

AMYLIN PHARMACEUTICALS, INC.

SYMLIN™ Injection
(pramlintide acetate)

NDA No. 21-332

Advisory Committee Briefing Document

26 July 2001

Available for Public Disclosure
without redaction.

EXECUTIVE SUMMARY

This document provides the key background information and data supporting the proposed indications regarding the use of SYMLIN™ Injection (pramlintide acetate) for glycemic and metabolic control in the treatment of patients with type 1 or type 2 diabetes mellitus who use insulin. Supporting information for the following points are presented in the main document.

BACKGROUND

- Pramlintide is a synthetic analog of the human hormone amylin.
- Amylin is a neuroendocrine peptide hormone with glucoregulatory properties which is cosecreted with insulin from pancreatic β -cells in response to meals.
- Nonclinical studies indicate that amylin is a neuroendocrine hormone that complements the actions of insulin in postprandial glucose homeostasis via several effects. These include a suppression of glucagon secretion at mealtime above and beyond that elicited by insulin, and a slowing of the rate of nutrient delivery from the stomach to the small intestine. Amylin therefore regulates the rate of endogenous (liver-derived) and exogenous (meal-derived) glucose influx into the circulation to better match the rate of insulin-stimulated glucose efflux.
- Pancreatic β -cell destruction (type 1) and dysfunction (type 2) renders patients deficient in both insulin and amylin.
- The vast majority of type 1 and insulin-using type 2 patients with diabetes do not achieve satisfactory glycemic control with insulin replacement therapy alone. At present, this patient population has no (type 1 diabetes) or limited (type 2 diabetes) adjunctive therapeutic options.
- Barriers to achieving satisfactory glycemic control with currently available insulin therapies include:
 - excessive postprandial glucose excursions
 - increased risk of severe hypoglycemia
 - undesired weight gain, with adverse effects on lipid profile and blood pressure

PRAMLINTIDE SUPPORTING DATA

- Pramlintide is a biosynthetic analog of human amylin that has been developed to allow replacement of amylin action at mealtime, as an adjunct to insulin. Pramlintide is to be administered via subcutaneous injection prior to meals.
- The proposed indication of pramlintide is to improve glycemic and metabolic control in type 1 and type 2 patients with diabetes treated with insulin or insulin plus oral hypoglycemic agent(s).
- In short-term studies in both type 1 and insulin-using type 2 patients with diabetes, prandial amylin replacement with pramlintide as an adjunct to insulin:
 - prevented the abnormal rise in glucagon after meals
 - slowed the rate of gastric emptying and, consequently
 - markedly improved postprandial glycemic excursions
- In controlled long-term (26 to 52 weeks) studies of both type 1 and insulin-using type 2 patients, addition of pramlintide (BID, TID, or QID with meals) to the existing insulin regimen:
 - improved overall glycemic control (reduction in HbA_{1c} and achievement of HbA_{1c} targets)
 - achieved better metabolic control evidenced by (1) no weight gain, (2) no increased insulin use, and (3) no increase in the overall severe hypoglycemia event rate
 - had no adverse effects on lipids or blood pressure
- Among 4493 patients exposed to pramlintide, the most commonly occurring treatment-emergent adverse events related to pramlintide treatment were nausea, anorexia, and vomiting, which were generally mild-to-moderate in intensity, more common in type 1 than in type 2 diabetes, dose-related, typically occurred early upon treatment, and dissipated over time.
- In conclusion, prandial amylin replacement with pramlintide, as an adjunctive therapy to insulin, is safe and efficacious in improving glycemic and metabolic control in type 1 and type 2 diabetic patients while addressing several important shortfalls of insulin therapy.

TABLE OF CONTENTS

LIST OF MAIN-TEXT TABLES.....	5
LIST OF MAIN-TEXT FIGURES	6
GLOSSARY OF TERMS.....	8
1. INTRODUCTION	9
2. SCIENTIFIC RATIONALE.....	9
3. TARGET POPULATION	11
4. UNMET MEDICAL NEED IN DIABETES PATIENTS TREATED WITH INSULIN	12
5. PRAMLINTIDE PHARMACOLOGY.....	15
6. SCOPE OF CLINICAL DEVELOPMENT PROGRAM.....	18
7. CLINICAL PHARMACOKINETICS.....	19
8. CLINICAL PHARMACODYNAMICS.....	21
9. CLINICAL DEVELOPMENT PROGRAM	25
9.1 Selection of Doses to Study in Clinical Trials.....	25
9.2 Study Design and Statistical Considerations	25
10. OVERVIEW OF CLINICAL FINDINGS: CONTROLLED STUDIES.....	31
10.1 Type 1 Diabetes	31
10.1.1 Short-Term Controlled Study	31
10.1.2 Long-Term Controlled Studies.....	32
10.2 Insulin-Using Type 2 Diabetes	39
10.2.1 Short-Term Controlled Study	39
10.2.2 Long-Term Controlled Studies.....	40
11. OVERALL ASSESSMENT OF EFFICACY.....	47
11.1 Dose Response.....	47
11.1.1 Dose Response in Type 1 Diabetes Studies.....	47
11.1.2 Dose Response in Type 2 Diabetes Studies.....	48
11.2 Joint Outcome: Relationship Between HbA _{1c} and Weight.....	49
11.3 Joint Outcome: Relationships Between HbA _{1c} and Insulin, and Weight and Insulin.....	51
11.4 Overall Summary of Efficacy	53
12. OVERALL ASSESSMENT OF SAFETY	54
12.1 Patient Disposition.....	54
12.2 Treatment-Emergent Adverse Events in Long-Term Controlled Studies.....	54
12.3 Gastrointestinal Adverse Events.....	55
12.4 Hypoglycemia.....	57
12.4.1 Definition of Sponsor-Defined Severe Hypoglycemia.....	57
12.4.2 Hypoglycemia Adverse Events.....	58
12.4.3 Sponsor-Defined Severe Hypoglycemia.....	60

12.4.4	Hypoglycemia and Injuries/Accidents.....	61
12.4.5	Hypoglycemic Override of Pramlintide Action.....	63
12.5	Other Notable Adverse Events	64
12.5.1	Retinal Disorders	64
12.5.2	Deaths	66
12.6	Drug-Drug Interactions.....	66
12.6.1	Drug-Drug Interaction Studies	66
12.6.2	Concomitant Medications of Particular Relevance to a Diabetic Population.....	67
12.7	Other Safety	68
13.	BENEFIT/RISK RATIO	69
14.	PROPOSED INDICATION AND DOSING RECOMMENDATION	73
15.	REFERENCES	74
	APPENDIX 1: PRAMLINTIDE CLINICAL DEVELOPMENT PROGRAM.....	77
	APPENDIX 2: PRAMLINTIDE PHARMACOKINETICS.....	84
	APPENDIX 3: PRAMLINTIDE PHARMACODYNAMICS.....	87
	APPENDIX 4: SYNOPSES OF CONTROLLED STUDIES	91
1.1	Short-term Controlled Study in Type 1 Diabetes	92
1.1.1	Study 137-105.....	93
1.2	Long-term Controlled Studies in Type 1 Diabetes	99
1.2.1	Study 137-112.....	100
1.2.2	Study 137-117.....	109
1.2.3	Study 137-121.....	116
1.3	Short-term Controlled Study in Type 2 Diabetes Using Insulin.....	123
1.3.1	Study 137-114.....	124
1.4	Long-term Controlled Studies in Type 2 Diabetes Using Insulin.....	130
1.4.1	Study 137-111.....	131
1.4.2	Study 137-123.....	139
1.4.3	Study 137-122.....	146
	APPENDIX 5: ADVERSE EVENTS AND PATIENT DEATHS DURING PRAMLINTIDE CLINICAL TRIALS.....	153
	APPENDIX 6: PRAMLINTIDE NONCLINICAL TOXICOLOGY	178

LIST OF MAIN-TEXT TABLES

Table 1: Prospectively Defined Statistical Analysis Approaches for Long-Term Controlled Studies29

Table 2: Pramlintide Treatment Arms for Which Change in HbA_{1c} Achieved Formal Statistical Significance Compared With Placebo, Using the Prospectively Defined Analysis Methods30

Table 3: Long-Term Controlled Studies in Type 1 Diabetes.....33

Table 4: Summary of Mean Change From Baseline in HbA_{1c}, Total Daily Insulin Dose, and Body Weight in Long-Term Studies in Patients With Type 1 Diabetes by Recommended Dose (Population: Evaluable).....35

Table 5: Change in HbA_{1c} at 26 Weeks and 52 Weeks for the Intent-to-Treat and Stable Insulin Populations (Study 137-121: Patients With Type 1 Diabetes)36

Table 6: Proportion of Patients (%) Achieving HbA_{1c} Reductions and Targets in Type 1 Study 137-121 at Recommended Doses (Population: Intent-to-Treat).....38

Table 7: Proportion of Patients (%) Achieving an HbA_{1c} Reduction of ≥0.5% at Week 4 in Type 1 Study 137-121 at Recommended Doses (Population: Intent-to-Treat).....38

Table 8: Long-Term Controlled Studies in Insulin-Using Type 2 Diabetes41

Table 9: Summary of Mean Change From Baseline in HbA_{1c}, Total Daily Insulin Dose, and Body Weight From Baseline in Long-Term Studies in Patients With Type 2 Diabetes by Recommended Dose (Population: Evaluable).....43

Table 10: Change in HbA_{1c} at 6 Months and 1 Year for the Intent-to-Treat and Stable Insulin Populations (Study 137-122: Patients With Type 2 Diabetes)44

Table 11: Change in HbA_{1c} From Baseline at Week 26: Patients With and Without Biguanides and Sulfonylureas (Long-term Controlled Studies in Patients With Type 2 Diabetes Using Insulin) ...45

Table 12: Proportion of Patients (%) Achieving HbA_{1c} Reductions and Targets in Type 2 Study 137-122 at Recommended Dose (Population: Intent-to-Treat).....46

Table 13: Proportion of Patients (%) Achieving an HbA_{1c} Reduction of ≥0.5% at Week 4 in Type 2 Study 137-122 at Recommended Doses (Population: Intent-to-Treat).....46

Table 14: Summary of Mean Change From Baseline in HbA_{1c}, Body Weight, and Total Daily Insulin Dose From Baseline in Long-Term Studies in Patients With Type 1 Diabetes by Nausea Categorization and Recommended Dose (Population: Intent-to-Treat)50

Table 15: Summary of Mean Change From Baseline in HbA_{1c}, Body Weight, and Total Daily Insulin Dose From Baseline in Long-Term Studies in Patients With Type 2 Diabetes by Nausea Categorization and Recommended Dose (Population: Intent-to-Treat)51

Table 16: Number (%) of Patients in the Long-Term Studies With Treatment-Emergent Adverse Events With an Overall Incidence of ≥5% in Pramlintide and an Incidence Greater in Pramlintide Than in Placebo (Population: Intent-to-Treat).....55

Table 17: Hypoglycemic Adverse Events Long-Term Controlled Studies in Patients With Type 1 and in Patients With Type 2 Diabetes Using Insulin.....59

Table 18: Sponsor-defined Hypoglycemia for Type 1 Studies 137-121, 137-112, and 137-117 Combined (Population: Intent-to-Treat)60

Table 19: Sponsor-defined Hypoglycemia for Type 2 Studies 137-122 and 137-123 Combined (Population: Intent-to-Treat)61

Table 20: Motor Vehicle and Other Accidents/Injuries Reported During the Pramlintide Clinical Development Program – Patient Incidence and Annual Event Rate per Patient63

Table 21: Pramlintide Does Not Affect the Counter-regulatory Response to Hypoglycemia in Patients With Type 1 Diabetes (Study AP93-04)64

Table 22: Incidence of Adverse Events Coding to Vision Disorders (Body System) and Retinal Disorder (Preferred Term) in Type 2 Diabetes Pramlintide Studies65

LIST OF MAIN-TEXT FIGURES

Figure 1:	Structure of Pramlintide and Human Amylin.....	10
Figure 2:	Pramlintide Target Population.....	11
Figure 3:	Absolute Risk of Sustained Retinopathy Progression as a Function of Mean HbA _{1c} During Follow-Up in the DCCT (Estimated From Poisson Regression Models) – Type 1 Diabetes.....	13
Figure 4:	Incidence Rate For Microvascular Complications During UKPDS – Type 2 Diabetes	13
Figure 5:	HbA _{1c} for the Insulin Group During the UKPDS – Type 2 Diabetes.....	14
Figure 6:	Three Fluxes Control Plasma Glucose	15
Figure 7:	Secretory Profiles of Amylin and Insulin in Nondiabetic Subjects.....	16
Figure 8:	Post-Meal Plasma Amylin Concentrations in Nondiabetic and Diabetic Subjects.....	16
Figure 9:	Glucoregulatory Actions of Amylin / Pramlintide	17
Figure 10:	Pramlintide Reduces Postprandial Glucose Concentrations in a Dose-related Manner (Patients With Type 1 Diabetes; Studies AP93-08, 137-104, 137-105).....	18
Figure 11:	Cumulative Duration of Exposure to Pramlintide (All Studies).....	19
Figure 12:	Plasma Pramlintide Concentrations Increase in Proportion to Dose in Healthy Subjects (Study 137-126).....	20
Figure 13:	Plasma Pramlintide Concentrations in Patients With Type 1 Diabetes (Study 137-143).....	20
Figure 14:	Plasma Pramlintide Concentrations in Patients With Type 2 Diabetes Who Use Insulin (Study 137-144).....	21
Figure 15:	Pramlintide Decreases Post-Meal Plasma Glucagon (Study AP93-08: Patients With Type 1 Diabetes)	22
Figure 16:	Single Dose Effect of Pramlintide Administered in Conjunction With Breakfast on Gastric Half-Emptying Times After Breakfast and Lunch (Study 137-118: Patients With Type 1 Diabetes)	22
Figure 17:	Pramlintide Decreases Post-Meal Plasma Glucose Concentrations (Study AP93-08: Patients With Type 1 Diabetes)	23
Figure 18:	Pramlintide Decreases Post-Meal Plasma Glucose Concentrations When Administered at Two Consecutive Meals (Study 137-107: Patients With Type 1 Diabetes).....	24
Figure 19:	Pramlintide in Combination With Insulin Lispro + Long-Acting Insulin Decreases Post-Meal Plasma Glucose Concentrations as Compared to Insulin Lispro+Long-Acting Insulin Alone (Study 137-130: Patients With Type 1 Diabetes).....	24
Figure 20:	Pramlintide Dose-Relationship of Glucose Lowering Effects and Nausea (Patients With Type 1 Diabetes; Studies AP93-08, 137-104, 137-105).....	25
Figure 21:	Long-Term Controlled Type 1 Diabetes Study Designs	26
Figure 22:	Long-Term Controlled Insulin-Using Type 2 Diabetes Study Designs.....	26
Figure 23:	Change in Serum Fructosamine (μmol/L) From Screening at 28 Days (Study 137-105: Short-Term Controlled Study in Patients With Type 1 Diabetes; Population: Evaluable).....	32
Figure 24:	Mean Change in HbA _{1c} From Baseline at Week 26 (Long-Term Controlled Studies in Type 1 Diabetes; Population: Intent-to-Treat, LOCF).....	34
Figure 25:	Mean Change in Weight From Baseline at Weeks 26 and 52 (Long-Term Controlled Studies in Type 1 Diabetes Combined; Population: Evaluable as Defined in Each Study)	34
Figure 26:	Change in HbA _{1c} Through 52 Weeks for the Intent-to-Treat Population (Study 137-121: Patients With Type 1 Diabetes).....	36
Figure 27:	Change in HbA _{1c} Through 52 Weeks for the Stable Insulin Population (Study 137-121: Patients With Type 1 Diabetes).....	36
Figure 28:	Reduction in HbA _{1c} Sustained Over 2 Years of Treatment With Pramlintide (Study 137-112 and Open-Label Extension; Population: Intent-to-Treat, Observed Values).....	37
Figure 29:	Difference in Treatment Means Between Pramlintide and Placebo (Treatment Effect), With 95% Confidence Intervals, for Change in HbA _{1c} From Baseline at Week 26 (Long-Term Controlled Studies in Type 1 Diabetes; Population: Intent-to-Treat).....	39
Figure 30:	Change in Serum Fructosamine (μmol/L) From Baseline at 28 Days (Study 137-114: Short-Term Controlled Study in Patients With Type 2 Diabetes Using Insulin; Population: Evaluable)	40
Figure 31:	Mean Change in HbA _{1c} From Baseline at Week 26 (Long-Term Controlled Studies in Patients With Type 2 Diabetes Using Insulin; Population: Intent-to-Treat).....	42

Figure 32:	Mean Change in Weight From Baseline at Weeks 26 and 52 (Long-Term Controlled Studies in Patients With Type 2 Diabetes Using Insulin Combined; Population: Evaluable as Defined in Each Study).....	42
Figure 33:	Change in HbA _{1c} Through 52 Weeks for the Intent-to-Treat Population (Study 137-122: Patients With Type 2 Diabetes).....	44
Figure 34:	Change in HbA _{1c} Through 52 Weeks for the Stable Insulin Population (Study 137-122: Patients With Type 2 Diabetes).....	45
Figure 35:	Difference in Treatment Means Between Pramlintide and Placebo (Treatment Effect), With 95% Confidence Intervals, for Change in HbA _{1c} From Baseline at Week 26 (Long-Term Controlled Studies in Insulin-Using Type 2 Diabetes; Population: Intent-to-Treat).....	47
Figure 36:	Mean Change and Standard Error in HbA _{1c} (%) From Baseline to Week 26 by Dose (Study 137-122: Long-Term, Controlled Study in Patients With Type 2 Diabetes Using Insulin; Population: Intent-to-Treat).....	49
Figure 37:	Joint Outcome – Change in HbA _{1c} and Insulin at 26 Weeks in Patients With Type 1 Diabetes (All Pramlintide Doses Pooled).....	52
Figure 38:	Joint Outcome – Change in HbA _{1c} and Insulin at 26 Weeks in Patients With Type 2 Diabetes (All Pramlintide Doses Pooled).....	53
Figure 39:	Percent of Patients Withdrawing From Pramlintide Clinical Trials.....	54
Figure 40:	Incidence of Nausea Over Time in Patients With Type 1 Diabetes (Population: Intent-to-Treat).....	56
Figure 41:	Cumulative Frequency Distribution of Time to First Onset of Nausea by Dose (Long-term Controlled Studies in Patients With Type 1 Diabetes).....	57
Figure 42:	Cumulative Frequency Distribution of Time to First Onset of Nausea by Dose (Long-term Controlled Studies in Patients With Type 2 Diabetes Using Insulin).....	57

GLOSSARY OF TERMS

ACE	angiotensin-converting enzyme
ADA	American Diabetes Association
AE	adverse event
Amylin	A 37-amino acid polypeptide of pancreatic β -cell origin that acts to modulate postmeal glucagon concentrations and the appearance of meal-derived nutrients in the peripheral circulation, thus reducing postprandial glucose concentration.
AUC	area under the curve
b	breakfast
BID	twice daily
C_{ave}	mean glucose concentrations
C_{max}	highest observed drug concentration during sampling period
d	dinner
DCCT	Diabetes Control and Complications Trial
dL	deciliter
ECG	electrocardiogram
EDIC	Epidemiology of Diabetes Interventions and Complications Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	hour
HbA _{1c}	glycosylated hemoglobin specific A _{1c} fraction; measure of glycemic control
HDL	high density lipoprotein cholesterol
HEDIS	Health Plan Employer Data and Information Set
ICH	International Conference on Harmonization (of regulatory guidelines)
IDDM	insulin-dependent diabetes mellitus; type 1 diabetes mellitus
IEMA	immunoenzymetric assay
Insulin	Used generically in this report to refer to any formulation of natural or biochemically produced insulin.
ITT	intent-to-treat
IV	intravenous(ly)
kg	kilogram
L	liter
l	lunch
LDL	low density lipoprotein cholesterol
LOCF	last observation carried forward
mg	milligram
min	minute
misc	miscellaneous
mL	milliliter
mmol	millimole
μ g	microgram
μ L	microliter
NA	not applicable
NDA	New Drug Application
NHANES	National Health and Examination Survey
NIDDM	non-insulin-dependent diabetes mellitus; type 2 diabetes mellitus
pg	picogram
PK	pharmacokinetic
pmol	picomole
pramlintide	The USAN-approved generic name for the amylin analog synthesized with prolines at positions 25, 28, and 29.
QID	four times daily
s	bedtime snack
SC	subcutaneous(ly)
$t_{1/2}$	half-life
TID	three times daily
T_{max}	time of the maximum observed/extrapolated concentration
UKPDS	United Kingdom Prospective Diabetes Study
WHOART	World Health Organization Adverse Reaction Terminology

1. INTRODUCTION

This document provides the key background information and data supporting the proposed indications put forth in NDA 21-332 regarding the use of SYMLIN™ Injection (pramlintide acetate) for glycemic and metabolic control in the treatment of patients with type 1 or type 2 diabetes mellitus who use insulin. In order to aid the reviewer, the approximately 70 pages of main text provide key summary data, with more detailed information in separate appendices located at the end, which are cross-referenced from the main text. The appendices contain the following information:

Appendix 1	Enumeration of study subjects, patient disposition, exposure, and demographics
Appendix 2	Overview of pramlintide clinical pharmacokinetics
Appendix 3	Overview of pramlintide clinical pharmacodynamics
Appendix 4	Synopses of the 6 long-term and 2 short-term controlled studies
Appendix 5	Summary of adverse events and patient deaths
Appendix 6	Summary of pramlintide nonclinical toxicology findings

For consistency throughout the remainder of this document (with the exception of Section 14 which presents the proposed indication), SYMLIN is referred to as pramlintide.

2. SCIENTIFIC RATIONALE

Pramlintide is a synthetic analog of the human hormone amylin (**Figure 1**). Amylin is a neuroendocrine hormone that was first described by investigators at Oxford University in 1987.¹ Amylin, and the amylin analog pramlintide, have been under investigation at Amylin Pharmaceuticals since 1989. Based on information derived from initial animal studies using supraphysiologic doses of the hormone,² the original proposed indication for pramlintide was for rescue from insulin-induced hypoglycemia. However, subsequent nonclinical and clinical studies demonstrated that at physiologic concentrations, amylin acts to decrease postprandial glucose concentrations. The clinical development program was therefore redirected at studying pramlintide as an adjunct to insulin in the treatment of type 1 and type 2 diabetes.

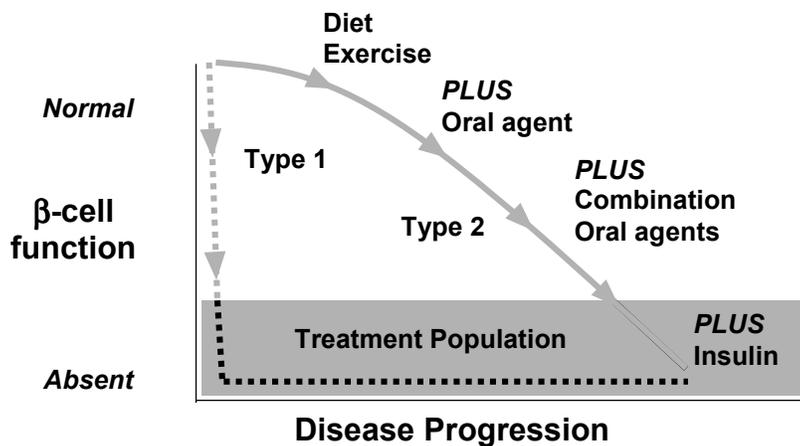
Pramlintide therapy is administered by subcutaneous injection prior to main meals to improve postprandial glucose homeostasis.

The benefits of pramlintide therapy include a further reduction in HbA_{1c} beyond the reduction observed with insulin alone, with the added benefit of improved weight control. The reduction in HbA_{1c} occurs without the overall increase in severe hypoglycemia and weight gain that is typically observed in patients who achieve this endpoint using insulin therapy alone, and this improvement occurs without increased insulin use. Pramlintide reduces postprandial glucose concentrations by decreasing postprandial glucagon secretion and modulating the rate of nutrient delivery into the small intestine. These effects optimize the rate of glucose appearance during the absorptive phase following a meal to better match the effect of insulin to increase glucose clearance. These complementary effects reduce the immediate postprandial glucose rise.

3. TARGET POPULATION

The target population for pramlintide use is all patients with diabetes with advanced β -cell failure (amylin and insulin deficiencies). As shown in **Figure 2**, the target population encompasses all patients with type 1 diabetes, since these patients are typically β -cell deficient and dependent on insulin at or shortly after the time of clinical diagnosis. In addition, the target population includes patients with type 2 diabetes mellitus who have gradually progressed to β -cell deficiency as evidenced by failure to achieve adequate glycemic control with oral hypoglycemic agents (OHAs), either singly or in combination, thereby necessitating the use of exogenous insulin. As mentioned earlier, patients who have progressed to this point have generally exhausted the available benefit from various oral therapies.

Figure 2: Pramlintide Target Population

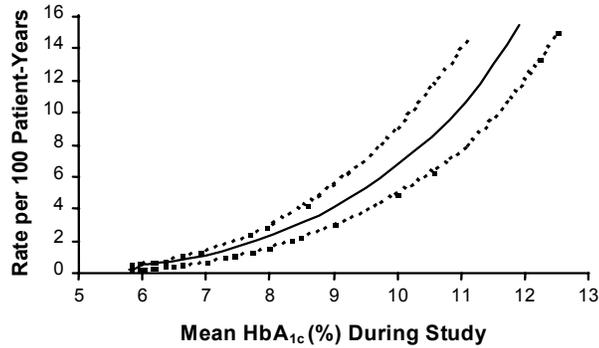


The clinical development program enrolled patients that were appropriate to assess efficacy and safety for this target population, given their level of glycemic control, use of insulin, and duration of disease (Appendix 1). The duration of pramlintide treatment (2109 patients exposed \geq 6 months and 1350 exposed \geq 12 months) was also adequate to make such assessments.

4. UNMET MEDICAL NEED IN DIABETES PATIENTS TREATED WITH INSULIN

Diabetes is a widespread disease with considerable morbidity and mortality. Sixteen million Americans have diabetes.⁷ Diabetes leads to considerable morbidity and mortality due to inadequate glucose control.^{8,9} Long-term microvascular consequences of the disease include blindness, end-stage renal disease, and lower limb amputations. Patients with type 1 and type 2 diabetes are also at significantly increased risk for macrovascular disease, which leads to an increase in myocardial infarctions, strokes, and premature death. Inadequate glucose control may also play a role in these processes although the relationship is less clear. Recent data suggest that postprandial hyperglycemia may be a risk factor for macrovascular disease.^{10,11} Long-term studies such as the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) have shown that any improvement in glucose control (measured by reductions in HbA_{1c}) reduces the risk of the long-term complications of diabetes.^{10,12,13,14} As shown in **Figure 3** and **Figure 4**, the relationship between increasing HbA_{1c} and progression of diabetic complications (e.g., retinopathy) in patients with type 1 or type 2 diabetes was found to be continuous and non-linear. Even modest reductions in HbA_{1c} conveyed benefit, and patients with higher initial HbA_{1c} benefited more from an absolute unit decrease in HbA_{1c} than did those with lower HbA_{1c}.

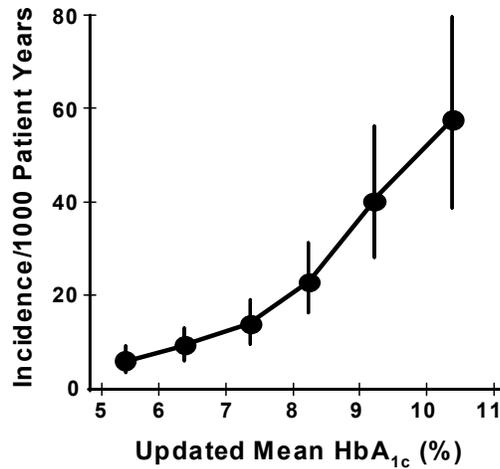
Figure 3: Absolute Risk of Sustained Retinopathy Progression as a Function of Mean HbA_{1c} During Follow-Up in the DCCT (Estimated From Poisson Regression Models) – Type 1 Diabetes



Solid line = regression line estimated as a function of the log of the mean HbA_{1c} value
Dotted line = 95% confidence interval

From Reference 13

Figure 4: Incidence Rate For Microvascular Complications During UKPDS – Type 2 Diabetes



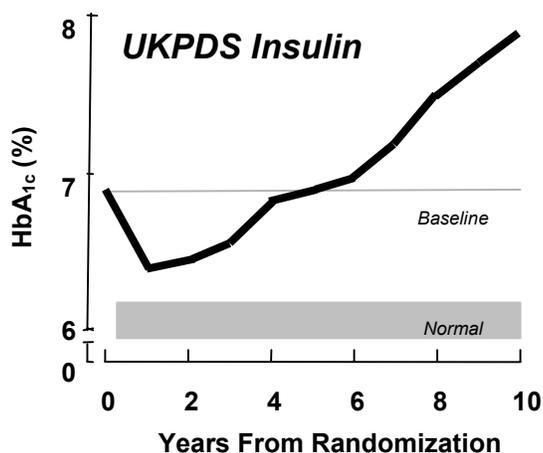
Error Bars = 95% confidence intervals

From Reference 10

Intensive insulin therapies lead to increased severe hypoglycemia and weight gain. In spite of a variety of currently available treatments, which predominantly impact fasting glucose concentrations, including multiple approaches to exogenous insulin therapy developed over decades, the β -cell deficient population continues to have inadequate glucose control. Furthermore, as shown in the DCCT, any improvement in glycemic control resulting from intensive insulin therapy is proportionally accompanied by an increase in severe hypoglycemia and weight gain. Several other studies and surveys (NHANES, HEDIS, EDIC, UKPDS) have also clearly demonstrated the difficulties encountered with insulin therapy in achieving and sustaining glycemic targets in patients with type 1 and type 2 diabetes.

Type 2 diabetes is a progressive disease. The results of the UKPDS clearly show that type 2 diabetes is a progressive disease. While HbA_{1c} increased steadily in the conventional (diet control) group during the study, the progressive nature of the disease is best illustrated by the group assigned to insulin monotherapy at the initial randomization. In the insulin group (**Figure 5**), HbA_{1c} decreased initially, then increased steadily, returning to baseline by Year 6 despite intensive therapeutic efforts. HbA_{1c} continued to progressively increase throughout the remainder of the study. This is consistent with a relentless loss of β -cell function making the patients more dependent upon the exogenous therapy, which as administered, was unable to compensate for the loss of endogenous insulin secretion.

Figure 5: HbA_{1c} for the Insulin Group During the UKPDS – Type 2 Diabetes



From Reference 14

Adequate glycemic control is not easily attainable using current therapies. The results of the DCCT and the UKPDS demonstrate that intensive therapy regimens which produced nearer-to-normal glucose concentrations markedly reduced the risk of long-term complications in type 1 and type 2 diabetes. The results of these studies also demonstrate that these intensive intervention strategies, even when applied by acknowledged experts working with highly motivated patients, do not normalize glucose concentrations or halt the progression of type 2 diabetes.

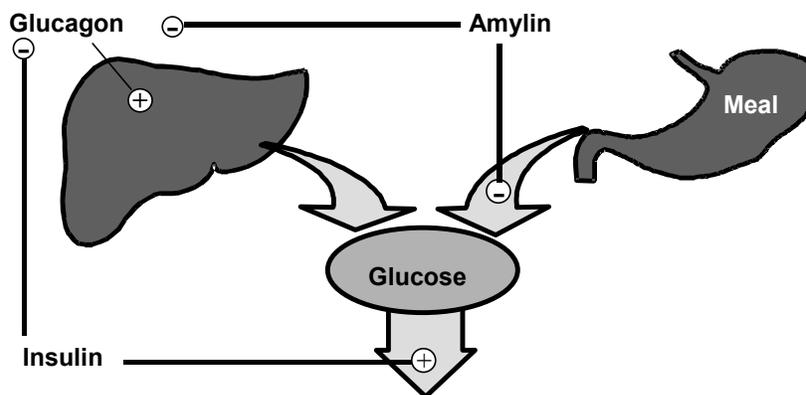
Thus, at the present time, insulin-using patients with diabetes are not achieving adequate glycemic control with insulin alone, which predominantly affects fasting glucose concentrations. Patients with type 2 diabetes who use oral hypoglycemic agents in addition to insulin generally fare no better. Therefore, for both type 1 and type 2 diabetes there remains a significant unmet medical need, particularly for a therapy that could be used as an adjunct to insulin to improve postprandial glycemic and metabolic control without

substantially increasing the risk of hypoglycemia and weight gain. Recent studies have indicated that those therapies which are focused on lowering postprandial glucose, rather than impacting predominantly fasting glucose, are effective at lowering HbA_{1c}.¹¹ HbA_{1c} is the accepted measure of prevailing glycemic status and the primary measure by which new diabetes therapies are assessed.¹⁵

5. PRAMLINTIDE PHARMACOLOGY

The integrated effects of amylin, insulin, and glucagon maintain euglycemia in healthy individuals. In healthy individuals, three principal fluxes provide for control of circulating glucose concentrations: glucose influx from meals, glucose influx from the liver, and glucose efflux from the circulation into peripheral tissues (**Figure 6**). In healthy individuals, insulin, glucagon, and amylin work together to maintain postprandial normoglycemia without precipitating reactive hypoglycemia. Insulin regulates glucose outflow from the plasma compartment by stimulating uptake of glucose by responsive tissues, while amylin regulates glucose inflow into the plasma compartment by inhibiting nutrient-stimulated glucagon secretion from the α -cell (reduction of endogenous glucose output) and modulating the rate of nutrient delivery (meal-derived glucose appearance) into the small intestine after ingestion of a meal.

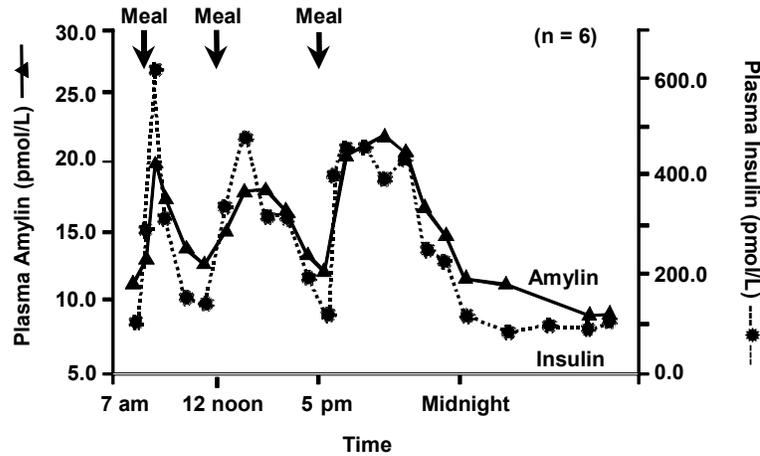
Figure 6: Three Fluxes Control Plasma Glucose



Diabetes is characterized by insulin and amylin deficiency and glucagon excess.

