (43.45)
Median	0.00	0.00	0.00	0.00	1.52
Range	-50.0, 100.0	-92.9, 50.0	-52.5, 125.0	-77.5, 102.5	-31.8, 177.8

Source: SDS 2.3.1

The data on insulin reduction from baseline in patients with type 2 diabetes are presented descriptively in Table 13. Consistent with previous pramlintide clinical studies, there was a reduction in the daily bolus/short-acting insulin use (median reductions of approximately 20%). There were minimal changes in the daily basal/long acting insulin use (-5% reductions). The total daily insulin use was reduced by approximately 10%.

Table 13: Insulin Percent Change from Baseline in Patients with Type 2 Diabetes (ITT Population, N=176)

Variable	Insulin Percent Change from Baseline				
	Week 4	Week 12	Month 6	Month 9	Month 12
Total daily insulin use (units)					
N	160	149	126	68	11
Mean(SD)	-13.11 (20.32)	-10.27 (26.82)	-6.55 (29.47)	-6.22 (28.43)	7.63 (59.354)
Median	-13.57	-10.19	-12.50	-9.66	-16.25
Range	-82.6, 81.3	-100, 100.0	-82.9, 100.0	-61.3, 77.8	-36.8, 160.0
Daily short acting/bolus insulin use (units)					
N	138	126	106	56	9
Mean(SD)	-21.65 (29.80)	-12.55 (43.06)	-10.44 (48.96)	-8.84 (37.32)	-5.60 (70.14)
Median	-21.58	-20.00	-18.38	-16.46	-22.22
Range	-100, 100.0	-100, 236.4	-92.7, 233.3	-56.3, 144.4	-66.7, 155.6
Daily long acting/basal insulin use (units)					
N	159	146	126	67	11
Mean(SD)	-8.46 (19.44)	-6.46 (23.39)	-4.36 (26.79)	-4.72 (27.66)	0.86 (25.144)
Median	0.00	-2.67	-5.31	-6.12	0.00
Range	-68.0, 100.0	-100, 100.0	-61.3, 100.0	-61.3, 80.0	-32.4, 50.0

Source: SDS 2.3.1

C.4 Summary of efficacy data

Type 1 diabetes

The efficacy observations made in patients with type 1 diabetes in this clinical trial can be summarized as follows:

- the mean absolute reduction in HbA1c relative to baseline was modest (approximately – 0.2 on average)
- body weight was reduced on average by approximately 2-4 kg (median values were more consistent at approximately –2.5 kg; some patients, however, lost as much as 20 kg)
- pramlintide use was associated with a reduction in daily bolus/short-acting insulin use (approx. 25%), nearly no change in daily basal/long-acting insulin use, and a net reduction in total daily insulin use (approximately 12%)
- individual responses for all efficacy measures (HbA1c, weight) and insulin use varied widely (range of absolute HbA1c changes at 6 months: -2.1 to +3.4; range of weight reduction at six months: -17.7 kg to +3.6 kg).

Type 2 diabetes

The efficacy observations made in patients with type 2 diabetes in this clinical trial can be summarized as follows:

- the mean absolute reduction in HbA1c relative to baseline was approximately – 0.6, larger that the mean reduction observed in patients with type 1 diabetes

- body weight was reduced on average by approximately 2-3 kg; some patients, however lost as much as 18-20 kg
- pramlintide use was associated with a reduction in daily bolus/short-acting insulin use (approx. 20%) , a minimal reduction in daily basal/long-acting insulin use (approx. 5%), and a net reduction in total daily insulin use (approximately 10%)
- individual responses for all efficacy measures (HbA1c, weight) and insulin use varied widely (range for absolute HbA1c changes at 6 months: -3.9 to +2.2; range of weight reduction at six months: -18.1 kg to +4.5 kg).

D. Safety

D.1 Type 1 diabetes

Deaths

There were no patient deaths.

Serious adverse events

Seventeen type 1 diabetes patients reported a total of 20 serious adverse events (applicant's Table 17). There were two cases of severe hypoglycemia (one occurred after the patient discontinued pramlintide, patient 31904). One SAE ("hip fracture") was due to an injury (the subject fell from a tree); the applicant does not report symptoms of hypoglycemia or glucose measurements at the time of this event.

Table 17: Serious Adverse Events (Study 137-155 – Type 1 Patients)

Pramlintide Dose (at time of event onset)	Patient Number	Serious Adverse Event	Investigator Assessment of Causality
60 µg TID	8203	Hypoglycemic Seizure	Possibly related
60 µg TID	9619	Dyspnea	Probably not related
60 µg TID	10201	Appendicitis Perforated	Unrelated
60 µg BID	21906	Uterine Fibroids	Unrelated
60 µg TID	30913	Stress Incontinence	Unrelated
15 µg TID	31301	Gastrointestinal Disorder NOS	Unrelated
60 µg TID	31904	Diabetic Ketoacidosis	Unrelated
60 µg TID	31904	Shock Hypoglycemic	Unrelated
60 µg TID	31904	Diabetic Ketoacidosis	Unrelated
60 µg TID	31904	Angina Unstable	Unrelated
60 µg TID	32001	Cholecystitis NOS	Probably not related
30 µg TID	32004	Gastroenteritis NOS	Probably not related
60 µg TID	32106	Appendicitis	Unrelated
60 µg TID	32108	Appendicitis	Unrelated
60 µg TID	32109	Hip Fracture	Unrelated
60 µg TID	32310	Deep Vein Thrombosis	Unrelated
60 µg QID	32804	Groin Abscess	Unrelated
60 µg TID	32401	Pneumothorax NOS	Probably not related
60 µg TID	34310	Cellulitis	Unrelated
60 µg TID	34306	Cellulitis	Unrelated

Note This table presents all serious adverse events reported in type 1 patients in ongoing Study 137-155 as of 30 June 2004

Adverse events leading to withdrawal

Twenty-one type 1 patients withdrew from the study prematurely due to adverse events: 14 withdrew due to gastrointestinal AEs and 3 patients withdrew prematurely due to hypoglycemia (Applicant's Table 18).

Table 18: Adverse Events Leading to Withdrawal (Study 137-155 – Type 1 Patients)

Pramlintide Dose (at time of event onset)	Patient Number	Adverse Event Leading to Withdrawal	Investigator Assessment of Causality
15 µg (dosing frequency not recorded)	9214	Nausea	Probably related
30 µg (dosing frequency not recorded)	9608	Abdominal Pain NOS	Possibly related
15 µg TID	32209	Nausea	Definitely related
15 µg TID	33012	Abdominal Pain Upper	Probably not related
15 µg TID	33202	Hypoglycemia NOS	Probably related
30 µg TID	10812	Nausea	Definitely related
30 µg TID	30907	Vomiting NOS	Definitely related
30 µg TID	30914	Abdominal Discomfort	Definitely related
30 µg TID	32301	Hypoglycemia NOS	Possibly related
30 µg TID	33704	Aerophagia	Probably not related
30 µg TID	33706	Fatigue	Probably related
45 µg BID	9215	Vomiting	Probably related
45 µg TID	31406	Malaise	Probably related
45 µg TID	31602	Nausea	Definitely related
45 µg TID	33002	Loss of Consciousness	Possibly related
60 µg TID	1310	Hypoglycemia NOS	Possibly related
60 µg TID	2201	Nausea	Definitely related
60 µg TID	18607	Nausea	Definitely related
60 µg TID	31506	Adenocarcinoma Pancreas	Unrelated
60 µg TID	32215	Rhinorrhea	Definitely related
60 µg TID	32902	Abdominal Distension	Possibly related

Note This table presents all adverse events leading to withdrawal in type 1 patients reported in ongoing Study 137-155 as of 30 June 2004

Frequent Treatment-Emergent Adverse Events

Of the 265 type 1 diabetes patients enrolled as of the 30 June 2004, 216 (81.5%) have reported at least one adverse event. Nausea (37%) and hypoglycemia (35%) were the most common adverse events (Applicant's Table 16). The majority of nausea events were, reportedly, mild or moderate in intensity and occurred mostly within the initial weeks of therapy. There were 432 hypoglycemic events reported; of these, 27 represented severe ("assistance") hypoglycemia. The applicant states that none of the AEs coded as injuries was associated with hypoglycemia and the only MVA reported was alcohol-related ("blood ethanol increased").

Table 16: Incidence of Frequent (5%) Adverse Events (Study 137-155 – Type 1 Patients)

Preferred Term	Number (%) of Patients (N=265)
Any Adverse Event	216 (81.5%)
Nausea	98 (37%)
Hypoglycemia	92 (35%)
Sinusitis	27 (10%)
Upper Respiratory Tract Infection NOS	23 (9%)
Vomiting	18 (7%)
Fatigue	12 (5%)
Diarrhea	13 (5%)

* Ninety-two type 1 patients reported a total of 432 hypoglycemic events. Of these, 23 type 1 patients had 27 severe (assisted) hypoglycemic events reported

D.2 Type 2 Diabetes

Deaths

There was one patient death. It occurred in a 66 year-old patient with type 2 diabetes and a pre-existing history of cardiovascular disease who developed a fatal myocardial infarction 102 days within the study. The event has been deemed as "probably not related" to the study medication by the investigator. Myocardial infarction has not been associated with pramlintide in clinical trials. Neither is it plausible mechanistically based on our current knowledge of the pramlintide's mechanism of action.

Serious adverse events

Fourteen type 2 diabetes patients have reported a total of 19 serious adverse events (applicant's Table 20). Ten of these led to premature withdrawal from the study (including the above-mentioned fatal MI). There were no cases of severe (assisted) hypoglycemia.

Table 20: Serious Adverse Events (Study 137-155 – Type 2 Patients)

Pramlintide Dose (at time of event onset)	Patient Number	Serious Adverse Event	Investigator Assessment of Causality
120 µg TID	7303	Detached Retina Repair	Probably not related
120 µg TID	7303	Chest Pain	Probably not related
120 µg TID	7303	Chest Pain	Probably not related
120 µg BID	16109	Coronary Artery Disease NOS	Probably not related
120 µg TID	18602	Cellulitis	Unrelated
120 µg TID	18602	Chest Pain*	Probably not related
120 µg BID	19906	Pancreatitis NOS*	Unrelated
120 µg BID	25203	Osteomyelitis NOS*	Unrelated
120 µg BID	31707	Ventricular Tachycardia*	Unrelated
120 µg TID	32002	Diabetes Mellitus Inadequate Control*	Unrelated
120 µg TID	32006	Angina Unstable*	Probably not related
120 µg TID	32206	Diabetic Ketoacidosis	Unrelated
120 µg TID	32402	Acute Myocardial Infarction (death)*	Probably not related
120 µg TID	32405	Osteoarthritis NOS*	Unrelated
120 µg BID	32503	Osteomyelitis	Unrelated
120 µg TID	33008	Cholecystitis NOS*	Probably not related
120 µg TID	33807	Acquired Pyloric Stenosis	Unrelated
120 µg TID	33807	Anemia	Unrelated
120 µg TID	34506	Depression*	Unrelated

Note: This table presents all serious adverse events reported in type 2 patients in ongoing Study 137-155 as of 30 June 2004

* Serious adverse events that led to withdrawal from the study.

Adverse events leading to withdrawal

A total of 20 patients with type 2 diabetes have withdrawn from the study prematurely due to adverse events. The most common AEs responsible for patient withdrawals were gastrointestinal, in general, and nausea, in particular. One patient withdrew due to hypoglycemia.

Table 21: Adverse Events Leading to Withdrawal (Study 137-155 – Type 2 Patients)

Pramlintide Dose (at time of event onset)	Patient Number	Adverse Event Leading to Withdrawal	Investigator Assessment of Causality
Dose not recorded	9613	Odema NOS	Possibly related
120 µg (dosing frequency not recorded)	9614	Nausea	Probably related
60 µg TID	16108	Abdominal Pain Upper	Probably not related
60 µg TID	17206	Nausea	Definitely related
120 µg QD	17207	Urticaria NOS	Probably related
120 µg BID	14904	Nausea	Definitely related
120 µg TID	8217	Nausea	Definitely related
120 µg TID	18602	Chest Pain	Probably not related
120 µg BID	19906	Pancreatitis	Unrelated
120 µg BID	25203	Osteomyelitis NOS	Unrelated
120 µg BID	31705	Nausea	Possibly related
120 µg BID	31707	Ventricular Tachycardia	Unrelated
120 µg TID	32002	Diabetes Mellitus Control Inadequate	Unrelated
120 µg TID	32006	Angina Unstable	Probably not related
120 µg TID	32402	Acute Myocardial Infarction (death)	Probably not related
120 µg TID	32405	Osteoarthritis NOS	Unrelated
120 µg TID	32903	Vomiting NOS	Definitely related
120 µg TID	33008	Cholecystitis NOS	Probably not related
120 µg TID	34104	Hypoglycemia NOS	Possibly related
120 µg TID	34506	Depression	Unrelated

Note: This table presents all adverse events leading to withdrawal reported in type 2 patients in ongoing Study 137-155 as of 30 June 2004

Frequent Treatment-Emergent Adverse Events

The most common adverse events reported in patients with type 2 diabetes mellitus were nausea (30%) and hypoglycemia (12%) (applicant's Table 19). The nausea, reportedly, was mostly in the mild and moderate category and occurred predominantly in the early phases of pramlintide treatment. Of the 83 hypoglycemic events reported, 3 represented severe (" assisted") hypoglycemia. None of the 10 events that were coded under the "injury, poisoning and procedural complications" was, reportedly, associated with hypoglycemia. The applicant does not report any MVAs in this study.

Table 19: Incidence of Frequent (. 5%) Adverse Events (Study 137-155 – Type 2 Patients)

Preferred Term	Number (%) of Patients (N=176)
Any Adverse Event	125 (71%)
Nausea	53 (30%)
Hypoglycemia	21 (12%)
Upper Respiratory Infection NOS	21 (12%)
Sinusitis	16 (9%)
Vomiting	13 (7%)
Diarrhea	11 (6%)
Depression	10 (6%)
Influenza	8 (5%)

* Twenty-one type 2 patients reported a total of 83 hypoglycemic events Of these, two type 2 patients had 3 severe (assisted) hypoglycemic events reported

E. Summary of safety data

Type 1 diabetes:

The safety observations made in patients with type 1 diabetes in the clinical trial can be summarized as follows:

- gastrointestinal adverse events (nausea, vomiting) and, to a less extent, hypoglycemia are the most frequent group of adverse events leading to patient withdrawal
- the most frequent TEAEs were nausea (37%) followed by hypoglycemia (35%)
- there were no new safety signals identified by this analysis
- the applicant does not report any injuries associated with hypoglycemia; the only MVA reported was alcohol related

Type 2 diabetes:

The safety observations made in patients with type 2 diabetes in the clinical trial can be summarized as follows:

- as noticed in type1 diabetes patients, nausea is the most frequent reason for discontinuation of the clinical trial
- there were no SAEs and only one withdrawal associated with hypoglycemia
- the most frequent AEs were nausea (30.1%), URI (11.9%), and hypoglycemia (11.9%)
- there were no new safety signals identified in this analysis

The absence of a control group limits further conclusions.

VII. Study 137-150E

A. Study design and objective

This study is a multicenter, open-label extension of clinical study 137-150. In clinical study 137-150 patients with type1 diabetes in relatively good glycemic control (mean baseline HbA1c of 8.1) were randomized to either pramlintide plus insulin injections or placebo plus insulin injections. Study 137-150 has been presented to the Agency and has been reviewed previously in detail by this reviewer (see review in DFS). The patients enrolled in this extension study were those who completed study 137-150 and were "deemed compliant as judged by the investigator and/or sponsor." The stated objective of the extension study was to evaluate the long-term safety profile of pramlintide (primary endpoint) and to collect data on HbA1c and weight (secondary endpoints) in type 1 diabetes patients on pramlintide/insulin regimen who completed protocol 137-150. All endpoints were to be summarized descriptively. The clinical protocol of study 137-150E was very similar to that of studies 137-150 and 137-155 and will not be described in detail. The extension study included two groups of type 1 diabetes patients: one group who received placebo plus insulin in the "core" study (i.e. pramlintide-naïve patients) and one group who received pramlintide plus insulin in the "core' study (i.e.pramlintide-

experienced patients). The applicant presents the safety and efficacy data for these two cohorts. In this review they will be identified as the "prior placebo" cohort and as the "prior pramlintide" cohort. The data cutoff for this submission is June 30, 2004.

B. Subject disposition

Subject disposition is presented in Table 14. Seventy-nine patients (72.5 %) in the "prior placebo" group and 89 (91.8 %) patients in the "prior pramlintide" group completed 6 months of treatment. The most common reasons for discontinuation from the clinical trial were similar to those noted in study 137-155: " withdrawal of consent", "adverse event," and "investigator decision."

Table 14: Subject disposition

Disposition	"Prior Placebo" N (%)	"Prior Pramlintide" N (%)
All subjects	109 (100.0)	97 (100.0)
Intent-to-Treat (ITT)*	108 (99.1)	97 (100.0)
Withdrew	62 (56.9)	38 (39.2)
Withdrawal of consent	27 (43.5)	20 (52.6)
Adverse Event	13 (21.0)	4 (10.5)
Investigator Decision	9 (14.5)	9 (23.7)
Protocol Violation	4 (6.5)	2 (5.3)
Lost to Follow-up	9 (14.5)	2 (5.3)
Administrative	0 (0.0)	1 (2.6)

Source: SDS 1.1

Baseline demographics characteristics are presented in Table 15. The data from the "parental" study 137-150 are also presented for each of the two cohorts of the extension study. The demographics and baseline characteristics were consistent with those of other phase III pramlintide clinical trials.

Table 15: Demographics and baseline characteristics (ITT Population)*

Variable	"Prior Placebo" (N = 108)		"Prior Pramlintide" (N = 97)	
	137-150	137-150E	137-150	137-150E
Age	42.3 (11.1)	42.9 (11.2)	42.9 (14.4)	43.3 (14.4)
Weight (kg)	81.9 (17.5)	83.5 (18.2)	83.6 (18.2)	82.0 (19.0)
BMI (kg/m2)	27.9 (4.9)	28.4 (5.0)	28.2 (4.7)	27.5 (4.9)
HbA1c (%)	8.1 (0.9)	7.6 (0.8)	8.0 (0.8)	7.5 (0.7)
Total daily insulin use (units)	56.1 (29.0)	58.4 (33.0)	56.0 (29.4)	52.8 (30.6)
Daily short acting/bolus insulin use	28.6 (17.0)	26.2 (18.3)	26.3 (14.9)	20.6 (17.7)
Daily long acting/basal insulin use	27.5 (16.8)	32.1 (19.2)	29.8 (19.8)	32.2 (17.9)

*Data presented as mean (SD) values.
Source: SDS 1.3

C. Efficacy

HbA1c

The efficacy data for HbA1c are presented descriptively in Table 16 as changes from the baseline of the extension period for the two cohorts: the "placebo" cohort and the "pramlintide" cohort. The "prior placebo" group showed a small deterioration in glycemic control (0.1). The "prior pramlintide" cohort also displayed a small loss of glycemic control (between 0.1 and 0.3).

Table 16: HbA1c change from extension baseline

"Prior Placebo" Cohort (ITT Population, N=108)						
Statistics	**% Hb Change from Extension Study Baseline**					
	Week 12	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
N	88	77	68	55	46	14
Mean(SD)	0.1 (0.6)	0.1 (0.8)	0.1 (0.9)	0.1 (0.8)	0.1 (0.7)	0.0 (0.7)
Median	0.2	0.0	0.1	0.1	0.0	-0.1
Range	-1.5 to 2.1	-1.6 to 2.6	-2.1 to 4.1	-1.5 to 2.4	-1.4 to 2.6	1.4 to 1.3
"Prior Pramlintide" Cohort (ITT Population, N=97)						
Statistics	**% Hb Change from Extension Study Baseline**					
	Week 12	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
N	91	87	71	61	55	17
Mean(SD)	0.1 (0.7)	0.2 (0.8)	0.1 (0.7)	0.3 (0.7)	0.2 (0.7)	0.2 (0.6)
Median	0.1	0.1	0.1	0.3	0.2	0.3
Range	-2.9 to 2.1	-1.8 to 2.3	-2.1 to 2.5	-1.8 to 1.7	-2.6 to 2.3	-1.0 to1.2

Source: SDS 2.2.1

Weight loss effect

The data on weight loss are presented descriptively in Table 17 as changes from the baseline of the extension period for the two cohorts: the "placebo" cohort and the "pramlintide" cohort separately. For the "prior placebo" cohort, initiation of pramlintide treatment resulted in a weight loss consistent with that observed in other pramlintide phase III clinical trials (approx. –2.7 kg). For the 'prior pramlintide" cohort the weight loss was maintained with time and even augmented by another 0.3-0.4 kg.

Table 17: Weight change from extension baseline

"Prior Placebo" Cohort (ITT Population, N=108)						
Statistics	**% Weight Change from Extension Study Baseline**					
	Week 12	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
N	88	79	68	55	45	14
Mean(SD)	-2.1 (2.3)	-2.8 (3.3)	-2.8 (3.8)	-2.6 (3.7)	-2.7 (4.0)	-2.6 (4.8)
Median	-2.1	-2.7	-2.7	-1.7	-2.1	-1.5
Range	-9.1 ; 3.4	-15.2; 3.6	-16.9; 4.3	-13.3; 5.5	-14.4; 6.3	-11.6; 5.5
"Prior Pramlintide" Cohort (ITT Population, N=97)						
Statistics	**% Weight Change from Extension Study Baseline**					
	Week 12	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
N	92	86	72	61	55	18
Mean(SD)	-0.1 (2.1)	-0.1 (3.1)	-0.4 (3.6)	-0.3 (4.3)	0.2 (4.5)	0.9 (3.0)
Median	-0.3	-0.2	0.0	0.4	0.3	1.5
Range	-4.8; 7.7	-8.6; 9.7	-15.3; 7.3	-23.3;10.3	-22.6; 8.6	-6.6; 4.5

Source: SDS 2.2.1

Insulin use

Total Daily Insulin Use

Total daily insulin use was reduced by approximately 15% in the "prior placebo" cohort following the initiation of pramlintide treatment. It remained virtually unchanged in the "prior pramlintide" cohort (Table 18).

Table 18: Total Daily Insulin Use as Percent Change from Extension Baseline

"Prior Placebo" Cohort (ITT Population, N=108)						
Statistics	**% Total Daily Insulin Use Change from Extension Study Baseline**					
	Week 12	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
N	87	78	66	54	45	14
Mean(SD)	-13.3 (16.6)	-13.9 (15.4)	-15.4 (16.5)	-13.3 (19.0)	-15.1 (21.7)	-14.9 (14.6)
Median	-16.0	-14.2	-15.1	-14.1	-18.2	-13.6
Range	-48.5; 51.0	-47.1; 31.8	-53.1; 27.2	-51.8; 37.9	-70.6; 56.8	-40;.5 7.1
"Prior Pramlintide" Cohort (ITT Population, N=97)						
Statistics	**% Total Daily Insulin Use Change from Extension Study Baseline**					
	Week 12	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
N	92	88	70	61	53	18
Mean(SD)	-2.5 (19.3)	-1.8 (20.9)	-2.1 (25.6)	0.5 (24.3)	1.2 (25.2)	6.2 (28.5)
Median	-1.5	-1.0	-0.5	0.0	0.0	4.7
Range	-36.8; 123.7	-56.5; 124.2	-69.4; 136.6	-42.9; 135.1	-56.5; 96.2	-36.9; 98.2

Source: SDS 2.3.1.1

Daily Short-Acting/Bolus Insulin Use

Daily bolus/short-acting insulin use was reduced by approximately 22-25% in the "prior placebo" cohort following the initiation of pramlintide treatment. It remained virtually unchanged in the "prior pramlintide" cohort (Table 19).

Table 19: Daily Short Acting/Bolus Insulin Use as Percent Change from Extension Baseline

"Prior Placebo" Cohort (ITT Population, N=108)						
Statistics	**% Short Acting/Bolus Insulin Use Change from Extension Study Baseline**					
	Week 12	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
N	87	78	66	54	45	14
Mean(SD)	-24.5 (31.7)	-26.1 (34.7)	-26.0 (31.2)	-22.3 (37.2)	-22.5 (48.8)	-23.7 (28.0)
Median	-25.0	-33.3	-27.4	-20.7	-28.4	-22.2
Range	-100.0; 79.4	-100.0; 90.9	-100.0; 53.6	-100.0; 111.1	-100.0; 211.1	-75.0; 16.7
"Prior Pramlintide" Cohort (ITT Population, N=97)						
Statistics	**% Short Acting/Bolus Insulin Use Change from Extension Study Baseline**					
	Week 12	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
N	92	88	70	61	53	18
Mean(SD)	0.2 (50.5)	3.8 (38.1)	-2.7 (38.1)	1.1 (43.8)	8.5 (53.0)	17.7 (53.8)
Median	0.0	0.0	0.0	0.0	0.0	15.1
Range	-81.3; 400.0	-100.0; 150.0	-100.0; 160.0	-100.0; 200.0	-100.0; 200.0	-87.5; 166.7

Source: SDS 2.3.1.1

Daily Long-Acting/Baseline Insulin Use

Daily basal/long-acting insulin use was minimally reduced (approximately 5%) in the "prior placebo" cohort following the initiation of pramlintide treatment. It remained virtually unchanged in the "prior pramlintide" cohort (Table 20).

Table 20: Daily Long-Acting/Basal Insulin Use as Percent Change from Extension Baseline

"Prior Placebo" Cohort (ITT Population, N=108)						
Statistics	**% Long-Acting/Basal Insulin Use Change from Extension Study Baseline**					
	Week 12	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
N	86	77	65	53	44	13
Mean(SD)	-2.8 (19.4)	-2.1 (21.2)	-6.5 (18.4)	-4.9 (25.3)	-5.3 (21.1)	-7.5 (16.7)
Median	0.0	0.0	-7.1	-1.5	-7.1	-9.1
Range	-50.0; 66.7	-50.0; 106.7	-50.0; 56.3	-100.0; 66.7	-43.2; 64.0	-30.0; 32.0
"Prior Pramlintide" Cohort (ITT Population, N=97)						
Statistics	**% Long-Acting/Basal Insulin Use Change from Extension Study Baseline**					
	Week 12	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
N	92	88	70	61	53	18
Mean(SD)	-0.5 (30.6)	-2.4 (30.4)	-0.7 (33.3)	1.4 (33.9)	-1.3 (33.0)	4.8 (47.0)
Median	0.0	0.0	0.0	0.0	0.0	-7.5
Range	-100.0; 233.3	-60.0; 233.3	-60.0; 233.3	-60.0; 233.3	-60.0; 177.8	-31.4; 177.8

Source: SDS 2.3.1.1

Summary of efficacy data

The efficacy observations made in patients with type 1 diabetes in this clinical trial can be summarized as follows:

The pramlintide naïve ("prior placebo") cohort

Patients with type 1 diabetes who received insulin and placebo injections during study 137-150 and were started on pramlintide in an open-label fashion during the extension study, showed a small deterioration in glycemic control (absolute HbA1c increase of 0.1) as well as a weight reduction which was consistent with that observed in previous clinical trials (approx. –2.7 kg). These changes were associated with a reduction in daily bolus/short-acting insulin use (-22-25%), nearly no change in basal/long-acting insulin use (approximately 5% reduction), and a net reduction (15%) of total daily insulin use.

The pramlintide experienced ("prior pramlintide") cohort

The "prior pramlintide" cohort" had a minimal loss of glycemic control (absolute HbA1c increase of 0.1 to 0.3), lost some additional weight (0.3-0.4 kg) and had no changes in daily insulin use.

D. Safety

Deaths

There have been no deaths reported in this study.

Serious Adverse Events

Overall, a total of 22 subjects reported 30 serious adverse events (applicant's Table 14). One of these serious adverse events led to premature withdrawal from the study (subject 23701, fractured tibia and MVA). Six adverse events of hypoglycemia were reported by 5 patients. Three adverse events were listed as inflicted injury (none was associated with hypoglycemia).

The applicant states that " eight (3.9%) subjects reported motor vehicle accidents. Five of these accidents were associated with hypoglycemia, one of which was associated with bodily injury (fractured tibia; patient 23701)." Absence of a comparator limits the ability to draw further conclusions. For an analysis and discussion of severe hypoglycemia across clinical trials, including study 137-150, see the clinical review section).

Table 14: Serious Adverse Events (Study 137-150E – Type 1 Subjects)

Pramlintide Dose (at time of event onset)	Subject Number	Serious Adverse Event Preferred Term	Investigator Assessment of Causality
30 µg TID	20305	Gastroenteritis	Unrelated
45 µg TID	00968	Fever	Unrelated
60 µg TID	11203	Hypoglycemia	Probably related
60 µg TID	11203	Syncope	Probably related
60 µg TID	11210	Hypoglycemia	Probably related
60 µg TID	11214	Hypoglycemia	Possibly related
60 µg TID	11214	Convulsions	Possibly related
60 µg TID	11405	Ketosis	Unrelated
60 µg TID	00901	Inflicted Injury*	Unrelated
30 µg TID	00904	Colitis*	Unrelated
60 µg TID	00912	Ketosis*	Unrelated
60 µg TID	00968	Skin Ulceration*	Unrelated
60 µg TID	01705	Ketosis*	Probably not related
60 µg TID	01708	Ketosis*	Probably not related
60 µg TID	01718	Renal Calculus*	Probably not related
60 µg TID	01728	Inflicted Injury*	Unrelated
30 µg QAM, 60 µg BID	02302	Anaphylactoid Reaction*	Unrelated
60 µg TID	02310	Coronary Artery Disorder*	Unrelated
60 µg TID	02318	Ketosis*	Unrelated
60 µg TID	02321	Hypoglycemia*	Unrelated
60 µg TID	02321	Syncope*	Unrelated
60 µg TID	11207	Hypoglycemia*	Unrelated
60 µg TID	11207	Hypoglycemia*	Unrelated
60 µg TID	11207	Syncope*	Unrelated
60 µg TID	11207	Pneumonia*	Unrelated
30 µg TID	11258	Ketosis*	Unrelated
30 µg BID 15 µg QD	11402	Thyroid Adenoma*	Unrelated
60 µg TID	21803	ECG Abnormal*	Unrelated
30 µg TID	21701	Inflicted Injury*^	Probably not related
30 µg TID	23501	Coronary Artery Disorder*	Unrelated

Note: This table presents all serious adverse events reported in ongoing Study 137-150e.

- Events reported since the data cutoff for the last safety update (30 April 2003). The current reporting period is 01 May 2003 to 30 June 2004

^ Serious adverse events that led to withdrawal from the study

Severe adverse events are presented by patient cohort ("prior placebo" vs. prior pramlintide") in Table 21. In pramlintide-naïve patients hypoglycemia (2.8%), ketosis (2.8%), coronary artery disorder (1.9%), and inflicted injury (1.9%) were the most frequent SAEs. In pramlintide-experienced the most frequent SAEs were ketosis (3.1%), syncope (3.1%) hypoglycemia (2.1%).

Table 21: Serious Adverse Events (ITT population, N=205)

Preferred Term	"Prior Placebo" Cohort (N=108)			"Prior Pramlintide" Cohort (N=97)		
	N	%	Events	N	%	Events
Any adverse event	13	12.0	19	9	9.3	11
Anaphylactoid reaction	1	0.9	1	0	0.0	0
Fever	1	0.9	1	0	0.0	0
Syncope	1	0.9	1	2	2.1	2
ECG Abnormal	1	0.9	1	0	0.0	0
Convulsions	1	0.9	1	0	0.0	0
Colitis	0	0.0	0	1	1.0	1
Gastroenteritis	1	0.9	1	0	0.0	0
Hypoglycemia	3	2.8	4	2	2.1	2

Ketosis	3	2.8	3	3	3.1	3
Coronary Artery Disorder	2	1.9	2	0	0.0	0
Thyroid adenoma	0	0.0	0	1	1.0	1
Pneumonia	1	0.9	1	0	0.0	0
Inflicted injury	2	1.9	2	1	1.0	1
Skin Ulceration	1	0.9	1	0	0.0	0
Renal Calculus	0	0.0	0	1	1.0	1

Source: SDS 3.2.4.1

Adverse Events Leading to Patient Withdrawals

Seventeen subjects withdrew due to adverse events (listed in applicant's Table 15). As seen in other clinical trials of pramlintide, gastrointestinal adverse events (in particular nausea) were the most frequent reason of patient withdrawal due to an adverse event. Two patients withdrew due to hypoglycemia.

Table 15: Adverse Events Leading to Withdrawal (Study 137-150E –Type 1 Subjects)

Pramlintide Dose (at time of event onset)	Subject Number	Adverse Event Leading to Withdrawal Preferred Term	Causality
15 µg TID	9811	Reduced Appetite	Probably related
30 µg TID	11101	Hypoglycemia	Unrelated
30 µg TID	9808	Creatine Phosphokinase Increased (not treatment-emergent)	Possibly related
30 µg TID	1722	Nausea	Probably related
30 µg TID	916	Nausea*	Definitely related
60 µg TID	933	Hypoglycemia*	Unrelated
60 µg TID	939	Nausea*	Definitely related
30 µg TID	1743	Convulsions*	Probably not related
60 µg BID, 30 µg QAM	2302	Angioedema*	Probably related
30 µg TID	2498	Nausea*	Probably related
60 µg TID	2499	Weight Increase*	Probably not related
60 µg QID	2410	Nausea*	Probably related
60 µg TID	10412	Nausea*	Definitely related
60 µg TID	19319	Nausea*	Probably related
30 µg TID	23701	Inflicted Injury*	Probably not related
60 µg TID	23504	Flatulence/Abdominal Bloating*	Probably related
60 µg TID	24505	Depression*	Unrelated

Note: This table presents all adverse events leading to withdrawal reported in ongoing Study 137-150I

* Events reported since the data cutoff for the last safety update (30 April 2003). The current reporting period is 01 May 2003 to 30 June 2004

A larger percentage of pramlintide –naïve patients withdrew due to an adverse event relative to pramlintide-experienced patients (11.1 % vs. 4.1%) (Table 22). The most common adverse event leading to withdrawal was nausea (6.5%) for pramlintide-naïve patients and hypoglycemia (2.1%) for pramlintide-exposed patients.

Table 22: Adverse Events Leading to Withdrawals (ITT population, N=205)

Preferred Term	"Prior Placebo" Cohort (N=108)			"Prior Pramlintide" Cohort (N=97)		
	N	%	Events	N	%	Events
Any adverse event	12	11.1	12	4	4.1	4
Convulsions	1	0.9	1	0	0.0	0
Flatulence/Abdominal fullness	1	0.9	1	0	0.0	0
Nausea	6	6.5	6	1	1.0	1
Reduced appetite	1	0.9	1	0	0.0	0
Hypoglycemia	0	0.0	0	2	2.1	2
Weight increase	0	0.0	0	1	1.0	1
Depression	1	0.9	1	0	0.0	0
Inflicted injury	1	0.9	1	0	0.0	0
Angioedema	1	0.9	1	0	0.0	0

Source: SDS 3.2.6

Frequent Treatment-Emergent Adverse Events

Overall, the most common adverse events were hypoglycemia (84%) and nausea (36%) (applicant's Table 13). Only three subjects (1.5%) reported nausea of severe intensity. The majority of hypoglycemic events were, reportedly, of mild intensity. Severe hypoglycemia was reported by 32 (15.6%) of patients. Six events of severe hypoglycemia were assessed as serious.

Table 13: Incidence of Frequent (≥5%) Adverse Events (Study 137-150E – Type 1 Subjects)

Preferred Term	Number (%) of Subjects (N =205)
Any Adverse Event	190 (93%)
Hypoglycemia*	173 (84%)
Nausea	73 (36%)
Upper Respiratory Infection	60 (29%)
Inflicted Injury	30 (15%)
Headache	17 (8%)
Urinary Tract Infection	17 (8%)
Sinusitis	16 (8%)
Infection	12 (6%)
Influenza-like Symptoms	13 (6%)
Syncope	11 (5%)
Gastroenteritis	11 (5%)
Diarrhea	10 (5%)
Ketosis	12 (6%)
Reduced Appetite	11 (5%)

* Within these 173 type 1 subjects, 32 subjects reported 61 episodes of severe (assisted) hypoglycemia

Treatment-emergent adverse events with a frequency ≥ 2 % in each cohort are presented by "preferred term" in Table 23. The most common TEAEs for pramlintide-naïve patients were hypoglycemia (85%), nausea (44.4%), URI (28.7%), inflicted injury (13 %) and headache (9.3%). For pramlintide-experienced patients the most common AEs were hypoglycemia (93.5%), nausea (25.8%), URI (29.9 %), inflicted injury 16.5%) and UTI (10.3 %).

Table 23: Treatment-Emergent Adverse Events with a Frequency ≥ 2 % Summarized by Body-System*

Body System	"Prior Placebo" Cohort (N=108)		"Prior Pramlintide" Cohort (N=97)		All subjects (N=205)	
	N	%	N	%	N	%
Hypoglycemia	92	85.2	81	83.5	173	84.4
Nausea	48	44.4	25	25.8	73	35.6
URI	31	28.7	29	29.9	60	29.3
Inflicted injury	14	13.0	16	16.5	30	14.6
Headache	10	9.3	7	7.2	17	8.3
UTI	7	6.5	10	10.3	17	8.3
Sinusitis	9	8.3	7	7.2	16	7.8
Influenza-like symptoms	9	8.3	4	4.1	13	6.3
Ketosis	7	6.5	5	5.2	12	5.9
Infection	7	6.5	5	5.2	12	5.9
Syncope	6	5.6	5	5.2	11	5.4
Gastroenteritis	5	4.6	6	6.2	11	5.4
Reduced appetite	5	4.6	6	6.2	11	5.4
Dizziness	6	5.6	4	4.1	10	4.9
Diarrhea	6	5.6	4	4.1	10	4.9
Allergic reaction	5	4.6	4	4.1	9	4.4
Shaking	4	3.7	5	5.2	9	4.4
Pharyngitis	4	3.7	5	5.2	9	4.4
Sweating Increased	4	3.7	5	5.2	9	4.4
Nervousness	4	3.7	4	4.1	8	3.9
Vomiting	4	3.7	3	3.1	7	3.4
Hyperglycemia	3	2.8	4	4.1	7	3.4
Depression aggravated	3	2.8	4	4.1	7	3.4
Motor vehicle accident	3	2.8	4	4.1	7	3.4
Vertigo	3	2.8	3	3.1	6	2.9
Myalgia	3	2.8	3	3.1	6	2.9
Anxiety	4	3.7	2	2.1	6	2.9
Infection fungal	4	3.7	2	2.1	6	2.9
Asthenia	3	2.8	3	3.1	6	2.9
Convulsions	3	2.8	3	3.1	6	2.9
Depression	3	2.8	2	2.1	5	2.4

Source: SDS 3.2.1.1

*Adverse events are listed in decreasing frequency in the "all subjects" column.

Thirty seven inflicted injuries were reported by 30 subjects. Four of these injuries, reportedly, occurred in association with an episode of severe hypoglycemia. Of these only one occurred in a patient who used both pramlintide and insulin prior to the meal. The applicant also reports eight motor vehicle accidents, recorded by seven patients. Of these, three, reportedly, were associated with hypoglycemia and in only two pramlintide was co-administered with insulin prior to the MVA; in the third one the patient, reportedly, skipped the pramlintide dose.

E. Summary of safety data

For pramlintide-naïve patients

- hypoglycemia (2.8%), ketosis (2.8%), coronary artery disorder (1.9%), and inflicted injury (1.9%) were the most frequent SAEs.
- the most common adverse event leading to withdrawal was nausea (6.5%)
- the most common TEAEs for paramlintide-naïve patients were hypoglycemia (85%), nausea (44.4%), URI (28.7%), inflicted injury (13 %) and headache (9.3%).

For pramlintide-experienced patients

- the most common adverse event leading to withdrawal was hypoglycemia (2.1%) for pramlintide-exposed patients.
- the most common AEs were hypoglycemia (83.5%), nausea (25.8%), URI (29.9 %), inflicted injury 16.5%) and UTI (10.3 %).
- the most frequent SAEs were ketosis (3.1%), syncope (3.1%) hypoglycemia (2.1%).

Overall, there were no new safety signals gleaned from this trial in either pramlintide-naïve or pramlintide-experienced patients. The absence of a control group limits further conclusions.

VIII. Study 137-140

This trial is an ongoing open-label study of pramlintide use in subjects with type 1 or 2 diabetes mellitus using insulin. The study was designed to provide an opportunity for subjects to continue with pramlintide treatment after completing one of the long-term phase III studies. The data are presented separately for patients with type 1 and type 2 diabetes (87 type 1 subjects and 52 type 2 subjects). The data cutoff for this safety analysis is April 30, 2004.

Type 1 diabetes

Deaths

One subject (6508) died to esophageal cancer after receiving 60 µg of pramlintide for over 1 year. The investigator assessed this death as unrelated to study medication.

Serious Adverse Events

Nine type 1 diabetes subjects have reported a total of fourteen serious adverse events (see applicant's Table 8, below). Eight of the 14 adverse events were hypoglycemia.

Table 8: Serious Adverse Events (Study 137-140 – Type 1 Subjects)

Pramlintide Dose (at time of event onset)	Subject Number	Serious Adverse Event	Investigator Assessment of Causality
30 µg TID	06210	Gastroenteritis/Dehydration	Unrelated
90 µg TID	00301	Hypoglycemia Hypoglycemia	Probably not related Probably not related
60 µg TID	00306	Coronary Artery Disease	Unrelated
60 µg TID	00405	Hypoglycemia/Syncope	Unrelated
60 µg TID 90 µg TID 60 µg TID 60 µg TID	00409	Hypoglycemia Dysfunctional Uterine Bleeding Hypoglycemia Hypoglycemia (discontinuation from study)	Unrelated Unrelated Possibly related Probably related
60 µg TID	00208	Hypoglycemia	Probably not related
60 µg QID	00604	Hypoglycemia	Probably related
90 µg TID	00613	Coronary Artery Disease Left Bundle Cell Leuk	Unrelated Unrelated
60 µg TID	06508	Esophageal Carcinoma (death)*	Unrelated

Note: This table presents all serious adverse events reported in type 1 subjects in ongoing Study 137-140 since study initiation (first subject's first dose on 5 May 1999) through the data cutoff date of 30 June 2004

- Events reported since the data cutoff for the last safety update (30 April 2003). The current reporting period is 01 May 2003 to 30 June 2004

Withdrawals due to adverse events

Withdrawals due to adverse events are listed in applicant's Table 9, below. Of the 11 patiens who withdrew two patients withdrew due to hypoglycemia and the rest due to gastrointestinal symptoms (mostly nausea, and dyspepsia).

Table 9: Adverse Events Leading to Withdrawal (Study 137-140 – Type 1 Subjects)

Pramlintide Dose (at time of event onset)	Subject Number	Adverse Event Leading to Withdrawal	Investigator Assessment of Causality
30 µg TID	00304	Intermittent hypoglycemia	Possibly related
30 µg TID	00309	Hypoglycemia	Probably related
30 µg TID	00405	Nausea	Possibly related
90 µg TID	00621	Nausea, Vomiting Diarrhea	Possibly related Possibly related
30 µg TID	00622	Diarrhea	Possibly related
30 µg TID	06503	Nausea	Probably related
90 µg TID	06507	Nausea	Related
60 µg TID	00603	Dyspepsia	Possibly related
60 µg TID	00609	Dyspepsia	Possibly related
15 µg TID	00312	Nausea*	Definitely related
60 µg TID	06514	Nausea*	Probably related

Note: This table presents all adverse events leading to withdrawal reported in type 1 subjects ongoing Study 137-140 since study initiation (first subject's first dose on 5 May 1999) through the data cutoff date of 30 June 2004

- Events reported since the data cutoff for the last safety update (30 April 2003). The current reporting period is 01 May 2003 to 30 June 2004

Frequent TEAEs

TEAEs with a frequency ≥ 5% are presented in applicant's Table 7, below. Nausea (43%), hypoglycemia (35%) and inflicted injury (14%) were the most frequent adverse events. The nausea was, reportedly, "mild or moderate in intensity and in most cases resolved within the initial weeks of pramlintide therapy". Fourteen subjects reported severe ("assisted") hypoglycemia. Of the twelve who reported inflicted injuries only one was, reportedly, associated with hypoglycemia (a fall with bruising). The applicant states that "no motor vehicle accidents have occurred during this study in type 1 Subjects".

Table 7: **Incidence of Most Frequent (≥5%) Adverse Events (Study 137-140 – Type 1 Subjects)**

Preferred Term	Number (%) of Subjects (N=87)
Nausea	37 (43%)
Hypoglycemia*	30 (35%)
Inflicted Injury	12 (14%)
Sinusitis	8 (9%)
Upper Respiratory Tract Infection	10 (11%)
Hyperlipidemia	10 (11%)
Dyspepsia	6 (7%)
Diarrhea	5 (6%)
Depression	4 (5%)
Urinary Tract Infection	4 (5%)
Vomiting	4 (5%)

* Within these 30 type 1 subjects, 14 subjects reported 21 episodes of severe (assisted) hypoglycemia

Type 2 diabetes

Deaths

No deaths were reported.

Serious adverse events

Eight type 2 diabetes subjects reported a total of 16 serious adverse events (applicant's Table 11). None of them were due to hypoglycemia. Most of them appear to represent known complications of type 2 diabetes (e.g. neuropathy, osteomyelitis, cellulitis, myocardial infarction)

Table 11: Serious Adverse Events (Study 137-140 – Type 2 Subjects)

Pramlintide Dose (at time of event onset)	Subject Number	Serious Adverse Event	Investigator Assessment of Causality
30 µg TID	11109	Worsening of perforated nasal septum	Unrelated
90 µg TID		Inflicted Injury*	Unrelated
60 µg TID	00605	Right hip pain	Probably not related
120 µg TID		Spinal stenosis	Unrelated
60 µg TID		Neuropathy*	Unrelated
90 µg TID	00607	Enlarged prostate	Probably not related
120 µg TID	00608	Exacerbation of right plantar ulcer	Unrelated
		Cellulitis right foot	Unrelated
		Cellulitis right foot and ankle	Unrelated
		Osteomyelitis*	Unrelated
120 µg BID	06523	Right Lower Extremity Cellulitis*	Unrelated
120 µg BID	06512	Atypical chest pain	Unrelated
		Resection of thymic mass	Probably not related
		Mediastinitis	Probably not related
120 µg TID	11107	Myocardial Infarction*	Probably not related/Unlikely
90 µg TID	11110	Renal Calculus*	Probably not related/unlikely

Note This table presents all serious adverse events reported in type 2 subjects in ongoing Study 137-140 since study initiation (first subject's first dose on 5 May 1999) through the data cutoff date of 30 June 2004

* Events reported since the data cutoff for the last safety update (30 April 2003) The current reporting period is 01 May 2003 to 30 June 2004

Withdrawals due to adverse events

Patient withdrawals secondary to adverse events are listed in applicant's Table 12, below. No hypoglycemia cases are reported. Two of the three patients withdrew due to nausea.

Table 12: Adverse Events Leading to Withdrawal (Study 137-140 – Type 2 Subjects)

Pramlintide Dose (at time of event onset)	Subject Number	Adverse Event Leading to Withdrawal	Investigator Assessment of Causality
60 µg TID	00602	Nausea	Probably related
		Vomiting	Probably related
90 µg BID	11102	Nausea*	Possibly related
90 µg TID	11115	Lymphoma-like Disorder*	Probably not related/unlikely

Note This table presents all adverse events leading to withdrawal reported in type 2 subjects in ongoing Study 137-140 since study initiation (first subject's first dose on 5 May 1999) through the data cutoff date of 30 Apr 2003

* Events reported since the data cutoff for the last safety update (30 April 2003) The current reporting period is 01 May 2003 to 30 June 2004

Frequent TEAEs

Nausea (44%) and hypoglycemia (35%) were the most commonly reported adverse events. Reportedly, all cases of nausea were mild or moderate in intensity and for most patients resolved within the initial weeks of pramlintide therapy. Of the 56 hypoglycemic events reported, two represented severe (assisted) hypoglycemia. While eight subjects experienced "inflicted injuries", none was, reportedly, associated with hypoglycemia. No motor vehicle accidents have been reported during this study in patients with type 2 diabetes.

Study summary

Type 1 diabetes

Nausea (43%), hypoglycemia (35%) and inflicted injury (14%) were the most frequent adverse events. Nausea and hypoglycemia were the most common reason for patient withdrawal. The most frequent SAE was hypoglycemia. No new safety signals were identified in this analysis.

Type 2 diabetes

Hypoglycemia was not reported as a cause of serious adverse events or patient withdrawals. Although a frequent TEAE, most hypoglycemia events are reported as mild/moderate. Gastrointestinal adverse events were the most frequent TEAEs, and in a few patients were severe enough to result in discontinuation from the trial. No new safety signals were identified in this analysis.

Overall, the absence of a control group limits further conclusions.

IX. Study 137-149

This was a single center, randomized, double-blind, placebo-controlled, cross-over study whose primary objective was to evaluate the acute effect of pramlintide on satiety and food intake. As a secondary objective, the study assessed the acute effect of pramlintide on postprandial metabolic and hormonal responses (glucose, triglycerides, total cholesterol, insulin, cholecystokinin, and glucagon-like peptide-1). The patient population consisted of normal-weight and obese non-diabetic subjects, and insulin-treated subjects with type 1 and type 2 diabetes (15 subjects for each category, 60 subjects overall). The subjects were given pramlintide and underwent a standardized meal test. The pramlintide dose was 30 µg for normal-weight non-diabetic patients and for type 1 diabetes patients, and 120 µg for obese, non-diabetic subjects and for subjects with type 2 diabetes. The change in food (caloric) intake relative to placebo for each of the four groups of subjects studied is presented in Table 24. In all the groups studies there was a reduction in caloric intake relative to placebo. This reduction was more robust in patients with diabetes: ~23% and ~21%, compared with placebo, in patients with type 2 and type 1 diabetes, respectively. These observations were statistically significant for the 11 patients with type 2 diabetes ($p=0.0088$) and showed a trend toward statistical significance for a small group of 6 patients with type 1 diabetes ($p=0.0170$).

Table 24: Percent Difference in Total Caloric Intake Relative to Placebo*

Descriptive statistics	Normal weight non-diabetic	Obese non-diabetic	Type 1 diabetes	Type 2 diabetes
N	15	15	6	11
Mean (SD)	-13.8 (32.8)	-15.9 (21.6)	-21.1 (22.4)	-22.9 (26.8)
Median	-12.7	-18.0	-29.4	-24.6
Range	-52.8 to 69.0	-58.3 to 39.3	-42.7 to 12.2	-60.1 to 36.6

Source: SDS 2.2.1

*Percent difference is (Pramlintide-Placebo)/Placebo and multiplied by 100.

There were no serious adverse events reported in this study. No patients withdrew from study due to study medication (the one subject who withdrew did it so prior to receiving the study medication). There were no adverse events of hypoglycemia during the pramlintide or placebo study periods.

X. Pramlintide's mechanism of action: an update

In healthy adults plasma amylin concentrations reach approximately 4 pmol/L fasting and 25 pmol/L postprandially. The normal postprandial amylin response is absent in patients with type 1 diabetes and blunted in insulin-using patients with type 2 diabetes.

Pramlintide mean C_{max} ranges from 36.5 - 41.9 pmol/L for the 30 μg dose to 64.5 - 74.4 pmol/L for the 60 μg dose in patients with type 1 diabetes (both doses are proposed to be used in the label); pramlintide concentrations in patients with type 2 diabetes reach a mean C_{max} of 74.0 to 117.4 pmol/L for the 120 μg dose (also a to-be-labeled dose) dose[41]. They are all in excess of the amylin peak postprandial concentration of approximately 25 pmol/L, indicating that pramlintide is pharmacological treatment and not physiological replacement.

Pramlintide has a complex mechanism of action which includes the following:

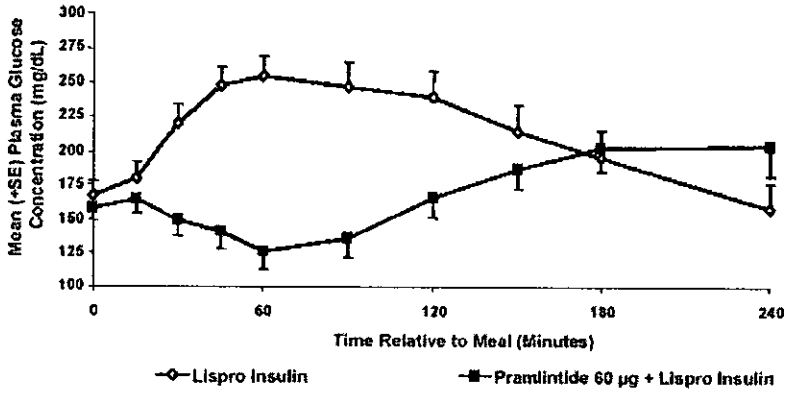
1) Effects on gastric emptying

Pramlintide lowers postprandial plasma glucose concentrations primarily via its effect on gastric emptying. Specifically, pramlintide slows down gastric emptying and the rate at which food is released from the stomach to the small intestine following ingestion of a meal. The postprandial glucose rise is reduced and delayed for approximately 3 hours following pramlintide administration (Figure 9). Importantly, however, pramlintide does not alter the net absorption of ingested carbohydrates; instead they are absorbed at a later time. There are three consequences to this phenomenon: 1) the suppression of the delayed glucose elevation (i.e. after 3 hours) depends on the action of the basal/long acting insulin, 2) the immediate postprandial glucose peaks are replaced by smaller late postprandial glucose elevations ("a smoothing out" of postprandial glucose profile), and 3) the reduction in postprandial glucose levels may be accompanied by a "dip" of the serum glucose below the preprandial levels (i.e. the postprandial "hump" is replaced by a

[41] See clinical pharmacology review in DFS (June 6, 2001).

biphasic, almost sigmoid profile with a below-baseline initial reduction followed by a late above-baseline elevation). This "dip" helps to explain the risk of severe hypoglycemia during the postprandial period ("mealtime hypoglycemia"). It should be mentioned that, the dip is more pronounced with rapid acting insulins than with regular insulin, and is more evident in patients with type 1 diabetes than in patients with type 2 diabetes.

Figure 9: **Mean Plasma Glucose Concentrations by Treatment: Study 137-151; Evaluable Population, Observed Data (Type 1 Patients Using Lispro Insulin; Pramlintide 60 µg; N=20)**



Notes Time=0 min is the average of glucose concentrations at times -30, -15, and -5 min.
Lispro insulin was administered according to package insert recommendations (t=0 min), and pramlintide was also injected immediately before the meal (t=0 min).

2) Reduction of food intake

The weight reduction consistently seen in association with pramlintide treatment during the phase III clinical trials in both type 1 and type 2 diabetes has been one of the most interesting and intriguing characteristics of pramlintide. It is not until the current submission that this effect has been studied (see Study 137-149 which assessed the acute effect of pramlintide on food intake). The results of this study indicate that, following a single dose of pramlintide, the total caloric intake was reduced by ~23% and ~21% (compared with placebo) in patients with type 2 and type 1 diabetes, respectively.

3) Reduction of postprandial glucagon secretion

In mechanistic studies pramlintide has been shown to reduce the postprandial glucagon concentrations in both type 2 and type 1 diabetes patients. It is important to recognize that this glucagon reduction is limited to a period of time of approximately 2-3 hours after meals. Taking into consideration that pramlintide treatment is administered 2-4 times per day, its suppressive effect on serum glucagon is not continuous during a 24-hour period. The exact contribution of the glucagonostatic effect to the overall glycemic control has not been quantified and is not known.

XI. Subject satisfaction questionnaire

Type 1 diabetes

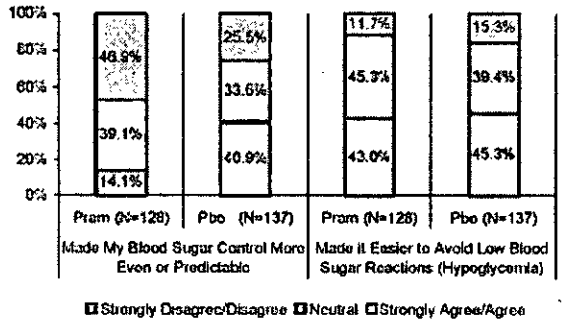
The applicant evaluated patients' satisfaction with pramlintide treatment in several clinical studies (137-150, 137-150E, and 137-155) employing a non-validated 14-item treatment satisfaction questionnaire. This questionnaire uses a 6-point scale that range from "strongly disagree" to "strongly agree." These evaluations were done in a placebo-controlled setting in trial 137-150 and in an open-label setting in studies 137-150E and 137-155.

Study 137-150

The applicant reports statistically significant differences between placebo and pramlintide patients at the end of the study in 12 of the 14 questions asked. The patients who remained on treatment[42] and completed the study perceived, reportedly, greater improvements in glucose, weight, and appetite control, compared with placebo-treated patients ($p<0.001$); in addition, the applicant reported improvements in patients' ability to function at home, work or school, how they felt overall, confidence in self-management (all $p\leq0.001$). The questionnaire indicates that pramlintide-treated patients felt that the benefits of pramlintide outweighed the need for additional injections ($p<0.001$). Consistent with pramlintide's known adverse event profile, pramlintide-treated patients were aware of more side effects related to treatment ($p=0.002$). Applicant's Figure 12 displays as a composite graph the perceived effects on blood glucose control. Consistent with the known effects of pramlintide on postprandial glucose measurements, 46.9% of pramlintide-treated subjects reported that pramlintide made blood sugar control more even and predictable compared to 25.5 % subjects treated with insulin and placebo.

[42] 21.5% of pramlintide-treated patients and 9.5% of placebo- (i.e. placebo plus insulin) treated patients discontinued treatment prior to study completion and could not be evaluated with the treatment satisfaction questionnaire.