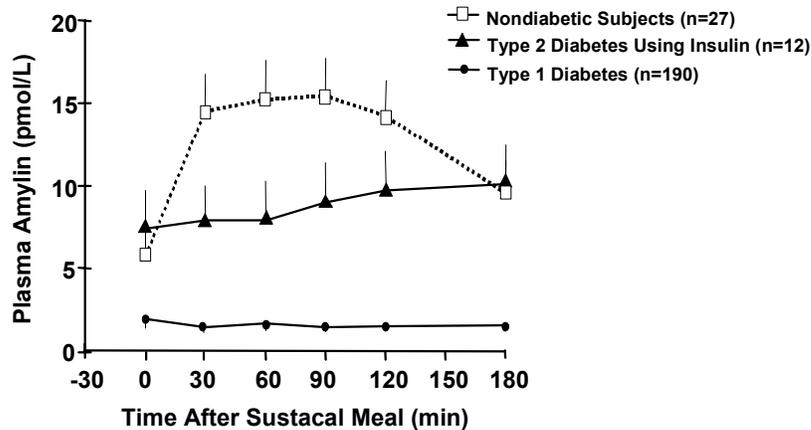
Evidence now exists indicating that diabetes is characterized by insulin deficiency, amylin deficiency, and glucagon excess during the postprandial period. The circulating profiles of amylin and insulin are similar in healthy subjects (**Figure 7**).¹⁶ In patients with type 1 diabetes (β -cell deficiency) and patients with type 2 diabetes who have progressed to β -cell failure, the integrated balance between plasma glucose inflow and outflow is disrupted by virtue of the reduced secretion of insulin and amylin from the β -cell (**Figure 8**).¹⁷

Figure 7: Secretory Profiles of Amylin and Insulin in Nondiabetic Subjects



From Reference 16

Figure 8: Post-Meal Plasma Amylin Concentrations in Nondiabetic and Diabetic Subjects

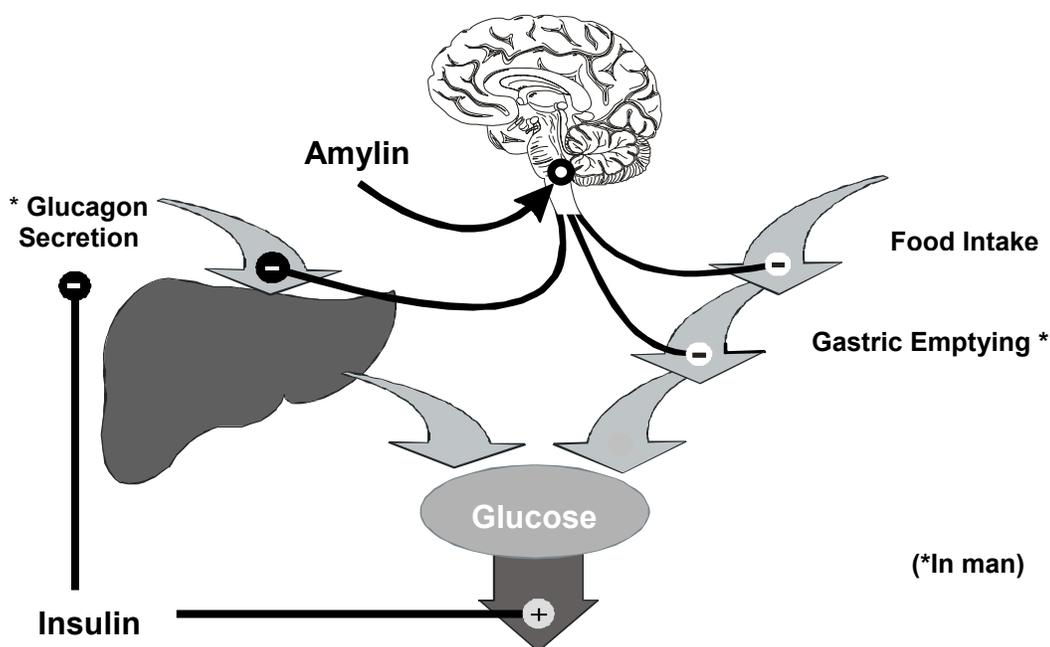


From Reference 17 and Amylin Pharmaceuticals, Inc. data on file

Pramlintide replaces deficient amylin. For patients with type 1 diabetes and patients with type 2 diabetes who use insulin, the impairment in the clearance of glucose from the plasma (outflow) during the postmeal period is redressed by insulin replacement therapy. However, there remains an unmet need to address the deficiency in the control of postmeal glucose appearance in the plasma (inflow), owing to a deficiency of amylin. Pramlintide replaces deficient amylin and, like amylin, inhibits postprandial glucagon secretion, thereby avoiding the effects of glucagon excess to drive hepatic glucose output during the postprandial period.^{18, 19} Pramlintide also regulates meal-derived nutrient delivery to the small intestine, an effect that optimizes the balance between glucose inflow and outflow during the absorptive period thereby reducing the postprandial surge in plasma glucose.^{20, 21}

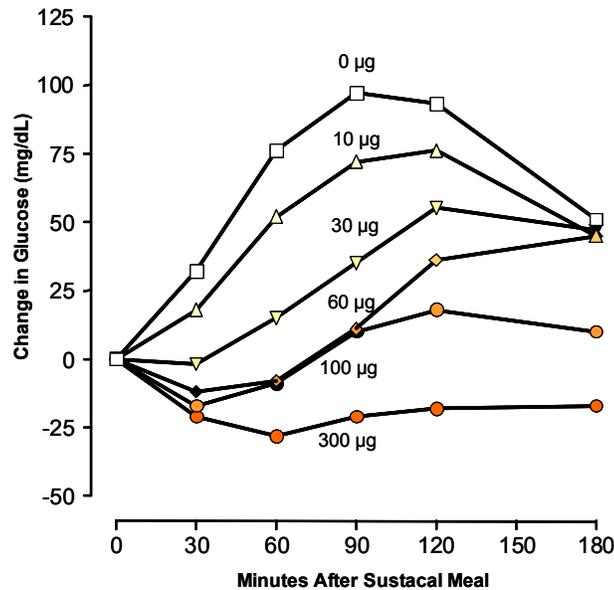
Importantly, there is no impediment of the counter-regulatory response to hypoglycemia when pramlintide is used to replace deficient amylin. In addition, the postmeal glucose-lowering actions of pramlintide are disabled during hypoglycemia, leaving intact the ability to treat hypoglycemia with oral carbohydrate. Finally, while there is no direct clinical evidence for a satiety effect of amylin, animal studies have shown that administration of either amylin or pramlintide results in reduced food intake.²² The observed weight loss in the long-term controlled clinical studies of pramlintide provides indirect support for such an effect in humans. The principal effects thought to contribute to the gluoregulatory activity of amylin are summarized in **Figure 9**.

Figure 9: Gluoregulatory Actions of Amylin / Pramlintide



Thus, pramlintide administration effectively replaces absent amylin agonist activity. Addition of pramlintide to insulin therapy safely redresses the tri-hormonal imbalance present in diabetes characterized by β -cell failure and α -cell dysregulation. Thus, pramlintide regulates the appearance of both meal-derived and endogenously produced glucose into the peripheral circulation and works in concert with insulin's effects to stimulate glucose disposal to mitigate postprandial hyperglycemia. This is evidenced by the ability of pramlintide to reduce postprandial glucose in a dose-related manner in patients with type 1 diabetes (**Figure 10**).

Figure 10: Pramlintide Reduces Postprandial Glucose Concentrations in a Dose-related Manner (Patients With Type 1 Diabetes; Studies AP93-08, 137-104, 137-105)

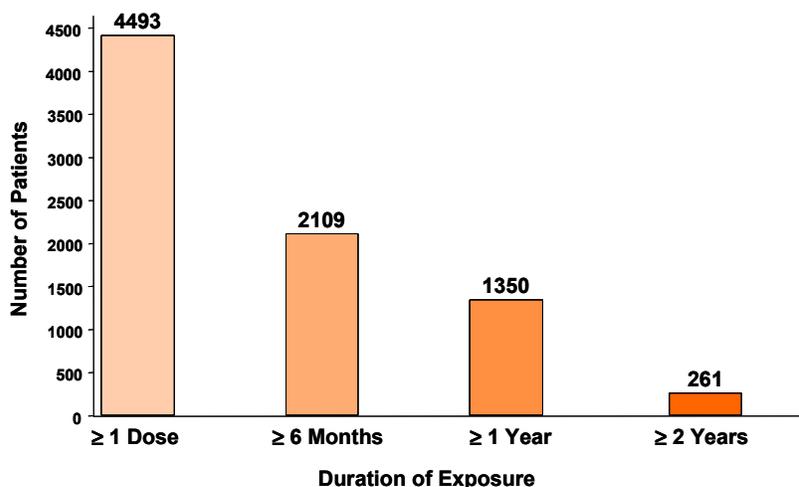


Data also presented in References 23, 24, and 25

6. SCOPE OF CLINICAL DEVELOPMENT PROGRAM

Pramlintide has been studied in 51 completed clinical trials enrolling a total of 5540 unique subjects (4493 pramlintide, 1504 placebo).^a There was a total of 2727 subject-years of pramlintide exposure, representing a mean exposure of 0.61 years per subject. Of subjects exposed to pramlintide, 1350 had exposure of ≥ 1 year and 261 had exposure of ≥ 2 years (**Figure 11**). The majority of study subjects were type 1 or insulin-using type 2 diabetes patients.

^a Patients in crossover studies and those in open-label extension studies who went from placebo to pramlintide treatment are counted in both the pramlintide and placebo categories.

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

Enumeration of subjects in the entire clinical development program (completed studies) is presented in Appendix 1. Also presented in Appendix 1 are summaries of subject disposition, subject exposure to pramlintide, and demographic characteristics.

7. CLINICAL PHARMACOKINETICS

Pramlintide is a short-acting subcutaneously injectable peptide therapy which is metabolized by proteolysis and cleared primarily via the kidney. In man, the N-terminal lysine residue is rapidly cleaved from pramlintide to form the fully active metabolite des-lys¹ pramlintide. The immunoassay used to detect plasma pramlintide is 100% cross-reactive with des-lys¹ pramlintide. Therefore, the assay measures all biologically active pramlintide (intact and metabolite).

Plasma concentrations of pramlintide increase in proportion to dose (30 to 120 µg) when administered subcutaneously to healthy volunteers (**Figure 12**). Following subcutaneous administration, pramlintide is quickly absorbed with a dose-independent T_{max} (~20 minutes) and mean C_{max} ranging from ~40 pmol/L (30 µg dose) to ~120 pmol/L (90 µg dose) in patients with type 1 diabetes (**Figure 13**). Concentrations in patients with type 2 diabetes tend to be lower (**Figure 14**), with a C_{max} range of ~30 pmol/L (60 µg dose) to ~166 pmol/L (180 µg dose). Observed pharmacokinetics are linear within the 30 to 180 µg dose range. The bioavailability of SC pramlintide is approximately 40%, and its kinetics are absorption-rate limited with an apparent elimination half-life of about 1 hour. Due to this short terminal half-life, multiple dose pharmacokinetics are the same as those following a single dose, and there is no evidence of pramlintide accumulation in plasma. In addition, as shown in Study 137-127, there was no significant effect of renal impairment on pramlintide pharmacokinetics. A list of the pramlintide pharmacokinetic clinical studies and their key findings is presented in Appendix 2.

Figure 12: Plasma Pramlintide Concentrations Increase in Proportion to Dose in Healthy Subjects (Study 137-126)

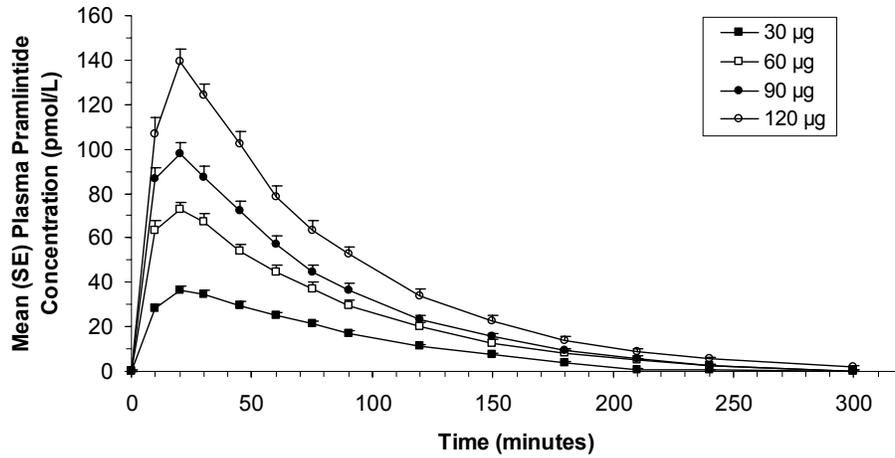


Figure 13: Plasma Pramlintide Concentrations in Patients With Type 1 Diabetes (Study 137-143)

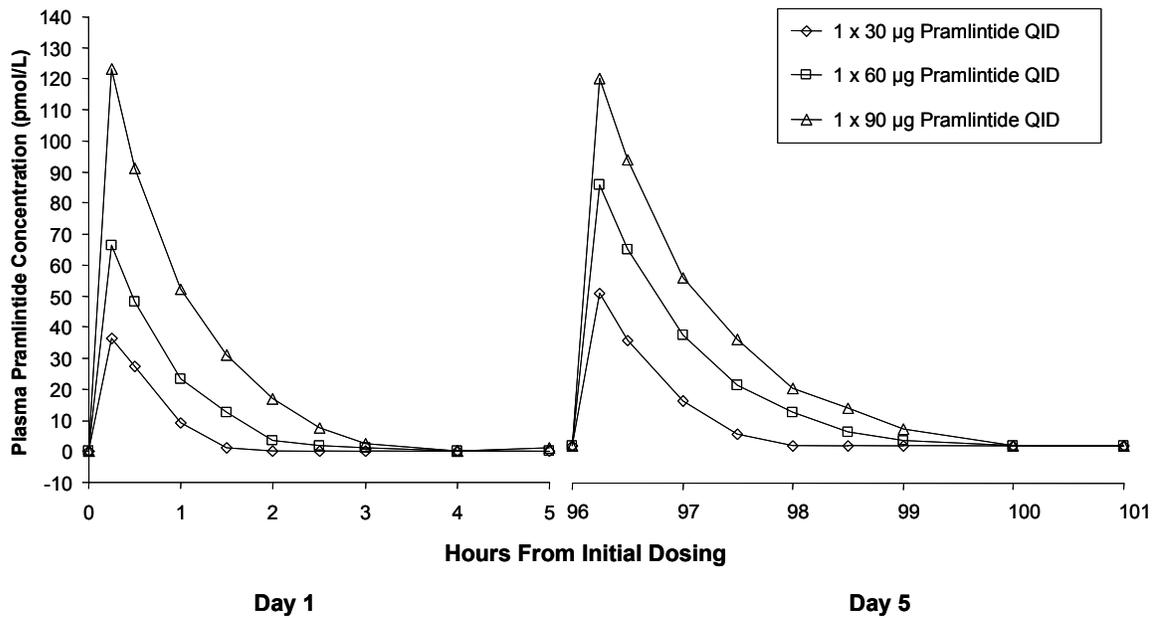
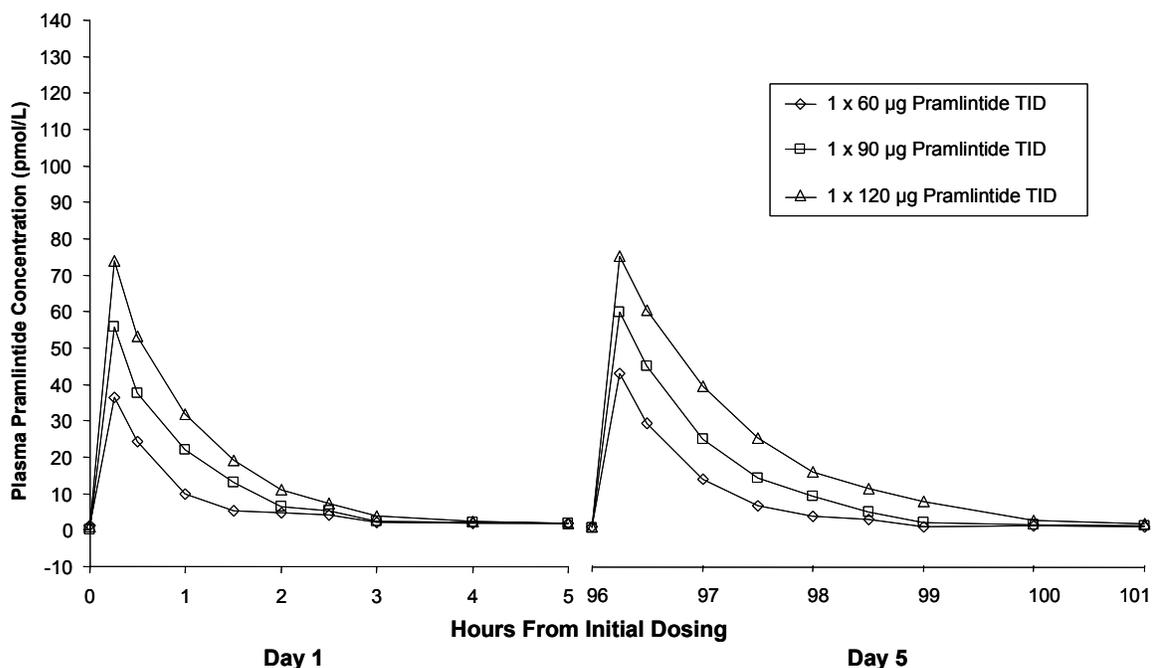


Figure 14: Plasma Pramlintide Concentrations in Patients With Type 2 Diabetes Who Use Insulin (Study 137-144)

8. CLINICAL PHARMACODYNAMICS

Pramlintide mechanism of action – reduced postprandial glucagon and modulation of gastric emptying. A reduction in postprandial hyperglycemia is the predominant pharmacodynamic effect of pramlintide therapy and is responsible for the reductions in HbA_{1c} observed in long-term controlled studies. Pramlintide administration is not associated with a reduction of fasting glucose concentrations in the targeted population (insulin-treated patients). Clinical studies have identified two principal mechanisms of action of pramlintide that are responsible for the reduction in postprandial plasma glucose concentrations observed following subcutaneous administration. They are:

- reduction of abnormal postprandial glucagon secretion (**Figure 15**); and
- modulation of the delivery rate of ingested nutrients into the small intestine (modulation of gastric emptying) (**Figure 16**).

These actions regulate the influx of both endogenously-produced and meal-derived glucose into the peripheral circulation and work in concert with the effects of insulin, which are primarily directed at stimulating glucose efflux into peripheral tissues. The effects of pramlintide are limited to the meal period immediately following dosing and do not carry over to a subsequent meal if no additional drug is administered (**Figure 16**). Both effects have been demonstrated in patients with type 1 and type 2 diabetes.

Figure 15: Pramlintide Decreases Post-Meal Plasma Glucagon (Study AP93-08: Patients With Type 1 Diabetes)

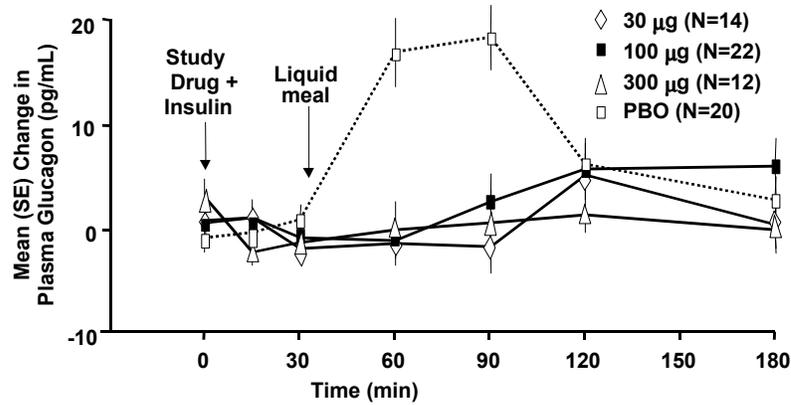
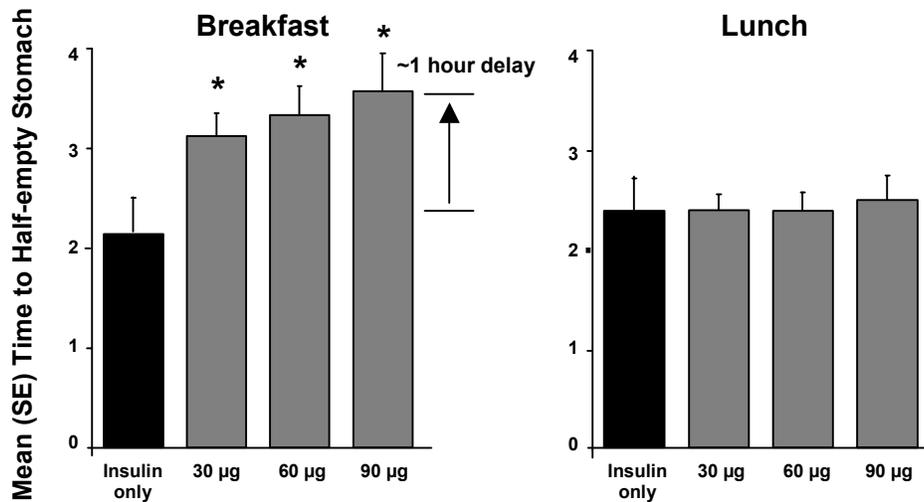


Figure 16: Single Dose Effect of Pramlintide Administered in Conjunction With Breakfast on Gastric Half-Emptying Times After Breakfast and Lunch (Study 137-118: Patients With Type 1 Diabetes)

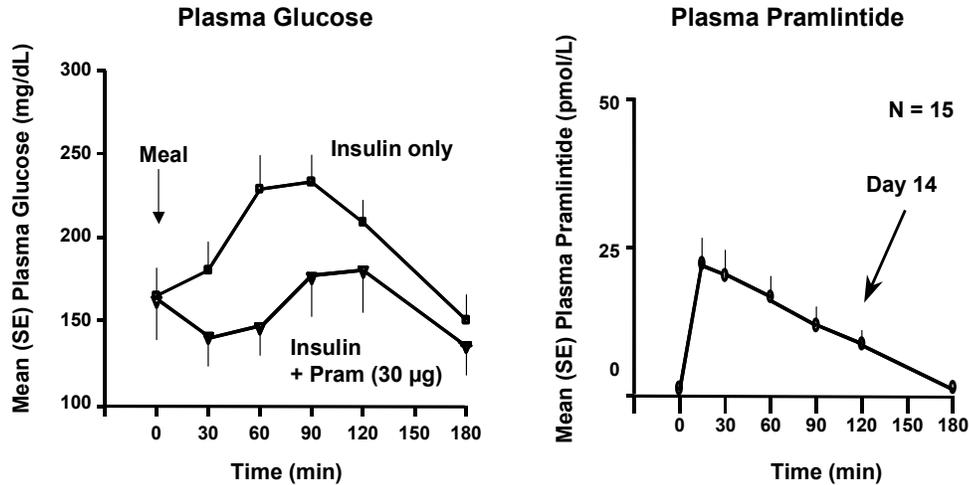


* p < 0.004 vs. placebo
 Single SC doses (N = 11, crossover);
 Tc-99m labelled pancake; solid component measured
 Note: no study medication administered at lunch.

Pramlintide reduces postprandial glucose in insulin-treated patients with diabetes. As shown in Figure 17, pramlintide reduces post-meal plasma glucose concentrations and

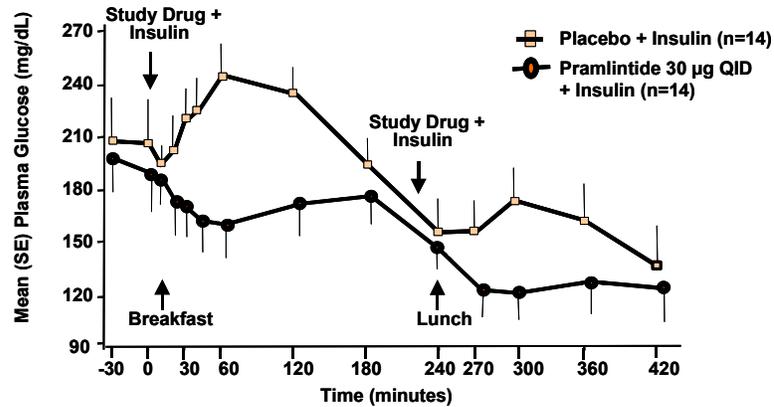
delays the time to maximum glucose concentration, as compared to placebo. The corresponding plasma pramlintide concentration profile is consistent with rapid absorption and a short elimination half-life for pramlintide. The plasma pramlintide concentrations achieved are similar to postprandial amylin concentrations in healthy subjects (**Figure 7**).

Figure 17: Pramlintide Decreases Post-Meal Plasma Glucose Concentrations (Study AP93-08: Patients With Type 1 Diabetes)



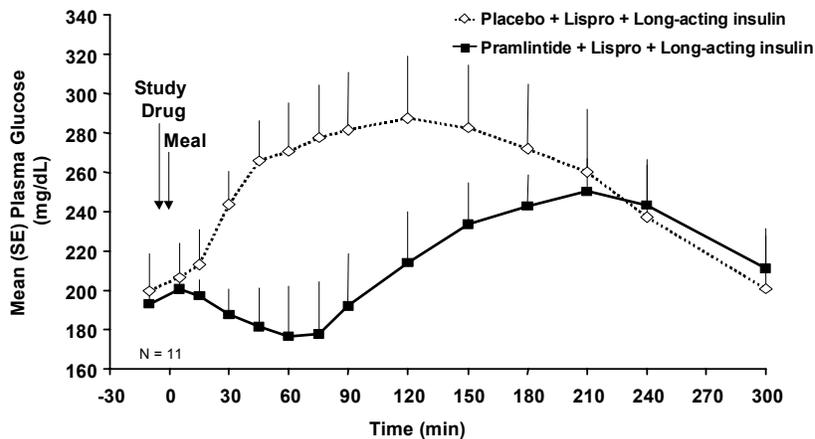
The acute effects of pramlintide on the reduction of postprandial hyperglycemia are also seen in the similar postprandial glucose profiles presented in **Figure 18** and **Figure 19**. As shown in **Figure 18**, injection of pramlintide at two consecutive meals (breakfast and lunch) resulted in reduction of postprandial plasma glucose concentrations at both meals. As noted earlier, however, there is no carryover effect of a single dose to a subsequent meal, and there is no effect on fasting glucose concentrations.

Figure 18: Pramlintide Decreases Post-Meal Plasma Glucose Concentrations When Administered at Two Consecutive Meals (Study 137-107: Patients With Type 1 Diabetes)



In addition, when pramlintide-treated patients were treated concomitantly with the short-acting insulin lispro (administered together with a long-acting insulin), a reduction in postprandial glucose was still observed, as compared to the patients receiving insulin lispro and long-acting insulin combination alone (**Figure 19**). This indicates that pramlintide achieves a postprandial glucose reduction over and above that produced by insulin lispro alone.

Figure 19: Pramlintide in Combination With Insulin Lispro + Long-Acting Insulin Decreases Post-Meal Plasma Glucose Concentrations as Compared to Insulin Lispro+Long-Acting Insulin Alone (Study 137-130: Patients With Type 1 Diabetes)



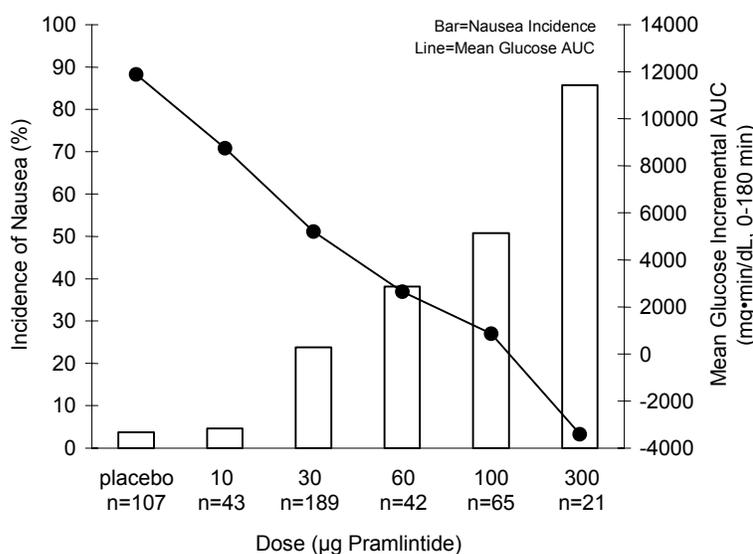
A list of pramlintide clinical pharmacodynamic studies and their key findings is presented in Appendix 3.

9. CLINICAL DEVELOPMENT PROGRAM

9.1 Selection of Doses to Study in Clinical Trials

As shown previously, evidence from clinical pharmacology studies indicates 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 (**Figure 10**). Dose-limiting side effects (which occurred at lower doses in patients with type 1 diabetes compared with type 2 diabetes) were limited to primarily nausea, vomiting, and anorexia. Based on the observed safety profiles (primarily nausea) relative to the dose-response for glucose lowering (**Figure 20**), a range of doses [(30 µg to 90 µg for type 1 diabetes studies) and (90 µg to 150 µg for type 2 diabetes studies)] was explored in the long- and short-term controlled studies. Information obtained from the early controlled studies were used to further refine the doses selected for later studies. As will be shown in the following sections, the recommended doses based on efficacy and safety outcomes of long-term controlled studies are 30 or 60 µg TID or QID for type 1 diabetes and 120 µg BID or TID for type 2 diabetes. These doses of pramlintide were administered in conjunction with meals based on the known primary effects of pramlintide on postprandial glucose, as has been demonstrated in both animal and human studies.

Figure 20: Pramlintide Dose-Relationship of Glucose Lowering Effects and Nausea (Patients With Type 1 Diabetes; Studies AP93-08, 137-104, 137-105)

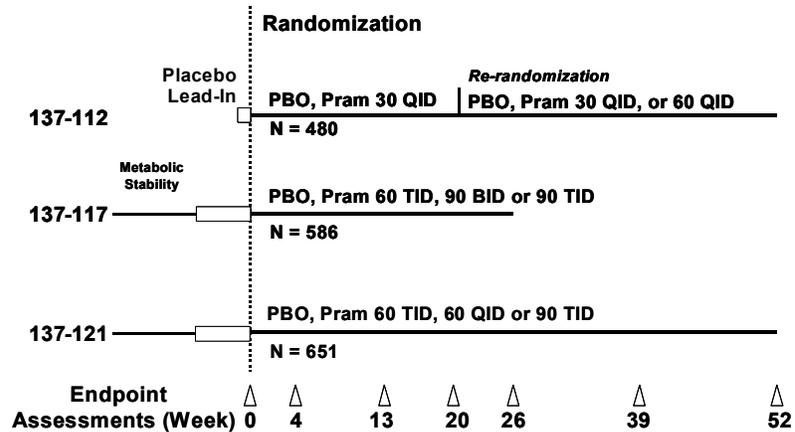


9.2 Study Design and Statistical Considerations

Controlled Study Trial Designs. Eight controlled efficacy and safety studies of pramlintide were conducted: four in patients with type 1 diabetes (Studies 137-105, 137-121, 137-112 and 137-117) and four in patients with type 2 diabetes treated with insulin (Studies 137-114,

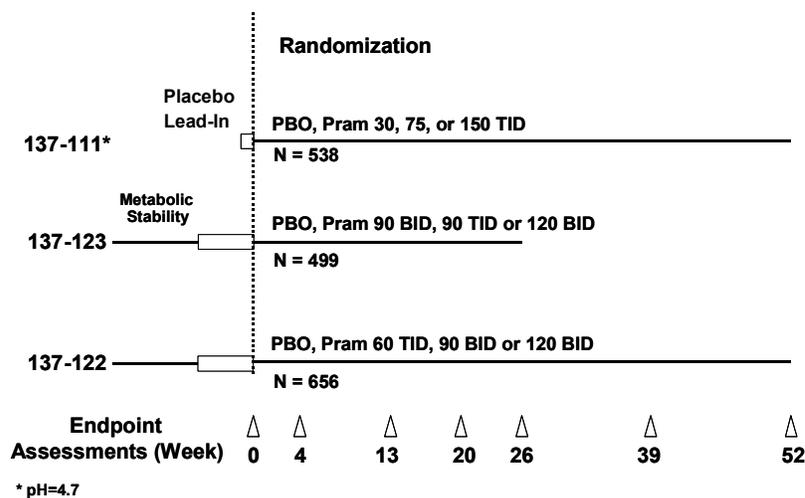
137-122, 137-111 and 137-123). In the terms of the ICH draft guidance, “E10 Choice of Control Group in Clinical Trials,” these were “add-on” placebo-controlled trials, with pramlintide being added on to insulin. Of these eight studies, six were conducted over a 6- to 12-month period. The key aspects of these six long-term controlled trials are illustrated in **Figure 21** and **Figure 22**.

Figure 21: Long-Term Controlled Type 1 Diabetes Study Designs



Type 1 Study 137-112 included a re-randomization (30 or 60 µg QID) of pramlintide-treated patients at Week 20 based on HbA_{1c} response at Week 13. As the results for patients appeared comparable irrespective of having received the 30 or 60 µg dose, these patients’ data were analyzed together and the active treatment arm in this study is referred to as 30/60 µg QID throughout this document.

Figure 22: Long-Term Controlled Insulin-Using Type 2 Diabetes Study Designs



Type 2 Study 137-111 was conducted using a formulation of pramlintide different from the intended commercial formulation that was used in Studies 137-122 and 137-123. The bioavailability of this formulation is decreased by approximately 30% relative to the intended commercial formulation. Therefore, while the results obtained using 150 µg TID in Study 137-111 are comparable to the results in the other studies using 120 µg BID, 150 µg TID is not a recommended dosage.

Entry criteria common to the six long-term controlled studies included an HbA_{1c} of ≥8.0% at screening, documented evidence of type 1 or type 2 diabetes (as appropriate for each study) for at least 1 year, stable weight, and clinical laboratory test results normal or abnormal but consistent with diabetes. Patients with clinically significant cardiac disease, untreated or poorly controlled hypertension, or a clinically significant history or presence of hepatic, renal, central nervous system, gastrointestinal, pulmonary, or hematologic disease were generally to be excluded from the studies. Concomitant medications frequently used by patients with diabetes (oral hypoglycemic agents with the exception of acarbose and glitazones, angiotensin-converting enzyme (ACE) inhibitors, anti-hypertensives, other cardiac medications and lipid lowering agents) were allowed. The use of prokinetic agents (including macrolide antibiotics), acarbose, bile acid sequestering resins, and dexfenfluramine was not allowed.

Insulin Use During Controlled Clinical Studies. Short-term controlled studies 137-105 and 137-114, and long-term controlled studies 137-112 and 137-111 simulated normal clinical care in that the insulin dose for each patient could be freely adjusted in accordance with good medical practice. In long-term studies, 137-121, 137-117, 137-123, and 137-122, investigators were encouraged to maintain each patient's insulin dose to within ±10% of the dose established for the patient during the study lead-in period. While this design was selected to better isolate the drug effect of pramlintide, many investigators and patients did change insulin regimens as needed to maintain glycemic control, particularly after the Week 4 visit. In the studies involving patients with type 2 diabetes, patients using oral hypoglycemic agents in conjunction with insulin continued these agents at a fixed dose throughout the study.