Figure 12: Subject Perceived Effects on Blood Glucose Control Q1 and Q4 Composite Outcome (ITT, N=295)

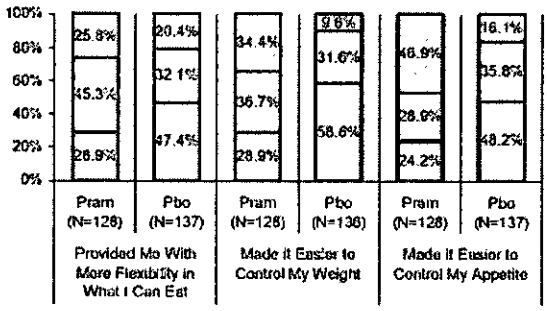


The category "strongly disagree disagree" corresponds to ESSQ responses 1 or 2, "neutral" corresponds to ESSQ responses 3 or 4, and "Strongly Agree/Agree" corresponds to ESSQ responses 5 or 6

Cross-reference Appendix 3.15

Applicant's Figure 13 displays as a composite graph the perceived effects on weight and appetite. Consistent with the previously observed effect of pramlintide on weight and appetite, 34.4% of pramlintide-treated patients perceived that pramlintide made it easier to control their weight relative to only 9.6% of those who received insulin plus placebo. Similarly 46.9% of pramlintide-treated patients perceived that pramlintide made it easier to control their appetite compared to only 16.1% of patients who received insulin plus placebo.

Figure 13: Subject Perceived Effects on Weight Appetite Control Q2, Q3 and Q5 Composite Outcome (ITT, N=295)



The category "strongly disagree disagree" corresponds to ESSQ responses 1 or 2, "neutral" corresponds to ESSQ responses 3 or 4, and "Strongly Agree Agree" corresponds to ESSQ responses 5 or 6

Descriptively, pramlintide had a favorable score relative to insulin alone in Study 137-150 (as well as 137-150E, see below) for the following questions: "Made my blood sugar more predictable," "Improved how I feel overall," "Made it easier to control my weight," "Provided me with more flexibility with what I can eat," Made it easier to control my appetite," "Provided me with benefits that insulin alone has not provided me," Reduced at least some of my worries about having diabetes," " Provided me enough benefit to outweigh the extra injections," Made me feel more confident about managing my diabetes," "Improved my ability to function at home, at work, or at school," and "I would recommend study medication to other people with diabetes."

Study 137-150-E

The applicant reports that the benefits perceived by pramlintide-treated patients at the end Study 137-150 under "blinded" conditions were sustained following 6 months of open-label pramlintide treatment in the extension study 137-150E. Patients who received insulin plus placebo in the core study, after receiving treatment with pramlintide in the extension study, reported similar results to those reported by pramlintide-treated patients in the core study.

Study 137-155

The applicant reports that "results from the treatment satisfaction questionnaire administered in type 1 patients in Study 137-155 are consistent with findings from blinded Study 137-150 and open-label extension Study 137-150E."

Type 2 diabetes

The same patient satisfaction questionnaire was given to patients with type 2 diabetes only in the open-label, uncontrolled, clinical practice study 137-155. When the questionnaire was applied to the patients who remained on pramlintide therapy[43] they reported perceived benefits at 1 month and 6 months which were similar to those observed in type 1 diabetes patients. The applicant states that the majority of patients reported eating less (with approximately half of patients perceiving a weight loss benefit), feeling better in general (53.3 % at Month 1 and 68.9% at Month 6) and having an improved outlook on life (38.1 % at Month 1 and 44% at Month 6). Approximately 95% of patients stated that they would continue pramlintide treatment.

XII. Labeling

The applicant's proposed label is acceptable as long as the following recommendations are incorporated:

- The boxed warning needs to be specific as to when severe hypoglycemia can occur in relationship with pramlintide administration; this information is extremely important from a safety standpoint it needs to be communicated clearly in the label.
- The comprehensive description of amylin's physiology in the "Clinical pharmacology" section should be abbreviated.
- The description of pramlintide as physiological replacement should be discouraged. Pramlintide is not simple physiological replacement but rather a complex pharmacological treatment.
- Descriptions of pramlintide's mechanism of action should emphasize the effect of pramlintide on gastric emptying because this process is central to the drug's activity

[43] In this study 23.5% patients discontinued treatment prior to the 6-month visit and thus, were not evaluated with the questionnaire; among these were "both patients who found the extra injections an excessive burden and patients who experienced persistent gastrointestinal tolerability issues."

from both an efficacy and safety standpoint. Instead, the applicant emphasizes the effect of pramlintide on postprandial glucagon concentrations.

- The description of the type 2 diabetes clinical trials should emphasize data obtained with the recommended dose of 120 µg; referencing any clinical data obtained with higher doses (which in final analysis have not been proven safe and effective) may be seen as an endorsement of such doses. The description of the efficacy results should be changed from [ ] to a numeric one and should include also the placebo-subtracted results, where applicable.
- The description of the type 1 diabetes clinical trials should follow the above-made recommendation for the type 2 clinical trials. In addition, the clinical data of the non-inferiority study 137-150 (omitted entirely by the applicant) should be included in the label because it was fundamental in developing the method of pramlintide initiation which is reflected in the proposed label. Equally important, study 137-150 is the only placebo-controlled clinical trial conducted in a patient population with relatively good glycemic control.
- The data on [ ] associated with pramlintide treatment in both type 1 and type 2 diabetes should be deleted from the label as it has been obtained with a non-validated questionnaire. In addition, these data were collected in an evaluable population and, thus, does not account for the fact that a good number of patients discontinue pramlintide treatment primarily for tolerability problems, and as many as 20% withdraw consent.

The specific changes to the proposed label are presented next. This label represents the currently negotiated label. Only minor changes (if any) are anticipated at this time. A Medication Guide, recently approved by the PISC, is still under review at this time.

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Dragos Roman
2/18/05 02:41:16 PM
MEDICAL OFFICER

David Orloff
2/23/05 05:41:30 PM
MEDICAL OFFICER

Memorandum

Date: December 12, 2003

From: Dragos Roman M.D., Medical Officer, HFD-510

Through: David Orloff, M.D., Acting Team Leader and Division Director, HFD-510

Subject: Addendum to NDA review of pramlintide acetate

To: File (NDA 21-332)

1. Background:

Pramlintide acetate is a new antidiabetic drug under review for possible approval. This memorandum to the file adds an additional analysis to the recently completed NDA review. Since several clinical investigators who participated in the Phase III clinical trials could not be certified with regard to a lack of a "significant equity interest" despite efforts made by the applicant (Amylin Pharmaceuticals Inc.), the Agency recently requested additional safety and efficacy data obtained from these investigators. The applicant's December 10, 2003 response to the Agency's request is the focus of this memorandum.

2. Summary:

There are three analyses that were requested from the applicant. They are summarized next.

2.1.The number of patients who experienced a) at least one episode of severe hypoglycemia, and b) the total number of severe hypoglycemic episodes reported by these investigators[1].

The applicant presents, as requested, such data from several Phase III clinical trials: studies 137-112, 137-117 (in patients with type 1 diabetes) and studies 137-111, 137-123 (in patients with type 2 diabetes). These data are summarized in table format bellow:

[1] Investigators who have not been certified with regard to the lack of a "significant equity interest"

Study 112	**Randomized N=480**		**Subject with at least one episode of severe hypoglycemia N=94**		**Total number of severe hypoglycemic episodes N=421**	
	Certified*	**Not certified**	**Certified**	**Not certified**	**Certified**	**Not certified**
	388 (81%)	92 (19%)	81 (86%)	13 (14%)	387 (92%)	34 (8%)
Study 117	**Randomized N=586**		**Subject with at least one episode of severe hypoglycemia N=120**		**Total number of severe hypoglycemic episodes N=329**	
	Certified	**Not certified**	**Certified**	**Not certified**	**Certified**	**Not certified**
	449 (77%)	137 (23%)	93 (77.5%)	27 (22.5%)	252 (77%)	77 (23%)
Study 111	**Randomized N=538**		**Subject with at least one episode of severe hypoglycemia N=14**		**Total number of severe hypoglycemic episodes N=27**	
	Certified	**Not certified**	**Certified**	**Not certified**	**Certified**	**Not certified**
	437 (81%)	111 (19%)	13 (93%)	1 (7.1%)	23 (85%)	4 (15%)
Study 123	**Randomized N=499**		**Subject with at least one episode of severe hypoglycemia N=24**		**Total number of severe hypoglycemic episodes N=42**	
	Certified	**Not certified**	**Certified**	**Not certified**	**Certified**	**Not certified**
	343 (69%)	156 (31%)	19 (79%)	5 (21%)	33 (79%)	9 (21%)

*Certified= has been certified with regard to the lack of a "significant equity interest."

Reviewer's comment: Although in three of the four clinical trials (137-112, 137-111, and 137-123) there is a trend suggesting that sites that were not certified with respect to "significant equity interest" reported a proportionally lower incidence and number of events of severe hypoglycemia, this fact does not influence the NDA safety conclusions. Irrespective of this observation, a clear imbalance in the incidence of severe hypoglycemia in pramlintide-treated patients relative to placebo-treated patients has been demonstrated in multiple clinical trials, for all doses and regimens tested.

2.2.Individual and mean hemoglobin A1c changes from baseline contributed to the primary efficacy analysis by patients enrolled in these sites[2] and how they compare with the mean HbA1c change from baseline for the entire study.

The applicant presents, as requested, the mean and individual HbA1c changes from baseline for all the sites requested. Most sites have a limited number of randomized patients overall; within

[2] Sites with investigators who have not been certified with regard to the lack of a "significant equity interest"

each site this limited number of patients is further divided in several treatment arms. As expected from such a small sample size, there is a considerable degree of variability in HbA1c changes from site to site and, within each site, from one treatment arm to another. Visual inspection of these datasets does not identify any site that clearly favors HbA1c changes in patients treated with pramlintide over those treated with placebo.

2.3.Safety and efficacy information contributed by Dr [redacted] site in study 137-117.

Dr. [redacted] s site randomized 9 subjects (7 to pramlintide, two to placebo). Two subjects (18 %) in the pramlintide group reported 13 episodes of severe hypoglycemia (the overall incidence of severe hypoglycemia in the intent-to-treat population was comparable at 21%). In addition, the efficacy results provided by this site are consistent with the results of the whole trial.

3. Conclusion

These analyses of the datasets provided by the applicant do not change the overall conclusions of the NDA, as already reviewed.

Dragos Roman M.D. Medical Officer, HFD-510

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/s/

Dragos Roman
12/12/03 11:32:05 AM
MEDICAL OFFICER

David Orloff
12/12/03 05:30:51 PM
MEDICAL OFFICER

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

APPLICATION #:	21-332	**APPLICATION TYPE:**	NDA resubmission
SPONSOR:	Amylin Pharmaceuticals	PROPRIETARY NAME:	Symlin
CATEGORY OF DRUG:	Amylin analog	GENERIC NAME:	Pramlintide acetate
		ROUTE:	Injectable (subcutaneous)
MEDICAL REVIEWER:	Dragos Roman, MD	REVIEW DATE	11-17-2003
		PDUFA DATE:	12-16-2003

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
06/16/2003	06/17/2003	NDA resubmission	

RELATED APPLICATIONS

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review: Symlin ™ (pramlintide acetate) is a synthetic analogue of human amylin. Injectable pramlintide acetate was developed as a glucose lowering drug to be used in combination with insulin in patients with type 1 and type 2 diabetes.

A New Drug Application for Symlin ™ was originally submitted to the Agency on December 08, 2000. Following an Advisory Committee in July 2001 and an extensive efficacy and safety review, the application was deemed approvable. The October 10, 2001 Action Letter issued by the Agency listed four clinical deficiencies. The current submission addresses satisfactorily three of the four clinical deficiencies. It fails, however to reduce the risk of severe hypoglycemia associated with pramlintide/insulin coadministration relative to insulin treatment alone that was observed repeatedly in clinical trials, particularly in patients with type 1 diabetes.

Recommended Regulatory Action: Approvable

Signed: Medical Reviewer: Dragos Roman M.D.
Date: 07/17/2003

Medical Team Leader: _____ Date: _____

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Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Clinical data provided in this sNDA failed to demonstrate an improvement in the safety profile of Symlin ™ (pramlintide acetate) when used in combination with insulin over the one established during the Phase III clinical trials and deemed not safe by the July 26, 2001 Endocrinologic and Metabolic Drug Advisory Committee and by the prior safety review. Therefore, this reviewer recommends against changing the prior "approvable" regulatory decision.

In order to improve the safety profile of pramlintide acetate, the applicant needs to reduce the increased risk of severe hypoglycemia (relative to insulin treatment alone) that was observed and confirmed in multiple clinical trials. One possible solution to this problem is to identify, prior to pramlintide treatment initiation, which patients have an exacerbated prolongation of gastric emptying and to exclude them from further clinical trials. Another option is to develop pramlintide treatment in patients with type 2 diabetes who do not use insulin.[1]

B. Recommendation on Phase 4 Studies and Risk Management Steps

Not applicable.

II. Summary of Clinical Findings

A. Background and Brief Overview of Clinical Program

Pramlintide acetate is a synthetic analogue of human amylin. Amylin is a 37-amino acid hormone that is co-secreted with insulin in response to nutrient stimuli. Amylin plays a role in glucose homeostasis via several mechanisms: (1) it reduces gastric motility following a meal and subsequently slows down the delivery of glucose to the systemic circulation, (2) it reduces food intake through effects on satiety, and (3) it regulates postprandial glucagon secretion. Pramlintide acetate was developed as a replacement to amylin in patients with β-cell failure in type 1 and type 2 diabetes. To this end, pharmacological treatment with pramlintide attempts to replace the lost endogenous amylin secretion. Pramlintide is administered as an injection given subcutaneously before meals, in addition to insulin. Pramlintide and insulin are not compatible in

[1] One of several recommendations made at the July 26, 2001 Endocrinologic and Metabolic Drug Advisory was to initiate a trial of pramlintide in patients with type 2 diabetes on metformin.

solution and, therefore, are administered at separate injection sites. Pramlintide is the first and only amylinomimetic in development to date. In a larger physiological context, it belongs to a group of antidiabetic drugs that, among other mechanisms of action, reduce gastric motility and secondarily blunt the postprandial glucose excursions.

A New Drug Application for Symlin ™ (pramlintide acetate) was originally submitted to the Agency on December 08, 2000 by Amylin Pharmaceuticals INC. Following an Advisory Committee in July 2001 and an extensive efficacy and safety review, the application was deemed approvable. The October 10, 2001 Action Letter issued by the Agency listed several deficiencies. Of these, four were clinical and are listed below:

1. The safety profile of Symlin ™ was found "unacceptable" due to an "increased risk of severe hypoglycemia relative to insulin alone" in patients with type 1 and type 2 diabetes, "particularly in the first month of therapy." An increased risk of serious adverse events associated with hypoglycemia (including motor vehicle accidents and other injuries) was also noted in patients with type 1 diabetes.
2. The application did not provide enough evidence to exclude a role for Symlin ™ in lowering the threshold for hypoglycemia awareness.
3. An apparent dose-dependent increase in progression of diabetic retinopathy associated with Symlin ™ therapy relative to insulin alone was observed in one study in patients with type 2 diabetes[2].
4. The applicant has not adequately characterized the antibody response to Symlin ™ produced by the drug substance manufactured by [redacted]

On June 17, 2003, Amylin Pharmaceuticals INC submitted a supplemental NDA (sNDA), containing data that address the above-listed deficiencies. This review analyzes the pramlintide acetate sNDA from a clinical perspective. The sNDA contains one clinical trial (137-150) and five pharmacokinetic/pharmacodynamic (PK/PD) studies.

Clinical trial 137-150 is a safety study. The study's objective was to evaluate the safety of a new treatment regimen in which pramlintide was titrated to tolerability for the initial 4 weeks and continued at a fixed dose of either 30-µg or 60-µg for the following 6 months of the trial (in order to reduce the incidence of severe hypoglycemia the insulin dose was also reduced during the pramlintide titration period and optimized only after a fixed pramlintide dose was established). The study was placebo-controlled, used an

[2] In a subsequent End-of-NDA-Review Meeting it was agreed by the Division that the potential increase in risk of retinopathy progression will be evaluated in an open-label Phase 4 study. This study will be conducted in approximately 500 patients with either type 1 or type 2 diabetes over 3 years.

add-on design (pramlintide was added to insulin), and was conducted in a group of patients with type 1 diabetes and relatively good glycemic control who have been free of severe hypoglycemia for the preceding 6 months. The primary endpoint of the trial was a comparison of the incidence of (severe) hypoglycemia between patients receiving pramlintide/insulin combination treatment and patients on insulin treatment alone (i.e. insulin plus placebo). This comparison was done in the context of similar efficacy between the two treatments measured statistically as equivalent HbA1c reduction at the end of the clinical trial[3]. In essence, study 137-150 asks the question as how does the safety of pramlintide/insulin combination treatment compare with the safety of insulin treatment alone for equivalent degrees of efficacy with respect to glycemic control. When compared to the Phase III efficacy clinical trials, study 137-150 was different in several ways: (1) it was a safety study, (2) it used a new regimen in which pramlintide was titrated to tolerability, (3) it was conducted in a group of patients with better glycemic control who were also stable with respect to severe hypoglycemia, and (4) insulin adjustments were made in a way consistent with clinical practice.

The five PK/PD studies investigated: (1) the effect of pramlintide on the subjects' ability to recognize symptoms of hypoglycemia, (2) the bioequivalence of pramlintide administration at different anatomical injection sites, (3) the effect of timing of pramlintide injections relative to meals on postprandial plasma glucose profiles, (4) the effects of pramlintide on the PK characteristics of acetaminophen, and (5) the effect of pramlintide on postprandial glucose fluctuations[4].

In the review of clinical trial 137-150 pramlintide plus insulin regimen will be often referred to as pramlintide/insulin combination treatment. Insulin plus placebo regimen will be referred to as insulin alone treatment. Similarly, when the term "pramlintide treatment" is used with reference to this clinical trial, it always means pramlintide plus insulin treatment; likewise, placebo means insulin alone.

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[3] Hypoglycemia, although a safety variable, can only be interpreted adequately in the context of the known efficacy of a glucose lowering drug or regimen. At the End-of-the-Review Meeting the applicant was given the choice to evaluate severe hypoglycemia in (1) a clinical trial that establishes the superiority of pramlintide/insulin regimen over the insulin alone regimen or (2) a clinical trial in which the two regimens showed similar degrees of efficacy (a non-inferiority trial design). The applicant elected the latter.

[4] All but the last of the listed PK/PD studies were requested by the Division following the October 10, 2001, "approvable" Action Letter.

B. Efficacy Conclusions

The efficacy of pramlintide has been evaluated during the Phase III clinical trials submitted with the original NDA in December 2000 (see Dr. Robert Misbin's efficacy review in DFS)[5]. Therefore, it will not be re-analyzed in this review.

The only clinical trial included in this sNDA (study 137-150) is a safety clinical trial which only secondarily evaluated several efficacy variables (changes in body weight, pattern of insulin use, and postprandial glucose measurements). By design, comparisons between treatment groups for efficacy and safety variables were done in a context of statistical non-inferiority for glycemic control (equivalent HbA1c reductions at the end of the trial).

B.1 Effects on weight

Consistent with previous observations, pramlintide treatment results in a modest weight loss: by the end of 29 weeks of pramlintide treatment patients lost on average 1.33 ± 0.31 kg relative to baseline (95% CI = 0.60 to 1.78). The full weight reduction was reached at 12 weeks and most of it persisted for the duration of the study. The treatment effect relative to insulin alone was a weight reduction of approximately 2.5 kg ($p<0.001$; 95% CI: 3.2 to 1.6 kg)[6].

B.2 Effect on insulin use

Consistent with observations made in the Phase III efficacy clinical trials, pramlintide treatment has been associated with a reduction in total daily insulin use at the end of the study: 11.7 % relative to baseline[7]. This total daily insulin reduction was primarily the result of a reduction in daily short-acting insulin[8] (approximately 23% on average). Consistent with the current understanding of pramlintide's mechanism of action (i.e. it delays but it does not abolish the absorption of glucose after a meal) the reduction in short acting insulin was associated with an increase in daily basal insulin[9] (12.2±58.3 percent change from baseline).

B.3 Effect on postprandial glucose reduction

Trial 137-150 provides ample evidence that the effect of pramlintide in the reduction of early postprandial glucose excursions is durable over the 29 weeks of the trial for the time points analyzed. This information comes from two sources: (1) postprandial plasma glucose evaluations

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[5] In essence, pramlintide/insulin combination treatment reduced HbA1c at 52 weeks relative to placebo by 0.31% in type 1 diabetes. In type 2 diabetes the HbA1c reduction at 52 weeks relative to placebo was 0.53%.

[6] Patients treated with insulin alone gained on average 1.25±0.24 kg for the duration of the trial (95% CI = 0.63 to 1.81).

[7] Patients treated with insulin alone had an overall increase in daily insulin use of 1.3% at the end of the study (19.7±71% increase in long-acting insulin and 2.3±35.8 % reduction in short-acting insulin).

[8] Short-acting insulin for patients on multiple dose injections and bolus insulin for patients on continuous subcutaneous insulin infusion.

[9] Long-acting insulin for patients on multiple dose injections and basal insulin for patients on continuous subcutaneous insulin infusion.

during a meal-test performed in a subgroup of patients at different timepoints during the clinical trial and (2) self-monitored blood glucose measurements done daily during the course of the clinical trial.

B.4 HbA1c observations

HbA1c reductions relative to baseline were similar between the pramlintide/insulin combination regimen and the insulin alone regimen.[10] Subgroup analyses showed no differences in HbA1c reduction for the two doses of pramlintide: 30-µg pramlintide (< 1/3 of patients) and 60-µg pramlintide (> 2/3 of patients)[11]. The insulin alone regimen resulted in a slightly higher percentage of patients who achieved HbA1c reductions ≤ 7% (ADA recommended)[12] or ≥ 5 % relative to baseline[13] at the end of the 29 weeks of treatment.

In summary, study 137-150 shows that pramlintide/insulin combination treatment results in (1) a modest weight loss relative to baseline, (2) a reduction in total daily insulin use relative to baseline (due primarily to a reduction in short-acting insulin), and (3) durability of effect with respect to the early reduction of postprandial plasma glucose concentrations. When compared with insulin treatment alone, the pramlintide/insulin combination treatment resulted in additional weight loss and a small additional reduction in total daily insulin use, both in the context of an equivalent Hg A1c reduction.

C. Safety Conclusions

Analysis of the safety data from study 137-150 confirms two safety signals already identified in pramlintide-treated patients during the Phase III clinical trials. They are: (1) gastrointestinal adverse events (nausea, vomiting, reduced appetite) and (2) severe hypoglycemia.

C.1 Gastrointestinal adverse events

Similar to observations made in the Phase III efficacy trials, gastrointestinal treatment-emergent adverse events had higher incidence rates in pramlintide treated patients relative to patients treated with insulin alone. To this end, nausea and vomiting occurred twice more frequently, and reduced appetite occurred 4.4 times more frequently in association with pramlintide.

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[10] The HbA1c reduction (LS Mean ±SE) was 0.49±0.07 for insulin alone and 0.47±0.07 for pramlintide/insulin combination. The trial has met the pre-designed non-inferiority margin of 0.4 % HbA1c change from baseline.
[11] Median HbA1c reduction was 0.4% for both doses.
[12] 24.2 % insulin alone and 19.6% insulin plus pramlintide.
[13] 48.9% insulin alone and 43.1 % insulin plus pramlintide.

The dose-titration regimen identified two subgroups of patients with two different degrees of tolerability to pramlintide: a subgroup who could not be titrated beyond 30-µg (< 1/3 of the ITT population) and a subgroup who tolerated the 60-µg dose (>2/3 of the ITT population). The least tolerant patients (the 30-µg subgroup) had a higher incidence of nausea, vomiting, and reduced appetite when compared to the more tolerant patients (60-µg subgroup)[14].

C.2 Severe hypoglycemia

The pramlintide titration regimen did not reduce the imbalance in severe hypoglycemia associated with pramlintide/insulin combination treatment relative to insulin alone treatment that was observed during the Phase III clinical trials. In study 137-150, **severe hypoglycemia occurred approximately twice more frequently in patients on pramlintide** during both the initiation and maintenance periods[15]. Similarly, serious adverse events associated with hypoglycemia occurred more frequently with pramlintide treatment[16]. This imbalance in the incidence of severe hypoglycemia occurs in the context of similar incidence rates of non-severe hypoglycemia.

An analysis of events associated with severe hypoglycemia indicates that gastrointestinal adverse events appear to be a contributing factor. To this end, a greater number of severe hypoglycemic events occurred in pramlintide-treated subjects when nausea was reported on the day of the hypoglycemic event; in addition, twice as many patients on pramlintide reported missed meals or ingested smaller meals in association with pramlintide treatment relative to insulin treatment alone[17].

Patients who showed the least tolerability to pramlintide (the subgroup that could not be titrated beyond 30-µg of pramlintide) displayed the highest incidence of severe

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[14] Nausea occurred twice more frequently with the 30-µg pramlintide dose subgroup relative to the 60-µg pramlintide dose subgroup during both the treatment initiation (first 4 weeks) and maintenance (4 weeks to 29 weeks) periods.

[15] The incidence of severe hypoglycemia was higher in pramlintide treated patients for the whole duration of the study (10.2% insulin alone, 21.6% pramlintide), for the "initiation period" (2.7% insulin alone, 4.7% pramlintide), and for the "maintenance period" (8.4% insulin alone, 17.7% pramlintide).

[16] One placebo patient (0.68%) and four pramlintide patients (2.7%) experienced serious adverse events associated with hypoglycemia.

[17] In a Gastrointestinal Symptom Questionnaire administered to patients who reported nausea and/or vomiting during the previous week of the clinical trial approximately 30% of subjects on pramlintide reported sustained nausea and approximately 3% reported missing a meal due to nausea.

hypoglycemia relative to insulin alone[18]. This observation applies both to the initiation and the maintenance periods. In addition, patients who could not be titrated beyond the 30-µg pramlintide dose appear to be particularly vulnerable to severe hypoglycemia during the first 2 months of insulin optimization as the insulin dose is allowed to increase in order to achieve better glycemic control[19].

C.3 Recognition of hypoglycemia symptoms

A concern that pramlintide may interfere with the patients' ability to recognize symptoms of hypoglycemia was raised during the original NDA review. Evidence from clinical trial 137-150 (similar incidence rates in reporting symptoms of hypoglycemia between the two treatment arms) and evidence from an in depth pharmacodynamic study, do not appear to be substantiate this concern.

C.4. Anti-pramlintide Antibodies

The — manufactured drug product which was tested in study 137-150 appears to be twice more immunogenic relative to the drug products which were evaluated in the efficacy Phase III clinical trials[20]. However, the antibody titers detected are low (1:5 to 1:25).

In summary, the new pramlintide regimen tested in the safety clinical trial 137-150 has not improved the safety of pramlintide/insulin combination treatment relative to insulin treatment alone. An imbalance in incidence of severe hypoglycemia relative to insulin persists even with pramlintide titration. By not succeeding in providing a safer way to initiate pramlintide therapy in patients with type 1 diabetes, the safety profile of pramlintide therapy has not changed significantly from the one observed during the Phase III efficacy trials.

D. Dosing

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[18] In the applicant's own characterization, the occurrence of severe hypoglycemia "*could largely be attributed to the small number of subjects who were unable to escalate beyond the 30 µg pramlintide dose, likely owing primarily to gastrointestinal side effects (nausea) and the resulting risk of temporarily mismatched insulin dose relative to meal size until the nausea resolves.*"

[19] Insulin optimization was started at the end of the 4-week initiation.

[20] An analysis of the antibody titers during the course of trial 137-150 indicates that 15.3 % of pramlintide treated-patients develop anti-pramlintide titers after 25 weeks of treatment compared to 6.1 % of the insulin alone treated patients. During the Phase III clinical trials, in studies up to one year duration, 6.8% and 8.5% of patients with type 1 and type 2 diabetes respectively had been shown to develop anti-pramlintide antibodies during treatment.

The safety trial 137-150 used the same doses of pramlintide (30 μg and 60 μg) and the same route of administration (subcutaneous) employed during the Phase III efficacy clinical trials in patients with type 1 diabetes[21]. It was different, however, in that pramlintide was administered immediately before meals ("0 min.") while in the Phase III clinical trials it was administered earlier ("–15 min.")[22]. The main contribution of the pramlintide titration regimen of study 137-150 with respect to drug administration is twofold: (1) it reduced the proportion of patients who discontinued early the clinical trial due to gastrointestinal adverse events and (2) it identified two relatively distinct patterns of tolerability to the drug; to this end, <1/3 of patients cannot be titrated beyond the 30-μg dose, while > 2/3 of patients tolerate the 60-μg dose.

E. Special Populations

See original NDA review. This sNDA does not provide any additional efficacy or safety analyses by age, race or ethnic background.

F. Risk/Benefit Analysis Conclusions

The new pramlintide regimen utilized in the safety trial 137-150 did not reduce the imbalance of severe hypoglycemia between patients treated with pramlintide/insulin combination and patients treated with insulin alone that was seen during the Phase III efficacy clinical trials and was deemed "unacceptable" in the October 10, 2001 Action Letter. Consequently, study 137-150 has not changed the risk/benefit analysis that formed the basis of the October 10, 2001 regulatory decision.

This reviewer's risk/benefit analysis is at variance with the applicant's risk/benefit assessment. The applicant states that hypoglycemia is "predictable and manageable," that it "should be largely avoidable by lowering the insulin dose during the initiation of pramlintide therapy." The study results indicate that, despite an initial lowering in insulin dose, the incidence of severe hypoglycemia was higher in pramlintide treated patients for the whole duration of the study (10.2% insulin alone, 21.6% pramlintide), for the "initiation period" (2.7% insulin alone, 4.7% pramlintide), and for the "maintenance period" (8.4% insulin alone, 17.7% pramlintide).

Study 137-150 has made important safety contributions to the understanding of the clinical effects of pramlintide. The results of clinical study 137-150 indicate that the change from a "fixed dose" pramlintide regimen to a "titration to tolerability" regimen was successful in reducing the initial impact of nausea. The pramlintide titration regimen dramatically reduced the

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[21] During trial 137-150 pramlintide was administered with the main meals of the day (breakfast, lunch, and dinner). An additional dose was given for large snacks (defined as snacks that contained >30 g of carbohydrates).

[22] Based on observations made during the pharmacokinetic study 137-151 the change from "–15 min." to "0 min." administration results in a slightly more vigorous reduction in postprandial plasma glucose concentrations. Although this change may result in a small increase in efficacy it may also increase the risk of postprandial hypoglycemia.

number of patients who discontinued the trial due to gastrointestinal adverse events. However, this benefit did not extend to a reduction in severe hypoglycemia relative to insulin treatment alone.

Based on our current understanding of pramlintide's mechanism of action, two factors prevent the safe use of pramlintide in patients with type 1 diabetes and appear to contribute to the high incidence of severe hypoglycemia when pramlintide is used in association with insulin: (1) pramlintide-induced gastrointestinal adverse events (nausea, reduced appetite) and (2) the remarkable variability in postprandial glucose reductions relative to preprandial glucose values.

(1) Pramlintide-induced gastrointestinal adverse events result in a reduction of meal size (or even skipped meals) and excess of insulin dose relative to the amount of ingested food. This problem may not be preventable since patients may not be aware of how much nausea they will have at any given meal; since both pramlintide and short-acting insulins are administered prior to meal ingestion, "after the fact" insulin adjustments are not possible. In addition, while the initial impact of pramlintide-induced gastrointestinal adverse events is reduced by the new pramlintide titration regimen, such events persist beyond the titration period[23].

(2) An additional concern to this reviewer is the remarkable magnitude and variability of postprandial reduction in serum glucose relative to preprandial glucose concentrations that is associated with pramlintide/insulin coadministration. In the pharmacodynamic study 137-151, patients had postprandial reductions in serum glucose concentrations as large as 100-120 mg below baseline. Depending, on the actual serum glucose concentrations prior to meal ingestion, the risk of postprandial severe hypoglycemia is

[23] For pramlintide-treated patients only 3 severe hypoglycemic events related to "skipped" or "reduced meals" occurred during the first month of the trial (days 13, 20, and 21), while 9 such events occurred during the rest of the trial (days 70, 74, 94, 100, 116, 124, 125, 156, and 204 respectively). For comparison, in the insulin alone group all severe hypoglycemia events associated with skipped/reduced meals occurred during the first month of the trial (days 4 and 24, respectively).

evident. The postprandial reduction in plasma glucose concentration relative to pre-meal glucose concentrations may be a mechanism independent of nausea/reduced appetite (i.e. related strictly to the large variability in gastric emptying time that follows pramlintide administration). The applicant does not provide any information that allows to predict which patients are at risk to have significant reductions in postprandial serum glucose concentrations.

Finally, since patients enrolled in study 137-150 were metabolically stable (absence of severe hypoglycemia over the preceding 6 months was an entry criterion), giving pramlintide to a less stable population has the potential risk of resulting in higher incidence rates of severe hypoglycemia.

In conclusion, clinical trial 137-150, has failed to improve the safety profile of this drug, when used in combination with insulin, over the one established during the Phase III clinical trials which was deemed not safe by the July 26, 2001 Endocrinologic and Metabolic Drug Advisory Committee and by the prior safety review.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Pramlintide acetate (brand name: SYMLIN™) is a synthetic analogue of human amylin. Amylin is a 37-amino acid hormone that is stored with insulin in secretory granules inside the pancreatic β-cell and is co-secreted with insulin in response to nutrient stimuli. Amylin plays a role in glucose homeostasis via several mechanisms: (1) it reduces gastric motility following a meal and subsequently slows down the delivery of glucose to the systemic circulation, (2) it reduces food intake through effects on satiety, and (3) it regulates postprandial glucagon secretion. Pramlintide is different structurally from human amylin in that amino acids at positions 25 (alanine), 28 (serine), and 29 (serine) are replaced with proline. Pramlintide maintains amylinomimetic effect while being more soluble and stable than the native amylin molecule.

Pramlintide acetate is a new molecular entity. It is the first and only amylinomimetic in development so far. In a larger physiological context, it belongs to a new group of antidiabetic drugs that, among other mechanisms of action, reduce gastric motility and secondarily blunt the postprandial glucose excursions.

The applicant's proposed indication for pramlintide acetate is: " [redacted]

The proposed doses of pramlintide acetate are 30-µg or 60-µg for patients with type 1 diabetes and 120-µg for patients with type 2 diabetes. Pramlintide acetate (further referred to as pramlintide) is to be administered immediately prior to major meals or any snack containing ≥30 g of carbohydrate. The age targeted for use is > 16 years.

B. State of Armamentarium for Indication

The treatment of type 1 diabetes is insulin. No drugs are currently approved for the treatment of type 1 diabetes in addition to insulin.

For type 2 diabetes, several drug products are currently approved, some to be used in conjunction with insulin (e.g. metformin, TZDs, sulphonylureas). They have mechanisms of action that are distinct from that of pramlintide.

C. Important Milestones in Product Development

This application is a resubmission of the SYMLIN™ (pramlintide acetate) NDA. A brief chronology of the main regulatory events that occurred following the original NDA submission follows:

December 08, 2000: Amylin Pharmaceuticals INC. submitted a New Drug Application in favor of pramlintide acetate.

July 26, 2001: The Endocrinologic and Metabolic Drugs Advisory Committee met and evaluated the efficacy and safety of pramlintide acetate in patients with type 1 and type 2 diabetes. The main questions asked by the Agency and the associated tally are presented in abbreviated form in Table 1. The Committee voted 8 to 1 against approval of pramlintide in type1 diabetes and 6 to 3 against approval of pramlintide in type 2 diabetes[24].

Table 1: Advisory Committee Response to Questions Regarding the Efficacy and Safety of Pramlintide

Question	Type 1 Diabetes		Type 2 Diabetes	
	Yes	No	Yes	No

[24] Source: Final Minutes of the July 26, 2001, Endocrinologic and Metabolic Advisory Committee.

Was the efficacy of pramlintide treatment in combination with insulin established?	8	1	8	1
Were the study designs adequate to guide physicians in the effective use of pramlintide in combination to insulin?	0	9	0	9
Are the data adequate to define the safety profile of pramlintide when used in combination with insulin?	1	8	2	7
Do you recommend approval of pramlintide for use in combination with insulin?	1	8	3	6

October 10, 2001: The Agency issued an approvable letter in response to the December 8, 2000 NDA. The agency listed several deficiencies. Of these, four were clinical and are listed below:

- The safety profile of Symlin ™ was found "unacceptable" due to an "increased risk of severe hypoglycemia relative to insulin alone" in patients with type 1 and type 2 diabetes, "particularly in the first month of therapy." An increased risk of serious adverse events associated with hypoglycemia (including motor vehicle accidents and other injuries) was also noted in patients with type 1 diabetes.
- The application did not provide enough evidence to exclude a role for Symlin ™ in lowering the threshold for hypoglycemia awareness.
- An apparent dose-dependent increase in progression of diabetic retinopathy associated with Symlin ™ therapy relative to insulin alone was observed in one study in patients with type 2 diabetes[25].
- The applicant has not adequately characterized the antibody response to Symlin ™ produced by the drug substance manufactured by — manufacturer.

November 21, 2001: An end-of-NDA review meting took place between the Agency and Amylin Pharmaceuticals representatives. The deficiencies listed in the approvable letter and the applicant's proposal for studies that would address these shortcomings were discussed.

April 9, 2002: A teleconference took place between the Division representatives and members of the Amylin Pharmaceuticals team in which the division provided further guidance concerning the protocol for study 137-150 (the clinical safety study included in this submission).

D. Other Relevant Information/Foreign Marketing History

Pramlintide is not currently approved in any country.

E. Important Issues with Pharmacologically Related Agents

Pramlintide acetate is the first drug in its class. Therefore there are no pharmacologically related medications.

[25] In a subsequent End-of-NDA-Review Meeting it was agreed by the Division that the potential increase in risk of retinopathy progression will be evaluated in an open-label Phase 4 study. This study will be conducted in approximately 500 patients with either type 1 or type 2 diabetes over 3 years.

II. Clinically Relevant Findings From Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The statistical review agrees with the applicant's statistical analysis of HbA1c reduction in study 137-150.

The biopharmaceutical review concludes with the following comments:

- The type 1 obese patients showed lower pramlintide exposure compared to that in other patient groups (i.e., type 1 non-obese, type 2 obese, and type 2 non-obese). In the original NDA, the pramlintide exposure in type 2 diabetes appeared to be lower than that in type 1 diabetes according to the observations. In this regard, the relative bioavailability difference between types of diabetic patient was not conclusive.
- The abdomen, arm and thigh were proposed as injection sites. The exposure after injection into thigh was not different from that after in abdomen. However, pramlintide exposure as AUC was 20-36% higher after arm injection compared to that in abdomen for obese patients. Therefore, arm should be cautiously considered as an alternative injection site for obese patients because of hypoglycemic safety concern with the higher exposure.
- The primary pharmacodynamic endpoint was the plasma glucose concentration-time curve from time zero to last time point ($AUC_{0\text{-}4hr}$). However, the AUC was not an optimal PD endpoint because of averaging nature between below and above the baseline (fasting glucose level).
- Inhibition of postprandial glucose excursion was one of the proposed beneficial effects of pramlintide. Mean maximum postprandial glucose elevation ($C_{max,glu}$) was observed as 87.2mg/dL for placebo (insulin alone), 77.7mg/dL for pramlintide dosing 15 minutes before breakfast, and 47.2mg/dL for pramlintide dosing immediate before breakfast in type 1 using lispro insulin group. However, the elevated glucose levels ($C_{max,glu}$) were observed at the last sampling of the study (i.e., 4 hours after breakfast). The some levels were as close as the maximum postprandial glucose elevations of placebo. In these regards, it was premature to assess the beneficial role of pramlintide to postprandial glucose excursion based on the results in the type 1 using lispro insluin. Comparison of individual data across treatments may provide further insight

of the results that were with significant inter-subject variability.

III. Human Pharmacokinetics and Pharmacodynamics

The applicant presents five newly conducted pharmacokinetic (PK) and pharmacodynamic (PD) studies. Four of these (studies 137-151, 137-152, 137-153, 137-154) are in response to the deficiencies listed in the Approvable Letter, dated October 10, 2001.

Pharmacokinetic Studies

Study 137-153[26]

The full title of study 137-153 is: "A Randomized, Open-Label, Crossover Study to Examine the Absolute Bioavailability of Pramlintide When Injected Subcutaneously at Various Anatomical Sites in Non-obese and Obese Subjects With Type 1 and Type 2 Diabetes Mellitus Using Insulin."

The primary objective of the study was to determine the effect of various anatomical injection sites and varying needle lengths upon the absolute bioavailability of pramlintide when injected subcutaneously. The patient population consisted in non-obese and obese subjects with type 1 and type 2 diabetes mellitus using insulin. On 4 consecutive study days, subjects received a single dose of pramlintide[27] administered subcutaneously (SC) into one of four injection sites. On the fifth study day, all subjects received a single intravenous (IV) bolus dose of pramlintide (20 μg). All doses were administered immediately prior to breakfast.

The study population consisted of four study groups defined by diabetes type and BMI:
Study Group 1: non-obese subjects with type 1 diabetes (BMI $\leq$27 kg/m^2)
Study Group 2: obese subjects with type 1 diabetes (BMI 30 kg/ m^2 to 45 kg/m^2, inclusive)
Study Group 3: non-obese subjects with type 2 diabetes (BMI $\leq$27 kg/m^2)
Study Group 4: obese subjects with type 2 diabetes (BMI 30 kg/ m^2 to 45 kg/m^2, inclusive)

[26] See clinical pharmacology review for analysis.

[27] The dose was 60 μg for subjects with type 1 diabetes and 120 μg for subjects with type 2 diabetes.

Subjects were randomly assigned to one of four treatment sequences. Each sequence was defined by the injection site and the size of the needle use as follows:

Sequence A: Abdomen (SC) 6.0-mm needle

Sequence B: Abdomen (SC) 12.7-mm needle

Sequence C: Arm (SC) 12.7-mm needle

Sequence D: Thigh (SC) 12.7-mm needle

Sequence E: IV bolus

The applicant proposes the following conclusions:

- In both subjects with type 1 and type 2 diabetes, SC injection of pramlintide into sites over the anterior abdominal wall appears optimal in terms of pramlintide bioavailability.
- In general, SC injection of pramlintide into the extremities (arm or thigh) provides a similar pattern of bioavailability to that seen following injection into the abdominal site.
- In both subjects with type 1 and type 2 diabetes, SC injection of pramlintide using either a 6.0 mm or 12.7-mm needle length resulted in similar pramlintide bioavailability.
- Body adiposity (BMI and skinfold thickness) do not appear to be a major contributor to the plasma pramlintide concentrations in subjects with type 1 or type 2 diabetes.
- The approximate two-fold increase in plasma pramlintide concentrations observed following a 120-µg dose in type 2 subjects, compared to a 60 µg dose in type 1 suggests that other factors than body adiposity contributes to the higher dosing requirements for type 2 subjects (e.g., amylin/pramlintide resistance).

Study 137-154[28]

The full title of study 137-154 is: "A randomized, single-blind, placebo-controlled, crossover study to examine the effect of pramlintide on the pharmacokinetics of an orally administered concomitant medication given at various times in relation to pramlintide dosing in subjects with type 2 diabetes."

[28] See pharmacology review for analysis.

The primary objective was to examine the effects of pramlintide on the pharmacokinetics of acetaminophen when administered at different times in relation to subcutaneous pramlintide injections. On consecutive study days, subjects with type 2 diabetes received one of six treatments in random order. Each treatment was defined primarily by the timing of oral acetaminophen administration[29] relative to the time of injection of study medication. Twenty-four subjects with type 2 diabetes were enrolled in the study. Primary and secondary endpoints were standard pharmacokinetic variables. The applicant concludes the following:

- pramlintide appeared to affect the rate of absorption but not the extent of exposure of acetominophen when it was administered with pramlintide or during the 2 h after pramlintide dosing
- for oral medications with rapid absorption profiles whose primary efficacy depends on rapid absorption and C_{max}, administration should occur at least 1 h prior to pramlintide administration or be postponed until approximately 3 h after pramlintide administration to insure that pramlintide does not impair the oral medication's efficacy
- oral medications whose efficacy depends primarily on the extent of absorption may be given at any time relative to pramlintide administration, with no loss of efficacy
- with the exception of analgesics, rapid acting sedatives, and certain antibiotics, most orally administered medications used by subjects with type 1 and type 2 diabetes treated with insulin, including commonly used oral hypoglycemic agents, "should not be impacted by the observed effects of pramlintide".

Pharmacodynamic Studies

[29] 1000 mg given at the following times relative to pramlintide injection: -2h, -1h, 0h, +1h, and +2h.

Study 137-146[30]

The full title of study 137-146 is: "A placebo-controlled, single-blind, pilot study to examine the effects of adjunctive pramlintide therapy on glucose fluctuations in subjects with type 1 diabetes mellitus utilizing continuous subcutaneous insulin infusion (CSII)."

The primary objective was to examine the effects of 4 weeks of adjunctive pramlintide treatment on glucose excursions during a 24-hour period as assessed using the [redacted] Continuous Glucose Monitoring System (CGMS) in subjects with type 1 diabetes mellitus utilizing continuous subcutaneous insulin infusion. Secondary objectives were: (1) to examine the effects of 4 weeks of adjunctive pramlintide treatment on glucose excursions after a standardized meal test and (2) to assess safety and tolerability.

Twenty-four male and female subjects age 16 and older with type 1 diabetes mellitus utilizing CSII for at least 6 months prior to screening received study medication. The study consisted of three periods (Baseline, On-Therapy, and Off-Therapy). During each period, subjects received a standardized breakfast and underwent 72-hour glucose monitoring using the CGMS. Study medication (pramlintide or placebo) was administered in a double-blind fashion TID at the same time as meals (breakfast, lunch, and dinner). Subjects had a 10%- to 20% reduction in preprandial boluses of short-acting insulin during the first 3 days of the On-Therapy period. After that time, preprandial insulin boluses were to be adjusted based on investigator discretion. The Pramlintide dose was 30-µg TID given as a subcutaneous injection.

The mean percent of interstitial fluid glucose measurements within selected concentration intervals during a 24-hr period are presented in Table 2 by treatment and by each of the three treatment periods: Baseline, On-Therapy, and Off-Therapy. During the Baseline period, subjects in the pramlintide group exhibited 24-hour interstitial fluid glucose fluctuations as follows: 58.2% of measurements above 140 mg/dL, 13.3% of measurements below 80 mg/dL, and 28.1% of measurements within the euglycemic

[30] See pharmacology review for analysis.

target range (80-140 mg/dL). After 4 weeks of pramlintide 30-μg TID (end of On-Therapy period), there was an increase in measurements within the euglycemic target range from 28.1 % to 37.2 (a 32% increase). For the placebo-treated subjects measurements within the euglycemic target range were similar between baseline and end of trial (24.5% and 27.8%, respectively).

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Table 2: Mean Percent of Interstitial Fluid Glucose Measurements Within Selected Concentration Intervals During a 24-Hour Period

Mean (SE) Percent of Interstitial Fluid Glucose Measurements Within Selected Concentration Intervals During a 24-Hour Period						
	Placebo (N=16)			Pramlintide 30 µg TID (N=16)		
Glucose (mg/dL)	Baseline	On-Therapy	Off-Therapy	Baseline	On-Therapy	Off-Therapy
240 - <80	26.5 (8.5)	19.4 (4.6)	26.1 (8.2)	13.3 (3.7)	15.1 (4.0)	16.0 (3.5)
80 - <140	24.5 (8.9)	27.8 (3.0)	29.0 (4.9)	28.1 (3.7)	37.2 (3.8)	26.4 (4.2)
>140	48.5 (9.1)	52.3 (7.0)	44.5 (9.8)	58.2 (5.6)	47.2 (5.7)	57.6 (6.2)
>200	28.8 (8.8)	25.3 (8.3)	25.7 (11.0)	30.4 (6.3)	21.6 (5.0)	28.7 (5.2)
>300	6.5 (4.3)	7.3 (4.4)	8.1 (6.8)	8.0 (2.9)	4.9 (2.2)	5.4 (2.7)

Source: Synopsis of Study 137-146.

The applicant concludes that, "in subjects with type 1 diabetes mellitus utilizing CSII, adjunctive SC administration of pramlintide 30 µg TID for 4 weeks elicited a reduction in glucose fluctuations as evidenced by a shift of glucose readings from the hyperglycemic to euglycemic range throughout a representative 24-hour period."

Study 137-151

The full title of Study 135-151 is: "A Randomized, Single-Blind, Placebo-Controlled, Crossover Study to Examine the Effect of Pramlintide Dose Timing on Postprandial Plasma Glucose Profiles in Subjects With Type 1 Diabetes Mellitus and Subjects With Type 2 Diabetes Mellitus Using Insulin."

The primary objective was to determine the effect of the timing of pramlintide injection relative to meal ingestion on postprandial plasma glucose profiles in subjects with type 1 and type 2 diabetes using insulin. Three study groups were defined by diabetes type and type of mealtime insulin used in their treatment regimen. They were:

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

In this five-way crossover study subjects received a single dose of one of five treatments (A, B, C, D, or E) in random order:

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

Each treatment (pramlintide or placebo) was administered subcutaneously within specified times relative to a standardized breakfast after an overnight fast. Subjects were randomly assigned to one of four treatment sequences according to a randomization schedule generated for each study group. Dosing differed for subjects with type 1 and type 2 diabetes so that subjects received, for the purposes of this study, the highest proposed dose of pramlintide for the type of diabetes they had. Subjects with type 1 diabetes received pramlintide 60-µg or placebo. Subjects with type 2 diabetes using insulin received pramlintide 120-µg or placebo. Fifty-nine subjects (21 type 1 subjects using insulin lispro, 19 type 1 subjects using regular insulin, and 19 type 2 subjects using insulin lispro) were enrolled in this study.

Table 3 displays the mean plasma glucose $AUC_{(0\text{-}4\ h)}$ for each of the three study groups and, within each study group, for each injection time and treatment. Within each study group, the mean plasma glucose $AUC_{(0\text{-}4\ h)}$ for each pramlintide injection time was lower than the value observed following placebo injection. In general, pramlintide injections given immediately before the meal ("0 min.") appeared to have the most robust effect on mean plasma glucose $AUC_{(0\text{-}4\ h)}$ when used in association with insulin lispro. This observation was more clearly made in patients with type 1 diabetes who received insulin lispro.

For subjects with type 1 diabetes receiving regular insulin, the "+30 min" timepoint showed comparative effectiveness to earlier timepoints. The maximum reduction in postprandial glucose excursions within the first 30 minutes following pramlintide dosing is consistent with the known pharmacokinetic characteristics of pramlintide (peak plasma pramlintide concentrations occur at ~20 min relative to pramlintide injection time).

Table 3: Incremental Mean Plasma Glucose $AUC_{(0-4\ h)}$ (mg·h/dL) Following a Standardized Breakfast by Study Group and by Treatment (Evaluable Subjects, N=57)

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

Source: Table 11/Summary

The effects of the timing of pramlintide injection on the postprandial plasma glucose excursions for each study group are presented graphically in the next three figures. Figure 1 presents the mean plasma glucose concentration-time profiles of pramlintide in subjects with type 1 diabetes using insulin lispro.

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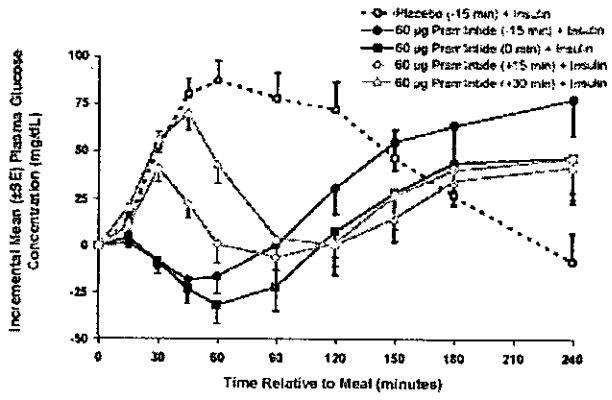
Figure 1: Mean (SE) Plasma Glucose Concentrations by Treatment (Evaluable Type 1 Subjects Using Insulin Lispro, N=20)



Source: Figure 7/Summary

The following observations are derived from this figure:

- The magnitude of reduction in postprandial glucose excursions was most pronounced for the "0 min" and "-15 min" pramlintide injection time points. These early reductions in plasma glucose concentrations were accompanied by a mean (± SE) reduction of plasma glucose below baseline values, which was lowest at 45 min (-18.3 ± 29.6 mg/dL) for the "–15 min" pramlintide injection and at 60 min (-31.9±43 mg/dL) for the "0 min" pramlintide injection, respectively[31].
- Pramlintide administration at 0 min appeared to have a greater impact on the reduction of postprandial glucose excursions during the first 2-hours of the postprandial period; it also was associated with the greatest reduction in plasma glucose concentration below baseline. This dose timing, which was selected for the

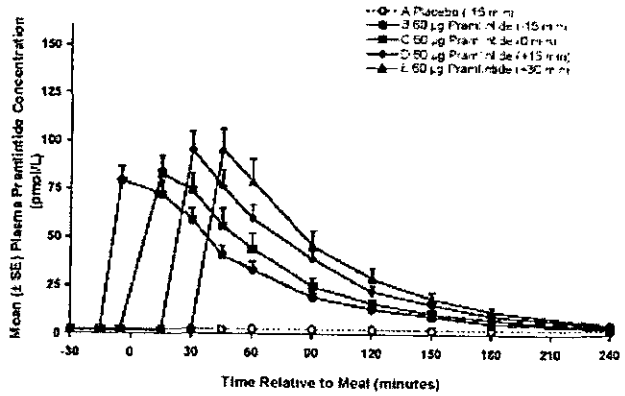
[31] Individual plasma glucose reductions were even lower as evidenced by the magnitude of the standard error and by the range of glucose changes (some were > 100 mg below premeal serum glucose concentration).

clinical trial 137-150, has the largest potential for clinical efficacy but also carries the highest risk of hypoglycemia.

- When pramlintide was administered at +15 and +30 minutes the pattern of postprandial plasma glucose was different than that observed for the –15 and 0 min. Plasma glucose concentrations increased immediately following ingestion of breakfast (somewhat similar to the early glucose rise observed with the placebo injection). Subsequently, the mean plasma glucose concentrations began to decrease reaching a minimum mean plasma glucose concentration observed at 90 min for +15 min (-6.3 ±65.1 mg/dL) and 120 min for +30 min (0.5 ± 51.1 mg/dL).

The above-summarized observations were made in the context of a study during which the pramlintide pharmacokinetic profiles were remarkably consistent and reproducible (similar mean plasma pramlintide concentration-time profiles: Figure 2).

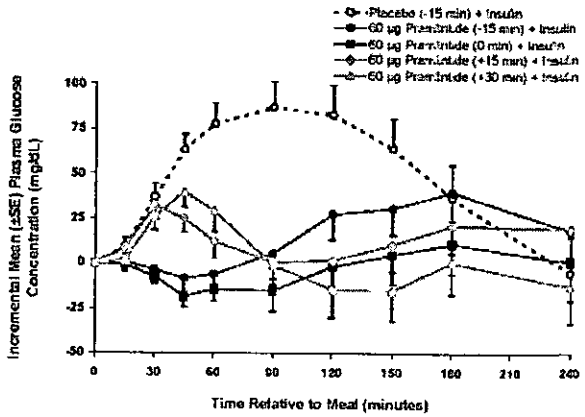
Figure 2: Mean (SE) Plasma Pramlintide Concentration-Time Curves by Treatment (Evaluable Type 1 Subjects Using Insulin Lispro N=20)



Source: Figure 8/Summary

Figure 3 presents the mean plasma glucose concentration-time profiles of pramlintide in subjects with type 1 diabetes using regular insulin.

Figure 3: Mean (SE) Plasma Glucose Concentrations by Treatment (Evaluable Type 1 Subjects Using Regular Insulin, N=18)



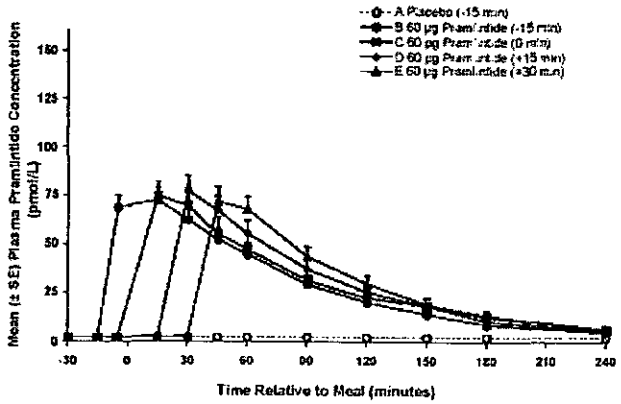
Source: Figure 9/Summary

The postprandial glucose profiles for regular insulin are, in general, similar to those observed for insulin lispro. Several differences are worth highlighting:

- The early reduction (relative to baseline) in postprandial plasma glucose concentrations seen with the –15 and 0 min pramlintide injection times is less pronounced with regular insulin when compared to insulin lispro. (To this end, pramlintide administration at "-15 min" and "0 min" results in mean decreases in plasma glucose concentrations below baseline values of -8.4 ± 37.6 mg/dL and -18.5 ± 24.6 mg/dL at 45 min, respectively.
- During the late part of the postprandial period, mean plasma glucose concentrations remain lower than placebo for longer periods of time (i.e. beyond 180 minutes following meal ingestion).

As it was the case for insulin lispro, the above-summarized observations were made in the context of a study during which pramlintide pharmacokinetic profiles were remarkably consistent and reproducible between different injections (similar mean plasma pramlintide concentration-time profiles: Figure 4).

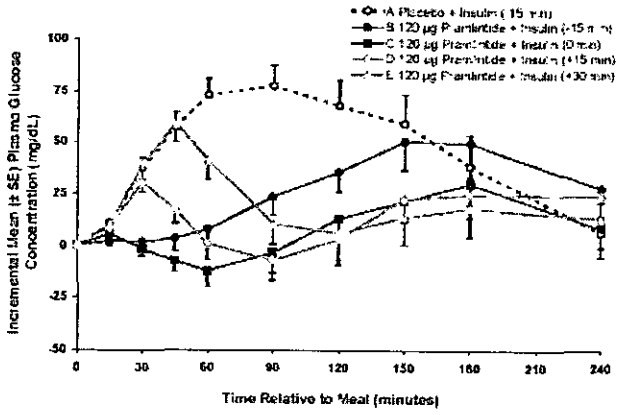
Figure 4: Mean (SE) Plasma Pramlintide Concentration-Time Curves by Treatment (Evaluable Type 1 Subjects Using Regular Insulin, N=18)



Source: Figure 10/Summary

Figure 5 presents the mean plasma glucose concentration-time profiles of pramlintide in subjects with type 2 diabetes using insulin lispro.