Efficacy Endpoints. In both short-term controlled studies (137-105 and 137-114), the primary efficacy endpoint was change in serum fructosamine from baseline to Day 28 of treatment. This endpoint was considered appropriate as serum fructosamine concentrations reflect the average blood glucose concentration of a patient over the prior 2 weeks.

In the two initial 1-year controlled studies (137-112 and 137-111) the primary efficacy endpoint was defined as the relative change (percent of baseline value) in HbA_{1c} from baseline to 52 weeks. For the other long-term controlled studies (137-117, 137-121, 137-123, and 137-122), the primary efficacy endpoint was defined as change in HbA_{1c} from

baseline to 26 weeks. These endpoints were considered appropriate as HbA_{1c} is a measure of long-term glycemic control, reflecting the average blood glucose concentration of a patient over the prior 3 months. The primary endpoints are summarized in **Table 1**.

In studies 137-112 and 137-111, change in HbA_{1c} from baseline was considered a secondary endpoint, while in the other four long-term controlled studies, relative change in HbA_{1c} was considered a secondary endpoint. Other secondary endpoints in all of the long-term controlled studies included changes in body weight and concomitant insulin use. Body weight was analyzed as the change from baseline to various time points within the study. Insulin use was analyzed as the percent change in total daily insulin dose from baseline to various time points within the study.

Analysis Populations. In the two initial 1-year controlled studies (137-112 and 137-111) the primary analysis population was the evaluable population, prospectively defined as those subjects who completed 52 weeks of therapy. The intent-to-treat population was defined as those patients randomized to a double-blind treatment group who received at least one dose of study medication and was a secondary analysis population. In the other long-term controlled studies, (137-117, 137-121, 137-123, and 137-122), the primary analysis population was the intent-to-treat population, prospectively defined the same as as in the two initial 1-year studies, although an evaluable population was also defined for these studies to provide a secondary analysis population. In general, the results obtained using the intent-to-treat and evaluable populations were comparable in all studies, both in terms of magnitude of effect and outcome of inferential statistical tests. The primary analysis populations are summarized in **Table 1**.

Statistical Analysis Methods. Analysis of variance (ANOVA) was used to analyze change in HbA_{1c} in all six long-term studies. In studies with multiple active treatment arms, specific predefined multiple comparison adjustment procedures were employed, as shown in **Table 1**.

Table 1: Prospectively Defined Statistical Analysis Approaches for Long-Term Controlled Studies

Diabetes	Study	Doses	Statistical Analysis Details				
			Primary Population	Primary Endpoint	Study Week	Method	Multiple Comparisons
Type 1	137-112	Placebo, 30/60 µg QID	Evaluable	%ΔHbA _{1c}	52	ANOVA	N/A
	137-117	Placebo, 90 µg BID, 60 µg TID, 90 µg TID	ITT	ΔHbA _{1c}	26	ANOVA	Step Down
	137-121	Placebo, 60 µg TID, 60 µg QID, 90 µg <i>TID</i>	ITT	ΔHbA _{1c}	26	ANOVA	Fisher's LSD
Type 2	137-111	Placebo, 30 µg TID, 75 µg TID, 150 µg TID	Evaluable	%ΔHbA _{1c}	52	ANOVA	Hochberg
	137-123	Placebo, 90 µg BID, 120 µg BID, 90 µg TID	ITT	ΔHbA _{1c}	26	ANOVA	Step Down
	137-122	Placebo, 60 µg <i>TID</i> , 90 µg BID, 120 µg BID	ITT	ΔHbA _{1c}	26	ANOVA	Fisher's LSD

In studies 137-121 and 137-122, the 90 µg TID and 60 µg TID treatment arms (shown in *italics*), respectively, were prospectively excluded from the analysis after agreement by the Agency.

A summary of the treatment arms in each study which formally achieved statistical significance using the prospectively defined analysis methods and populations is summarized in **Table 2**.

Table 2: Pramlintide Treatment Arms for Which Change in HbA_{1c} Achieved Formal Statistical Significance Compared With Placebo, Using the Prospectively Defined Analysis Methods

Study	Primary HbA _{1c} Endpoint	Significant Difference From Placebo ^a	Other Results and Statistical Interpretation
137-112	Relative Change at Week 52, Evaluable	30/60 µg QID	<ul style="list-style-type: none"> 30/60 µg QID ΔHbA_{1c} at Week 26 (Intent-to-Treat) statistically significant^b
137-117	Change at Week 26, Intent-to-Treat	None	<ul style="list-style-type: none"> For 1^o analysis, initial multiple comparison not significant, so other groups not tested 60 µg TID ΔHbA_{1c} at Week 26 (Intent-to-Treat) statistically significant^c
137-121	Change at Week 26, Intent-to-Treat	60 µg TID 60 µg QID	<ul style="list-style-type: none"> 90 µg TID prospectively excluded from analysis
137-111	Relative Change at Week 52, Evaluable	None	<ul style="list-style-type: none"> For 1^o analysis, initial multiple comparison not significant, so other groups not tested 75 µg TID and 150 µg TID ΔHbA_{1c} at Week 26 (Intent-to-Treat) statistically significant^b
137-123	Change at Week 26, Intent-to-Treat	None	<ul style="list-style-type: none"> For 1^o analysis, initial multiple comparison not significant, so other groups not tested 120 µg BID ΔHbA_{1c} at Week 26 (Intent-to-Treat) statistically significant^c Due to imbalance in baseline HbA_{1c}, reanalyzed using post hoc ANCOVA – 90 µg BID, 120 µg BID, 90 µg TID ΔHbA_{1c} at Week 26 (Intent-to-Treat) statistically significant
137-122	Change at Week 26, Intent-to-Treat	120 µg BID	<ul style="list-style-type: none"> 60 µg TID prospectively excluded from analysis

^a Using prospectively-defined primary (1^o) endpoint and analysis method.

^b Prospectively-defined secondary (2^o) endpoint; statistically significant difference compared with placebo.

^c Prospectively-defined secondary (2^o) endpoint; nominally (i.e., not taking into account multiple comparisons) statistically significant (p<0.05) difference compared with placebo.

As shown in **Table 2**, a consistent finding of statistically significant changes in HbA_{1c} (based on prospectively-defined endpoints and analysis methods) was observed in type 1 studies 137-112 and 137-121, and in type 2 study 137-122. Other studies showed statistical significance in pre-specified secondary analyses supportive of the overall findings and recommended doses. In studies 137-111 and 137-123, the baseline HbA_{1c} values were imbalanced across the treatment arms. Using analysis of covariance (ANCOVA) with baseline HbA_{1c} in the model, both of these type 2 diabetes studies achieved statistical significance for their primary pre-specified endpoints. In type 2 study 137-122, statistical significance was achieved using either the ANOVA or ANCOVA techniques.

Since there are slight differences in the specifics of the prospective primary endpoints across the six studies, it was felt useful to apply a consistent approach to presenting data across studies. For this purpose, the common endpoint examined in the NDA and in this document is change in HbA_{1c} from baseline at Week 26, analyzed using the intent-to-treat population with last observation carried forward (LOCF). This was the prospectively defined method for four of the six studies (137-117, 137-121, 137-123, 137-122). The details of the other statistical analyses can be seen in the individual report synopses (see Appendix 4).

10. OVERVIEW OF CLINICAL FINDINGS: CONTROLLED STUDIES

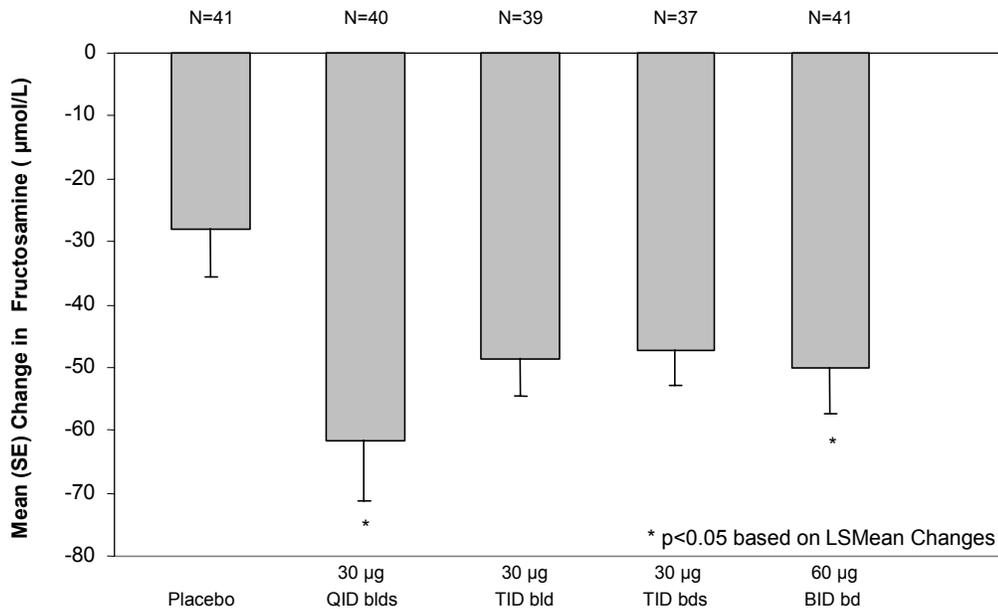
10.1 Type 1 Diabetes

All four controlled studies (137-105, 137-112, 137-117, and 137-121) demonstrate or support the effectiveness of pramlintide in improving glycemic control in patients with type 1 diabetes. Study 137-105 was a short-term (1-month) controlled study, and the other three were long-term controlled studies. Studies 137-121 and 137-112 were each 12 months in duration, and Study 137-117 was 6 months in duration. All four studies were placebo-controlled.

10.1.1 Short-Term Controlled Study

In Study 137-105, 4 weeks of pramlintide administration (30 µg QID) significantly reduced 24-hour plasma glucose AUC_(0-1440 min) and mean glucose concentrations (C_{ave}), Sustacal test meal plasma glucose AUC_(0-180 min), and serum fructosamine concentrations (Appendix 4; Section 1.1.1). Treatment with 60 µg BID also resulted in a statistically significant reduction in fructosamine concentrations after 4 weeks (**Figure 23**). These effects were not due to increased insulin use, as 24-hour serum insulin AUC_(0-1440 min) and Sustacal test meal serum insulin AUC_(0-180 min) profiles were reduced in pramlintide patients as compared to placebo. Results from the other TID and BID pramlintide dosing regimens in the study displayed similar trends. Pramlintide treatment not only reduced 24-hour plasma glucose AUC_(0-1440min) but also appeared to reduce the variability in plasma glucose concentrations throughout the day. This reduction in the amplitude of glucose fluctuations is evidenced by a reduction in the mean range and standard deviation of plasma glucose concentrations.

Figure 23: Change in Serum Fructosamine (µmol/L) From Screening at 28 Days (Study 137-105: Short-Term Controlled Study in Patients With Type 1 Diabetes; Population: Evaluable)



b, breakfast; l, lunch; d, dinner; s, bedtime snack.

10.1.2 Long-Term Controlled Studies

Demographic and Baseline Characteristics. A total of 1717 patients with type 1 diabetes (1179 pramlintide, 538 placebo) entered the long-term controlled studies (**Table 3**). Of these, 778 (66%) of the pramlintide patients and 403 (75%) of the placebo patients completed the studies. There were approximately equal numbers of males and females in the pramlintide and placebo groups. Consistent with the known demographics of type 1 diabetes, the majority of patients enrolled were white (93-95%); 2% were black and 3% were Hispanic. The mean age of patients was approximately 40 years. Baseline HbA_{1c} concentrations after placebo lead-in ranged from 5.7% to 13.7% (mean approximately 9.0%), and duration of diabetes prior to entering the study ranged from 1.0 to 58.0 years (mean approximately 19 years). Demographic and baseline characteristics appeared well-matched across treatment groups. In all studies, patients' usual insulin therapy was continued. Demographic and baseline characteristics for the long-term controlled studies in patients with type 1 diabetes are presented in Appendix 1.

Table 3: Long-Term Controlled Studies in Type 1 Diabetes

Study No. Location	Study design	Treatment	No. of Patients	Duration (Weeks)
137-112 US	multicenter, parallel group, double-blind	pramlintide pH 4.0 30/60 µg QID , SC, blds*† placebo	243 237	52
137-117 Europe/Canada	multicenter, parallel group, double-blind	pramlintide pH 4.0 90 µg BID, SC, bd 60 µg TID , SC, bld 90 µg TID, SC, bld placebo	144 148 147 147	26
137-121 US/Canada	multicenter, parallel group, double-blind	pramlintide pH 4.0 60 µg TID , SC, bld 60 µg QID , SC, blds 90 µg TID, SC, bld placebo	164 161 172 154	52

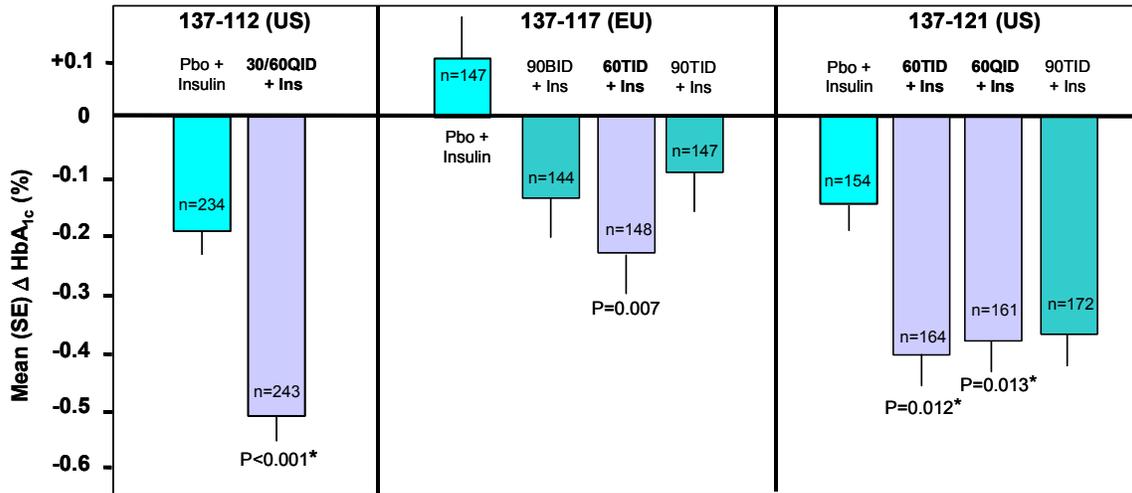
Recommended doses are shown in **bold**.

* b, breakfast; l, lunch; d, dinner; s, bedtime snack.

† Initial randomization to either 30 µg or placebo, with second randomization of 30 µg patients to either 30 µg or 60 µg at Week 20 based on HbA_{1c} response at Week 13.

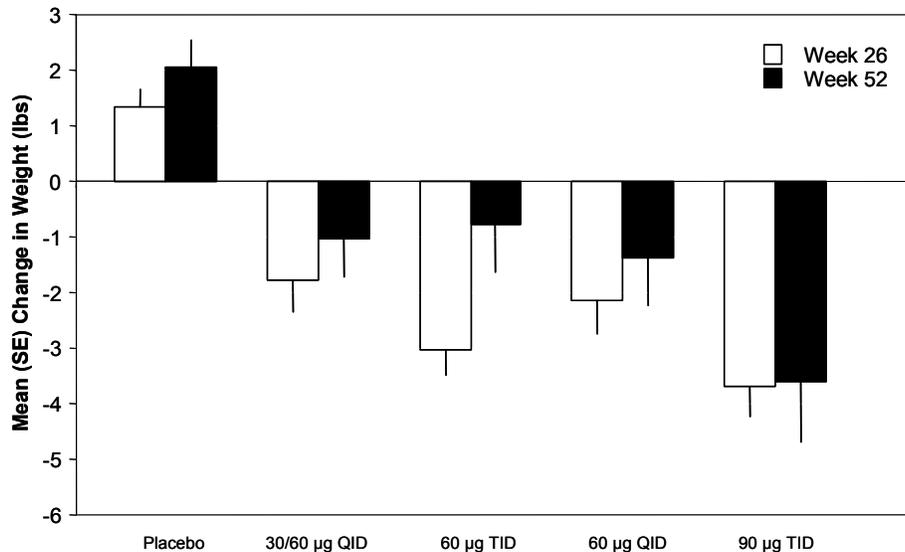
Pramlintide effects on HbA_{1c}, body weight, and insulin use. All three long-term, controlled studies demonstrated a favorable, statistically significant effect of pramlintide on glycemic control in patients with type 1 diabetes. At all the pramlintide dosage regimens tested in combination with insulin, clinically significant mean absolute reductions from baseline in HbA_{1c} at Week 26 (**Figure 24**) and at Week 52 (two studies) were observed that were greater than those observed with placebo+insulin. The reductions in HbA_{1c} were achieved without a concomitant increase in total daily insulin dose; mean total daily doses of insulin in patients treated with pramlintide either decreased or, in the case of the 30/60 µg QID group in Study 137-112, remained approximately the same in contrast to the larger increases in insulin dose observed in the placebo group. There was a decrease in body weight among patients with type 1 diabetes treated with pramlintide, compared with mean increases in weight among insulin+placebo patients (**Figure 25**).

Figure 24: Mean Change in HbA_{1c} From Baseline at Week 26 (Long-Term Controlled Studies in Type 1 Diabetes; Population: Intent-to-Treat, LOCF)



Note: A p-value with an asterisk indicates that statistical significance of the primary study endpoint was achieved using the prospectively defined criteria for each study. A p-value without an asterisk indicates nominal significance at the p<0.05 level. Recommended doses are shown in **boldface**.

Figure 25: Mean Change in Weight From Baseline at Weeks 26 and 52 (Long-Term Controlled Studies in Type 1 Diabetes Combined; Population: Evaluable as Defined in Each Study)



In the two 1-year studies, the clinically and statistically reductions in HbA_{1c} and body weight were maintained throughout the 52 weeks of treatment for the evaluable population using the recommended doses (30 or 60 µg TID or QID) identified for type 1 diabetes (**Table 4**). In addition, patients treated with pramlintide generally decreased insulin use throughout the three studies whereas patients treated with insulin+placebo generally increased insulin use.

Table 4: Summary of Mean Change From Baseline in HbA_{1c}, Total Daily Insulin Dose, and Body Weight in Long-Term Studies in Patients With Type 1 Diabetes by Recommended Dose (Population: Evaluable)

	Mean Change in HbA _{1c} (%) ¹		Mean Relative (%) Change in Total Daily Insulin ²		Mean Change in Weight (lbs) ³	
	Week 26	Week 52	Week 26	Week 52	Week 26	Week 52
137-112						
Placebo	-0.18	-0.12	9.69	10.03	1.65	2.22
Pramlintide 30/60 µg QID	-0.58*	-0.39*	1.05	2.27	-1.76*	-1.03*
137-117						
Placebo	0.08	NA	0.94	NA	0.75	NA
Pramlintide 60 µg TID	-0.19†	NA	-2.20	NA	-3.43*	NA
137-121						
Placebo	-0.21	0.05	3.55	-0.28	1.50	1.76
Pramlintide 60 µg TID	-0.54†	-0.35*	-0.10	-2.52	-2.57*	-0.77
Pramlintide 60 µg QID	-0.40	-0.33*	-4.16	-6.07	-2.16*	-1.36*

¹ Analysis of covariance procedure with treatment regimen and site as factors in the model and baseline HbA_{1c} as a covariate.

² Relative change from baseline; statistical difference between treatments not assessed for this variable.

³ Analysis of variance procedure with treatment regimen and site as factors in the model, outliers removed prior to unblinding.

* Statistically significant difference from placebo + insulin.

† Pairwise comparison was statistically significant at nominal < 0.05 level

NA, not applicable (6-month study).

Note: Values presented are unadjusted means for the evaluable population (defined as having completed 26 weeks [137-117, 137-121] or 52 weeks [137-112]).

While investigators in studies 137-117 and 137-121 were encouraged to maintain each patient's insulin dose to within $\pm 10\%$ of the dose established for the patient during the study lead-in period, many investigators and patients did change insulin regimens following the initial weeks of therapy as clinically indicated to avoid hypoglycemia and maintain glycemic control. This variation in insulin doses reflects standard clinical practice, but it presents a confounding factor in evaluating the drug effect of pramlintide. Therefore, to better isolate the drug effect of pramlintide over and above that of insulin, a stable insulin population (patients who did not alter total daily insulin dose by more than 10%) was evaluated. Overall, the stable insulin population represents about 30% of the patients (both pramlintide and placebo) enrolled in the three long-term, controlled studies.

Data from 1-year study 137-121 illustrate that in general, a larger reduction in HbA_{1c} from baseline was observed for the stable insulin population compared with the intent-to-treat population for patients with type 1 diabetes (**Table 5**). While the pattern of HbA_{1c} reduction for the two populations was similar throughout the course of the study, the magnitude of effect seen with pramlintide relative to placebo was greater in the stable insulin population, the true drug effect group, than the intent-to-treat at all time points (**Figure 26** and **Figure 27**).

Table 5: Change in HbA_{1c} at 26 Weeks and 52 Weeks for the Intent-to-Treat and Stable Insulin Populations (Study 137-121: Patients With Type 1 Diabetes)

Intent-to-Treat	Placebo	60 µg TID	60 µg QID	90 µg TID
	(N=154)	(N=164)	(N=161)	(N=172)
Baseline HbA _{1c} (%)	8.9	9.0	8.9	8.9
Change in HbA _{1c} (%) from baseline at Week 26	-0.18	-0.41	-0.39	-0.38
Change in HbA _{1c} (%) from baseline at Week 52	-0.04	-0.29	-0.34	-0.26
Stable Insulin	Placebo	60 µg TID	60 µg QID	90 µg TID
	(N=36)	(N=30)	(N=30)	(N=18)
Baseline HbA _{1c}	9.0	9.2	8.7	9.1
Change in HbA _{1c} (%) from baseline at Week 26	-0.23	-0.83	-0.64	-0.73
Change in HbA _{1c} (%) from baseline at Week 52	0.13	-0.59	-0.57	-0.74

Figure 26: Change in HbA_{1c} Through 52 Weeks for the Intent-to-Treat Population (Study 137-121: Patients With Type 1 Diabetes)

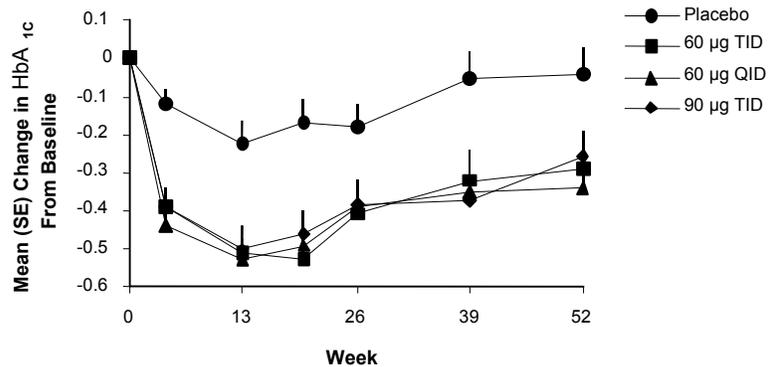
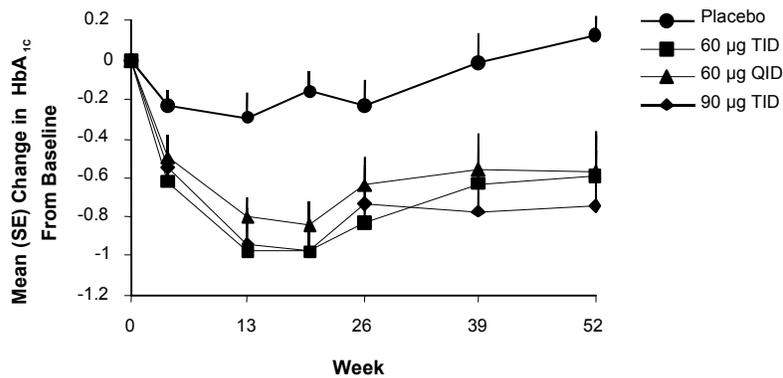
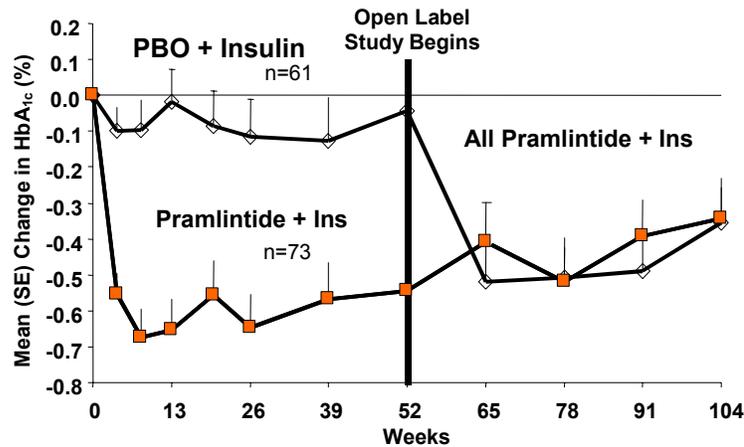


Figure 27: Change in HbA_{1c} Through 52 Weeks for the Stable Insulin Population (Study 137-121: Patients With Type 1 Diabetes)



As shown previously (**Table 4**), clinically and statistically significant reductions in HbA_{1c} concentrations were observed at the dosage regimens of 30/60 µg QID, 60 µg TID, and 60 µg QID, which were maintained throughout 52 weeks of the study. The long-term effectiveness of pramlintide on glycemic control in patients with type 1 diabetes was further demonstrated for up to 104 weeks of treatment in the uncontrolled study 137-112E (**Figure 28**).

Figure 28: Reduction in HbA_{1c} Sustained Over 2 Years of Treatment With Pramlintide (Study 137-112 and Open-Label Extension; Population: Intent-to-Treat, Observed Values)



Pramlintide treatment is associated with reaching HbA_{1c} targets. In addition to examining change in HbA_{1c}, the proportion of patients achieving specific HbA_{1c} targets was assessed. In all three long-term controlled type 1 studies, more patients treated with pramlintide+insulin achieved HbA_{1c} concentrations that reached defined targets for control of diabetes than did patients treated with insulin only (placebo); this is exemplified by data from type 1 study 137-121 (**Table 6**).

Table 6: Proportion of Patients (%) Achieving HbA_{1c} Reductions and Targets in Type 1 Study 137-121 at Recommended Doses (Population: Intent-to-Treat)

HbA _{1c} Parameter*	Percent of Patients					
	Week 26			Week 52		
	Placebo	Pramlintide 60 µg		Placebo	Pramlintide 60 µg	
		TID	QID		TID	QID
Reduction						
≥0.50%	52	74	77	65	79	81
≥0.75%	35	52	62	44	66	59
≥1.00%	27	39	47	31	55	43
Target†						
<8.0%	28	47	46	30	51	52
<7.0%	3	11	12	4	14	13
Reduction ≥0.50% and HbA _{1c} <8.0%	24	44	45	28	50	51

* Includes only patients who had baseline HbA_{1c} values above specified targets. Proportion of patients calculated as: 1 - Kaplan-Meier estimate based on survival analysis; excludes patients without baseline values; no data imputation.

In addition to the targets described above, a subpopulation was defined to include those patients who achieved a reduction in HbA_{1c} at Week 4 of ≥0.5%. More patients treated with pramlintide+insulin than patients treated with insulin only (placebo) had this magnitude of reduction in HbA_{1c} at Week 4 (**Table 7**). It is noteworthy that those patients achieving a ≥0.5% reduction in HbA_{1c} at Week 4 exhibited HbA_{1c} reductions at Week 26 of approximately 0.6% to 0.9% in type 1 study 137-121. Nevertheless, clinically relevant decreases in HbA_{1c} and weight were observed in many patients even if this early robust response in HbA_{1c} was not achieved.

Table 7: Proportion of Patients (%) Achieving an HbA_{1c} Reduction of ≥0.5% at Week 4 in Type 1 Study 137-121 at Recommended Doses (Population: Intent-to-Treat)

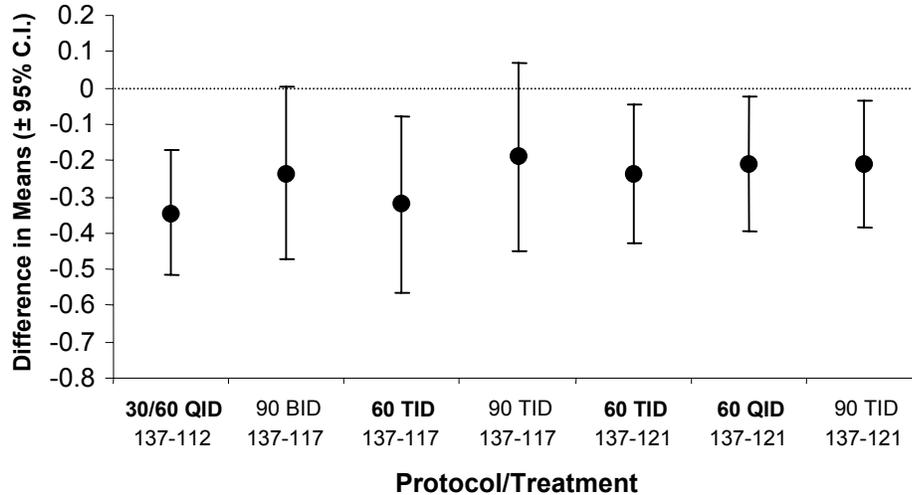
HbA _{1c} Parameter*	Percent of Patients		
	Placebo	Pramlintide 60 µg	
		TID	QID
Reduction of ≥0.50% at Week 4	20	38	42

* Includes only patients who had baseline HbA_{1c} values above specified targets. Proportion of patients calculated as: 1 - Kaplan-Meier estimate based on survival analysis; excludes patients without baseline values; no data imputation.

Summary of efficacy findings in type 1 diabetes. In all three long-term controlled studies, patients with type 1 diabetes treated with the recommended doses of pramlintide (30 or 60 µg TID or QID) for 26 weeks consistently experienced mean decreases in HbA_{1c} (**Figure 29**) and body weight compared with patients treated with placebo. Pramlintide-treated patients also appeared to use less insulin than placebo-treated patients. The effects were sustained throughout 1-year in two studies, and in at least one extension study, the reduction in HbA_{1c}

was maintained for 2 years. Although not shown in this document, pramlintide had no adverse effects on lipid profiles in patients with type 1 diabetes studied in the three long-term controlled trials.

Figure 29: Difference in Treatment Means Between Pramlintide and Placebo (Treatment Effect), With 95% Confidence Intervals, for Change in HbA_{1c} From Baseline at Week 26 (Long-Term Controlled Studies in Type 1 Diabetes; Population: Intent-to-Treat)



Note: Recommended doses are shown in **boldface**.

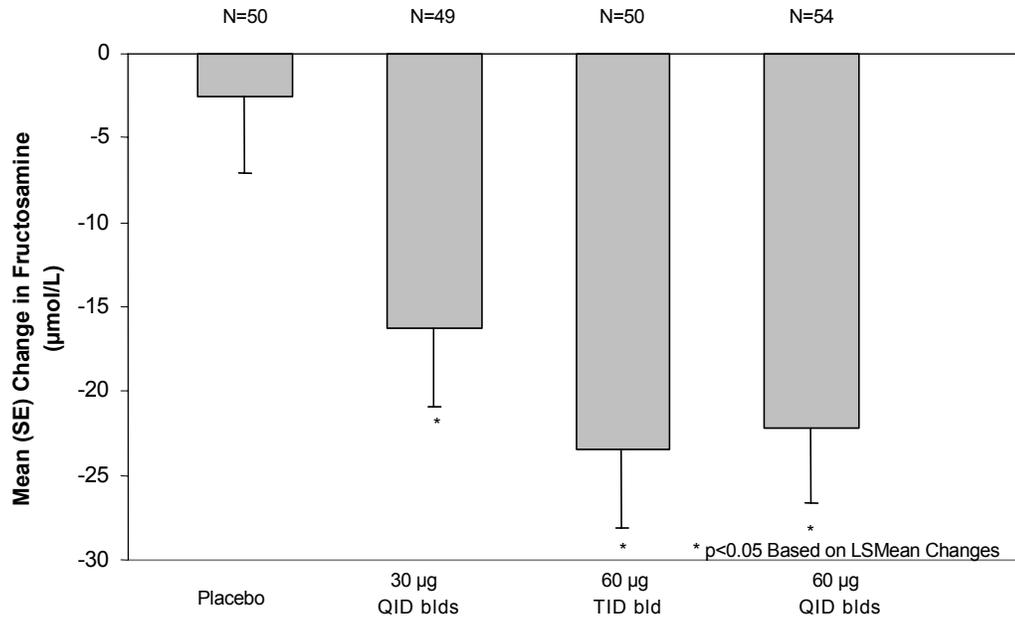
10.2 Insulin-Using Type 2 Diabetes

All four controlled studies (137-114, 137-111, 137-123, and 137-122) demonstrate or support the effectiveness of pramlintide in improving glycemic control in patients with type 2 diabetes who use insulin. Study 137-114 was a short-term (1-month) controlled study, and the other three were long-term controlled studies. Studies 137-122 and 137-111 were each 12 months in duration, and Study 137-123 was 6 months in duration. All four studies were placebo-controlled.

10.2.1 Short-Term Controlled Study

As measured both by changes in serum fructosamine concentrations (**Figure 30**) and HbA_{1c} concentrations in short-term controlled Study 137-114, pramlintide, self-administered subcutaneously at dosages of 30 µg QID, 60 µg TID, and 60 µg QID for 4 weeks, significantly improved glycemic control in patients with type 2 diabetes mellitus using insulin (Appendix 4.1, Section 1.3.1). There also was a suggestion that pramlintide, at the dosages used in this study, and particularly at a dosage of 60 µg TID, was associated with a decrease in weight during the 4-week treatment period.

Figure 30: Change in Serum Fructosamine (µmol/L) From Baseline at 28 Days (Study 137-114: Short-Term Controlled Study in Patients With Type 2 Diabetes Using Insulin; Population: Evaluable)



b, breakfast; l, lunch; d, dinner; s, bedtime snack.

10.2.2 Long-Term Controlled Studies

Demographic and Baseline Characteristics. A total of 1693 patients with type 2 diabetes (1273 pramlintide, 420 placebo) entered the long-term controlled studies (**Table 8**). Of these, 968 (76%) of the pramlintide patients and 321 (76%) of the placebo patients completed. There were slightly more males than females in the pramlintide and placebo groups. Of the 1273 type 2 patients treated with pramlintide and 420 type 2 patients treated with placebo in the long-term controlled studies, the majority (83%) were white; 8-9% were black and 7-8% were Hispanic. The mean age of the patients was approximately 56 to 58 years. Baseline HbA_{1c} concentrations ranged from 5.7% to 15.8% (mean approximately 9.0%), and duration of diabetes ranged from 0.7 to 58.0 years (mean approximately 12 years). In all studies, patients' insulin therapy (and if applicable, oral hypoglycemic agent therapy) was continued. Demographic and baseline characteristics for the long-term controlled studies in patients with type 2 diabetes are presented in Appendix 1.

Table 8: Long-Term Controlled Studies in Insulin-Using Type 2 Diabetes

Study No. Location	Study design	Treatment	No. of Patients	Duration (Weeks)
137-111 US	multicenter, parallel group, double-blind	pramlintide pH 4.7* 30 µg TID, SC, bld † 75 µg TID, SC, bld 150 µg TID, SC, bld placebo	122 136 144 136	52
137-123 Europe/Canada	multicenter, parallel group, double-blind	pramlintide pH 4.0 90 µg BID, SC, bd 120 µg BID , SC, bd 90 µg TID, SC, bld placebo	121 126 129 123	26
137-122 US/Canada	multicenter, parallel group, double-blind	pramlintide pH 4.0 90 µg BID, SC, bd 60 µg TID, SC, bld 120 µg BID , SC, bd placebo	171 158 166 161	52

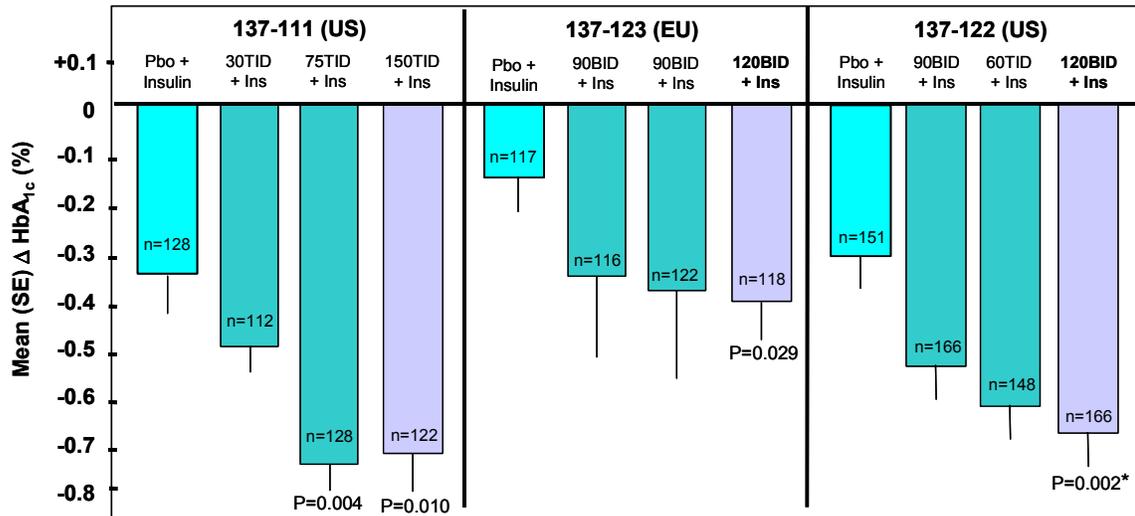
Recommended doses are in **bold**.

* Bioavailability approximately 70% of the pH 4.0 formulation, as shown in study 137-125.

† b, breakfast; l, lunch; d, dinner.

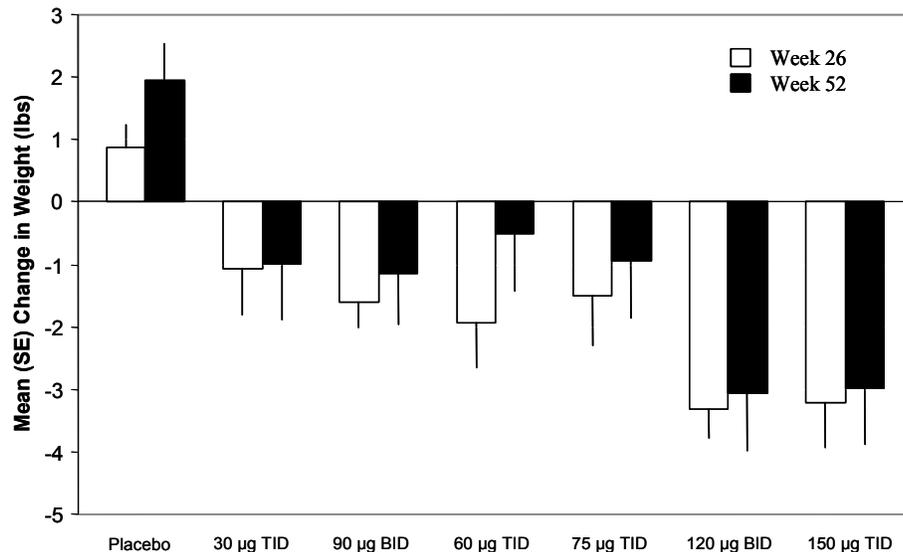
Pramlintide effects on HbA_{1c}, body weight, and insulin use. All three long-term, controlled studies demonstrated a favorable, statistically significant effect of pramlintide on glycemic control in patients with type 2 diabetes using insulin with or without oral hypoglycemic agents. Pramlintide added to insulin, particularly at a dosage regimen of 120 µg BID, produced absolute reductions from baseline in HbA_{1c} at Week 26 (**Figure 31**) and Week 52 (two studies) that were greater than those observed with insulin+placebo. The reductions in HbA_{1c} were achieved without a concomitant increase in total daily insulin dose, relative to increased insulin use among placebo patients. There was a decrease in body weight among patients with type 2 diabetes using insulin treated with pramlintide, compared with mean increases in weight among insulin+placebo patients (**Figure 32**).

Figure 31: Mean Change in HbA_{1c} From Baseline at Week 26 (Long-Term Controlled Studies in Patients With Type 2 Diabetes Using Insulin; Population: Intent-to-Treat)



Note: A p-value with an asterisk indicates that statistical significance of the primary study endpoint was achieved using the prospectively defined criteria for each study. A p-value without an asterisk indicates nominal significance at the p<0.05 level. For Study 137-111, mean changes at Week 26 for the 75 and 150 µg dose groups were significantly different from placebo using the prospectively-defined multiple comparison procedure. Recommended doses are shown in **boldface**.

Figure 32: Mean Change in Weight From Baseline at Weeks 26 and 52 (Long-Term Controlled Studies in Patients With Type 2 Diabetes Using Insulin Combined; Population: Evaluable as Defined in Each Study)



In the two 1-year studies, the clinically and statistically significant reductions in HbA_{1c} and body weight were maintained throughout the 52 weeks of treatment for the evaluable

population using the recommended dose (120 µg BID) identified for type 2 diabetes (Table 9). In addition, patients treated with pramlintide generally used less insulin throughout the three studies.

Table 9: Summary of Mean Change From Baseline in HbA_{1c}, Total Daily Insulin Dose, and Body Weight From Baseline in Long-Term Studies in Patients With Type 2 Diabetes by Recommended Dose (Population: Evaluable)

	Mean Change in HbA _{1c} (%) ¹		Mean Relative (%) Change in Total Daily Insulin ²		Mean Change in Weight (lbs) ³	
	Week 26	Week 52	Week 26	Week 52	Week 26	Week 52
137-111						
Placebo	-0.38	-0.16	14.72	15.40	2.00	2.40
Pramlintide 150 µg TID	-0.81†	-0.60†	6.05	9.00	-3.21*	-2.97*
137-123						
Placebo	-0.14	NA	7.17	NA	0.15	NA
Pramlintide 120 µg BID	-0.38†	NA	-0.37	NA	-3.43*	NA
137-122						
Placebo	-0.27	-0.14	2.69	3.22	0.53	1.52
Pramlintide 120 µg BID	-0.73*	-0.68*	-0.83	3.32	-3.23*	-3.06*

¹ Analysis of covariance procedure with treatment regimen and site as factors in the model and baseline HbA_{1c} as a covariate.

² Relative change from baseline; statistical difference between treatments not assessed for this variable.

³ Analysis of variance procedure with treatment regimen and site as factors in the model, outliers removed prior to unblinding.

* Statistically significant difference from placebo + insulin.

† Pairwise comparison was statistically significant at nominal < 0.05 level

NA, not applicable (6-month study).

Note: Values presented are unadjusted means for the evaluable population (defined as having completed 26 weeks [137-123, 137-122] or 52 weeks [137-111]).

Due to the lower bioavailability of the formulation used in 137-111 (approximately 70% of the to-be-marketed pH 4.0 formulation), the data from the 150 µg TID dose of 137-111 can be compared with the 120 µg dose of the pH 4.0 formulation used in studies 137-122 and 137-123.

As described earlier for type 1 diabetes studies, a stable insulin population (patients who did not alter total daily insulin dose by more than 10%) was evaluated to better isolate the drug effect of pramlintide over and above that of insulin. Overall, the stable insulin population represents about 50% of the type 2 diabetes patients (both pramlintide and placebo) enrolled in the three long-term, controlled studies.

Data from 1-year study 137-122 illustrate that in contrast with the results for type 1 diabetes patients, changes in HbA_{1c} for the intent-to-treat population and stable insulin population in type 2 diabetes patients were similar, suggesting that in this disease population the magnitude of drug effect was evident regardless of any variations in insulin usage that may have occurred (Table 10). In addition, patients with type 2 diabetes are less sensitive to relatively

small variations in insulin use, possibly also contributing to this finding. This finding was consistent throughout the course of the study (**Figure 33** and **Figure 34**).

Table 10: Change in HbA_{1c} at 6 Months and 1 Year for the Intent-to-Treat and Stable Insulin Populations (Study 137-122: Patients With Type 2 Diabetes)

Intent-to-Treat	Placebo	90 µg BID	60 µg TID	120 µg BID
	(N=161)	(N=171)	(N=158)	(N=166)
Baseline HbA _{1c} (%)	9.3	9.1	9.0	9.0
Change in HbA _{1c} (%) from baseline at Week 26	-0.32	-0.54	-0.62	-0.68
Change in HbA _{1c} (%) from baseline at Week 52	-0.25	-0.35	-0.53	-0.62
Stable Insulin				
	(N=55)	(N=64)	(N=69)	(N=70)
Baseline HbA _{1c} (%)	9.2	9.0	9.0	8.7
Change in HbA _{1c} (%) from baseline at Week 26	-0.29	-0.56	-0.62	-0.64
Change in HbA _{1c} (%) from baseline at Week 52	0.01	-0.25	-0.53	-0.57

Figure 33: Change in HbA_{1c} Through 52 Weeks for the Intent-to-Treat Population (Study 137-122: Patients With Type 2 Diabetes)

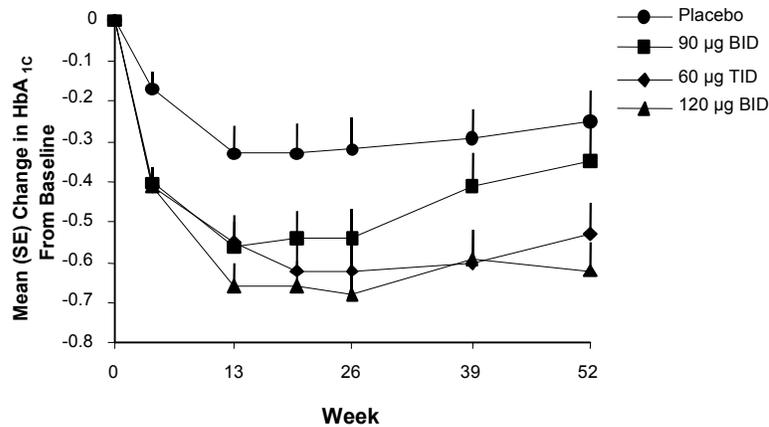
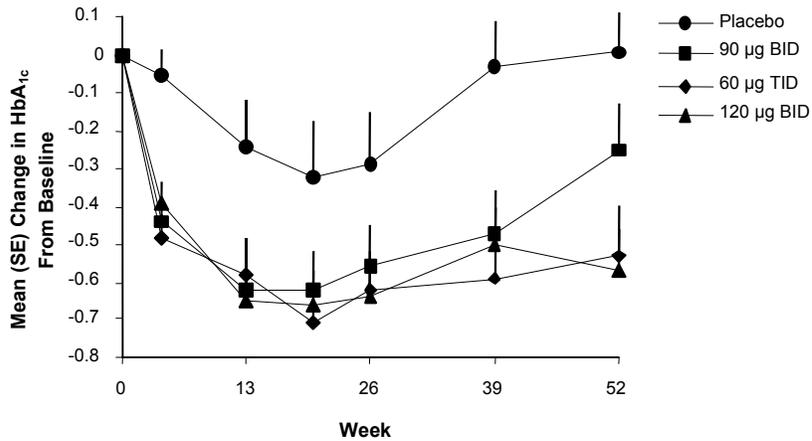


Figure 34: Change in HbA_{1c} Through 52 Weeks for the Stable Insulin Population (Study 137-122: Patients With Type 2 Diabetes)



Pramlintide effects on HbA_{1c} with and without oral hypoglycemic agents. In the long-term controlled studies in patients with type 2 diabetes, the effects on HbA_{1c} in those insulin-using patients on pramlintide therapy, with or without biguanides or sulfonylureas were examined (Table 11). In all cases, the addition of pramlintide therapy resulted in a greater decrease in HbA_{1c} than in those patients taking an oral hypoglycemic agent and insulin alone.

Table 11: Change in HbA_{1c} From Baseline at Week 26: Patients With and Without Biguanides and Sulfonylureas (Long-term Controlled Studies in Patients With Type 2 Diabetes Using Insulin)

Oral Hypoglycemic Agent Use	Number of Patients and Change in HbA _{1c} at Week 26			
	Placebo		All Pramlintide	
	N	ΔHbA _{1c} (SE)	N	ΔHbA _{1c} (SE)
Biguanides				
Yes	34	0.27 (0.16)	95	-0.59 (0.12)
No	269	-0.27 (0.06)	741	-0.56 (0.04)
Sulfonylureas				
Yes	31	-0.28 (0.18)	91	-0.73 (0.12)
No	272	-0.26 (0.06)	745	-0.55 (0.04)

Pramlintide treatment is associated with reaching HbA_{1c} targets. In addition to examining change in HbA_{1c}, the proportion of patients achieving specific HbA_{1c} targets was assessed. In all three long-term controlled type 2 studies, more patients treated with pramlintide+insulin achieved HbA_{1c} concentrations that reached defined targets for control of

diabetes than did patients treated with insulin only (placebo); this is exemplified by data from type 2 study 137-122 (**Table 12**).

Table 12: Proportion of Patients (%) Achieving HbA_{1c} Reductions and Targets in Type 2 Study 137-122 at Recommended Dose (Population: Intent-to-Treat)

HbA _{1c} parameter*	Percent of Patients			
	Week 26		Week 52	
	Placebo	Pramlintide 120 µg BID	Placebo	Pramlintide 120 µg BID
Reduction				
≥0.50%	57	82	65	84
≥0.75%	41	63	51	72
≥1.00%	29	53	40	61
Target†				
<8.0%	26	41	30	51
<7.0%	3	9	5	14
Reduction ≥0.50% and HbA _{1c} <8.0%	22	40	25	48

* Includes only patients who had baseline HbA_{1c} values above specified targets. Proportion of patients calculated as:
1 - Kaplan-Meier estimate based on survival analysis; excludes patients without baseline values; no data imputation.

In addition to the targets described above, a subpopulation was defined to include those patients who achieved a reduction in HbA_{1c} at Week 4 of ≥0.5%. More patients treated with pramlintide+insulin than patients treated with insulin only (placebo) had this magnitude of reduction in HbA_{1c} at Week 4 (**Table 13**). It is noteworthy that those patients achieving a ≥0.5% reduction in HbA_{1c} at Week 4 exhibited HbA_{1c} reductions at Week 26 of approximately 1.0% in type 2 study 137-122. Nevertheless, clinically relevant decreases in HbA_{1c} and weight were observed in many patients even if this early robust response in HbA_{1c} was not achieved.

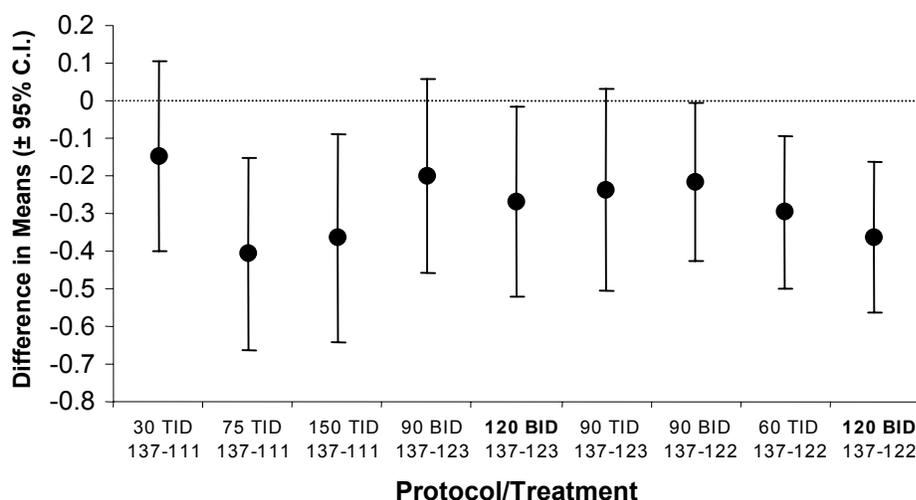
Table 13: Proportion of Patients (%) Achieving an HbA_{1c} Reduction of ≥0.5% at Week 4 in Type 2 Study 137-122 at Recommended Doses (Population: Intent-to-Treat)

HbA _{1c} Parameter*	Percent of Patients	
	Placebo	Pramlintide 120 µg BID
Reduction of ≥0.50% at Week 4	23	41

* Includes only patients who had baseline HbA_{1c} values above specified targets. Proportion of patients calculated as:
1 - Kaplan-Meier estimate based on survival analysis; excludes patients without baseline values; no data imputation.

Summary of efficacy findings in type 2 diabetes studies. Clinically and statistically significant reductions in HbA_{1c} concentrations were consistently observed at Week 26 at the dosage regimens of 120 µg BID and 150 µg TID (**Figure 35**), which persisted throughout 52 weeks of the study. The long-term effectiveness of pramlintide on glycemic control in insulin-using patients with type 2 diabetes with or without oral hypoglycemic agents was further evidenced for up to 2 years in one extension study. Pramlintide-treated patients also lost weight, compared with placebo patients who generally gained weight throughout the studies. Pramlintide-treated patients also appeared to generally use less insulin than placebo-treated patients. Although not shown in this document, pramlintide had no adverse effects on lipid profiles in insulin-using patients with type 2 diabetes studied in the three long-term controlled trials.

Figure 35: Difference in Treatment Means Between Pramlintide and Placebo (Treatment Effect), With 95% Confidence Intervals, for Change in HbA_{1c} From Baseline at Week 26 (Long-Term Controlled Studies in Insulin-Using Type 2 Diabetes; Population: Intent-to-Treat)



Note: Recommended doses are shown in **boldface**.

11. OVERALL ASSESSMENT OF EFFICACY

11.1 Dose Response

11.1.1 Dose Response in Type 1 Diabetes Studies

Results of several clinical studies provide evidence that pramlintide exerts its activity in a dose-related manner. Although a formal analysis of dose and response was not performed in any of the controlled studies in patients with type 1 diabetes, a wide range of doses was explored in these studies, and additional regimens were explored in the 14-day clinical pharmacology studies, AP93-08 and 137-104. In Study 137-104, effects of subcutaneously

administered pramlintide on the plasma glucose $AUC_{(0-180 \text{ min})}$ after administration of a Sustacal test meal to patients with type 1 diabetes were examined. Changes in the Sustacal incremental $AUC_{(0-180 \text{ min})}$ after 14 days of dosing were approximately + 12%, -17%, -57%, and -75% in the placebo, 10 μg , 30 μg , and 100 μg pramlintide treatment groups, respectively, after post-meal plasma glucose concentrations were adjusted for pre-meal glucose concentrations. The treatment differences were statistically significant for comparisons of placebo with 30 μg pramlintide ($p=0.0144$) and 100 μg pramlintide ($p=0.0006$). Evidence of dose-response for glucose lowering was also observed in Study AP93-08 in which patients with type 1 diabetes were treated with pramlintide 30 μg , 100 μg , or 300 μg TID administered subcutaneously for 14 days. The changes in incremental $AUC_{(0-180 \text{ min})}$ from baseline after 14 days of dosing were -646, -6351, -6690, and -8509 $\text{mg}\cdot\text{min}/\text{dL}$ for the placebo, 30 μg , 100 μg , and 300 μg pramlintide treatment groups, respectively. Interestingly, the reduction in postprandial plasma glucagon concentrations observed in this study were maximal at the lowest dose (30 μg) suggesting unique dose response relationships for postprandial glucagon and postprandial glucose.

No dose response relationship relative to efficacy was observed in the long-term controlled type 1 studies, though a dose-relationship was seen for the adverse event nausea (see Section 12.3).

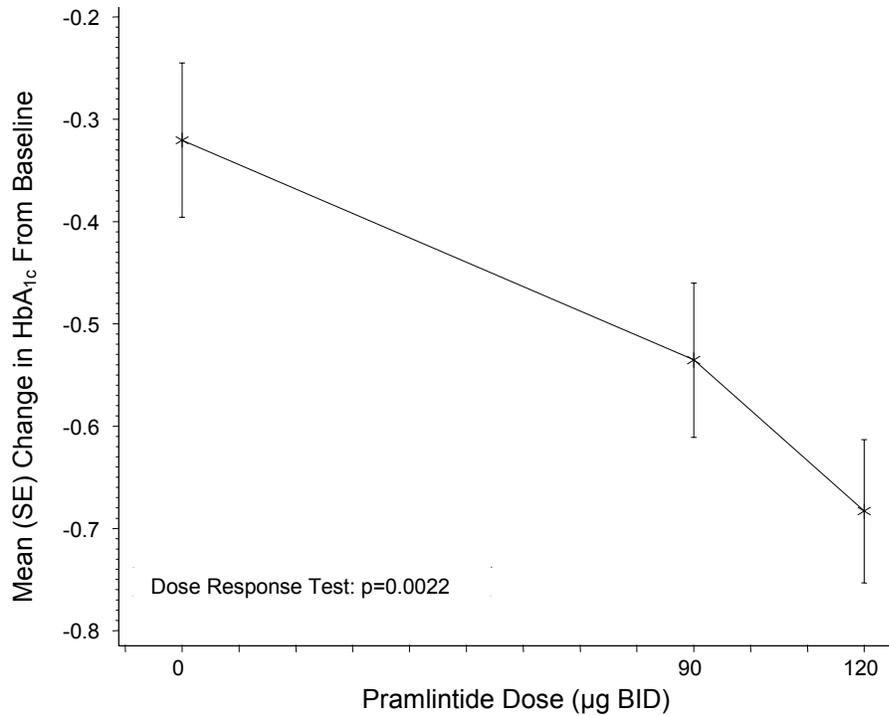
Study 137-118 examined the effect of three single subcutaneous doses of pramlintide (30 μg , 60 μg , and 90 μg) on the rate of gastric emptying in patients with type 1 diabetes. Half-emptying time of the solid-component of the test meal increased in a dose-related fashion relative to placebo treatment (difference from placebo of 59, 69, and 86 minutes for the pramlintide 30 μg , 60 μg , and 90 μg treatment groups, respectively) (**Figure 16**). In study 137-103, a continuous intravenous infusion of pramlintide 25 $\mu\text{g}/\text{hr}$ resulted in half emptying times that were much greater than observed at the highest dose in study 137-118 (90 μg) indicating that a maximum subcutaneous dose for the gastric emptying effect has not been identified.

11.1.2 Dose Response in Type 2 Diabetes Studies

A formal dose response analysis (linear trend test based on linear contrast with one degree of freedom) was conducted in the three long-term controlled studies in patients with type 2 diabetes using insulin. In Study 137-122, a significant dose-response relationship ($p=0.0022$) was found for the absolute reduction from baseline in HbA_{1c} at Week 26 in the intent-to-treat population for the range of doses from 0 to 120 μg BID (**Figure 36**). A similar dose response was found in Study 137-123 ($p=0.0213$) for the same range of doses (0 to 120 μg BID). In Study 137-111, significant dose response relationships were found for the range of doses from 0 to 150 μg TID for the absolute reduction from baseline in HbA_{1c} at Week 52 in the evaluable ($p=0.0349$) population. The dose response findings were

confirmed for the absolute reduction from baseline in HbA_{1c} at Week 52 in the intent-to-treat population (p=0.0074) as well as for the relative change from baseline in HbA_{1c} at Week 52 for both the intent-to-treat (p=0.0093) and evaluable (p=0.0360) populations.

Figure 36: Mean Change and Standard Error in HbA_{1c} (%) From Baseline to Week 26 by Dose (Study 137-122: Long-Term, Controlled Study in Patients With Type 2 Diabetes Using Insulin; Population: Intent-to-Treat)



Taken together, from the perspective of effectiveness, the three long-term controlled studies indicate that for patients with type 2 diabetes using insulin, a dosage of pramlintide 120 µg BID given before meals would be appropriate for initiation of therapy, and that the dosage could be increased in this population to 120 µg TID (total daily dose of 360 µg) if required.

11.2 Joint Outcome: Relationship Between HbA_{1c} and Weight

A joint outcome analysis of HbA_{1c} and weight was undertaken for the three long-term, controlled studies of pramlintide in patients with type 1 diabetes and two of the three studies in patients with type 2 diabetes using insulin with or without oral hypoglycemic agents. The purpose of the joint outcome analysis was to explore whether improved glycaemic control with pramlintide treatment was associated with a decrease in body weight, and whether the decrease in body weight was associated with the most frequently observed adverse event, nausea (see Section 12.2). The majority of patients treated with pramlintide had a drug effect

(i.e., a decrease both in HbA_{1c} and in body weight, a decrease in HbA_{1c} with minimal change in body weight, or a decrease in body weight with minimal change in HbA_{1c}), compared with patients in the combined placebo groups. As depicted in **Table 14** and **Table 15**, patients in the pramlintide treatment group exhibited a favorable drug effect whether or not they experienced nausea.

Table 14: Summary of Mean Change From Baseline in HbA_{1c}, Body Weight, and Total Daily Insulin Dose From Baseline in Long-Term Studies in Patients With Type 1 Diabetes by Nausea Categorization and Recommended Dose (Population: Intent-to-Treat)

		Mean Change in HbA _{1c}	Mean Change in Weight	Mean Change in Total Daily Insulin
Occurrence of Nausea	N	(%)	(lbs)	(%)
0-4 Weeks				
Nausea				
Placebo	41	-0.1	0.44	1.4
Pramlintide Recommended Dose	268	-0.5	-1.54	-1.7
No Nausea				
Placebo	497	-0.2	0.88	1.4
Pramlintide Recommended Dose	448	-0.5	-0.88	-1.1
4-26 Weeks				
Nausea				
Placebo	24	0.2	1.76	16.3
Pramlintide Recommended Dose	66	-0.5	-2.86	-0.1
No Nausea				
Placebo	478	-0.1	1.32	4.6
Pramlintide Recommended Dose	570	-0.4	-2.20	0.6
26-52 Weeks				
Nausea				
Placebo	19	-0.4	-1.10	9.4
Pramlintide Recommended Dose	22	-0.6	-0.88	-1.6
No Nausea				
Placebo	284	-0.1	2.20	5.5
Pramlintide Recommended Dose	385	-0.4	-0.88	-0.1

Only nausea events occurring during the specified weeks are included. The exposure for an individual patient is limited to the specified weeks (0-4, 4-26, 26-52) of the study.

Type 1 diabetes study 137-112, 137-117, and 137-121 data were pooled.

The type 1 diabetes recommended doses are 30/60 µg QID, 60 µg TID, and 60 µg QID.

Table 15: Summary of Mean Change From Baseline in HbA_{1c}, Body Weight, and Total Daily Insulin Dose From Baseline in Long-Term Studies in Patients With Type 2 Diabetes by Nausea Categorization and Recommended Dose (Population: Intent-to-Treat)

		Mean Change in HbA _{1c}	Mean Change in Weight	Mean Change in Total Daily Insulin
Occurrence of Nausea	N	(%)	(lbs)	(%)
0-4 Weeks				
Nausea				
Placebo	14	-0.1	2.20	1.7
Pramlintide Recommended Dose	55	-0.5	-2.64	-2.2
No Nausea				
Placebo	270	-0.1	0.66	1.0
Pramlintide Recommended Dose	237	-0.4	-1.54	0.5
4-26 Weeks				
Nausea				
Placebo	14	-0.3	0.44	4.5
Pramlintide Recommended Dose	25	-0.5	-3.30	2.7
No Nausea				
Placebo	253	-0.2	0.66	4.5
Pramlintide Recommended Dose	245	-0.6	-3.30	-1.1
26-52 Weeks				
Nausea				
Placebo	8	-1.3	-0.00	4.3
Pramlintide Recommended Dose	5	-0.8	2.86	11.8
No Nausea				
Placebo	116	-0.0	1.10	3.1
Pramlintide Recommended Dose	126	-0.7	-3.08	3.3

Only nausea events occurring during the specified weeks are included. The exposure for an individual patient is limited to the specified weeks (0-4, 4-26, 26-52) of the study. Type 2 diabetes studies 137-122 and 137-123 data were used. The type 2 diabetes recommended dose is 120 µg BID.

11.3 Joint Outcome: Relationships Between HbA_{1c} and Insulin, and Weight and Insulin

The purpose of this joint outcome analysis was to explore whether or not the decreases in HbA_{1c} concentrations from baseline observed in the pramlintide treatment groups were associated with an increase in total daily insulin dose. As shown in **Figure 37** and **Figure 38**, the majority of patients with type 1 diabetes and patients with type 2 diabetes using insulin with or without oral hypoglycemic agents had either a decrease in both HbA_{1c} and total daily insulin use (>10%) or a decrease in HbA_{1c} with minimal change in total daily insulin use (within ±10%) as compared to placebo groups. Of note is that when insulin usage increased among pramlintide-treated patients, the effect on reducing HbA_{1c} was maintained

or even more pronounced. However, this was associated with a smaller effect on body weight.

Figure 37: Joint Outcome – Change in HbA_{1c} and Insulin at 26 Weeks in Patients With Type 1 Diabetes (All Pramlintide Doses Pooled)

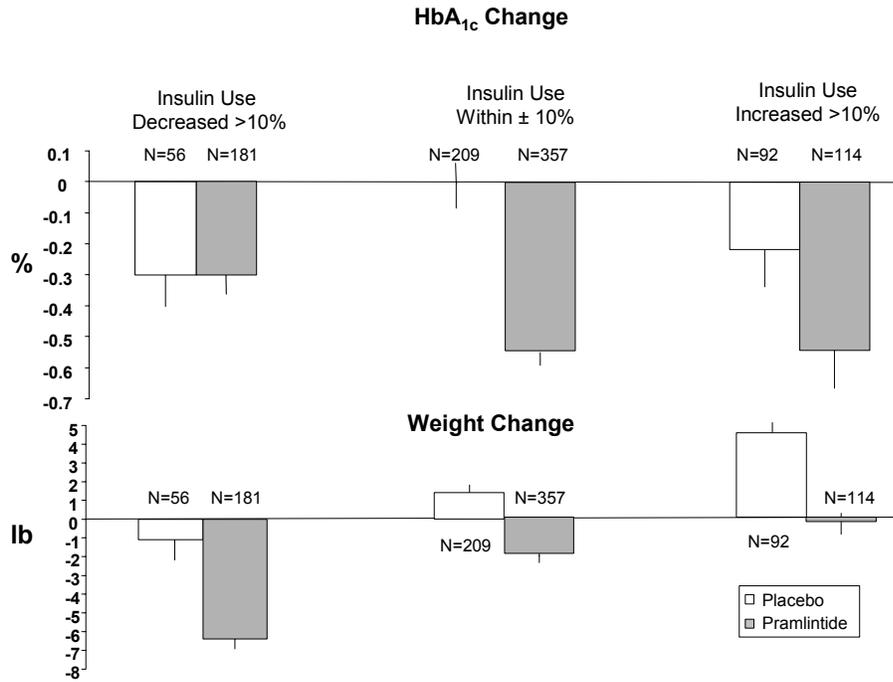
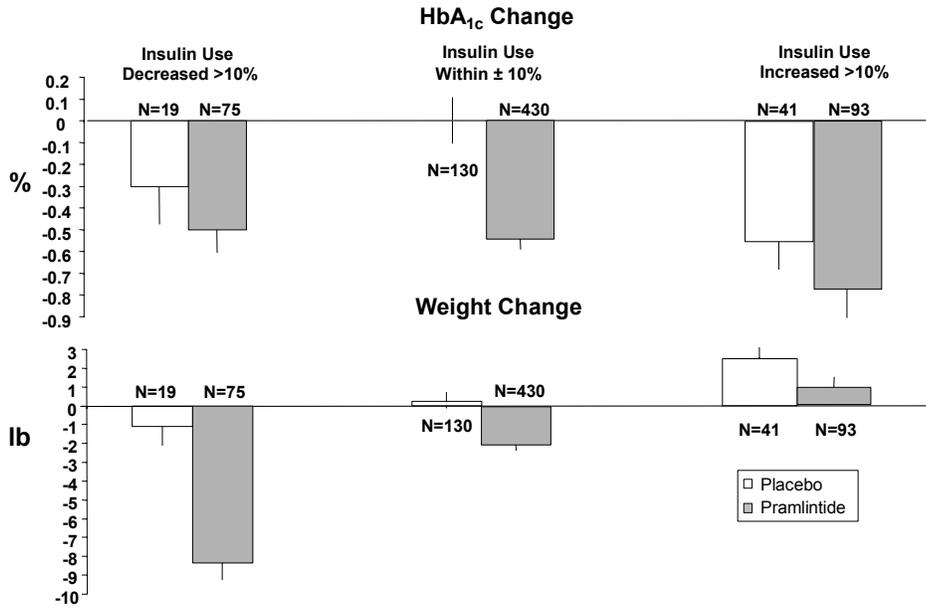


Figure 38: Joint Outcome – Change in HbA_{1c} and Insulin at 26 Weeks in Patients With Type 2 Diabetes (All Pramlintide Doses Pooled)



11.4 Overall Summary of Efficacy

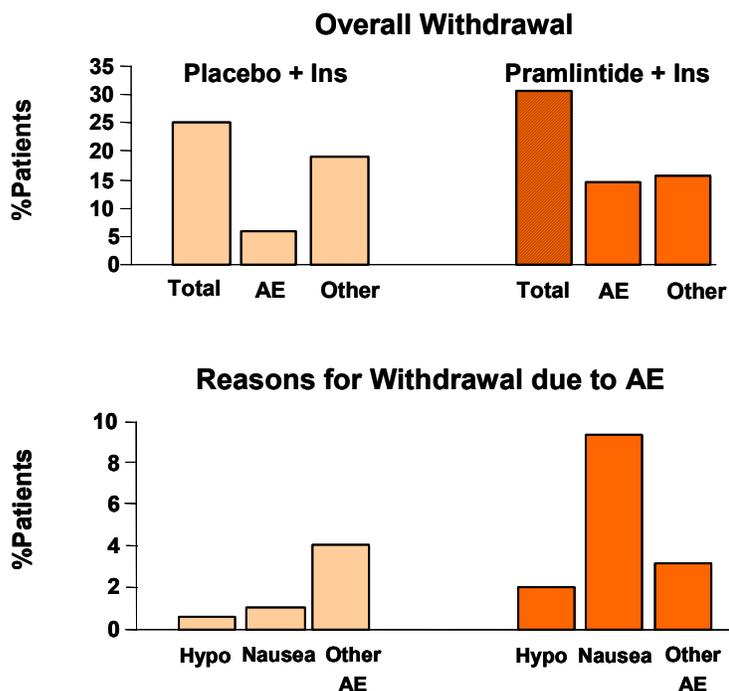
Patients (type 1 and type 2 using insulin) treated with pramlintide in the long-term controlled studies exhibited clinically and statistically significant benefits in terms of reduced HbA_{1c}, body weight, and insulin use. These effects were sustained throughout the course of studies up to 1-year in duration. In addition, more pramlintide patients than placebo patients achieved defined target reductions in HbA_{1c}. Pramlintide dose response was demonstrated based on both long-term study outcomes such as HbA_{1c}, and in the context of acute effects such as postprandial glucose. Joint outcome analyses were used to examine the relationship between the various clinical outcomes. Such analyses show that in general, reductions in HbA_{1c} and body weight occurred irrespective of how insulin usage was altered during the clinical studies. In addition, it was shown that reductions in HbA_{1c} and body weight, or insulin use occurred both in patients who experienced nausea, and those who never experienced this adverse event, indicating that the positive clinical outcomes were not merely a result of nausea-induced weight loss.