Figure 5: Mean (SE) Plasma Glucose Concentrations by Treatment (Evaluable Type 2 Subjects Using Insulin



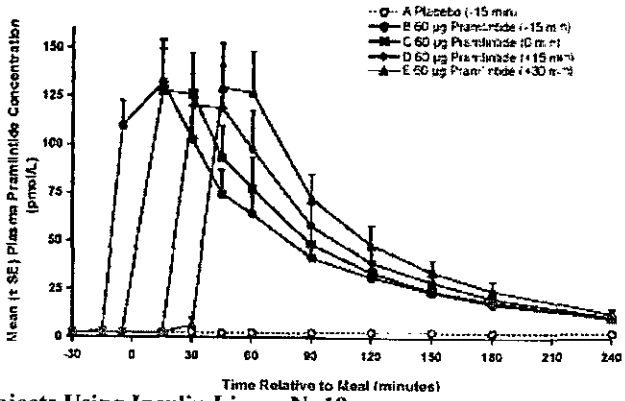
lispro, N=19)

Source: Figure 11/Summary

In general, the postprandial glucose profiles for insulin lispro in patients with type 2 diabetes share similarities with both the insulin lispro and regular insulin profiles in type 1 diabetes patients. It should be noted that the reductions in plasma postprandial glucose concentrations below baseline values were less marked in type 2 diabetes patients relative to type 1 diabetes patients despite using the same type of insulin (insulin lispro) but different doses of pramlintide. Thus, with pramlintide administration at "-15 min" and "0 min", the maximum decreases in mean postprandial plasma glucose concentrations were observed at 30 min (1.7 ± 16.2 mg/dL) and 60 min (-12.3 ± 33.3 mg/dL), respectively. For the "+15 min" and "+30 min" pramlintide injections the minimum mean plasma glucose concentrations were

observed at 90 min (-7.2 ± 40.6 mg/dL) and 120 min (5.7 ± 54.8 mg/dL), respectively. These observations were made in the context of a study during which pramlintide pharmacokinetic profiles were remarkably consistent and reproducible between different injections (similar mean plasma pramlintide concentration-time profiles: Figure 6).

Figure 6: Mean (SE) Plasma Pramlintide Concentration-Time Curves by Treatment (Evaluable Type 2



Subjects Using Insulin Lispro N=19

Source: Figure 12/Summary

The applicant concludes that "in subjects with type 1 diabetes and insulin-using subjects with type 2 diabetes, subcutaneous administration of pramlintide immediately prior to meal ingestion (0 min) is optimal in terms of reduction in postprandial glucose excursions". This conclusion, however, relates primarily to the efficacy of the drug. With respect to safety, this study identifies a vulnerability to glucose reductions below baseline, in particular for patients with type 1 diabetes using insulin lispro. In this study group, the lowest mean serum glucose concentration below baseline was (-31.9 ± 43 mg/dL). In some patients, such a reduction can be significant depending on how low the baseline serum glucose value is. Such glucose reductions can produce postprandial serum glucose values in the hypoglycemic range.

Study 137-152

The full title of this study is: "A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study in Healthy Volunteers to Assess the Effects of Pramlintide Upon the Recognition of Hypoglycemic Symptoms."

The primary objective of the study was to assess the effect of pramlintide on the subjects' ability to recognize symptoms associated with hypoglycemia during a three-stepped hypoglycemic clamp in healthy volunteers (the three glycemic target levels were 70 mg/dL, 55 mg/dL, and 45 mg/dL),. The primary study endpoint was the change from baseline in the average percent scores for each of the 11 questions on the hypoglycemic symptom questionnaires administered at the end (50- and 60-min timepoints) of each hypoglycemic clamp step[32]. The secondary objective was to assess the effect of pramlintide on plasma catecholamine concentrations[33].

The study consisted in two 6-day treatment periods during which subjects were domiciled. Utilizing a cross-over design, subjects were randomly assigned to one of two treatment sequences (A:B or B:A), where A was placebo and B was pramlintide 60 µg. During both treatment periods, subjects received 0.1 mL of study medication (pramlintide [60 µg] or placebo) three times daily (TID) for 5 consecutive days (Days 1 through 5). Study medication was administered subcutaneously within 15 minutes prior to meals. On Day 6, subjects underwent a 3-hour, three-stepped, hypoglycemic clamp[34]. Each subject's blood glucose concentration was clamped at three glycemic target levels (70 mg/dL, 55 mg/dL, and 45 mg/dL), each hypoglycemic clamp step lasting for approximately 60 minutes[35].

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[32] Individual hypoglycemic symptoms assessed by the questionnaire were grouped into autonomic symptoms (sweating, palpitation/heart pounding, shaking/trembling, hunger, and nausea/sickness) and neuroglycopenic symptoms (confused/muddled, drowsy/sleepy, odd/strange behavior, difficulty speaking, incoordination, and headache).

[33] The secondary study endpoints included the plasma catecholamine concentrations (epinephrine and norepinephrine) measured at 30- and 60-min intervals and the change from baseline in plasma catecholamine concentrations measured at 30- and 60-min intervals of each clamp step.

[34] Subjects received 0.1 mL of study medication (pramlintide [60 µ] or placebo) SC at approximately 0800 within 15 minutes prior to breakfast. After consuming breakfast, subjects were to fast. At approximately 1530, subjects were connected to an artificial pancreas. — A 60-min baseline period (t=0 min to t=60 min) began and plasma glucose concentrations were recorded. Throughout the 3-hour clamp procedure, a primed (~4 g pramlintide or equivalent volume of placebo), continuous intravenous (IV) infusion of study medication (pramlintide [~16 g/h] or placebo [equivalent volume/h]) was administered from t=60 min until the end of the clamp (t=240 min). Timing was relative to the start of the baseline period (t=0 min).

[35] In eight subjects who were resistant to reaching the final blood glucose target (45 mg/dL), the clamp period was extended beyond the allotted 60 minutes in order to provide a total 60-minute period at the glucose target (45 mg/dL). A validated, standardized, hypoglycemic symptom questionnaire was

Mean (SD) Baseline and Mean (SD) Changes From Baseline in Composite Hypoglycemic Symptoms Questionnaire Scores by Symptom Group and Treatment (Population: Evaluable Subjects in Protocol 137-152; N=17)

		Placebo			Pramlintide		
Symptom Group	Glucose Concentration	n	Mean	SD	n	Mean	SD
Autonomic[*]	Baseline[‡]	17	2.1	3.7	17	1.0	1.8
		Change From Baseline[§]					
	70 mg/dl.	17	+0.4	0.8	17	+0.4	1.4
	55 mg/dl.	17	+5.3	7.2	17	+2.3	3.8
	45 mg/dl.	17	+13.9	13.7	17	+13.4	11.4
Neuroglycopenic[†]	Baseline[‡]	17	0.7	1.9	17	1.0	1.7
		Change From Baseline[§]					
	70 mg/dl.	17	+0.5	1.2	17	+0.8	1.4
	55 mg/dl.	17	+1.9	4.6	17	+1.1	2.1
	45 mg/dl.	17	+1.6	3.3	17	+0.9	2.1

[*] Questions regarding sweating, palpitation heart pounding, shaking trembling, hunger, and nausea sickness.
[†] Questions regarding confused muddled, drowsy sleepy, odd strange behavior, difficulty speaking, incoordination, and headache.
[‡] Baseline scores were the average of the percent scores at 50 and 60 minutes during the baseline period
[§] Change from baseline is the average of the percent scores at 50 and 60 minutes during the hypoglycemic clamp steps minus the average of the percent scores at 50 and 60 minutes during the baseline period.

The mean changes from baseline in composite hypoglycemic symptoms questionnaire by symptom group (autonomic vs. neuroglycopenic) and treatment (placebo vs. pramlintide) are presented above (Table 4). In general, the changes in hypoglycemic symptoms scores were similar between the two treatment groups. The changes from baseline in autonomic symptom scores were very similar at the 70 mg/dl glucose concentration [+0.4(±0.8) placebo and +0.4(± 1.4) pramlintide] and at the 45 mg glucose, which was the lowest level achieved [+13.9(±13.7) placebo and 13.4 (±11.4) pramlintide]. An imbalance between treatment groups in autonomic symptom scores changes from baseline was noticed for the 55 mg/dl glucose concentration.

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The changes from baseline in neuroglycopenic symptom scores were lower in the pramlintide group for both the 55 mg/dl glucose concentration [+1.9(± 4.6) placebo and

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administered employing Visual Analog Scales at the 50- and 60-min timepoints of each 60-min interval. Blood samples for the measurement of plasma glucose, insulin, pramlintide, epinephrine, and norepinephrine concentrations were collected at baseline and at 30-min intervals throughout the clamp. At the end of the clamp, glucose was infused to allow plasma glucose concentrations to return to the normal range, and subjects ate a meal with continued blood glucose monitoring. Subjects were to remain domiciled for observation until discharge the next morning (Day 7).

1.1(±2.1) pramlintide] and the 45 mg/dl glucose concentration [1.6(±3.3) placebo and 0.9(±2.1) pramlintide].

Mean catecholamine concentrations measured during the hypoglycemic clamp were similar between the two treatment groups (Table 5, below).

Mean (SD) Baseline and Mean (SD) Changes From Baseline in Catecholamine Concentrations During the 3-hour, Three-stepped Hypoglycemic Clamp Procedure by Treatment (Population: Evaluable Subjects in Protocol 137-152; N=17)

		Placebo			Pramlintide		
Variable	Clamp Step/ Glucose Concentration	n	Mean	SD	n	Mean	SD
Epinephrine (pg/mL)	Baseline*	17	178.4	105.2	17	162.2	108.2
		60-min Change From Baseline†					
	70 mg/dl	17	+54.2	170.8	17	−39.9	102.4
	55 mg/dl	17	+713.4	361.6	17	+611.5	425.5
	45 mg/dl	17	+2169	1260.6	17	+2588.4	1609.3
Norepinephrine (pg/mL)	Baseline*	17	1135.7	308.0	17	1114.8	245.4
		60-min Change From Baseline†					
	70 mg/dl	17	-27.6	449.4	17	+163.5	341.9
	55 mg/dl	17	+300.2	318.2	17	+144.4	321.0
	45 mg/dl	17	+581.9	393.5	17	+465.5	473.0

*Average of the baseline concentrations measured at 30 and 60 minutes
†Change from baseline is the concentration during the hypoglycemic clamp step minus the average of the 30 and 60-min concentrations during the baseline period

Changes from baseline in autonomic symptoms scores for individual subjects are presented below. With the exemption of an outlier in the placebo group (subject 9017) the responses were similar during pramlintide and placebo administration (applicant's Figure 4).

Figure 4: Changes From Baseline in Composite Autonomic Symptoms Scores (%) By Subject (Population: Evaluable Subjects in Protocol 137-152; N=17)

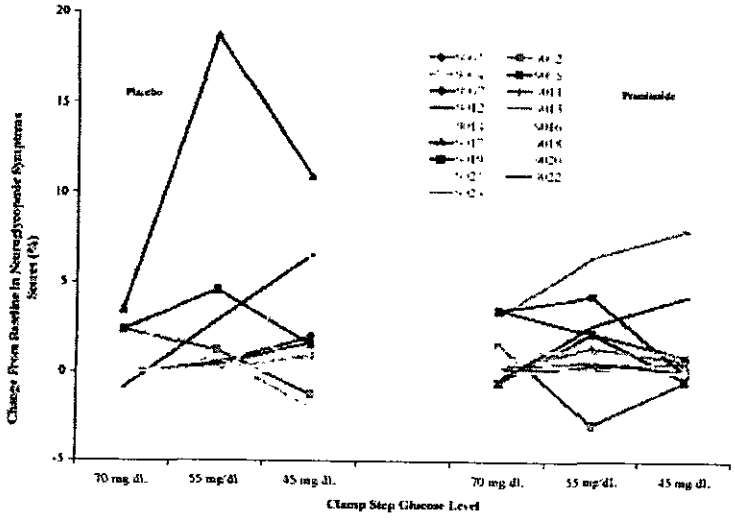

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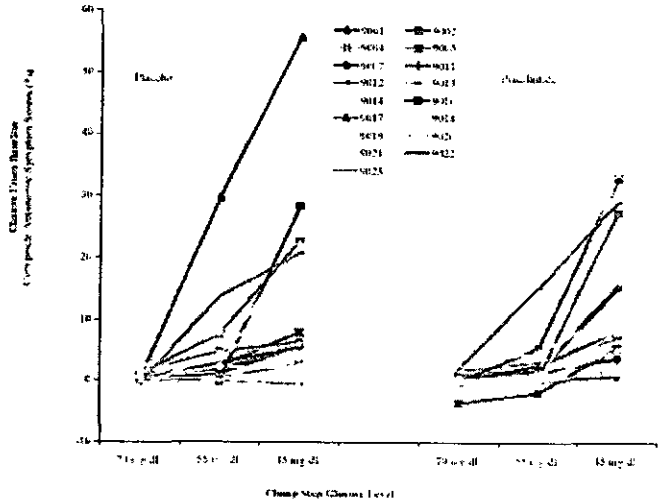
Figure 5: Change From Baseline in Composite Neuroglycopenic Symptoms Scores (%) By Subject (Population Evaluable Subjects in Protocol 137-152. N 17)



In conclusion, study 137-152 does not identify any consistent differences between pramlintide[36] and placebo administration in terms of (1) mean autonomic and (2) mean neuroglycopenic symptom responses to plasma glucose concentrations as low as 45 mg/dL. Individual subject analyses reveal various degree of variability for the components evaluated. This study corroborates the observations made in the clinical trial 137-150 which showed similar incidence of symptoms of hypoglycemia recognized by patients on pramlintide or placebo.

IV. Description of Clinical Data and Sources

A. Overall Data

The main source of clinical data in this review is study 137-150. This clinical trial was conducted in response to the Approvable Letter issued by the Agency on October 10, 2001. Two pharmacokinetic and three pharmacodynamic studies were also submitted along to study 137-150. All but oneof these studies were requested by the Division at the end of the first review cycle.

[36]Pramlintide infusion rate of 16 µg/h.

B. Tables Listing the Clinical Trials

The safety clinical trial 137-150 and the five pharmacokinetic/pharmacodynamic studies are listed in Table 6.

Table 6: Summary of Studies Reviewed

Study number	Objective	Type of Study/Patient population
137-150	To compare the incidence of severe hypoglycemia between a cohort of patients treated with combined pramlintide and insulin regimen and a cohort of patients treated with insulin alone (i.e. insulin and placebo)	Safety clinical study/type 1 diabetes patients
137-151	To study the effect of timing of pramlintide injection relative to meals on postprandial plasma glucose profiles in patients with diabetes using insulin	Pharmacodynamic study/type 1 and type 2 diabetes patients
137-152	To study the effect of pramlintide on recognition of hypoglycemic symptoms and counter-regulatory hormone responses	Pharmacodynamic study/healthy volunteers
137-153	To study the effect of anatomical injection site and needle length on pramlintide bioavailability	Pharmacokinetic study/lean and obese type 1 and type 2 diabetes patients
137-154	To study the effect of pramlintide on the pharmacokinetics of orally administered acetaminophen when acetaminophen was administered at various times relative to pramlintide injection	Pharmacokinetic study/ type 2 diabetes patients
137-146	To study the effect of pramlintide on postprandial glucose fluctuations	Pharmacodynamic study/type 1 diabetes patients

C. Postmarketing Experience

Pramlintide is new molecular entity under review for possible market approval. Therefore, at this time there is no postmarketing experience with this drug.

D. Literature Review

The applicant references 66 publications pertaining to pramlintide or amylin; they include 31 journal articles and 35 abstracts. There are no new large scale clinical trials beyond those already submitted to the Agency. There is no new critical safety information published in the medical literature.

Of particular interest are two observations made in a publication by Vella et al.[37] First, in both type 1 and type 2 diabetes patients, the 30-µg and the 60-µg dose had similar effects on gastric emptying as seen in the figure below. The authors conclude that: "a dose-dependent effect of pramlintide could not be demonstrated in either group of participants with diabetes. The magnitude of the delay in gastric emptying was not different in types 1 and 2

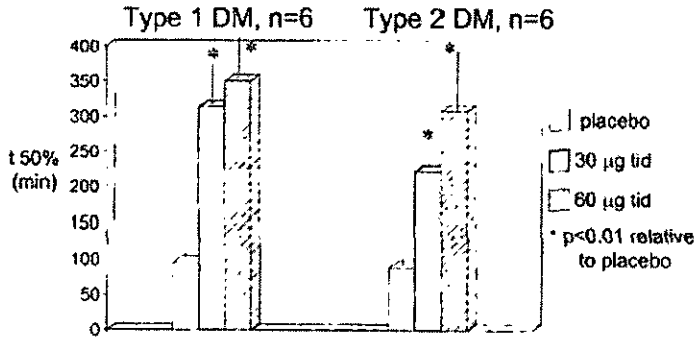


Figure 2 Dose-related effects of pramlintide on gastric emptying in people with type 1 or type 2 diabetes mellitus ($n = 6$ per group, mean ± SEM). The effect of pramlintide did not differ in people with type 1 and type 2 diabetes.

diabetics." It was statistically different from placebo treated patients.

The second observation of interest of this study is the remarkable degree of variability in gastric emptying following pramlintide administration as measured by "gastric emptying t 50%", illustrated below (the figure correlates the gastric emptying t 50% with measurements of pancreatic polypeptide but the figure is presented in the review as a descriptive look of the pharmacodynamic effect of pramlintide on gastric emptying).

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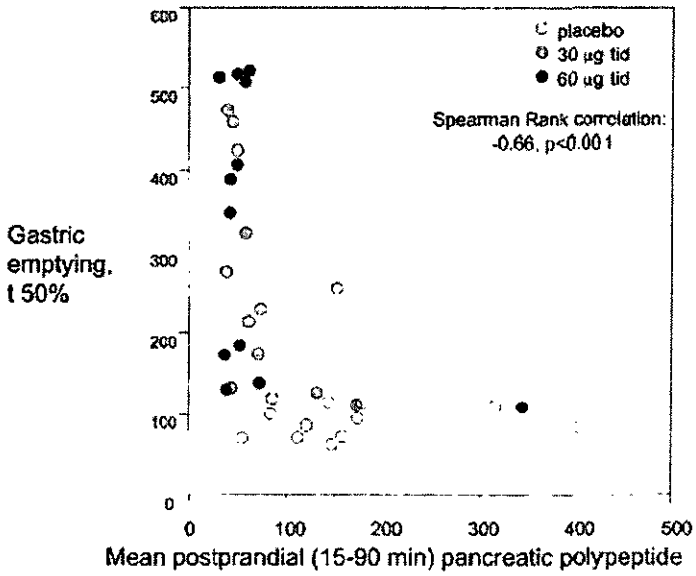
[37] A.Vella et al: Effects of pramlintide, an amylin analogue, on gastric emptying in type 1 and type 2 diabetes. *Neurogastroienterol.Mot.*(2002) **14**, 123-131.



V. Clinical Review Methods

A. Overview of Materials Consulted in Review

This clinical review has been conducted from the electronic submission of this NDA. The original NDA data (submitted in December 2000) was accessed primarily, but not exclusively, through the DFS Safety and Efficacy Reviews (efficacy review by Dr. Robert Misbin and safety review by this reviewer). Both the FDA and the Amylin Pharmaceuticals July 26, 2001 Endocrinologic and Metabolic Advisory Committee Briefing Documents were consulted.

B. Ethics Review/ Ethical Conduct of the Study

With respect to the ethical conduct of clinical study 137-150, the sponsor states that

- it was conducted in compliance with current Good Clinical Practices and Title 21 Part 56 of the United States of America Code of Federal Regulations relating to Institutional Review Boards
- it was conducted in accordance with the "Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects" contained in the Declaration of Helsinki, and its revisions

- it was conducted in compliance with Title 21 Part 50 of the United States of America Code of Federal Regulations pertaining to informed consent; "at the first visit, prior to initiation of any study-related procedures, subjects gave their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits."

C. Financial Disclosure

Financial disclosure documents are provided for (1) studies cited in the Approvable Letter[38] and (2) studies conducted as a result of the Approvable Letter, and (3) "ongoing and other studies".

The applicant provided the following financial disclosure information:

- Form OMB No. 0910-0396. The applicant certifies that Amylin Pharmaceuticals "has not entered into any financial agreement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study".
- An extensive list of investigators who completed the financial disclosure forms is provided. None of these investigators (1) owned or entered into an agreement to own a proprietary interest in pramlintide, (2) received, or entered into an agreement to receive, payments, grants and/or equipment from Amylin Pharmaceuticals, Inc. having a monetary value exceeding $25,000, (3) owned or entered into an agreement to own, Amylin Pharmaceuticals stock and/or stock options that exceed $50,000.00 in value.
- A list of investigators who could not be certified with regard to the lack of a significant equity interest as defined in 21 CFR 54.2(b) despite due diligence on

[38] The Approvabe Letter dated October 10, 2001 states that "financial disclosure information in accordance with 21 CFR Part 54 must be submitted for efficacy studies 137-111, 137-112, 137-117, and 137-123." All these were phase III studies in patients with either type 1 or type 2 diabetes.

behalf of the applicant to obtain from this information, including the reasons for failing to provide the information.

- A list of investigators who have participated in financial agreements or hold financial interest is provided. It includes four subinvestigators and one principal investigator. The only principal investigator was [ ] who purchased approx. 10,000 shares of Amylin stock worth $149,500 at the time of financial disclosure; Dr. [ ] was an investigator in study [ ] An analysis of [ ] information [ ] collected from Dr. [ ] site in study [ ] was consistent with the information collected at other sites.

D. Data Quality and Integrity

There was no DSI audit. The submitted data appeared complete and no critical inconsistencies or errors were identified between tables and text in different sections of the submission.

VI. Integrated Review of Efficacy

A. Efficacy Conclusions

The efficacy of pramlintide has been evaluated during the Phase III clinical trials submitted with the original NDA in December 2000 (see Dr. Robert Misbin's efficacy review in DFS)[39]. Therefore, it will not be re-analyzed in this review.

The only clinical trial included in this sNDA (study 137-150) is a safety clinical trial which only secondarily evaluated several efficacy variables (changes in body weight, pattern of insulin use, and postprandial glucose measurements). By design, comparisons between treatment groups for efficacy and safety variables were done in a context of statistical non-inferiority for glycemic control (equivalent HbA1c reductions at the end of the trial).

A.1 Effects on weight

Consistent with previous observations, pramlintide treatment results in a modest weight loss: by the end of 29 weeks of pramlintide treatment patients lost on average 1.33 ± 0.31 kg relative to baseline (95% CI = 0.60 to 1.78). The full weight reduction was reached at 12 weeks and most of it persisted for the duration of the study. The treatment effect relative to insulin alone was a weight reduction of approximately 2.5 kg ($p<0.001$; 95% CI: 3.2 to 1.6 kg)[40].

A.2 Effect on insulin use

Consistent with observations made in the Phase III efficacy clinical trials, pramlintide treatment has been associated with a reduction in total daily insulin use at the end of the study: 11.7 % relative to baseline[41]. This total daily insulin reduction was primarily the result of a reduction in daily short-acting insulin[42] (approximately 23% on average). Consistent with the current understanding of pramlintide's mechanism of action (i.e. it delays but it does not abolish the absorption of glucose after a meal) the reduction in short acting insulin was associated with an increase in daily basal insulin[43] (12.2±58.3 percent change from baseline).

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[39] In essence, pramlintide/insulin combination treatment reduced HbA1c at 52 weeks relative to placebo by 0.31% in type 1 diabetes. In type 2 diabetes the HbA1c reduction at 52 weeks relative to placebo was 0.53%.

[40] Patients treated with insulin alone gained on average 1.25±0.24 kg for the duration of the trial (95% CI = 0.63 to 1.81).

[41] Patients treated with insulin alone had an overall increase in daily insulin use of 1.3% at the end of the study (19.7±71% increase in long-acting insulin and 2.3±35.8 % reduction in short-acting insulin).

[42] Short-acting insulin for patients on multiple dose injections and bolus insulin for patients on continuous subcutaneous insulin infusion.

[43] Long-acting insulin for patients on multiple dose injections and basal insulin for patients on continuous subcutaneous insulin infusion.

A.3 Effect on postprandial glucose reduction

Trial 137-150 provides ample evidence that the effect of pramlintide in the reduction of early postprandial glucose excursions is durable over the 29 weeks of the trial for the time points analyzed. This information comes from two sources: (1) postprandial plasma glucose evaluations during a meal-test performed in a subgroup of patients at different timepoints during the clinical trial and (2) self-monitored blood glucose measurements done daily during the course of the clinical trial.

A.4 HbA1c observations

HbA1c reductions relative to baseline were similar between the pramlintide/insulin combination regimen and the insulin alone regimen.[44] Subgroup analyses showed no differences in HbA1c reduction for the two doses of pramlintide: 30-μg pramlintide (< 1/3 of patients) and 60-μg pramlintide (> 2/3 of patients)[45]. The insulin alone regimen resulted in a slightly higher percentage of patients who achieved HbA1c reductions ≤ 7% (ADA recommended)[46] or ≥ 5 % relative to baseline[47] at the end of the 29 weeks of treatment.

In summary, study 137-150 shows that pramlintide/insulin combination treatment results in (1) a modest weight loss relative to baseline, (2) a reduction in total daily insulin use relative to baseline (due primarily to a reduction in short-acting insulin), and (3) durability of effect with respect to the reduction of postprandial plasma glucose concentrations. When compared with insulin treatment alone, the pramlintide/insulin combination treatment resulted in additional weight loss and a small additional reduction in total daily insulin use, both in the context of an equivalent Hg A1c reduction.

B. General Approach to Review of the Efficacy of the Drug

The clinical study 137-150 submitted in this application is reviewed extensively in the next section. The human pharmacokinetic and pharmacodynamic studies submitted with this application were in general summarized and some were reviewed in detail. Original data and tables were re-formatted in order to follow the structure of this clinical review (the NDA source for each re-formatted table is listed at the bottom of the table). Extensive data in table format are included in the clinical review to serve as references for future inquires by primary, secondary, and tertiary reviewers.

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[44] The HbA1c reduction (LS Mean ±SE) was 0.49±0.07 for insulin alone and 0.47±0.07 for pramlintide/insulin combination. The trial has met the pre-designed non-inferiority margin of 0.4 % HbA1c change from baseline.
[45] Median HbA1c reduction was 0.4% for both doses.
[46] 24.2 % insulin alone and 19.6% insulin plus pramlintide.
[47] 48.9% insulin alone and 43.1 % insulin plus pramlintide.

C. Detailed Review of Trials by Indication

C.1. Clinical Study 139-150

C.1.1 Objective

The primary objective of this study was to compare the incidence of hypoglycemia (in general) and severe hypoglycemia (in particular) between a pramlintide-treated group and a placebo-treated group of patients with type 1 diabetes under relatively good glycemic control. This comparison was to be made for several intervals during the trial: initial 4 weeks, Week 4 to Week 29, and the entire 29 weeks of treatment.

The secondary objectives were:

- To examine the changes in HbA1c at specific times during the trial (Week 4, Week 8, Week 12, Week 16, Week 21, Week 25, and Week 29).
- To evaluate the change in postprandial glucose concentration during a standardized meal-test compared to baseline (at Week 4, Week 16, and Week 29).
- To examine the change in body weight from baseline at specific times during the trial (Week 4, Week 8, Week 12, Week 16, Week 21, Week 25, and Week 29).
- To examine the pattern of daily insulin use over the 29-week treatment period.

C.1.2 Study Design

This clinical trial was a randomized, triple-blind, placebo-controlled, multicenter study conducted in subjects with type 1 diabetes mellitus treated with insulin. Insulin was administered as multiple daily injections (MDI) or as continuous subcutaneous insulin infusion (CSII). This study was 29 week-long and included two treatment periods: a 4-week "pramlintide initiation /insulin reduction period" and a 25-week "pramlintide maintenance/insulin dose-optimization period." Study medication was administered immediately prior to meals, three times a day (TID) or four times a day (QID) depending on the subject's meal pattern. The study design is summarized in Table 7.

During the 4-week pramlintide initiation period, pramlintide treatment (or equivalent volume of placebo) was initiated at a dose of 15 µg and titrated toward a maintenance dose of 30 µg or 60 µg (with an intermediate transitional dose of 45 µg prior to achieving the 60-µg level). Titration of pramlintide dose was done weekly based on whether

subjects experienced repeated clinically significant nausea[48]. Insulin doses (primarily preprandial doses of short-acting insulin) were decreased with the initiation of study medication to obviate the risk of hypoglycemia. Upon completion of the 4-week pramlintide initiation period, all subjects were on a maintenance dose of pramlintide of 30 µg or 60 µg (or equivalent volume of placebo).

During the 25-week pramlintide maintenance period all subjects continued pramlintide at either 30 µg or 60 µg dose (or equivalent volume of placebo).[49] Insulin doses (both mealtime and basal components) were adjusted based on self-monitored blood glucose concentrations with the aim of reaching ADA[50] glycemic targets. The 25-week pramlintide maintenance period is also referred to as insulin optimization period.

[48] Clinically significant nausea (CSN) was defined as nausea symptoms that (1) interfered with the subject's ability to eat regular meals or (2) substantially reduced food intake.

[49] If a subject experienced repeated CSN at any time during the 25-week maintenance period, the subject was to decrease to pramlintide 30 µg or placebo (equivalent volume) and remain on this dose for the remainder of the study.

[50] ADA = American Diabetes Association.

4-Week Initiation Period				25-Week Insulin Dose Optimization Period
Progressive Pramlintide Dose-titration (Insulin Dose Reduction)				Pramlintide Dose Maintenance (Ongoing Insulin Adjustment)
Pramlintide or Placebo				Pramlintide or Placebo
Level 1	Level 2	Level 3	Level 4	
			60 µg	60 µg
		45 µg		
	30 µg[†]	*30 µg*[†]	*30 µg*[†]	*30 µg*[†]
15 µg	*15 µg*[*]			
Week 1 Days 1-7	Week 2 Days 8-14	Week 3 Days 15-21	Week 4 Days 22-28	Week 5 – Week 29 Days 29-203

[*]Subjects experiencing repeated CSN symptoms on any of the last 3 days of Level 1 remained on pramlintide 15 µg (or equivalent volume of placebo) during Level 2. After Level 2, these subjects increased to pramlintide 30 µg (50 µL) and remained on this dose for the remainder of the study

[†]Subjects experiencing repeated CSN symptoms on any of the last 3 days of Level 2 remained on pramlintide 30 µg (50 µL) (or equivalent volume of placebo) for the remainder of the study. Subjects experiencing repeated CSN symptoms on any of the last 3 days of Level 3 or Level 4 decreased to pramlintide 30 µg (50 µL) (or equivalent volume of placebo) for the remainder of the study

[‡]Subjects experiencing repeated CSN symptoms during the 25-week insulin dose-optimization period that were deemed clinically significant by the investigator and likely related to study medication decreased to pramlintide 30 µg (50 µL) (or equivalent volume of placebo) for the remainder of the study

Table 7: Study Design (Clinical Trial 137-150)

Source: Table 1.

A total of 296 subjects with type 1 diabetes mellitus who had been free of severe hypoglycemia for the past 6 months and had an HbA1c 7.5% to 9.0% were enrolled. Randomization was stratified according to Screening HbA1c values [(< 8.0%), (≥ 8.0% to ≤ 8.5%), (>8.5%)] to ensure balanced distribution of subjects across treatment groups with respect to their HbA1c values. Subjects were randomized within each stratum at the ratio of 1:1 (pramlintide:placebo).

Guidelines on insulin adjustments were given for each of the two periods of the clinical trial (pramlintide initiation and pramlintide maintenance). Thus, during the pramlintide initiation period all subjects were instructed to reduce their total daily insulin (and in particular their preprandial insulin dose) by ~30% to 50%. Subsequently, the following recommendations for insulin adjustment were provided for subjects whose glucose values were consistently out-of-range (Table 8)

Table 8: Guidelines for Insulin Adjustment During 4-Week Pramlintide Initiation Period*

Blood Glucose Value	Insulin Component	Reduce Insulin Dose if:	Increase Insulin Dose if:
Preprandial	Basal	glucose <130 mg/dl.	glucose >180 mg/dl.
Postprandial*	Preprandial Bolus	glucose <160 mg/dl.	glucose >240 mg/dl.

*90 min to 120 min post-meal

Source: Table 3.

Stricter recommendations for insulin adjustment were given to patients during the pramlintide maintenance/insulin optimization phase (Table 9):

Table 9: Guidelines for Insulin Adjustment During 25-Week Insulin Dose-optimization Period*

Blood Glucose Value	Insulin Component	Reduce Insulin Dose if:	Increase Insulin Dose if:
Preprandial	Basal	glucose <110 mg/dl	glucose >140 mg/dl.
Postprandial*	Preprandial Bolus	glucose <130 mg/dl	glucose >180 mg/dl.

*90 min to 120 min post-meal

Source: Table 4.

During the trial, subjects maintained a daily electronic diary which recorded (1) pre- and postmeal glucose measurements for breakfast, lunch, dinner, and large snacks[51], (2) information on insulin use, and (3) information on the occurrence of symptoms of hypoglycemia.[52]

A subset of subjects underwent a standardized meal-test at baseline, Week 4 (end of pramlintide initiation period), Week 16, and Week 29 (end of trial).

C.1.3 Main Inclusion and Exclusion Criteria

The main inclusion criteria were:

- Age 18 or older with a clinical diagnosis of type 1 diabetes mellitus requiring treatment with insulin for a minimum of 1 year (otherwise healthy).

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[51] A large snack was defined as containing >30 grams carbohydrate. Blood glucose (preprandial and postprandial) was monitored at least 6 times each day, including breakfast, lunch, dinner, and snacks. Postprandial blood glucose monitoring was performed 1 to 2 hours after the meal.

[52] Patients were to record symptoms of hypoglycemia upon awakening in the morning and retiring in the evening.

- Patients used either CSII or preprandial short-acting insulin (regular, lispro, or aspart) prior to each meal.
- Patients used self-blood glucose monitoring at least 3 times/day and used the data to adjust insulin treatment.
- Patients had an HbA1c of 7.5% to 9.0%, inclusive, at screening.
- Patients were free of symptoms of severe hypoglycemia (defined as episodes that require intravenous glucose, glucagon, or the assistance of another individual) for 6 months prior to screening.
- Patients had "stable weights" (weight was to be within ± 2.5 kg of the weight at screening, as documented by a weight within 2 to 6 months prior to screening).
- Patients had to have a valid driver's license.
- All laboratory test values had to be within 25% of the specified normal range or determined to be clinically insignificant by the investigator and approved by the sponsor. Abnormalities of plasma glucose, serum lipids, urinary glucose, and urinary protein consistent with type 1 diabetes mellitus were acceptable.
- Patients were euthyroid.

Excluded were patients who had evidence of significant cardiac disease, untreated or poorly controlled hypertension, chronic diseases, gastroparesis, malignancies, received antidiabetic medications or drugs that directly affect gastrointestinal motility.

C.1.4. Protocol amendments

Study 137-150 was initiated on April 17, 2002 and was completed on March 28, 2003. The study had one protocol amendment ("Amendment 1"), dated July 22, 2002 and three "Administrative Letters." The first administrative letter was incorporated in "Amendment 1".

"Amendment 1" contained mostly clarifications to the protocol. With respect to the hypoglycemia and glucose monitoring, the following were included:

- guidance was provided for the reporting of multiple hypoglycemic events that occur within 4 h of each other;[53] in addition, the definition of severe hypoglycemia was clarified

[53] Multiple hypoglycemic events that occurred within 4 hours of each other were to be considered a single hypoglycemic episode.

- the frequency of self-blood glucose monitoring (both preprandial and postprandial) was modified to at least 6 times per day (including breakfast, lunch, dinner, and snacks); postprandial self-monitored blood glucose measurements were to be taken approximately 1 to 2 h postmeal
- the definition of mild hypoglycemia was clarified[54]

The Administrative Letter 2 (dated 10 September 2002) incorporated an ECG assessment at the end of the study.

The Administrative Letter 3 (dated 13 Feb 2003) changed the medical monitor during the study.

The definition of protocol deviation was changed prior to the final analysis. Two criteria (visit window and study procedures) were no longer used to define protocol deviations.

None of the protocol changes mentioned above appear to have had a significant influence on the results or the conclusions of the study.

C.1.5. Interim Analysis

An interim analysis of data from the initial 16 weeks of treatment for all subjects was prepared prior to the completion of the study. This interim analysis (which was not specified in the protocol) was completed 3 months before the completion of the study in response to a request by the Swiss Regulatory Authorities. The applicant sought advice from the Division during this process. The Division agreed with the applicant's plan to conduct the interim analysis. Unblinding of the data was confined to selected personnel within the company who did not have any involvement in the study until the study was completed and unblinded to all. It was agreed by the Division that the protocol-defined significance level (0.05) was not to be adjusted for the final analyses. The applicant provided a copy of the interim summary to the agency prior to the submission of the NDA.

[54] Asymptomatic hypoglycemic episodes associated with a blood glucose measurement < 60 mg/dL were to be considered "mild" by definition. Symptomatic hypoglycemic episodes associated with a blood glucose measurement < 60 mg/dL were to be assigned severity based on a hypoglycemia workshet.

C.1.6 Patient Disposition

Patient Disposition by Treatment Arm (Pramlintide vs. Placebo) and by Time on Trial

A total of 296 subjects were randomized: 149 subjects to pramlintide and 147 subjects to placebo. Of these, 117 (78.5%) completed the study in the pramlintide group, and 133 (90.5%) completed the study in the placebo group. Patient disposition and the reasons for patient withdrawal from the clinical trial are presented in Table 10. Overall twice as many pramlintide-treated patients withdrew than placebo-receiving patients (21.5% vs. 9.5%). Withdrawal of consent was the most common reason for withdrawal and it was twice more common in the pramlintide group (8.1% pramlintide vs. 3.4 % placebo). Similarly, twice as many pramlintide-treated patients withdrew due to adverse events (5.4%) relative to placebo (2%)[55].

Table 10: Patient Disposition and Reasons for Patient Withdrawal

Patient Category	Placebo N (%)	Pramlintide N (%)	All subjects N (%)
Randomized	147 (100)	149 (100)	296 (100%)
Completed	133 (90.5%)	117 (78.5%)	250 (84.5%)
Withdrawn	14 (9.5)	32 (21.5)	46 (15.5)
Reasons for withdrawal			
Withdrawal of Consent	5 (3.4)	12 (8.1)	17 (5.7)
Adverse Event	3 (2.0)	8 (5.4)	11 (3.7)
Investigator Decision	0 (0.0)	5 (3.4)	5 (1.7)
Protocol Violation	3 (2.0)	3 (2.0)	6 (2.0)
Lost to Follow- up	3 (2.0)	4 (2.7)	7 (2.4)

Source:Supporting Data Summary 1.1

Patient withdrawal by time on trial (first month vs. the rest of the trial) is presented in Table 10A.

Table 10A: Patient Disposition by Time on Trial

Withdrawal Period	Placebo N = 147 n (%)	Pramlintide N =149 n (%)

[55] Compared to the Phase III clinical trials in patients with type 1 diabetes fewer patients withdrew in study 137-150. Thus, 25% and 34 % withdrew during the Phase III clinical trials in the placebo and pramlintide groups, respectively. Withdrawals due to adverse events were also reduced in trial 137-150 overall (6% and 18 % placebo and pramlintide, respectively withdrew in the phase III clinical trials). The ratio of pramlintide to placebo withdrawals was similar across trials (approximately 3)

Whole Trial	14 (9.5)	32 (21.5)
Initiation period	4 (2.7)	6 (4)#
Maintenance Period	10 (6.8)	26 (17.4)

#One patient withdrew prior to receiving any medication. Excluding this patient only 5 (3.3%) patients withdrew during the first month.

Patient Disposition for Pramlintide-Treated Patients by Dose and by Time on Trial

At the end of the initiation period the pramlintide treatment arm included patients on two pramlindide doses (30µg or 60µg)[56]. Due to the fact that patients were titrated to either pramlintide dose based on tolerability, the two dose groups were not balanced at the end of the trial. Thus, of the 117 pramlintide-treated subjects completing the trial, the majority [91(77.8%)] were at the 60-µg level, while [24 (20.5%)] were at the 30-µg level.

Table 11 presents subject disposition by dose group and by trial period (pramlintide initiation phase vs. pramlintide maintenance phase). Overall, 32 subjects withdrew prematurely: 1 (3.1%) withdrew prior to receiving any study medication, 5 (15.6%) withdrew during the initiation period, and 26 (81.2%) withdrew during the maintenance period. During the initiation period patients withdrew at lower doses exclusively (15µg and 30µg only; no patients withdrew while receiving the 45µg and 60µg doses). During the maintenance period, more patient withdrawals occurred at the 30-µg dose level [14 (43.8%)] than at the 60-µg dose level [10 (31.3%)].

Table 11: Subject Disposition for Pramlintide-Treated Subjects by Dose and Time on Trial (Randomized Pramlintide; N=149)*

Subjects Withdrawing Prior to Completion of 29 Weeks of Pramlintide Treatment (N=32)†				
	15 µg	30 µg	45 µg	60 µg
Withdrew	3 (9.4%)	17 (53.1%)	1 (3.1%)	10 (31.3%)
Initiation Period	2 (6.3%)	3 (9.4%)	0 (0.0%)	0 (0.0%)
Maintenance Period	1 (3.1%)	14 (43.8%)	1 (3.1%)	10 (31.3%)

*Dose is assigned as last treatment dose taken in the study, with the exception of subjects 1708 and 1101 (Section 4.6), who are assigned to the dose taken at Week 16 for purposes of data reconciliation

†One of the 33 subjects (02 B05) randomized to pramlintide-treatment withdrew prior to receiving a single dose of pramlintide, and is therefore not included in the four-dose levels

Source: Table 8.

[56] Two patients were maintained against protocol recommendations at the 15µg and the 45µg dose (one for each dose).

*Percentages are based on the number of patients withdrawn for a specific dose or period out of the overall (32) number of patients who withdrew.

C.1.7. Protocol deviations

The applicant presents the protocol deviations in the following categories: (1) inclusion/exclusion criteria violations, (2) out-of-range screening HbA1c values, (3) previous exposure to pramlintide, (4) study medication overdose, (4) other study medication deviation, (5) restricted concomitant medication change, and (6) "other." Protocol deviations are summarized in Table 12. The applicant approved all protocol deviations on the grounds that they would have "minimal impact" on study outcomes and would "pose no added safety risks". A large proportion of patients had protocol deviations (81 % in the placebo group and 86.5 % in the pramlintide group). The majority of the deviations were related to the inclusion/exclusion criteria and, in particular, to out-of range HgA1c values. Reportedly, the HbA1c changes were "minimally outside of the range prespecified in the protocol and were all sponsor allowed"[57]. The protocol deviations were, in general, balanced between the two treatment groups.

Table 12: Protocol Deviations by Treatment (ITT; N=295)

	Subject Group			
Deviation Type	**Placebo (N=147)**		**Pramlintide (N=148)**	
	n	%	n	%
Total	119	(81.0)	128	(86.5)
All Inclusion/Exclusion Criteria	68	(46.3)	81	(54.7)
HbA_{1c} Value Above 9.0%	24	(16.3)	20	(13.5)
HbA_{1c} Value Below 7.5%	22	(15.0)	24	(16.2)
Has previously received pramlintide	3	(2.0)	8	(5.4)
Study Medication Overdose	1	(0.7)	0	(0.0)
Other Study Medication Deviation	11	(7.5)	18	(12.2)
Restricted Concomitant Medication Change	9	(6.1)	3	(2.0)
Other	0	(0.0)	0	(0.0)

Source: Table 11.

In addition to the protocol deviations tabulated above, several minor "study procedural deviations" occurred. None appear to have an impact on the interpretability of the study.

C.1.8 Treatment compliance

[57] Appendix 3.6 lists "Protocol Deviations of Interest" which include mostly the following terms: (1) study medication not titrated per protocol, (2) concomitant medication added, (3) missed study medication, and (4) study medication taken after eating.

Compliance with study drug was comparable between placebo and pramlintide treated patients. The compliance in the 30-μg subgroup was slightly lower than that in the 60-μg subgroup.

C.1.9 Demographic and Baseline Patient Characteristics

Table 13 presents the main demographic and baseline characteristics for the ITT population by treatment (placebo vs. pramlitide) and by dose (30-μg and 60-μg) for the pramlintide arm. Overall, there were only minor differences in baseline age, weight, BMI, duration of diabetes, history of severe hypoglycemia, and HbA1c levels between the patients in the placebo and pramlintide treatment arms. The same can be said about the patients receiving the 30-μg and the 60-μg doses within the pramlintide arm.

The mean values for the above mentioned baseline variables indicate that the patients enrolled in the study were around 40 years of age, have had type 1 diabetes for half of their life, were mildly overweight (BMI approx. 27) were relatively well controlled on insulin (HbA1c = 8.1), and were mostly free of severe hypoglycemia prior to the study initiation. Similar numbers of males and females were enrolled in the study.

Table 13: Demographic and Baseline Characteristics by Treatment (ITT; N=295)

		Pramlintide		
Variable	Placebo (N=147)	*All* (N=148)	30 µg* (N=41)	60 µg* (N=101)
Gender n (%)				
Male	60 (40.8)	72 (48.6)	15 (36.6)	54 (53.5)
Female	87 (59.2)	76 (51.4)	26 (63.4)	47 (46.5)
Race n (%)				
n	147	148	41	101
Caucasian	134 (91.2)	134 (90.5)	35 (85.4)	93 (92.1)
Black	3 (2.0)	5 (3.4)	2 (4.9)	3 (3.0)
Asian	1 (0.7)	1 (0.7)	1 (2.4)	0 (0.0)
Hispanic	9 (6.1)	8 (5.4)	3 (7.3)	5 (5.0)
Age (yr)				
n	147	148	41	101
Mean (SD)	41.4 (12.4)	40.8 (14.2)	36.4 (13.3)	41.1 (15.5)
Median	42.0	40.0	43.0	40.0
Min, Max	15.0, 72.0	15.0, 78.0	20.0, 65.0	15.0, 78.0
Weight (kg)	147	148	41	101
Mean (SD)	80.9 (17.1)	81.4 (16.9)	77.0 (12.4)	83.1 (18.1)
Median	79.6	78.7	76.7	80.3
Min, Max	49.2, 130.6	52.5, 137.9	57.6, 105.6	52.5, 137.9
BMI (kg/m^2)				
n	136	136	41	69
Mean (SD)	27.8 (4.8)	27.7 (4.6)	27.3 (3.8)	28.1 (4.9)
Median	27.4	27.5	27.0	27.7
Min, Max	17.5, 43.9	19.3, 44.7	19.4, 35.9	19.3, 42.7
Duration of Diabetes (yr)				
n	147	148	41	101
Mean (SD)	20.5 (12.1)	19.4 (11.7)	18.8 (12.5)	19.0 (12.2)
Median	21.2	17.6	19.1	17.1
Min, Max	1.6, 52.7	1.1, 52.5	2.9, 52.5	1.1, 50.6
Severe Hypoglycemia History				
None	136 (92.5)	136 (91.9)	39 (95.1)	91 (90.1)
One Episode	8 (5.4)	5 (3.4)	2 (4.9)	3 (3.0)
Two or More Episodes	3 (2.0)	7 (4.7)	0 (0.0)	7 (6.9)
Baseline (Day 1) HbA$_{1c}$ (%)				
n	147	148	41	101
Mean (SD)	8.1 (0.8)	8.1 (0.8)	8.2 (0.7)	8.1 (0.8)
Median	8.1	8.1	8.2	8.0
Min, Max	6.7, 10.7	6.5, 10.7	6.9, 10.5	6.5, 10.7
Strata (Baseline)				
<8.0%	68 (44.9)	65 (44.0)	19 (39.0)	47 (46.5)
≥8.0% to <9.5%	37 (26.5)	52 (35.1)	15 (36.6)	34 (33.7)
≥9.5%	42 (28.6)	31 (20.9)	7 (24.5)	20 (19.8)

*Dose as assigned as last dose taken in the study, with the exception of subjects 1718 and 1133 (Section 4.9), who are assigned to the Week 16 dose for purposes of data reconciliation. The six subjects receiving 15 µg or 45 µg as the last dose in the study are included in the *all* pramlintide column as described in Table 7.

†A few subjects were missing baseline data for BMI; thus, the n's for these specified variables do not reconcile with the N's for the treatment.

Table 14 presents the information on baseline insulin use for the patients enrolled in the study. Patients in the placebo and pramlintide treatment groups received similar amounts of daily insulin (56 units) divided almost equally between short- and long-acting insulins. Insulin was administered via one of two modalities: continuous subcutaneous insulin infusion (CSII) or multiple daily injection (MDI). Overall, approximately equal number of patients received CSII (52.2 %) and MDI (47.5%). CSII subjects were using less insulin to achieve glycemic control (placebo: 49.6 units, pramlintide: 47.3 units), compared to MDI subjects (placebo: 63.7 units, pramlintide: 66.5 units). For both CSII and MDI subsets, similar patterns of insulin use were observed across the placebo and pramlintide populations.

Table 14: Total Daily Insulin Use at Baseline (Day 1) by Treatment (ITT; N=295)

All Subjects (N=295)[a]		Pramlintide		
Insulin (units)	Placebo (N=147)	All (N=148)	30 µg[a] (N=41)	60 µg[a] (N=101)
Daily Insulin				
n	138	128	37	86
Mean (SD)	56.5 (28.9)	50.0 (28.1)	54.0 (23.5)	56.5 (30.3)
Median	49.5	49.3	47.7	49.6
Daily Short-Acting/Bolus Insulin				
n	138	128	37	86
Mean (SD)	28.3 (16.3)	26.5 (14.2)	25.2 (11.6)	27 (15.4)
Median	24.3	25.0	26.2	24.6
Daily Long-Acting/Basal Insulin				
n	138	128	37	86
Mean (SD)	28.1 (17.5)	29.4 (19.6)	28.8 (17.7)	29.5 (20.6)
Median	23.9	25.9	24.0	25.7
CSII Subjects (N=155)[a]		Pramlintide		
Insulin (units)	Placebo (N=70)	All (N=82)	30 µg[a] (N=24)	60 µg[a] (N=54)
Daily Insulin				
n	70	78	22	44
Mean (SD)	44.6 (23.3)	47.3 (27.2)	45.9 (33.5)	47.1 (21.4)
Median	41.7	43.1	39.0	44.2
Daily Bolus Insulin				
n	70	78	22	44
Mean (SD)	25.7 (14.3)	23.9 (13.6)	23.7 (13.6)	22.3 (11.2)
Median	22.2	21.8	22.9	19.2
Daily Basal Insulin				
n	70	78	22	44
Mean (SD)	23.3 (13.0)	24.3 (13.9)	22.2 (11.2)	24.7 (15.4)
Median	21.5	21.3	23.3	21.6
MDI Subjects (N=140)[a]		Pramlintide		
Insulin (units)	Placebo (N=74)	All (N=66)	30 µg[a] (N=17)	60 µg[a] (N=47)
Daily Insulin				
n	68	58	15	42
Mean (SD)	68.7 (32.4)	50.5 (32.5)	65.8 (26.5)	66.4 (35.1)
Median	64.4	47.1	58.7	56.7
Daily Short-Acting Insulin				
n	68	58	15	42
Mean (SD)	31.2 (17.7)	30.8 (16.5)	27.4 (13.1)	31.9 (17.7)
Median	27.1	29.1	25.2	29.0
Daily Long-Acting Insulin				
n	68	58	15	42
Mean (SD)	32.5 (20.3)	35.7 (23.2)	38.4 (21.1)	34.4 (24.2)
Median	28.4	30.0	34.4	29.8

[a]Dose as assigned as last dose taken in the study with the exception of subjects 1708 and 11101 (Section 4.0), who are assigned to the Week 16 dose for purposes of data reconciliation. The six subjects receiving 15 µg or 45 µg as the last dose in the study are included in the all pramlintide columns as described in Table 7.

[b]Several subjects were missing baseline data due to default in subjects receiving electronic diaries at Screening and/or due to subject errors in electronic diary data entries during the baseline period. Therefore the n's for these specified variables do not necessarily match the N's for the treatment.

C.1.10.1. Data sets analyzed

The applicant conducted data analysis in the following five patient populations:

- Randomized: All randomized subjects.
- Intent-to-Treat (ITT): All randomized subjects who received at least one injection of study medication.

- Evaluable: All ITT subjects who remained in the study through the whole trial with no major deviations from the protocol[58].
- Meal-Test: All subjects participating in the standardized meal-test.
- Evaluable Meal-Test: All subjects participating in the standardized meal-test who had adequate data for evaluation of the pharmacodynamic parameter AUC(0-3 h) at baseline and end of trial[59].

Table 15 displays the number and percentage of patients included in the main efficacy/safety populations (ITT and evaluable).

Table 15: Patient Populations Analyzed

Population	Pramlintide N (%)	Placebo N (%)	All subjects N (%)
Randomized	149 (100%)	147 (100%)	296 (100%)
ITT*	148 (99.3%)	147 (100%)	295 (99.7)[60]
Evaluable**	117 (78.5%)	133 (90.5%)	250 (84.5%)

N=number of patients. % is percentage of patients within each group (column).
*ITT = Intent-to-treat (all randomized patients who received study medication).
** All ITT subjects who remain in the study through Week 29 with no major deviations from the protocol.
Source:Supporting Data Summary 1.2

C.1.10.2 Efficacy variables and statistical plan

Efficacy variables

The efficacy variables (all secondary endpoints) were: HbA1c, postprandial glucose concentrations during a standardized meal-test, body weight, and daily insulin use. The June 11, 2003 statistical plan included the following efficacy/safety analyses:

HbA1c Analysis

HbA1c results were to be summarized by visit and treatment using descriptive statistics. Change in HbA1c from Baseline (Day 1) to Week 29 (Visit 12) was to be analyzed parametrically both within treatment groups and between treatment groups on both the ITT (LOCF[61]) and Evaluable

[58] Any subject not taking study medication for a period of more than 14 consecutive days was excluded from the evaluable population.

[59] For a subject's data at a particular visit to be considered adequate, both of the following had to be true: (1) the plasma glucose time profile at the visit did not contain missing concentrations at more than two consecutive timepoints; (2) The subject had to have taken study medication (pramlintide or placebo) prior to the meal-test (post-baseline visits only).

[60] One randomized subject had a waiver request for a screening HbA1c value of 6.8%, which was denied and the subject was discontinued from the study prior to receiving study medication. This subject was excluded from the ITT population (N=148) and was only included in the randomized population (N=149).

[61] ITT = intent to treat; LOFC = last observation carried forward.

populations. Non-inferiority of the pramlintide treatment compared with the placebo treatment was to be done using a general linear model. In addition, descriptive summaries of HbA1c were to be presented by treatment and visit for the following: number and percent of subjects who achieve an HbA1c value of $\leq 7\%$, number and percent of subjects who achieve an HbA1c value of $\leq 8\%$, number and percent of subjects who achieve an HbA1c reduction of $\geq 0.5\%$.

Weight Analyses

Weight changes were to be summarized by visit and treatment using descriptive statistics. Change in weight from Baseline (Day 1) to Week 29 (Visit 12) was to be analyzed parametrically between treatment groups on both the ITT (LOCF) and Evaluable populations.

Insulin Use Analysis

Total daily insulin (and percent change in total daily insulin from baseline) were to be summarized by visit and treatment for the ITT and Evaluable populations using descriptive statistics.

Pharmacodynamic and Pharmacokinetic Analysis

An extensive statistical plan was available for the PK/PD endpoints analyzed (see biopharm and statistical review).

Hypoglycemia

Severe hypoglycemia was to be summarized descriptively by treatment and dose, presenting subject incidence and the number of events. Kaplan-Meier estimates for the time to first incidence of severe hypoglycemia were to be presented by treatment. Additionally, the annual event rate per subject and the event rate per subject-year of observation for each treatment were to be summarized for severe hypoglycemia using descriptive statistics. No inferrential statistics were planned for the analysis of severe hypoglycemia.

Severe hypoglycemia was to be examined for 3 distinct study time periods: (1) treatment initiation (initial 4 weeks of treatment), (2) maintenance period (Week 4 to Week 29), and the whole duration of the trial (initiation and maintenance periods together).

C.1.10.5. Efficacy Results

Efficacy analyses were secondary analyses in this safety clinical trial (the primary analysis was a comparison of the incidence of severe hypoglycemia and overall hypoglycemia during pramlintide treatment relative to placebo treatment).

C1.10.5.1 HbA1c Evaluations

Table 16 presents the change from baseline to Week 29 in HbA1c for placebo and pramlintide treatments for the ITT population . Both "within group" and "between group" analyses are presented. Within group analysis indicate that the mean changes from baseline to Week 29 in HbA1c were statistically significant for both the placebo and pramlintide group (p-values <0.0001 for both analyses). The between group comparison indicates non-inferiority, as the upper one-sided 95% confidence limit was 0.19, which is less than the pre-defined non-inferiority boundary of 0.4.

Table 16: HbA1c Change From Baseline to Week 29: Within Group and Between Group Parametric Analyses (ITT LOCF; N=295)

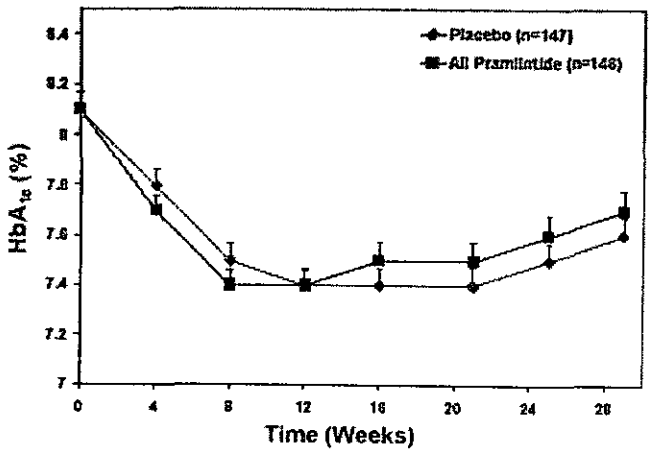
	Placebo (N=143)	Pramlintide (N=143)	Difference (Pramlintide-Placebo)
HbA_{1c} Change From Baseline to Week 29			
Arithmetic Mean Change (SE)	-0.47 (0.07)	-0.39 (0.07)	0.08 (0.10)
LSMean Change (SE)	-0.49 (0.07)	-0.47 (0.07)	0.03 (0.10)
95% CI	-0.63, -0.35	-0.61, -0.33	-
P-Value (Within Group)	<.0001	<.0001	-
Upper One-Side 95% CI	-	-	0.19

Source: Table 15

Figure 7 displays the on-trial mean HbA1c concentrations by treatment group (pramlintide vs. placebo) as a function of time for the ITT population. The data include measurements collected at baseline and at end of trial as well as the following intermediary timepoints: weeks 4, 8, 12, 16, 20, and 24. Both placebo-and pramlintide-treated subjects had identical mean baseline HbA1c (8.1%)[62]. On treatment, both treatment groups displayed similar trends in HgA1c changes. Pramlintide-receiving patients had better initial response (up to 8 weeks). This trend reversed after week 12 for the rest of the trial. At the end of 29 weeks of treatment, both placebo- and pramlintide-treated subjects had better glycemic control relative to baseline. The mean HbA1c at Week 29 was 7.6% and 7.7% for the placebo and pramlintide groups, respectively.