12. OVERALL ASSESSMENT OF SAFETY

12.1 Patient Disposition

Approximately 30% of pramlintide patients withdrew prematurely from clinical trials across the development program, compared with approximately 25% of placebo patients (Figure 39). Among pramlintide-treated patients, the majority of withdrawals due to adverse events were on account of nausea, the most common adverse event associated with pramlintide treatment.

Figure 39: Percent of Patients Withdrawing From Pramlintide Clinical Trials



12.2 Treatment-Emergent Adverse Events in Long-Term Controlled Studies

In the long-term controlled studies in patients with type 1 diabetes and in patients with type 2 diabetes using insulin the treatment-emergent adverse events with an overall incidence of $\geq 5\%$ in pramlintide or placebo patients and for which the incidence for the pramlintide group was greater than the incidence for the placebo group (after rounding) were nausea, anorexia, vomiting, abdominal pain, fatigue, dizziness, dyspepsia, and hypoglycemia (Table 16). In addition, the integrated safety database was examined to determine if there was any increase in adverse events in patients on oral hypoglycemic therapy. Based on these evaluations, there does not appear to be any evidence of an interaction of pramlintide and any of the oral hypoglycemic agents evaluated.

Tables summarizing the incidence of all adverse events throughout the clinical development program are provided in Part 1 of Appendix 5.

Table 16: Number (%) of Patients in the Long-Term Studies With Treatment-Emergent Adverse Events With an Overall Incidence of $\geq 5\%$ in Pramlintide and an Incidence Greater in Pramlintide Than in Placebo (Population: Intent-to-Treat)

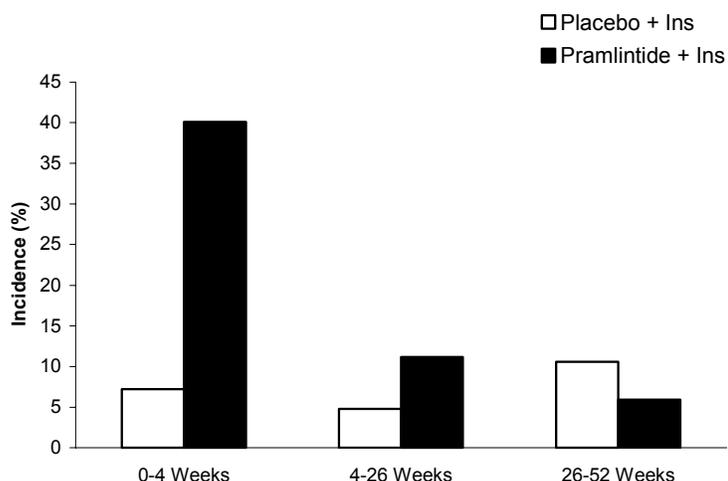
Adverse Event	Pramlintide n = 2452	Placebo n = 958
Nausea	909 (37)	149 (16)
Anorexia	307 (13)	25 (3)
Vomiting	239 (10)	59 (6)
Abdominal pain	186 (8)	63 (7)
Fatigue	163 (7)	39 (4)
Dizziness	115 (5)	38 (4)
Dyspepsia	118 (5)	29 (3)
Hypoglycemia*	678 (28)	216 (23)

* Includes all hypoglycemic adverse events, not just Sponsor-defined severe events.

12.3 Gastrointestinal Adverse Events

The majority of nausea, vomiting, and anorexia adverse events were reported as mild or moderate in intensity, and were more common in pramlintide-treated patients with type 1 diabetes than with type 2 diabetes. Although 37% of pramlintide-treated patients experienced nausea, only 5% reported severe nausea. Nausea was generally reported during the first few weeks of treatment, was dose-related, and decreased over time (**Figure 40**). The decreased occurrence of nausea over time was not due to differential withdrawal from the study across active and placebo treatment groups.

Figure 40: Incidence of Nausea Over Time in Patients With Type 1 Diabetes (Population: Intent-to-Treat)



Nausea was the only treatment-emergent adverse event with strong evidence for a dose response in the long-term controlled studies in patients with type 1 diabetes. Nausea was the most commonly reported adverse event in this population (51% overall), and was reported more frequently in patients exposed to a total daily dose of 270 µg (59%) than in patients exposed to lower total daily doses: 120-<180 µg (47%), 180-<225 µg (49%), and 240 µg (34%). Nausea was also the only treatment-emergent adverse event with strong evidence for a dose response in the long-term controlled studies in patients with type 2 diabetes.

The incidence of nausea was explored as a function of time from start of treatment and by dose, as shown in **Figure 41** and **Figure 42**, which display Kaplan-Meier plots of the cumulative frequency distribution of the time to first onset of nausea for the respective pramlintide doses employed in the long-term controlled studies. These displays make clear that not only do most pramlintide-treated patients who report nausea report it within the first 4 weeks, but also that the reporting incidence increases with increasing dose. Of note, the incidence of nausea in type 2 patients is less than for type 1 patients for any given dose.

Figure 41: Cumulative Frequency Distribution of Time to First Onset of Nausea by Dose (Long-term Controlled Studies in Patients With Type 1 Diabetes)

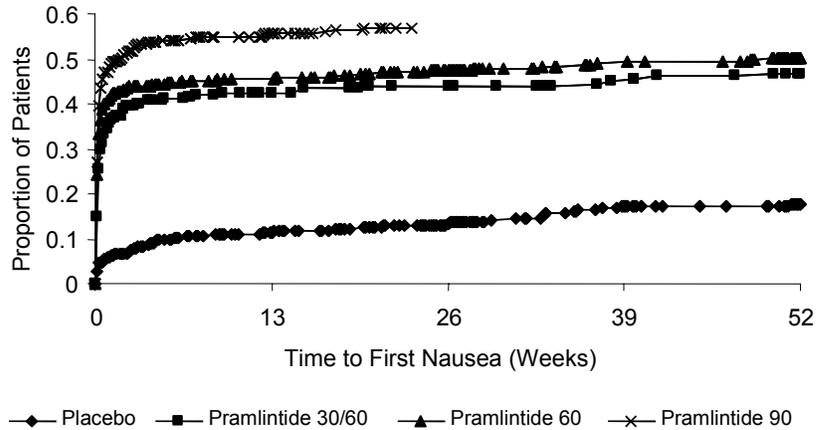
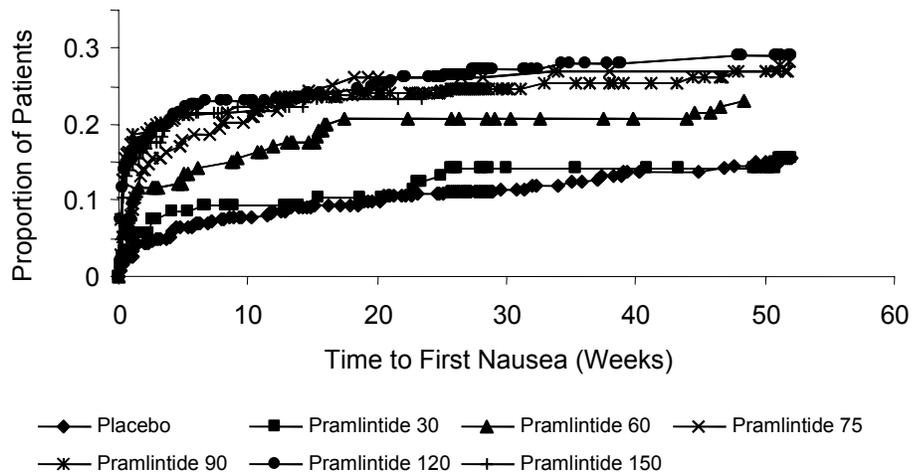


Figure 42: Cumulative Frequency Distribution of Time to First Onset of Nausea by Dose (Long-term Controlled Studies in Patients With Type 2 Diabetes Using Insulin)



12.4 Hypoglycemia

12.4.1 Definition of Sponsor-Defined Severe Hypoglycemia

Hypoglycemia was assessed in the pramlintide clinical development program in two principal ways. First, an examination of the incidence of all hypoglycemic adverse events in the context of all other treatment-emergent adverse events was undertaken in order to account for all adverse events deemed to be hypoglycemia by the investigator. The major drawback of this approach is that many of the events recorded are not well characterized with regard to some objective measure of severity that would result in a reliable assessment by

disparate observers. For this reason, a second assessment of “Sponsor-Defined Severe Hypoglycemia” was made, using the same definition as that employed in the DCCT:²⁶

- requiring the assistance of another individual (including aid in ingestion of oral carbohydrate)
- requiring the administration of glucagon injection or intravenous glucose

This definition was used for assessing hypoglycemia in five of the six long-term controlled studies in the pramlintide clinical development program (data collection methods in Study 137-111 precluded assessment of Sponsor-Defined Hypoglycemia in that study, although hypoglycemic adverse events were assessed in the context of all other treatment-emergent adverse events in this study).

12.4.2 Hypoglycemia Adverse Events

Table 17 summarizes the incidence of hypoglycemic adverse events in the long-term controlled studies of pramlintide in patients with type 1 diabetes or insulin-using type 2 diabetes. The incidence of hypoglycemic adverse events was slightly higher in the pramlintide groups compared with the placebo groups. The majority of the hypoglycemic adverse events were judged by the investigator to be related to the study medication in both pramlintide- and placebo-treated patients with type 1 diabetes. In the long-term controlled studies in type 1 diabetes, 14% and 8% of patients in the pramlintide and placebo groups, respectively, had severe hypoglycemia as assessed by the investigator. These intensity ratings do not take into account the “Sponsor-Defined Severe Hypoglycemia” definition. Hypoglycemia was reported as a serious adverse event in 9% of pramlintide patients and 4% of placebo patients in the long-term controlled studies in patients with type 1 diabetes.

There were proportionally fewer hypoglycemic events in patients with type 2 diabetes using insulin than in patients with type 1 diabetes (**Table 17**). The majority of the hypoglycemic events were judged by the investigator to be related to the study medication in both the pramlintide- and placebo-treated patients with type 2 diabetes using insulin. The proportion of patients with type 2 diabetes using insulin who had a hypoglycemic event judged by the investigator to be severe ranged from 2% to 3%. Relatively few (1% to 2%) of the pramlintide- or placebo-treated patients with type 2 diabetes using insulin had a hypoglycemic event that met the definition of a serious adverse event.

**Table 17: Hypoglycemic Adverse Events
Long-Term Controlled Studies in Patients With Type 1 and in Patients With Type 2 Diabetes Using Insulin^[1]**

Hypoglycemic Events ^[2]	Type 1						Type 2 Using Insulin						Total					
	Pramlintide		Placebo		Pramlintide		Placebo		Pramlintide		Placebo		Pramlintide		Placebo			
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n		
All Hypoglycemic Events	323 (27.40)	747	101 (18.77)	309	88 (10.10)	164	19 (6.69)	45	411 (20.05)	911	120 (14.60)	354						
Mild Events	37 (3.14)	94	17 (3.16)	25	21 (2.41)	68	5 (1.76)	11	58 (2.83)	162	22 (2.68)	36						
Moderate Events	131 (11.11)	313	52 (9.67)	106	37 (4.25)	61	8 (2.82)	23	168 (8.20)	374	60 (7.30)	129						
Severe Events	165 (13.99)	338	43 (7.99)	178	30 (3.44)	35	6 (2.11)	11	195 (9.51)	373	49 (5.96)	189						
Sponsor-defined Severe Hypoglycemic Events ^[2]	295 (25.02)	791	96 (17.84)	428	76 (8.73)	139	17 (5.99)	40	371 (18.10)	930	113 (13.75)	468						
Serious Hypoglycemic Events	106 (8.99)	197	23 (4.28)	39	21 (2.41)	22	4 (1.41)	6	127 (6.20)	219	27 (3.28)	45						

[1] The studies included for Type 1 are 137-112, 137-117 and 137-121. The studies included for Type 2 are 137-122 and 137-123.

[2] The mild, moderate and severe classifications under all hypoglycemic events and the serious classification were investigator-determined, as indicated on the adverse event forms.

[3] Sponsor-defined severe hypoglycemic events were defined as hypoglycemia requiring the assistance of another individual or the administration of IV glucose or glucagon.

12.4.3 Sponsor-Defined Severe Hypoglycemia

In the individual long-term controlled studies in both type 1 and type 2 diabetes, the event rate per patient-year of observation for Sponsor-defined severe hypoglycemia (requiring assistance of another individual, administration of glucagon, or administration of intravenous glucose) was higher in the pramlintide groups than in the placebo treated groups during the initial 4 weeks of therapy (**Table 18** and **Table 19**). This observation is consistent with adding an additional agent capable of lowering plasma glucose without adjusting pre-existing hypoglycemic treatment regimens, including insulin. After patients had an opportunity to adjust to the addition of pramlintide to their regimen (i.e., after the first 28 days of treatment), there was no difference in the event rate per patient-year for Sponsor-defined severe hypoglycemia among patients who received pramlintide plus insulin compared with those who received placebo plus insulin. For the overall study period, in patients with type 1 diabetes the event rate for severe hypoglycemia was 1.11 per patient-year with pramlintide and 1.12 per patient-year with placebo. In patients with type 2 diabetes, the overall event rate for severe hypoglycemia was 0.24 per patient-year with pramlintide and 0.22 per patient-year with placebo.

Table 18: Sponsor-defined Hypoglycemia for Type 1 Studies 137-121, 137-112, and 137-117 Combined (Population: Intent-to-Treat)

	First 4 Weeks		4 Weeks to the end of the study		Whole study	
	Placebo (N=538)	Pram (N=1179)	Placebo (N=538)	Pram (N=1179)	Placebo (N=538)	Pram (N=1179)
Number and incidence of patients with at least one episode of hypoglycemia	30 (6%) ^a	154 (13%)	85 (16%) ^a	220 (19%)	96 (18%) ^a	295 (25%)
Patient time (years)	39.9	83.9	343	629	383	713
Number of hypoglycemic events	64	267	362	518	428	791
Number of hypoglycemic events per one year of patient time	1.6	3.2	1.05	0.82	1.12	1.11

^a Includes 1 placebo patient in study 137-112 who had 128 hypoglycemic events.

Table 19: Sponsor-defined Hypoglycemia for Type 2 Studies 137-122 and 137-123 Combined (Population: Intent-to-Treat)

	First 4 Weeks		4 Weeks to the end of the study		Whole study	
	Placebo (N=284)	Pram (N=871)	Placebo (N=284)	Pram (N=871)	Placebo (N=284)	Pram (N=871)
Number and incidence of patients with at least one episode of hypoglycemia	2 (0.7%)	23 (3%)	16 (6%)	63 (7%)	17 (6%)	76 (9%)
Patient time (years)	21.2	64.6	166	523	188	587
Number of hypoglycemic events	4	29	36	110	40	139
Number of hypoglycemic events per one year of patient time	0.2	0.5	0.22	0.21	0.21	0.24

These observations indicate that in clinical practice it will be prudent to reduce the patient’s insulin dose, particularly short-acting insulin administered preprandially, by 10-20% at the time of initiation of pramlintide therapy. Further reductions in insulin doses may be indicated if the patient encounters the nausea side-effect. Once pramlintide therapy has been successfully initiated, insulin doses should be adjusted according to the standards of clinical practice based upon self blood glucose monitoring data to optimize the patient’s glycemic control.

12.4.4 Hypoglycemia and Injuries/Accidents

In response to a request made by the Agency, an effort was made to ascertain whether or not there was an undue number of accidents, especially in the context of hypoglycemia, among pramlintide-treated patients. To this end, a thorough search of the integrated safety database was combined with a manual review of serious adverse event (SAE) reports related to motor vehicle accidents and other injuries which occurred during the pramlintide clinical development program. The details of the approach taken are described below:

- All treatment-emergent adverse events in the integrated safety database which coded to the preferred terms **FALL**, **INFLECTED INJURY**, or **JOINT DISLOCATION** were identified.^a
- The integrated safety databases were searched for any treatment-emergent adverse event, which contained the words **ACCIDENT**, **AUTOMOBILE**, **AUTO**, **BUS**, **CAR**, **DRIVING**, **MOTOR**, **MOTORCYCLE**, **MVA**, **TRACTOR**, **TRAFFIC**, or **VEHICLE** within the verbatim term. Some of these events were the same as those captured in the first step,

^a The term **accidental trauma** only comprised a single adverse event in the program (Study 137-124, patient 101; pressure injury to left great toe) and was therefore not included in this search.

- while others were unique (e.g., hypoglycemia that was motor vehicle accident-related would have been coded to the preferred term hypoglycemia).
- The narrative serious adverse event (SAE) reports were searched for the same keywords as in the second bullet above, in order to glean any additional information on treatment-emergent adverse events related to accidents and injuries that was not formally recorded on patient case report forms.
 - A manual cross-review of these three data sources was done to arrive at the subset of all accident- or injury-related treatment-emergent adverse events. It should be noted that in 10 instances, particular adverse events (e.g., hypoglycemia, confusion, syncope) were described in SAE reports as having occurred in the context of driving, although there was no related motor vehicle or other accident reported. In addition, one patient was reported in the integrated safety database as having a non-serious hypoglycemic event while driving, but there was no motor vehicle accident reported. These events are not included in the subset of patients or related summaries of motor vehicle-related and other accidents.
 - To insure that no event was omitted or discounted, relatedness to a hypoglycemic adverse event was assumed if there was a hypoglycemic adverse event reported on the same day as the accident/injury. For this purpose, any hypoglycemic adverse event was considered and the assessment was not limited to Sponsor-defined severe hypoglycemic events.

The information described above was used to generate **Table 20** summarizing the patient incidence and annual event rate per patient-year of **motor vehicle accidents or related injuries and other accidents and related events**, both overall, and those deemed as related to a hypoglycemic event. Overall, the incidences of motor vehicle accident-related events and other accident/injury-related events were similar between pramlintide- and placebo-treated patients (both type 1 and type 2). Also included in **Table 20** for completeness is the incidence of automobile-related adverse events for which there was no motor vehicle accident reported.

Table 20: Motor Vehicle and Other Accidents/Injuries Reported During the Pramlintide Clinical Development Program – Patient Incidence and Annual Event Rate per Patient

Type of Adverse Event	Number (%) of Patients Annual Event Rate (SE)			
	Type 1 Diabetes		Type 2 Diabetes Using Insulin	
	Pramlintide (N=2573)*	Placebo (N=904)*	Pramlintide (N=1663)*	Placebo (N=532)*
Motor Vehicle Accident-Related Events				
Total	28 (1.08%) 0.025 (0.004)	7 (0.77%) 0.018 (0.007)	18 (1.08%) 0.017 (0.004)	3 (0.56%) 0.023 (0.009)
Hypoglycemia-Related†	17 (0.66%) 0.017 (0.003)	2 (0.22%) 0.005 (0.004)	1 (0.06%) 0.008 (0.001)	0 NA
Other Accident/Injury-Related Events				
Total	197 (7.65%) 0.160 (0.011)	53 (5.86%) 0.159 (0.020)	194 (11.67%) 0.204 (0.123)	55 (10.34%) 0.199 (0.025)
Hypoglycemia-Related†	10 (0.39%) 0.007 (0.002)	2 (0.22%) 0.005 (0.004)	2 (0.12%) 0.002 (0.001)	1 (0.19%) 0.003 (0.003)
Automobile-Related Hypoglycemic Adverse Events With No Motor Vehicle Accident Reported ‡				
Total	8 (0.31%) 0.006 (0.002)	0 NA	1 (0.06%) 0.002 (0.001)	1 (0.19%) 0.003 (0.003)

* N refers to all patients with diabetes enrolled in clinical studies, including those not in the controlled and uncontrolled study categories.

† Hypoglycemia-Related is defined as there being a hypoglycemia adverse event recorded on the same day as the accident/injury.

‡ Hypoglycemic adverse events which apparently occurred in the context of driving, or were otherwise automobile-related, but for which there are no indications of a motor vehicle accident having occurred.

NA = not applicable

12.4.5 Hypoglycemic Override of Pramlintide Action

It is important to know whether pramlintide has any adverse effect on the usual counter-regulatory hormones which come into play under conditions of insulin-induced hypoglycemia. This is particularly important given the observation that a key mechanism of pramlintide action is to inhibit *postprandial* glucagon secretion. Studies in animals have shown that the presence of pramlintide does not affect hypoglycemia-induced release of glucagon.

To further explore this in humans, a study (AP93-04) was done in which patients with type 1 diabetes were first subjected to euglycemic conditions (5 mmol/L) in a glucose-clamp

setting. Pramlintide (275 µg total dose) or placebo was administered by intravenous infusion in a two-way crossover design. After beginning the study medication infusion, glucose was allowed to decline to 2.8 mmol/L (hypoglycemic phase). Concentrations of various plasma counter-regulatory hormones were measured throughout the euglycemic and hypoglycemic phases to assess any effect of pramlintide on counter-regulatory response. **Table 21** shows that there was no detrimental effect of pramlintide on any of the hormones measured, indicating that rescue from hypoglycemia by endogenous mechanisms or by administration of exogenous glucagon presents no safety concern for patients treated with pramlintide. It is noteworthy that these observations were made at circulating pramlintide concentrations approximately 4- to 5-times greater than those achieved using subcutaneous administration of the recommended doses.

Table 21: Pramlintide Does Not Affect the Counter-regulatory Response to Hypoglycemia in Patients With Type 1 Diabetes (Study AP93-04)

Hormone	Mean (SE) Incremental AUC – Hypoglycemic Phase	
	Pramlintide (N=7)	Placebo (N=7)
Insulin (pmol•min/L)	45000 (5000)	49000 (8000)
Glucagon (ng•min/L)	1201 (271)	289 (325)
Growth Hormone (µg•min/L)	722 (117)	281 (261)
Cortisol (nmol•min/L)	10000 (2000)	6000 (2000)
Epinephrine (pmol•min/mL)	107 (43)	69 (32)
Norepinephrine (pmol•min/mL)	33 (9)	32 (6)

Note: there were no statistically significant differences between pramlintide and placebo.

NA = not applicable.

12.5 Other Notable Adverse Events

12.5.1 Retinal Disorders

During the review of safety results from type 2 Study 137-111, an apparent increase in the incidence of retinal disorder (WHOART preferred term) was noted in the pramlintide 150 µg TID treatment group (10.4%) relative to the incidence among placebo-treated patients (5.1%) (**Table 22**). Investigator-described events that mapped to this preferred term include the following: diabetic retinopathy (described variously as background, exacerbated, proliferation, or increased), retinopathy (red dots, increased, hypertensive grade 1, proliferation of, others unspecified), laser surgery secondary to retinopathy, photocoagulation treatment, microaneurysms (fundi, leaky, others unspecified), torn retina, and ocular inflammation. Although patients with unstable retinopathy were to have been excluded from study participation, and no exceptions were reported, there were no specific assessments of retinopathy (i.e., fundus photography) at study baseline. It is possible that the longer duration of disease in the pramlintide 150 µg TID treatment group (mean, 13.3 years) compared with the other treatment groups (range of means: 11.3 to 11.9 years) may have

been related to a greater degree of baseline retinopathy that was not noted at study entry in that group of patients. Based on detailed medical review of individual patient information, it is likely that the reported retinal disorder events represent progression of pre-existing underlying conditions, rather than the appearance of new conditions secondary to pramlintide treatment. This judgment was based on the unlikelihood of having many (if any) newly-emergent advanced retinal disorders within the timeframe of a 1-year clinical study, as opposed to identification of steadily progressing pre-existing cases, a common occurrence in this patient population.

The lack of an adverse effect of pramlintide on vision in patients with type 2 diabetes is further supported by the data from studies 137-122 and 137-123, in which there was no apparent pramlintide-related increase in the incidence of retinal disorder, or any of the terms which code to the body system Vision Disorders, at doses of up to 120 µg BID (**Table 22**).

Based on the information presented, it is felt that retinal disorder (and vision disorders in general) do not present a safety concern for type 2 patients treated with pramlintide at the recommended doses. It is also noteworthy that there was no evidence for increased incidence of vision disorders in any of the long-term controlled type 1 diabetes studies.

Table 22: Incidence of Adverse Events Coding to Vision Disorders (Body System) and Retinal Disorder (Preferred Term) in Type 2 Diabetes Pramlintide Studies

Study Number Adverse Event	Number (%) of Patients			
	Placebo (N=136)	Pram 30 µg TID (N=122)	Pram 75 µg TID (N=136)	Pram 150 µg TID (N=144)
137-111				
Vision Disorders	20 (14.7%)	19 (15.6%)	25 (18.4%)	29 (20.1%)
Retinal Disorders	7 (5.1%) ^a	7 (5.7%)	8 (5.9%) ^b	15 (10.4%) ^c
137-122				
Vision Disorders	31 (19.3%)	23 (13.5%)	22 (13.9%)	28 (16.9%)
Retinal Disorders	10 (6.2%)	10 (5.8%)	6 (3.8%)	7 (4.2%)
137-123				
Vision Disorders	9 (7.3%)	11 (9.1%)	8 (6.2%)	9 (7.1%)
Retinal Disorders	3 (2.4%)	2 (1.7%)	1 (0.8%)	3 (2.4%)

^a Does not include 1 patient with an event coded as retinal hemorrhage.

^b Does not include 2 patients with events coded as retinal hemorrhage.

^c Does not include 2 patients with events coded as retinal hemorrhage.

Note: “Vision Disorders” is a WHOART Body System encompassing all preferred terms related to vision, while “Retinal Disorders” is a WHOART Preferred Term encompassing a variety of investigator terms related to retinal disorders.

12.5.2 Deaths

Of the 5540 patients enrolled in the 51 clinical trials, 17 patients (10 [0.2%] pramlintide, 7 [0.5%] placebo) died. Sixteen of the seventeen deaths were clearly not related to study drug. Cardiovascular disease was the most frequent cause of death due to an adverse event (nine deaths in total; five pramlintide and four placebo). Consistent with their diabetes, all nine of the patients who died from cardiovascular disease had a medical history of a cardiovascular abnormality prior to study entry. There were no important differences between pramlintide and placebo with regard to the number of deaths due to other adverse events. Only one pramlintide-treated patient (randomized to pramlintide 30 µg) died due to adverse events (convulsions and hypoglycemia) that were considered possibly related to study medication; this death was also attributed to coronary artery disease that was considered probably not related to study medication. Brief narrative descriptions of all deaths occurring in the pramlintide clinical development program are provided in Part 2 of Appendix 5.

12.6 Drug-Drug Interactions

12.6.1 Drug-Drug Interaction Studies

Drug-drug interaction studies have examined the potential interaction of pramlintide with orally administered medications (Studies 137-133 and 137-134), and the possible interaction with various types of insulin (Studies 137-115, 137-119, 137-120, and 137-130).

One mechanism of action of pramlintide is to modulate gastric emptying, a process that may have an effect on the absorption of concomitantly administered oral drugs. To determine whether the gastric emptying rate alters the pharmacokinetics of common concomitantly administered drugs, pramlintide was co-administered with low-dose oral contraceptive Lo/Ovral® (ethinyl estradiol/norgestrel) (Study 137-133), and it was co-administered with Penbritin® (ampicillin) (Study 137-134), an antibiotic which is relatively stable in the acidic gastric secretion and is moderately well absorbed from the gastrointestinal tract after oral administration. Pramlintide was shown to have no effect on the pharmacokinetic profile of ethinyl estradiol, but it substantially reduced the rate but not the extent of absorption of norgestrel. Since uniformity in the extent of absorption is probably more important for efficacy of an oral contraceptive, it is unlikely that contraceptive efficacy would be compromised with co-administration of pramlintide. Similarly, pramlintide significantly delayed the onset of absorption of ampicillin, but its extent of absorption and the C_{max} were essentially unchanged and therefore, the efficacy of ampicillin should not be affected by co-administration with pramlintide. Neither study evaluated the effect of co-administering Lo/Ovral or ampicillin on the pharmacokinetics of pramlintide.

Generally, pramlintide does not appear to have an effect on the extent of absorption of the drug, but since pramlintide may cause a delay in gastric emptying, it may affect the rate of

absorption of an orally administered concomitant drug. This effect is similar to the food effect; therefore patients should be advised that, if administration schedules result in some doses of concomitant medications being taken with pramlintide while others are not, the patient needs to be consistent in the co-administration schedule and take the concomitant medication at least 1 hour before the pramlintide dose. In situations where therapeutic plasma concentrations of orally administered medications need to be reached quickly, e.g., analgesics, prophylactic antibiotics for dental procedures, etc., the oral medications should be administered at least 1 hour prior to pramlintide administration.

In most pramlintide clinical studies, patients with diabetes who required insulin self-administered their appropriate doses of insulin and pramlintide as separate subcutaneous injections. Four studies investigated the pharmacodynamic effects on glucose and/or pharmacokinetic effects on insulin and pramlintide following mixing and simultaneous administration of various combinations of pramlintide and insulin.

The effects of co-administration of placebo versus pramlintide with lispro insulin and NPH, lente, or ultralente insulin (administered as three separate subcutaneous injections) were examined (Study 137-130). Also examined were the effects of co-administration of pramlintide and 70/30 insulin mixed together and as separate single injections (Study 137-115). Effects of co-administration of pramlintide versus placebo plus NPH and regular insulin (137-119) or isophane and soluble insulin (137-120) mixed together and as separate single injections in patients with type 1 diabetes were also performed. All studies showed that although individual responses were variable, a single dose of pramlintide reduced the early plasma glucose response following a meal, with a delay in time of onset for postprandial increases in glucose in the pramlintide-treated group, and substantial reduction in baseline corrected glucose C_{max} and AUC. However, mixing pramlintide with insulin changed the pharmacokinetic parameters of pramlintide in all cases, and of insulin in some cases, suggesting that these drugs should not be mixed in the same syringe prior to administration. The pharmacodynamic effects of co-administration were less conclusive for glucose, indicating that inadvertent mixing should not result in any undue acute risk to patients with regard to glucose response.

12.6.2 Concomitant Medications of Particular Relevance to a Diabetic Population

Treatment-emergent adverse events occurring in long-term controlled and uncontrolled studies in patients with type 1 diabetes and in the long-term controlled and uncontrolled studies in patients with type 2 diabetes using insulin with or without oral hypoglycemic agents were reviewed for potential clinical manifestations of drug-drug interactions. In the type 1 population, the following classes of frequently prescribed concomitant medications were evaluated: fibrates, statins, ACE inhibitors, beta blockers, calcium channel blockers, and thiazide diuretics. In addition, while not taken frequently by patients with type 1 diabetes, α -glucosidase inhibitors, biguanides, glitazones, sulfonylureas were also evaluated.

In the type 2 population, the following classes of frequently prescribed concomitant medications were evaluated: α -glucosidase inhibitors, biguanides, glitazones, sulfonylureas, fibrates, statins, ACE inhibitors, beta blockers, calcium channel blockers, and thiazide diuretics. Based on these evaluations, there did not appear to be any evidence of an interaction between pramlintide and any of the classes of concomitant medications evaluated in patients with type 1 diabetes and type 2 diabetes. In particular, a thorough review revealed no evidence that pramlintide administration reduced the efficacy of any of these classes of frequently prescribed concomitant medications.

12.7 Other Safety

Vital signs, clinical laboratory measures, electrocardiograms, and physical examinations. In the long-term controlled studies in patients with type 1 and type 2 diabetes mellitus, treatment with pramlintide had no adverse effect on vital signs, clinical laboratory measures, electrocardiograms, or physical examinations. This is consistent with information obtained from the nonclinical toxicology program, a summary of which is provided in Appendix 6.

Pregnancy. Pregnant subjects were to be excluded from all studies in the pramlintide development program. However, it is not uncommon for a few pregnant women to inadvertently be exposed to a new drug during development, and this was indeed the case in the pramlintide clinical development program. A total of 17 subjects (12 pramlintide, 5 placebo) in the development program became pregnant. Of these, 8 (6 pramlintide, 2 placebo) ended in miscarriage/spontaneous abortion or elective abortion. One subject (pramlintide), who underwent an elective abortion, was also diagnosed with cervical cancer at that time. Six subjects (4 pramlintide, 2 placebo) gave birth to healthy infants without complications. One subject (pramlintide) gave birth to a baby boy who was macrosomal and had circulatory shock complicated by shocklung and pyelonephritis. One subject (placebo) developed preclampsia and pregnancy-induced hypertension and was placed on bed rest; her baby was born five weeks premature but is now healthy. One subject (pramlintide) had a normal delivery but the baby girl exhibited signs of mental retardation; this subject previously had six spontaneous abortions and since delivered a healthy baby boy.

Based on the above information, the following statement is proposed for labeling:

There are no adequate and well-controlled studies of pramlintide acetate in pregnant women. Pramlintide acetate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose concentrations during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality,

most experts recommend that insulin be used during pregnancy to maintain blood glucose concentrations as close to normal as possible.

Adverse reactions that are serious but very unusual in the absence of drug therapy.

FDA's "Guidance for Industry: Content and Format of the Adverse Reaction Section of Labeling for Human Drugs and Biologics" of May 2000 states that there are certain events, e.g., liver failure, agranulocytosis, significant purpura, intussusception, and acute renal failure, that are serious but very unusual in the absence of drug therapy. The integrated safety database was, therefore, systematically searched for these events. There were no reports of liver failure, agranulocytosis, significant hemolytic anemia, rhabdomyolysis, idiopathic thrombocytopenic purpura, or intussusception in any of the clinical studies. Thrombocytopenia was reported in two patients, one treated with pramlintide and one treated with placebo. Acute renal failure was reported in four patients, three treated with pramlintide and one treated with placebo. A case-by-case review indicated that neither thrombocytopenia nor acute renal failure could reasonably be associated with the use of pramlintide. In addition, there was no adverse effect of pramlintide on liver or kidney function tests or plasma lipids.