Figure 7: Mean (+SE) HbA1c Values by Visit and Treatment (ITT Observed; N=295)

[62] Although placebo and pramlintide treatment groups had identical mean HbA1c at baseline (8.1%), a slightly higher percentage of placebo subjects entered the study in poorer glycemic control (a larger percentage of patients were in the HbA1c >8.5% stratum in the placebo arm compared to the pramlintide arm: 28.6% placebo vs. 20.3% pramlintide).



Source: Figure 7.

Table 17 summarizes descriptively the HgA1c changes on trial (baseline to week 29) by treatment (placebo vs. pramlintide) and by dose for the pramlintide treatment group (30-µg vs. 60-µg). The HbA1c changes on trial were similar for both the 30 µg (-0.3%) and 60 µg (-0.4%) subgroups. The results for the 30-µg subgroup were, reportedly, impacted by one outlier (subject 0967).[63] Median reduction from baseline in HbA1c was equivalent for both pramlintide subgroups (-0.4%) and was identical to median HbA1c reduction in the placebo group.

Table 17: HbA1c Values and Change from Baseline to End of Treatment (ITT Population, N=295)

Variable	Placebo (N=147)		Pramlintide					
			All (N=148)		30-µg (N=41)		60-µg (N=101)	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Screening HgA1c	8.2 (0.8)	8.1	8.2 (0.8)	8.2	8.3 (0.8)	8.1	8.2 (0.8)	8.2
Baseline HgA1c	8.1 (0.8)	8.1	8.1 (0.8)	8.0	8.2 (0.7)	8.1	8.1 (0.8)	8.0
Week 29 HgA1c	7.6 (0.9)	7.6	7.7 (0.9)	7.6	7.8 (1.1)	7.6	7.6 (0.8)	7.6
HgA1c change from baseline	-0.5 (0.9)	-0.4	-0.4 (0.9)	-0.4	-0.3 (1.2)	-0.4	-0.4 (0.8)	-0.4

Source: SDS 2.1.1.1.1

Table 18 summarizes descriptively the HgA1c changes on trial (baseline to Week 29) by treatment (placebo vs. pramlintide) and by type of insulin administration (CSII and MDI). In addition, for the pramlintide treatment group, data for the 30-µg and 60-µg subgroups are presented. The mean change in HbA1c from baseline to Week 29 was comparable for both placebo (-0.3%) and pramlintide (-0.4%) CSII subjects. The mean change in HbA1c from baseline to Week 29 was slightly greater for placebo (-0.6%) MDI subjects, compared to pramlintide (-0.4%) MDI subjects. This suggests that, for patients receiving insulin via MDI regimen, better control was achieved in the placebo tratment group (-0.6% placebo vs. –0.4% pramlintide). This observation was more striking in the 30-µg subgroup (-0.6% placebo vs.

[63] Subject (0967) experienced a 4.0% increase in HbA1c at Week 29.

+0.2% in the "30-µg subgroup"). It is not clear whether this observation reflects a real phenomenon or reflects variability of this point estimate due to the small number of patients in the 30-µg subgroup (N=17).

Table 18: HbA1c Change from Baseline to End of Treatment by Type of Insulin Administration (ITT Population, N=295)

Variable	Placebo		Pramlintide					
			All		30-µg		60-µg	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
CSII*	-0.3 (0.8)	-0.4	-0.4 (0.8)	-0.3	-0.5 (0.7)	NA	-0.3 (0.8)	NA
MDI**	-0.6 (0.9)	-0.7	-0.4 (1.0)	-0.5	0.2 (1.8)		-0.5 (0.8)	

* CSII = continuous subcutaneous insulin infusion (N = 155). **MDI = multiple dose injection (n =140). NA = not available
For CSII: placebo = 73, pramlintide all = 82, "30µg"=24, and "60 µg"= 54 subjects, respectively.
For MDI: placebo = 74, pramlintide all = 66, "30µg"=17, and "60 µg"= 47 subjects, respectively.
Source: SDS 2.1.1.1.2 and SDS 2.1.1.1.3

Table 19 presents the number and percent of patients who achieved pre-specified HbA1c targets (including the recommended ADA target values of < 7 %) at the end of treatment. The data are presented by treatment (placebo vs. pramlintide) and by pramlintide dose (30-µg and 60-µg). Although, the overall percentage of patients achieving Hg A1c ≤ 8% was the same for the placebo and pramlintide treatment groups (54%), the precentage of patients who achieved the ADA glycemic target of ≤ 7% was slightly higher in the placebo group (24.2% placebo vs. 19.6% pramlintide). Similarly, more subjects in the placebo group achieved HbA1c réductions ≥0.5% (48.9% placebo vs. 43.1 % pramlintide). Among patients in the pramlintide group, similar proportions of subjects in the 30 µg and 60 µg subgroups achieved ≥0.5% HbA1c reductions. A larger proportion in the 30 µg subgroup achieved HbA1c < 8% when compared to the 60 µg subgroup (72% of patients in the 30 µg subgroup vs. 51% of patients in the 60 µg subgroup).

Table 19: Percent of Subjects Achieving Target HbA1c Values at Week 29 by Treatment (ITT Observed; N=295)

Variable Visit	Placebo n/N Percent	Pramlintide* *All* n/N Percent	 30 µg n/N Percent	 60 µg n/N Percent
Subjects Achieving HbA_{1c} Value ≤7% at Week 29	30/124 (24.2%)	21/107 (19.6%)	4/23 (17.4%)	17/83 (20.5%)
Subjects Achieving HbA_{1c} Value ≤8% at Week 29	39/71 (54.9%)	29/53 (54.7%)	8/11 (72.7%)	21/41 (51.2%)
Subjects Achieving HbA_{1c} Reduction ≥0.5% at Week 29	65/133 (48.9%)	50/116 (43.1%)	11/24 (45.8%)	39/90 (43.3%)

*Dose is assigned as last dose taken in the study, with the exception of subjects 1708 and 11101 (Section 4.0), who are assigned to their Week 16 dose for purposes of data reconciliation. The six subjects receiving 15 µg or 45 µg as the last dose in the study are included in the *all* pramlintide column as described in Table 7

Source: Table 16.

In conclusion, in the context of a non-inferiority clinical trial conducted in patients with type 1 diabetes and relatively good glycemic control:

- both placebo and pramlintide treated subjects improved glycemic control by the end of the 29 weeks of treatment relative to baseline
- for the patients in the pramlintide treatment group the 30 µg and 60 µg subgroups showed similar efficacy results
- the pattern of HbA1c changes on trial was slightly different in the pramlintide and placebo groups despite similar results at the end of the trial (better response to pramlintide during the first 8-12 weeks followed by better response for placebo after week 12)
- a larger proportion of placebo treated patients reached ADA recommended glycemic targets that pramlintide treated patients
- a larger proportion of placebo treated patients achieved reductions in HbA1c ≥ 0.5%
- non-inferiority of pramlintide treatment relative to placebo treatment was demonstrated during the trial

C.1.10.5.2 Insulin Use Evaluations

Insulin use ("pattern of daily insulin use over the 29-week treatment period") was a prespecified secondary endpoint. Table 20 presents data on daily insulin use by treatment (placebo vs. pramlintide) for bolus/short-acting and for basal/long-acting insulins[64]. The data are presented as changes from baseline at the end of the pramlintide initiation period (Week 4) and at the end of the trial (Week 29)[65]. While the protocol recommended a 30% to 50% reduction in bolus/short-

[64] CSII subjects received a continuous basal insulin infusion supplemented with boluses of short-acting insulin with meals. MDI subjects received intermittent long-acting insulin injections supplemented with short-acting insulin injections with meals.

[65] The applicant submits that the median values are a more appropriate reflection of the actual percent change from baseline in insulin use because"four subjects were identified as significant outliers." Subject 6603 (pramlintide CSII) did not record basal insulin use at baseline and had an "improbable" percent change from baseline in total daily insulin use (~755%) at Week 29 (this patient was excluded from the analysis). Subjects 3312 (placebo MDI), 20710 (placebo CSII), and 24402 (pramlintide MDI) exhibited increases greater than 300% in total daily insulin use and/or basal/long-acting use. These data were not excluded.

acting insulin doses with the initiation of study medication in order reduce the risk of hypoglycemia, the applicant states that "this recommendation was not followed for all subjects."

Bolus/Short-Acting Insulins

The median daily bolus/short-acting insulin use was reduced in both the placebo- and pramlintide-receiving treatment groups during the 4-week initiation period (Table 20 and Figure 8). This reduction was more significant in the pramlintide treatment group (-29.8% pramlintide vs. -8.3 % placebo). The reduction in the bolus/short-acting insulin use persisted in the pramlintide-treatment group by the end of the trial (-28.4%) and diminished in the placebo group (-3.5%).

Basal/Long-Acting Insulins

There was no reduction in the median daily basal/long acting insulin by the end of the pramlintide initiation period (Week 4) in either treatment group. For the remainder of the clinical trial there was an increase in the use of basal/long acting insulin. This change was greater for the placebo group by the end of the trial (10.3% placebo vs. 2.9% pramlintide).

Combined Insulin Use

Upon completion of 29 weeks of treatment, placebo-treated subjects had an overall increase in total daily insulin dose of 1.3%. In contrast, pramlintide-treated subjects had a an overall decrease in total daily insulin dose of 11.7% for the same length of treatment.

Table 20: Total Daily Insulin Use and Percent Change From Baseline (ITT; N=295)

	Bolus/Short-Acting Insulin				Basal/Long-Acting Insulin			
Insulin Use (units)	**Placebo (N=147)**		**Pramlintide (N=148)**		**Placebo (N=147)**		**Pramlintide (N=148)**	
Visit	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**
Baseline	28.4 (16.3)	24.3	26.5 (14.2)	25.0	28.1 (17.5)	23.9	29.4 (19.5)	25.9
Week 4	-7.5 (30.9)	-8.3	-22.0 (42.3)	-29.8	8.9 (44.2)	0.0	3.9 (38.2)	0.0
Week 29	-2.3 (35.8)	-3.5	-22.8 (39.1)	-28.4	19.7 (71.3)	10.3	12.2 (58.3)	2.9

Source: Table 17

Figure 8 displays graphically the median daily insulin percent change from baseline by visit and treatment (placebo and pramlintide). Data are presented for bolus/short-acting insulin and for basal/long-acting insulin.

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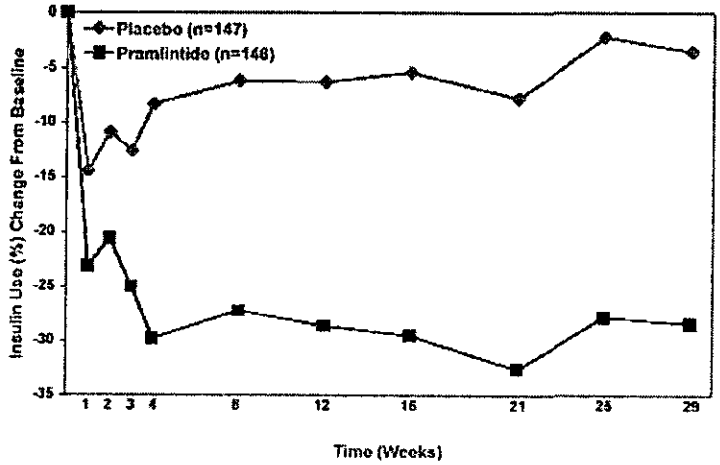
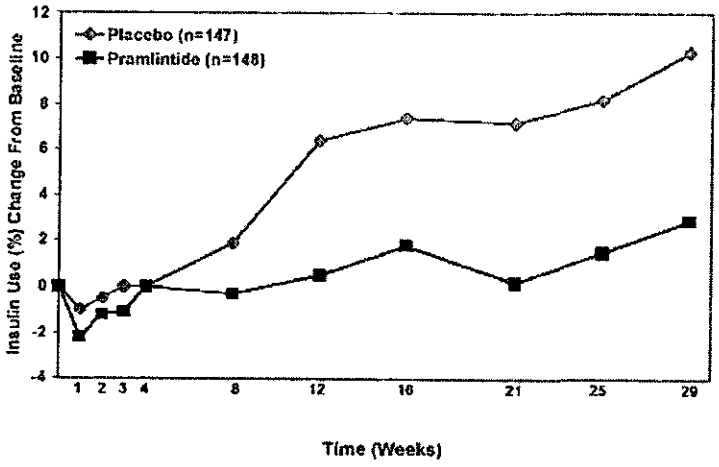
Figure 8: Median Total Daily Insulin Percent Changes from Baseline by Treatment and Visit (ITT; N=295)

Bolus/Short-Acting Insulin



Basal/Long-Acting Insulin



Source: Figure 8.

The pattern of insulin use for the 30-µg and 60-µg subgroups was in general similar to the overall pattern of insulin use noted in the pramlintide treatment arm. To this end, bolus/short-acting insulin was distinctly reduced while basal/long-acting insulin was slightly increased at the end of the trial (Table 21). Subjects receiving the 30-µg pramlintide dose needed less basal/long-acting insulin at the end of trial than subjects receiving 60-µg (there was only a 4.2% increase in basal/long-acting insulin use for the 30-µg dose compared with a 14.2 % increase in the 60-µg dose subgroup). The

reduction in bolus/short-acting insulin at the end of the clinical trial was similar for the two dose subgroups (approx. 22%). Overall, pramlintide-receiving patients treated with 30-µg had a greater reduction in insulin use (-10.8%) than patients treated with 60-µg vs. (–6.4%).

Table 21: Daily Insulin Use and Percent Change From Baseline in Subjects Patients Receiving Pramlintide (ITT, N=148)

	Total Daily Insulin		Bolus/Short-Acting Insulin		Basal/Long-Acting Insulin	
Insulin Use (units)	30-µg (N=41)	60-µg (N=101)	30-µg (N=41)	60-µg (N=101)	30-µg (N=41)	60-µg (N=101)
Visit	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Baseline	54.0 (23.5)	56.5 (30.3)	25.2 (11.6)	27.0 (15.4)	28.8 (17.7)	29.5 (20.6)
Week 4 (% Change from Baseline)	-8.1 (18.4)	-5.9 (37.1)	-24.3 (30.5)	-20.0 (42.9)	8.5 (28.9)	6.4 (49.5)
Week 29 (% Change from Baseline)	-10.8 (20.9)	-6.4 (36.5)	-22.6 (41.7)	-22.9 (39.0)	4.2 (32.2)	14.2 (64.0)

Source: SDS 2.3.1.1.1

Table 22 presents information on daily insulin use for the subgroup of patients who used continuous subcutaneous insulin infusion (CSII). The data are presented by treatment (placebo vs. pramlintide) and by type of insulin treatment used (bolus/short-acting vs. basal/long-acting). By the end of the trial, bolus insulin was reduced by 30.1% in CSII pramlintide-treated subjects, compared to 3.5% in CSII placebo-treated subjects. In contrast, basal insulin increased by 2.9% in CSII pramlintide-treated subjects, compared to 7.2% in CSII placebo-treated subjects. The median change from baseline in total daily insulin use was +1.8% for placebo and -11.9% for pramlintide). These observations are similar to those recorded for the overall pramlintide group (MDI and CSII together, Table 22).

Table 22: Total Daily Insulin Use and Percent Change From Baseline in Subjects Employing CSII (ITT CSII; N=155)

	Bolus/Short-Acting Insulin	Basal/Long-Acting Insulin

Insulin Use (units)	Placebo (N=73)		Pramlintide (N=82)		Placebo (N=73)		Pramlintide (N=82)	
Visit	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Baseline	25.7 (14.3)	22.2	23.0 (10.9)	21.8	23.9 (13.0)	21.5	24.3 (13.9)	21.1
Week 4 (% Change from Baseline)	-8.6 (29.9)	-9.6	-20.1 (50.8)	-33.5	9.1 (50.3)	0.0	3.5 (28.1)	0.0
Week 29 (% Change from Baseline)	-3.2 (31.9)	-3.5	-23.8 (39.2)	-30.1	23.4 (74.8)	7.2	6.9 (27.6)	2.9

Source: Table 18

Table 23 presents information on daily insulin use for the subgroup of patients who used multiple doses of insulin (MDI). The data are presented by treatment (placebo vs. pramlintide) and by type of insulin treatment used (bolus/short-acting vs. basal/long-acting). By the end of the trial, short-acting insulin was reduced by 25.3% in MDI pramlintide-treated subjects, compared to 3.8% in MDI placebo-treated subjects. Long-acting insulin increased by 3.2% in MDI pramlintide-treated subjects, compared to 11.0% in MDI placebo-treated subjects. The median change from baseline in total daily insulin use was +0.5% for placebo and -10.2% for pramlintide for subjects employing MDI insulin therapy. These observations are similar to those recorded for the overall pramlintide group (MDI and CSII together, Table 20).

Table 23: Total Daily Insulin Use and Percent Change From Baseline in Subjects Employing MDI (ITT MDI; N=140)

	Bolus/Short-Acting Insulin				Basal/Long-Acting Insulin			
Insulin Use (units)	Placebo (N=74)		Pramlintide (N=66)		Placebo (N=74)		Pramlintide (N=66)	
Visit	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Baseline	31.2 (17.7)	27.4	30.8 (16.5)	29.1	32.5 (20.3)	28.4	35.7 (23.2)	30.0
Week 4	-6.4 (32.2)	-7.3	-24.4 (28.7)	-28.2	8.7 (36.9)	0.2	4.5 (47.8)	0.0
Week 29	-1.3 (39.7)	-3.8	-21.5 (39.5)	-25.3	15.8 (67.8)	11.0	19.0 (82.8)	3.2

Source: Table 19

In conclusion:

- pramlintide-receiving patients used less insulin daily at the end of 29 weeks of treatment relative to placebo-receiving patients (+1.3% placebo; -11.7% pramlintide,)

- the pattern of bolus/short-acting insulin changes in pramlintide-treated patients consisted in a reduction in insulin use at the end of the pramlintide titration period (-29.8%) which persisted at the end of the trial (-28.4%)
- the pattern of basal/long-acting insulin changes in pramlintide-treated patients did not change by the end of the pramlintide titration period and increased slightly by the end of the trial (2.9%)
- patients treated with 30-µg of pramlintide had a greater reduction in total daily insulin use (-10.8%) than patients treated with 60-µg (–6.4%); this insulin reduction was due primarily to changes in basal/long-acting insulin (the reduction in bolus/short-acting insulin was similar for the two dose subgroups)

C.1.10.5.3 Body Weight Evaluations

Body weight evaluations ("the change in body weight from baseline at specific times during the trial") were a predefined secondary endpoint. Table 24 presents a pramlintide-to-placebo comparison of weight changes from baseline to Week 29. Placebo- (i.e. insulin alone) treated patients gained on average approximately 1.25 kg at the end of the trial. In contrast, pramlintide treated patients lost on average approximately 1.3 kg. The mean treatment effect for weight loss is approximately 2.5 kg for 29 weeks of treatment. The weight reduction in the pramlintide group was statistically significant when compared to the weight change in the placebo group (p-value <0.0001).

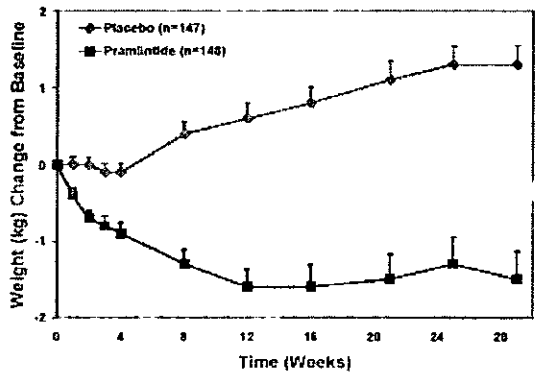
	Placebo (N=145)	Pramlintide (N=147)	Difference (Pramlintide-Placebo)
Weight (kg) Change From Baseline to Week 29			
Arithmetic Mean Change (SE)	1.25 (0.24)	-1.33 (0.31)	-2.57 (0.39)
LSMean Change (SE)	1.22 (0.30)	-1.19 (0.30)	-2.41 (0.40)
95% CI	0.65, 1.81	-1.78, -0.60	-3.20, -1.63
P-Value (Between Group)	-	-	<0.0001

Table 24: Weight* Change From Baseline to Week 29 (ITT, LOCF; N=295)
*In kg. Source: Table 20.

Figure 9 displays graphically the mean weight change from baseline by visit and treatment (placebo vs. pramlintide). The baseline mean weight was comparable between placebo and pramlintide treatments groups (81.1 kg placebo; 81.5 kg pramlintide). For placebo-treated subjects weight appeared constant during the 4-week initiation period; following entry into the insulin optimization period, weight increased progressively and reached a plateau at the end of the trial. For pramlintide-treated patients weight decreased steadily during the pramlintide initiation period; during the pramlintide maintenance period it continued to decrease until approximately 12 weeks of treatment and was followed by a slight increase for the rest of the trial.

The mean weight reduction (relative to baseline) for the pramlintide dose subgroups (30 µg and 60 µg) was not equivalent. The weight reduction was larger for the 30-µg subgroup (-2.4 kg), compared to the 60-µg subgroup(-1.2 kg). For subjects employing CSII, the weight reduction relative to baseline was –2.2 kg and relative to placebo was 3.6 kg (+1.4 kg placebo; -2.2 kg pramlintide). For subjects employing MDI, the weight reduction relative to baseline was –0.4 kg and relative placebo was 1.7 kg (+1.3 kg placebo; -0.4 kg pramlintide).

Figure 9: Mean (+SE) Change From Baseline to Week 29 in Weight (ITT; N=295)



Source: Figure 9.

In conclusion:

- pramlintide-treated patients lost on average 1.33 (±0.31) kg after 29 weeks of treatment, while placebo (i.e. insulin alone)-treated patients gained on average 1.25 (±0.24) kg (mean treatment effect = 2.5 kg; 95% CI: 3.2 kg to 1.6 kg)
- the loss of weight associated with pramlintide reached a plateau at approximately 12 weeks; thereafter a slight loss of effect was noted
- the weight reduction relative to baseline was larger for the 30-µg dose subgroup (2.4 kg), compared to the 60-µg dose subgroup (1.2 kg)
- subjects employing CSII had a larger weight reduction (2.2 kg) relative to subjects employing MDI (0.4 kg). Consequently, subjects employing CSII had a larger treatment effect relative to and placebo (3.6 kg) compared with subjects employing MDI (treatment effect relative to placebo = 1.7 kg)

C.1.10.5.4 Postprandial Glucose Evaluations

The applicant submits an extensive body of data collected during the clinical trial 137-150 that evaluates the effect of pramlintide on postprandial glucose excursions. These data include:

- an analysis of the postprandial plasma glucose concentration-profiles during standardized meal-tests

- an analysis of self-monitored blood glucose concentrations
- an analysis of the number and proportion of patients who achieved postprandial glucose targets

Standardized meal-test

Evaluation of postprandial plasma glucose concentration-profiles during standardized meal-tests was a prespecified secondary endpoint. These evaluations were done in a subgroup of patients at different times during the course of the clinical trial (baseline, Week 4, Week 16, and Week 29). The purpose of this evaluation was to demonstrate a sustained effect of pramlintide use on postprandial plasma glucose concentrations.[66]

Of the 100 subjects (50 placebo; 50 pramlintide) enrolled in the standardized meal-test 77 (77.0%) were considered evaluable at Week 29 (44 placebo; 33 pramlintide)[67]. Patients received a pramlintide or placebo injection (in addition to insulin) immediately prior to a standardized breakfast. Subsequently, plasma glucose concentrations were measured over a 3-hour period. For the baseline meal-test no study medication was administered. Detailed description of the standardized meal-test results are presented in the Appendix. In summary:

- Administration of pramlintide resulted in statistically significant within group reductions in postprandial mean plasma glucose $AUC_{(0\text{-}3\ h)}$ and C_{ave}.
- The reduction in the pramlintide group was greater than that observed for placebo, although between-group differences did not achieve statistical significance.
- Pramlintide treatment resulted in a reduction of the postprandial plasma glucose concentrations rise throughout the initial 1 to 1.5 hours of the postprandial period; beyond that point, a progressive rise was observed throughout the remainder of the 3 hour observation period. Data beyond three hours are not available.

The reduction in postprandial glucose is also visually evident in the postprandial plasma glucose concentration-time profiles (Figure 10). These profiles also point out a phenomenon demonstrated in many Phase II pharmacodynamic studies: when pramlintide is administered in addition to insulin, the postprandial plasma glucose concentrations may reach levels below the preprandial plasma glucose level. This postprandial plasma glucose concentration dip has the following characteristics:

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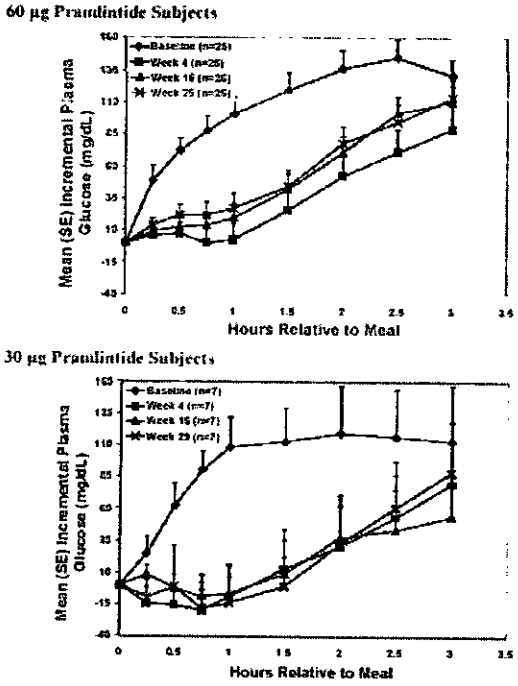
[66] A reduction in postprandial plasma glucose concentrations was established short-term (at 2 weeks and 4 weeks, respectively) in previous studies.

[67] Twenty-two subjects failed to meet the evaluable criteria due to withdrawing from the study, failure to achieve adequate IV access for sampling, etc.

- it generally occurs within the first postprandial hour
- it is variable among patients (as illustrated by the size of the standard error around the mean glucose concentration)
- it is more pronounced in the 30 µg pramlintide subgroup.

The implication of this observation is central to understanding the safety of pramlintide because, **depending on the preprandial plasma glucose concentration, pramlintide (when used in addition to a short acting insulin) may induce a postprandial reduction in serum glucose concentration in the hypoglycemic range.**

Figure 10: Mean Plasma Glucose Concentration-Time Profiles Following a Standardized Breakfast at



Baseline, Week 4, Week 16, and Week 29
Source: Figure

Self-Monitored Blood Glucose Concentrations

During the clinical trial, patients measured capillary glucose concentrations both before meals and 1-2 hours after meal ingestion. Self-monitored blood glucose (SMBG) values were recorded in an electronic diary across the entire 29-week study duration. The applicant presents graphic depictions of such data collected at breakfast, lunch, and dinner throughout the trial (see Appendix). This approach provides data in a setting that

mimics "real use" as opposed to the more constrained setting of the standardized meal test. While prior to initiation of study medication, subjects in both treatment arms exhibited very similar patterns of postprandial changes in blood glucose, on treatment there was an almost immediate separation evident between the pramlintide-treated patients and the placebo (i.e. insulin alone)- treated patients. To this end, pramlintide treatment was associated with consistently lower postprandial glucose concentrations when compared with placebo treatment. This effect is observed throughout the 29-week treatment period during all three meals: breakfast, lunch, and dinner[68]. Thus, the pramlintide effect on postprandial glucose concentrations measured in all patients during trial 137-150 is similar to the observations made in the standardized meal tests measured in a subgroup of patients.

Postprandial Glucose Targets

The applicant reports that throughout the 29-week study duration, a greater proportion of pramlintide subjects achieved the recently recommended ADA target for postprandial glucose control (<180 mg/dL) each day compared to placebo. A total of 68.2% (breakfast), 71.2% (lunch), and 69.5% (dinner) pramlintide-treated subjects achieved postprandial concentrations below the ADA recommended target of 180 mg/dL, compared to 51.0% (breakfast), 60.7% (lunch), and 58.7% (dinner) of placebo- (i.e. insulin alone) treated subjects.

In conclusion:

- pramlintide reduces postprandial glucose concentrations in both the experimental setting (during standardized meal-test) and during actual use (self-monitored blood glucose concentration); these drug effect is sustained throughout 29 weeks of treatment
- a larger proportion of pramlintide-treated patients achieve ADA recommended postprandial glucose concentration targets
- when pramlintide is used in association with a short acting insulin, during the first hour following pramlintide use, the serum glucose concentrations may reach levels below the preprandial glucose level; depending on the actual preprandial serum glucose concentration, some patients may be susceptible to postprandial serum glucose reductions in the hypoglycemic range

[68] The standardized meal-test was conducted at breakfast only.

- as illustrated in the previous paragraph, a large proportion of patient reach these targets on insulin alone

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VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety study 137-150 confirms the same safety signals identified during the Phase III clinical trials: (1) gastrointestinal adverse events (nausea, vomiting, reduced appetite) and (2) severe hypoglycemia (serious adverse events associated with hypoglycemia and "assisted hypoglycemia").

Similar to observations made in the Phase III efficacy trials, gastrointestinal treatment-emergent adverse events had higher incidence rates in patients treated with pramlintide/insulin combination relative to patients treated with insulin alone. Patients reported nausea and vomiting twice more frequently, and reduced appetite 4.4 times more frequently in association with pramlintide treatment. The dose-titration regimen identified two subgroups of patients with two different degrees of tolerability to pramlintide: a subgroup who could not be titrated beyond 30-µg (< 1/3 of the ITT population) and a subgroup who tolerated the 60-µg dose (>2/3 of the ITT population).[69]

Severe hypoglycemia occurred approximately twice more frequently in patients on pramlintide/insulin treatment when compared to patients who used insulin alone. Similarly, serious adverse events associated with hypoglycemia occurred more frequently with pramlintide treatment[70]. The twofold increase in incidence of severe hypoglycemia in pramlintide treated patients occurred both during the pramlintide initiation and pramlintide maintenance periods. The imbalance in incidence of severe hypoglycemia contrasts with the observation that non-severe hypoglycemia incidence rates were similar in both treatment groups. Gastrointestinal adverse events appear to be a contributing factor to severe hypoglycemia. Patients who could not be titrated beyond 30-µg of pramlintide displayed the highest incidence of severe hypoglycemia relative to patients who received insulin alone; in addition, this subgroup appears to be particularly vulnerable to severe hypoglycemia during the first two months

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[69] Nausea occurred twice more frequently with the 30-µg pramlintide dose subgroup relative to the 60-µg pramlintide dose subgroup during both the treatment initiation (first 4 weeks) and maintenance (4 weeks to 29 weeks) periods.

[70] One placebo patient (0.68%) and four pramlintide patients (2.7%) experienced serious adverse events associated with hypoglycemia.

of insulin optimization as the insulin dose was allowed to increase in order to achieve better glycemic control.[71]

A concern that pramlintide may interfere with the patients' ability to recognize symptoms of hypoglycemia was raised during the original NDA review. Evidence from clinical trial 137-150 (similar incidence rates in reporting symptoms of hypoglycemia between the two treatment arms) and evidence from an in depth pharmacodynamic study, do not appear to be substantiate this concern.

The — manufactured drug product which was tested in trial 137-150 appears to be twice more immunogenic relative to the drug products which were evaluated in the efficacy Phase III clinical trials[72]. However, the antibody titers detected are low (1:5 to 1:25).

B. Description of Patient Exposure

A total of 295 subjects were exposed to study medication in trial 139-150 (148 pramlintide; 147 placebo). Patient exposure to pramlintide during this trial is summarized (by dose and time on trial) in Table 25.

Table 25: Pramlintide Exposure in Study 137-150 (ITT Pramlintide; N=148)

[71] Insulin optimization was started at the end of the 4-week initiation period.

[72] An analysis of the antibody titers during the course of trial 137-150 indicates that 15.3 % of pramlintide treated-patients develop anti-pramlintide titers after 25 weeks of treatment compared to 6.1 % of the insulin alone treated patients. During the Phase III clinical trials, in studies up to one year duration, 6.8% and 8.5% of patients with type 1 and type 2 diabetes respectively had been shown to develop anti-pramlintide antibodies during treatment.

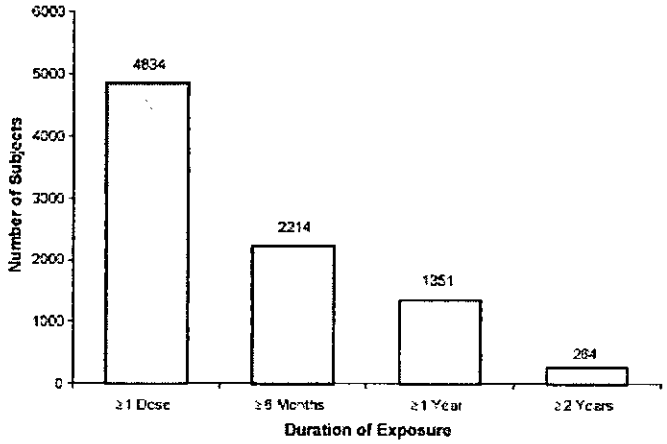
Extent of Pramlintide Exposure During the 4-Week Initiation Period (N=148)				
Visit*	15 µg	30 µg	45 µg	60 µg
Week 1 (n 147)	147 (99.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 2 (n 145)	13 (8.8%)	132 (89.2%)	0 (0.0%)	0 (0.0%)
Week 3 (n 143)	2 (1.4%)	26 (17.6%)	118 (79.7%)	0 (0.0%)
Week 4 (n 143)	1 (0.7%)	33 (22.3%)	5 (3.4%)	106 (71.6%)
Extent of Pramlintide Exposure During the Maintenance Period (N=142)				
	15 µg	30 µg	45 µg	60 µg
Week 8 (n 134)	2 (1.4%)	34 (23.9%)	2 (1.4%)	100 (70.4%)
Week 12 (n 128)	1 (0.7%)	30 (21.1%)	2 (1.4%)	95 (66.9%)
Week 16 (n 124)	1 (0.7%)	28 (19.7%)	1 (0.7%)	94 (66.2%)
Week 21 (n 120)	2 (1.4%)	25 (17.6%)	0 (0.0%)	93 (65.5%)
Week 25 (n 116)	1 (0.7%)	23 (16.2%)	0 (0.0%)	92 (64.8%)
Week 29 (n 117)	1 (0.7%)	24 (16.9%)	0 (0.0%)	92 (64.8%)

*At each visit (Week X), the n represents the number of subjects exposed to pramlintide between the prior visit and who are still exposed at the current visit. However any subject who withdrew from the study prior to the visit is not included in the n. As a subject could be exposed to more than one pramlintide dose between two study visits, a subject can be counted in more than one dose column, thus, (1) the n for exposure across pramlintide doses may be larger than the overall n for the specific visit, (2) the n for each dose at Week 29 will not reconcile with the last dose that subjects completed in the study (Table 8), and (3) the n for a specific visit be smaller than the n for a preceding visit if a subject was outside a specified visit window.

Source: Table 21

The patient exposure to pramlintide during trial 137-150 is only a fraction of the total patient exposure during the entire pramlintide development program, which is illustrated in Figure 11. A total of 4834 unique subjects with type 1 and type 2 diabetes have been exposed to pramlintide so far. Of these, 1351 have exposures of ≥1 year and 264 have exposures of ≥2 years. The total pramlintide exposure is 2801 subject-years and the mean pramlintide exposure is 0.58 years per subject.

Figure 11: Cumulative Duration of Exposure to Pramlintide (All Completed Studies)



Source: Figure 29.

C. Methods and Specific Findings of Safety Review

This safety review was conducted from the electronic submission of NDA 21-332. After detailed analysis, the applicant's datasets and tables were selectively re-formatted in order to better integrate into the structure of this review. Whenever a table was re-formatted, references to the original table or dataset were made at the bottom of the table. Selected datasets submitted in JMP were also reviewed.

Clinical Study 139-150

Safety summaries are based on data collected from all subjects exposed to study medication (ITT population, N=295)[73].

C.1. Deaths

No deaths were reported during the study.

C.2. Serious Adverse Events

[73] The sponsor defined the ITT population as "all randomized patients who received at least one injection of study medication." The ITT population (N=295) is one patient short of the "all randomized population" (N=296). One randomized subject (pramlintide treatment group) had a waiver request for a screening HbA1c value of 6.8%, which was denied and the subject was discontinued from the study prior to receiving study medication.

Nine (6.1%) placebo-treated subjects and fourteen (9.5%) pramlintide-treated subjects experienced serious adverse events (SAEs) during the study (Table 26). Of these, hypoglycemia occurred in one placebo-receiving patient (subject 11108) and in four pramlintide-receiving patients (subjects 0904, 24503, 202, and 9804)[74].

Table 26: Serious Treatment-Emergent Adverse Events (ITT; N=295)*

Subject	Treatment (and Dose)	SAE
0907	Placebo	Cholelithasis
0968	Placebo	Cellulitis
1743	Placebo	Ketosis
2403	Placebo	Myocardial Infarction
2417	Placebo	Tachycardia
3307	Placebo	Influenza-likeSymptoms
11108	Placebo	Hypoglycemia
19319	Placebo	Viral Illness
20402	Placebo	Ketosis
0904	Pramlintide(30 μg)	Hypoglycemia/Convulsion
11114	Pramlintide (30 μg)	Depression
20302	Pramlintide (30 μg)	Gastritis
24501	Pramlintide (30 μg)	Ketosis Hyperglycemia
24503	Pramlintide (30 μg)	Hypoglycemia Coma**
202	Pramlintide (60 μg)	Convulsions/Hypoglycemia
203	Pramlintide (60 μg)	Depression
925	Pramlintide (60 μg)	Coronary Artery Disorder
1209	Pramlintide (60 μg)	Ketosis
1718	Pramlintide (60 μg)	GERD
2301	Pramlintide (60 μg)	Ketosis
9804	Pramlintide (60 μg)	Inflicted Injury/MVA**
11103	Pramlintide (60 μg)	Cystitis
20303	Pramlintide (60 μg)	Chest Pain, Vomiting (separate events)

Source: Table 26
*Highlighted are patients who had hypoglycemia.
**Withdrew from the trial.

Motor Vehicle Accidents

The applicant reports a total of nine motor vehicle accidents (MVAs) during the course of the study in four (2.7%) placebo-treated subjects and five (3.4%) pramlintide-treated subjects. For most events the time of MVA occurrence is not specified and, therefore, correlation with the last pramlintide or insulin dose cannot be made. The applicant states that hypoglycemia was not implicated in any of the events by the investigator. One patient (9804, pramlintide 60 μg) appears to have had a hypoglycemic event associated with an MVA.

[74] Patient 9804 had hypoglycemic symptoms at the time of the event without a measured glucose level. The SAE in the placebo group occurred on day 51. The SAEs in the pramlintide group occurred on the following days of treatment: day 31(patient 202), day 74 (patient 24503), day 81 (patient 0904), and day 156 (patient 9804). Only two SAEs in the pramlintide group were also reported as severe hypoglycemia (patients 24503 and 9804).

Two additional MVAs associated with hypoglycemia are described in the NDA Resubmission safety Update # 2 during the extension phase of study 137-150: patient 11210 (60 μg) and patient 11203 (60 μg) had these events on days 42 and 82 of the open-label extension trial 137-150E, respectively.

C.3. Patient Discontinuations Due to Adverse Events

Three (2.0%) placebo-treated subjects and eight (5.4%) pramlintide-treated subjects withdrew due to an adverse event during the clinical trial. They are listed in Table 27. Patients who had hypoglycemia at the time of the withdrawal (both in the pramlintide treatment group, both also recorded as serious adverse events) are highlighted.

Table 27: Treatment-Emergent Adverse Events Leading to Withdrawal (ITT; N=295)

Subject	Treatment (and Dose)	AE Leading to Withdrawal
5504	Placebo	Speech Disorder
11409	Placebo	Weight Increase
24507	Placebo	Nausea
11105	Pramlintide(15 μg)	Nausea
11407	Pramlintide (15 μg)	Depression
19307	Pramlintide (15 μg)	Nausea
9805	Pramlintide (30 μg)	Bilirubinemia
11114	Pramlintide (30 μg)	Depression
24501	Pramlintide (30 μg)	Hyperglycemia
24503	Pramlintide (30 μg)	Hypoglycemic coma
9804	Pramlintide (60 μg)	Inflicted Injury*

Source: Table 27
*MVA with symptoms of hypoglycemia

C.4. Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs)[75] are presented in Table 28. Only TEAEs with a frequency ≥ 5% are included. Among these, several TEAEs occurred more frequently in the pramlintide treatment group. They were: asthenia, headache, nausea, reduced appetite, vomiting, pharyngitis, sinusitis, and increased sweating. Among them, the gastrointestinal TEAEs clearly displayed higher incidence rates in the pramlintide group relative to placebo. Patients reported nausea and vomiting twice more frequently in the pramlintide group relative to placebo. "Reduced appetite" was reported

[75] Hypoglycemia is not included in this analysis. Instead, it is analyzed separately in the next section of the review.

4.4 times more frequently with pramlintide treatment. Of interest, nausea, vomiting, and reduced appetite occurred at a greater incidence in the pramlintide 30-µg subgroup, compared to the pramlintide 60-µg subgroup[76]. Other events that occurred at a higher incidence in the 30-µg subset group, compared to the 60-µg subset group, were asthenia, influenza-like symptoms, fatigue, headache, and sinusitis.

Table 28: Frequent Treatment-Emergent Adverse Events (Overall Occurrence Rate ≥ 5%, ITT; N=295)*

Adverse Event (AE)	Placebo (N=147)		Pramlintide (N=148)	
	n (%)	Events	n (%)	Events
All AEs	118 (80.3)	673	127 (85.8)	716
Injection Site Reaction	14 (9.5)	16	6(4.1)	8
Asthenia	6 (4.1)	14	9 (6.1)	49
Fatigue	17 (11.6)	49	13 (8.8)	17
Influenza-Like Symptoms	10 (6.8)	10	9 (6.1)	9
Dizziness	24 (16.3)	71	16 (10.8)	85
Headache	18 (12.2)	33	19 (12.8)	29
Shaking	27 (18.4)	147	21 (14.2)	66
Diarrhea	17 (11.6)	19	15 (10.1)	18
Gastroenteritis	10 (6.8)	10	6 (4.1)	6
Nausea	53 (36.1)	83	93 (62.8)	206
Reduced Appetite	3 (2.0)	3	13 (8.8)	14
Vomiting	9 (6.1)	10	20 (13.5)	22
Infection	9 (6.1)	11	8 (5.4)	9
Pharyngitis	11 (7.5)	11	12 (8.1)	16
Sinusitis	13 (8.8)	16	22 (14.9)	30
URI	51 (34.7)	64	38 (25.7)	55
Inflicted Injury	17 (11.6)	25	15 (10.1)	17
Sweating Increased	18 (12.2)	72	21 (14.2)	51
Urinary Tract Infection	9 (6.1)	9	7 (4.7)	9

Source: Table 22.
*Hypoglycemia TEAEs are excluded.
URI = upper respiratory tract infection.
TEAEs occurring more frequently in the pramlintide group are highlighted.

C.5. Clinically Significant Treatment-Emergent Adverse Events: Hypoglycemia and Nausea

C.5.1 Hypoglycemia

[76] For the 30-µg subgroup (41 patients) the n (%) of gastrointestinal adverse events were as follows: nausea = 39 (95.1) , reduced appetite = 6 (14.6), vomiting = 7 (17.1) . For the 60-µg subgroup (101 patients) the n (%) of gastrointestinal adverse events were as follows: nausea: = 49 (48.5), reduced appetite = 7 (6.9), vomiting = 12 (11.9).

Information regarding hypoglycemic events was collected from two sources: (1) the patients'electronic diaries and (2) the hypoglycemic event CRF page.

C.5.1.1 Collection of Hypoglycemic Event Information

Electronic Diary

The electronic diary prompted subjects twice a day (morning and evening) to record *symptoms of hypoglycemia that interfered with daily activities*. In addition, patients recorded preprandial and prandial glucose measurements in the electronic diary. All recorded glucose values <60 mg/dL were evaluated by the clinical site staff with the study subjects to ascertain whether these events represented severe hypoglycemic episodes[77].

CRF Page

A hypoglycemic event CRF page was completed at each visit based on information from the electronic diaries. The information recorded included: (1) the date and time of the event, (2) whether the corresponding glucose measurement was <60 mg/dL, ≥ 60 mg/dL, or unknown, and (3) whether or not the intensity of the event was severe. If the event intensity was severe, the causality of the event was to be recorded (i.e. insulin administration, missed meal or snack, smaller meal, increased exercise, or unknown)[78]. If severe hypoglycemia was reported, study site staff were to ascertain whether the subject was operating a motor vehicle at the time severe hypoglycemia occurred.

C.5.1.2 Categorization of Hypoglycemia

The intensity of hypoglycemia was characterized as mild, moderate, or severe as follows.

Mild hypoglycemia:

- the subject reported symptoms consistent with hypoglycemia but hypoglycemia was not verified by glucose measurement
- the symptoms did not greatly interrupt or interfere with the subject's daily activities

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[77] Defined as requiring the assistance of another individual, treatment with IV glucose, treatment with IM glucagon.

[78] Severe hypoglycemic events that were associated with a glucose measurement of <60 mg/dL were also recorded on the adverse event page as hypoglycemia. If the event recorded on the hypoglycemic event CRF page was associated with a glucose measurement of ≥ 60 mg/dL, only the individual symptoms of the event were recorded on the adverse event CRF page (i.e. the event was not be recorded as an adverse event of hypoglycemia).

- the symptoms dissipated spontaneously, or upon eating
- the subject did not experience symptoms but reported a glucose meter measurement of less than 60 mg/dL (i.e. if an asymptomatic hypoglycemic event was recorded due to a blood glucose measurement of less than 60 mg/dL, the hypoglycemic event was recorded as mild in intensity).

Moderate hypoglycemia:

- the subject reported symptoms consistent with hypoglycemia that may or may not have been documented by glucose monitoring
- symptoms interrupted or interfered with the subject's daily activities and required immediate self-treatment (carbohydrate ingestion)

Severe hypoglycemia:

- the subject *required* the assistance of another person to obtain treatment for the event
- the subject required treatment for the event with intravenous glucose or intramuscular glucagon
- the subject was in a life-threatening situation as a result of the episode (e.g., seizure or loss of consciousness while driving a car).

C.5.1.3. Non-Severe Hypoglycemia

Symptoms of hypoglycemia were reported with comparable frequency in the pramlintide and placebo treatment groups for the whole duration of the trial (placebo: 91.2% and pramlintide: 91.9%). A slightly higher proportion of pramlintide-receiving patients displayed symptoms of hypoglycemia during the pramlintide initiation phase (placebo: 70.1% ; pramlintide: 79.1%). During the pramlintide maintenance period, as insulin optimization was pursued, the trend was reversed: more patients in the placebo (i.e. insulin only) group experienced symptoms of hypoglycemia (placebo: 88.8% and pramlintide 82.5%).

Blood glucose values <60 mg/dL (hypoglycemia range) were also reported with comparable frequency in the pramlintide and placebo treatment groups for the whole duration of the trial (placebo: 93.9% and pramlintide: 95.3%). Slightly more pramlintide-receiving patients

recorded blood glucose values < 60 mg/dl during the pramlintide initiation period (placebo: 78.9% and pramlintide: 83.1%). During the pramlintide maintenance/ insulin optimization period similar percentages of patients reported blood glucose values < 60 mg/dl (placebo: 93.7% and pramlintide: 93.0%).

In summary, no significant treatment-specific[79] differences in the incidence of symptoms indicative of non-severe hypoglycemia or glucose values in the hypoglycemic range (<60 mg/dL) were recorded during the study.

C.5.1.4 Severe Hypoglycemia

The main objective of study 137-150 was to evaluate whether a new regimen consisting in an initial dose-titration of pramlintide therapy combined with a transient reduction in short-acting insulin dose would reduce the increased risk of severe hypoglycemia observed during the pramlintide Phase III clinical trials in diabetic patients.[80]

Figure 11 presents Kaplan-Meier plots for the time to first incidence of severe hypoglycemia by treatment (pramlintide vs. placebo) and by pramlintide dose (30µg vs. 60µg). Separate Kaplan-Meier plots are presented for the following study periods:

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[79] Pramlintide plus insulin combination vs. insulin alone.

[80] During the Phase III, placebo-controlled pramlintide clinical trials presented with the original NDA on December 7, 2000, an increased incidence of severe hypoglycemia was noted in association with pramlintide treatment relative to insulin alone. To this end, during the initial 4 weeks of therapy hypoglycemia was observed in 5.6% of placebo-receiving patients and in 13.1% of pramlintide-receiving patients (an annual event rate of 1.6 for placebo and 3.2 for pramlintide, respectively). After the initial 4 weeks of treatment, the incidence of severe hypoglycemia was still higher in the pramlintide-treated group (16.9% for the placebo group and 21.1% for the pramlintide group; the annual event rate was 1.05 for the placebo and 0.74 for the pramlintide group. Since one outlier in the placebo group contributing almost 1/3 of all hypoglycemic events the event rate data is not informative. For the whole duration of the trial 18% placebo patients and 25% pramlintide patients experienced severe hypoglycemia.

- Baseline to Week 4. During these four weeks (" initiation period") pramlintide dose was titrated weekly to patient tolerability according to a predefined dose escalation plan, while insulin dose (primarily short-acting insulin) was reduced by 30-50% in order to avoid hypoglycemia.
- Week 4 to Week 29. During this period ("maintenance period") pramlintide was maintained at the dose tolerated by individual patients at the end of the "initiation period" (30μg vs. 60μg) while insulin dose was adjusted with the goal of achieving ADA-recommended targets of glycemic control.
- Week 16 to 29. This is the last part of the "maintenance period" when both pramlintide and insulin regimens are the most stable. Analysis of severe hypoglycemia for his period was not specified in the protocol's objectives; however it is an informative additional assessment. The applicant calls this period the "pramlintide dose-maintenance/insulin dose-maintenance" phase.

During the initiation period, twice as many pramlintide-treated patients experienced severe hypoglycemia. Thus, four (2.7%) placebo-treated subjects experienced severe hypoglycemia compared to seven (4.7%) pramlintide-treated subjects (annual event rates of 0.42 and 0.75, respectively). Of interest, a higher proportion of pramlintide subjects in the 30-μg subgroup (three subjects, 7.3%) experienced severe hypoglycemia, compared to subjects in the 60-μg subgroup (four subjects, 4.0%); the annual event rate was 1.53 for the 30 μg subgroup and 0.48 for the 60 μg subset group. Although the annual event rate was similar between the placebo and the 60-μg subgroup (0.42 vs. 0.48), the 30-μg subgroup had a disproportionately higher number of severe hypoglycemic events. The applicant states that "*as this was the same group with greater nausea, the increased incidence of severe hypoglycemia is possibly an indirect consequence of decreased food intake secondary to the higher incidence of gastrointestinal side effects.*".

Similar to the observations made during the initiation period, during the maintenance period, twice as many pramlintide-treated patients experienced severe hypoglycemia:

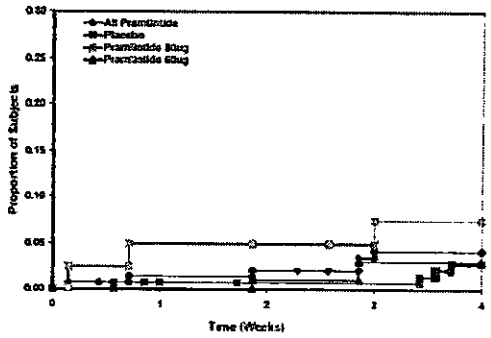
12 (8.4%) placebo-treated subjects and 25 (17.7%) pramlintide-treated subjects (annual event rate of 0.28 and 0.54 for the placebo and all pramlintide groups, respectively). The incidence of severe hypoglycemia was higher in the 30-µg subgroup (9 subjects or 24.3%) compared to the 60-µg subgroup (16 subjects or 16.0%). The annual event rate for the 60 µg subgroup (which included the majority of pramlintide-treated subjects) was 0.41, higher than the placebo group. The annual event for the 30 µg subgroup was the highest (1.00).

The applicant presents the Kaplan-Meier plot for Week 16 through Week 29 as a measure of hypoglycemia risk when both a maintenance dose of pramlintide and optimization of insulin treatment have been achieved. During this period, 7 (5.1%) placebo-treated subjects and 8 (6.6%) pramlintide-treated subjects experienced severe hypoglycemia. A comparable annual event rate was observed for the placebo (0.31) and all pramlintide (0.32) groups, respectively. Comparable incidences and annual event rates were also observed for the pramlintide subset groups. A total of two (7.4%) subjects from the 30-µg subset and six (6.5%) subjects from the 60-µg subset groups experienced severe hypoglycemia (annual event rates of 0.33 and 0.32, respectively).

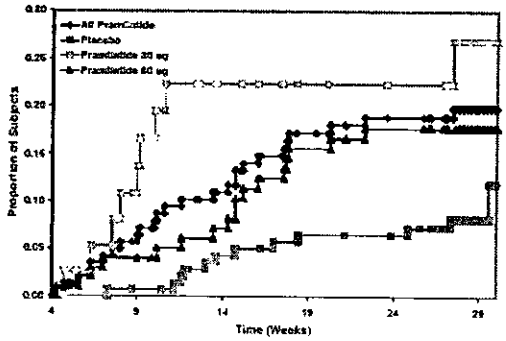
The "Week 4 to Week 29" Kaplan-Meier plot indicates that the first two months of the pramlintide maintenance are a period when patients who receive the 30 µg pramlintide dose regimen are particularly susceptible to the risk of severe hypoglycemia. This is also the time when insulin optimization is initiated. A different trend (i.e. a gradual increase in incidence of severe hypoglycemia as insulin optimization is initiated) can be noted for the 60 µg treatment arm.

Figure 11:Time to First Incidence of Severe Hypoglycemic Adverse Event (ITT; N=295)

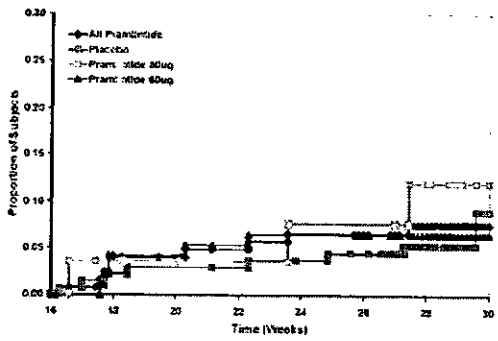
Baseline (Day 1) to Week 4: Pramlintide Dose-Escalation/Insulin Dose-Reduction



Week 4 to Week 29: Pramlintide Dose-Maintenance/Insulin Dose-Intensification



Week 16 to Week 29: Pramlintide Dose-Maintenance/Insulin Dose-Maintenance



*Dose is assigned as last dose taken in the study, with the exception of subjects 1708 and 11101 (Section 4.0), who are assigned to their Week 16 dose for purposes of data reconciliation. The six subjects receiving 15 µg or 45 µg as the last dose in the study are included in the *all* pramlintide column as described in **Table 7**.

Source: Figure 10.

Table 29 summarizes factors that contributed to the occurrence of severe hypoglycemia (such as excess insulin, missed meal, increased exercise, alcohol use) as well as information on the temporal association between severe hypoglycemia ans nausea. Two observations are of particular interest:

- a larger proportion of pramlintide-receiving patients who experienced severe hypoglycemia had evidence of nausea on the day of the event (14.6% pramlintide vs. 4.3% placebo)
- a larger proportion of pramlintide-receiving patients (51.2 %) used insulin in excess of their physiological needs compared to 21.7 % of placebo patients[81].

Table 29: Severe Hypoglycemia – Contributing Factors and Relationship with Nausea (ITT; N=295).

	Placebo (N=23 Events)	**Pramlintide** (N=41 Events)
	Number (%) of Events	
Relationship Between Severe Hypoglycemic Events and Nausea		
Nausea Prior to Day of Event	8 (34.8%)	23 (56.1%)
Nausea on Day of Event	1 (4.3%)	6 (14.6%)
Contributing Factors to Severe Hypoglycemic Events		
Excess Insulin	5 (21.7%)	21 (51.2%)
Missed Meal	5 (21.7%)	9 (21.9%)
Increased Exercise	3 (13.0%)	2 (4.9%)
Alcohol	0 (0.0%)	1 (2.4%)
Other	1 (4.4%)	0 (0.0%)
Unknown	9 (39.1%)	8 (19.5%)

Source: Table 24

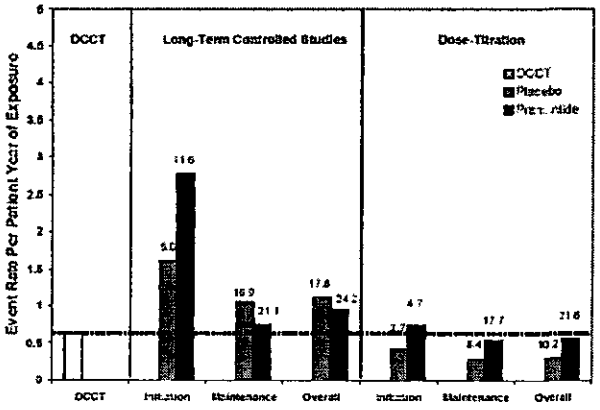
Figure 12 presents the annual event rate and the incidence of severe hypoglycemia from study 137-150 juxtaposed with the severe hypoglycemia information from the

[81] The applicant states that all the available information related to the severe hypoglycemia events was assessed by a single reviewer to ensure consistency throughout. It should be mentioned that the information in this table (applicant's Table 24) is not consistent with the information provided in Appendix.3.11.9. identified as "Severe Hypoglycemic events (CRF Page 54A) By-Subject DataListing in the NDA. The latter lists 8 subjects with "missed meal or snack" in the pramlintide group and 2 subjects in the placebo group. Three additional patients in the pramlintide group had causality for severe hypoglycemia identified as "small meal" with none in the placebo group. In total, 11 subjects (27%) in the pramlintide group and 2 (13%) in the placebo group missed or had smaller meals as a cause of the severe hypoglycemic event. According to this observation twice as many subjects in the pramlintide group missed or had smaller meals when compared to placebo. All such severe hypoglycemia events occurred during the first month of the trial for placebo-treated patients (days 4 and 24, respectively); for pramlintide-treated patients 3 events occurred during the first month of the trial (days 13, 20, and 21), and 9 events during the rest of the trial (days 70, 74, 94, 100, 116, 124, 125, 156, and 204 respectively).

pramlintide Phase III trials[82] and the Diabetes Control and Complications (DCCT) trial. Although the absolute incidence and event rate of severe hypoglycemia in pramlintide-treated patients was lower in trial 137-150 when compared to the Phase III trials, a similar pramlintide to placebo imbalance in incidence and annual event rates for severe hypoglycemia is observed (approximately 2:1 pramlintide:placebo). This pramlintide-to-placebo imbalance occurred despite dose-titration of pramlintide. It occurred during both the initiation and the maintenance periods. In this respect, clinical trial 137-150 replicates the observations made during the Phase III clinical trials of pramlintide in patients with type 1 diabetes: despite a similar incidence of non-severe hypoglycemia in both pramlintide and placebo (i.e. insulin alone) treated patients, pramlintide-treated patients have twice the incidence of severe hypoglycemia relative to placebo-treated patients. Importantly, the patients enrolled in study 137-150 were different in two respects: (1) they had better glycemic control at baseline and (2) they were selected to be free of severe hypoglycemia for 6 months before enrollment (in contrast, during the Phase III clinical trials patients had to be free of severe hypoglycemia for only two weeks). It is this reviewer's opinion that a historical comparison of incidence rates of severe hypoglycemia is not particularly relevant since the patient populations in various clinical trials are different. This observation applies also to the comparison made with the DCCT data.

Figure 12: Annual Event Rate and Incidence of Severe Hypoglycemia (DCCT*, Study 137-150, and Type 1 Long-term Controlled Trials 137-112, 137-117, and 137-121; ITT Recommended Doses)

[82] It should be noted that the sponsor's presentation of the placebo data for the Phase III trials includes an outlier in the placebo group that had contributed almost 1/3 of all hypoglycemic events. There are some minor differences between this table and the tables presented to the Agency that tabulate severe hypoglycemia in the pramlintide treatment group: however, the trends are consistent. See also footnote # 78.



*DCCT intensified insulin group [21]

Source: Figure 11.

Table 30 presents the incidence and annual rates of severe hypoglycemia from study 137-150, Phase III pramlintide clinical trials and DCCT in table format. In addition, it provides dose-specific incidence and annual rates for severe hypoglycemia in trial 137-150.

Table : 30: Annual Event Rate and Incidence of Severe Hypoglycemia (DCCT*, Study137-150, and Type 1 Long-term Controlled Trials 137-112, 137-117, and 137-121; ITT Recommended Doses)

Study Treatment	Initiation Period (Week 0 – 4)		Maintenance Period* (Week 4 – Week 29)		Overall	
	Incidence (%)	Event Rate	Incidence (%)	Event Rate	Incidence (%)	Event Rate
137-150						
Placebo	2.7	0.42	8.4	0.28	10.2	0.30
Pramlintide Total	4.7	0.75	17.7	0.54	21.6	0.57
Pramlintide 60 µg♦	0.9	0.46	16.0	0.41	19.8	0.42
Pramlintide 30 µg♦	*1.4*	*0.79*	*24.3*	*1.00*	*29.3*	*1.10*
Type 1 Long-term Controlled Trials						
Placebo	5.6	1.60	16.9	1.05	17.8	1.12
Pramlintide	11.6	2.78	21.1	0.74	24.2	0.96
DCCT†						
Intensive Insulin					65.0	0.62

*For the type 1 long-term controlled trials the maintenance period was Week 4 – Week 26. Overall was Week 0 – Week 26.

†Representing 6.5 years of follow-up [21]

♦Represents actual dose taken during the initiation period at the time of the severe hypoglycemia and the last dose taken during the maintenance period

Source: Table 25.

It should be noted that the data for the 30-µg and 60-µg subgroups during the initiation period presented in Table 30 represents only the severe hypoglycemia occurring at the dose that was eventually tolerated by individual patients (in order to achieve such a dose, a patient had to escalate through one or more doses, during which time severe hypoglycemia could have occurred). Indeed, when all severe hypoglycemic events are taken into consideration (a situation that reflects closer clinical practice) the severe hypoglycemia incidence and annual event rates for the first month of treatment are quite different (Table 30A)[83].

Table 30 A: Incidence and Annual Event Rate of Severe Hypoglycemia During the Pramlintide Initiation Period (Study 137-150)*

Study Treatment and Dose	Initiation Period (Week 0-4)	
	Number and (%)	Event Number and (Event Rate)
Placebo	4 (2.7)	5 (0.42)
Pramlintide Total	7 (4.7)	9 (0.75)
Pramlintide 60-µg	4 (4)	4(0.48)
Pramlintide 30-µg	3 (7.3)	5 (1.73)

*Source: SDS 3.2.14.3. For this period hypoglycemic events were defined as those that began on or after the first data of study medication administration and up to and including the Week 4. Dose is assigned as the last dose received in the study.

In conclusion:

- the results of the current study largely replicates observations made in the pramlintide Phase III clinical trials with respect to the increased incidence of severe hypoglycemia in pramlintide-treated patients relative to insulin treatment alone
- while non-severe hypoglycemia occurred at comparable rates in insulin alone-treated patients and pramlintide-treated patients, severe hypoglycemia occurred twice more often in pramlintide-treated patients (21.6%) than in patients receiving

[83] Final Clinical Study Report for Study 137-15o, on page 141 of the NDA states: "During the initiation period, four (2.7%) placebo-treated subjects experienced severe hypoglycemia compared to seven (4.7%) pramlintide-treated subjects, with an annual event rate of 0.42 and 0.75, respectively. Based on last dose received in the study (SDS 3.2.14.3), a somewhat higher proportion of pramlintide subjects in the less tolerant 30-µg subset group (three subjects, 7.3%) experienced severe hypoglycemia, compared to subjects in the 60-µg subset (four subjects, 4.0%). The annual event rate for the 60 µg subset group, which was achieved by the majority (N=101) of pramlintide-treated subjects was 0.48, was comparable the placebo group. In contrast, the 30 µg subset (N=41) had an annual event rate of 1.53, which appears to be another manifestation of the decreased tolerance of pramlintide.

placebo and insulin (10.2%) for the whole duration of the clinical trial; this 2:1 ratio of severe hypoglycemia (pramlintide:placebo) is seen for both the initiation and the maintenance periods[84]

- patients who received the 30-µg (low dose) pramlintide regimen displayed a disproportionately higher incidence and annual event rate of severe hypoglycemia relative to patients who tolerated and received the higher dose (60-µg)[85]
- the first two months of the pramlintide maintenance period appears to be associated with an increased risk of severe hypoglycemia relative to placebo in particular for patients treated with the 30 µg pramlintide dose (this coincides with the beginning of the insulin optimization period)
- nausea appears to be a contributing factor to severe hypoglycemia (a greater number of severe hypoglycemic events in pramlintide-treated subjects occurred when nausea was reported on the day of the hypoglycemic event; twice as many patients on pramlintide reported missed meals or ingested smaller meals in association with pramlintide treatment relative to insulin alone

C.5.2 Nausea

Table 31 presents the incidence of treatment-emergent nausea by treatment (pramlintide vs. placebo), treatment period (initiation vs. maintenance periods), and symptom intensity. During the initiation period, a higher incidence of nausea was observed in the pramlintide group (28.6% placebo vs. 55.4% pramlintide)[86]. During the maintenance period, the incidence of nausea was twice higher in the pramlintide group (28.0%) relative to the placebo group (14.7%). As seen in the Phase III clinical trials, the incidence of nausea decreased after the first 4 weeks of treatment but nausea did nor disappear. Consistent with the observations made during the Phase III clinical trials, most of the nausea was

[84] Pramlintide initiation period : 2.7 % placebo, 4.7 % pramlintide. Pramlintide maintenance period: 8.4% placebo and 17.7 % prmlintide.

[85] Overall incidence: 19.9% for the 60 µg dose subgroup vs. 29.3 for the 30 µg subgroup. Overall annual event rate: 0.42 for the 60 µg dose subgroup vs. 1.10 for the 30 µg subgroup.

[86] During the Phase III clinical trials the overall incidence of nausea for the equivalent first four weeks of treatment was 8.6 % in the placebo group vs. 47 % in the pramlintide group.

reported as mild. Some imbalance in "moderate" nausea was noticeable[87]. Severe nausea was seen in a small number of patients but predominantly in association with pramlintide. Although the majority of patients experiencing nausea were labeled as having "mild" nausea, it should be emphasized that the clinical significance of the different intensities of nausea (and how it relates to severe hypoglycemia) is not clear. The dose-titration regimen resulted also in a marked reduction of nausea-related patient withdrawals in study 137-150. Thus, two (1.4%) pramlintide-treated subjects withdrew due to nausea, compared to one (0.7%) placebo-treated subject. The incidence of patient withdrawals due to nausea was significantly reduced in this study (1.4%), compared to the Phase III clinical trials (9.0% for the 30-µg and 60-µg doses).

[87] Initiation period: 6.1% placebo vs.16.2 % pramlintide. Maintenance period: 1.4% placebo vs. 4.9 % pramlintide.

Table 31: Incidence of Treatment-Emergent Nausea by Intensity and Treatment (ITT; N=295)

Study Period / Intensity	Placebo (N=147)		Pramlintide* All (N=148)		15 µg (N=148)		30 µg (N=145)		45 µg (N=120)		60 µg (N=110)	
	n	(%)			n	(%)	n	(%)	n	(%)	n	(%)
Initiation	**42**	(28.6)	**82**	(55.4)	**52**	**(35.1)**	**31**	**(21.4)**	**23**	**(19.2)**	**9**	**(8.2)**
Mild	33	(22.4)	69	(46.6)	42	(28.4)	27	(18.6)	17	(14.2)	7	(6.4)
Moderate	9	(6.1)	24	(16.2)	11	(7.4)	6	(4.1)	7	(5.8)	2	(1.8)
Severe	0	(0.0)	4	(2.7)	1	(0.7)	2	(1.4)	0	(0.0)	1	(0.9)
			Pramlintide†									
Study Period / Intensity	**Placebo (N=143)**		***All*** **(N=143)**				**30 µg (N=38)**				**60 µg (N=101)**	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Maintenance	**21**	(14.7)	**40**	(28.0)	NA	NA	**17**	**(44.7)**	NA	NA	**20**	**(19.8)**
Mild	18	(12.6)	33	(23.1)	NA	NA	14	(36.8)	NA	NA	16	(15.8)
Moderate	2	(1.4)	7	(4.9)	NA	NA	3	(7.9)	NA	NA	4	(4.0)
Severe	1	(0.7)	3	(2.1)	NA	NA	0	(0.0)	NA	NA	3	(3.0)

*During the initiation period, dose is assigned as the dose at time of the nausea event.

†During the maintenance period, dose is assigned as last dose taken in the study, with the exception of subjects 1708 and 1130 (Section 4.0), who are assigned to their Week 36 dose for purposes of data reconciliation. The six subjects receiving 15 µg or 45 µg as the last dose in the study are included in the *all* pramlintide column as described in **Table 7**

Source: Table 23

The applicant provides the results of a Gastrointestinal Symptom Questionnaire administered to patients who reported nausea and/or vomiting during the previous week of the clinical trial. This questionnaire consisted of a series of questions designed to assess the reported nausea in greater detail. The results of the questionnaire are summarized by the applicant by treatment group.

The following observations were made for the placebo (insulin alone) group:

- the majority of subjects who experienced nausea reported intermittent nausea (≤4 days/week) throughout the study
- nausea was generally episodic in nature, occurred one or two times a day, and decreased after the initiation period
- the occurrence, timing, and association of nausea with meals were random throughout the day.
- nausea did not interrupt daily activities

The following observations were made for the pramlintide group:

- the majority of subjects who experienced nausea reported frequent events (>4 days/week) during the initiation period, followed by a progressive shift towards intermittent nausea during the maintenance period
- nausea was primarily episodic in nature during the initiation period; approximately 30% of subjects reported sustained nausea

- nausea decreased after the initiation period and, when persistent, it occurred one to three times a day during the maintenance period
- the occurrence of nausea was slightly higher during the morning, compared to other times of the day
- in terms of timing, nausea occurred during or after the meal resulting in decreased food intake; less than 3% of the respondents at any visit reported missing a meal due to nausea
- subjects experiencing nausea reported discomfort but indicated daily activities were not interrupted

In conclusion:

- This new pramlintide titration regimen reduced the impact of pramlintide on nausea-related patient withdrawals (1.4% in this clinical trial vs. 9 % in the Phase III clinical trials.
- Twice as many patients experienced nausea in the pramlintide-treatment group relative to the placebo group
- Although most nausea was reported as mild in intensity in general, a significant proportion of patients reported moderate nausea (among these, the paramlintide-to placebo inbalance was almost threefold; severe nausea occurred occasionally but mostly in pramlintide-treated patients. The relationship between the intensity of nausea (mild, moderate, and severe) in pramlintide-treated patients and severe hypoglycemia is not fully characterized
- The GI questionnaire indicates that "in terms of timing, nausea occurred during or after the meal resulting in decreased food intake;" in addition, up to 3% of the respondents at any visit reported missing a meal due to nausea and 30 % of subjects reported sustained nausea

C.6. Clinical Laboratory

Clinical laboratory data are presented as "laboratory values of potential clinical importance (PCI)" at study exit (week 29). The PCI laboratory values were defined as values outside the reference range for each analyte. Table 32 presents a summary of PCI values at the end of the study. The number of potentially clinically important laboratory values at Week 29 were similar between the placebo and pramlintide group. Some minor imbalances between the two treatment groups are noted but the number of observations is so small that firm conclusions cannot be drawn. Several analytes related to renal function (urine protein, serum BUN, serum creatinine and serum potassium) were higher in the pramlintide group. Nephropathy is a known complication of long-standing diabetes and a minor imbalance between groups in patients with diabetic nephropathy may account for the differences[88].

[88] Abnormal creatinine values were: (1) Placebo group: one patient (screening creatinine 1.6 mg/dl); (2) Pramlintide group, five parients: I) creatinine at week 29: 1.6 mg/dl; II) creatinine at week 29: 1.7 mg/dl; III) creatinine at screening of 1.8 mg/dl, day 1 of 1.8 mg/dl, and week 29 of 1.8 mg/dl; IV) creatinine at screening of 1.6 mg/dl, day 1 of 1.7 mg/dl, and week 29 of 1.7 mg/dl; V) creatinine at week 29 of 10.4 mg/dl.

Table 32: Number of Laboratory Values of Potential Clinical Importance at Week 29 by Treatment

Variable	Treatment Group					
	Placebo (N=147)			Pramlintide (N=148)		
	Number of PCI Values	Total Number of Lab Values	%	Number of PCI Values	Total Number of Lab Values	%
Hematology						
Hemoglobin (g/dL)	0	130	0.0	1	112	0.9
Platelet Count ($x10^3$/UL)	0	128	0.0	1	107	0.9
Urinalysis						
Protein	2	132	1.5	6	113	5.3
Urine Glucose	22	132	16.7	21	113	18.6
Clinical Chemistry						
ALT (IU/L)	1	133	0.8	1	116	0.9
Bicarbonate (meq/L)	1	132	0.8	1	115	0.9
BUN (mg/dL)	0	133	0.0	2	116	1.7
Calcium (mg/dL)	0	133	0.0	3	116	2.6
Total Cholesterol (mg/dL)	0	132	0.0	2	115	1.7
Total CPK (IU/L)	3	133	2.3	1	116	0.9
Creatinine (mg/dL)	1	133	0.8	5	116	4.3
GGT (IU/L)	1	133	0.8	0	116	0.0
Glucose (mg/dL)	0	128	0.0	2	113	1.8
Phosphorous (mg/dL)	0	133	0.0	1	116	0.9
Potassium (meq/L)	2	133	1.5	4	116	3.4
Sodium (meq/L)	0	133	0.0	3	116	2.6
Total Bilirubin (mg/dL)	0	133	0.0	1	116	0.9
Triglyceride (mg/dL)	0	132	0.0	1	115	0.9

Cross-references: SDS 3.3.4, 3.3.5, and 3.3.6; Appendices 3.12.3, 3.12.7, and 3.12.11

(ITT; N=295)
Source: Table 28.

Table 32A displays treatment-emergent urinary adverse events by treatment group (placebo vs pramlintide) for the maintenance period. No clear differences are identifiable.

Table 32A: Treatment-emergent Adverse Events Codes Under the Preferred Term of Urinary System

Preferred Term	Placebo N=143 n (%)	Pramlintide N=143 n (%)
Cystitis	2 (1.4%)	2 (1.4%)
Hematuria	0	1 (0.7 %)
Nephropathy toxic	1 (0.7%)	0
Renal calculus	1 (0.7%)	0
Renal Function Abnormal	0	1 (0.7%)
Urinary Tract Infection	9 (6.3%)	7 (4.9%)

*Source SDS 3.2.8. N =number (%)

C.7 Vital Signs/ECG

Mean blood pressure measurements by visit and treatment are presented in Table 33. No consistent changes between treatment groups are noted. A discreet trend toward an increase in mean systolic blood pressure was present in both treatment groups. Heart rate changes over time were, reportedly, "unremarkable." The applicant reports only one clinically significant abnormal ECG (right bundle branch block) in a placebo patient.

Table 33: Mean Blood Pressure by Visit and Treatment (ITT; N=295)*

	Placebo (N 147)	Pramlintide (N 148)
Visit	Systolic (SD) / Diastolic (SD)	Systolic (SD) / Diastolic (SD)
Baseline	120 3 (13 6) 72 5 (7 7)	120 0 (15 3) 73 4 (8 6)
Week 1	120 6 (12 9) 72 2 (8 0)	120 6 (14 3) 73 2 (9 2)
Week 2	117 9 (12 5) 70 3 (8 4)	120 8 (16 5) 72 6 (9 8)
Week 3	118 6 (14 0) 70 4 (8 3)	121 4 (14 9) 72 7 (11 1)
Week 4	118 7 (13 8) 71 7 (8 5)	121 5 (14 9) 72 3 (10 1)
Week 8	120 0 (13 7) 72 4 (8 6)	122 1 (14 5) 71 7 (8 6)
Week 12	119 7 (13 0) 71 3 (8 6)	121 3 (14 1) 72 8 (8 5)
Week 16	121 3 (15 7) 72 7 (8 6)	122 8 (15 3) 73 5 (9 5)
Week 21	122 6 (14 2) 72 7 (8 8)	123 5 (15 3) 72 8 (9 4)
Week 25	121 6 (14 1) 72 7 (8 8)	123 6 (15 9) 73 1 (11 1)
Week 29	121 4 (14 9) 72 4 (8 4)	123 8 (15 4) 73 2 (8 6)

Source: Table 29.

*Data are presented as mean and standard deviation. Blood pressure is measured in mmHg.

C.8 Other Safety Observations

Pregnancies

Two pregnancies occurred during the course of the study in patients on pramlintide treatment. One was followed by an elective "pharmacological abortion." The other was carried to term (the duration of the *in utero* exposure to pramlintide was estimated at 21 days). The infant was born with trisomy 21, but this chromosomal abnormality is commonly associated with advanced maternal age (the patient was 44 years of age).

Anti-Pramlintide Antibodies

The Approvable Letter dated 10 October 2001 requested additional information regarding the
immunogenicity of pramlintide for the drug product containing — material due to differences in methods of peptide synthesis of pramlintide acetate.

During study 137-150, the 284 subjects who had not participated in previous studies were treated
exclusively with drug product containing — material, with assessments done at Day 1 (prior to drug exposure), Week 16, and Week 25. Among subjects with baseline and Week 25 assessments (excluding those with a positive response at baseline) a total of 7 (6.1%) of placebo-treated subjects and 15 (15.3%) of pramlintide-treated subjects had, reportedly, a "low-titer" treatment-emergent positive anti-pramlintide antibody result at Week 25[89]. The applicant states that "there was no evidence of a relationship between development of antibodies and loss of pramlintide clinical activity, injection site reactions, or allergic symptoms." No other clinical analyses are provided. Visual inspection of the listed individual antibody titer results confirms that most patients had low titers (1:5 or 1:25). In addition, data from an ongoing study (137-140), in which patients were switched to the — drug product, confirm low antibody titers to pramlintide in 7 patients who became antibody positive.

[89] Supporting Data Summary 3.7.2. During the Phase III clinical trials, in studies up to one year duration, 6.8% and 8.5% of patients with type 1 and type 2 diabetes respectively had been shown to develop anti-pramlintide antibodies during treatment.

D. Adequacy of Safety Testing

The safety information presented in this NDA is adequate to allow a regulatory action. Trial 137-150 was designed with the purpose of evaluating the incidence of severe hypoglycemia in a cohort of patients with type 1 diabetes who were treated with a new pramlintide/insulin regimen. The collection and presentation of the information on severe hypoglycemia was extensive and followed guidance provided by the Division in previous meetings and discussions with the applicant. Similarly, nausea has been evaluated extensively and presented in detail. In addition to hypoglycemia and nausea, standard adverse events, vital signs, and clinical laboratory have also been evaluated. All safety evaluations requested by the agency at the end of the review cycle have been addressed by the applicant[90].

E. Summary of Critical Safety Findings and Limitations of Data

Analysis of the safety data from study 137-150 confirms two safety signals already identified in pramlintide-treated patients during the Phase III clinical trials. They are: (1) gastrointestinal adverse events (nausea, vomiting, reduced appetite) and (2) severe hypoglycemia.

E.1 Gastrointestinal adverse events

Similar to observations made in the Phase III efficacy trials, gastrointestinal treatment-emergent adverse events had higher incidence rates in pramlintide treated patients relative to patients treated with insulin alone. To this end, nausea and vomiting occurred twice more frequently, and reduced appetite occurred 4.4 times more frequently, in association with pramlintide.

The importance of the pramlintide-induced gastrointestinal adverse events goes beyond a tolerability issue because of their relationship with another adverse event: severe hypoglycemia. This NDA provides evidence that the nausea and the reduction in appetite that follow pramlintide administration may result in decreased or even missed meals. Because the short-acting insulins are given prior to the ingestion of a meal, the reduction in meal size may result in an unpreventable mismatch between the dose of insulin and the actual amount of food ingested (i.e. the insulin dose is overestimated). If the mismatch is severe, hypoglycemia may follow. There is

[90] It has been agreed by the agency to evaluate the incidence of retinopathy as Phase IV study.

no factor that can predict for any given meal when a patient will have a level of nausea that will result in smaller or missed meals[91].

E.2 Severe hypoglycemia

Despite the fact that it used a different pramlintide regimen (initial pramlintide titration and concomitant reduction in short-acting insulin), study 137-150 records a pattern of hypoglycemia similar to that observed during the Phase III clinical trials: while non-severe hypoglycemia occurred with similar frequencies in patients treated with insulin alone and in patients treated with pramlintide/insulin combination therapy, severe hypoglycemia was approximately twice more frequent in patients treated with pramlintide/insulin combination.[92]

An analysis of events associated with severe hypoglycemia indicates that pramlintide-induced gastrointestinal adverse events appear to be a contributing factor. To this end, a greater number of severe hypoglycemic events occurred in pramlintide-treated subjects when nausea was reported on the day of the hypoglycemic event; in addition, twice as many patients on pramlintide reported missed meals or ingested smaller meals in association with severe hypoglycemia. Thus, trial 137-150 makes a major contribution in understanding the etiology of severe hypoglycemia because it clarifies the mechanistic link between the gastrointestinal adverse events and the severe hypoglycemia: pramlintide induces nausea, nausea results in smaller meals and an imbalance between the insulin dose and the size of the food ingested. Additional data from the pharmacodynamic trial 137-151 shows that, when pramlintide is used in combination with a short-acting insulin, early postprandial serum glucose concentrations can fall substantially below the baseline serum glucose levels, potentially in the hypoglycemic range.

E.3 Recognition of hypoglycemia symptoms

A concern that pramlintide may interfere with the patients' ability to recognize symptoms of hypoglycemia was raised during the original NDA review. Evidence from clinical trial 137-150 and from a pharmacodynamic study (137-152), does not appear to be substantiate this concern.

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[91] Additional information about nausea obtained from a Gastrointestinal Symptom Questionnaire indicates that (1) patients using pramlintide experience nausea during and after the meal, (2) up to 3% of pramlintide users reported missing a meal due to nausea at any visit, and (3) 30% of subjects reported sustained nausea on pramlintide.

[92] The incidence of severe hypoglycemia was higher in pramlintide treated patients for the whole duration of the study (10.2% insulin alone, 21.6% pramlintide), for the "initiation period" (2.7% insulin alone, 4.7% pramlintide), and for the "maintenance period" (8.4% insulin alone, 17.7% pramlintide). In addition, more patients had serious adverse events associated with hypoglycemia in the pramlintide/insulin group (four patients) relative to the insulin alone group (1 patient). Two patients withdrew due to hypoglycemia (coma and injury) in the pramlintide treated-group (none in the insulin alone group).

Trial 137-150 provides information that indicates the lack of a discernable difference in the incidence of symptoms of hypoglycemia between the two treatment regimens. Combined with the results of the pharmacodynamic study 137-152 which does not identify differences between pramlintide and placebo treated patients in their ability to recognize symptoms of hypoglycemia, this responds favorably to one of the safety concerns raised by the initial safety review and the October 10, 2001 Action Letter which stated that "investigations to date have not excluded the role of Symlin™ in altering (lowering) the threshold for hypoglycemia awareness or in otherwise impairing patient responses to hypoglycemia."

E.4 Antibody response

An analysis of the antibody titers during the course of trial 137-150 indicates that 15.3 % of pramlintide treated-patients develop anti-pramlintide titers after 25 weeks of treatment compared to 6.1 % of the insulin alone treated patients. Although the — -manufactured drug product appears to be twice as immunogenic relative to those previously tested in the Phase III clinical trials for different durations, the antibody titers are low (1:5 to 1:25).

In conclusion, the new pramlintide regimen tested in the safety clinical trial 137-150 (initial titration of pramlintide associated with concomitant lowering of the insulin dose) has not improved the safety of pramlintide/insulin combination treatment relative to insulin treatment alone. An imbalance in incidence of severe hypoglycemia relative to insulin treatment alone persists even with pramlintide titration. By not succeeding in providing a safer way to initiate pramlintide therapy in patients with type 1 diabetes, the safety profile of pramlintide therapy has not changed significantly from the one observed during the Phase III efficacy trials.

VIII. Dosing, Regimen, and Administration Issues

The safety trial 137-150 used the same doses of pramlintide (30 µg and 60 µg) and the same route of administration (subcutaneous) employed during the Phase III efficacy clinical trials in patients with type 1 diabetes[93]. It was different, however, in that pramlintide was administered immediately before meals ("0 min.") while in the Phase III clinical trials it was administered earlier ("–15 min.")[94]. The main contribution of study 137-150 with respect to pramlintide administration is twofold: (1) it reduced the proportion of patients who discontinued early the clinical trial due to gastrointestinal adverse events and (2) it identified two relatively distinct patterns of tolerability to the drug as a result of pramlintide titration (to this end, approximately 1/3 of patients cannot be titrated beyond the 30-µg dose, while the remainder 2/3 of patients tolerate the 60-µg dose).

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[93] During trial 137-150 pramlintide was administered with the main meals of the day (breakfast, lunch, and dinner). An additional dose was given for large snacks (defined as snacks that contained >30 g of carbohydrates).

[94] Based on observations made during the pharmacodynamic study 137-151 the change from"–15 min." to " time 0 min." administration results in a slightly more vigorous reduction in postprandial plasma glucose concentrations. Although this change may result in a small increase in efficacy it may also increases the risk of postprandial hypoglycemia.

Evidence provided in the bioequivalence study 137-153 suggests that body adiposity may not be a major contributor factor to the plasma concentrations of pramlintide, an issue raised in the original efficacy review. This study suggests that the larger pramlintide doses required in patients with type 2 diabetes (120-µg) relative to patients with type 1 diabetes (up to 60-µg) are due to factors other than obesity (possibly "amylin resistance").

IX. Use in Special Populations

A. Gender Effects Analyses

See original NDA review. This sNDA does not provide any additional efficacy or safety analyses by age, race or ethnic background.

B. Age, Race, or Ethnicity Effects on Safety or Efficacy

See original NDA review. This sNDA does not provide any additional efficacy or safety analyses by age, race or ethnic background.

C. Pediatric Program

See original NDA review. This sNDA does not provide any pediatric data.

D. Special Populations

See original NDA review. This sNDA does not provide any additional efficacy or safety analyses in patients with chronic renal or hepatic disease. Pregnant patients were excluded from the clinical trial.

X. Risk-Benefit Analysis, Recommendations, and Labeling

A. Risk Benefit Analysis

The safety study 137-150[95] has been designed to address deficiencies identified during the review of the first pramlintide NDA submission of December, 2000. These deficiencies, listed in the Agency's Action Letter dated October 10, 2001 included an "unacceptable safety profile" due to "an increased risk of severe hypoglycemia relative to insulin alone, particularly in the first month of therapy, in trials of Type 1 and Type 2 diabetes."

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[95] Study 137-150 was different from the Phase III efficacy trials in several ways: (1) it was a safety study, (2) it used a new regimen in which pramlintide was titrated to tolerability, (3) it was conducted in a group of patients with better glycemic control who were also stable with respect to severe hypoglycemia, (4) insulin adjustments were made in a way consistent with clinical practice, and (5) it was not a superiority trial; instead it compared pramlintide/ insulin combination treatment to insulin alone in the context of equivalent efficacy in lowering HbA1c.

The new pramlintide regimen utilized in the safety trial 137-150 did not reduce the imbalance of severe hypoglycemia between patients treated with pramlintide/insulin combination and patients treated with insulin alone that was seen during the Phase III efficacy clinical trials. Consequently, study 137-150 has not changed the risk/benefit analysis that formed the basis of the October 10, 2001 regulatory decision.

This reviewer's risk/benefit analysis is at variance with the applicant's risk/benefit assessment. The applicant states that hypoglycemia is "predictable and manageable," that it "should be largely avoidable by lowering the insulin dose during the initiation of pramlintide therapy." The study results indicate that, despite an initial lowering in insulin dose, the incidence of severe hypoglycemia was higher in pramlintide treated patients for the whole duration of the study (10.2% insulin alone, 21.6% pramlintide), for the "initiation period" (2.7% insulin alone, 4.7% pramlintide), and for the "maintenance period" (8.4% insulin alone, 17.7% pramlintide).

Study 137-150 has made important safety contributions to the understanding of the clinical effects of pramlintide. The results of clinical study 137-150 indicate that the change from a "fixed dose" pramlintide regimen to a "titration to tolerability" regimen was successful in reducing the initial impact of nausea. The pramlintide titration regimen dramatically reduced the number of patients who discontinued the trial due to gastrointestinal adverse events. However, this benefit did not extend to a reduction in severe hypoglycemia relative to insulin treatment alone.

Based on our current understanding of pramlintide's mechanism of action, two problems prevent the safe use of pramlintide in patients with type 1 diabetes and appear to contribute to the high incidence of severe hypoglycemia when pramlintide is used in association with insulin: (1) pramlintide-induced gastrointestinal adverse events (nausea, reduced appetite) and (2) the remarkable variability in early postprandial glucose reductions relative to preprandial glucose values.

(1) Pramlintide-induced gastrointestinal adverse events result in a reduction of meal size (or even skipped meals) and excess of insulin dose relative to the amount of ingested food. This problem may not be preventable since patients may not be aware of how much nausea they will have at any given meal; since both pramlintide and short-acting insulins are administered prior to meal ingestion, after the fact insulin adjustments are not possible. In addition, while the initial impact of pramlintide-induced

gastrointestinal adverse events is reduced by the new pramlintide titration regimen, such events persist beyond the titration period[96].

(2) An additional concern to this reviewer is the remarkable magnitude and variability of postprandial reduction in serum glucose concentrations relative to preprandial glucose concentrations associated with pramlintide/insulin co-administration. In the pharmacodynamic study 137-151, patients had early postprandial reductions in serum glucose concentrations as large as 100-120 mg below baseline. Depending, on the actual serum glucose concentrations prior to meal ingestion, the risk of postprandial severe hypoglycemia is evident. The applicant does not provide any information that allows to predict which patients are at risk to have significant reductions in postprandial serum glucose concentrations. The postprandial reduction in plasma glucose concentration relative to pre-meal glucose concentrations may be a mechanism independent of nausea/reduced appetite (i.e. related strictly to the large variability gastric emptying time that follows pramlintide administration).

Finally, since patients enrolled in study 137-150 were metabolically stable (absence of severe hypoglycemia over the preceding 6 months was an entry criterion), giving pramlintide to a less stable population has the potential risk of resulting in higher incidence rates of severe hypoglycemia.

B. Recommendations

As clinical trial 137-150, did not succeed in improving the safety of pramlintide /insulin combination treatment relative to insulin treatment alone over the one established during the Phase III clinical trials which was deemed not safe by the July 26, 2001 Endocrinologic and Metabolic Drug Advisory Committee and by the prior safety review, this reviewer recommends against changing the "approvable" regulatory decision.

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[96] For pramlintide-treated patients only 3 severe hypoglycemic events related to skipped or reduced meals occurred during the first month of the trial (days 13, 20, and 21), while 9 such events occurred during the rest of the trial (days 70, 74, 94, 100, 116, 124, 125, 156, and 204 respectively). For comparison, in the insulin alone group all severe hypoglycemia events associated with skipped/reduced meals occurred during the first month of the trial (days 4 and 24, respectively).

C. Labeling

No labeling recommendations are made since the recommended regulatory decision is "approvable".

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/s/

Dragos Roman
11/21/03 10:53:31 AM
MEDICAL OFFICER

David Orloff
12/4/03 05:15:23 PM
MEDICAL OFFICER

Memorandum

Date: 9/4/01

From: Saul Malozowski, MD, Ph.D., MBA
Medical Team Leader

Subject: Symlin (Amylin); NDA 21-332; Team Leader Memorandum to the File

To: David Orloff, MD
Division Director, DMEDP

Recommendation:
This drug should not be approved.

This memorandum addresses issues that arose during this NDA review and supports my recommendation for non-approval. The issues are as follows:

1) Was the design of the clinical studies adequate and what level of efficacy was shown?

Since the early 1990s the American Diabetes Association has recommended intensive therapy to improve glucose control in subjects with diabetes. This recommendation emanated from results from multiple clinical studies demonstrating that good glucose control was associated with substantial decrease in complications, particularly those affecting the retina.

Although, during the process of drug development, it may be permissible to expose patients to some degree of discomfort to properly define the safety and efficacy of a drug, a clinical development plan should address the efficacy and safety of a drug under the best clinical practices possible. Use of artificial constraints could result in inappropriate study design.

This is indeed what happened with the studies performed by this sponsor: a) Insulin doses were kept constant in most studies and, b) the effects of Symlin were studied under inadequate glucose control. These shortcomings were discussed with the sponsor on multiple occasions, during the early stages of the drug development program, in an attempt to remedy these problems. Specifically the sponsor was asked to explore the use of Symlin in subjects with good glycemic control. This is important because at that time there were theoretical arguments to suggest that Symlin use will not be associated to hypoglycemia.

Because the sponsor refused to follow this repeated advice, we are faced with results that are difficult to interpret because they were obtained in a context that differs substantially from clinical practice.

There is no question that under inadequate glucose control with insulin therapy Symlin is able to reduce HbA1c both in patients with type 1 and 2 diabetes. These statistically significant reductions (~0.3%) are small in magnitude. It is not clear however, whether these modest reductions could be also expected in patients with adequate or good glucose control because no attempts were made to answer this question. If the benefit risk balance of Symlin were good, it could be only approved for the treatment of patients with inadequate insulin therapy.

It is important to stress that increasing the insulin dose would have matched and undoubtedly surpass the improvement obtained by adding Symlin, as it has been previously shown in many studies.

Insulin and Symlin can not be mixed. Mixing alters the pH of both products and may substantially affect Symlin and insulin pharmacological activities.

Symlin failed to show a dose response relationship. Some studies showed an effective dose of 30 µg TID while larger doses (60 µg TID) were less efficacious or failed to be efficacious in various studies. These anomalous results, in the context of an overall modest efficacy, limit our ability to recommend a rationale dosing regimen that could be consistently effective, if the benefit risk balance were positive. It is also important to stress that patients with the poorest control experienced the largest reductions in HbA1c. These results also question the effects of Symlin on better controlled patients.

Moreover, the level of efficacy consistently deteriorated with time. These findings are disturbing because the benefits are borderline and they may disappear with time.

Patients receiving Symlin lost weight in comparison to placebo treated patients. The weight decrease was seen in both type 1 and 2 patients treated with Symlin. The weight loss was modest (~2% of body weight) and occurred in the first 12-13 weeks of therapy.

Thereafter, weight remained unchanged. There was no relationship between weight loss and improvements in HbA1c. The degree of HbA1c change was similar regardless of weight changes. Thus, the anorexigenic effects of Symlin do not explain, by themselves, the modest reductions in HbA1c associated with Symlin use.

No improvements in lipids accompanied the fairly small changes in HbA1c. This questions the clinical significance of the HbA1c changes exerted by this drug. The expectation is that improvements in HBA1c will also improve lipid profiles. This did not occur.

No improvements were seen in blood pressure. Neither the diastolic nor the systolic values showed favorable changes.

The lack of changes in lipids and BP suggest that this drug is able to reduce HbA1c but the degree of benefit is so limited that other critical metabolic parameters in patients with diabetes are not affected despite this favorable change.

2) Is Symlin therapy, as currently administered, a "physiological replacement therapy"?

Contrary to the endogenous peptide amylin which is directly secreted into the portal circulation Symlin is given subcutaneously. As a result, Symlin reaches systemic supraphysiological levels. Thus, Symlin therapy, as currently administered, can not be in earnest defined as a "physiological replacement therapy." In addition, the timing of injection should also mimic what happens when food reaches the GI tract. This goal is difficult to be achieved.

These two barriers may explain, in part, the excess rate of nausea reports associated with Symlin (probably secondary to its central nervous system effects) and the subsequent significant increase in dropouts observed in the Symlin treated patients. In patients with type 1 diabetes three times more patients withdrew from the Symlin arm than in the placebo group (18% vs. 6 %, respectively). When comparing the effects of Symlin vs. placebo in type 1 diabetes the reports of nausea were 51% vs. 17%, of anorexia 18% vs. 2%, of hypoglycemia 27% vs. 19% respectively. Vomiting and fatigue were two times more frequent in the Symlin treated group.

Therefore these nausea reports are important in nature and gravity. These adverse events limited the retention of patients in the study. These undesirable effects may substantially restrict the use of this product if approved.

3) What is the impact of the failure to develop analytical methods in addressing Symlin biological properties?

Many times sponsors are unable to properly address a drug mechanism of action or develop adequate analytical tools to study a compound. These shortcomings have in general not been critical for drug approval, where the focus is mainly in the balance of safety and efficacy.

Symlin's sponsor has not been able to develop an adequate bioassay and it is questionable whether the analytical tools to measure the circulating levels of Symlin are up to standards.

The absence of adequate tools may be limiting our ability to properly address this compound physiology that may be critical to explain the lack of a dose response relationship and other outcomes seen in the clinical studies.

4) Is there a discrepancy between the pharmacodynamic (PD) studies and the results observed in the clinical studies?

The pharmacodynamic studies showed that when Symlin was added to insulin, **the combination** was able to induce significant reductions in post-prandial glucose (PPG) excursions. This salutary effects, however, did not manifest as expected in the clinical studies where the HbA1c reduction were only ~0.3%.

Decreases in PPG have been reported with regular insulin, rapid acting insulins, and oral secretagogues.

In numerous clinical studies, despite a rapid and more potent early response affecting the PPG when compared to regular insulin and sulfonylureas, both rapid acting insulin and non-sulfonylurea secretagogues were not able to achieve better control in HbA1C when compared to regular insulin or sulfonylureas, respectively. No claims of improved glucose controls are currently labeled in any product effectively affecting PPG because these changes were not associated with improved HbA1c levels.

It appears that rapid changes in an early phase of PPG excursion may be overcome by rapid deterioration in glucose profiles once the effect of the rapid acting drug wanes. Indeed this is what has happened with all the rapid acting drugs.

Although Symlin (plus insulin) significantly affected PPG in PD studies, the results of the clinical studies appear to question the long lasting effects of these modifications on this short window.

PD studies are conducted under close medical supervision. Diet and other parameters critical in the evaluation of PD parameters are closely monitored. In contrast, clinical studies mimic, to some extent, real use of a medicine. Patients need to self-administer the medication as indicated, they need to follow dietary advice and also need to receive the insulin as planned. These many variables may not be as easy to monitor as in the context of the clinic where these as well as other variables are properly controlled.

Because Symlin has such a short effect, it is entirely possible that minor modification in the timing of insulin dosages, food intake, food composition and Symlin dosage may have altered the interaction of these critical elements. Indeed, it is well recognized that the level of compliance tends to decrease when time elapses.

The need for larger dosages in patients with type 2 diabetes may be explained in part by the different PK/PD profile in these subjects. This may be due to the increased subcutaneous fat in this population (BMI ~30.)

It is clear from the studies submitted in the NDA that Symlin, per se, has no hypoglycemic properties. The effects of Symlin appear to be related to a delay in gastric emptying. Co-administration of insulin is necessary to induce reduction in glucose

levels. Diabetes progression is associated with development of peripheral neuropathy. At the same time, autonomic neuropathy develops. Patients may have different degrees of alterations in their gastric motility. While in normal volunteers the administration of Symlin could result in a predictable sequence of gastric emptying, in patients with diabetes, this sequence may be quite altered. This may explain, in part, the discrepancies observed in the results of the studies and the lack of a dose response relationship.

Food composition and quantity may also affect gastric emptying. Because patients in daily life do have a large option of food this ample variability may have also impacted the results of the studies presented. These issues were not properly elucidated during drug development.

5) Motor vehicle crashes (and other "accidents")

Because Symlin alone does not induce hypoglycemia, many speculated that this product could result in fewer hypoglycemic episodes than most of the currently available product for the treatment of diabetes. The results of the studies were disappointing in this regard because there was a statistically increase in hypoglycemia in patients with type 1 diabetes. In addition, and more important, there was an increase of episodes involving car "accidents". Only one episode involving a car accident occurred in the placebo group while 18 such episodes occurred in subjects receiving Symlin. This was limited to patients with type 1 diabetes. Thus, due to the randomization scheme motor vehicle crashes or near crashes were 7 times more frequent in subjects receiving Symlin. This occurred more frequently during the first month of therapy but the events were present throughout the duration of the double blinded studies.

Events involving cars are troublesome because not only the subjects receiving the medication are at risk but also bystanders as well as passenger could be affected. This was properly addressed in Dr. Misbin's review.

An issue that has not been resolved by this NDA is the true incidence of these events. I presume that the studies in the NDA underestimate the number of MVA. As stated before it was not foreseen that hypoglycemia would occur. As a result, no effort was undertaken to capture information related to motor vehicle use. We do not know how many patients enrolled were drivers, how many drove, how frequently, etc, etc.

In addition, most of the MVA were clustered in US studies. Many of subjects with type 1 diabetes were studied in Europe, where public transportation is used much more commonly than in the US. Moreover, some of the studies were done in countries (Czech Republic, Hungary) where the number of cars is fewer than in the US. In this context, it is possible, that events involving car accidents or events were underestimated and/or not properly captured. Hence future studies should prospectively address these concerns and variables.

6) CNS and Hypoglycemia

It is clear that Symlin has effects on the CNS. The anorexigenic actions and the early effects inducing nausea cannot but be attributed to Symlin. Although it was not prospectively studied many of the effects attributed to hypoglycemia may be linked to CNS effects of this compound. The definition of hypoglycemia encompasses events where glycemia was not necessarily determined. Thus, some of these episodes where glycemic levels were not assessed may reflect this central action of Symlin. In the absence of measured glucose levels this remains a hypothetical speculation.

7) What is the benefit risk balance?

Of concern in the safety review are the significantly increased number of reports of hypoglycemia and motor crashes in patients receiving Symlin when compared to placebo. These findings are alarming in the context of the poor glucose control (HbA1c ~8.5%) achieved for a drug whose mechanism of action is not to induce hypoglycemia. It is quite rare to find statistically significant levels of serious adverse events in drug applications. In this case hypoglycemia and MVAs, two life-threatening adverse effects, reached this level of significance not previously seen in other antidiabetic medications.

The level of concern that these adverse events elicit needs to be overcome by the benefits that the medication provides. Symlin offers very modest reductions in HbA1c in the context of poor glucose control without affecting lipids. With time, these beneficial effects wane. Symlin administration is associated with significant increase risks for hypoglycemia and motor crashes. It seems that the benefits that could be reached using 3-4 preprandial Symlin injections do not overcome the potential significant risks that emerged during the drug development process.

8) What will be necessary to fill the existing gaps in the drug development process to gain approval?

The main question that has not been yet answered in this NDA is how to use this drug under the best clinical conditions. A long term study will be necessary to address this issue where insulin could be used as it is under current recommended norms and not kept fixed as it was on most studies in this NDA. These studies will need to prospectively assess the real risk of hypoglycemia, MVAs, and personal injury and develop strategies to decrease these risks. Decreasing the insulin doses will probably improve these prospects but will also probably impinge on the main outcome: reductions in HbA1c. Because most of the improvement were seen at the beginning of the studies the effects of initially reducing insulin and then increasing its dose remain unknown. Similar uncertainties are present if the Symlin doses were to be modified.

In patients with type 2 diabetes, the sponsor will need first to clarify the discrepancies in PK/PD before undertaking any long term study.

However, due to what has already been learned with this compound one questions the rationale to proceeding with these studies. It is clear that at the most the expected improvement will not be more than a reduction of 0.4% in HBA1c. If approved, this would be the smallest HbA1c improvement that will be granted market access. I consider that this will be a bad precedent in the context of the poor safety profile of this drug. A safety profile that leads to significant drop out rates associated with nausea as well as significant increases in hypoglycemia, anorexia, injury, and MVA could be tolerated if the benefits would outweigh these risks. This, unfortunately, is not the case with this drug.

Because the expectation for improvement is very modest, how would the consent documents fairly disclose the benefits and risks and what would be the subjects' motivations to enroll in a study where the risks greatly outweigh the benefits in new studies? Finally, how could such studies be construed as ethical?

If my recommendations are not followed and this product is approved either now or after new research is undertaken, it will be imperative to disclose this safety information in a black box to prevent, or attempt to prevent, episodes of hypoglycemia, and or associated MVAs. Wording similar to that used in drugs that affect conscience and limit the ability to drive or operate heavy machinery should be inserted in such black box.

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/s/

Saul Malozowski
9/6/01 12:12:28 PM
MEDICAL OFFICER

Secondary Review

David Orloff
9/27/01 07:43:12 PM
MEDICAL OFFICER
Noted. See DD memo for my analyses and recommendations.

Safety Review

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	09-06-2001
		PDUFA DATE:	10-08-2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

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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.

The following safety concerns are raised by this review:

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 in both type 1 and type 2 diabetes patients.
2) Increased incidence of severe hypoglycemia is associated with an increased number of serious adverse events, including driving-related events, other types of injuries, coma and seizures in type 1 diabetes patients.
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.

Recommended Regulatory Action:

1) Type 1 diabetes: Non-approval.
1) Type 2 diabetes: Approvable from a safety standpoint if an additional study that titrates both insulin and pramlintide, is able to prove reduction in first month severe hypoglycemia while still preserving drug efficacy.

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

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Executive Summary (Safety Review)

I. Recommendations:

A. Recommendations on approvability

Type 1 diabetes

Given that pramlintide is a glucose-lowering agent with marginal efficacy (0.3 % HbA1c reduction over placebo) and major safety issues, a risk benefit assessment of this NDA submission argues against approval of this drug in patients with type 1 diabetes.

Of primary concern is the increased risk of **severe hypoglycemia** and **hypoglycemia associated with serious adverse events** (including **motor vehicle accidents, other injuries, coma, and seizures)** observed with the use of pramlintide in patients with type 1 diabetes. Most importantly, this reviewer cannot identify any features of the motor vehicle accidents (MVAs) that would allow to predict which patients are at risk for this life-threatening event.

Type 2 diabetes

The limited efficacy of pramlintide in type 2 diabetes patients coupled with the fourfold risk of severe hypoglycemia during the first month of treatment argues, from a clinical perspective, against the use of pramlintide in this patient population.

If the sponsor were able to demonstrate that a titration study of pramlintide and insulin against insulin alone would eliminate severe hypoglycemia during the first month of treatment, the safety profile of pramlintide would be markedly improved.

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) Extent of Safety Testing:

Overall, 4493 subjects have been exposed to pramlintide and 1504 subjects received placebo in 51 completed clinical trials. The mean pramlintide exposure time per subject is 0.61 years and the total exposure time is 2727 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 refers to pramlintide plus insulin, and placebo treatment refers to 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 (SAEs):

2.A. Deaths

There are seventeen **deaths** recorded during the pramlintide clinical trials, most due to cardiovascular events such as myocardial infarction, sudden death, arrhythmias. The are no major numerical differences between the pramlintide and placebo treatment groups. Two deaths (both in patients receiving pramlintide) may have been related to hypoglycemia (one being a motor vehicle accident). A third death (also in a pramlintide-receiving patient) lacks a cohesive explanation and does not allow for any definitive conclusions.

2. B. Serious adverse events other than deaths:

Hypoglycemia is the leading cause of serious adverse events associated with pramlintide treatment in both type 1 and type 2 diabetes trials. Hypoglycemia associated with SAEs occurs twice more frequently in pramlintide-treated patients over placebo in both types of diabetes. The incidence of SAEs associated with hypoglycemia is higher in type 1 diabetes trials: 9%, compared to 2 % in type 2 diabetes patients.

Although the full range of hypoglycemia-related SAEs responsible for the pramlintide-to-placebo differences is not completely understood, motor vehicle accidents, non-MVA

injuries, comas and seizures constitute an important segment of SAEs in patients with **type 1 diabetes**. Driving-related events associated with hypoglycemia occur 4-8 times more frequently in the pramlintide group, depending on the dataset analyzed. About 1/3 of them take place during the first month of pramlintide treatment with the rest occurring at unpredictable times later on during the trial. Non-MVA injuries associated with hypoglycemia are four times more frequent in pramlintide-treated patients. As stated above, one fatal MVA may have been associated with hypoglycemia in type 1 diabetes. There are no discernable features of the MVAs that allow for the prevention of these events. None of the injuries associated with hypoglycemia has been prospectively assessed and they may represent an underestimation of the true incidence and potential risk to patients.

Weak safety signals are provided by **central and peripheral nervous system** adverse events (in type 1 and type 2 diabetes), **syncope** (type 1 diabetes only), and **inflicted injury** (type 1 diabetes only).

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. Patients treated with pramlintide withdraw three times more frequently due to adverse events during the type 1 diabetes trials (18% pramlintide vs 6 % placebo) compared to only 1.3 times in type 2 diabetes trials (9% pramlintide vs 7 % placebo). Trial completion rates are lower in pramlintide–treated patients in type 1 diabetes (66% compared to 75% for placebo treated patients). Trial completion rates are equal in type 2 diabetes trials (75% for both treatments).

Gastrointestinal (GI) adverse events (in particular **nausea**, but also **anorexia** and **vomiting**) are the main cause of patient withdrawal in both type 1 and type 2 diabetes patients treated with pramlintide. In the type 1 diabetes trials nausea-related withdrawals take place in 12 % of pramlintide patients (twelve times more frequent than placebo). In type 2 diabetes trials the pramlintide-to-placebo difference is only 1.5 times. The vast majority of the nausea-related withdrawals occur during the first month of treatment.

Hypoglycemia is the second most common reason for subject withdrawal for pramlintide-treated type 1 diabetes patients. It is <u>not</u> an important reason for withdrawal in type 2 diabetes patients.

Somnolence, **fatigue**, and **inflicted injury** are unexpected reasons for subject withdrawals in patients treated with pramlintide during the type 1 diabetes trials.

4) Common Adverse Events:

The most common adverse events associated with pramlintide treatment in the type 1 diabetes trials are: **nausea** (51%), **anorexia** (18%), **hypoglycemia** (27%), **vomiting**, and

fatigue. Nausea and anorexia are 3 times and 9 times more frequent, respectively, in pramlintide-treated patients compared to placebo.

The most common adverse events associated with pramlintide in the type 2 diabetes trials are: **nausea** (24%), and **anorexia** (8%). They are approximately twice more common in the pramlintide group over the placebo group. Several CNS symptoms (headache, fatigue, dizziness, and anxiety) are encountered more frequently in association with pramlintide treatment.

Nausea is an extremely frequent adverse event accompanying pramlintide treatment in both types of diabetes, but more so in type 1 diabetes patients. Most subjects develop nausea early in the treatment (within the first four weeks). Nausea has a high rate of recurrence. Nausea occurs at all pramlintide doses that result in glucose lowering effect (clearly demonstrated in type 1 diabetes).
Nausea is the main reason for subject withdrawal for both type 1 and type 2 diabetes subjects in the long-term controlled trials. Nausea-related withdrawals are 17 times more frequent than placebo in type 1 diabetes patients during the first month of treatment and twice more frequent than placebo in type 2 diabetes patients for the same time interval.

Severe hypoglycemia (defined as any episode of hypoglycemia that requires the assistance of another individual for treatment) is a major safety issue in both type 1 and type 2 diabetes patients treated with pramlintide. It is particularly common during the first month of pramlintide treatment (twice more frequent than placebo in type 1 diabetes, and four times over placebo in type 2 diabetes). Following the first month of treatment the incidence differences in severe hypoglycemia between pramlintide and placebo treatment groups persist but to a much lower extent; this observation is more consistently seen in type 1 diabetes patients. Reduction of severe hypoglycemia after the first month of treatment occurs in the context of waning drug efficacy and first month nausea-related withdrawals (i.e. drug-susceptible patients appear to withdraw early in the treatment). Overall, the incidence of severe hypoglycemia is higher in type 1 diabetes patients on pramlintide when compared to type 2 diabetes patients receiving the same treatment (four times more frequent during the first month and approximately 2.7 times higher in the remainder of the trial).

5) Relationship of side effects with animal toxicity

There is some degree of correlation between animal toxicity data and the pramlintide adverse profile observed in humans, in particular with respect to gastrointestinal-related findings. The use of pramlintide in animals is associated, at pharmacological doses, with reduced gastric emptying time, decreased appetite, and lower body weight. All these findings are observed in humans as well.
The relationship between the transient decrease in blood pressure noted in dogs and the small (and apparently clinically insignificant) decrease in diastolic blood pressure in type 1 diabetes by the end of the first month of pramlintide treatment is unclear. A correlation between animal and human data with respect to the absence of significant serum

chemistry abnormalities and organ-specific toxicity (e.g. renal, cardiac, hepatic) is also noted. Other correlations are difficult to make.

6) Drug-drug interactions

The information concerning concomitant use of pramlintide and other medications is limited to only a few drugs: ampicillin (reduced absorbtion), oral contraceptives (mixed effect but overall delayed $T_{max.}$), insulin lispro (no increase in severe hypoglycemia in a small study). Data concerning drug-drug interactions between pramlintide and frequently used medications in type 1 and type 2 diabetes patients (such as statins, ACE inhibitors, other glucose lowering drugs, etc.) are limited. The way this information has been presented in the submission further limits meaningful interpretation (the data derived from the controlled and the uncontrolled studies are mixed, thus making pramlintide-to-placebo comparisons difficult to interpret).

7) Trial exposure versus marketing exposure

Patient exposure to pramlintide appears large enough in both duration and number to predict the most frequent safety issues associated with this drug. The doses tested during the long-term controlled clinical trials are similar to the doses intended for clinical use. **However, it is not at all clear how pramlintide therapy should be initiated in either type 1 and type 2 diabetes patients.** In the face of a high incidence of adverse events (especially severe hypoglycemia and nausea) taking place during the first month of treatment, the sponsor is proposing low pramlintide initiation dose and a form of insulin titration. This approach however has never been tested in clinical trials. Preservation of drug efficacy under these new conditions is unknown. Therefore, these issues have not been resolved.

8) Effects of trial exclusion on safety profile versus expected marketed population.

The type 1 diabetes and type 2 diabetes patients studied during the phase 3 pramlintide trials represent a relatively stable patient population. In order to have been enrolled in the studies the patients had to have a stable insulin regimen for at least two months prior to the lead-in period, and no evidence of severe hypoglyemia for two weeks prior to screening. They also had a mean HbA1c of about 9% and normal clinical laboratory tests. If marketed, pramlintide is likely to be used in a more heterogenous population that may include metabolically unstable patients (for which the sponsor has no information), and patients with a broader range of HbA1c (including patients at the lower end of the HbA1c spectrum). Among the latter, there is a potentially higher risk of severe hypoglycemia since this adverse event is known to be inversely related to the patient's HbA1c level.
Limited safety information is available for patients excluded from the clinical studies such as those with cardiac disease, hypertension, hepatic or renal disease, seizures, eating

disorders. In particular the effects of pramlintide use in patients using drugs that affect gastric motility or in patients with gastric autonomic neuropathy is unknown. No data is available about pediatric patients, particularly for those with type 1 diabetes.

9) Recommended warnings

If pramlintide were to be approved, warnings should describe the risk of hypoglycemia in both type 1 and type 2 diabetes patients. These warnings should emphasize that the hypoglycemia-risk is not limited to the first month of treatment, especially in type 1 diabetes. SAEs associated with hypoglycemia (MVAs, non-MVA injuries, coma, seizures) should be mentioned in association with potential pramlintide use in type 1 diabetes. Consideration should be given to a black box warning on the potential for MVAs and injuries during high risk activities. The frequent occurrence and severity of gastrointestinal events should be included in the label. In addition, systemic symptoms such as fatigue, somnolence, syncope (in type 1 diabetes) and CNS adverse events (headache, fatigue, dizzines, anxiety, in type 2 diabetes) need to be listed in the label.