13. BENEFIT/RISK RATIO

The data reviewed in this document indicate that pramlintide reduces postprandial plasma glucose concentrations in patients with type 1 and type 2 diabetes treated with insulin. This improvement in postprandial glucose control is accomplished by inhibiting postprandial glucagon secretion and reducing the rate at which nutrients are delivered to the small intestine for absorption. These effects complement the action of insulin, are sustained over time, and lead to a clinically meaningful reduction in HbA_{1c} beyond that achieved with insulin alone. Since these mechanisms for lowering plasma glucose are not shared with other glucose-lowering agents, pramlintide represents a novel and unique addition to the armamentarium for achieving glycemic control in patients with diabetes. Furthermore, since pramlintide is being proposed as an adjunct to insulin, its use offers the ability to improve glycemic control in the subset of patients with diabetes who have exhausted all other therapeutic options but who continue to have suboptimal glucose control.

Patients treated with pramlintide have improvements in HbA_{1c} which should lead to reduced risk of long-term complications. Patients receiving pramlintide in the long-term, controlled trials exhibited a wide range of responses with a substantial proportion reaching and maintaining target values as defined by the American Diabetes Association. The data from the stable insulin cohort in both the type 1 and type 2 trials suggest that the true effect of the addition of pramlintide is an HbA_{1c} reduction of approximately 0.7 units in patients with entry values of ~9.0%. Data from the DCCT indicate that a 10% reduction in HbA_{1c} from baseline, i.e., a reduction of 0.9 units in subjects with baseline values of 9.0%, reduces

the risk for the development and/or progression of microvascular complications by ~45%. Thus, these data indicate that the improvement in glycemic control achieved with pramlintide, without an increase in insulin use, should lead to an approximately 30-40% reduction in the risk of long-term complications. The UKPDS demonstrated a similar relationship between reductions in HbA_{1c} and diabetic complications. Such a reduction in risk of microvascular complications is expected to be significant in terms of improved well-being and quality-of-life, and containment of health care costs. Not only are the benefits significant, but they accrue to patients whose options for improving their position in the struggle against diabetes are limited. Patients with type 1 diabetes have only insulin as a therapeutic option at present and in spite of the progress represented by fast-acting analogs and continuous subcutaneous infusion therapy, the vast majority of patients with type 1 diabetes fall short of achieving desired therapeutic goals. Patients with type 2 diabetes who have progressed to insulin therapy have usually extracted the benefits conveyed to them by the various oral agents. Thus, they are also stranded without other beneficial therapeutic alternatives at the present time.

The benefits of pramlintide treatment cannot be achieved by increasing insulin dose.

One might ask, however, couldn't a patient's insulin dose simply be increased to achieve similar benefits? While that appears intuitively correct given that insulin is the most potent glucose lowering agent available, clinical experience in terms of the ability to achieve the desired level of glycemic control has been extraordinarily disappointing. In the DCCT, multiple daily insulin injections were successfully employed to lower HbA_{1c} in the intensive treatment group. This "success" however, did not achieve HbA_{1c} values <7.0% as presently recommended by the American Diabetes Association and was accompanied by a 3-fold increase in severe hypoglycemia and significant weight gain, the latter leading to atherogenic changes in plasma lipid parameters and appreciable increases in blood pressure. Taken together, these changes convey significant additional risk for atherosclerotic cardiovascular disease to patients. Most importantly, subsequent follow-up of the subjects 4 years following withdrawal of the extensive support provided by the DCCT treatment team indicates that the improvements in glycemic control have not been maintained as evidenced by mean HbA_{1c} values of ~8.0%. In terms of type 2 diabetes treated with insulin, the UKPDS data clearly show that HbA_{1c} values tended to rise, not fall, during chronic insulin therapy in a clinical trial setting where skilled clinicians were striving to normalize the values. These type 2 patients also struggled with increased weight gain and hypoglycemia. Collectively, these data from intervention trials reflect the frustrations associated with attempts to effect glycemic control using insulin alone. Unlike thyroid or adrenal corticosteroid replacement where addition of the deficient hormone readily restores near-normal physiology, therapeutic success utilizing insulin therapy has proven to be a much more elusive goal as evidenced by where we are today after over 80 years of refinement.

Pramlintide has manageable side effects. Attempts to improve glucose control by more aggressive use of insulin are plagued by increased risks of hypoglycemia and weight gain, factors which represent major barriers to achieving and maintaining adequate glycemic control for both patients and healthcare providers. Risks associated with the use of currently available oral hypoglycemic agents include hypoglycemia, weight gain, lactic acidosis and edema. In comparison, the risks of pramlintide therapy include mild to moderate nausea, anorexia and vomiting (37%, 13%, and 10% respectively in the six long-term controlled studies) which are usually transient in nature, and increased insulin-induced severe hypoglycemia during the initial 4 weeks of therapy when insulin doses were not reduced with the initiation of therapy. The increased risk for insulin-induced hypoglycemia resolve with continued therapy. These observations indicate that in clinical practice it will be prudent to reduce the patient's insulin dose, particularly short-acting insulin administered preprandially, by 10-20% at the time of initiation of pramlintide therapy. Further reductions in insulin doses may be indicated if the patient encounters the nausea side-effect. Once pramlintide therapy has been successfully initiated, insulin doses should be adjusted according to the standards of clinical practice based upon self blood glucose monitoring data to optimize the patient's glycemic control.

Pramlintide does not exhibit drug-induced idiosyncratic adverse reactions that are serious but very unusual in the absence of drug therapy. There were no reports of liver failure, agranulocytosis, significant hemolytic anemia, rhabdomyolysis, idiopathic thrombocytopenic purpura, or intussusception in any of the clinical studies. None of the few reports of thrombocytopenia or acute renal failure could reasonably be associated with the use of pramlintide. In addition, there was no adverse effect of pramlintide on liver or kidney function tests or plasma lipids.

The risks of pramlintide therapy relative to the risk of no therapy or continuing current therapies. In considering the use of pramlintide in patients with diabetes, one needs to consider the risks of: (1) no therapy; (2) continuing current therapies; and (3) the addition of pramlintide. No therapy in patients with type 1 diabetes would result in death and in patients with type 2 diabetes leads to significant deterioration in metabolic control. Continuation of current therapies is associated with the risk of hypoglycemia, weight gain associated with its deleterious consequences, lactic acidosis, edema, and the residual long-term risk for microvascular and macrovascular disease imparted by the failure to achieve the desired level of glycemic control. The risks associated with the addition of pramlintide as adjunctive therapy to insulin in these individuals include the need for additional injections, transient mild to moderate nausea, anorexia, and vomiting, and an increase in insulin-induced severe hypoglycemia during the first 4 weeks of therapy when the insulin dose is not reduced.

The burden of increased injections appears to be acceptable to the majority of patients as evidenced by approximately 70% of subjects completing the 1-year controlled trials opting to

continue on into an open-label extension study requiring them to continue the incremental injections. The gastrointestinal side effects, which are more prominent in type 1 than type 2 patients, are transient in nature and usually dissipate during the initial 4 to 6 weeks of therapy. Nausea, anorexia and vomiting resulted in cessation of therapy in 7%, 1%, and 1% of patients respectively. The increased risk for hypoglycemia can be managed by judicious reductions of insulin upon initiation of pramlintide therapy.

The benefit/risk equation for pramlintide. Assessing the benefit/risk equation of pramlintide as adjunctive therapy to insulin in patients with type 1 and type 2 diabetes leads to a positive conclusion in favor of pramlintide. Pramlintide has been shown to offer an improvement in glycemic control above that achieved with insulin alone in approximately 70% of patients, with over 90% of patients exhibiting a reduction in HbA_{1c}, a reduction in body weight, or both. These beneficial results were achieved at the expense of transient gastrointestinal side effects (a tolerability issue) and an increased risk for severe hypoglycemia during the first 4 weeks of therapy. The increased hypoglycemia occurred under double-blind study conditions following the addition of an agent now shown to significantly reduce plasma glucose concentrations, with both patients and investigators encouraged to limit changes in insulin doses. These conditions are not representative of routine clinical practice where prudent changes in insulin dosing will be recommended as outlined above at the time of initiation of therapy to reduce the risk of these undesired events. Following initiation of therapy in the clinical practice setting, patients should be encouraged to modify their insulin regimens according to usual standards of practice based upon self blood glucose monitoring as a means of optimizing their control. Used in this manner, patients should be able to improve their glycemic control while avoiding weight gain and not increasing their insulin use. This represents a significant advance for these patients compared to the challenge of accomplishing this goal with insulin alone, a battle in which most of the patients have found themselves on the losing side for years. Experience indicates that the negative consequences of achieving the same goals with insulin alone will lead the patients and their providers to maintain the status quo. To do so leaves the patients exposed to an increased risk for the long-term complications of diabetes that has negative impacts upon both the patient's lifestyle/quality-of-life and healthcare costs.

Benefit/Risk Summary. Pramlintide is the first novel therapy for patients with type 1 diabetes since the introduction of insulin. For patients with type 2 diabetes who have progressed through treatment with the various oral agents, require insulin therapy, and are still not achieving the desired level of glycemic control, pramlintide offers an additional therapeutic option for improving both glycemic and metabolic control. As such, it offers the potential of improved glycemic and metabolic control to patients who have limited or no other options. In addition to clinically meaningful reductions in HbA_{1c}, pramlintide treatment effects weight stabilization or reduction in the overweight individual, as well as the ability to reduce insulin dose. While there are dose-related adverse events, particularly in the

gastrointestinal system, and treatment requires the administration of additional injections, the side effects dissipate with continued time on therapy, and the injections did not appear to be an impediment to patient acceptance during long-term controlled and uncontrolled trials, in which some patients were treated for up to 2 years. Reducing insulin dose at the outset of starting pramlintide therapy can likely mitigate the nausea and hypoglycemia that occurs mostly at the initiation of therapy.

When assessed in total, the benefits that pramlintide affords to patients with diabetes, as well as to the health care system as a whole, exceed the risks of pramlintide use in this patient group. With time, the optimal ways in which to use pramlintide will be refined beyond the current recommendations regarding dosing and initial adjustment to insulin dose. The risks of pramlintide therapy should be manageable, but as is the case for all therapies, will not be tolerated by all. However, having pramlintide available will allow health care providers and patients to better manage glycemic and metabolic control in the context of limited other therapeutic options.

14. PROPOSED INDICATION AND DOSING RECOMMENDATION

Based on data provided in the NDA and summarized in this document the following indications are proposed:

SYMLIN is indicated as adjunctive therapy to insulin to improve glycemic and metabolic control in people with type 1 or type 2 diabetes mellitus with or without oral hypoglycemic agents.

SYMLIN should be added to patients' existing diabetes treatment regimens, which should include nutritional counseling, exercise, and weight management as needed. Weight management is important not only in the primary treatment of diabetes, but also to maintain the efficacy of drug therapy. SYMLIN has been shown to reduce body weight in people with diabetes.

The benefits of SYMLIN (pramlintide acetate) therapy can be obtained without an increase in the hypoglycemia annual event rate and with no increase in insulin use.

In patients with type 1 diabetes, SYMLIN therapy should be initiated at 30 or 60 µg per dose, administered as a separate subcutaneous injection. The number of SYMLIN doses per day should be based upon frequency of meals and snacks, not to exceed 4 doses per day. In patients with type 2 diabetes, SYMLIN therapy should be initiated at 120 µg per dose, administered as a separate subcutaneous injection. The number of SYMLIN doses per day should be based upon frequency of meals, not to exceed 3 doses per day. For all patients, SYMLIN should be given within 15 minutes before a meal. SYMLIN therapy should be

adjusted to optimize glycemic and weight control, or to minimize gastrointestinal side effects. Adjustments to patients' insulin or other therapies should be considered as a means to optimizing glycemic control while minimizing safety concerns (particularly insulin-induced hypoglycemia) when pramlintide therapy is first introduced.

15. REFERENCES

- 1 Cooper GJ, Willis AC, Clark A, Turner RC, Sim RB, Reid KB. Purification and characterization of a peptide from amyloid-rich pancreases of type 2 diabetic patients. *Proc Natl Acad Sci USA*. 1987;84:8628-8632.
- 2 Cooper GJ, Leighton B, Dimitriadis GD, Parry-Billings M, Kowalchuk JM, Howland K, et al. Amylin found in amyloid deposits in human type 2 diabetes mellitus may be a hormone that regulates glycogen metabolism in skeletal muscle. *Proc Natl Acad Sci USA*. 1988;85:7763-7766.
- 3 Gebre-Medhin S, Olofsson C, Mulder H. Islet amyloid polypeptide in the islets of Langerhans: friend or foe? *Diabetologia*. 2000;43:687-695.
- 4 Beaumont K, Kenney MA, Young AA, Rink TJ. High affinity amylin binding sites in rat brain. *Mol Pharmacol*. 1993;44:493-497.
- 5 Sexton PM, Paxinos G, Kenney MA, Wookey PJ, Beaumont K. In vitro autoradiographic localization of amylin binding sites in rat brain. *Neuroscience* 1994;62:553-567.
- 6 Jodka C, Green D, Young A, Gedulin B. Amylin modulation of gastric emptying in rats depends upon an intact vagus nerve. *Diabetes*. 1996;45 (suppl 2):235A.
- 7 Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National estimates and general information on diabetes in the United States. Revised edition. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 1998.
- 8 Murphy SL. Deaths: Final Data for 1998. *Natl Vit Stat Rep*. 2000;48(11):1-105.
- 9 American Diabetes Association. Economic consequences of diabetes mellitus in the U.S. in 1997. *Diabetes Care*. 1998;21:296-309.
- 10 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412.
- 11 Bastyr EJ III, Stuart CA, Brodows RG, Schwartz S, Graf CJ, Zagar A, Robertson KE, IOEZ Study Group. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA_{1c}. *Diabetes Care*. 2000;23:1236-1241.

- 12 Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977-986.
- 13 Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes.* 1995;44:968-983.
- 14 UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352(9131):837-853.
- 15 Nathan DM, Singer DE, Hurxthal K, Goodson JD. The clinical information value of the glycosylated hemoglobin assay. *N Engl J Med.* 1984;310:341-346.
- 16 Koda JE, Fineman MS, Kolterman OG, Caro JF. 24 hour plasma amylin profiles are elevated in IGT subjects vs. normal controls. *Diabetes.* 1995;44 (suppl 1):238A.
- 17 Fineman MS, Giotta MP, Thompson RG, Kolterman OG, Koda JE. Amylin response following Sustacal® ingestion is diminished in type II diabetic patients treated with insulin. *Diabetologia.* 1996;39(suppl 1):A149.
- 18 Gedulin BR, Rink TJ, Young AA. Dose-response for glucagonostatic effect of amylin in rats. *Metabolism.* 1997;46:67-70.
- 19 Nyholm B, Ørskov L, Hove KY, Gravholt CH, Møller N, Alberti KGMM, et al. The amylin analog pramlintide improves glycemic control and reduces postprandial glucagon concentrations in patients with type 1 diabetes mellitus. *Metabolism.* 1999;48:935-941.
- 20 Young AA, Gedulin BR, Vine W, Percy A, Rink TJ. Gastric emptying is accelerated in diabetic BB rats and is slowed by subcutaneous injections of amylin. *Diabetologia.* 1995;38:642-648.
- 21 Kong M-F, Stubbs TA, King P, Macdonald IA, Lambourne JE, Blackshaw PE, et al. The effect of single doses of pramlintide on gastric emptying of two meals in men with IDDM. *Diabetologia.* 1998;41:577-583.
- 22 Watkins J, Bhavsar S, Young AA. Effect of amylin to inhibit food intake in rats can be blocked with the selective amylin receptor antagonist, AC187. *Program and Abstracts of the 10th International Congress of Endocrinology.* 1996; 419.
- 23 Kolterman OG, Schwartz S, Corder C, Levy B, Klaff L, Peterson J, et al. Effect of 14 days' subcutaneous administration of the human amylin analogue, pramlintide (AC137), on an intravenous insulin challenge and response to a standard liquid meal in patients with IDDM. *Diabetologia.* 1996;39:492-499.
- 24 Thompson RG, Peterson J, Gottlieb A, Mullane J. Effects of pramlintide, an analog

- of human amylin, on plasma glucose profiles in patients with IDDM. results of a multicenter trial. *Diabetes*. 1997;46:632-636.
- 25 Thompson RG, Pearson L, Kolterman OG. Effects of 4 weeks' administration of pramlintide, a human amylin analogue, on glycaemia control in patients with IDDM: effects on plasma glucose profiles and serum fructosamine concentrations. *Diabetologia*. 1997;40:1278-1285.
- 26 DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med*. 1991;90:450-459.

APPENDIX 1: PRAMLINTIDE CLINICAL DEVELOPMENT PROGRAM

**Enumeration of Subjects in the Pramlintide Clinical Development Program
 (Completed Studies)**

Study Group Placebo	No. of Studies	No. of Subjects †	No. Exposed Pramlintide	(Previously Exposed)*
CLINICAL PHARMACOLOGY	29	912	805	353
Bioavailability/Bioequivalence (Healthy)	3	116	116 (0)	0 (0)
Human PK Safety/Tolerance (Healthy)	2	82	77 (0)	17 (0)
Human PK Safety/Tolerance (Diabetics)	4	85	76 (0)	9 (0)
PK in Diabetic Population (Intrinsic Factors)	1	21	21 (0)	0 (0)
PK in Healthy Population (Extrinsic Factors)	2	30	30 (0)	29 (0)
PK in Diabetic Population (Extrinsic Factors)	4	103	101 (0)	72 (0)
Human Pharmacodynamics (Healthy)	1	10	10 (0)	10 (0)
Human Pharmacodynamics (Diabetics)	12	465	374 (0)	216 (0)
SUBJECTS WITH TYPE 1 DIABETES	8	2431	1970	581
Short-term, Controlled Studies	1	215	172 (0)	43 (0)
Long-term, Controlled Studies	3	1717	1179 (0)	538 (0)
Uncontrolled Studies (long-term)	4	758	758 (139)	0 (0)
SUBJECTS WITH TYPE 2 DIABETES	6	1896	1512	470
Short-term, Controlled Studies	1	203	153 (0)	50 (0)
Long-term, Controlled Studies	3	1693	1273 (0)	420 (0)
Uncontrolled Studies (long-term)	2	342	342 (256)	0 (0)
OTHER STUDIES	8	301	206	100
Misc Pramlintide Studies: SC administration	6	283	200 (0)	83 (0)
Misc Pramlintide Studies: IV administration	1	6	6 (0)	5 (0)
Vehicle only administration	1	12	0 (0)	12 (0)
GRAND TOTAL	51	5540	4493	1504

* Number previously exposed refers to exposure in an earlier clinical study
 † Unique subjects

**Subject Disposition During the Pramlintide Clinical Development Program
(Completed Studies)**

Disposition Reason	Clinical Pharmacology [2]		Type 1				Uncon- trolled	Type 2 Using Insulin				Other		
	Pram	Pbo	Controlled		Pram	Controlled		Uncon- trolled	Pram	Pbo	Pram	Pbo		
			Short-term Pram	Long-term Pbo		Short-term Pram							Long-term Pbo	
Total Population	805	353	172	43	1179	538	758	153	50	1273	420	342	206	100
Completed Trial (%)	767(95)	347(98)	158(92)	39(91)	778(66)	403(75)	163(22)	148(97)	49(98)	968(76)	321(76)	0(0)	189(92)	98(98)
Withdrawn (%)	38(5)	6(2)	14(8)	4(9)	401(34)	135(25)	595(78)	5(3)	1(2)	305(24)	99(24)	342(100)	17(8)	2(2)
Non-Compliance	1(<1)	0(0)	0(0)	0(0)	34(3)	23(4)	20(3)	0(0)	0(0)	36(3)	19(5)	6(2)	0(0)	2(2)
Withdrawal of Consent	4(<1)	1(<1)	4(2)	0(0)	80(7)	43(8)	164(22)	1(1)	0(0)	82(6)	26(6)	41(12)	0(0)	0(0)
Adverse Event	20(2)	4(1)	6(3)	0(0)	217(18)	31(6)	142(19)	2(1)	1(2)	117(9)	31(7)	18(5)	12(6)	0(0)
Investigator Decision	2(<1)	0(0)	1(1)	1(2)	9(1)	3(1)	8(1)	0(0)	0(0)	13(1)	2(<1)	8(2)	0(0)	0(0)
Protocol Violation	7(1)	0(0)	0(0)	1(2)	9(1)	10(2)	11(1)	1(1)	0(0)	20(2)	9(2)	10(3)	3(1)	0(0)
Lost to Follow-up	0(0)	1(<1)	0(0)	0(0)	39(3)	19(4)	43(6)	1(1)	0(0)	22(2)	8(2)	6(2)	0(0)	0(0)
Administrative Reason	4(<1)	0(0)	3(2)	2(5)	13(1)	6(1)	207(27)	0(0)	0(0)	15(1)	4(1)	253(74)	2(1)	0(0)

[1] Each patient is counted once per column.

[2] Two patients in Study AP93-02 completed all required study activities and were reported in the CSR as completing the study. However, the patients did deviate from the protocol and are reported in this table as withdrawing from the study.

**Subject-Years of Exposure to Pramlintide During the Clinical Development Program
 (Completed Studies)**

Study Group	Total Number of Subjects	Mean Years of Exposure per Subject	Subject-Years of Exposure
CLINICAL PHARMACOLOGY	805	0.0162	13.07
Bioavailability/Bioequivalence (Healthy)	116	0.0078	0.90
Human PK Safety/Tolerance (Healthy)	77	0.0069	0.53
Human PK Safety/Tolerance (Diabetics)	76	0.0205	1.56
PK in Diabetic Population (Intrinsic Factors)	21	0.0027	0.06
PK in Healthy Population (Extrinsic Factors)	30	0.0027	0.08
PK in Diabetic Population (Extrinsic Factors)	101	0.0082	0.83
Human Pharmacodynamics (Healthy)	10	0.0055	0.05
Human Pharmacodynamics (Diabetics)	374	0.0242	9.05
SUBJECTS WITH TYPE 1 DIABETES	1970	0.7286	1435.38
Short-term, Controlled Studies	172	0.0740	12.72
Long-term, Controlled Studies	1179	0.7177	846.17
Uncontrolled Studies (long-term)	619	0.9313	576.49
SUBJECTS WITH TYPE 2 DIABETES	1512	0.8391	1268.69
Short-term, Controlled Studies	153	0.0746	11.42
Long-term, Controlled Studies	1273	0.9197	1170.77
Uncontrolled Studies (long-term)	86	1.0058	86.50
OTHER STUDIES	206	0.0502	10.33
Misc Pramlintide Studies: SC administration	200	0.0516	10.32
Misc Pramlintide Studies: IV administration	6	0.0027	0.02
TOTAL	4493	0.6070	2727.47

 For patients that went from pramlintide in parent protocol (controlled) to pramlintide in extension (uncontrolled), all exposure is counted in the long term controlled row.

**Demographic Characteristics of Subjects Enrolled in the Pramlintide Clinical Development Program
(Completed Studies)**

Demographic Category	Clinical Pharmacology		Type 1				Type 2 Using Insulin				Other			Total			
	Pram	Pbo	Controlled		Uncon- trolled	Controlled		Uncon- trolled	Pram	Pbo	Pram	Pbo	Pram	Pbo	Pram	Pbo	All
			Short-Term Pram	Long-Term Pbo		Short-Term Pram	Long-Term Pbo										
N	805	353	172	43	1179	538	758	153	50	1273	420	342	206	100	4493	1504	5540
Sex n (%)																	
Male	597 (74)	261 (74)	131 (76)	28 (65)	596 (51)	290 (54)	398 (53)	75 (49)	27 (54)	656 (52)	223 (53)	201 (59)	141 (68)	74 (74)	2568 (57)	903 (60)	3174 (57)
Female	208 (26)	92 (26)	41 (24)	15 (35)	583 (49)	248 (46)	360 (47)	78 (51)	23 (46)	617 (48)	197 (47)	141 (41)	65 (32)	26 (26)	1925 (43)	601 (40)	2366 (43)
Race n (%)																	
White	670 (83)	322 (91)	168 (98)	42 (98)	1119 (95)	503 (93)	718 (95)	122 (80)	42 (84)	1058 (83)	347 (83)	290 (85)	172 (83)	95 (95)	3966 (88)	1351 (90)	4899 (88)
Black	31 (4)	9 (3)	1 (1)	0 (0)	21 (2)	12 (2)	14 (2)	11 (7)	2 (4)	110 (9)	32 (8)	27 (8)	3 (1)	1 (1)	196 (4)	56 (4)	239 (4)
Hispanic	87 (11)	12 (3)	1 (1)	1 (2)	32 (3)	17 (3)	22 (3)	17 (11)	5 (10)	86 (7)	34 (8)	21 (6)	28 (14)	4 (4)	277 (6)	73 (5)	333 (6)
Other	17 (2)	10 (3)	2 (1)	0 (0)	7 (1)	6 (1)	4 (1)	3 (2)	1 (2)	19 (1)	7 (2)	4 (1)	3 (1)	0 (0)	54 (1)	24 (2)	69 (1)
Age (Years)																	
Mean	34.9	35.2	35.3	35.6	39.6	40.2	41.3	59.5	57.5	57.5	56.2	57.9	45.8	38.9	45.1	43.9	45.1
SD	11.94	11.87	10.73	11.62	12.65	12.84	11.96	9.95	10.74	9.97	10.30	9.84	16.11	14.87	14.95	14.77	14.92
Min	17.0	18.0	18.0	19.0	16.0	16.0	16.0	33.0	25.0	22.0	26.0	27.0	16.0	16.0	16.0	16.0	16.0
Max	75.0	75.0	66.0	64.0	83.0	75.0	80.0	78.0	74.0	84.0	81.0	76.0	74.0	73.0	84.0	81.0	84.0
n	805	353	172	43	1179	538	756	153	50	1272	420	342	206	100	4491	1504	5539
Number (%)																	
16<=age<18	1 (<1)	0 (0)	0 (0)	0 (0)	19 (2)	8 (1)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2)	1 (1)	29 (1)	9 (1)	38 (1)
18<=age<65	786 (98)	345 (98)	170 (99)	43 (100)	1122 (95)	508 (94)	727 (96)	93 (61)	35 (70)	941 (74)	326 (78)	245 (72)	171 (83)	91 (91)	3942 (88)	1348 (90)	4868 (88)
65<=age	18 (2)	8 (2)	2 (1)	0 (0)	38 (3)	22 (4)	25 (3)	60 (39)	15 (30)	331 (26)	94 (22)	97 (28)	30 (15)	8 (8)	520 (12)	147 (10)	633 (11)
Weight (kg)																	
Mean	76.1	74.6	77.5	76.0	75.1	75.2	74.8	88.8	86.8	92.3	91.2	91.7	81.4	80.5	81.2	80.3	81.2
SD	12.36	11.74	14.79	11.67	13.82	14.70	13.57	16.82	16.24	19.63	19.15	17.36	14.30	15.90	17.44	17.12	17.52
Min	47.2	47.2	45.9	57.2	37.7	39.5	44.0	46.8	58.1	47.7	40.0	46.6	49.9	44.5	37.7	39.5	37.7
Max	120.9	109.0	127.1	114.0	143.0	166.0	126.2	138.9	130.3	194.9	177.5	170.5	119.0	124.4	194.9	177.5	194.9
n	794	343	172	43	1169	533	752	153	50	1263	416	341	204	99	4456	1484	5495
Number (%)																	
0<=wt< 80	510 (63)	235 (67)	103 (60)	32 (74)	772 (65)	355 (66)	508 (67)	49 (32)	20 (40)	352 (28)	118 (28)	78 (23)	97 (47)	53 (53)	2316 (52)	813 (54)	2871 (52)
80<=wt<110	274 (34)	108 (31)	63 (37)	10 (23)	374 (32)	165 (31)	237 (31)	89 (58)	26 (52)	699 (55)	237 (56)	218 (64)	99 (48)	39 (39)	1848 (41)	585 (39)	2259 (41)
110<=wt	10 (1)	0 (0)	6 (3)	1 (2)	23 (2)	13 (2)	7 (1)	15 (10)	4 (8)	212 (17)	61 (15)	45 (13)	8 (4)	7 (7)	292 (6)	86 (6)	365 (7)

[1] Each patient is counted once per column.

**Demographic Information by Study and Pooled Dose For Long-term Controlled Type 1 Diabetes Studies
Population: Intent-to-Treat**

Variable	Type 1 Diabetes					
	137-112		137-117		137-121	
	Placebo (N=237)	Pramlintide (N=243)	Placebo (N=147)	Pramlintide (N=439)	Placebo (N=154)	Pramlintide (N=497)
Race						
White	219 (92.4)	232 (95.5)	145 (98.6)	438 (99.8)	139 (90.3)	449 (90.3)
Black	6 (2.5)	2 (0.8)	0 (0.0)	0 (0.0)	6 (3.9)	19 (3.8)
Hispanic	9 (3.8)	7 (2.9)	1 (0.7)	0 (0.0)	7 (4.5)	25 (5.0)
Other	3 (1.3)	2 (0.8)	1 (0.7)	1 (0.2)	2 (1.3)	4 (0.8)
Gender						
Male	130 (54.9)	133 (54.7)	78 (53.1)	213 (48.5)	82 (53.2)	250 (50.3)
Female	107 (45.1)	110 (45.3)	69 (46.9)	226 (51.5)	72 (46.8)	247 (49.7)
Age (Years)						
n	237	243	147	439	154	497
Mean (Std)	40.4 (12.1)	40.3 (11.6)	38.8 (13.1)	38.0 (12.7)	41.3 (13.6)	40.7 (13.0)
Median	38.0	39.0	38.0	38.0	40.5	41.0
(Min,Max)	(16.0,70.0)	(16.0,70.0)	(16.0,71.0)	(16.0,83.0)	(16.0,75.0)	(16.0,76.0)
Weight (kg)						
n	235	240	146	436	151	495
Mean (Std)	75.6 (13.3)	75.0 (13.8)	72.5 (12.7)	73.3 (12.5)	76.8 (15.8)	76.9 (14.6)
Median	74.4	74.8	71.0	71.7	75.7	75.7
(Min,Max)	(46.9,121.6)	(46.3,113.4)	(40.5,113.6)	(48.0,143.9)	(50.3,135.2)	(36.7,131.3)
BMI (kg/m²)						
n	234	238	144	434	150	489
Mean (Std)	25.8 (3.5)	25.2 (3.3)	25.0 (3.9)	25.3 (3.7)	26.4 (4.8)	26.5 (4.3)
Median	25.1	25.2	24.5	24.8	25.3	25.8
(Min,Max)	(18.9,39.6)	(18.7,33.1)	(17.8,37.9)	(17.5,45.4)	(18.6,48.4)	(15.8,51.7)
HbA1c (%)						
n	234	240	145	436	153	488
Mean (Std)	8.9 (1.5)	8.7 (1.3)	9.1 (1.1)	9.0 (1.1)	9.0 (1.1)	8.9 (1.0)
Median	8.6	8.4	8.9	8.9	8.8	8.7
(Min,Max)	(6.4,13.7)	(6.3,13.2)	(5.7,12.8)	(6.5,13.5)	(7.2,13.6)	(6.9,12.9)
Duration of Diabetes (Years)						
n	236	242	147	439	154	497
Mean (Std)	17.1 (10.5)	16.5 (10.0)	15.8 (11.0)	16.0 (9.6)	18.2 (10.5)	18.8 (11.0)
Median	16.0	16.0	13.0	14.5	18.2	17.0
(Min,Max)	(1.3,57.0)	(1.1,50.0)	(1.1,52.0)	(1.0,48.0)	(1.3,47.0)	(1.0,58.0)

Note: -Race, Gender, Age, and Duration of Diabetes are summarized from the demographic page of each study (screening).
-BMI, Weight, and HbA1c are summarized from the baseline visit of each study.

**Demographic Information by Study and Pooled Dose for Long-term Controlled Type 2 Diabetes Studies
Population: Intent-to-Treat**

Variable	Type 2 Diabetes					
	137-111		137-122		137-123	
	Placebo (N=136)	Pramlintide (N=402)	Placebo (N=161)	Pramlintide (N=495)	Placebo (N=123)	Pramlintide (N=376)
Race						
White	110 (80.9)	309 (76.9)	120 (74.5)	377 (76.2)	117 (95.1)	372 (98.9)
Black	11 (8.1)	53 (13.2)	19 (11.8)	57 (11.5)	2 (1.6)	0 (0.0)
Hispanic	14 (10.3)	33 (8.2)	20 (12.4)	53 (10.7)	0 (0.0)	0 (0.0)
Other	1 (0.7)	7 (1.7)	2 (1.2)	8 (1.6)	4 (3.3)	4 (1.1)
Gender						
Male	84 (61.8)	226 (56.2)	83 (51.6)	250 (50.5)	56 (45.5)	180 (47.9)
Female	52 (38.2)	176 (43.8)	78 (48.4)	245 (49.5)	67 (54.5)	196 (52.1)
Age (Years)						
n	136	401	161	495	123	376
Mean (Std)	55.5 (10.6)	56.8 (10.0)	56.4 (10.2)	57.6 (10.2)	56.7 (10.1)	58.1 (9.6)
Median	57.0	58.0	56.0	58.0	57.0	58.0
(Min,Max)	(26.0,76.0)	(27.0,76.0)	(31.0,81.0)	(22.0,84.0)	(33.0,76.0)	(23.0,79.0)
Weight (kg)						
n	136	398	160	494	121	373
Mean (Std)	91.0 (16.9)	91.4 (17.7)	96.6 (20.4)	97.9 (21.7)	84.2 (17.7)	85.4 (15.9)
Median	90.5	91.2	94.3	96.8	82.0	85.2
(Min,Max)	(40.4,137.1)	(47.0,164.7)	(52.4,175.7)	(48.6,193.7)	(47.0,149.7)	(50.0,133.0)
BMI (kg/m²)						
n	134	395	160	489	120	372
Mean (Std)	30.3 (4.7)	30.9 (5.2)	33.7 (7.2)	34.0 (7.0)	30.3 (5.9)	30.7 (5.2)
Median	30.2	30.6	33.1	33.2	30.1	30.3
(Min,Max)	(16.3,44.4)	(17.1,51.4)	(19.2,63.5)	(17.9,71.2)	(18.4,50.2)	(17.8,51.2)
HbA1c (%)						
n	135	398	160	489	120	371
Mean (Std)	9.1 (1.2)	9.2 (1.2)	9.2 (1.3)	9.0 (1.2)	9.5 (1.4)	9.3 (1.2)
Median	8.9	9.0	8.9	8.9	9.2	9.3
(Min,Max)	(6.9,12.3)	(6.9,12.3)	(5.5,13.1)	(5.7,13.1)	(7.1,15.8)	(6.2,13.8)
Duration of Diabetes (Years)						
n	136	402	161	494	123	376
Mean (Std)	11.8 (7.7)	12.2 (7.5)	12.4 (7.0)	11.9 (6.9)	13.2 (7.0)	13.6 (7.6)
Median	11.0	10.0	11.0	11.0	12.0	12.2
(Min,Max)	(1.0,35.2)	(0.7,45.0)	(2.0,41.0)	(0.8,46.0)	(1.3,36.2)	(1.3,58.0)

Note: -Race, Gender, Age, and Duration of Diabetes are summarized from the demographic page of each study (screening).
-BMI, Weight, and HbA1c are summarized from the baseline visit of each study.