10) Relashionship of safety profile to other glucose lowering drugs

Pramlintide is a new molecular entity with a new proposed mechanism of reduction in prandial hyperglycemia and therefore it has no standard to be compared against in its class. Hypoglycemia (the main event observed in the pramlintide clinical trials) is not an uncommon adverse event among marketed glucose lowering drugs. It is closely linked to the efficacy of each particular compound. Therefore, an acceptable level of hypoglycemia has to be judged in the context of the overall risk-benefit analysis of the drug. At this point, in the absence of a way to safely initiate pramlintide therapy (i.e. a titration study which results in reduction of severe hypoglycemia) the risk is considerably higher than the benefit that pramlintide may bring to both type 1 and type 2 diabetes patients.

The gastrointestinal adverse events may ultimately prove to be a class effect for several new drugs in development which decrease gastric motility and reduce prandial glycemia. An overlap between pharmacological and toxic effects may impact on the final tolerability and dose selection for these new drugs. Although it is not proven, the potential interplay between two medications (pramlintide and insulin in this submission) and a variable meal content, may result in **mealtime hypoglycemia**. Safety signals observed in this review should result in prospective search of meal-related hypoglycemia and hypoglycemic serious adverse events in other submissions.

11) Unsolved safety issues:

The are major safety concerns associated with the use of pramlintide injection in addition to insulin injection in the treatment of both type 1 and type 2 diabetes patients, but more so in type 1 diabetes. Since safety profiles are different between type 1 and type 2 diabetes, they will be addressed separately.

Type 1 diabetes

The most significant **safety signals** associated with pramlintide use in type 1 diabetes are:

1) A three fold increase in patient withdrawal due to **adverse events** overall.
2) A 50 % incidence of **nausea** that is highly recurrent.
3) A three fold increase in **nausea** and nine times increase in **anorexia** over placebo treatment.
4) Twelve times higher chance of discontinuing the drug due to **nausea.**
5) A small increase in **syncope, inflicted injury**, and CNS-related SAEs (such as **coma** and **seizures**).
6) A two fold increase in **severe hypoglycemia** during the first month of treatment.
7) A two fold increase in **hypoglycemia**-related SAEs overall.
8) In addition and most importantly, a 4-8 fold increased risk of **driving-related events** associated with **hypoglycemia** (including a possible MVA-related death) and a four fold increased risk of **non-MVA injuries** associated with **hypoglycemia.**
9) Most MVAs are recorded in a study which takes place in the U.S.A. and uses higher single pramlintide doses (study 137-121) when compared to a European and Canadian study (137-117) or a U.S.A. study which employs smaller single doses (137-112). This suggests that **driving habits** and **magnitude of single pramlintide dose** may play a role in the occurrence of driving-related events associated with hypoglycemia.
10) Possibly **hypoglycemia** unawareness (subject to debate but without data to reassure that this is not a safety issue).
11) A tendency toward a lower diastolic blood pressure at the end of the first month of treatment which subsequently resolves.

The following safety issues remain unsolved in type 1 diabetes patients:

- **The two fold increased incidence of severe hypoglycemia during the first month of treatment.** All the dose regimens used in the long-term trials (including the lowest dose of 30 μg) have been associated with an increase in severe hypoglycemia incidence during the first month of treatment. Shortcomings in trial design (which attempted to keep insulin levels relatively constant) appear to have contributed to this problem. There are no data that assess safety and efficacy with lower doses of insulin.

- **The increased incidence of driving-related accidents, other types of injuries, and CNS-related SAEs associated with hypoglycemia.** These events are more frequent

during the first month and persist throughout the study. A clear predictive factor was not identified and as a result I cannot envision a strategy to prevent them from happening.

- **The remarkably high incidence and intensity of gastrointestinal symptoms.** Although not life-threatening, these adverse events need to be weighed against the limited benefit of the drug or the desire of the patient to accept it.

Type 2 diabetes

The most significant **safety signals** associated with pramlintide use in type 2 diabetes are:

1) A slightly higher incidence of patient withdrawal due to **adverse events** overall.
2) A 12% incidence of **nausea** which abates only gradually toward the end of the first year.
3) A two fold increase in **nausea** and **anorexia** over placebo treatment.
4) A 1.5 fold increase in **nausea**-related withdrawals over placebo-treated patients.
5) A possible dose-related increase in **retinopathy.**
6) A two fold increase in **hypoglycemia**-related SAEs overall.
7) Most importantly, a four fold increase in severe **hypoglycemia** during the first month of treatment.
8) A small increase in **CNS-related TEAEs.**

The following safety issues remain unsolved in type 2 diabetes patients:

- **The high incidence of severe hypoglycemia during the first month of treatment.** Similar to type 1 diabetes, shortcomings in trial design, which attempted to keep insulin levels relatively constant, appear to have contributed to this problem. There are no data that assess safety and efficacy with lower doses of insulin.

- **The high incidence and intensity of gastrointestinal symptoms.** This level of discomfort, although much less than noticed in type 1 diabetes and not associated with life-threatening events, needs to be weighed against the limited benefit of the drug, the desire of the patient to accept it.

- **A small increase in CNS-related TEAEs.**

Integrated Review of Safety:

A) Conclusions:

Type 1 diabetes

The type 1 diabetes safety review identifies severe hypoglycemia as the most important safety issue in the type 1 diabetes long-term clinical trials. There is a two fold increased risk of severe hypoglycemia during the first month of pramlintide treatment and a 4-8 fold increased incidence of driving-related events associated with hypoglycemia for the whole duration of the trials (as well as a four fold increased incidence of non-MVA injuries associated with hypoglycemia). A remarkably high incidence and intensity of gastrointestinal adverse events and a small but consistent CNS safety signal consisting in comas, seizures (both hypoglycemia-related), syncope, somnolence and fatigue are also noted.

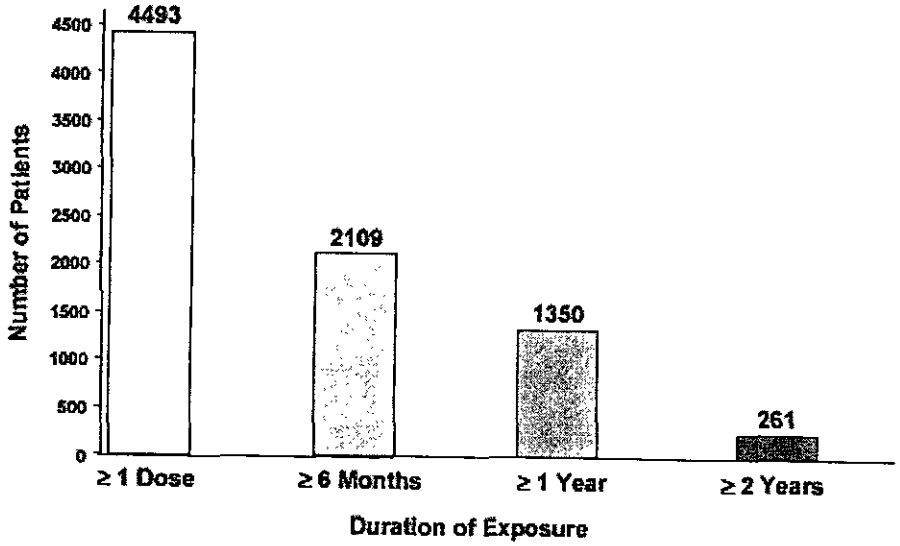
Type 2 diabetes

Hypoglycemia is the most important safety issue in the type 2 diabetes long-term trials as indicated by a four fold increase in severe hypoglycemia during the first month of pramlintide treatment and a two fold overall increase in incidence of SAEs associated with hypoglycemia. The incidence of severe hypoglycemia is lower in type 2 diabetes patients on pramlintide when compared to type1 diabetes patients receiving the same treatment. Gastrointestinal adverse events are also an important safety signal but comparatively less than in type 1 diabetes. A difficult to rule out, dose-related retinopathy associated with pramlintide use is present; incompletely collected data limit definitive conclusions. CNS-related TEAEs are encountered more frequently than in placebo-treated patients.

B) 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 51 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, 4493 subjects have been exposed to pramlintide and 1504 subjects received placebo. The mean pramlintide exposure time per subject is 0.61 years and the total exposure time is 2727 subject-years. Of subjects exposed to pramlintide, 1350 had exposure of ≥1 year and 261 had exposure of ≥2 years. The majority of study subjects were type 1 and insulin-using type 2 diabetes patients. 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*)



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

	Type 1 diabetes		Type 2 diabetes	
Treatment	**Pramlintide**	**Placebo**	**Pramlintide**	**Placebo**
Number of Subjects	1179	538	1273	420

C) Methods and Specific Findings of Safety Review

This review was conducted from the electronic submission and paper copies of Integrated Safety Summary (ISS) reports of NDA 21-322. In addition, individual clinical study reports, pharmacology studies, supportive data summaries (SDS), appendixes, patient narratives, CRF and CRT reports were reviewed as they related to safety data from the ISS. Data reports submitted by the sponsor at the Agency's request were also reviewed along with the Amylin Advisory Committee Briefing Document.

Deaths:

Seventeen patients died during the pramlintide clinical trials. The distribution of deaths among controlled and uncontrolled clinical trials is presented in table 2:

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

	Type 1 diabetes					Type 2 diabetes				
Type of Study	Controlled				Uncntr.	Controlled				Uncntr.
	Short-term		Long-term			Short-term		Long-term		
Treatment	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 that included older subjects with multiple comorbidities.

Three deaths that occurred during the long-term controlled type 1 diabetes studies in the pramlintide group deserve further discussion. It should be noted that serum glucose levels are not available for any of these cases.

Subject 137-117-3501 (pramlintide 90 µg TID):

The subject was a 35-year-old male with a 6-year history of type 1 diabetes and no other significant medical history. The patient died on the first day of pramlintide treatment. The following description is provided:

"On [ ], approximately one day after starting double-blind therapy, the subject was involved in a motor vehicle accident that resulted in his death the same day (SAE #1205). Study medication was unblinded by the investigator at the request of the coroner without discussion or consent by Amylin Pharmaceuticals. The investigator assessed this event as severe in intensity and probably not related to study medication. This was an unexpected (not previously labeled in the Investigator Brochure) event. Due to the fact that food was present in the stomach at the post-mortem examination, indicating that the subject had eaten lunch prior to the event, a role for hypoglycemia due

to study medication was judged unlikely. The Sponsor assessed this event as not related to study medication."

Reviewer's comments: This death raises most concerns. The presence of food in the stomach is not by any means reassuring when the patient is receiving a drug which delays gastric emptying in a dose dependent manner. On the contrary, it raises the concern that, when given in conjunction with insulin, pramlintide may induce postprandial hypoglycemia through delayed glucose delivery to the gut.

Subject 137-112-2804 (pramlintide 30 µg QID):

The subject was a 48-year-old male with a 12-year history of diabetes mellitus and a history of "diabetes-related seizures." The patient's death occurred 229 days within the trial. The following description of his death is provided:

" On [redacted], after 229 days of double-blind therapy, his wife awoke at approximately 0400 hours and discovered that the subject was having a seizure. She left the bedside to obtain some orange juice and when she returned she noticed he was not breathing. She began CPR with the assistance of her son after calling the paramedics. The paramedics arrived and were unable to resuscitate the subject. He was pronounced dead at the hospital." An autopsy was performed and showed a 50 % narrowing of the right coronary artery but no coronary obstruction was described. Although the cause of death was listed as "coronary arteriosclerosis" and "hypoglycemic seizure" on the CRF termination page, the sponsor acknowledges that "based on the available information, it appeared that the subject had a seizure possibly related to hypoglycemia."

Reviewer's comments: The death of this subject seems to be related to a hypoglycemic episode (seizure). The coronary findings noticed at autopsy appear to be coincidental. We have no information in the submission as to when the subject had his last meal (he was on a QID regimen which included a pramlintide injection prior to a bedtime snack).

Subject 137-117-7010 (pramlintide 90 µg BID):

The subject was a 31-year old male with a 4-year history of type 1diabetes and no other medical problems. The death took place on day 165 of pramlintide treatment. The following description of the event is given:

"On [redacted], approximately 165 days after starting double-blind therapy, the subject was admitted to the emergency room where he subsequently died (SAE #1307) on the same day. The investigator spoke with the medical doctor who was on duty at the hospital the evening the subject died. The cause of death was felt to be due to alcohol abuse over a two-day period. The subject reportedly had stopped taking study medication on [redacted] The investigator subsequently spoke with the subject's family and was told that the subject had not been abusing alcohol at the time of his death. By their report, he had two glasses of wine during a family meeting after which he experienced nausea, vomiting, and loss of appetite. The subject stayed in bed the following day. The

paramedics were called, but when they arrived the subject had already expired. The family indicated the amount of alcohol consumed by the subject was "average" in comparison to what he generally consumed, and that the subject had not discontinued study medication. An autopsy was not performed. The investigator assessed this event as serious, of severe intensity, and probably not related to study medication. This was an unexpected (not previously labeled in the Investigator Brochure) event. As the details in this case were unclear, a role for study medication could not be ruled out. Based upon the available information, the Sponsor classified this event as possibly related to study medication."

Reviewer's comments: The description of the events surrounding the death of this patient has numerous contradictions with respect to the amount of alcohol ingested, the place and nature of the death, the description of the events prior to the death, whether the patient has discontinued insulin and pramlintide, etc. The study termination page does not shed any additional light; it states that "patient probably stopped study drug, meals and insulin from [redacted]" (i.e. two days before death occurred). In summary, one cannot find a cohesive explanation for this death.

Conclusions:

- **Only a small number of deaths occurred during the pramlintide long-term clinical trials. Therefore, a numerical pramlintide-to-placebo comparison does not provide a concerning safety signal.**
- **A review of patient narratives identifies two deaths possibly associated with hypoglycemia (one being a motor vehicle accident) and one death which does not have a cohesive explanation, all in the pramlintide treatment group.**

Serious Adverse Events (SAEs) Other Than Deaths:

Table 3 presents the cumulative incidence of SAEs recorded during the long-term type 1 and type 2 diabetes trials. Type 1 diabetes trials describe an increased incidence of SAEs in the pramlintide group (14 %) compared to the placebo treatment group (10%). In contrast, cumulative SAE incidence did not show any difference between treatment groups in the type 2 diabetes trials.

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

	Type 1 diabetes		Type 2 diabetes	
	Pramlintide (n=1179)	Placebo (n=538)	Pramlintide (n=1273)	Placebo (n=420)
Incidence	170 (14%)	53 (10%)	173 (14%)	61 (15%)

n=total number of subjects
Source: ISS, SDS 136.

Type 1 diabetes:

Hypoglycemia is the leading cause of serious adverse events in the type 1 diabetes trials (9% incidence in the treatment group and 4% in the placebo group). Table 4 reports SAEs occurring with a frequency difference between pramlintide and placebo **higher or equal to 1 %**. Indeed, 62% of all SAEs are due to hypoglycemia in the pramlintide group compared to 43% in the placebo group. Hypoglycemia is the only SAE that occurrs at a rate in the pramlintide group at least 1% greater than in placebo.

When groups of related signs and symptoms ("body systems") are considered, only three categories (body as a whole, metabolic/nutritional system, and nervous system) meet the ≥ 1% pramlintide-to-placebo difference criterion.

In the metabolic/nutritional category, hypoglycemia is the main contributor for both treatment groups (90 % of pramlintide SAEs and 74 % of placebo SAEs).
The most frequently reported SAE in the body as a whole system is **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 are 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 the inflicted injury category includes eleven SAEs reported in the pramlintidet 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*

Type 1 Diabetes						
		Pramlintide (n=1179)		**Placebo** (n=538)		**Fold difference**
		n	%	n	%	
Symptom	**Hypoglycemia**	106	9%	23	4%	2.2 X
Body System	**Metabolic/Nutritional**	119	10%	31	6%	1.7 X
	Body as a Whole	19	2%	7	1%	2 X
	Nervous System	10	1%	0	0	NA

*included are only symptoms occurring with a frequency of 1% or greater over placebo; one patient could have experienced more than one SAE n=number of patients; %=percentage of patients.
Source: ISS, SDS 136.

Other serious treatment-emergent adverse events, each reported by just **one subject and only in the pramlintide-treated subjects**, include asthenia, cerebrovascular disorder, gastric dilatation, gastrointestinal hemorrhage, angina pectoris, acute renal failure, weight decrease, lympocytic leukemia, amnesia, depression, pulmonary granuloma, ocular hemorrhage, retinal disorder, vitreous disorder, and lymphadenopathy.

Type 2 diabetes:

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. Table 5 reports SAEs occurring with a frequency difference between pramlintide and placebo **higher or equal to 1 %**. In type 2 diabetes studies hypoglycemia is present less frequently. It is found in only 2% of the pramlintide-treated subjects and 1% of the placebo group, thus representing only 12% and 7%, respectively, of all SAEs). On the other hand there is not a single SAE, other than hypoglycemia, which occurred with an incidence 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). 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-to-placebo difference.
For the metabolic/nutritional system however, hypoglycemia is the main contributor (87 % of SAEs in the pramlintide group and 67 % in the placebo group).

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

Type 1 Diabetes						
		Pramlintide (n=1273)		**Placebo** (n=420)		**Fold difference**
		n	%	n	%	
Symptom	**Hypoglycemia**	21	2%	4	1%	2 X
Body System	**Gastrointestinal**	20	2 %	5	1%	2 X
	Metabolic/Nutritional	24	2 %	6	1%	2 X
	Vascular (extracardiac)	20	2 %	5	1 %	2 X

*included are only symptoms occurring with a frequency of 1% or greater over placebo; one patient could have experienced more than one SAE n=number of patients; %=percentage of patients.
Source: ISS, SDS 136.

Although only 1% of pramlintide-treated subjects reported serious adverse events in the central and peripheral nervous system, it is noteworthy that (except for abnormal gait and neuritis which were only reported by placebo subjects), all the SAEs – dizziness, convulsions, neuralgia, neuropathy, aphasia, ataxia, headache, hemiplegia, paresis, and vertigo - were reported by pramlintide subjects.

Other noteworthy serious treatment-emergent adverse events, each reported by <1% of pramlintide subjects but not by any placebo subjects, included syncope, ECG abnormal, intestinal obstruction, gastric dilatation, bradycardia, extrasystoles, cardiac fibrillation, tachycardia, jaundice, biliary pain, bone disorder, confusion, anemia, cystitis, renal function abnormal, transient ischemic attack, and retinal disorder.

Conclusions:

- **Hypoglycemia is the most common cause of SAEs in both type 1 and type 2 diabetes trials but much more so in type 1 diabetes patients.**
- **Central nervous system-related SAEs, although infrequent, occur predominantly in the pramlintide treatment group in both type 1 and type 2 diabetes.**
- **A small safety signal which occurs predominantly in the pramlintide group is provided by the "inflicted injury" category.**

Withdrawals:

Adverse events are the major reason for patient withdrawal in the long-term controlled type 1 and type 2 diabetes trials. The incidence of adverse event-related withdrawals is summarized in table 6 along with the trial completion rates.

Adverse event-related withdrawals are three times more frequent in the pramlintide treatment group in the type 1 diabetes patients when compared to placebo. In contrast, in type 2 diabetes patients pramlintide-related withdrawals are only 1.3 times over placebo.

53 % and 37.5 % of all patient withdrawals are due to adverse events in type 1 and type 2 diabetes trials, respectively, in the pramlintide treatment groups (versus 24 % in the placebo group in type 1 diabetes and 29 % in the placebo group in type 2 diabetes).

Table 6: Withdrawals Due to Adverse Events in the Long-term Type 1 and Type 2 Diabetes Trials

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

Reasons for withdrawal other than adverse events (such as non-compliance, withdrawal of consent, protocol violation, lost to follow-up, investigator decision, administrative reasons) have equal or very close rates between the treatment and placebo arms. Individually, they account for a relatively small percentage of the enrolled patients who withdrew.

Differences in the adverse event withdrawal profile exist between type 1 and type 2 diabetes patients. Therefore withdrawals are presented for each condition separately.

Type 1 Diabetes:

The gastrointestinal adverse events are the most frequent cause of patient withdrawal. Table 7 displays adverse events with an incidence **higher than 1 %** between pramlintide and placebo.

Among the GI symptoms, nausea is the main reason for patient withdrawal due to an adverse event. **12 % of all pramlintide-treated patients withdrew due to nausea. Nausea-related withdrawals took place twelve times more frequently in the pramlintide treatment group than in the placebo group.**

The next most frequently reported adverse events are hypoglycemia and anorexia. Withdrawals due to hypoglycemia are three times more frequent in the pramlintide treatment group. Surprisingly, somnolence is a reason for patient withdrawal.

Table 7: Adverse Events Leading to Withdrawal in the Controlled, Long-term Type1 Diabetes Trials*

Type 1 Diabetes					
Adverse Event	**Pramlintide** (n=1179)		**Placebo** (n=538)		**Fold difference**
	n	%	n	%	
Nausea	138	12 %	6	1 %	**12 X**
Hypoglycemia	37	3 %	3	1 %	**3 X**
Anorexia	20	2 %	0	0 %	NA
Vomiting	25	2 %	3	1 %	2 X
Dyspepsia	6	1 %	0	0 %	NA
Somnolence	6	1 %	0	0 %	NA

**included are only symptoms with occur with a frequency of 1% or greater over placebo.
n=number of subjects. %=percent patients experiencing an AE. Fold difference is % pramlintide divided by % placebo. A patient can list more than one symptom as reason for withdrawal.
Source: ISS, SDS 119.

Individual adverse events that do not reach a **1%** incidence difference but appeare to occur either exclusively or predominantly in the pramlintide group are: asthenia, syncope, back pain, hot flushes, influenza-like symptoms, malaise, and pain.

Fatigue is another adverse event found more frequently in the pramlintide group when compared to placebo (11 pramlintide subjects=1%, and 2 placebo subjects or <1%).

Inflicted injury is a reason for which five patients withdrew in the pramlintide group compared to none in the placebo group.

The long-term uncontrolled studies provide similar information. The withdrawals in the gastrointestinal system (13%), metabolic/nutritional system (3%) and body as a whole (1%, with fatigue as a main contributor) followed the same pattern observed in the controlled studies.

Only one subject listed medication error as a reason for withdrawal.

Type 2 Diabetes:

The adverse evenst leading to patient withdrawal with an incidence higher than **1 %** between pramlintide and placebo are presented in table 8. Similar to the observations made in type 1 diabetes trials, the GI system adverse events are the most frequent causes of subject dropout in the long-term controlled type 2 diabetes studies. However this does

not happen to the same extent. Nausea does not stand out to the same degree among all other gastrointestinal symptoms (it has only1.5 fold higher incidence in the pramlintide treatment group over placebo).

Hypoglycemia, the second most common individual reason for withdrawal in type 1 diabetes studies, is 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: Adverse Events Leading to Withdrawal in the Controlled, Long-term Type 2 Diabetes Trials*

Type 2 Diabetes					
Adverse Event	**Pramlintide** (n=1273)		**Placebo** (n=420)		**Fold difference**
	n	%	n	%	
Nausea	39	3 %	7	2 %	**1.5 X**
Abdominal pain	8	1 %	0	0 %	NA
Anorexia	7	1 %	0	0 %	NA

**included are only symptoms with occur with a frequency of 1% or greater over placebo.
n=number of subjects. %=percent patients experiencing an AE. Fold difference is % pramlintide divided by % placebo. A patient can list more than one symptom as reason for withdrawal.
Source: ISS, SDS 119.

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

Conclusions:

- **Gastrointestinal adverse events (in particular nausea, anorexia, vomiting and abdominal pain) are the most common cause of trial withdrawal in both type 1 and type 2 patients treated with pramlintide.**
- **In type 1 diabetes trials nausea-related withdrawals take place in 12 % of pramlintide treated patients (twelve times more frequently than placebo).**
- **The vast majority of nausea-related withdrawals occur during the first month of treatment (17 times more frequent in the pramlintide treatment group over placebo.).**
- **In type 2 diabetes patients, nausea-related withdrawals occur only 1.5 times more frequently in the pramlintide group over placebo.**
- **Hypoglycemia is the second most important reason for patient withdrawal in type 1 diabetes but is not a factor in type 2 diabetes.**
- **Somnolence, fatigue, and inflicted injury are unexpected reasons for subject withdrawals in type 1 diabetes patients.**

Treatment Emergent Adverse Events (TEAEs)

Pramlintide-treated type 1 and type 2 diabetes patients have different adverse event profiles. Therefore the treatment-emergent adverse events are analyzed separately for each condition.

Type 1 Diabetes

Gastrointestinal adverse events are the most common TEAEs observed in the long-term controlled type 1 diabetes trials. Table 9 displays TEAEs with an incidence difference **higher than 1 %** between pramlintide and placebo. Nausea is by far the most frequent individual TEAE and is experienced by 51% of pramlintide-treated patients, followed by hypoglycemia (27 %). Anorexia, although less frequent than nausea and hypoglycemia, shows the highest fold difference over placebo (nine fold). Fatigue, an unexpected adverse event, occurs twice more frequently in pramlintide treated patients. Hypoglycemia is more frequent in the pramlintide treatment group but it also has a higher placebo incidence (27 % vs 19 %).

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)*

Type 1 Diabetes					
Adverse Event	Pramlintide		Placebo		Fold
	n=1179	%	n=538	%	difference
Nausea	601	51%	92	17%	**3 X**
Hypoglycemia	323	27%	101	19%	1.4 X
Anorexia	209	18%	12	2%	**9 X**
Vomiting	154	13%	36	7%	1.9 X
Fatigue	80	7%	22	4%	1.8 X

*individuals experiencing multiple AEs within the same category are counted once.
n=number of subjects. %=percent patients experiencing an AE. Fold difference is % pramlintide divided by % placebo.
Source:ISS, Table 15.

Treatment-emergent adverse events with a frequency of **1%** (and no higher than 1%) in the pramlintide group compared to the placebo group are: abdominal pain, dyspepsia, flatulence/abdominal fullness, arthralgia, **inflicted injury**, urinary tract infection, **syncope**, hypertension (aggravated), weight decrease, myalgia, angina pectoris, post-operative pain, and foot callus.

Type 2 Diabetes

Gastrointestinal adverse events are the most common TEAEs but they do not dominate the adverse event profile to the same extent as in type 1 diabetes patients. Table 10

displays TEAEs with an incidence difference **higher than 1 %** between pramlintide and placebo in the long-term controlled type 2 diabetes trials. Similar to observations made in type 1 diabetes patients, nausea is the most frequent GI adverse event reported (24%) and anorexia is the GI adverse event with the highest fold difference over placebo (2.7). However, in contrast to type 1 diabetes hypoglycemia is not as frequent a TEAE. Small differences in the incidence of central nervous system and psychiatric adverse events (e.g. headache, fatigue, dizziness, anxiety, etc.) become apparent. Most TEAE show a 1.5 to 2 fold difference over placebo..

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)*

Type 2 Diabetes					
Adverse Event	**Pramlintide**		**Placebo**		**Fold difference**
	n=1273	%	n=420	%	
Nausea	308	24 %	57	14%	1.7 X
Headache	154	12 %	37	9 %	1.3 X
Anorexia	98	8 %	13	3%	**2.7 X**
Abdominal pain	97	8 %	27	6 %	1.3 X
Vomiting	85	7 %	23	5 %	1.4 X
Fatigue	83	7 %	17	4 %	1.8 X
Dyspepsia	76	6 %	12	3 %	2 X
Dizziness	71	6 %	17	4 %	1.5 X
Anxiety	53	4 %	9	2 %	2 X
Gastroenteritis	47	4 %	10	2 %	2 X
Neuropathy	34	3 %	6	1 %	3 X
Cellulitis	33	3 %	5	1 %	3 X

*individuals experiencing multiple AEs within the same category are counted once.
n=number of subjects. %=percent patients experiencing an AE. Fold difference is % pramlintide divided by % placebo.
Source:ISS, Table 15, SDS 77.

Treatment emergent adverse events with a frequency of **1%** (and no higher than 1%) in the pramlintide group compared to the placebo group are: allergic reaction, **hypoglycemia**, infection, pharyngitis, rhinitis, abnormal vision, fever, chest pain, edema, leg pain, dependent edema, flatulence/abdominal fullness, ear disorder, depression, somnolence, abrasion, fungal dermatitis, skin ulceration, nail disorder, and abnormal vision.

Thrombocytopenia is reported in two subjects, one treated with pramlintide (in type 1 diabetes extension study 137-112E, a transient finding) and one treated with placebo (a subject with type 2 diabetes).

Acute renal failure is reported in four subjects, three treated with pramlintide (one with type 1 diabetes and two with type 2 diabetes) and one with placebo (type 2 diabetes).

There are no reports of liver failure, agranulocytosis, significant hemolytic anemia, rhabdomyolysis, idiopathic thrombocytopenic purpura, or intussusception in any of the clinical studies.

Conclusions:

- **Gastrointestinal adverse events (nausea, anorexia, vomiting) are the most frequent TEAE in both type 1 and type 2 diabetes patients.**
- **Type 1 diabetes patients are more susceptible than type 2 diabetes patients to the GI adverse events of pramlintide (as manifested in both incidence and fold difference over placebo).**
- **Hypoglycemia is a frequent adverse event in type 1 diabetes but does not stand out in type 2 diabetes trials.**
- **Among the non-GI adverse events fatigue provides a signal over placebo in type 1 diabetes. In type 2 diabetes, several CNS symptoms (headache, fatigue, dizziness, anxiety) are encountered more frequently in pramlintide-treated patients (1.3 to 2 fold difference).**

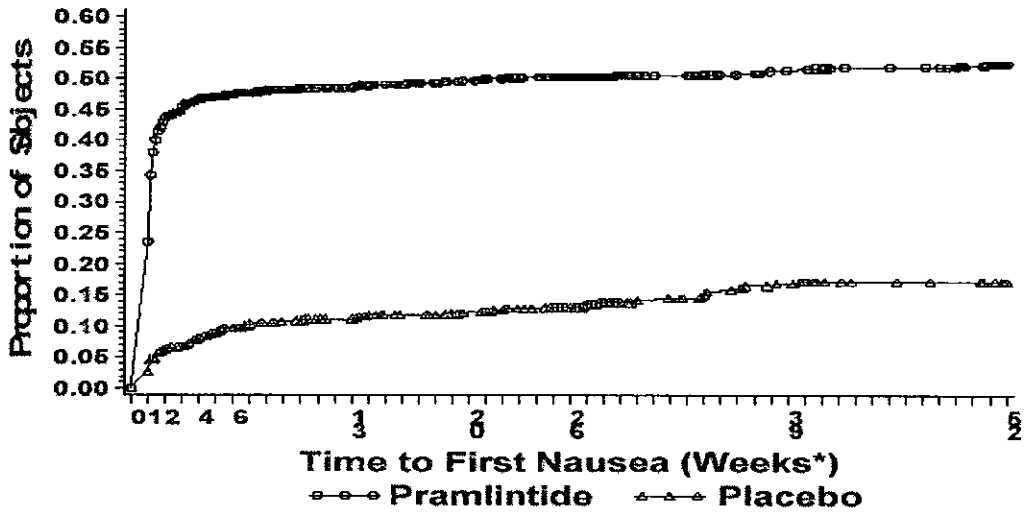
Nausea:

· Nausea is a pervasive adverse event associated with pramlintide treatment. 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. It occurs early during the pramlintide treatment and has a high recurrence rate.

Nausea is an early event in both type 1 and type 2 diabetes trials:

The majority of pramlintide-treated subjects who report nausea do so within the first few weeks of therapy. Figure 2 presents a cumulative Kaplan-Meier plot of the time to first episode of nausea in type 1 diabetes trials, comparing pramlintide and placebo patients. The proportion of subjects who report nausea increases sharply during the first four weeks of therapy and grows only minimally thereafter. Out of the 601 pramlintide-treated patients who reported nausea, 552 (92%) had the onset during the first week of treatment. There is approximately a four fold difference between the frequency of this adverse event in the pramlintide and the placebo arms.

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

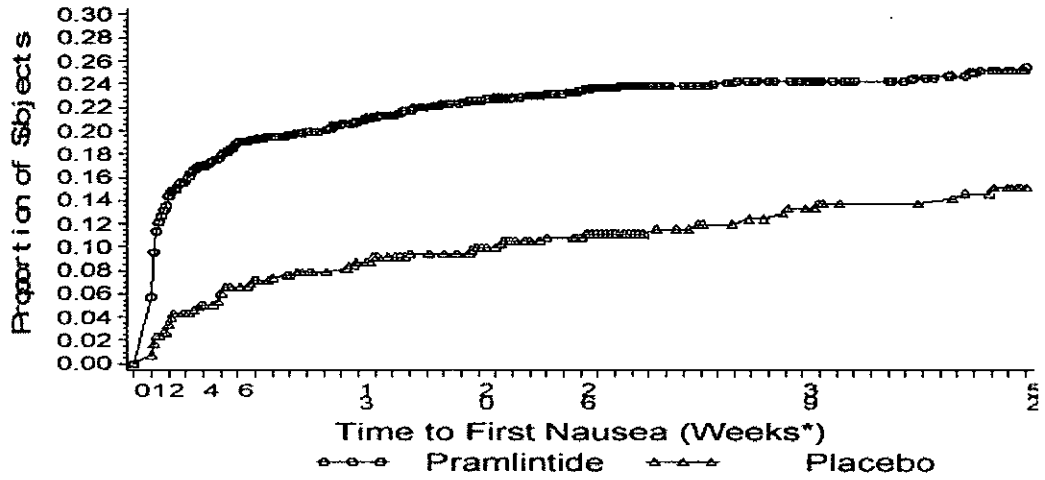


Source: ISS, Figure 7.

A similar observation is made in the type 2 diabetes trials, i.e. nausea occurs early in the course of pramlintide treatment. Figure 3 displays a cumulative Kaplan-Meier plot of the time to first episode of nausea in type 2 diabetes trials, comparing pramlintide and placebo subjects. Similar to the type 1 diabetes trials, the proportion of subjects who report nausea increases sharply during the first four weeks of therapy and only minimally thereafter. Out of the 308 pramlintide-treated patients who reported nausea, 224 (73%) do

so during the first week of treatment. There is a two fold difference between the frequency of this adverse event in the pramlintide and placebo arms. This difference is less than observed in the type 1 diabetes trials (four fold).

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



Source: ISS, Figure 8.

Nausea is a recurring symptom in both type 1 and type 2 diabetes trials:

Table 11 tabulates the number of patients (pramlintide and placebo) who develop nausea during the first month of treatment and re-experience this symptom in the following months up to the end of the long term controlled type 1 diabetes trials. Out of the 1179 patients enrolled in the pramlintide treatment group, 552 (47%) had their first episode of nausea during the first four weeks of treatment (compared to only 8.6% placebo treated patients). Recurrence of nausea among the pramlintide patients who already experienced it during the first month is high. By the end of the first year 49 % of pramlintide patients are still experiencing nausea compared to only 21% of the placebo patients.

Even though the time intervals provided by the sponsor in this analysis are not equal in duration and even though there is a decline in incidence of nausea with time, there is also a high rate of recurrence in the pramlintide group.

Table 11 #: Recurrence of Nausea After Four Weeks of Treatment (Long-Term Controlled Studies in Subjects With Type 1 Diabetes)

	Pramlintide				Placebo			
Time Period (weeks)	Subjects Randomized n	Nausea n (%)	Subjects at Risk# n	Recurrence of Nausea* n (%)	Subjects Randomized	Nausea n (%)	Subjects at Risk# n	Recurrence of Nausea* n (%)
>0-4	1179	552(47%)			538	46(8.6%)		
>4-13			535	374 (70%)			45	18 (40%)
>13-20			497	267 (54%)			41	12 (29%)
>26-39			272	144 (53%)			29	6 (21%)
>39-52			262	128 (49%)			28	6 (21%)

***Recurrence of nausea** is defined as any episode of nausea after four weeks that is observed for a subject who experienced nausea in the first four weeks. If a subject withdrew from a trial due to nausea they are counted as having a recurrence of nausea in each of the remaining periods. If an occurrence of nausea continues into more than one period it is counted in all periods in which it was present.
#Subjects at risk is the number of subjects who had nausea in the first four weeks of the trial and who remain in the trial during the defined periods. If a subject withdrew from a trial due to nausea they are counted as being at risk in each of the remaining periods.
Source ISS, Table 20

A similar pattern of early occurrence and high recurrence was observed during the type 2 diabetes trials. Table 12 depicts the number of patients (pramlintide and placebo) who develop nausea during the first month of treatment and re-experience this symptom in the following months up to the end of the long term controlled type 2 diabetes trials. Out of 1273 patients enrolled in the pramlintide treatment group, 224 (18%) had their first episode of nausea during the first four weeks of treatment (compared to 6 % of patients in the placebo group. Recurrence of nausea was higher in the pramlintide group up to week 39. By the end of the year the recurrence rate was similar in both treatment groups (36 % pramlintide, 37 % placebo). However, it should be noted that the number of patients in the placebo group is very small and therefore the ability to draw any robust conclusion is limited.

Thus, two differences emerge in type 2 diabetes patients with respect to nausea when compared to the type 1 diabetes counterparts. Recurrence rates are somewhat lower during most of the treatment and may disappear toward the end of the first year of study.

Table 12: Recurrence of Nausea After Four Weeks of Treatment (Long-Term Controlled Studies in Subjects With Type 2 Diabetes)

	Pramlintide				Placebo			
Time Period (weeks)	Subjects Randomized n	Nausea n (%)	Subjects at Risk# n	Recurrence of Nausea* n (%)	Subjects Randomized	Nausea n (%)	Subjects at Risk# n	Recurrence of Nausea* n (%)
>0-4	1273	224(18%)			419	25 (6%)		
>4-13			220	133 (60%)			23	10 (43%)
>13-20			211	92 (44%)			23	5 (22%)
>26-39			134	53 (40%)			17	4 (23%)
>39-52			129	46 (36%)			16	6 (37%)

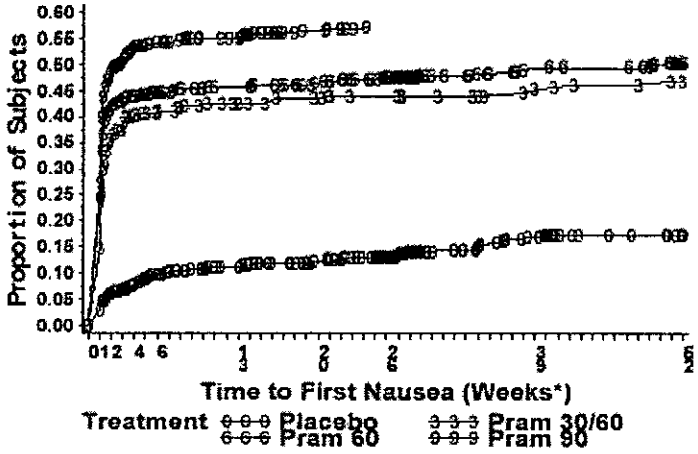
***Recurrence of nausea** is defined as any episode of nausea after four weeks that is observed for a subject who experienced nausea in the first four weeks. If a subject withdrew from a trial due to nausea they are counted as having a recurrence of nausea in each of the remaining periods. If an occurrence of nausea continues into more than one period it is counted in all periods in which it was present.
#Subjects at risk is the number of subjects who had nausea in the first four weeks of the trial and who remain in the trial during the defined periods. If a subject withdrew from a trial due to nausea they are counted as being at risk in each of the remaining periods.

Source ISS, Table 21

Nausea is the only symptom that shows a dose-response relationship with praminlintide treatment in both type 1 and type 2 diabetes trials:

Figure 4 presents the occurrence of nausea as a function of dose for the type 1 diabetes trials. It clearly illustrates that nausea not only occurs early in the course of the treatment (most subjects report it within the first four weeks) but reporting incidence increases with increasing dose. The 90 µg dose is associated with the highest proportion of subjects who report nausea, followed by the 60 µg dose, and the 30/60 µg dose.

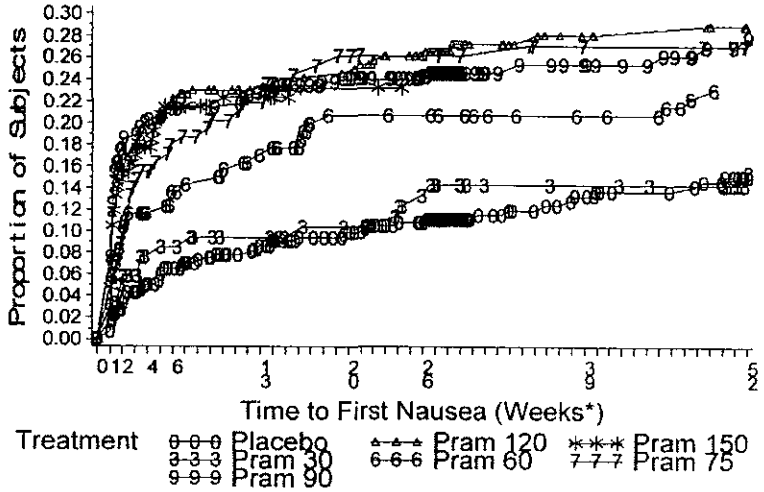
Figure 4: Cumulative Frequency Distribution of Time to First Onset of Nausea by Dose (Long-term Controlled Studies in Subjects With Type 1 Diabetes)



Source: ISS, Figure 9

The type 2 diabetes trials allow for the same observation to be made: nausea occurs early in the course of the treatment and reporting incidence increases with increasing dose. Figure 5 presents the time to first episode of nausea as a function of pramlintide dose. The high doses (75 to150 µg) are associated with the highest proportion of subjects with nausea. Nausea occurres less in association with the 60 µg and 30 µg doses. In contrast to type 1 diabetes, the resolution between doses is not as clear especially above 75 µg.

Figure 5: Cumulative Frequency Distribution of Time to First Onset of Nausea by Dose (Long-term Controlled Studies in Subjects With Type 2 Diabetes)



Source: ISS, Figure 10

Quantitative differences 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. The percentage of subjects who experience nausea among the type 1 diabetics is roughly twice that observed in type 2 diabetes subjects exposed to comparable doses.

Table 13 provides further evidence of a dose-response relationship trend in both type 1 and type 2 diabetes for nausea. A higher drug dose tends to be associated with a higher proportion of subjects who experience nausea. This observation applies to both type 1 and type 2 diabetes patients.

Table 13: Number and Percentage of Subjects With Treatment Nausea by Total Daily Dose of Pramlintide (Type 1 and Type 2 Long-term Controlled Diabetes Studies)

Dose	90-<120µg	120-<180µg	180-<225µg	225-<240µg	240µg	270µg
Nausea (type 1)	_	113 (47%)	224 (49%)	_	76 (34%)	188 (59%)
Nausea (type 2)	18 (15%)	_	105 (23%)	36 (26%)	81 (28%)	35 (27%)

Source: ISS, SDS 207 and 208

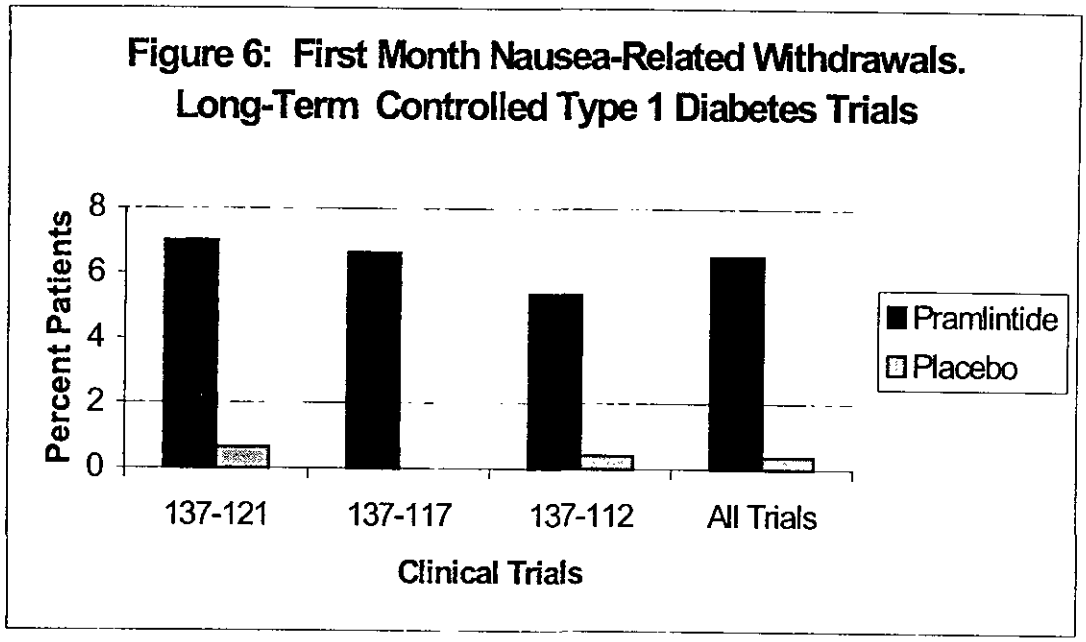
The observation that nausea occurs in a dose-dependent manner is consistent with the findings from the clinical pharmacology trials which indicated a dose response relationship between pramlintide and gastric emptying in patients with type 1 diabetes (study 137-118).

Intensity of nausea: nausea is an important cause of treatment discontinuation during pramlintide therapy.

Of the 51% of subjects who reported nausea as an adverse event during the pramlintide treatment in the type 1 diabetes trials, over half experienced severe or moderate nausea. Another measure of the severity of nausea is the degree to which it contributes to patient withdrawal in the clinical studies. Nausea is the most common reason for subject withdrawal in both type 1 and type 2 diabetes long–term trials. The implication of this observation is that it reaches such a degree of discomfort that even motivated patients who decide to participate in a clinical trial may not be able to tolerate it.

Not only does nausea reach such a level of discomfort that the patient decides to withdraw from the clinical trial but also most withdrawals take place early in the treatment. Figure 6 presents the incidence of first month withdrawals during the type 1 diabetes trials (individual and combined).

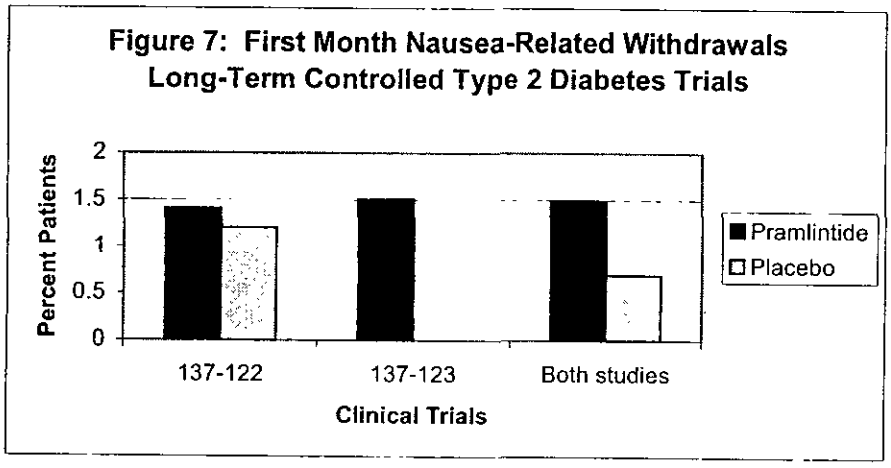
On the average there is a 17-fold ratio between percent of nausea-related withdrawals in the pramlintide group and the placebo group respectively. The first month withdrawals occur at all doses (including the lowest used dose of 30 µg in study 137-112)



Source: ISS,SDS 3.2.5.3. and 3.2.8.2

In all three type 1 diabetes trials the withdrawals occurred early (mostly during the first 4-6 weeks of treatment). Withdrawals following the first 4-8 weeks of the trial are infrequent.

First month withdrawals take place in type 2 diabetes subjects as well, although they do not reach the same magnitude as in type 1 diabetes trials. Figure 7 presents first month nausea-related withdrawals in type 2 diabetes patients. Overall, they occur twice more frequently in the pramlintide group than in the placebo group (this is four times less frequent than observed in the type 1 diabetes trials). After the first month of treatment the number of subjects with nausea-related withdrawals is small.

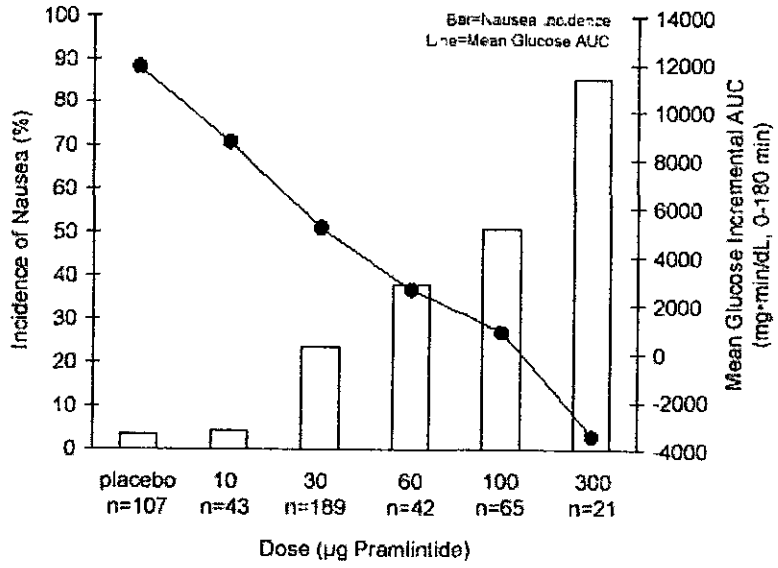


Source: ISS, SDS 3.2.5.3

Nausea is an integral part of any pramlintide dose regimen associated with glucose lowering effect in type 1 diabetes.

Clinical pharmacology studies indicate that a broad range of pramlintide doses (30 to 300 μg TID) reduce postprandial plasma glucose concentrations, while 10 μg QID appears to have a minimal effect. Dose-limiting side effects (which occurred at lower doses in patients with type 1 diabetes compared with type 2 diabetes) were primarily nausea, vomiting, and anorexia. Figure 8 juxtaposes the incidence of nausea and the glucose lowering effect (measured as mean glucose AUC) for various doses tested. It is apparent that the only pramlintide dose which is not associated with nausea (10 μg) also lacks glucose lowering effect. The next higher dose of 30 μg (which is also the lowest dose tested in the long–term controlled trials) has glucose lowering effect but is associated with nausea as well. Higher doses (up to 300 μg) have glucose lowering effects proportional to the magnitude of the dose but they are also associated with dose-proportional increases in nausea incidence.

Figure 8:
Pramlintide Dose-Relationship of Glucose Lowering Effects and Nausea (Patients With Type 1 Diabetes; Studies AP93-08, 137-104, 137-105)



Source:Amylin AC Briefing Document, Figure 20

Conclusions:

- **Nausea is a pervasive adverse event associated with pramlintide therapy.**
- **Nausea occurs at all pramlintide doses that result in glucose lowering effect (clearly demonstrated in type 1 diabetes patients).**
- **Nausea incidence is higher in 1 diabetes patients when compared to type 2 diabetes patients.**
- **Nausea occurs early in the treatment and often is severe enough to result in study discontinuation.**
- **Nausea is the most frequent reason for patient withdrawal in both type 1 and type 2 diabetes patients.**
- **Nausea-related withdrawals occur predominantly during the first month of treatment.**
- **Among patients who experience it, nausea is a recurrent symptom, more so in type 1 diabetes patients.**

Severe Hypoglycemia

Definition

Several definitions of hypoglycemia have been used during the pramlintide clinical program. This limits to some extent trial to trial comparisons.
Severe hypoglycemia has been most consistently captured under the Diabetes Control and Complication Trial (DCCT) definition. It describes severe hypoglycemia 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 during five of the six 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 sponsor excludes the long-term study 137-111 (type 2 diabetes) due to inconsistent methodology in data collection.

Table 14 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 is higher in the type 1 diabetes trials (compared to the type 2 diabetes trials) and that it is consistently higher than placebo for both types of diabetes subjects.

Table 14: Number and (%) of Subjects With at Least One Episode of Severe Hypoglycemia in Type 1 and Type 2 Long-term Diabetes Trials*:

	Type 1 Diabetes		Type 2 Diabetes	
	Pramlintide	**Placebo**	**Pramlintide**	**Placebo**
Subjects enrolled	N=1179	N=538	N=871	N=284
Number and (%) subjects with hypoglycemia	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.
Source: ISS, Table 25.

Individual subjects experienced a variable number of severe hypoglycemic events. While most patients had only a few events, some experienced a considerable number of events (up to 128 in a placebo subject). The distribution of severe hypoglycemic events per subject is displayed in Table 15:

Table 15: 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.**

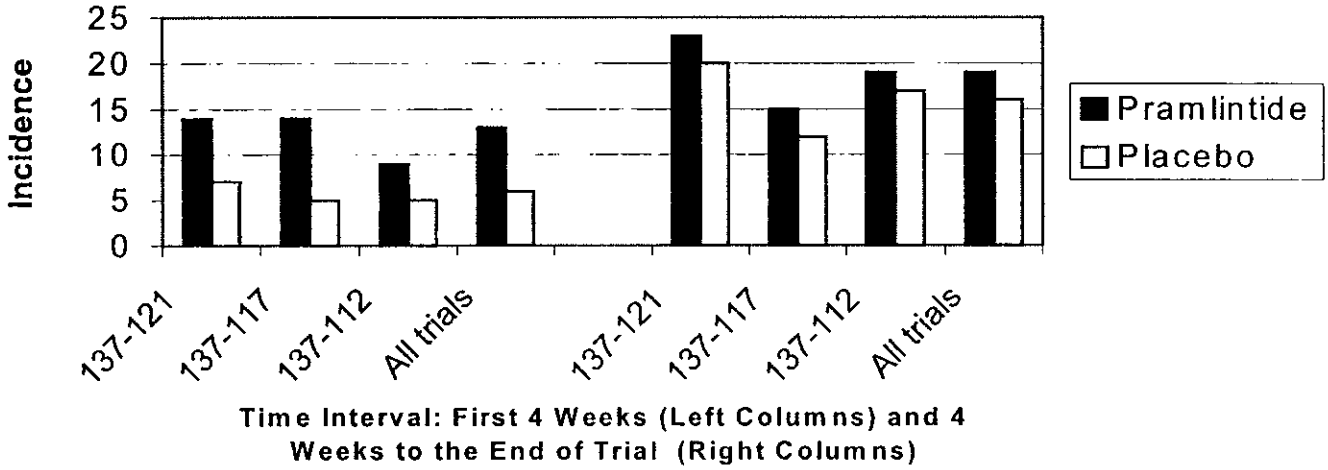
n=number of subjects enrolled in the study.

Type 1 Diabetes

Information about the time of occurrence of severe hypoglycemia was presented in this submission stratified by two time intervals: the first four weeks of the trial and the period following the first four weeks to the end of the trial. (End of trial is six months to one year). Figure 9 displays the **incidence** of severe hypoglycemia during both time intervals for each study (137-121, 137-117, and 137-112) and for all three studies combined.

Overall, severe hypoglycemia is twice more common in the pramlintide group during the first month of the treatment. This observation is consistently observed within each trial. Following the first month of treatment the difference between pramlintide and placebo groups declines but it is still seen consistently in each major trial. It should be noted that the time intervals selected by the sponsor are not equivalent (first interval is four weeks, while next interval is 5 to 11 month depending on the trial analyzed).

Figure 9: Incidence of Severe Hypoglycemia Stratified By Time:Type 1 Diabetes



Source: Addendum to ISS.

Analysis of severe hypoglycemic **events** stratified by the same time interval, leads to similar conclusions. It shows 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).

Following the first four weeks of treatment a similar rate of events is recorded across both groups. However, event rate analysis is more susceptible to the presence of outliers. It is precisely for this reason that long-term controlled study 137-112 is left out from this analysis. Remarkably, this study includes one placebo subject who had no fewer 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.

It should be noted that the reduction in incidence and event rate of severe hypoglycemia after the first month occurs in the context of waning efficacy of the drug, in a population of patients that has been deprived of drug-susceptible patients through early nausea-related withdrawals.

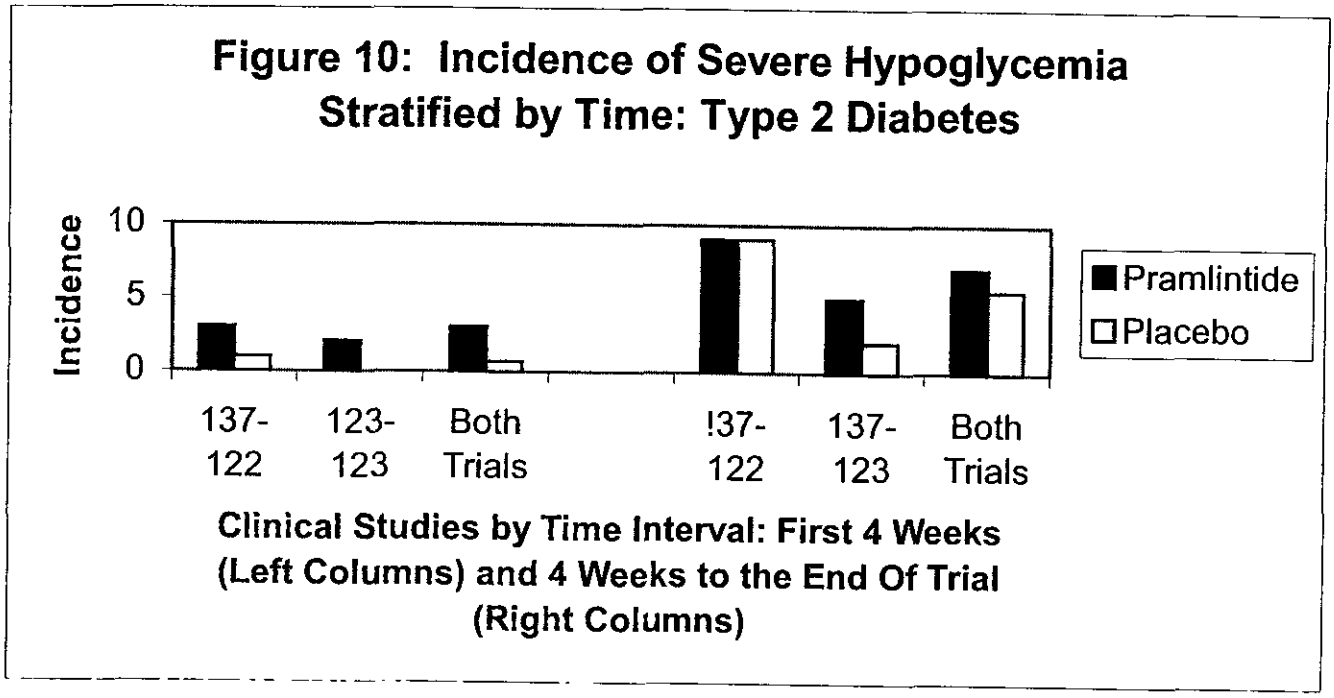
Table 16: Number of Severe Hypoglycemic Events per Year of Patient Time in the Long-term Controlled Type 1 Diabetes Trials (Studies 137-121 and 137-117)

Study Number	First 4 Weeks		4 Weeks to the End of Study		Whole Study	
	Pram	**Pbo**	**Pram**	**Pbo**	**Pram**	**Pbo**
137-121	3.7	1.0	0.9	0.6	1.2	0.7
137-117	3.2	1.7	1	1	1.4	1.1
Combined	3.45	1.35	0.95	0.8	1.3	0.9

Pram=pramlintide. Pbo=placebo.

Type 2 Diabetes

The time of occurrence of severe hypoglycemia during the type 2 diabetes trials is presented in this submission stratified by the same two time intervals: the first four weeks of the trial and the period following the first four weeks to the end of the trial. (End of trial is six months to one year). Figure 10 displays the **incidence** of severe hypoglycemia during both time intervals for individual studies 137-122, 137-113 and for both studies combined. Overall there is a four-fold incidence difference between pramlintide and placebo treatment groups during the first month of treatment. This observation is consistently observed in each trial. After the first month of treatment the differences between the pramlintide and placebo treatment groups are inconsistent (trial 137-122 shows no difference, while trial 137-123 indicates a 2.5 fold difference, pramlintide over placebo). It should be noted that the time intervals selected by the sponsor are not equivalent (first interval is four weeks, while next interval is 5 to 11 month depending on the trial analyzed).



Source: Addendum to ISS.

Table 17 presents the distribution of severe hypoglycemic **events** during the two periods selected. An almost two fold increase in the number of events during the first month of treatment is present in the pramlintide group; for the remainder of the treatment no differences are noted between drug and placebo.

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
137-122	0.4	0.3	0.23	0.3	0.23	0.3
137-123	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).

The same concerns expressed for type 1 diabetes apply to type 2 diabetes patients. The reduction in incidence and event rate of severe hypoglycemia after the first month occurs

in the context of waning efficacy of the drug, in a population of patients that has been deprived of drug-susceptible patients through early nausea-related withdrawals.

It is important to recognize that the incidence of severe hypoglycemia is lower in type 2 diabetes compared to type 1 diabetes patients (four times less frequent during the first month and approximately 2.7 times for the rest of the trial).

Conclusions:

- **Severe hypoglycemia is twice more frequent in the pramlintide treatment group over placebo during the first month of treatment in type 1 diabetes.**

- **Similarly, pramlintide treatment in type 2 diabetes patients is associated with a four fold increased incidence of severe hypoglycemia.**

- **Following the first month of treatment the incidence differences in severe hypoglycemia between pramlintide and placebo treatments groups are still present but to a lower extent; this observation is more consistently seen in type 1 diabetes patients.**

- **Reduction of severe hypoglycemia after the first month of treatment occurs in the context of decreased drug efficacy and first month nausea-related withdrawals.**

- **The incidence of severe hypoglycemia is higher in type 1 diabetes compared to type 2 diabetes patients (four times more frequent during the first month and approximately 2.7 times in the remainder of the trial).**

Hypoglycemia Associated With Serious Adverse Events: Motor Vehicle Accidents (MVAs), Other Injuries, and CNS Events (Coma and Seizures)

Hypoglycemia is the single most common cause of serious adverse events in the long-term controlled type 1 and type 2 diabetes trials (table 18). The association of hypoglycemia with an SAE occurs twice more frequently in the pramlintide treated group.

Table 18: Hypoglycemia Associated with SAEs in Type 1 and Type 2 Long-term Diabetes Trials*:

	Type 1 Diabetes			Type 2 Diabetes		
	Pram.	**Pbo.**	**Fold Diff.**	**Pram.**	**Pbo.**	**Fold Diff.**
Total subject number	N=1179	N=538		N=1273	N=420	
Number and (%) subjects with hypoglycemia and SAEs	106 (9%)	23 (4%)	2.25 X	21 (2%)	4 (1%)	2 X

* N=number of patients. Fold diff.=fold difference between pramlintide and placebo.
Pram.=pramlintide. Pbo.=placebo.
Source: ISS, Table 25.

This drug-to placebo difference prompted a search for the specific nature of the serious adverse events associated with hypoglycemia. The observation that the inflicted injury category is associated with subject withdrawal and SAEs in type 1 diabetes patients focused the search on injuries associated with hypoglycemia. The patients' narratives describing 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** associated with hypoglycemia (table 19). Subsequent review clarified that one of the placebo subjects experienced the MVA after the termination of the trial, thus reducing this number of patients in the placebo group to only one (subject 137-121-8405).

It should be noted that the MVA data were not presented in this manner in the NDA submission but were generated based on emerging evidence during the review process. It is indeed possible that the sponsor may not have been aware of these life-threatening events associated with pramlintide use in type 1 diabetes.

Table 19: Driving-related Events Associated with Hypoglycemia (Type 1 and Type 2 Diabetes, All Studies)

	Type 1 Diabetes					Type 2 Diabetes				
	Controlled Trials				Uncntr	Controlled Trials				Uncntr.
	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	1	3	0	0	1	0	0

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

The nature of the driving-related events covers a wide spectrum of severity that ranges from motor vehicle crashes (resulting in trauma and hospital admission) to events in which the subject becames "confused" or "disoriented" at the wheel but is apparently able to avoid a collision. Most of them require paramedic intervention, emergency room visits, parenteral glucose administration. The only motor vehicle crash, which does not have a clearly documented association with hypoglycemia, involves a 35-year-old subject who had a fatal MVA.

The driving-related events in the pramlintide group occur predominantly during the first month (40%) with two of them occurring during the first day of the trial. The remaining events, which occur after the first month, do not show any particular time-related distribution. The event rate per year of exposure is 4:1 pramlintide to placebo. A list of the subjects involved in the driving-related events is presented in table 20:

Table 20: Driving-Related SAEs associated With Hypoglycemia: Type 1 Diabetes Controlled Studies

Study/Subject number	Treatment group	Age	Duration of treatment	Comments
137-121-0808	Pramlintide	42 y	1 day	Hypoglycemic episode while driving/ER visit/i.v.glucose.
137-121-0810	Pramlintide	38 y	186 days	Hypoglycemic episode while driving/ER visit/i.v.glucose/fractured ribs/laceration repair/possibly kidney trauma.
137-121-0906	Pramlintide	32 y	59 days	Severe hypoglycemic episode while driving. Hospital admission for an A_3 pillion fracture.
137-121-3940	Pramlintide	69 y	240 days	Pulled the car to the side of the road and became unconscious (serum glucose=33 mg/dl.)
137-121-4401	Pramlintide	56 y	15 days	Hypoglycemic episode while driving/ER visit/i.v.glucose.

137-121-6806	Pramlintide	34 y	7 days	Became confused while driving and drove the wrong way on the highway/ER visit/i.v.glucose.
137-121-9301	Pramlintide	41 y	111 days	Felt like she was going to pass out; hit another vehicle (blood glucose=43 mg/dl.).
137-121-10003	Pramlintide	44 y	330 days	Hypoglycemic episode while driving/ER visit/i.v.glucose.
137-121-10503	Pramlintide	33 y	242 days	Stopped by police for driving erratically (blood glucose=39 mg/dl.).
137-121-10911	Pramlintide	42 y	3 days	Hypoglycemia/became unconscious while driving and ran off the road.
137-112-1306	Pramlintide	37 y	142 days	Hypoglycemia/lost consciousness while driving.
137-112-1718	Pramlintide	53 y	349 days	Hypoglycemic event. This event "probably led to an MVA at the time"(paramedic intervention and i.v. glucose).
137-117-3501	Pramlintide	35 y	1 day	Motor vehicle accident that resulted in death.
137-117-3702	Pramlintide	47 y	18 days	Lost consciousness while driving a car and hit a roadside guardrail. Recovered and ate sugar which reversed symptoms.
137-117-1105	Pramlintide	35 y	35 days	Severe hypoglycemic episode during which he "blacked out" and his car hit another vehicle.
137-121-8405	Placebo	63 y	169 days	While driving her car after lunch she became confused; police found her in the parking lot with damage to her vehicle (blood glucose=50 mg/dl.).

Three additional cases of hypoglycemia resulting in MVAs were identified in the open label type 1 diabetes studies and are summarized in table 21. Subsequently an additional patient was identified in this group (patient 137-112E-0923).

Table 21: Motor Vehicle Accidents and Near Missed MVAs in Type 1 Diabetes Uncontrolled Studies:

Study/Subject number	Treatment group	Age	Duration of treatment	Comments
137-112E-0820	Pramlintide	34 y	189 days open label	Became unconscious while driving and hit a tree (serum glucose=16 mg/dl)
137-112E-1209	Pramlintide	59 y	86 days open label	Hypoglycemic episode while driving/ER visit/i.v.glucose.
137-113-1916	Pramlintide	34 y	610 days	Severe hypoglycemic episode while driving the car/ER visit.
137-112E-0923	Pramlintide	34 y	64 days open label	Became unconscious while driving and hit a telephone pole (serum glucose=137 mg/dl)

The search did not identify pramlintide-to-placebo differences in driving-related events during the type 2 diabetes trials.

Driving is not the only form of trauma associated with severe hypoglycemic adverse events. Three non-MVA injuries associated with hypoglycemia were also identified, all in the pramlintide group. One subject (137-117-6304) was admitted to the hospital for surgical repair of a broken elbow after he fell out of a tree during a severe hypoglycemic episode. Another subject (137-117-7201) required hospital admission for temporal bone and cranial base skull fracture following an episode of loss of consciousness/fall "possibly due to hypoglycemia". Subject 137-117-5030 had a fall and a subsequent nose laceration associated with a hypoglycemic episode.

There is a discrepancy between the number of injuries found during the search and the number of events recorded in the inflicted injury category of the NDA. This is due to the fact that some of the injuries associated with hypoglycemia are coded only to the preferred term hypoglycemia.

Faced with this safety signal the Agency requested an analysis of all MVAs and trauma occurring in association with hypoglycemia during the pramlintide clinical program. The data submitted to the Agency are displayed in Table 22. for the whole pramlintide clinical program.

Table 22: Motor Vehicle and Other Accidents/Injuries Reported During the Pramlintide Clinical Development Program-Patient Incidence

Number and % of Patients				
	Type 1 Diabetes		Type 2 Diabetes	
Type of Adverse Event	Pramlintide (n=2573)	Placebo (n=904)	Pramlintide (n=1663)	Placebo (n=532)
Motor Vehicle Accident-Related Events				
Total	28 (1.09%)	7 (0.77%)	18 (1%)	3 (0.56%)
Hypoglycemia-Related	17 (0.66 %)	2 (0.22%)	1 (0.06 %)	0 (0%)
Other Accident/Injury-Related Events				
Total	197 (7.6%)	53 (5.9%)	194 (11.7%)	55 (10%)
Hypoglycemia-Related	10 (0.39%)	2 (0.22%)	2 (0.12%)	1 (0.19%)
Automoblie-Related Hypoglycemic Adverse Events With No Motor Vehicle Accident Reported				
	8 (0.3%)	0 (0%)	1 (0.06%)	1 (0.2%)

It should be noted that this analysis contains all the patients enrolled in clinical studies, not only those in the controlled trials. This type of analysis does not look at the occurrence of MVAs strictly in the context of the clinical trials and thus limits the pramlintide-to-placebo comparison. Even so, a few observations can be made:

- Most of the hypoglycemia-related injuries occur in patients with type 1 diabetes.
- Hypoglycemia-related injuries show a higher pramlintide to placebo discrepancy than the "total injury" category.
- The division of events in two categories ("motor vehicle accident-related events" and "automobile-related hypoglycemic adverse events with no motor vehicle accident reported") is artificial. Both categories may represent different facets of the same phenomenon (hypoglycemic adverse events occurring in the context of driving).

In order to make pramlintide-to-placebo comparisons in the context of long-term controlled clinical trials, only the patients who were enrolled in the phase 3 type 1 diabetes studies are counted in table 23:

Table 23: Driving-Related Events and Other Injuries Associated With Hypoglycemia in the Long-Term Controlled Type 1 Diabetes Trials

Number and % of Patients					
	Pramlintide (n=1179)		**Placebo** (n=538)		**Fold Difference**
	n	%	n	%	
Driving-Related	18	1.53 %	1	0.18%	**8.5 X**
Other Injuries	9	0.76 %	1	0.18 %	**4.2 X**
All injuries	27	2.29 %	2	0.37	**6.2 X**

Note that the two driving categories from the previous table are unified and that only one placebo patient is counted (patient 137-121-9317 had an MVA **after** the completion of the trial and is therefore excluded). This table does not include the fatal MVA.
Also note that two additional subjects are added to the sponsor's list in the pramlintide "other injury" category. They are subject 137-117-6304 (hypoglycemia/fall/broken elbow) and 137-117-5030 (hypoglycemia/fall/nose laceration). These reports were missed by the sponsor.

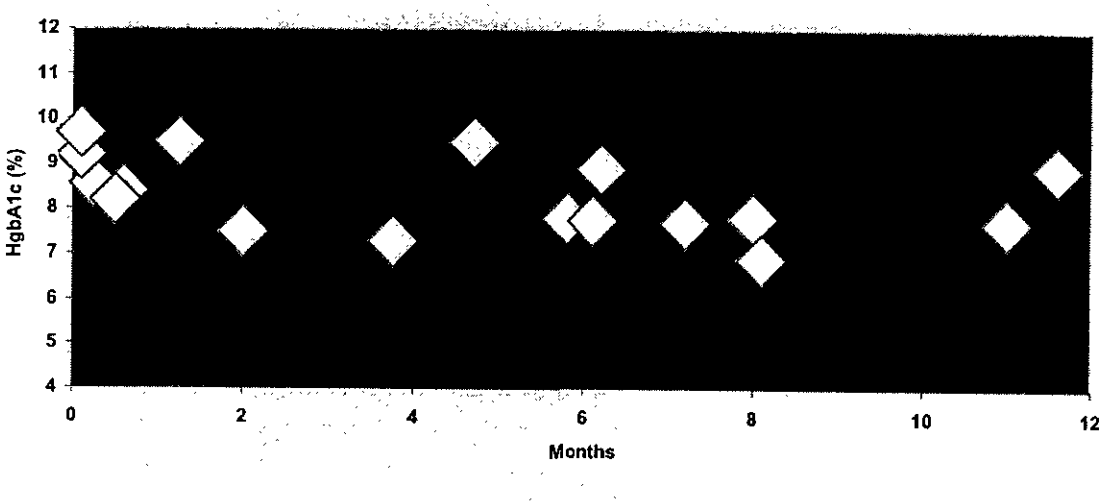
Based on this analysis type 1 diabetes patients treated with pramlintide experience anywhere between 4 to 8 times more driving-related events associated with hypoglycemia than the placebo-treated patients. This observation is consistent with "other types of injury" category associated with hypoglycemia (i.e. four-fold difference).

It should be noted that minor differences exist between the reviewer's list and the list provided by the sponsor. However they both contain the same "core" of subjects with MVAs and **only one** placebo patient.

Particularly troublesome is the fact that the injuries associated with hypoglycemia have not been prospectively assessed and that they may represent an underestimation of the true incidence and potential risk to patients.

It is of particular importance to understand the time distribution of driving-related events associated with hypoglycemia within the clinical trials in order to consider potential preventive interventions. Figure 11 displays the relationship between of the driving-related events, time to event in the trial (in the pramlintide treatment group), and the HbA1c at the time of the event. Less than 1/3 of all the events take place during the first month of drug exposure. This is consistent with the previously observed higher incidence of severe hypoglycemia during the first month of the trials. However, over 2/3 of events take place at different times during the rest of the trials with no predictable time of occurrence. They also happen at relatively high HbA1c levels that normally are associated with lower incidence of hypoglycemic events.

Figure 11: Time of Driving-Related Events vs HbA1c*



*Each diamond shape represents an individual driving-related event associated with hypoglycemia in the pramlintide treatment group.

Equally important is to understand when these driving-related events occur during the day, particularly if there is any relation with the mealtime. This information is not presented systematically in the submission. Although some of the events clearly occur after a meal and some others take place at times which can be inferred as mealtimes, the quality of the information available does not allow any sound conclusions.

Analysis of serious adverse events in type 1 diabetes allow the observation that **all SAEs in the central and peripheral nervous system category are in the pramlintide treatment group and none in the placebo-treated group. Among these, all four**

patients with hypoglycemic convulsions and all three subjects with hypoglycemic coma received pramlintide treatment.

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. 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 despite showing adequate counter-regulatory responses. The role of these endocrine markers in the recognition of hypoglycemia is not clear (see appendix).

On the other hand, pramlintide is known to delay gastric emptying in a dose-dependent manner. It is theoretically possible that variations in gastric emptying time due to different meal content and pharmacodynamic interactions between pramlintide and insulin may result in variable delivery of nutrients (including glucose) to the intestine. This possible scenario brings to mind the patient with a fatal MVA who, at autopsy, had food in the stomach.

It is also important to recognize the fact that we do not have any information about how many subjects enrolled in the clinical trials own a car or what their driving habits are. None of this information has been taken into consideration at the time of randomization. Therefore it is difficult to predict the impact of the hypoglycemic events occurring in the context of driving on the type 1 diabetes patient population if pramlintide were to be used on a large scale. An observation which may have particular significance is the fact that **most driving-relating events associated with hypoglycemia are recorded in study 137-121 (10 out of 15 events on the reviewer's list and 13 out of 18 on the sponsor's list). This study includes almost exclusively U.S. patients (there were 102 centers: 100 from U.S.A. and two from Canada) and used higher doses (60 to 90 μg).** In contrast, study 137-117 included 51 European, 13 Canadian, and no U.S.sites). Study 137-112 was completed in the U.S.A. but the doses used were smaller (30 μg for the first 20 weeks and 30 and 60 μg thereafter). The number of pramlintide-receiving patients was about the same in studies 137-121 and 137-117 and smaller in 137-112. **Thus, there is a suggestion that that the driving-related events are associated with increased driving (such as in the U.S. population) and magnitude of the pramlintide dose.**

Conclusions:

- **Pramlintide therapy is associated with a two-fold increase in serious adverse events associated with hypoglycemia in both type 1 and type 2 diabetes patients.**
- **The incidence of SAEs associated with hypoglycemia is higher in type 1 diabetes patients (9% compared with 2 % in type 2 diabetes subjects).**

- **Although the range of hypoglycemic SAEs responsible for the pramlintide-to-placebo difference is not completely understood, injuries and CNS events represent an important component in type 1 diabetes patients.**
- **Driving-related events associated with hypoglycemia occur 4-8 times more frequently in the pramlintide group depending on the dataset analyzed.**
- **Less than 1/3 of driving-related events take place during the first month of treatment. The rest of the MVAs occur at unpredictable times during pramlintide treatment and at relatively high levels of HbA1c.**
- **There is a disproportionate number of MVAs in study 137-121 (done in U.S.A.) when compared to study 137-117 (done in Canada and Europe) or study 137-112 (which used lower pramlintide doses).**
- **Non-MVA injuries associated with hypoglycemia are four times more frequent in pramlintide treated patients in type 1 diabetes compared to placebo counterparts.**
- **One fatal MVA may have been associated to hypoglycemia in a type 1 diabetes patient.**
- **There are no discernable features of the MVAs that allow the prevention of these events.**
- **The injuries associated with hypoglycemia have not been prospectively assessed and they may represent an underestimation of the true incidence and potential risk to the patient.**
- **CNS-related SAEs, such as coma and seizures occur only in the pramlintide treatment group and all are associated with hypoglycemia.**

Retinopathy

Study 137-111 (phase 3, type 2 diabetes) shows a dose-related increase in incidence of adverse events captured by the term "retinal disorder" (table 24). The following events are mapped to this term: "diabetic retinopathy, retinopathy, laser surgery secondary to retinopathy, photocoagulation treatment, microaneurysms, torn retina, and occular inflammation." This observation stands alone in this study and is not confirmed by any of the other two long-term type 2 diabetes studies.

Table 24 Incidence of Adverse Events Coding to Retinal Disorder in Type 2 Diabetes Long-Term Pramlintide Studies

Study Number Adverse Event	Number (%) of Patients			
137-111	**Placebo** (n=136)	**Pramlintide 30 µg TID** (n=122)	**Pramlintide 75 µg TID** (n=136)	**Pramlintide 150 µg TID** (n=144)
Retinal Disorders	7 (5.1%)*	7 (5.7%)	8 (5.9%)**	15 (10.4 %)***
137-122	Placebo (n=161)	**Pramlintide 90 µg BID** (n=171)	**Pramlintide 60 µg TID** (n=158)	**Pramlintide 120 µg BID** (n=166)
Retinal Disorders	10 (6.2%)	10 (5.8%)	6 (3.8 %)	7 (4.2 %)
137-123	**Placebo** (n=123)	**Pramlintide 90 µg BID** (n=121)	**Pramlintide 90 µg TID** (n=129)	**Pramlintide 120 µg BID** (n=126)
Retinal Disorders	3 (2.4 %)	2 (1.7 %)	1 (0.8 %)	3 (2.4 %)

* Does not include one patient with an event coded as retinal hemorrhage.
** Does not include two patients with events coded as retinal hemorrhage.
*** Does not include two patients with events coded as retinal hemorrhage.
Source: ISS and Amylin AC Briefing Document Table 22.

It is important to remember that there were no specific assessments of retinopathy (i.e. fundus photography) at study baseline to allow comparative assessment later on. The sponsor points out that the duration of disease was longer in the 150 µg TID treatment group (mean, 13.3 years) compared to the other treatment groups (means of 11.3 and 11.9 years). Thus, patients in this arm may have had more time to develop this complication.

It seems unlikely that this signal is real, although in absence of confirmatory solid data such a statement has major limitations. On one hand there is no consistent dose-related increase in retinal disorder incidence in the other two long-term studies (for instance, the 90 µg BID arm in study 137-122 has a higher incidence of retinopathy than 120 µg BID; similarly, in study 137-123 the 90 µg TID arm has a lower incidence of retinopathy than the 120 µg BID arm despite a higher daily dose of pramlintide). In addition, study 137-111 employed a pramlintide formulation with a pH of 4.7 which is known to exhibit a 25% reduction in bioavailability compared to the pH 4.0 formulation used in the other

studies (i.e. 150 µg TID dose ought to be equivalent to a dose of approx. 110 µg TID of the to-be-marketed preparation).

Conclusions:

- **A signal of dose-related retinopathy is present in a single study in type 2 diabetes patients. It occurs in the treatment arm that uses the highest daily dose of pramlintide administered in any trial. The available information limits further interpretation of this finding.**

Vital Signs

Vital signs data collected during the pramlintide studies are height, weight, blood pressure and pulse rate. Of these, only blood pressure and pulse rate are analyzed in this safety review. Weight is considered as an efficacy parameter in the pramlintide program and is not be part of this review section. Height was used for determining body mass index (BMI).

Clinical pharmacology trials

The clinical pharmacology studies do not provide any safety signal related to pramlintide treatment. The sponsor does not report any clinically important effect of pramlintide on blood pressure or heart rate in any of these trials which explore a wide range of doses and routes of administration. Thus, the observation made in dogs that pramlintide lowers transiently the blood pressure through 25 minutes post-administration at 300 μg/kg did not translate in any evidence of hypotension during these studies.

Long-term controlled trials in type 1 and type 2 diabetes patients

The long-term studies in subjects with type 1 and type 2 diabetes provide the largest dataset for blood pressure and pulse data. The vast majority of subjects enrolled in the long-term controlled trials had a baseline and at least one subsequent vital sign measurement.

Table 25 shows blood pressure and pulse rate changes from baseline recorded in the long-term controlled type 1 and type 2 diabetes trials. These changes are presented as mean values for both pramlintide and placebo subjects.

Mean baseline and post-baseline values are within the normal range for both pramlintide and placebo subjects. Little or no change in blood pressure or pulse from baseline to the last visit are seen in either pramlintide or placebo subjects in these studies.

Table 25: Pulse and Blood Pressure: Mean Values at Baseline and Mean Change from Baseline to Last Visit in the Long-Term Controlled Studies in Subjects With Type 1 and Type 2 Diabetes

			Type 1 Diabetes		Type 2 Diabetes	
Variable			**Pram** (n=1179)	**Pbo** (n=538)	**Pram** (n=1273)	**Pbo** (n=420)
Pulse (bpm)	**Supine**	n	1172	537	1271	419
		Baseline	74	73	75	76
		Change	**1**	**1**	**0**	**-1**
	Standing	n	1172	537	1268	418
		Baseline	79	78	78	79
		Change	**1**	**1**	**-1**	**-1**
Systolic BP (mmHg)	**Supine**	n	1174	537	1271	419
		Baseline	123	122	133	132
		Change	**0**	**1**	**1**	**2**
	Standing	n	1174	537	1268	419
		Baseline	121	120	131	130
		Change	**-1**	**0**	**0**	**2**
Diastolic BP (mmHg)	**Supine**	n	1174	537	1271	419
		Baseline	76	76	78	78
		Change	**0**	**0**	**0**	**1**
	Standing	n	1174	537	1268	419
		Baseline	77	77	79	78
		Change	**0**	**0**	**0**	**0**

N=number of enrolled patients; n= number of patients with a baseline and at least a subsequent measurement. Pram=pramlintide; Pbo=placebo.
Change= value at last visit minus baseline value.
Source: ISS, Table 36.

Vital sign changes in individual patients are captured under the category of "potentially clinically important" measurements. This information is displayed in table 26 . Overall, the percentage of subjects with potentially clinically important blood pressure is similar in the pramlintide and placebo groups in both type 1 and type 2 diabetes patients.

Table 26: Incidence of Potentially Clinically Important Blood Pressures in the Long-Term Controlled Trials

		Type 1 Diabetes		Type 2 Diabetes	
		Pram (n=1179)	**Pbo** (n=538)	**Pram** (n=1273)	**Pbo** (n=420)
Hypertension	**Systolic BP>140 and change from baseline>20**	164 **(13.9%)**	104 **(19.3%)**	454 **(35.7%)**	155 **(36.9%)**
	Systolic BP>180	8 **(0.7%)**	2 **(0.4%)**	40 **(3.1%)**	11 **(2.6%)**
	Diastolic BP>90 and change from baseline>20	51 **(4.3%)**	21 **(3.9%)**	79 **(6.2%)**	31 **(7.4%)**
	Diastolic BP> 105	10 **(0.8%)**	3 **(0.6%)**	25 **(2.0%)**	6 **(1.4%)**
Hypotension	**Systolic BP<90**	42 **(3.6%)**	24 **(4.5%)**	27 **(2.1%)**	7 **(1.7%)**
	Diastolic BP<60	152 **(12.9%)**	69 **(12.8%)**	127 **(10.0%)**	41 **(9.8%)**

BP measurements in mmHg.
Source: ISS, Table 37.

In the uncontrolled studies in subjects with type 1 diabetes and in subjects with type 2 diabetes using insulin, the percentage of subjects with potentially clinically important **diastolic hypotension** (type 1 -15.7%, type 2 - 14.3%) was higher than in pramlintide subjects in the corresponding long-term controlled studies (type 1 – 12.9%, type 2 – 10.0%). In the absence of a placebo arm this information has limited value.

Short-term controlled trials in type 1 and type 2 diabetes

One observation concerning the short-term controlled studies deserves notice. In this studies the percentage of subjects with potentially clinically important **diastolic hypotension** is higher in pramlintide group than in placebo group (table 27). This observation stands in contrast with the data collected in the long-term controlled studies which shows no treatment specific differences.

Table 27: Incidence of Potentially Clinically Important Blood Pressures (Short-Term Studies, Type 1 and Type 2 Diabetes Trials)

	Type 1 Diabetes		Type 2 Diabetes	
	Pram (n=172)	**Pbo** (n=43)	**Pram** (n=153)	**Pbo** (n=50)
Systolic Hypotension (BP<90 mmHg)	4 (2.3%)	0 (0%)	1 (0.7%)	1 (2.0%)
Diastolic Hypotension (BP< 60mmHg)	29 **(16.9%)**	4 **(9.3%)**	12 **(7.8%)**	2 **(4.0%)**

A small reduction in the mean change from baseline to last visit in diastolic blood pressure can also be seen during the short-term controlled studies in type 1 diabetes patients (Table 28). This observation does not apply to type 2 diabetes.

Table 28: Diastolic Blood Pressure: Mean Values at Baseline and Mean Change from Baseline to Last Visit in the Short-Term Controlled Studies in Subjects With Type 1 Diabetes and in Subjects With Type 2 Diabetes

			Type 1 Diabetes		Type 2 Diabetes	
			Pram (n=172)	**Pbo** (n=43)	**Pram** (n=153)	**Pbo** (n=50)
Diastolic BP (mmHg)	**Supine**	n	172	43	150	50
		Baseline	75	74	77	77
		Change	**-3**	**-1**	**0**	**0**
	Standing	n	N/A	N/A	148	49
		Baseline	N/A	N/A	77	78
		Change	N/A	N/A	**0**	**-1**

N=number of enrolled patients; n= number of patients with a baseline and at least a subsequent measurement Pram=pramlintide; Pbo=placebo.
Change= value at last visit minus baseline value.
Source: ISS, SD179.

Adverse Events Associated With Blood Pressure and Pulse Rate Changes

Due to the presence of a safety signal of dyastolic hypotension noticed in patients with type 1 diabetes in the short-term controlled studies, adverse events related to blood pressure and pulse rate were reviewed.

Hypotension

Hypotension is an infrequent cause of serious adverse events or subject withdrawal.
There are two SAEs associated with hypotension during the long-term type 2 diabetes controlled studies (one in each treatment group).
Only one patient withdrew during the long term type 2 diabetes controlled trials (in the pramlintide group).
Hypotension is an infrequent treatment-emergent adverse event in either type 1 or type 2 diabetes subjects (table 29). Adverse events of "hypotension" and "hypotension postural" occur only in association with pramlintide treatment in type 1 diabetes albeit in low numbers.

29: Treatment Emergent Adverse Events Related to Blood Pressure and Pulse Rate (Long-Term Controlled Type 1 and Type 2 Diabetes Trials)

	Type 1 Diabetes		Type 2 Diabetes	
	Pramlintide (n=1179)	**Placebo** (n=538)	**Pramlintide** (n=1273)	**Placebo** (n=420)
Hypotension	2 (<1%)	0 (0%)	8 (1%)	3 (1%)
Hypotension postural	7 (1%)	0 (0%)	7 (1%)	2 (<1%)
Hypertension	28 (2%)	19 (4%)	75 (6%)	24 (6%)
Hypertension aggravated	6 (1%)	0 (0%)	26 (2%)	11 (3%)
Blood pressure fluctuation	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tachycardia	8 (1%)	7 (1%)	17 (1%)	2 (<1%)
Bradycardia	0 (0%)	0 (0%)	4 (<1%)	3 (1%)

Source:ISS, SDS 77

Bradycardia

One SAE is reported in a type 2 diabetes patient receiving pramlintide. TEAEs are infrequent (table 29).

Tachycardia

One SAE and one withdrawal are reported in the pramlintide treatment group during the long-term controlled type 2 diabetes trials. TEAEs are infrequent (table 29).

Hypertension
One SAE is reported in a type 2 diabetes patient receiving pramlintide and two SAEs in the 1 type diabetes long-term controlled trials. TEAEs are infrequent (table 29).

Conclusions:

- **Pramlintide treatment is not associated with blood pressure and pulse rate changes in patients with type 2 diabetes.**
- **Pramlintide treatment in type 1 diabetes patients may be associated with a tendency toward lower diastolic blood pressure in the first month of treatment which subsequently disappears. This does not appear to be a clinically important issue (i.e. SAEs and withdrawals due to blood pressure or pulse abnormalities are infrequent).**

Clinical Laboratory

The degree of laboratory testing varies among trials. This is largely due to the diverse nature of studies performed. Therefore, in analyzing the potential effects of pramlintide on the various analytes, emphasis is being placed on the long-term controlled studies in both type 1 and type 2 diabetes. They provide anywhere between six months to one full year of drug exposure.

Hematology, chemistry analytes and urinalysis have been measured before the beginning of the study, at baseline, and periodically through the end of the studies.

Hematology variables include: hemoglobin, hematocrit, red cell indices, WBC (total and differential) counts, platelet counts, and HbA1c.

Chemistry measurements include: electrolytes, liver function tests, renal function tests (BUN, creatinine), creatinine kinease.

Lipid measurements include: cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and LDL/HDL ratio.

Urine studies include pH measurement.

Criteria for laboratory changes of potential clinical importance were pre-defined. The number and percent of potentially clinically important laboratory values are summarized for each visit for the selected analytes. The denominator for the calculation is the number of subjects with an available laboratory value at that visit for the analyte.

It should be noted that most (albeit not all) of the subjects enrolled in the phase 3 studies have at least a baseline and a post-baseline measurement for most of the laboratory measurements included. An exemption to this observation is HDL/LDL testing (done in about one fifth of the subjects in the long-term controlled studies) and total cholesterol (done in only in 75% of type 1 diabetes patients).

Table 30 summarizes the incidence of chemistry laboratory abnormalities which meet the "potential clinical importance definition" criterion.

Table 30: Incidence of Potentially Clinically Important Laboratory Abnormalities (Chemistry) in the Long-term Controlled Trials (Type 1 and Type 2Diabetes)*

	Type 1 Diabetes		Type 2 Diabetes	
Chemistry Variable	**Pramlintide** (N=1179)	**Placebo** (N=538)	**Pramlintide** (N=1273)	**Placebo** (N=420)
Total	330 (28%)	197 (37%)	385 (30%)	151 (36%)
ALT	8 (<1%)	5 (<1%)	10 (<1%)	3 (<1%)
AST	6 (<1%)	4 (<1%)	6 (<1%)	2 (<1%)
Albumin	4 (<1%)	2 (<1%)	5 (<1%)	0 (0%)
Alk Phos.	2 (<1%)	1 (<1%)	2 (<1%)	0 (0%)
Bicarbonate	10 (<1%)	4 (<1%)	21 (2%)	11 (3%)
CK	39 (3%)	28 (5%)	35 (3%)	19 (5%)
Calcium	1 (<1%)	2 (<1%)	1 (<1%)	0 (0%)
Cholesterol	2 (<1%)	1 (<1%)	8 (<1%)	3 (<1%)
Creatinine	9 (<1%)	1 (<1%)	5 (<1%)	2 (<1%)
GGT	10 (<1%)	5 (<1%)	34 (3%)	9 (2%)
Phosphorus	69 (6%)	38 (7%)	48 (4%)	12 (3%)
Potassium	54 (5%)	16 (3%)	21 (2%)	12 (3%)
Serum Glucose	145 (12%)	79 (15%)	39 (3%)	28 (7%)
Sodium	25 (2%)	24 (4%)	16 (1%)	7 (2%)
Total Bilirubin	14 (1%)	5 (<1%)	8 (<1%)	2 (<1%)
Triglycerides	30 (3%)	32 (6%)	165 (13%)	65 (15%)
Urea	23 (2%)	16 (3%)	63 (5%)	23 (5%)
Uric Acid	4 (<1%)	1 (<1%)	48 (4%)	14 (3%)

*Highlighted are the individual analytes which show a difference of at least one percent in the pramlintide group over the placebo group.

There are no strong signals among chemistry laboratory tests. Potassium (in type 1 diabetes) and GGT, phosphorus, and uric acid (in type 2 diabetes) show higher incidence over placebo (≥1%). Serum potassium is the single analyte that shows >1% incidence difference between pramlintide and placebo.

Table 31 summarizes the incidence of hematology and urine analysis abnormalities which meet the "potential clinical important" definition criterion.

Table 31: Incidence of Potentially Clinically Important Laboratory Abnormalities (Hematology and Urine Analysis) in the Long-term Controlled Trials (Type 1 and Type 2Diabetes)*

	Type 1 Diabetes		Type 2 Diabetes	
Variable	**Pramlintide** (N=1179)	**Placebo** (N=538)	**Pramlintide** (N=1273)	**Placebo** (N=420)
Hematology (total)	**24 (2%)**	**17 (3%)**	**29 (2%)**	**14 (3%)**
HbA1c	**1 (<1%)**	**5 (<1%)**	**3 (<1%)**	**2 (<1%)**
Hematocrit	**17 (1%)**	**11 (2%)**	**22 (2%)**	**11 (3%)**
Hemoglobin	**14 (1%)**	**7 (1%)**	**11 (<1%)**	**6 (1%)**
Platelets	**0 (0%)**	**1 (<1%)**	**0 (0%)**	**0 (0%)**
WBC	**0 (0%)**	**2 (<1%)**	**1 (<1%)**	**0 (0%)**
Urine Analysis	**169 (14%)**	**189 (35%)**	**207 (16%)**	**94 (22%)**
Urine Glucose	**166 (14%)**	**186 (35%)**	**189 (15%)**	**90 (21%)**
Urine Ketones	**2 (<1%)**	**2 (<1%)**	**0 (0%)**	**0 (0%)**
Urine Protein	**13 (1%)**	**13 (2%)**	**33 (3%)**	**8 (2%)**

*Highlighted is the individual analyte which shows a difference of at least one percent in the pramlintide group over the placebo group.

There are no strong safety signals in the hematology and urine analysis laboratories abnormalities. Urine protein is the only measurement that shows a higher incidence in the pramlintide group over placebo (1%). Not a single analyte shows >1% incidence difference between pramlintide and placebo in either type 1 and type 2 diabetes subjects.

In addition to analyzing "potentially clinically important" laboratory abnormalities, the sponsor also provides data concerning mean laboratory values at baseline and post-baseline. Overall, the mean baseline and post-baseline laboratory values are described "within the normal range". Mean changes from baseline in laboratory values are "generally similar for subjects treated with pramlintide and subjects treated with placebo." Exemptions are summarized in table 32:

Table 32: Mean Changes From Baseline in Laboratory Values Showing Differences Between the Pramlintide and Placebo Groups:

	Type 1 Diabetes		Type 2 Diabetes	
Analyte	**Pramlintide**	**Placebo**	**Pramlintide**	**Placebo**
ALT	↑ 1.29 U/L	↑ 5.2 U/L	↑ 0.59 U/L	↑ 0.52 U/L
CK	↓ 3.38 U/L	↑ 11.86 U/L	↓ 1.45 U/L	↑ 5.13 U/L
Glucose	↓ 6.83 mg/dl	↑1.42 mg/dl	↓ 5.38 mg/dl	↑ 3.38 mg/dl
Triglycerides	↑ 4.97 mg/dl	↓ 0.13 mg/dl	↓10.10 mg/dl	↑ 7.71 mg/dl

None of the above mean changes provide a strong safety signal. As expected, the serum glucose levels are lower in the pramlintide treatment groups, consistent with the glucose-lowering effect of the drug. A small decrease in serum creatinine kinase levels is consistently observed in association with pramlintide in both type 1 and type 2 diabetes patients.

Special emphasis is placed on the laboratory data as it relates to several organ systems such as the kidneys and the liver. A summary of these analyses in the long-term controlled studies is provided in the following subsection.

Renal function test abnormalities:

Blood urea nitrogen (BUN). A total of 94 pramlintide-receiving subjects have at least one blood urea nitrogen measurement in the abnormal range (defined as BUN>30 mg/dL) during the long-term controlled studies compared to 43 placebo-treated subjects. Pramlintide to placebo comparisons by type of diabetes in the long term studies are presented in table 33:

Table 33: Number and Incidence of Abnormal BUN Values in Long-term Controlled Type 1 and Type 2 Diabetes Studies

	Type 1 Diabetes		Type 2 Diabetes	
	Pramlintide (N=1179)	**Placebo** (N=538)	**Pramlintide** (N=1273)	**Placebo** (N=420)
Number	28	17	66	26
Incidence	2.4 %	3.1%	5.2%	6.2%

The differences between the active drug and placebo are too small to raise any safety concerns.

Serum creatinine. A total of thirteen subjects have an elevated serum creatinine (defined as a rate blanked creatinine >2 mg/dL) while on pramlintide compared to only 4 subjects on placebo during the long-term controlled studies. Pramlintide to placebo comparisons by type of diabetes during the long term studies are presented in table 34.

Table 34: Number and Incidence of Abnormal Creatinine Values in Long-Term Controlled Type 1 and Type 2 Diabetes Studies:

	Type 1 Diabetes		Type 2 Diabetes	
	Pramlintide (N=1179)	**Placebo** (N=538)	**Pramlintide** (N=1273)	**Placebo** (N=420)
Number	9	1	4	3
Incidence	0.76%	0.18%	0.31%	0.71%

There is an approximately four-fold incidence difference in abnormal creatinine elevations between the active drug and placebo in type 1 diabetes patients. In absence of any other corroborating safety signals (e.g. BUN and urine changes are in the opposite direction) this signal is too small to allow for any definitive conclusions.

Serum creatinine and BUN combined: A total of eleven subjects have a combined elevation of serum creatinine and BUN on pramlintide compared to 3 subjects on placebo. Pramlintide to placebo comparisons by diabetes type in the long term studies are presented in table 35:

Table 35: Number and Incidence of Abnormal Creatinine and BUN Values Combined in Long-Term Controlled Type 1 and Type 2 Diabetes Studies:

	Type 1 diabetes		Type 2 diabetes	
	Pramlintide (N=1179)	**Placebo** (N=538)	**Pramlintide** (N=1273)	**Placebo** (N=420)
Number	7	0	4	3
Incidence	0.59%	0%	0.31%	0.71%

The differences between the active drug and placebo mimic the findings of the abnormal creatinine elevations. The signal is too weak to raise any clear safety concerns.

Liver enzyme abnormalities:

Abnormalities of serum bilirubin. Several subjects had isolated total bilirubin levels. Table 36 summarizes the number the incidence of isolated hyperbilirubinemia (defined as a serum total bilirubin level >2 mg/dL without specification whether it is direct or indirect).

Table 36: Incidence of Hyperbilirubinemia During the Long-Term Controlled Type 1 and Type 2 Diabetes Studies:

	Type 1 Diabetes		Type 2 Diabetes	
	Pramlintide (N=1179)	**Placebo** (N=538)	**Pramlintide** (N=1273)	**Placebo** (N=420)
Number	15	5	9	2
Incidence	1.27%	0.92%	0.7%	0.47%

The differences between the active drug and placebo are too small to raise any safety concerns.

Abnormalities of serum bilirubin combined with elevated ALT/AST levels. Since the association between elevated serum transaminases and bilirubin correlates with at least a 10% chance of severe liver injury, a search of subjects with this combination of abnormal analytes was done. Four such subjects were identified, all in the long-term controlled studies Table 37):

Table 37: Subjects With Combined Elevations of Serum Bilirubin and Transaminases (Alkaline Phosphatase and GGT levels are also included)*:

Subject/Study	SGOT (U/L)	SGPT (U/L)	GGT (U/L)	Total Bilirubin (mg/dL)	Alkaline Phosphatase (U/L)
137-112-1815	858	2175	489	11.1	547
137-121-7402	278	204	585	4.5	549
137-122-5507	184	422	921	2.3	172 (normal)
137-122-6601	195	278	414	2.4	166 (normal)

*Highlighted subjects are in the pramlintide group.

Several observations can be made concerning this group of subjects:

- There is an equal number of subjects in each treatment group.
- Both pramlintide subjects completed the study and had normalized liver function tests on repeat measurement. Subject 137-122-5507 had an identified adverse event of cholecistitis.
- Both placebo subjects were discontinued from the study, one for cardiac failure and one for protocol violation.

Conclusions:

- **Pramlintide treatment has minimal effect over standard analytes with the exemption of serum and urine glucose levels that are to be expected from a glucose-lowering drug.**

- **A weak safety signal of increased serum creatinine is present in type 1 diabetes patients but it is not supported by other renal findings such as BUN and urine protein concentrations.**

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Electrocardiogram (ECG) Findings:

ECG data collection is inconsistent among different studies. Most of the 26 clinical pharmacology studies include an ECG evaluation either at the initial screening, or both at screening and at the end of the study.
All long-term studies have an ECG evaluation performed at baseline. Most have several subsequent evaluations (up to four, including one at the end of the trial). Two studies (both six months in duration) have one ECG at baseline and one at the end of the study.

It should be noted that timing of ECGs in the clinical studies was not planned to correspond to peak plasma concentrations of pramlintide.

No QT prolongation is reported in either type 1 or type 2 diabetes subjects.

Table 38 shows the incidence of new ECG abnormalities in the short term and the long-term controlled studies.
The short-term type 2 diabetes trial 137-114 (one month duration) is the only trial to show an increase in ECG abnormalities in the pramlintide group over placebo (two fold). None of the other studies record drug-to-placebo differences.

Table 38 Incidence of New ECG Abnormalities (Type 1 and Type 2 Diabetes Long-Term Controlled Studies)

	Type 1 Diabetes				Type 2 Diabetes			
	Short-term		Long-term		Short-term		Long-term	
	Pram.	Pbo.	Pram.	Pbo.	Pram.	Pbo.	Pram.	Pbo.
Subjects enrolled	172	43	1179	538	153	50	1273	420
Subjects with baseline and follow-up ECGs	167	42	1082	500	150	50	1186	389
New ECG abnormalities (number and %)*	13 (8%)	3 (7%)	130 (12%)	71 (14%)	20 (13%)	3 (6%)	191 (16%)	65 (17%)
New clinically significant ECG abnormalities (number and %)*	0 (0%)	0 (0%)	3 (<1%)	1 (<1%)	0 (0%)	0 (0%)	5 (<1%)	8 (2%)

*In investigator's judgement.
Pram.=pramlintide. Pbo.=placebo.
Source: SDS 190.

In addition to the above analysis, the sponsor provides narratives describing ECG findings considered "clinically significant" by the investigator or "noteworthy" by the sponsor's medical reviewer. This information (verified against the CRT individual profile information is summarized in table 39). It should be noted that the number of ECGs found to be "clinically significant" in the narratives does not match the ones identified in the previous table.

Table 39: Categories of Clinically Significant Treatment-Emergent ECG Findings (Long-term Controlled Type 1 and Type 2 Diabetes Trials)

	Type 1 Diabetes		Type 2 Diabetes	
	Pramlintide	**Placebo**	**Pramlintide**	**Placebo**
Conduction abnormalities	1	0	2	0
Arrhythmias	1	0	2	2
Myocardial infarction	3	0	2	4
Ischemia	1	1	5	4
Ventricular hypertrophy	0	0	0	1

The differences between the treatment groups are too small to draw any conclusions or identify any signals of concern.

Conclusion:

- **The use of pramlintide in addition to insulin in patients with type1 and type 2 diabetes does not appear to be associated with any increase in ECG abnormalities. An isolated pramlintide-to-placebo difference noted during the short-term type 2 diabetes trials is not confirmed during the long-term trials.**
- **QT prolongation is not reported in either type 1 or type 2 diabetes.**

Drug-drug interactions:

Pramlintide has three proposed mechanisms of action: inhibition of postprandial glucagon secretion, food intake reduction, and reduction of the delivery rate of ingested carbohydrate into the small intestine. This last mechanism is secondary to a dose-dependent delay in gastric emptying for both liquids and solids.

There are two immediate consequences of the gastric motility effects induced by pramlintide: reduced absorption of concomitantly administered drugs and cumulative effect with drugs that alter gastric motility (e.g. erythromycin, metoclopramide, atropine) or agents that alter the intestinal absorption of nutrients (e.g. α -glucosidase inhibitors).

Experience from clinical pharmacology studies.

There are six studies that investigate the interactions between pramlintide and other drugs. Only two of these, (studies137-133 and 137-134, both conducted in healthy volunteers) evaluate the pharmacokinetic interactions of a single 90 µg SC dose of pramlintide with oral medications: contraceptives (ethinyl estradiol and norgestrel) and ampicillin, respectively.

Four additional studies evaluate the potential pharmacokinetic and pharmacodynamic effects of co-administering pramlintide with various brands and types of insulin in subjects with type 1 diabetes. One study evaluates the safety and pharmacodynamic effects of co-administering insulin lispro and 60 µg SC pramlintide as separate injections. Three studies are insulin mixing studies (they look at the effects of mixing pramlintide 30 µg with various brands and types of insulin in the same syringe).

Close temporal administration of pramlintide (90µg) and Ampicillin (500 mg) results in a T_{max}. delay of 60 minutes for ampicillin without changes in C_{max} and AUC.

Pramlintide has a mixed effect on low-dose oral contraceptives. For ethinyl estradiol (30µg) it delays the drug's Tmax by 30 minutes without changing the C_{max}, $AUC_{(0-\infty)}$ or $t_{1/2}$. For norgestrel (300 µg) pramlintide delays the drug's Tmax by 45 minutes and it reduces the C_{max} by 30 % without alteration of the $AUC_{(0-\infty)}$ or $t_{1/2}$.

Experience from clinical trials.

The type 1 diabetes trials include patients on fibrates, statins, ACE inhibitors, beta blockers, calcium channel blockers, and thiazide diuretics. Less frequently used drugs were alpha glucosidase inhibitors, biguanides, glitazones, sulphonylureas.
The type 2 diabetes trials include the following classes of frequently prescribed concomitant medications: alpha glucosidase inhibitors, biguanides, glitazones, sulphonylureas, fibrates, statins, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, and thiazide diuretics.

The sponsor presents the data combined for the long-term controlled and uncontrolled studies, thus making pramlintide-to-placebo comparisons uninterpretable. In order to provide a sense of the concomitant use of pramlintide and the above mentioned drugs table 40 is provided.

Table 40: Number of Subjects Exposed to Concomitant Medications Among Subjects Receiving Pramlintide (Controlled and Uncontrolled Clinical Studies)

	Type 1 Diabetes (n=1798)	Type 2 Diabetes (n=1339)
α-glucosidase inhibitors	0	3
Biguanines	6	160
Glitazones	1	7
Sulphonylureas	1	172
Statins	92	220
ACE inhibitors	371	532
β-blockers	77	219
Ca channel blockers	110	298
Fibrates	29	148
Thiazides	39	127

Source: ISS, SDS 192 and 193.

The sponsor's analysis concludes that "overall, there does not appear to be any evidence of an interaction between pramlintide and any of the classes of concomitant medications commonly used and evaluated in subjects with type 1 diabetes".
A small safety signal is found in type 2 diabetes subjects in the cardiovascular system for patients taking concomitantly thiazide diuretics and pramlintide. Twice as many overall adverse events and an increased incidence of "aggravated hypertension" occurs. However, the nature of analysis conducted limit the ability to draw any conclusions at this time.

Conclusions:

- **There is not enough information to draw any meaningful conclusions about potential drug-drug interactions between pramlintide and frequently used medications such as antihypertensives, statins, other antidiabetic medications, diuretics.**
- **Concomitant use of thiazide diuretics in patients with type 2 diabetes taking pramlintide may be associated with increased incidence of adverse events.**
- **Concomitant use of pramlintide and orally administered ampicillin or contraceptives delays the oral drug absorbtion as it is to be expected from the known effect of pramlintide on gastric emptying. Thus, it is very likely that pramlintide will interact with other orally administered medications and with medications that alter gastric motility.**

Anti-pramlintide antibody response

The immunogenicity of pramlintide was explored in 10 clinical studies ranging from clinical pharmacology to short-term and along-term clinical trials. Two methods of antibody detection were used during the program: a radioimmunoassay (RIA) (a high affinity antibody assay) and an enzyme-linked immunoabsorbant assay (ELISA) (both a low and a high affinity antibody assay).
The RIA has been used in four clinical pharmacology studies and one type 1 diabetes, short-term controlled study. The ELISA assay has been used for the determination of anti-pramlintide antibody in two of the long-term controlled studies and two ongoing studies.
Four clinical pharmacology studies (AP92-02, AP92-03, AP93-08, and 137-104) and a short-term controlled study (137-105) were negative for the presence of anti-pramlintide antibodies. They were all short studies (pramlintide exposure between 5 days to four weeks) and all used the RIA method for antibody detection at 4-6 weeks after the start of exposure. The pramlintide preparation used during all these studies was manufactured from a single source [ ]

Anti-pramlintide antibody response in **type 1 diabetes** studies was measured in study 137-112. The assay used was ELISA. Some of the patients were exposed to pramlintide formulations from one manufacturer [ ]; while others were exposed to a pramlintide mixture derived from two different manufacturers [ ] and [ ] Table 41 displays the number and percent of subjects with anti-pramlintide antibodies in study 137-112 (intent to treat population):

Table 41: Anti-Pramlintide Antibodies: Study 137-112

Treatment	Number tested at Least Once	Number Positive at Least Once	% Positive
Placebo	233	7	3.0%
Pramlintide (30 µg)	240	21	8.8%

Source: ISS Table 39, SDS 3.5.1/3.5.2

It should be noted that anti-pramlintide antibodies were present at randomization in two placebo patients and 5 pramlintide patients. If the subjects with antibodies at randomization are excluded the % positives are 2.25 for placebo and 6.8% for pramlintide. The percent of patients who developped anti-pramlintide antibodies among those which were exposed to the pramlintide mixture was about the same (approx. 8.7%). The sponsor states that review of the HbA1c values in the antibody positive subjects "did not suggest a relationship between development of anti-pramlintide antibodies and loss of clinical activity of pramlintide", thus inferring that they are not neutralizing antibodies. There were no reported events of hypersensitivity or anaphylaxizs in the study.

The generation of anti-pramlintide antibodies following long-term exposure in subjects

with **type 2 diabetes** using insulin was assessed in Study 137-111. The assay used was ELISA. All patients were exposed to pramlintide formulation made by one manufacturer [ ]. Table 42 displays the number and percent of subjects with anti-pramlintide antibodies in study 137-111 (intent to treat population):

Table 42: Anti-Pramlintide Antibodies: Study 137-111

Treatment	Number tested at Least Once	Number Positive at Least Once	% Positive
Placebo	131	6	4.6 %
Pramlintide (30 µg)	116	6	5.2 %
Pramlintide (75 µg)	131	16	12.2 %
Pramlintide (150 µg)	139	20	14.4 %

Source: ISS Table 39, SDS 3.5.1/3.5.2

It should be noted that anti-pramlintide antibodies were present at randomization in three placebo patients and 10 pramlintide patients. If the subjects with antibodies at randomization are excluded the % positives are 2.3%, 3.5%, 8.7%, and 12.5% for the placebo, pramlintide 30 µg, pramlintide 70 µg, and pramlintide 150 µg group, respectively. The sponsor states that review of the HbA1c values in the antibody positive subjects "did not suggest a correlation between development of anti-pramlintide antibodies and loss of clinical activity of pramlintide", thus inferring that they are not neutralizing antibodies.
There were no reported events of hypersensitivity or anaphylaxis in the study.

Results from two on-going studies (137-143 and 137-144) (twenty four patients, 14-day duration, different manufacturer: [ ] identified only one subject with a positive ELISA which at a later date was reported negative.

A pramlintide-to-placebo comparison of allergy-related symptoms does not identify any evidence of allergic reactions associated with type 1 or type 2 diabetes patients (table 43).

Table 43: Number and % of Subjects With Allergic Reactions: Long-term Controlled Type 1 and Type 2 Diabetes Studies

	Type 1 Diabetes		Type 2 Diabetes	
Body System Preferred Term	Pramlintide (n=1179)	Placebo (n=538)	Pramlintide (n=1273)	Placebo (n=420)
Injection Site Reaction	78 (7 %)	50 (9%)	78 (6%)	28 (7%)
Allergic Reaction	59 (5 %)	28 (5%)	65 (5%)	18 (4%)
Edema	7 (1%)	7 (1%)	37 (3%)	8 (2%)
Asthma	8 (1%)	3 (1%)	14 (1%)	2 (<1%)
Bronchospasm	6 (1%)	1 (<1%)	13 (1%)	5 (1%)
Rash	28 (2%)	24 (4%)	41 (3%)	15 (4%)

Rash Erythematous	9 (1%)	7 (1%)	12 (1%)	4 (1%)
Urticaria	7 (1%)	1 (<1%)	13 (1%)	1 <1%)
Rash Maculo-Papular	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)
Rash Pustular	0 (0%)	0 (0%)	1 (<1%)	0 (0%)

Source: ISS Table 40.

Conclusions:

- **Pramlintide use is associated with minor immunogenicity in two long-term studies (type 1 and type 2 diabetes).**
- **There is no evidence of allergic reactions to pramlintide in either type 1 or type2 diabetes patients.**

Special Populations:

There are no specific studies designed to investigate the effects of age, race or gender on the pharmacokinetics and pharmacodynamics of pramlintide. The long-term efficacy and safety studies include a large number of patients of different age groups, various races and both genders. The long-term controlled clinical trials are the main source of information for the drug-demographic interactions for the variables age, sex or race.

1) Age:

Table 44 summarizes the age distribution for the top five adverse events in patients with **type 1 diabetes**. The age groups analyzed are: < 18 years, 18-65 years and ≥65 years. It should be noted that the largest number of patients are in the 18-64 year group. The <18 year group is minimally represented. So is the > 65 year group.

Table 44 Most Frequent Treatment-Emergent Adverse Events: Incidence by Age- Type 1 Diabetes

Adverse Event	Treatment Group	<18 Years*	18-64 Years**	≥65 years***
Nausea	**Pramlintide**	**11 (58%)**	**574 (51%)**	**16 (42%)**
	Placebo	3 (38%)	87 (17%)	2 (9%)
Anorexia	**Pramlintide**	**2 (11%)**	**197 (18%)**	**10 (26%)**
	Placebo	1 (13%)	11 (2%)	0 (0%)
Hypoglycemia	**Pramlintide**	**5 (26%)**	**307 (27%)**	**11 (29%)**
	Placebo	1 (13%)	92 (18%)	8 (36%)
Vomiting	**Pramlintide**	**3 (16%)**	**148 (13%)**	**3 (8%)**
	Placebo	1 (13%)	34 (7%)	1 (5%)
Fatigue	**Pramlintide**	**0 (0%)**	**77 (7%)**	**3 (8%)**
	Placebo	0 (0%)	22 (4%)	0 (0%)

*The <18 year group includes: 19 patients for pramlintide and 8 patients for placebo.
** The 18-64 year group includes: 1122 patients for pramlintide and 508 patients for placebo.
*** The ≥ 65 year group includes: 38 patients for pramlintide and 22 patients for placebo.