APPENDIX 2: PRAMLINTIDE PHARMACOKINETICS

A total of 25 studies investigated the pharmacokinetics of pramlintide either directly, or indirectly via its pharmacodynamic effects on glucose. During the conduct of the pramlintide clinical program, modifications were made to both the formulation of pramlintide and assay methods used to measure plasma concentrations of pramlintide. Of the pH, volume, and concentrations assessed, only pH was shown to have an effect on the pharmacokinetics of pramlintide (Study 137-125). This document focuses on the 14 studies that used the pH 4.0 acetate salt formulation of pramlintide and the IEMA method to measure plasma pramlintide concentrations as these most adequately reflect the pharmacokinetics and bioavailability of the intended market formulations of pramlintide acetate. In some cases, studies explored both the pharmacokinetic and pharmacodynamic effects of pramlintide. In such cases, the studies are listed here and in Appendix 3.

Pramlintide Pharmacokinetic Clinical Studies Using the Intended Market Formulation

Study	Design	Key Pharmacokinetic Findings
Bioavailability/Bioequivalence (Healthy Subjects)		
137-125	Single-center, crossover, open-label	<ul style="list-style-type: none"> Bioavailability of pH 4.7 formulation ~70% that of pH 4.0 Bioavailability of 60 µg SC pH 4.0 formulation ~38-40% compared to 60 µg IV pH 4.0 Injection volume does not affect bioavailability of pH 4.0 formulation
137-142	Single-center, crossover, open-label	<ul style="list-style-type: none"> Pen-cartridge and vial-syringe bioequivalent (60 µg, SC)
137-145	Single-center, crossover, open-label	<ul style="list-style-type: none"> Formulations (60 µg, SC) using bulk drug from two manufacturers (Bachem and UCB) are bioequivalent
Human PK Safety/Tolerance (Healthy Subjects)		
137-126	Single-center, crossover, open-label	<ul style="list-style-type: none"> Dose proportionality over 30 to 120 µg (SC) range
Human PK Safety/Tolerance (Diabetics)		
137-143	Single-center, open-label, three-treatment, three-way crossover, two-group, parallel (type 1)	<ul style="list-style-type: none"> Pramlintide did not accumulate in plasma during 5 days of SC treatment with 30, 60, or 90 µg TID or QID Mean C_{max} and AUC_(0-t) increased relatively proportionally with increasing doses of pramlintide across the 30 to 90 µg dosing range

Pramlintide Pharmacokinetic Clinical Studies Using the Intended Market Formulation

Study	Design	Key Pharmacokinetic Findings
Human PK Safety/Tolerance (Diabetics) - continued		
137-144	Single-center, open-label, three-treatment, three-way crossover, two-group, parallel (type 2 using insulin)	<ul style="list-style-type: none"> • Pramlintide did not accumulate in plasma during 5 days of SC treatment with either 60, 120, or 180 µg BID or 60, 90, or 120 µg TID • Mean C_{max} and AUC_(0-t) increased relatively proportionally with increasing doses of pramlintide across the 60 to 180 µg dosing range
PK in Diabetic Special Populations		
137-127	Single-center, open-label, parallel group (renally impaired type 1)	<ul style="list-style-type: none"> • No significant effect of renal impairment on pramlintide (60 µg, SC) pharmacokinetics
PK in Healthy Subjects – Drug Interactions: Orally Administered Medications		
137-133	Single-center, double-blind, placebo-controlled, crossover (oral contraceptive interaction)	<ul style="list-style-type: none"> • No clinically significant interactions of pramlintide (90 µg, SC) with oral contraceptive
137-134	Single-center, double-blind, placebo-controlled, crossover (antibiotic interaction)	<ul style="list-style-type: none"> • Results consistent with effects of pramlintide on modulating the rate of nutrient delivery from the stomach; ampicillin T_{max} delayed approximately 1 hour following single 90 µg SC dose
PK in Diabetic Population – Drug Interactions: Insulin		
137-115	Single-center, open-label, crossover (insulin mixing in type 1)	<ul style="list-style-type: none"> • No major change in plasma concentration profiles of insulin or pramlintide (30 µg, SC) when mixed in the same syringe • No change in plasma glucose profiles
137-119	Single-center, open-label, placebo-controlled, crossover (insulin mixing in type 1)	<ul style="list-style-type: none"> • Plasma glucose pharmacodynamics not adversely affected by mixing • Pramlintide (30 µg, SC) pharmacokinetic parameters significantly altered, suggesting that the two drugs should not be mixed in the same syringe
137-120	Single-center, open-label, placebo-controlled, crossover (insulin mixing in type 1)	<ul style="list-style-type: none"> • Plasma glucose pharmacodynamics not adversely affected by mixing • Pramlintide (30 µg, SC) pharmacokinetic parameters significantly altered, suggesting that the two drugs should not be mixed in the same syringe
137-130	Single-center, open-label, placebo-controlled, crossover (insulin lispro co-administration in type 1)	<ul style="list-style-type: none"> • Pramlintide (60 µg, SC) provides better early postprandial glucose control than achieved with lispro alone • Pramlintide administered with insulin lispro does not produce exaggerated hypoglycemia

APPENDIX 3: PRAMLINTIDE PHARMACODYNAMICS

Studies have identified two principal actions of amylin and pramlintide that may be of therapeutic use in insulin-treated patients with diabetes: reduction of abnormal postprandial glucagon secretion and modulation of the delivery rate of ingested nutrients into the small intestine, thereby reducing the rate of appearance of meal-derived circulating glucose into peripheral circulation. The following table provides an overview of studies that predominantly focus on pharmacodynamics.

Pramlintide Clinical Studies That Predominantly Focus on Pharmacodynamics

Study	Design	Key Pharmacodynamic Findings
Studies Demonstrating Effects on Glucagon		
137-107	Single-center, double-blind, placebo-controlled, crossover (glucagon and glucose profile in type 1)	<ul style="list-style-type: none"> Pramlintide (30 µg SC, QID) caused no change in hepatic glucagon responsiveness, but reduced postprandial plasma glucose and glucagon during 26 to 28 days of treatment
137-106	Single-center, single-blind, placebo-controlled, crossover (post-meal glucose profile in type 2)	<ul style="list-style-type: none"> Pramlintide (500 µg, IV over 5 hours) significantly lowered postprandial hyperglycemia
Studies Demonstrating Effects on Gastric Emptying		
137-103	Single-center, double-blind, placebo-controlled, crossover (gastric emptying in type 1)	<ul style="list-style-type: none"> High dose IV infusion of pramlintide (125 µg, 25 µg/h over 5 hours) markedly slowed rate of emptying of both solid and liquid components of the test meal
137-118	Single-center, single-blind, placebo-controlled, crossover (gastric emptying in type 1)	<ul style="list-style-type: none"> Pramlintide regulates the rate of gastric emptying of solid and liquid components of a test meal administered with pramlintide (30 to 90 µg SC), but not a subsequent meal given 4 hours later Mean C_{max} and AUC₍₀₋₂₄₀₎ increased relatively proportionally with increasing doses of pramlintide across the 30 to 90 µg dosing range, whereas T_{max} was essentially unaffected by dose.
137-137	Single-center, double-blind, placebo-controlled, crossover (gastric emptying in type 2 using insulin)	<ul style="list-style-type: none"> Pramlintide regulates the rate of gastric emptying following a single 90 µg SC injection
137-138	Single-center, open-label, placebo-controlled, crossover (gastric emptying, plasma glucose, and insulin secretion in healthy volunteers)	<ul style="list-style-type: none"> Dose-dependent effect of pramlintide (30, 90 µg SC) on gastric emptying in healthy subjects
137-133	Single-center, double-blind, placebo-controlled, crossover (oral contraceptive interaction)	<ul style="list-style-type: none"> No clinically significant interactions of pramlintide (90 µg SC) and oral contraceptive
137-134	Single-center, double-blind, placebo-controlled, crossover (antibiotic interaction)	<ul style="list-style-type: none"> Results consistent with effects of pramlintide on modulating the rate of nutrient delivery from the stomach; ampicillin T_{max} delayed approximately 1 hour following single 90 µg SC dose

Pramlintide Clinical Studies That Predominantly Focus on Pharmacodynamics

Study	Design	Key Pharmacodynamic Findings
Studies Demonstrating Effects on Postprandial Glucose		
AP93-01	Multicenter, single-blind, placebo-controlled, crossover (post-meal glucose profile in type 1)	<ul style="list-style-type: none"> Pramlintide treatment (30, 100, 300 µg, IV) reduced postprandial hyperglycemia
AP93-08	Multicenter, double-blind, placebo-controlled, parallel group (post-meal glucose profile in type 1)	<ul style="list-style-type: none"> Pramlintide treatment (30, 100, or 300 µg SC, TID) results in reduced postprandial hyperglycemia, suppression of postprandial glucagon, and no effect on response to a standardized insulin-induced hypoglycemic challenge during 14 days of treatment No alteration in counter-regulatory hormone response to hypoglycemia
137-101	Single-center, single-blind, placebo-controlled, crossover (post-meal glucose profile in type 1)	<ul style="list-style-type: none"> Pramlintide treatment (125, 250 µg, IV over 5 hours) reduced postprandial hyperglycemia after a standardized meal, but not after IV glucose load
137-104	Multicenter, double-blind, placebo-controlled, parallel group (24-hour glucose profile in type 1)	<ul style="list-style-type: none"> Pramlintide (30 or 100 µg SC, QID) lowers mean 24-hour plasma glucose concentrations during 14 days of treatment A no effect dose of 10 µg SC identified
137-105	Multicenter, double-blind, placebo-controlled, parallel group (post-meal glucose profile, preprandial plasma glucagon in type 1)	<ul style="list-style-type: none"> Pramlintide (30 µg TID or QID, or 60 µg BID, SC) significantly lowered postprandial hyperglycemia during 28 days of treatment No effect on preprandial glucagon
137-114	Multicenter, double-blind, placebo-controlled, parallel group (fructosamine in type 2 using insulin)	<ul style="list-style-type: none"> Pramlintide (30 µg QID, or 60 µg TID or QID, SC) significantly lowered fructosamine during 28 days of treatment, providing evidence for effects in lowering postprandial glucose
137-119	Single-center, open-label, placebo-controlled, crossover (insulin mixing in type 1)	<ul style="list-style-type: none"> Plasma glucose pharmacodynamics not adversely affected by mixing Pramlintide (30 µg, SC) pharmacokinetic parameters significantly altered, suggesting that the two drugs should not be mixed in the same syringe
137-120	Single-center, open-label, placebo-controlled, crossover (insulin mixing in type 1)	<ul style="list-style-type: none"> Plasma glucose pharmacodynamics not adversely affected by mixing Pramlintide (30 µg, SC) pharmacokinetic parameters significantly altered, suggesting that the two drugs should not be mixed in the same syringe

Pramlintide Clinical Studies That Predominantly Focus on Pharmacodynamics

Study	Design	Key Pharmacodynamic Findings
Studies Demonstrating Effects on Postprandial Glucose - continued		
137-130	Single-center, open-label, placebo-controlled, crossover (insulin lispro co-administration in type 1)	<ul style="list-style-type: none"> • Pramlintide (60 µg, SC) provides better early postprandial glucose control than achieved with lispro alone • Pramlintide administered with insulin lispro does not produce exaggerated hypoglycemia
Studies Demonstrating Effects on Counter-regulatory Hormones and Insulin Sensitivity		
AP93-02	Multicenter, double-blind, placebo-controlled, parallel group (hypoglycemic challenge in type 1)	<ul style="list-style-type: none"> • Pramlintide (100 to 1000 µg SC) had no negative impact on counter-regulatory hormone response to hypoglycemia
AP93-03	Single-center, single-blind, placebo-controlled, parallel group (hypoglycemic challenge in type 1)	<ul style="list-style-type: none"> • Pramlintide (0.1 to 0.25 µg SC, QID) had no effect on the severity of hypoglycemia induced by a standardized IV insulin infusion, or the response of counter-regulatory hormones to hypoglycemia
AP93-04	Single-center, double-blind, placebo-controlled, crossover (glucose clamp in type 1)	<ul style="list-style-type: none"> • Pramlintide (275, 412.5, 550 µg, IV over 5.5 hours) does not produce insulin resistance with acute administration • Pramlintide does not impair the counter-regulatory response to hypoglycemia • No observed effect on hepatic or peripheral insulin sensitivity

APPENDIX 4: SYNOPSES OF CONTROLLED STUDIES

1.1 Short-term Controlled Study in Type 1 Diabetes

There was one short-term controlled study in subjects with type 1 diabetes [137-105]. This was a randomized, placebo-controlled, parallel-group, double-blind, multicenter study in subjects with type 1 diabetes mellitus, designed to assess the tolerability and effects on glycemic control of four dosing regimens of subcutaneously administered pramlintide [30 µg QID blds,^a 30 µg TID bld, 30 µg TID bds, 60 µg BID bd] versus placebo administered QID for 28 days.

^a b = breakfast; l = lunch; d = dinner; s = snack

1.1.1 Study 137-105

Title of Study: Four Week, Multicenter, Double-Blind, Parallel, Placebo and Tripro-Amylin Dose Frequency Study of Plasma Glucose Profiles and Pharmacokinetics in Subjects with Juvenile-Onset Diabetes Mellitus

Investigators and Study Centers: 20 Investigators at 20 US study centers

Key Publication (Reference):

Thompson RG, Pearson L, Kolterman OG. Effects of four weeks' administration of pramlintide, a human amylin analogue, on glycaemia control in patients with IDDM: effects on plasma glucose profiles and serum fructosamine concentrations. *Diabetologia* 1997;40:1278-1285.

Studied Period: November 1994 – July 1995

Phase of Development: 2

Objectives: Primary Objectives: To determine the effect of four dose frequency regimens of pramlintide versus placebo on changes in 24-hour plasma glucose profiles from baseline to four weeks of treatment, through comparison of areas under the curve (AUC). To determine the safety of four dose frequency regimens of pramlintide versus placebo when administered by subcutaneous injection. Secondary Objectives: To determine the effect of four dose frequency regimens of pramlintide versus placebo on HbA_{1c} at baseline compared to the end of treatment. To determine the effects of four dose frequency regimens of pramlintide on glucose concentrations following a standardized meal tolerance test as compared to placebo. To determine the effect of four dose frequency regimens of pramlintide versus placebo on fructosamine concentrations at baseline compared to end of treatment; compare results from placebo baseline to changes at four weeks of dosing of mean 24-hour glucose profiles and changes in C_{max} and C_{min} glucose; compare the incidence and severity of hypoglycemia between the four dose frequency regimens of pramlintide versus placebo based on protocol-defined criteria.

Methodology: Randomized, placebo-controlled, parallel-group, double-blind, multicenter study in subjects with type 1 diabetes mellitus, designed to assess the tolerability and effects of four dosing regimens of pramlintide (30 µg QID blds, 30 µg TID bld, 30 µg TID bds, 60 µg BID bd) versus placebo administered QID for four weeks. The letters b, l, d, and s refer to doses administered with breakfast, lunch, dinner, and the bedtime snack, respectively.

Number of Subjects: Two hundred fifteen subjects (26% female, 74% male; mean age 35.4 years) were enrolled in this study. The number of subjects enrolled in each treatment group

was: 45 pramlintide 30 µg QID blds; 41 pramlintide 30 µg TID bld; 44 pramlintide 30 µg TID bds, 42 pramlintide 60 µg BID bd; and 43 placebo. Of the 215 subjects enrolled, 197 (91.6%) completed the study.

Diagnosis and Main Criteria for Inclusion: Subjects with type 1 diabetes mellitus for at least two years but not exceeding 25 years; aged between 18 and 60 years, who met all other protocol defined inclusion and exclusion criteria.

Test Form, Dose and Mode of Administration, Batch No.: Pramlintide acetate 0.3 mg/mL (AC-0137-F10), 0.1 mL per subject, subcutaneous administration, Lot number: 94-0906FB; Pramlintide acetate 0.6 mg/mL (AC-0137-F11), 0.1 mL per subject, subcutaneous administration, Lot number: 94-0904FB.

Duration of Treatment: Eight-day single-blind placebo lead-in followed by four weeks of randomized treatment.

Reference Form, Dose and Mode of Administration, Batch No.: Placebo, 0.1 mL per subject, subcutaneous administration, Lot number: 94-0608FE.

Criteria for Evaluation:

Efficacy: Efficacy was assessed for the evaluable population. Comparison of 24-hour plasma glucose profiles ($AUC_{(0-1440 \text{ min})}$) at baseline and after four weeks of randomized treatment. Comparison of prandial plasma glucose concentrations ($AUC_{(0-930 \text{ min})}$, C_{ave} , C_{SD} , and C_{range}) at baseline and after four weeks of randomized treatment. Comparison of the glucose response to the Sustacal® test meal ($AUC_{(0-180 \text{ min})}$ and incremental $AUC_{(0-180 \text{ min})}$) at baseline, and after two and four weeks of randomized treatment. Comparison of fructosamine and HbA_{1c} at baseline and after four weeks of randomized treatment.

Clinical Pharmacology: Clinical pharmacology was assessed for the evaluable population. Comparison of 24-hour serum insulin profiles $AUC_{(0-1440 \text{ min})}$ at baseline and after four weeks of randomized treatment. Comparison of insulin profiles to the Sustacal test meal ($AUC_{(0-180 \text{ min})}$) at baseline and after two and four weeks of randomized treatment. Comparison of preprandial plasma glucagon, epinephrine, and norepinephrine concentrations at baseline and after four weeks of randomized treatment. Comparison of 24-hour plasma pramlintide profiles after four weeks of treatment ($AUC_{(0-1440 \text{ min})}$), and Sustacal test meal pramlintide profiles after two and four weeks of treatment ($AUC_{(0-180 \text{ min})}$, C_{max} , T_{max} , and $t_{1/2}$).

Safety: Safety was assessed for the intent-to-treat population. Adverse events, clinical laboratory values, vital signs, electrocardiograms (ECGs), physical examination findings, anti-pramlintide antibodies, and hypoglycemic episodes were assessed.

Statistical Methods:

Efficacy: Change in the plasma glucose 24-hour profiles ($AUC_{(0-1440 \text{ min})}$) was compared across treatments after four weeks of randomized treatments using an analysis of variance model (ANOVA) with terms of treatment and center for all evaluable subjects. Change in the prandial plasma glucose concentrations ($AUC_{(0-930 \text{ min})}$, C_{ave} , C_{SD} , and C_{range}) were compared across treatments after four weeks of randomized treatment using an ANOVA with terms of treatment and center for all evaluable subjects. Ninety-five percent (95%) confidence intervals for the difference in the LSmeans were obtained. ANOVA was also used to analyze the change in the plasma glucose response, $AUC_{(0-180 \text{ min})}$ (both absolute and incremental), to the Sustacal test meal from baseline to two and four weeks of randomized treatment. Changes in fructosamine and HbA_{1c} from baseline to four weeks of treatment were also analyzed using ANOVA.

Clinical Pharmacology: The 24-hour serum insulin profiles ($AUC_{(0-1440 \text{ min})}$) were compared for change from baseline to four weeks of randomized treatment using ANOVA across treatment groups. ANOVA was also used to compare the change in the serum insulin profiles ($AUC_{(0-180 \text{ min})}$) after a Sustacal test meal from baseline to two and four weeks of randomized treatment across treatment groups. Preprandial plasma glucagon, epinephrine, and norepinephrine concentrations at baseline and after four weeks of randomized treatment were presented using descriptive statistics.

Pharmacokinetic parameters for the pramlintide concentrations collected after four weeks of treatment (24-hour profile) and for the pramlintide profiles obtained after a Sustacal test meal after two and four weeks of treatment were obtained using WinNonlin and were summarized.

Safety: Adverse events, clinical laboratory values, and vital signs were presented using descriptive statistics.

SUMMARY CONCLUSIONS:

EFFICACY – RESULTS: Change in 24-Hour Plasma Glucose AUC:

Following four weeks of treatment (Visit 6), mean plasma glucose AUC_(0-1440 min) decreased from baseline (Visit 3) in all pramlintide groups, while it increased for the placebo group. The difference in the change from baseline was statistically significant (p=0.0142) between pramlintide 30 µg QID blds and placebo.

Plasma Glucose AUC_(0-1440 min) (mg·min/dL): Change from Baseline (Visit 3) after Four Weeks of Treatment (Visit 6)		
Treatment Group	Change from Baseline (Visit 3) after Four Weeks of Treatment (Visit 6)	Pairwise Comparisons of LS Means Difference from Placebo (p-value)
	Mean (SD)	
Placebo	3247 (79334)	NA
30 µg QID blds	-33336 (65371)	0.0142
30 µg TID bld	-1556 (86540)	0.6034
30 µg TID bds	-2176 (57975)	0.5426
60 µg BID bd	-16603 (79281)	0.1329

Prandial Period (0-930 min): Following four weeks of treatment (Visit 6), mean prandial plasma glucose AUC_(0-930min) decreased from baseline (Visit 3) in all pramlintide groups, while it increased for the placebo group. The difference in the change from baseline was statistically significant between pramlintide 30 µg QID blds and placebo (p=0.0073) and pramlintide 60 µg BID bd and placebo (p=0.0230). Following four weeks of treatment (Visit 6), the difference in the change from baseline (Visit 3) in mean prandial plasma glucose C_{ave} was statistically significant between pramlintide 30 µg QID blds and placebo (p=0.0145), and pramlintide 60 µg BID bd and placebo (p=0.0113). Four weeks of treatment with pramlintide 30 µg QID blds and pramlintide 60 µg BID bd was also associated with reductions in the mean prandial plasma glucose C_(range) and C_{SD}, suggesting a reduction in the large variability in plasma glucose, compared to placebo.

Sustacal Test Meal: Greater mean reductions in glucose AUC_(0-180 min) and incremental AUC_(0-180 min) were observed for all pramlintide groups after two (Visit 5) and four weeks (Visit 6) of treatment, compared to placebo. After four weeks of treatment (Visit 6), the difference in the change from baseline (Visit 3) in incremental mean glucose AUC_(0-180 min) was statistically significant between pramlintide 30 µg QID blds and placebo (p=0.0244), pramlintide 30 µg TID bds and placebo (p=0.0226), and pramlintide 60 µg BID bd and placebo (p=0.0146).

Fructosamine and HbA_{1c} Analyses: Greater mean reductions from screening (Visit 1) in mean fructosamine concentration were observed for all pramlintide groups after four weeks (Visit 6) of treatment, compared to placebo. The difference in the mean change from screening (Visit 1) in serum fructosamine concentration was statistically significant between

pramlintide 30 µg QID blds and placebo (p=0.0014) and 60 µg BID bd and placebo (p=0.0433). Following four weeks of treatment (Visit 6), the greatest reduction from screening (Visit 1) in mean HbA_{1c} was observed for the pramlintide 30 µg QID blds regimen.

CLINICAL PHARMACOLOGY RESULTS:

Change in Serum Insulin AUC_(0-1440 min): Following four weeks of study drug administration, reductions from baseline (Visit 3) in serum insulin AUC_(0-1440 min) were observed for all pramlintide groups, while an increase in serum insulin AUC_(0-1440 min) was observed for the placebo group. The difference in the change from baseline in mean serum insulin AUC_(0-1440 min) was statistically significant (p=0.0248) between the 30 µg QID blds group and placebo at Visit 6.

Change in Serum Insulin AUC_(0-180 min): A mean serum insulin AUC_(0-180 min) reduction from baseline (Visit 3) was observed for the pramlintide 30 µg TID bds group at two weeks of treatment (Visit 5), and the pramlintide 30 µg QID blds, 30 µg TID bld, and 30 µg TID bds groups at four weeks of treatment (Visit 6).

Preprandial Plasma Glucagon and Catecholamine Concentrations: Four weeks of pramlintide treatment had no effect on preprandial plasma glucagon, epinephrine, and norepinephrine concentrations.

SAFETY RESULTS:

Adverse Events: Of the 215 randomized subjects, 206 (95.8%) experienced at least one treatment-emergent adverse event. The most commonly occurring treatment-emergent adverse events were hypoglycemia (92.1%), nausea (20.9%), headache (18.1%), upper respiratory tract infection (8.4%), pharyngitis (6.5%), and anorexia (5.6%). With the exception of nausea and anorexia, the incidence of frequently reported adverse events was similar between the placebo and pramlintide treatment groups.

The incidence of hypoglycemic events was similar across the placebo and pramlintide groups (88.6% to 93.3%). These results were only slightly higher than the incidence (78.0% to 88.4%) of hypoglycemic events reported during the placebo lead-in period. The majority of hypoglycemic events were assessed by the investigator as mild in intensity (86.0%).

Deaths: None

Serious Adverse Events: Subject 2040 (pramlintide 30 µg QID blds) experienced two serious treatment-emergent adverse events (ketosis and peripheral edema). The investigator assessed the ketosis as serious, of moderate intensity and probably not related to study

medication, and the edema peripheral as serious, of mild intensity and probably not related to study medication.

Adverse Events Leading to Withdrawal: Six pramlintide-treated subjects withdrew from the study due to adverse events, which were primarily gastrointestinal in nature.

Clinical Laboratory Values: There were no unexpected changes for this study population in clinical laboratory values, nor any relationship between pramlintide treatment and the incidence of potentially clinically important laboratory values. A mean decrease from screening (Visit 1) was observed in serum glucose after four weeks of treatment (Visit 6) for all four pramlintide treatment groups whereas an increase from screening (Visit 1) was observed for the placebo group. A lower incidence of clinically important urine glucose concentrations was observed for the pramlintide treatment groups as compared to the placebo treatment group at four weeks of treatment (Visit 6), suggesting an improved level in glucose control.

Vital Signs, Electrocardiograms, and Physical Examinations: In general, no clinically meaningful or unexpected changes were reported in vital signs, ECGs, and physical examinations.

CONCLUSIONS:

Four weeks of treatment with pramlintide 30 µg QID blds resulted in significant improvement in overall 24-hour glucose control, glucose control during the meal-derived, prandial period (15.5 hours), and glucose control during the controlled, three-hour Sustacal meal period. Results from other TID and BID pramlintide dosing regimens displayed similar trends, suggesting that less frequent dosing may be adequate in some subjects.

Four weeks of treatment with pramlintide 30 µg QID blds and 60 µg BID bd produced reductions in mean prandial glucose C_{SD} and $C_{(range)}$ consistent with a reduction in the larger daily variability in plasma glucose concentrations which characterize patients with type 1 diabetes.

Pramlintide administration was associated with reductions in insulin doses mean serum insulin AUC while both insulin dose and mean serum insulin AUC increased in placebo subjects.

The subcutaneous administration of four dose frequency regimens of pramlintide (30 µg QID blds, 30 µg TID bld, and 30 µg TID bds, and 60 µg BID bd) versus placebo for four weeks appeared to be safe and well-tolerated. The incidence of hypoglycemic events was similar among treatment groups. Pramlintide improved glycemic control without an increased risk of hypoglycemic events.

1.2 Long-term Controlled Studies in Type 1 Diabetes

There were three long-term, controlled studies in subjects with type 1 diabetes. Two of these studies (137-121 and 137-112) were conducted in the US and Canada (1 year duration) and one (137-117) was conducted in Europe and Canada (6 month duration). A brief summary of each of the three studies is provided in the following sections.

1.2.1 Study 137-112

Title of Study: Fifty-Two Week, Multicenter, Double-Blind, Parallel Group, Placebo Controlled Study to Evaluate Glycated Hemoglobin and Safety of Pramlintide (AC137) Versus Placebo in Patients With Type I Diabetes Mellitus.

Investigators and Study Centers: 37 investigators at 35 centers in the USA.

Key Publications (Reference):

1. Rosenstock J, Whitehouse F, Schoenfeld S, Dean E, Blonde L, Kolterman, O. Effect of Pramlintide on Metabolic Control and Safety Profile in People With Type 1 Diabetes. *Diabetes* 1998;47 (suppl 1):A88
2. Whitehouse F, Ratner R, Rosenstock J, Schoenfeld S, Kolterman, O. Pramlintide Showed Positive Effects on Body Weight in Type 1 and Type 2 Diabetes. *Diabetes* 1998;47 (suppl 1):A9
3. Bone H, Hurley MA, Goldstein H, Fineman MS, Kolterman, OG. Effects of Administration of Pramlintide for 12 Months on Bone Metabolism Markers in People With Type 1 Diabetes. *Endocrine Society 81st Annual Meeting Programs and Abstracts* 1999:447 (abstract P3-42)

Studied Period: September 1995 to December 1997

Phase of Development: 3

Objectives:

The primary objectives of this study were to:

1. determine the effects of pramlintide on glucose control as reflected by hemoglobin A_{1c} (HbA_{1c}) obtained at baseline (Visit 1), at 13 weeks (Visit 5), and at 52 weeks of treatment (Visit 9) compared to placebo in subjects with type 1 diabetes mellitus; and
2. determine the safety of two doses of pramlintide compared to placebo when administered by subcutaneous injection.

The key secondary objectives of this study were to:

1. determine the effect of pramlintide on long-term glucose control defined as baseline (Visit 1) HbA_{1c} compared to HbA_{1c} obtained at 4, 8, 13, 20, 26, 39 and 52 weeks of treatment with pramlintide;

2. determine the effect of pramlintide versus placebo on HbA_{1c} in a subset analysis based on entry HbA_{1c} (evaluable patients across all dosage groups and placebo were to be divided into upper, middle and lower two-third cohorts for this analysis)
3. determine the portion of the population treated with pramlintide having a decrease in HbA_{1c} obtained at baseline (Visit 1) and after 13 weeks (Visit 5) of treatment less than 1%;
4. determine change in HbA_{1c} in this population at 26, 39 and 52 weeks after re-randomization at 20 weeks (Visit 6) to 30 µg or 60 µg four times a day.

Methodology: This was a randomized, 52-week, multicenter, double-blind, parallel group, placebo-controlled study. Subjects who satisfied all inclusion and exclusion criteria and successfully completed the screening visit began a 20-week treatment period (pramlintide 30 µg QID or placebo QID) according to a predetermined randomization schedule. At Week 20, subjects who had a reduction in HbA_{1c} of <1% at Week 13, compared to baseline, were re-randomized to either 30 µg or 60 µg QID of pramlintide for the duration of the study period. Subjects who had a reduction of HbA_{1c} of ≥1%, compared to baseline, remained at the same dosage for the duration of the study period. Subjects initially randomized to placebo were re-randomized to placebo for the duration of the study period regardless of HbA_{1c} value. For most summaries and analyses, subjects who were re-randomized to either 30 µg or 60 µg pramlintide are grouped together with non-re-randomized pramlintide subjects in this report, in order to assess the efficacy and safety of the pramlintide QID regimen overall. Subjects received insulin throughout the study. Adjustments were to be made as needed to a subject's insulin regimen, consistent with good medical practices.

Number of Subjects: Four hundred eighty subjects between the ages of 16-70 years (mean age, 40.4 years), inclusive, were randomized (54.8% males, 45.2% females). A total of 342 subjects (71.3%) completed 52 weeks of treatment.

Diagnosis and Main Criteria for Inclusion: Males, females using appropriate contraception, or females who were post-menopausal or surgically sterile with type 1 diabetes mellitus who met all inclusion and exclusion criteria were eligible for study inclusion.

Test Product, Dose and Mode of Administration, Batch No: Pramlintide, 0.1 mL (30 µg), subcutaneous injection, Lot Nos. 95-0503GB (AC-0137-F16), 95-0902GB (AC 0137-F21). Pramlintide, 0.1 mL (60 µg), subcutaneous injection, Lot No. 95-0501GB (AC-0137-F17).

Duration of Treatment: 52 weeks.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo, 0.1 mL, subcutaneous injection, Lot No. 95-0504GE.

Criteria for Evaluation:

Efficacy: Efficacy evaluations consisted of measurements of HbA_{1c}. The Statistical Analysis Plan defined the primary efficacy parameter as the relative change in HbA_{1c} from baseline to Week 52. Key secondary efficacy criteria included the change in HbA_{1c} from baseline to Weeks 13, 26, and 52, the relative change in HbA_{1c} from baseline to Week 13 and from baseline to Week 26, and the number and percent of subjects achieving an HbA_{1c} value <8%. Additional post hoc analyses performed included the percentage of subjects achieving HbA_{1c} <7% or achieving a decrease in HbA_{1c} ≥0.5%. Other secondary efficacy endpoints included body weight, fasting serum lipids, and episodes of severe hypoglycemia.

Safety: Safety evaluations included reports of adverse events, serious adverse events, deaths, withdrawals due to adverse events, clinical laboratory evaluations (including plasma anti-pramlintide antibodies), vital signs, electrocardiograms, physical examinations, and evaluations of nausea over time.

Other: Serum and urine markers of bone turnover were measured in all subjects. Bone mineral density was determined using dual energy x-ray absorptiometry at selected investigator sites.

Statistical Methods:

Efficacy: The protocol stated that the statistical analysis of the efficacy data was to be performed for all completed (evaluable) subjects and for all randomized subjects (intent-to-treat). The Statistical Analysis Plan specified that the evaluable population would be the primary population for the efficacy evaluations. The Statistical Analysis Plan also defined the Stable Insulin Population as an additional population to isolate the treatment effect of pramlintide independent of effects of changes in insulin dose. Parametric two-way analysis of variance (ANOVA) of relative change and change from baseline (HbA_{1c}, lipids, and weight), repeated measures ANOVA (HbA_{1c}), and survival log-rank test of HbA_{1c} <8%, and severe hypoglycemia, were all conducted as two-tailed tests with a significance level of 0.05, with the exception of the log-rank test for severe hypoglycemic events (significance level of 0.10).

Safety: Detailed listings and summaries were prepared showing pre-treatment and post-treatment values, as well as change from pre-treatment values, to provide descriptive comparisons for the pramlintide treatment regimens and placebo. Adverse events were tabulated by incidence, severity, and study drug attributability, and compared between treatment regimens.