Analysis of the most frequent treatment-emergent adverse events in relationship to age does not identify a particular age susceptibility for type 1 diabetes patients. This observation covers any adverse events with an incidence ≥ 5%.
The inflicted injury category occurrs twice as frequently in the <18 year group receiving pramlintide. However, the total number of patients in this group is overall small.

Table 45 summarizes the age distribution for the top five adverse events in patients with **type 2 diabetes**. The age groups analyzed are the same as in type 1 diabetes shown

above. It should be noted that, for type 2 diabetes patients, the group over 65 years is well represented while the <18 year group is absent. This is consistent with the fact that type 2 diabetes is mainly a disease of the adult and elderly population. The pediatric type 2 diabetes population is not represented in these studies.

Table 45: Most Frequent Treatment-Emergent Adverse Events: Incidence by Age- Type 2 Diabetes

Adverse Event	Treatment Group	18-64 Years*	≥65 years**
Nausea	**Pramlintide**	**235 (25%)**	**73 (22%)**
	Placebo	48 (15%)	9 (10%)
Anorexia	**Pramlintide**	**71 (8%)**	**27 (8%)**
	Placebo	10 (3%)	3 (3%)
Headache	**Pramlintide**	**130 (14%)**	**24 (7%)**
	Placebo	30 (9%)	7 (7%)
Fatigue	**Pramlintide**	**60 (6%)**	**23 (7%)**
	Placebo	12 (4%)	5 (5%)
Dyspepsia	**Pramlintide**	**53 (6%)**	**23 (7%)**
	Placebo	9 (3%)	3 (3%)

*The 18-64 year group includes: 941 patients for pramlintide and 326 patients for placebo.
** The ≥ 65 year group includes 331 patients for pramlintide and 94 patients for placebo.

Analysis of the most frequent treatment-emergent adverse events in relationship to age does not identify any obvious age-related susceptibility for type 2 diabetes patients. This is true for any adverse events with an incidence ≥ 5%.

A few observations can be made though: headaches are twice more common in the 18-64 year group. Not in the above table is the information that dizziness and back pain are more frequent in the ≥ 65 year group compared to the 18-64 year group (8% vs 5% for dizziness and 95 vs 7% for back pain).

Sex:

There is an equal distribution of males and females across the entire study population in both type 1 and type 2 diabetes long-term controlled studies. Table 46 displays the incidence by sex for the five most frequent treatment-adverse events in **type 1 diabetes**.

Table 46: Most Frequent Treatment-emergent Adverse Events: Incidence by Sex- Type 1 Diabetes

Adverse Event	Pramlintide		Placebo	
	Male (n=596)	Female (n=583)	Male (n=290)	Female (n=248)
Nausea	273 (46%)	328 (56%)	35 (12%)	57 (23%)
Anorexia	105 (18%)	104 (18%)	3 (1%)	9 (4%)
Hypoglycemia	158 (27%)	165 (28%)	47 (16%)	54 (22%)
Vomiting	69 (12%)	85 (15%)	15 (5%)	21 (8%)
Fatigue	35 (6%)	45 (8%)	8 (3%)	14 (6%)

Analysis of treatment-emergent adverse events in relationship with sex does not identify any obvious sex-related susceptibility for type 1 diabetes patients. These observations cover any adverse events with an incidence ≥ 5%.

A few adverse events (headaches, dizziness, and diarrhea) are more frequent in the female group but they mimic the same distribution in the placebo group.
Similar observations can be extended to the type 2 diabetes studies, as shown in table 47, below:

Table 47: Most Frequent Treatment-Emergent Adverse Events: Incidence by Sex- Type 2 Diabetes

Adverse Event	Pramlintide		Placebo	
	Male (n=656)	Female (n=617)	Male (n=223)	Female (n=197)
Nausea	124 (19%)	184 (30%)	22 (10%)	35 (18%)
Anorexia	47 (7%)	51 (8%)	5 (2%)	8 (4%)
Headache	49 (7%)	105 (17%)	17 (8%)	20 (10%)
Fatigue	42 (6%)	41 (7%)	5 (2%)	12 (6%)
Dyspepsia	36 (5%)	40 (6%)	6 (3%)	6 (3%)

Most treatment-emergent adverse events occur with similar incidence between sex groups. Women appear to be 1.6 times more susceptible to nausea in the pramlintide group (30% vs 19%), a ratio similar to the one noted in the placebo group (1.8). Pramlintide treated female patients are 2.5 more susceptible to headaches than men (female-to-male placebo incidence ratio is 1.25 times only in the placebo group).

Race:

The relatively small number of subjects in the African-American and Hispanic groups limits the analysis of adverse events incidence by race. Table 48 illustrates the five most frequent adverse events in type 1 diabetes and their distribution by racial group.

Table 48: Most Frequent Treatment-Emergent Adverse Events: Incidence by Race- Type 1 Diabetes*

Adverse Event	Pramlintide			Placebo		
	White (n=1119)	Black (n=21)	Hispanic (n=32)	White (n=503)	Black (n=12)	Hispanic (n=17)
Nausea	568 (51%)	9 (43%)	21 (66%)	83 (17%)	1 (8%)	7 (41%)
Anorexia	199 (18%)	4 (19%)	3 (9%)	12 (2%)	0 (0%)	0 (0%)
Hypoglycemia	309 (28%)	7 (33%)	5 (16%)	95 (19%)	0 (0%)	4 (24%)
Vomiting	145 (13%)	1 (5%)	7 (22%)	31 (6%)	0 (0%)	4 (24%)
Fatigue	77 (7%)	2 (10%)	1 (3%)	21 (4%)	0 (0%)	1 (6%)

*Non-white, non-black, non-Hispanic categories not included due to the extremely low number of subjects in this category.

Analysis of the most frequent treatment-emergent adverse events in relationship to race does not identify a particular race susceptibility for type 1 diabetes patients. Although only the top five adverse events are presented in the table, this observation coverso any adverse events with an incidence ≥ 5%. Further observations are limited by the small number of subjects in the black and Hispanic group.

The race distribution of subjects during the **type 2 diabetes** trials is different than noted in the type 1 diabetes trials. A larger number of subjects are in the non-caucasian race groups. Table 49 summarizes the most frequent adverse events by race in the type 2 long-term diabetes trials.

Table 49: Most Frequent Treatment-Emergent Adverse Events: Incidence by Race- Type 2 Diabetes*

Adverse Event	Pramlintide			Placebo		
	White (n=1058)	Black (n=110)	Hispanic (n=86)	White (n=347)	Black (n=32)	Hispanic (n=34)
Nausea	266 (25%)	21 (19%)	19 (22%)	48 (14%)	5 (16%)	3 (9%)
Anorexia	90 (9%)	7 (6%)	0 (0%)	10 (3%)	1 (3%)	2 (6%)
Headache	117 (11%)	17 (15%)	17 (20%)	26 (7%)	4 (13%)	7 (21%)
Fatigue	70 (7%)	6 (5%)	6 (7%)	14 (4%)	1 (3%)	2 (6%)
Dyspepsia	65 (6%)	8 (7%)	3 (3%)	9 (3%)	2 (6%)	1 (3%)

*Non-white, non-black, non-Hispanic category is not included due to the low number of subjects in this category.

Minimal variations in the incidence of gastrointestinal adverse events can be noted but there is no consistent pattern. Although only the top five adverse events are presented in table 49, this observation covers any adverse events with an incidence ≥ 5%.

Conclusions:

- **Pramlintide therapy does not appear to be associated with any distinct age, sex, or race specific susceptibility.**
- **The validity of this observation is limited by the poor representation of certain subgroups of patients (e.g. pediatric and elderly patients), and racial groups (particularly African-Americans, Hispanics, and non-white, non-black, non-Hispanics).**
- **There is no pramlintide PK/PD information for any age, sex, or age population subgroups.**

D) Adequacy of safety testing:

Patient exposure to pramlintide during the long-controlled studies appears large enough to predict common TEAEs, clinical laboratory, ECG, and vital signs changes.
The following shortcomings and limitations are identified:

- Faced with of a high incidence of adverse events during the first month of treatment the sponsor is proposing lower **pramlintide initiation doses** and concomitant insulin titration (Advisory Committee Meeting, July 26, 2001). This approach however has not been tested or proven safe in any clinical trial and has not been shown to be associated with preservation of drug efficacy in either type1 or type 2 diabetes patients.
- The data collection has been inadequate for the evaluation of **retinopathy**. The absence of baseline fundoscopic photographs does not allow an accurate interpretation of the finding of dose-related increased retinopathy observed in one of the type 2 diabetes trial.
- The pharmacological studies investigating **hypoglycemia unawareness** provide inconsistent results and fail to convince that patients on pramlintide are not at risk for this complication.
- The information concerning **concomitant use of pramlintide and other medications** is limited. An important part of this database is presented in a format that limits the ability to interpret the data (the information derived from the controlled and the uncontrolled studies is mixed, thus making pramlintide-to-placebo comparisons difficult to interpret).
- The patients enrolled in the pramlintide clinical trials are relatively stable patients with type 1 and type 2 diabetes. How the body of safety data accumulated during phase 3 trials applies to **patients excluded** from the trials is not known (e.g. among the patients excluded are those suffering from cardiac disease, hypertension, hepatic or renal disease, seizures, eating disorders gastric autonomic neuropathy). No data is available about pediatric patients.
- The sponsor enrolled patients with relatively high Hg A1c levels. Therefore the safety data generated in the clinical trials (in particular the risk of hypoglycemia) cannot be predicted for patients with lower Hb A1c levels who have an intrinsically higher hypoglycemia risk.
- Most importantly, the sponsor failed to prospectively study **motor vehicle accidents** and **trauma** although this has been one of the major safety issues anticipated and investigated in major trials such the Diabetes Control and Complication Trial. In addition, the misclassification of some MVAs associated with hypoglycemia under the hypoglycemia preferred term lead to an underestimation of these events.

E) Summary of critical safety findings as they relate to labeling:

Type 1 diabetes

The following **safety signals** are associated with pramlintide use in type 1 diabetes and should be included in the label if the drug were to be approved:

- **Adverse events overall**: a three fold increase in patient withdrawal due to adverse events.
- **Nausea**: high incidence (50 % and three fold higher than placebo), high recurrence rate, major cause of early subject withdrawal (twelve times over placebo), dose-response relationship.
- **Anorexia**: nine time increase over placebo treatment.
- Increased incidence of other **GI adverse events** (vomiting, abdominal pain,etc.)
- **SAEs**: higher than placebo (14 % vs 10% incidence).
- **Syncope, inflicted injury**, and **CNS-related SAEs** (such as **coma** and **seizures**): small increase over placebo treatment.
- A two fold increase in **severe hypoglycemia** during the first month of treatment.
- A two fold increase in **hypoglycemia**-related SAEs overall.
- A 4-8 fold increased risk of **driving-related events** associated with **hypoglycemia** (including a possible MVA-related death) and a four fold increased risk of **non-MVA injuries** associated with **hypoglycemia.**
- Possibility of **hypoglycemia** unawareness.
- A tendency toward a **lower diastolic blood pressure** at the end of the first month of treatment which subsequently resolves.

Type 2 diabetes

The following **safety signals** are associated with pramlintide use in type 2 diabetes and should be included in the label if the drug were to be approved:

- **Adverse events overall**: increase in patient withdrawal due to adverse events (95 vs 7%).
- **Nausea**: high incidence (12 % and two fold higher than placebo), high recurrence rate; abates toward the end of the first year of treatment; important cause of early subject withdrawal (1.5 times over placebo), dose-response relationship.
- **Anorexia**: a two fold increase over placebo treatment.
- Increased incidence of other **GI adverse events** (vomiting, abdominal pain,etc.).
- A possible dose-related increase in **retinopathy.**
- A two fold increase in **hypoglycemia**-related SAEs overall.
- Most importantly, a four fold increase in severe **hypoglycemia** during the first month of treatment.
- A small increase in **CNS-related TEAEs.**

F) 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 50 illustrates the results of the insulin-induced hypoglycemic challenge in study AP93-02:

Table 50: Distribution of Subjects With Subjective Symptoms of Hypoglycemia During Hypoglycemic Challenge (AP93-02 Study)

	Pramlintide Peak			Pramlintide trough			Placebo		
	Subjects	Aware	%	Subjects	Aware	%	Subjects	Aware	%
Baseline	12	7	58	12	7	58	8	6	75
End of trial	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 51:

Table 51: Distribution of Subjects With Subjective Symptoms of Hypoglycemia During Hypoglycemic Challenge (AP93-03 Study)

	Pramlintide Peak			Pramlintide trough			Placebo		
	Subjects	Aware	%	Subjects	Aware	%	Subjects	Aware	%
Baseline	20	19	95	12	9	75	12	10	83
End of trial	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 52).

Table 52: Patient Rating of Hypoglycemic Symptoms (AP93-08 Study)

	Pramlintide			Placebo
Dose	300 µg	100 µg	30 µg	
Baseline Score	1.4±0.5	1.2±0.3	1.1±0.3	1.4±0.4
End of Trial Score	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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/s/

Dragos Roman
9/6/01 04:53:39 PM
MEDICAL OFFICER

Saul Malozowski
9/7/01 02:20:46 PM
MEDICAL OFFICER

David Orloff
9/27/01 07:46:55 PM
MEDICAL OFFICER
Noted. See DD memo for final recommendations.

Efficacy

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	21-332	APPLICATION TYPE:	NDA Review
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:	8/30/01

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
12/07/00	12/08/00	Original NDA	
7/26/01		Briefing document	For Advisory committee

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: NON-APPROVAL

Special care should be taken to make sure that patients on pramlintide do not injure themselves or others in motor vehicle accidents. The Sponsor should agree to these precautions before enrolling new patients. Otherwise, the IND should be placed on clinical hold.

Signed: **Medical Reviewer: Robert I Misbin MD** ____ **Date: August 30, 2001**

Medical Team Leader: Saul Malozowski MD **Date: September 7, 2001**

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 (about 0.3% units) 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. In one 12-month study in type 2 diabetes, there was a dose-dependent increase in reporting of diabetic retinopathy in patients treated with pramlintide.

The NDA should not be approved.

B. Additional Studies:

The Sponsor should perform trials 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. These should 12-month placebo-controlled trials in which patients are instructed to titrate their insulin doses in order to optimize glycemic control. Reduction in HbA1c without an increase in hypoglycemia should be criteria for a successful trial. Retinal photography should be done at baseline and endpoint.

Review of the results from clinical pharmacology studies raises concern about the possibility that a five-day exposure to pramlintide could cause hypoglycemia unawareness. The studies were small and the differences were not statistically significant. In addition, no evidence of hypoglycemia unawareness was found in the 14-day study. Still, the possible danger of hypoglycemia unawareness is sufficiently important that this issue should be answered definitively, particularly in view of the large number of motor vehicle and other accidents in patients on pramlintide. Prior to undertaking the 12-month trials described above, the Sponsor should investigate the possibility that pramlintide causes hypoglycemia unawareness in study with adequate power.

Prior to initiating a pivotal study in patients with type 2 diabetes, the Sponsor needs to determine why the bioavailablity of pramlintide is so much lower in patients with type 2 diabetes than in normal controls or in patients with type 1 diabetes. This information is needed to provide a rationale for dose selection in a pivotal trial.

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 Sponsor was urged to do an insulin-titration study and to use hypoglycemia as a primary outcomes variable**. 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."

In a meeting that took place at FDA on December 8, 1998

" The Agency expressed skepticism that the application would be approvable even if the current ongoing studies turn out to be positive.'

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 and motor vehicle accidents. There were three deaths that I believe may have been related to use of pramlintide. 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. In one 12-month study in type 2 diabetes, there was a dose-dependent increase in reporting of diabetic retinopathy in patients treated with pramlintide.

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. Additional sites should be inspected after the Sponsor has been given adequate opportunity to correct any deficiencies.

D. Dosing:

The clinical trials do not provide enough information to determine the dose-response relationships of pramlintide. In type 1diabetes, 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. According to the PK review, the bioavailablity of pramlintide in patients with type 2 diabetes is lower than 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 as recommended by the American Diabetes Association (ADA).

E. Special Populations:

Not applicable

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 pertinent 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. The bioavailablity 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. This issue needs to be resolved in a PK study.

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 patients 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. The results of these inspections raise doubts about the reliability of the safety database. Of a total of 44 patient records examined, there was one episode of severe hypoglycemia and one motor vehicle accident that had not been entered into the database. Additional sites should be inspected after the Sponsor has been given adequate opportunity to correct any deficiencies.

C. Ethical and patient care 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.

C. Debarment and financial disclosure

Amylin has certified that it did not and will not use an any capacity the services of any person debarred under section 306 of the Federal Food , Drug and Cosmetic act.

The following financial disclosure information has been submitted:

1 Form OMB No. 0910-0396. The applicant certifies that it has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study.
2 The applicant further certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in Amylin Pharmaceuticals.and/or stock options exceeding $50,000
3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment from Amylin Pharmaceuticals with monetary value in excess of $25,000
4 List of investigators from whom completed financial disclosure forms were received.
5 Certification pursuant to 21 CFR 54.5(c) that the applicant acted with due diligence to obtain financial disclosure information from a list of investigators from whom completed forms were never received.
6 List of investigators not submitting financial disclosure information and the studies to which they contributed data.

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 and efficacy of pramlintide in patients whose HbA1c is 8% or less.

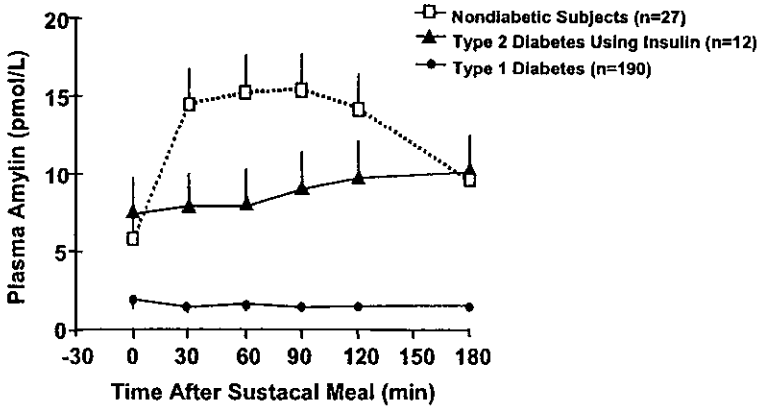
Weight loss was a consistent feature of pramlintide treatment. Whereas patients on insulin alone tended to gain weight, patients on pramlintide generally lost weight. The mean weight loss in pramlintide-treated patients was about 1-2 kg in 26 weeks.

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. There were three deaths that I believe may have been related to the use of pramlintide. 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.

Preliminary studies:

Plasma amylin levels are low in patients with type 1 diabetes. Basal levels are generally normal in insulin-treated patients with type 2 diabetes, but these patients do not show the rapid rise of plasma amylin level to about 15 pM normally seen after food ingestion. (see figure below)

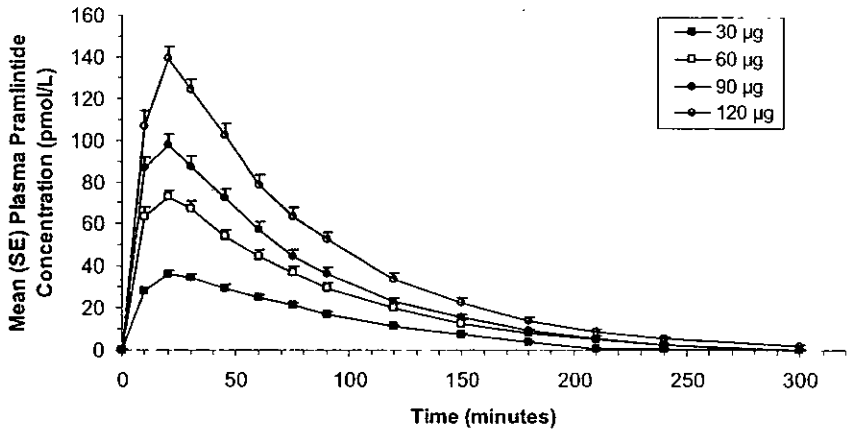
Post-Meal Plasma Amylin Concentrations in Nondiabetic and Diabetic Subjects



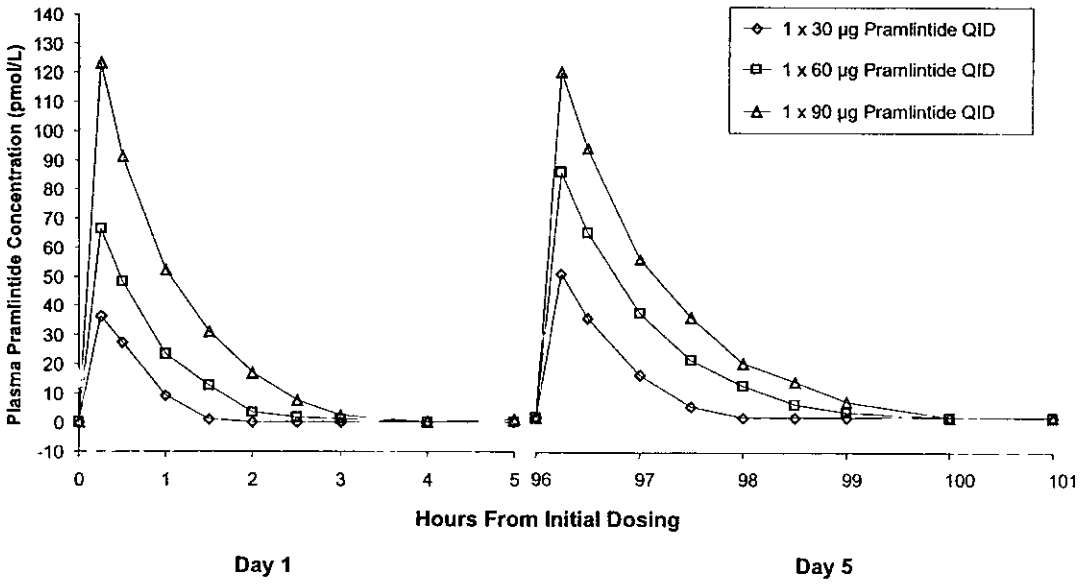
From Reference 17 and Amylin Pharmaceuticals, Inc. data on file

A dose of 30 ug of pramlintide sc in normal subjects and patients with type 1 diabetes results in plasma pramlintide levels similar to or greater than the amylin levels normally seen after eating. In patients with type 2 diabetes, a dose of 60 ug is required to give approximately the same result (see figures below).

Plasma Pramlintide Concentrations Increase in Proportion to Dose in Healthy Subjects (Study 137-126)

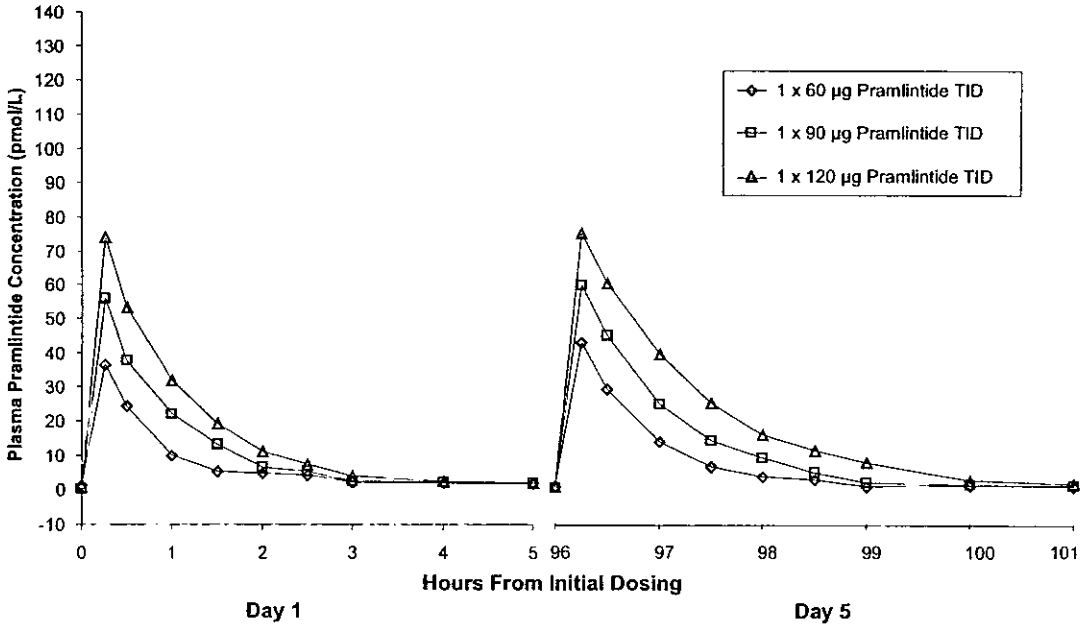


Pramlintide concentrations in patients with type 1 diabetes



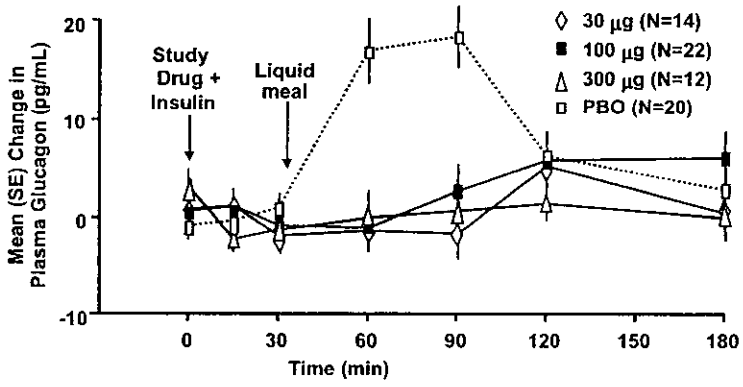
In patients with type 2 diabetes, a dose of 60 ug is required to give approximately the same result.

Plasma Pramlintide Concentrations in Patients With Type 2 Diabetes Who Use Insulin (Study 137-144)

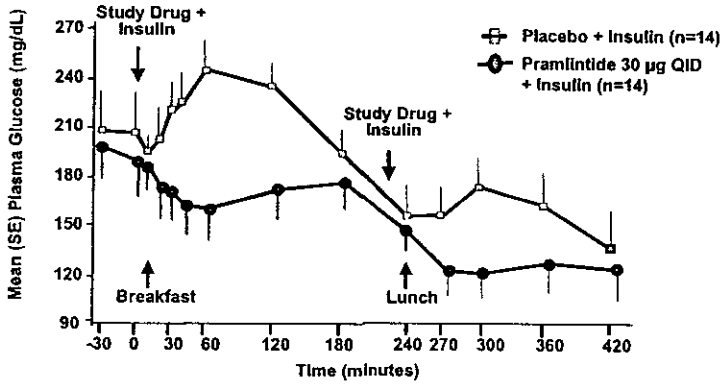


Pramlintide administrations blocks post-prandial glucagon secretion (see figure below) and also delays gastric emptying

Pramlintide Decreases Post-Meal Plasma Glucagon (Study AP93-08: Patients With Type 1 Diabetes)



As shown in the figure below, these effects appear to result in the reversal of postprandial glucose spike that normally occurs after eating.



Postprandial glucose spikes are exaggerated in patients with diabetes and contribute to elevated levels of HbA1c in patients with poorly controlled diabetes. Pramlintide treatment would be expected to lead to a decrease in postprandial hyperglycemia and hence, HbA1c levels. **But the results in the figure shown above would suggest that there is also the potential danger of postprandial hypoglycemia**. In general, patients expect their blood glucose levels to rise after eating. From the graph shown above, it is clear that pramlintide given with insulin may result in a fall in glucose levels after eating. Thus, if the preprandial glucose level is nearly normal, one would expect that hypoglycemia may develop.

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 the 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(3 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

Volume 157, table 9

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 glycemic responders" to be patients whose HbA1c dropped by at least 0.5% units at four weeks. The overall efficacy in "Early Glycemic 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_{1c}	9.78	9.27	9.25	9.14
HbA_{1c} 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_{1c} 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 HbA1c 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 HbA1c. The mean reduction of HbA1c 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 HbA1c 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 HbA1c 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 [ ] 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.

Overall Efficacy in "Early Glycemic Responder" Subgroup – Observed Cases (Type 1 Diabetes Study 137-121)

	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_{1c}	9.39	9.22	8.93	9.11
HbA_{1c} 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_{1c} 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

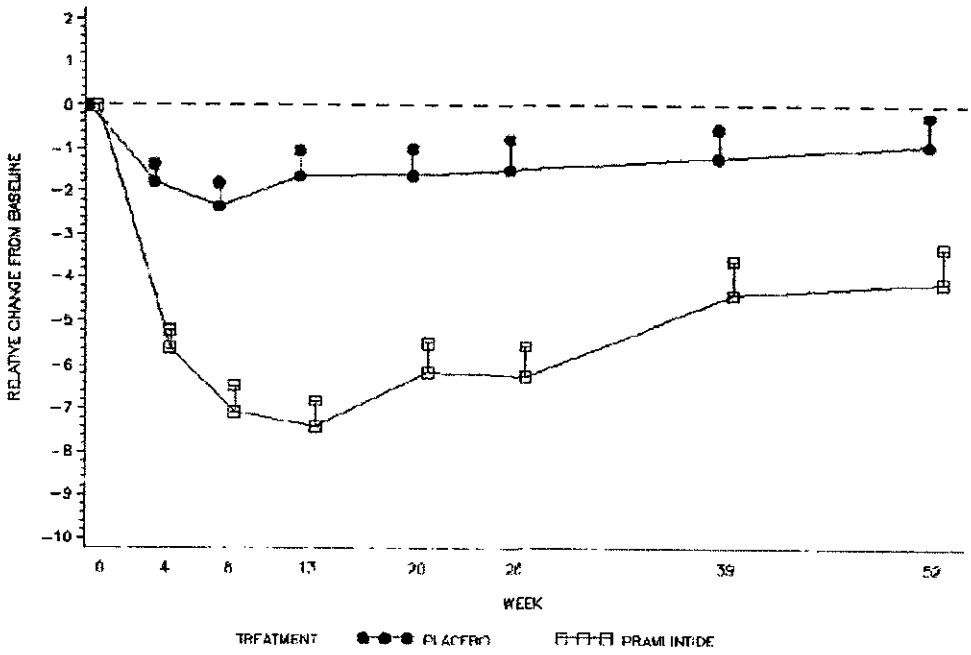
This study was conducted from September 7 1995 through December 27, 1997.

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



[1] Relative Change = {[HbA_{1c} (post-baseline) - HbA_{1c} (baseline)] / HbA_{1c} (baseline)}*100

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

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.

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 a single placebo 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".

1: Overall Efficacy in "Early Glycemic Responder" Subgroup – Observed Cases (Type 1 Diabetes Study 137-112)

	Placebo (N=56)	Pram 30/60 µg QID (N=105)
% of ITT	24%	44%
Baseline Mean HbA_{1c}	9.72	9.22
BA_{1c} 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_{1c} 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.

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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 [redacted] 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).

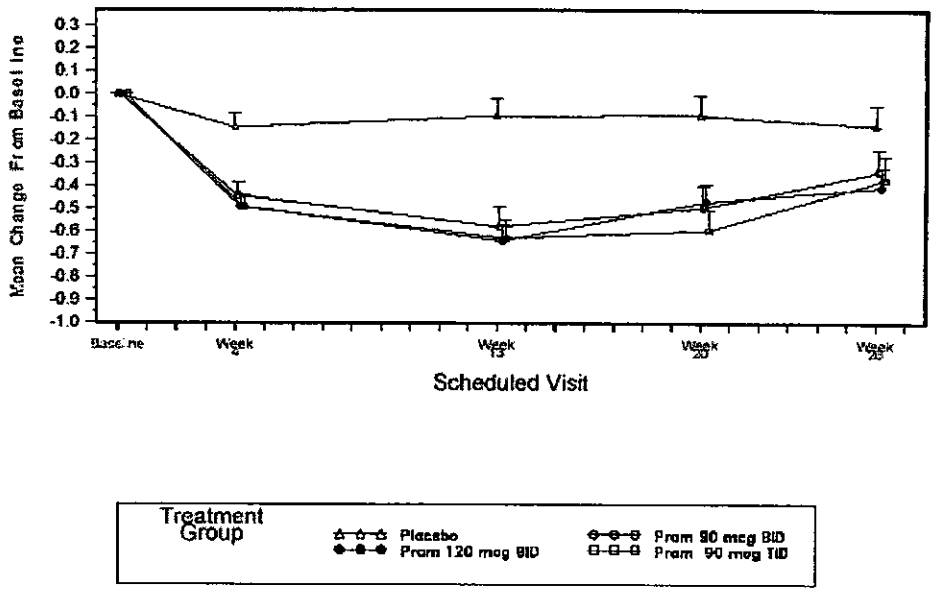
Mean lipids in molar units were

- 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 poplulation, 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 4 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, there were no statistically significant lipid changes either between pramlintide and placebo or between baseline and endpoint.

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 only.

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 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.

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 Sponsor was urged to do an insulin-titration study and to use hypoglycemia as a primary outcomes variable. 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"

In a meeting that took place at FDA December 8, 1998

" The Agency expressed skepticism that they application would be approvable even if the current ongoing studies turn out to be positive.'

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).

Overall Efficacy in "Early Glycemic Responder" Subgroup - Observed Cases (Type 1 Diabetes Studies 137-121, 137-112, and 137-117 Combined)			
	All Placebo Combined (N=123)	All Pram Combined (N=480)	
% of ITT	24%	44%	
Baseline HbA_{1c}	9.65	9.16	
HbA_{1c} 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_{1c} 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.

3. Relationship between HbA1c reduction and Weight reduction

Background and regulatory issues:

Treatment of poorly controlled diabetes with insulin is almost invariably associated with weight gain. Calories are stored as fat that would have been lost as glycosuria in the untreated state. Treatment of type 2 diabetes with insulin, insulin secretagogues and insulin sensitizers (thiazolidinediones) are generally associated with weight gain also. This is generally considered undesirable because patients with type 2 diabetes are often obese and obesity itself is associated with insulin resistance.

Voluntary weight reduction is usually associated with improvement in hyperglycemia, especially in patients with type 2 diabetes. This has been reported with the antiobesity drugs Orlistat (Diabetes Care 21, August 1998) and dexfenfluramine (Diabetes Care 22 900, 1999), and with gastric bypass surgery (Diabetes Care 22, 651, 1999). As a whole, the patients in these studies were much more obese than in the pramlintide trials, and had HbA1c levels that were not nearly as high. For example, with Orlistat, the baseline weight was 99 kg, and BMI 34. After 52 weeks placebo subtracted weight loss was 1.9 kg (6.2 vs. 4.3). Mean HbA1c at baseline was 8%. The placebo-subtracted reduction in HbA1c was 0.46 (-0.28 vs. +0.18).

From data on the use of behavioral modification shown below, it can be seen that the act of losing weight is a more important determinant of HbA1c than reducing the level of obesity itself. A ten-kilogram weight loss at 20 weeks was associated with a drop in HbA1c of nearly 2 % units. About 2/3 of the weight loss was retained after a one year, but gaining back just a few kilograms resulted in HbA1c returning to a value that was even higher than baseline.

	Weight, kg	BMI	HbA1c
Baseline	104.5	37.8	10.4
20 weeks, behavioral therapy	94.4	34.2	8.6
1 year follow-up	97.7	35.4	11.8

From Wing et al. Arch Int Med 151, 1334, 1991

With dexfenfluramine, the maximum placebo-subtracted reduction in weight and HbA1c occurred at four months. Although the effects of the drug on weight and HbA1c reduction waned over time, the weight reduction was more persistent than the reduction in HbA1c.

Before considering the relationship between weight loss and reduction in HbA1c for pramlintide, it is important to bear in mind that a precedent would be set if FDA approved a new drug to treat type 2 diabetes whose mechanism of action was reduction in body fat. This issue was discussed at the Endocrine and Metabolic Drugs Advisory Committee meeting March 12, 1998.

The FDA has required longer placebo-controlled trials for approval of drugs to treat obesity than for drugs to treat type 2 diabetes. Two years of placebo-comparison were included in the Orlistat label, 12 months in the Sibutramine label. Most drugs to treat type 2 diabetes have been approved with six months of placebo comparison. With Pioglitazone, the duration of placebo comparison was 16 weeks. While not wishing to oversimplify, the higher standard for antiobesity drugs reflects the recognition that these drugs must be very safe because they are often used (some one say **ab**used) under conditions where the need for treatment is not compelling. The unhappy experience with Redux/fen-phen illustrates this point (see Dispensing With the Truth by Alicia Mundy, St Martin's Press 2001). The need to show superiority to placebo after 12 months discourages development of drugs designed to be a quick fix.

During the public session of the FDA Advisory Committee Meeting that considered the Pramlintide NDA on July 26, 2001, Dr John Pullman had positive comments about the ability of pramlintide to encourage weight loss. From page 197 of the transcript, he stated " Weight loss, which can be trivialized to five or ten percent, can mean a lot when you weigh 180 pounds and you go down to 162. People would kill for those things." Regrettably this sentiment rings remarkably true when one considers that the risk of primary pulmonary hypertension from Redux was known at the time of FDA approval. It should also be noted that the average weight loss in patients on pramlintide was only about 2%.

Approval of a drug to treat diabetes whose mechanism of action was weight loss through anorexia would set a dangerous precedent and encourage drugs aimed at obese patients to be masqueraded as drugs to treat patients with diabetes. This is not to say, however, that drugs already approved for weight reduction should not be used in obese patients with diabetes. Weight loss can generally be expected to improve hyperglycemia in obese patients with type 2 diabetes. The distinction that needs to be made is that the standard of approval for antiobesity agents should not be relaxed because these drugs may be useful in diabetes.

My caveat about safety does not necessarily apply to pramlintide. 1350 patients have been exposed to pramlintide for 52 weeks or longer, 261 patients for 104 weeks or longer. No major toxicity has been identified. The danger of hypoglycemia due to pramlintide pertains to patients treated with insulin. This danger would not be present in patients with simple obesity. Given that pramlintide must be given by injection, it is less likely to be abused than a drug that is given orally. Nevertheless, it is important to try to determine if pramlintide's primary antidiabetic activity is related to anorexia and weight loss.

Relationship between Weight Loss and Reduction in HbA1c in Pramlintide Trials:

Because so many patients on pramlintide complain of nausea, the possibility was considered that the pramlintide's primary antidiabetic action is to cause nausea and anorexia leading to decreased caloric intake and weight reduction. The Sponsor did joint outcome analysis for HbA1c and body weight in which "drug effect" was defined as follows:

HbA1c category	Weight decrease 1 kg or more	Weight change within 1 kg	Weight increase 1 kg or more
Increase 0.3 units or more	Intermediate	No	No
Change within 0.3 % units	Drug Effect	Intermediate	No
Decrease 0.3% units or more	Drug Effect	Drug Effect	Intermediate

This classification is based on an arbitrary definition of therapeutic response. In my judgment, reductions in HbA1c of 0.3% units or weight loss of 1 kg should be considered minimal thresholds for a clinically meaningful response.

Pooled data for mean reductions in HbA1c and body weight in the patients who had a "drug effect" are shown in the table below:

Joint Outcome Analysis at 26 weeks

	Type 2	Type 1
Placebo: % drug effect	34%	29%
HbA1c, change	-0.78	-0.64
Weight, kg	-1.59	-1.47
HbA1c change/kg	0.49	0.44
Pramlintide: all regimens % drug effect	58%	54%
HbA1c,change	-0.97	-0.72
Weight, kg	-2.46	-2.35
HbA1c change/kg	0.39	0.31

The effectiveness of pramlintide in this joint outcome analysis is demonstrated by the finding that there were more patients with "drug effect' in the pramlintide group (58% for type 2 diabetes and 54% for type 1) than in the placebo group (34% for type 2 diabetes and 29% for type 1 diabetes). Otherwise, the relationship between weight loss and reduction in HbA1c (reduction in Hb1c per kilogram lost) are similar between pramlintide and placebo and between type 2 and type 1 diabetes. The patients with "drug effect" in the placebo group presumably were more adherent to recommendations for diet and exercise. For patients with type 2 diabetes on placebo, the mean HbA1c reduction was 0.49 units for each kg of body weight they lost. For patients in the pramlintide group, the mean reduction in HbA1c was 0.39 units for each kg of body weight they lost. Thus, the antidiabetic activity of pramlintide in these patients is completely accounted for by pramlintide's weight-reducing activity. For patients with type 1 diabetes on placebo, the mean HbA1c reduction was 0.44 units for each kg of body weight they lost. For patients in the pramlintide group, the mean reduction in HbA1c was 0.31 units for each kg of body weight they lost. Again, the antidiabetic activity of pramlintide in these patients is completely accounted for by pramlintide's weight-reducing activity.

My previous comments pertain only to patients classified by the Sponsor as having a " drug effect" (both weight loss and reduction in HbA1c) in the joint outcome analysis shown above. Using the entire patient population, FDA statistician, Dr David Hoberman found no relationship between changes in weight and hemoglobin A1c. Dr Hoberman defined two strata: 1) subject who lost weight and 2) subjects who gained weight or whose weight remained the same. As illustrated by the following table, mean HbA1c change in pramlintide-treated patients was not different between patients who lost weight and patients who gained weight.

Type 1 diabetes	Trial 112		Trial 117		Trial 121	
	Loss	Gain	Loss	Gain	Loss	Gain
Change in HbA1c	-0.31	-0.50	-0.13	-0.15	-0.18	-0.57

Type 2 diabetes	Trial 111		Trial 122		Trial 123	
	Loss	Gain	Loss	Gain	Loss	Gain
	-0.70	-0.94	- 0.61	-0.77	-0.44	-0.23

This analysis does not take into account the magnitude of the weight change or the reproducibility of the measurement. The average weight loss among all pramlintide-treated patients was only about 1 kg. This is probably very close to the error in reproducibility of the measurement. An analysis that would not be influenced by a single spurious value would be to plot weight as a function of time and correlate the slope of the plot, expressed as kg/year, with change in HbA1c (since HbA1c is a very reproducible measurement no procedure to account for spurious value is required). But an additional problem is that changes in insulin dose affect HbA1c and body weight. An increase in insulin dose would be expected to cause a rise in body weight and reduction in HbA1c. A decrease in insulin dose would normally result in loss of body weights (due to glycosuria) and rise in HbA1c. Given the complexity of the relationship between change in weight and change in HbA1c in these trials, I doubt that any analysis we could do would yield a definitive result.

Effects of nausea on changes in body weight and changes in HbA1c

The Sponsor submitted a subgroup analysis which suggested that there was little if any relationship between nausea, and change in HbA1c or change in weight. This is shown in the next several tables. Many more patients reported nausea/vomiting on pramlintide than on placebo, but reporting of nausea/vomiting did not seem to have much influence on changes in HbA1c.

HbA1c Type 1 diabetes at 26 weeks ITT patients table 24 ISE

	Placebo	All Pramlintide
With Nausea/vomiting		
N=	102	452
LS Mean HbA1c diff	-0.14	-0.34
Mean diff		-0.20
Without N/V		
N=	393	437
LS Mean HbA1c diff	-0.11	-0.25
Mean diff		-0.14

HbA1c Type 2 diabetes at 26 weeks ITT patients table 57 ISE

	Placebo	All Pramlintide
With Nausea/vomiting		
N=	57	270
LS Mean HbA1c diff	-0.34	-0.55
Mean diff		-0.20
Without N/V		
N=	339	769
LS Mean HbA1c diff	-0.23	-0.57
Mean diff		-0.34

Data for the Evaluable population taken directly from the submission of May 2001 are found in the next two tables for type 1 and type 2 diabetes respectively.

For patients with type 1 diabetes, the mean change in body weight at 26 weeks was – 1.10 kg on pramlintide (all groups) compared to 0.61 on placebo. The placebo-subtracted change attributable to pramlintide was –1.69 kg. However, patients who reported nausea/vomiting had approximately the same change in weight (1.86 kg) as those who did not (1.51 kg).

Body weight in Type 1 diabetes at 26 weeks evaluable patients table 28 ISE

	Placebo	All Pramlintide
With Nausea/vomiting		
N=	80	328
Weight change, kg	0.56	-1.39
Mean diff		-1.86 (-2.53,-1.19)
Without N/V		
N=	311	340
Weight, change kg	0.62	-0.82
Mean diff		-1.51 (-2.00, -1.03)

Nausea/vomiting appears to have some influence on weight change in patients with type 2 diabetes, particularly those on placebo, but there is little evidence that reporting of nausea/vomiting contributed much to weight change in patients on pramlintide.

Body weight Type 2 diabetes at 26 weeks evaluable patients table 59 ISE

	Placebo	All Pramlintide
With Nausea/vomiting		
N=	44	209
Weight change, kg	-0.09	-1.29
Mean diff		-1.13 (-2.16, -0.10)
Without Nausea/Vomiting		
N=	258	622
Weight, change kg	0.49	-0.97
Mean diff		-1.47 (-1.90, -1.03)

In summary, weight loss and reduction in HbA1c in pramlintide-treated patients do not seem to be strongly associated with reporting of nausea. But a major flaw in this analysis is that patients were dicotomized (with nausea or without nausea) without regard for when the nausea occurred or its severity. Drug-related nausea at the beginning of the trial would be expected to cause weight loss and reduction in HbA1c if the severity of the nausea were sufficient to cause anorexia. On the other hand, mild nausea occurring toward the end of the study would have little effect on change in body weight or HbA1c.

VII Integrated review of Safety

The integrated review of safety was done by Dr Dragos Roman. His complete review is in a companion document. I have listed what I believe to be the most important points raised by Dr Roman and have included additional comments about retinopathy.

Hypoglycemia

Motor vehicle accidents and other types of trauma associated with hypoglycemia were major causes of morbidity in patients with type 1 diabetes, and occurred at least four times more frequently in patients on pramlintide than in patients on insulin alone. Approximately 1/3 of these events occurred during the first month of pramlintide treatment. 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

Central Nervous System Adverse events:

According to Dr Roman's review, CNS-related adverse events occurred predominantly in pramlintide-treated patients. He points out that 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 were reported more frequently in the pramlintide group among serious adverse events, albeit in low numbers. Coma and seizures in pramlintide-treated patients were due to hypoglycemia, but there were no episodes of coma or seizures in patients on insulin only. That pramlintide does not interfere with the normal recognition of hypoglycemia has not been excluded either. Elsewhere he has noted that "Somnolence is the top non-GI and non-nutritional single symptom cause of subject withdrawal."

When viewed in light of the motor vehicle-related events and accidents in patients on pramlintide, these CNS findings suggest the possibility that pramlintide may directly interfere with a person's normal ability to avoid danger, in addition to increasing the risk of hypoglycemia.

Patients deaths

There was no difference between pramlintide and placebo with respect to the total number of deaths. But Dr Roman listed three deaths in pramlintide-treated patients as deserving special mention. It is not possible, in any of these cases, to be confident in attributing the death to pramlintide. But these cases must be evaluated in light of our knowledge about the adverse event profile of pramlintide: 1) Pramlintide increases the risk of severe hypoglycemia, particularly during the first month of treatment;

2) Pramlintide increases the risk of being involved in a motor vehicle accident;
3) Pramlintide is associated with a high incidence of nausea, vomiting, and anorexia.
It is also worth noting that in the DCCT trial, there were no deaths, myocardial infarctions or strokes directly attributable to hypoglycemia (although two patients died in MVA's). My own view is that it is more likely than not that each of these three deaths was related to pramlintide treatment. Particularly distressing is that all three patients were reasonably young.

A 48-year-old male with a 12-year history of type 1 diabetes had a witnessed, early morning seizure during sleep, followed by cardiac arrest. Resuscitation attempts were unsuccessful. The patient had been taking 30 ug pramlintide qid, and typically took a dose with his evening meal at about 11:00 pm.

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. There was food in is stomach indicating that he had recently eaten lunch, but that the food had not been absorbed (see fig on p 13)

A 31 year old man with a four year history of type 1 diabetes and no other medical problems died on day 165 of pramlintide treatment. The exact circumstances surrounding his death are unclear. It appears that he experienced nausea, vomiting, and loss of appetite and died a day or so later.

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 borne in mind that the greater reporting of diabetic retinopathy occurred in only one trial. I might dismiss this observation entirely were it not for the fact that the finding occurred in the high dose arm of a 52 week trial, and that this was the highest dose used in any of the phase three trials.* Even more important is that fundic photography was not done routinely in any of the trials. Thus, increased reporting of diabetic retinopathy as a dose-dependent adverse event must be taken seriously, as a possible signal of progression of diabetic retinopathy in pramlintide-treated patients

*(The dose issue is complicated because the bioavailability of pramlintide is lower in patients with type 2 diabetes than type 1. Also, this study was done with a formulation whose bioavailability was somewhat less than the formulations used in later trials.)

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 not straightforward. Fundic photography should be done in any future long-term studies.

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. It would have been desirable to perform a clinical trial in which lower doses were used. 10 ug qid or 15 ug tid would be reasonable starting doses with up-titration as needed for efficacy. Based on the data submitted in the NDA, one could support 30 ug qid or 60 ug tid as standard doses 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 bioavailablity 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 (type 1 patients tend to be thin, while type 2 patients are usually obese). But this leaves open the question of how to dose patients with type 1 diabetes who are obese or patients with type 2 diabetes who are thin. This issue needs to be resolved in a PK study. Since patients who use insulin usually rotate their insulin injection sites, it would also be of interest to know if the absorption of pramlintide is different depending on the site of injection.

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 Recommendation of the Advisor Committee Meeting, July 26, 2001

Type 1 diabetes:

The advisory committee voted 8/1 against approval of pramlintide for type 1 diabetes.

The only vote in favor of approval for type 1 diabetes was from Dr William Tamborlane. His dissent appeared to be based on the ability of pramlintide to reduce postprandial hyperglycemia. He noted (p 229 in the transcript) that many of his patients have high postprandial glucose values even though their HbA1c levels might be reasonably "well controlled" . Dr Tamborlane stated that he was proud to have been part of the DCCT study that established HbA1c as a surrogate endpoint (p 252), but appears now to favor using improvement in postprandial glucose as a measure of efficacy (p259).

The FDA position has been that reduction of postprandial hyperglycemia may be a useful strategy to reduce overall hyperglycemia, but that there is little, if any, evidence that reduction of postprandial hyperglycemia **per se** confers any benefit. Earlier this year, the American Diabetes Association convened a consensus conference to attempt to answer the question whether targeting postprandial hyperglycemia is worthwhile.

The opinion of the ADA's panel, as published in a position paper in Diabetes Care 24, 775, 2001, is that "it is unclear whether excessive excursions of postprandial glucose have a significant impact on the development of diabetic microvascular and macrovascular complications independent of HbA1c levels." Therefore, the position of the American Diabetes Association is essentially the same as that of the FDA.

Speaking about pramlintide for Amylin Pharmaceuticals, Dr Orville Kolterman stated "The reductions in postprandial glucose were done as acute studies, single center studies in very carefully controlled, if you will, metabolic ward conditions (page 233 of the transcript)."

It should be noted also that studies showing reductions in postprandial hyperglycemia with pramlintide were done at or before 28 days of pramlintide treatment. FDA has not reviewed data addressing whether this reduction in postprandial hyperglycemia is sustained. Given that the reduction in HbA1c and incidence of hypoglycemia peaked early in the trials, it seems likely that reduction in postprandial hyperglycemia is also not sustained.

In summary, I do not think that FDA should accept the reduction in postprandial glucose levels observed in short-term studies as a reason to approve pramlintide.

Type 2 diabetes:

The vote was 6/3 against approval of pramlintide for type 2 diabetes.

Less concern was voiced regarding hypoglycemia in patients with type 2 diabetes than in patients with type 1 diabetes. The benefit of weight reduction in patients with type 2 diabetes was also noted. While voting against approval, Dr Grady suggested that a study be done in which pramlintide is given to patients taking insulin plus metformin.

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. Three additional pramlintide-treated patients sustained injuries (two fractures and one laceration) during hypoglycemic events unrelated to motor vehicle accidents. One patient died in a motor vehicle accident the day after starting pramlintide. A second patient on pramlintide died during what was probably a hypoglycemic seizure. A third patient developed nausea and anorexia after pramlintide and died soon afterwards for no apparent reason.

The benefit /risk assessment of pramlintide is clearly negative. The long-term reduction in HbA1c is small and the decrease in body weight achieved with pramlintide is more than offset by the risk of hypoglycemia. Pramlintide-treated patients are much more likely to be involved in automobile-related events than patients on insulin alone. In this regard one should be mindful that there were three deaths due to MVA's in the DCCT study (N Eng J Med 1993;329:977-86), but just two involved study patients. The third death occurred in a person who " was killed in a motor vehicle accident involving a car driven by a patient in the intensive-therapy group who was probably hypoglycemic." **Were it approved, the harm that would result from pramlintide would not be limited to patients alone, but would likely involve bystanders who may be injured by patients under the influence of pramlintide**. In accordance with the efforts of government and private organizations, such as MADD (Mothers Against Drunk Driving), to prevent motor vehicle-related injury, it is incumbent upon FDA not to approve pramlintide until it can be shown that pramlintide can be used in such a way that it does not increase the risk of motor-vehicle accidents. **If further testing of pramlintide**

is to be done, special precautions should be taken to insure that patients do not injure themselves or others. Patients should be informed about the potential risk of pramlintide-related injury and be advised to refrain from driving or use of dangerous equipment. Unless these safety criteria are met, the IND should be put on clinical hold.

Need for additional studies

Review of the results from clinical pharmacology studies raises concern about the possibility that a five-day exposure to pramlintide in patients with type 1 diabetes could cause hypoglycemia unawareness. The studies were small and the differences were not statistically significant. In addition, no evidence of hypoglycemia unawareness was found in the 14-day study. Still, the possible danger of hypoglycemia unawareness is sufficiently important that this issue should be answered definitively, particularly in view of the large number of accidents in patients on pramlintide. Prior to exposing any new patients, the Sponsor should exclude the possibility that pramlintide causes hypoglycemia unawareness. Hypoglycemia should be induced by an intravenous insulin infusion. The rate of infusion should be gradually increased until the patient exhibits signs/symptoms of hypoglycemia. If no signs/symptoms of hypoglycemia develop, the infusion should be terminated when the blood glucose concentration falls to 2 mM. **The object of the study is to determine the plasma glucose threshold at which signs/symptoms of hypoglycemia develop.** Samples should be obtained for determination of glucose and pramlintide levels. Glucose threshold values at baseline should be compared to values obtained after five days of pramlintide 120 ug tid or placebo. The timing of the pramlintide dose and the insulin infusion should be planned so that the peak pramlintide concentration and glucose nadir will occur at nearly the same time. Subjects should be instructed not to drive or operate machinery during the five days of treatment. Even better would be to perform the study on a clinical research ward. The study should be done in patients with type 1 diabetes who are in reasonably good control (HbA1c 6.5- 8.5 on constant insulin regimen) or in non-obese normal volunteers.

Assuming that the study outlined above does not show that pramlintide causes hypoglycemia unawareness, the Sponsor should perform studies 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. These should be 12-month placebo-controlled trials with reduction in hemoglobin A1c levels as the primary measure of efficacy. In order to avoid hypoglycemia in patients with type 1 diabetes, I would suggest a starting dose of pramlintide of 15 ug tid with titrations to 30 ug, and 60 ug tid as needed (or 10 ug qid with titration up to 30 ug qid). The dose of pramlintide should remain constant for the last 6 months of the study. Reduction in HbA1c from baseline without an increase in hypoglycemia should be criteria for a successful trial. In order to prevent hypoglycemia early in the trial, it might be advisable to instruct patients to reduce their short acting preprandial insulin dose* when starting test drug. After the first week or so, patients should be instructed to adjust their insulin dose as needed to achieve good glycemic control. I would presume that placebo patients would need to resume their

previous insulin dose while patients on pramlintide might continue on the lower insulin dose. Patients should be instructed to titrate their insulin dose in order to optimize glycemic control. They should be informed both in writing and verbally of the finding that pramlintide appears to increase the risk of hypoglycemia and motor vehicle accidents. They should be advised to avoid driving or use of machinery.

*(reducing the insulin dose will mean that glucose levels will rise. That glucose levels may rise **less** in pramlintide-treated patients than in patients on placebo should not be considered a positive result. For the trial to be considered positive, HbA1c levels should be lower at endpoint than at baseline.)

Prior to initiation of additional studies in patients with type 2 diabetes, the Sponsor should determine why the bioavailability of pramlintide is so much lower in patients with type 2 diabetes than in patients with type 1 diabetes. This issue is discussed by Dr Johnson in the Biopharmacy review. One presumes that the difference in bioavailability is related to the distribution of body fat, but this has not been clearly established.

The Sponsor should consider a trial of pramlintide vs placebo in obese insulin-treated patients with type 2 diabetes who are also taking metformin (2g/d or greater). The study should be 12 months in duration.

In both 12-month trials, retinal photography should be performed at baseline and at endpoint with a fundoscopic exam at about 6 months. In view of the finding in study 111, inclusion criteria should be developed to exclude patients believed to have clinically important or unstable retinopathy.

Additional studies needed for an approvable package can be summarized as follows:

Phase 2 studies:

1) Investigate hypoglycemia unawareness
2) Bioavailability

Phase 3 studies

12 month trials in patients with type 1 and type 2 diabetes with insulin titration and fundic photography. The dose of pramlintide should start low and be increased as needed for efficacy during the first six months. The dose should be kept constant for the last six months in order to demonstrate the durability of response.

Recommended regulatory action:

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

If new patients are to be exposed to pramlintide, special care should be taken to make sure that they do not injure themselves or others in motor vehicle accidents. Unless the Sponsor agrees to these precautions, the IND should be placed on clinical hold.

Robert I Misbin MD
HFD 510
Medical Officer
August 30, 2001
Finalized with minor revisions on September 6, 2001.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Misbin
9/7/01 02:51:19 PM
MEDICAL OFFICER

Saul Malozowski
9/7/01 02:52:32 PM
MEDICAL OFFICER

David Orloff
10/2/01 05:50:54 PM
MEDICAL OFFICER
Noted. See DD memo for my recommendations