SUMMARY-CONCLUSIONS:

EFFICACY RESULTS:

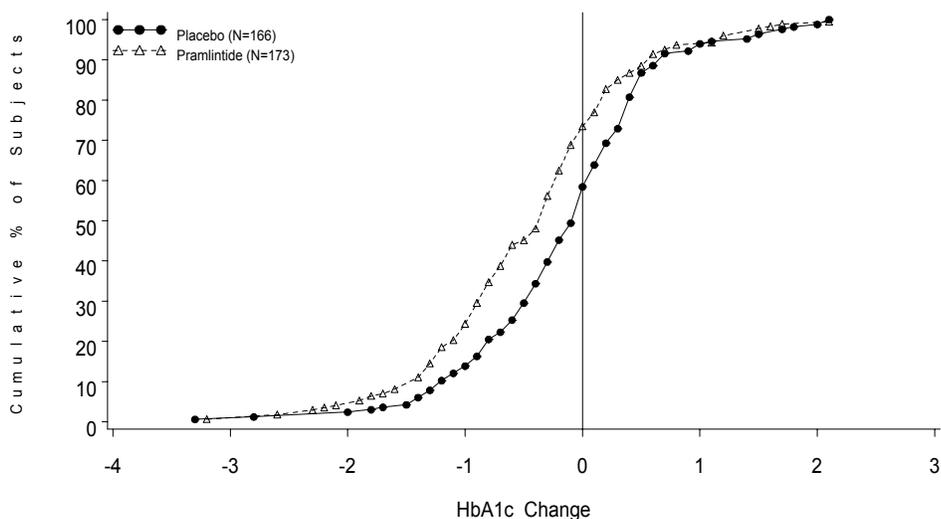
HbA_{1c} Results: Pramlintide QID was effective in significantly improving glycemic control as determined by a clinically and statistically significant difference from placebo in the primary efficacy parameter, relative change from baseline at Week 52 in HbA_{1c} in the evaluable population. Results in the intent-to-treat and stable insulin populations were consistent with the results obtained for the evaluable population. Results for secondary efficacy parameters associated with HbA_{1c} measurements (the change in HbA_{1c} from baseline at Weeks 13, 26, and 52, the relative change in HbA_{1c} from baseline at Weeks 13 and 26, and the number and percent of subjects achieving various HbA_{1c} target values) were all consistent with the primary efficacy parameter. A summary of key HbA_{1c} variables is provided in the following table.

<u>SUMMARY OF KEY HbA_{1c} VARIABLES</u>		
	Placebo (N=168)	Pramlintide QID (N=174)
<u>HbA_{1c} relative change (%) from Baseline at Week 26^[1]</u>		
LSMEAN (SE)	-1.96 (0.76)	-6.80 (0.75)
LSM difference	4.84	
Pairwise p-value	.0001	
<u>HbA_{1c} relative change (%) from Baseline at Week 52^[1]</u>		
LSMEAN	-1.27 (0.78)	-4.35 (0.76)
LSM difference	3.08	
Pairwise p-value	.0039	
<u>HbA_{1c} change (%) from Baseline at Week 26^[1]</u>		
LSMEAN	-0.22 (0.07)	-0.63 (0.07)
LSM difference	0.41	
Pairwise p-value	0.0001	
<u>HbA_{1c} change (%) from Baseline at Week 52^[1]</u>		
LSMEAN	-0.16 (0.07)	-0.42 (0.07)
LSM difference	0.26	
Pairwise p-value	0.0071	
Early Glycemic Responders (%) ^[2]	24	44
<u>Kaplan-Meier estimate of proportion of subjects achieving targets by Week 52</u>		
HbA _{1c} <8% ^[3,5]	0.360	0.579
p=0.0002 ^[4]		
HbA _{1c} <7% ^[3,5]	0.117	0.232
p=0.0024 ^[4]		
Decrease of ≥0.5% ^[3,6]	0.662	0.809
p=0.0001 ^[4]		
<p>^[1] Evaluable population; ANOVA with treatment and site as factors in the model.</p> <p>^[2] Intent-to-treat subjects who achieved a reduction in HbA_{1c} of ≥0.5% at Week 4.</p> <p>^[3] Intent-to-treat population without imputation.</p> <p>^[4] Log-rank test for the overall comparison of time to first achieving target HbA_{1c} value.</p> <p>^[5] Kaplan-Meier estimate of the proportion of subjects with HbA_{1c} at baseline above target value who achieved an HbA_{1c} value below the target value by Week 52.</p> <p>^[6] Kaplan-Meier estimate of the proportion of subjects achieving a ≥0.5% decrease from baseline in HbA_{1c} by Week 52.</p>		

To further characterize the pramlintide treatment effect, the change in HbA_{1c} from baseline at Weeks 4, 13, 20, 26, 39, and 52, as well as the average change from baseline for Weeks 4 – 26 and Weeks 4 – 52, was analyzed including baseline HbA_{1c} in the ANOVA model. These additional analyses confirmed the analyses without baseline HbA_{1c} as a covariate. With the exception of Week 26 in the stable insulin population, all comparisons between pramlintide and placebo were statistically significant (p≤0.0420) with pramlintide exhibiting a greater reduction from baseline than placebo.

The following figure shows cumulative percent of subjects vs. change in HbA_{1c} from baseline at Week 52. The points on the curve represent the cumulative percentage of subjects (Y axis) assigned to a particular treatment group who completed 52 weeks of treatment and who achieved a change in HbA_{1c} from baseline at least as large as the HbA_{1c} change value given on the X axis. A negative change from baseline represents improved glucose control; a positive change indicates worsening of glucose control. As shown in the following figure, the cumulative percent of subjects who had a decrease in HbA_{1c} from baseline of $\geq 0.5\%$ or more at Week 52 was 45% in the pramlintide group compared with 30% in the placebo group. The cumulative percent of subjects who had a decrease from baseline in HbA_{1c} of $\geq 1.0\%$ at Week 52 was 24% in the pramlintide group compared with 14% in the placebo group. That the pramlintide curve is shifted to the left relative to the placebo curve indicates more improvement in glucose control for pramlintide subjects than for placebo subjects.

**Week 52 Cumulative Percent of Subjects who Achieved
 Changes in HbA_{1c} From Baseline
 Population: Intent-to-Treat -- Observed Values**



Note: Subject 9462 (Trt=Pramlintide, HbA_{1c} Change=4.4%) is not shown.

For subjects who had a reduction in HbA_{1c} of $< 1.0\%$ after 13 weeks of treatment with 30 μg pramlintide QID and who were re-randomized to pramlintide 60 μg QID, the increased dose did not appear to result in further improvement in glycemic control.

Pramlintide treatment also was associated with a significant reduction in weight and LDL/HDL ratio. The incidence of severe hypoglycemic events was 19.6% for placebo (33

out of 168 subjects), and 26.4% for pramlintide treated subjects (46 out of 174 subjects). The event rate per subject-year of observation was 0.74 for both placebo (excluding a single placebo subject who reported 128 events) and pramlintide QID. Pramlintide treatment appeared to lead to an earlier onset of severe hypoglycemia, as evidenced by the calculated mean time to first experiencing a severe hypoglycemic event being shorter in the pramlintide group (41.6 weeks) than in the placebo group (46.2 weeks), and the log-rank test showed a significant trend ($p=0.0696$).

SAFETY RESULTS:

Adverse Events: Two hundred thirty-two (95.5%) pramlintide-treated subjects and 220 (92.8%) placebo-treated subjects reported one or more treatment-emergent adverse events. Forty-eight subjects (30 pramlintide, 18 placebo) withdrew from the study prematurely due to adverse events. The most common adverse events were gastrointestinal in nature, most notably nausea which occurred in more than twice as many pramlintide-treated subjects as placebo-treated subjects. Anorexia was the second most common gastrointestinal adverse event reported for pramlintide-treated subjects. The majority of nausea and anorexia events were assessed as mild in intensity.

A higher prevalence of nausea was observed for pramlintide-treated subjects as compared to placebo-treated subjects throughout most of the study. Nausea was most pronounced at Week 2. A higher occurrence of withdrawals due to nausea was observed for pramlintide at Weeks 2 and 8 as compared to placebo. A total of 18 pramlintide-treated subjects withdrew due to nausea, with the majority (12/18) of withdrawals occurring at Week 2.

The incidence of hypoglycemic adverse events was similar between pramlintide and placebo. Fifty-nine (24.3%) pramlintide-treated subjects experienced 113 hypoglycemic events, whereas 42 (17.7%) placebo-treated subjects experienced 164 hypoglycemic events. An increased incidence of hypoglycemic events was observed among the 62 subjects re-randomized to pramlintide 60 µg QID as compared to the 71 subjects re-randomized to pramlintide 30 µg QID.

Fifteen (24.2%) subjects from the pramlintide 60 µg QID treatment group experienced 24 hypoglycemic events, whereas nine (12.7%) subjects from the pramlintide 30 µg QID treatment group experienced 15 hypoglycemic events.

Deaths: There were two deaths reported in this study. One subject in the pramlintide group died as a result of coronary artery arteriosclerosis, which is consistent with the increased risk of cardiovascular disease with diabetes. Since a relationship to study medication could not be ruled out, this event was assessed as possibly related to study medication. One subject in the placebo group died as a result of ventricular fibrillation and cardiac arrest during hospitalization

for pneumonia, which, by patient history, appears to represent aspiration pneumonia. This event was assessed as probably not related to study medication.

Serious Adverse Events: There were 82 serious adverse events in this study. Twenty-two (9.1%) pramlintide-treated subjects and 17 (7.2%) placebo-treated subjects reported 43 and 39 serious treatment-emergent events, respectively. The most common serious adverse event was hypoglycemia.

Clinical Laboratory Values: Laboratory parameters were not adversely affected by pramlintide treatment.

Vital Signs, Physical Examinations and ECGs: Pramlintide treatment appeared to have no effect on vital signs, physical examinations and electrocardiogram measurements.

Anti-Pramlintide Antibodies: Five placebo subjects and 16 pramlintide subjects who had negative anti-pramlintide antibody results at baseline had a positive antibody assay at some time during the treatment period. Review of individual subject HbA_{1c} listings did not suggest a relationship between development of antibodies and loss of pramlintide clinical activity.

Bone Metabolism Results: Pramlintide treatment resulted in no harmful effects on bone metabolism and no clinically significant effect on bone mass. In post-menopausal subjects with type 1 diabetes mellitus, pramlintide treatment appeared to show a modest effect on markers of bone turnover, favoring new bone formation.

Conclusion: This adequate and well-controlled study supports the following conclusions:

Pramlintide 30 µg QID given as an adjunct to insulin was effective in significantly improving glycemic and metabolic control in subjects with type 1 diabetes. The drug was associated with a decrease in mean HbA_{1c} and weight, and exhibited a favorable effect on lipids. The effects were observed without any increase in the mean total daily dose of insulin. The drug did not significantly increase severe hypoglycemia in this population. Although pramlintide appears to lead to an earlier onset of severe hypoglycemia than placebo, consistent with initiation of a drug effect, it does not alter the overall event rate for severe hypoglycemia.

For subjects with type 1 diabetes mellitus who had a reduction in HbA_{1c} of <1.0% after 13 weeks of treatment with 30 µg of pramlintide QID, increasing the pramlintide dosage to 60 µg QID did not on average result in further improvement in glycemic control.

At Week 13, a decrease from baseline of ≥1.0% in HbA_{1c} concentration was observed in 32% of evaluable subjects in the pramlintide group compared with 13% of evaluable subjects in the placebo group.

The early glycemic responder population, which had a decrease $\geq 0.5\%$ in HbA_{1c} at Week 4, was comprised of 44% of the subjects in the pramlintide group compared to 24% of the subjects in the placebo group.

Pramlintide, at the doses used in this study, appears to be safe for use as an adjunct to insulin in the treatment of type 1 diabetes.

While approximately 10% of pramlintide QID subjects had a treatment-emergent positive anti-pramlintide antibody assay result at some time during treatment, there is no evidence of a relationship between development of antibodies and loss of pramlintide clinical activity.

Pramlintide, at the doses used in this study, appears to have a modest effect on bone turnover favoring new bone formation in post-menopausal women with type 1 diabetes.

1.2.2 Study 137-117

Title of Study: A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC-137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients With Type I Diabetes Mellitus

Investigators and Study Centers: 64 principal investigators at 64 sites (51 European, 13 Canadian).

Key Publication (Reference):

Fineman M, Bahner A, Gottlieb A, Kolterman O. Effects of six months administration of pramlintide as an adjunct to insulin therapy on metabolic control in people with type 1 diabetes. *Diabetes* 1999;48(Supplement 1):A113-A114 (Abstract 0489).

Studied Period (Years): 1996 - 1998

Phase of Development: 3

Objectives: The primary objectives of this study were to 1) determine the effects of three different dosage regimens of pramlintide compared with placebo on glycemic control as determined by change in hemoglobin A_{1c} (HbA_{1c}) from baseline to Week 26 in subjects with type 1 diabetes mellitus and 2) determine the safety of three different dosage regimens of pramlintide. The secondary objectives of this study included examining the effect of pramlintide on body weight, lipid parameters, insulin dose, and severe hypoglycemic events.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate glycemic control in subjects with type 1 diabetes mellitus on three different dosage regimens of pramlintide. Subjects who met the enrollment criteria and successfully completed screening were to complete 28 to 32 days of single-blind placebo lead-in. Following the stabilization lead-in period, all subjects enrolled in the study were randomized to one of the four treatment regimens (90 µg pramlintide BID, 60 µg pramlintide TID, 90 µg pramlintide TID, or placebo) for a 26-week, double-blind treatment period.

Number of Subjects: 802 subjects entered the placebo lead-in period; 586 subjects (50.3% female, 49.7% male) between the ages of 16 (except subjects in Germany and Austria where the age limitations were different) and 83 (mean age = 38.2 years) were randomized in the study. A total of 130 (88.4%), 96 (66.7%), 121 (81.8%), and 100 (68.0%) subjects completed the study in the placebo, pramlintide 90 µg BID, pramlintide 60 µg TID, and pramlintide 90 µg TID groups, respectively.

Diagnosis and Main Criteria for Inclusion: Male and female subjects with type 1 diabetes mellitus were enrolled. Females were required to use appropriate contraception if they were not post-menopausal or surgically sterilized.

Test Product, Dose and Mode of Administration, Batch No.: Pramlintide 0.6 mg/mL (AC-0137-F22), 0.1 mL (60 µg), subcutaneous administration. Lot Nos. 96-0503JB, 96-0805JB, 96-1103JB, and 97-0401JB. Pramlintide 0.9 mg/mL (AC-0137-F24), 0.1 mL (90 µg), subcutaneous administration. Lot Nos. 96-0506JB, 96-1002JB, and 97-0606JB.

Duration of Treatment: 26 weeks

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo, 0.1 mL, subcutaneous injection. Lot Nos. 96-0302JE, 95-0803GE, 96-1010JE, and 97-0101GE.

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the change in HbA_{1c} values from baseline at Week 26 for the intent-to-treat population. Secondary efficacy variables were the proportion of early glyemic responders (subjects who achieved a $\geq 0.5\%$ reduction in HbA_{1c} at Week 4), the proportion of durable glyemic responders (subjects who achieved a $\geq 0.5\%$ reduction from baseline in HbA_{1c} at Weeks 4 and 26), the change in HbA_{1c} from baseline at Weeks 4, 13, 20, and 26 as well as the average change from baseline for Week 4 to 26, the relative change in HbA_{1c} from baseline at each study visit, and the cumulative frequency for HbA_{1c} change from baseline at Weeks 4, 13, and 26. The proportion of subjects in each treatment group who achieved each of four different HbA_{1c} target values was determined, and a joint outcome analysis of HbA_{1c} and total daily insulin administered was performed. Other secondary efficacy variables were changes in total daily insulin dose, weighted average change from baseline in total daily insulin dose, weight, and fasting lipids, as well as the incidence of severe hypoglycemia.

Safety: Safety was assessed throughout the study period by monitoring adverse events, clinical laboratory data, vital signs, physical examination findings, and ECGs.

Statistical Methods:

Efficacy: Two-way analysis of variance (ANOVA) models were used to assess change in HbA_{1c} from baseline, relative change in HbA_{1c} from baseline, change in weight, and relative change in lipid profile. Pairwise comparisons between each pramlintide group and the placebo group were done by using a step-down procedure for HbA_{1c} variables. In addition, post-hoc ANOVA analysis of change in HbA_{1c} from baseline was performed that included baseline HbA_{1c} as a covariate in the model. The primary analyses of HbA_{1c} were performed on the intent-to-treat population, and additional analyses were done on the evaluable

population and the stable insulin subgroup. Change in HbA_{1c} from baseline was also summarized by gender and by age. A repeated measures analysis was used to evaluate change in HbA_{1c} from baseline values at post-randomization visits in the intent-to-treat population. The proportions of early and durable glycemic responders were analyzed by using the Cochran-Mantel-Haenszel test in the intent-to-treat population. An analysis of the time to first achieving an HbA_{1c} value <8% was performed. A post-hoc analysis of the time to first achieving three additional HbA_{1c} targets was also performed. A log-rank test was performed to compare the time to first achieving each of the four target values among treatment groups. The Kaplan-Meier estimate of the survival function corresponding to the time to first achieving each of the target values is presented for each of the four treatment groups. An analysis of joint outcomes for HbA_{1c} change from baseline and relative change from baseline for total daily insulin was undertaken at Weeks 4, 13, 20, and 26 in the observed cases dataset for the intent-to-treat population. The mean HbA_{1c} change from baseline and the mean of relative change from baseline for total daily insulin are displayed in a joint graph for the post-randomization visits. At a given visit, only subjects who had observed data for both variables were included in the sample. A subject's joint outcome for HbA_{1c} and insulin was classified at each visit as (1) a drug effect, (2) an indeterminate drug effect, or (3) no drug effect. At each visit, the frequency of the joint outcome classifications for the four treatment groups is displayed in a histogram. An overall treatment comparison of the ordinal distribution of the joint outcomes was undertaken at each visit by using van Elteren's test. Change in weight was analyzed in the evaluable population and in evaluable subjects with body mass indices of <27 or ≥27 kg/m². Changes in serum lipid concentrations were analyzed in the evaluable population. The total number of severe hypoglycemic events per subject year of observation was analyzed by using Poisson regression. A log rank test for time to first severe hypoglycemic event was performed. All statistical testing was two-tailed.

All tests for overall treatment effects were conducted with a significance level of 0.05, with the exception of the log-rank test and Poisson regression for severe hypoglycemia, which were carried out at the 0.10 level.

Safety: Detailed listings and summaries were prepared showing pretreatment and post-randomization values as well as change from pretreatment to provide descriptive comparisons of the pramlintide groups with the placebo group. Adverse events were tabulated by incidence, severity, and causality, and compared between treatment regimens.

SUMMARY - CONCLUSIONS:

EFFICACY RESULTS:

HbA_{1c}:

Key HbA_{1c} results for the intent-to-treat population, including the primary efficacy parameter (analysis of change in HbA_{1c} from baseline at Week 26 analyzed without baseline HbA_{1c} in the ANOVA model), are shown in the table below.

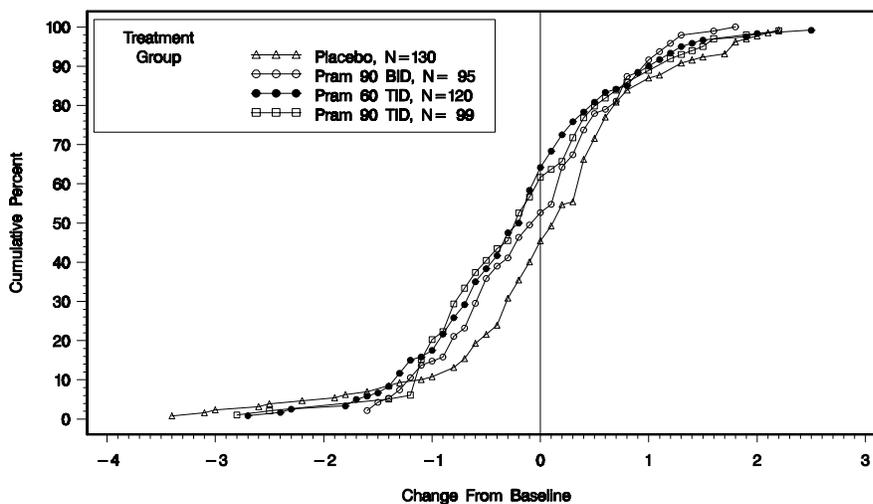
SUMMARY OF EFFICACY RESULTS					
	<u>Placebo</u>	<u>Pramlintide 60 µg TID</u>	<u>Pramlintide 90 µg BID</u>	<u>Pramlintide 90 µg TID</u>	<u>Overall p value</u>
<u>HbA_{1c} change from Baseline at Week 26^[1]</u>					0.049*
N	147	148	144	147	
LSM	0.08	-0.24	-0.15	-0.10	
SE	0.09	0.09	0.09	0.09	
LSM difference		-0.32	-0.23	-0.19	
Pairwise p-value		0.007	0.053	0.123	
Early Glycemic Responders (%) ^[2]	24.83	43.54	40.85	43.84	0.001 ^[4]
Durable Glycemic Responders (5) ^[3]	8.97	21.09	16.20	21.92	0.010 ^[4]
<u>Kaplan-Meier estimate of proportion of subjects achieving targets by Week 26</u>					
HbA _{1c} <8% ^[5,7]	0.236	0.406	0.316	0.361	0.027 ^[6]
HbA _{1c} <7% ^[5,7]	0.061	0.064	0.047	0.103	0.405 ^[6]
Decrease of ≥0.5% ^[5,8]	0.439	0.747	0.699	0.742	<0.001 ^[6]
HbA _{1c} <8% and Decrease of ≥0.5% ^[5,7,8]	0.185	0.375	0.279	0.355	0.002 ^[6]
^[1] Intent-to-treat population with imputation by last observation carried forward ^[2] Intent-to-treat subjects who achieved a reduction in HbA _{1c} from baseline of ≥0.5% at Week 4 ^[3] Intent-to-treat subjects who achieved a reduction in HbA _{1c} from baseline of ≥0.5% at Weeks 4 and 26 ^[4] Statistically significant difference among treatment regimens using Cochran-Mantel-Haenszel test ^[5] Intent-to-treat population without imputation ^[6] Log-rank test for the overall comparison of time to first achieving target HbA _{1c} value. ^[7] Kaplan-Meier estimate of the proportion of subjects with HbA _{1c} at baseline above target value who achieved an HbA _{1c} value below the target value by Week 26. ^[8] Kaplan-Meier estimate of the proportion of subjects achieving an 0.5% decrease from baseline in HbA _{1c} by Week 26. * Indicates statistical significance for the overall comparison of the treatment regimens using an F-test.					

The parametric analysis of the primary efficacy parameter revealed a statistically significant difference among the treatment groups (p=0.049). For the pairwise comparisons at Week 26, the first comparison in the step-down procedure outlined in the statistical analysis plan

(pramlintide 90 µg TID versus placebo) was not significant ($p=0.123$). However, the pairwise comparison of the pramlintide 60 µg TID group versus placebo was nominally statistically significant ($p=0.007$).

To further characterize the estimate of the pramlintide treatment effect size, the ANOVA was also performed including baseline HbA_{1c} in the model; the results confirmed the results without baseline HbA_{1c} in the model. The analysis in the evaluable population did not show a statistically significant difference among the treatment groups ($p=0.204$), but the pairwise comparison of the pramlintide 60 µg TID group versus placebo was nominally significant ($p=0.041$). The parametric analysis of the change from baseline in HbA_{1c} at Week 26 in the stable insulin subgroup approached statistical significance for the overall comparison among treatment groups ($p=0.052$), and revealed a statistically significant difference between the three pramlintide groups combined and the placebo group ($p=0.020$).

Secondary efficacy results associated with HbA_{1c} measurements (the proportion of early glycemic responders, the proportion of durable glycemic responders, the raw change in HbA_{1c} from baseline at Weeks 4, 13, and 20, as well as the average change from baseline for Weeks 4 to 26, and the relative change in HbA_{1c} from baseline to each study visit) were consistent with the primary efficacy parameter. The plot below shows cumulative percent of subjects vs. change in HbA_{1c} from baseline at Week 26. In all three pramlintide treatment groups the curves are shifted to the left of the placebo curve, indicating improvement in glucose control for subjects treated with pramlintide compared with subjects treated with placebo. The cumulative percent of subjects who had a decrease in HbA_{1c} from baseline of 0.5% or more at Week 26 was 36%, 38% and 40% in the pramlintide 90 µg BID, 60 µg TID, and 90 µg TID groups, respectively, compared with 22% in the placebo group. Also at Week 26, the cumulative percent of subjects who had a decrease in HbA_{1c} from baseline of 1.0% or more was 15%, 18% and 20% in the pramlintide 90 µg BID, 60 µg TID, and 90 µg TID groups, respectively, compared with 11% in the placebo group.

Week 26 Cumulative Percent of Subjects who Achieve Changes in HbA_{1c} From Baseline

The decreases in HbA_{1c} in all three pramlintide treatment groups were accompanied by decreases in the mean total daily insulin dose, illustrating that the effect of pramlintide on HbA_{1c} was independent of any concomitant increase in insulin dose. In contrast, insulin use in the placebo group increased at all time points. In each treatment group, mean total daily units varied by ≤ 1.6 units from baseline to Week 26.

Weight: Pramlintide-treated subjects lost weight during the study (range of means: -0.7 to -1.6 kg), and placebo-treated subjects gained weight (0.3 kg; $p < 0.001$). Subjects treated with pramlintide $60 \mu\text{g}$ TID and $90 \mu\text{g}$ TID lost the most weight.

Lipids: Pramlintide had no significant effect on serum lipid concentrations during the study.

Severe Hypoglycemia: Subjects treated with placebo or pramlintide $60 \mu\text{g}$ TID had similar rates of severe hypoglycemia. Subjects treated with pramlintide $90 \mu\text{g}$ BID or $90 \mu\text{g}$ TID had higher rates of severe hypoglycemia.

SAFETY RESULTS:

Adverse Events: Four hundred seventy-nine subjects (81.7%) experienced at least one treatment-emergent adverse event during the study. Three hundred thirty-eight subjects (57.7%) had gastrointestinal adverse events. A total of 255 (43.5%) subjects had a treatment-emergent adverse event of nausea. Nausea occurred in 15% of placebo, 51.4% of pramlintide $60 \mu\text{g}$ TID, 49.3% of pramlintide $90 \mu\text{g}$ BID, and 58.5% of pramlintide $90 \mu\text{g}$ TID groups. Nausea decreased from Week 2 to Week 26 in all treatment groups. The total number of subjects who withdrew from the study due to an adverse event was 98 (16.7%). Subjects in the placebo (4.1%) and the pramlintide $60 \mu\text{g}$ TID (13.5%) groups had a lower incidence of withdrawal due to adverse events when compared with the pramlintide $90 \mu\text{g}$ BID (23.6%) and $90 \mu\text{g}$ TID (27.2%) groups. Nausea (9.6%) was the most common treatment-emergent adverse event that

led to withdrawal. Severe nausea was reported by 6.8 to 7.6% of subjects in the pramlintide groups compared with 0.7% of subjects in the placebo group.

Deaths: Three subjects died during the study: one (pramlintide 90 µg TID) in a motor vehicle accident, one (pramlintide 90 µg BID) of suspected alcohol abuse, and one (placebo) of a myocardial infarction. None of the deaths were deemed as study drug related.

Serious Adverse Events: The incidences of serious adverse events were placebo 9.5%, pramlintide 60 µg TID 10.8%, pramlintide 90 µg BID 16.0%, and pramlintide 90 µg TID 15.0%. The most frequent serious adverse event in all treatment groups was hypoglycemia: placebo 4.1%, pramlintide 60 µg TID 5.4%, pramlintide 90 µg BID 11.8%, and pramlintide 90 µg TID 10.9%.

Clinical Laboratory Values: Laboratory values were similar for placebo- and pramlintide-treated subjects throughout the study.

CONCLUSION:

Results of this study support the conclusion that pramlintide 60 µg TID for 6 months was effective as an adjunct to insulin therapy in improving glycemic control in subjects with type 1 diabetes. Pramlintide administration resulted in mean decreases in HbA_{1c} and weight, and with no adverse effects on lipids. Decreased HbA_{1c} was not associated with an increase in the mean total daily dose of insulin. Pramlintide administered for 26 weeks at 60 µg TID was well-tolerated. The 90 µg dosages used in this study were less well tolerated.

1.2.3 Study 137-121

Title of Study: A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Subjects With Type 1 Diabetes Mellitus

Investigators and Study Centers: Multicenter: 102 centers with randomized subjects, 100 in the United States and 2 in Canada

Publication (Reference):

Gottlieb A, Velte M, Fineman M, Kolterman O. Pramlintide as an adjunct to insulin therapy improved glycemic and weight control in people with type 1 diabetes during treatment for 52 weeks. *Diabetes* 2000;49(suppl 1) :A109 (abstract 439-P).

Studied Period (Years): 1996 - 1999

Phase of Development: 3

Objectives:

The primary objectives of the study were:

to determine the effect of several different dose regimens of pramlintide when compared to placebo, on glycemic control as determined by change in hemoglobin A_{1c} (HbA_{1c}) obtained at baseline (Week 0) and Week 26 in subjects with type 1 diabetes mellitus treated with insulin; and to determine the safety of several different dose regimens of pramlintide.

Methodology: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate glycemic control in subjects with type 1 diabetes mellitus. Subjects were to be randomized to one of four treatment regimens (pramlintide 60 µg TID, 60 µg QID, 90 µg TID, or placebo) after a three-month subject stabilization period (two months of documented insulin stability followed by one month of placebo lead-in medication). Subjects continued with their usual diabetes regimen that may have included diet and exercise in addition to insulin. Subjects were to be treated with double-blind study medication for a 52-week treatment period. HbA_{1c} measurements were to be blinded to the investigator, subject, and medical monitor during the trial. However, investigators were to be notified if a subject's HbA_{1c} during the trial increased two or more percentage points from baseline (e.g. increased from 9.2% to 11.2%).

Number of Subjects: Six hundred fifty-one subjects age 16 or older (mean age 40.8 years) were randomized into this study. Approximately equal numbers of female (49.0%) and male (51.0%) subjects were enrolled. A total of 390 (59.9%) subjects completed the 52 weeks of

treatment: 103 (66.9%), 95 (57.9%), 106 (65.8%), and 86 (50.0%) in the placebo, pramlintide 60 µg TID, pramlintide 60 µg QID, and pramlintide 90 µg TID groups, respectively.

Diagnosis and Main Criteria for Inclusion: Male and female subjects with a history of type 1 diabetes mellitus requiring treatment with insulin for a minimum of one year at study screen visit.

Test Product, Dose and Mode of Administration, Batch No.: Pramlintide 60 µg TID and QID [AC-0137-F22 0.6 mg/mL (0.1 mL)] subcutaneous injection, Lot Nos. 96-0503JB, 96-0805JB, 96-1104JB, 97-0401JB, pramlintide 90 µg TID [AC-0137-F24 0.9 mg/mL (0.1 mL)] subcutaneous injection, Lot Nos. 96-0506JB, 96-1002JB, 97-0606JB.

Duration of Treatment: 52 weeks

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo QID (0.1 mL) subcutaneous injection, Lot Nos. 96-0302JE, 96-1010JE, 96-1009JE and 97-0101GE.

Criteria for Evaluation:

Efficacy: The primary criterion was the change in HbA_{1c} from baseline (Week 0) at Week 26 in the intent-to-treat population. Secondary efficacy parameters associated with HbA_{1c} measurements included the proportion of early glycemic responders (i.e., subjects who achieved a 0.5% reduction in HbA_{1c} at Week 4), the proportion of durable glycemic responders (i.e., subjects who an 0.5% reduction from baseline in HbA_{1c} at Week 4 and at Week 26), the change in HbA_{1c} from baseline at Weeks 4, 13, 20, 39 and 52 as well the average change from baseline for Weeks 4 – 26 and Weeks 4 – 52, and the relative change in HbA_{1c} from baseline to each study visit. The proportion of subjects in each treatment group that achieved each of four different HbA_{1c} target values or changes was determined and a joint outcome analysis of HbA_{1c} and total daily insulin was performed. Other secondary efficacy parameters included changes in insulin regimen, weight, and fasting lipids, as well as the incidence of severe hypoglycemia.

Safety: Safety was assessed throughout the study period by monitoring adverse events, clinical laboratory data, vital signs, physical examination findings and ECGs.

Statistical Methods:

Efficacy: In accordance with a statistical analysis plan finalized before the blind was broken and the results known, all inferential testing excluded the pramlintide 90 µg TID group. Two-way ANOVA models were used for assessing change in HbA_{1c} from baseline, relative

change in HbA_{1c} from baseline, change in weight, and relative change in lipid profile. Pairwise comparisons between each pramlintide group and the placebo group were done using Fisher's protected LSD procedure for HbA_{1c} variables. In addition, ANOVA analysis of change in HbA_{1c} from baseline that included baseline HbA_{1c} as a covariate in the model was performed. The primary analyses of HbA_{1c} were performed on the intent-to-treat population, and additional analyses were done on the evaluable population and the stable insulin and treatment-compliant subgroups. Change from baseline in HbA_{1c} was also summarized by gender and by age. An analysis of joint outcomes for HbA_{1c} change from baseline and relative change from baseline for total daily insulin was undertaken at Weeks 4, 13, 20, 26, 39, and 52 in the observed cases dataset for the intent-to-treat population. A subject's joint outcome for HbA_{1c} and insulin was classified at each visit as (1) a drug effect, (2) an indeterminate drug effect, or (3) no drug effect. All testing was two-tailed. All tests for overall treatment effects were conducted with a significance level of 0.05.

Safety: Detailed listings and summaries were prepared showing pre-treatment and post-treatment values, as well as change from pre-treatment values, to provide descriptive comparisons for the pramlintide treatment regimens and placebo. Adverse events were tabulated by incidence, severity, and study drug attributability, and compared between treatment regimens.

SUMMARY - CONCLUSIONS:

EFFICACY RESULTS:

Key HbA_{1c} results for the intent-to-treat population, including the primary efficacy parameter (analysis of change from baseline in HbA_{1c} at Week 26 analyzed without baseline HbA_{1c} in the ANOVA model), are shown in the table below.

SUMMARY OF EFFICACY RESULTS				
	<u>Placebo</u>	<u>Pramlintide 60 µg TID</u>	<u>Pramlintide 60 µg QID</u>	<u>Overall p value</u>
<u>HbA_{1c} change from Baseline at Week 26^[1]</u>				0.016*
N	154	164	161	
LSMEAN	-0.19	-0.44	-0.44	
SE	0.08	0.07	0.07	
LSM difference	-0.25	-0.25		
Pairwise p-value		0.012*	0.013*	
Early Glycemic Responders (%) ^[2]	20.26	38.36	42.41	0.001 ^[4]
Durable Glycemic Responders (%) ^[3]	9.80	23.27	22.15	0.002 ^[4]
Kaplan-Meier estimate of proportion of subjects achieving targets by Week 26				
HbA _{1c} <8% ^[5,7]	0.280	0.466	0.458	0.003 ^[6]
HbA _{1c} <7% ^[5,7]	0.032	0.109	0.118	0.019 ^[6]
Decrease of ≥0.5% ^[5,8]	0.519	0.741	0.768	<0.001 ^[6]
^[1] Intent-to-treat population with imputation ^[2] Intent-to-treat subjects who achieved a reduction in HbA _{1c} of ≥0.5% at Week 4 ^[3] Intent-to-treat subjects who achieved a reduction in HbA _{1c} of ≥0.5% at Weeks 4 and 26 ^[4] Statistically significant difference among treatment regimens using Cochran-Mantel-Haenszel test ^[5] Intent-to-treat population without imputation ^[6] Log-rank test for the overall comparison of time to first achieving target HbA _{1c} value. ^[7] Kaplan-Meier estimate of the proportion of subjects with HbA _{1c} at baseline above target value who achieved an HbA _{1c} value below the target value by Week 26. ^[8] Kaplan-Meier estimate of the proportion of subjects achieving an 0.5% decrease from baseline in HbA _{1c} by Week 26. * Statistically significant difference using Fisher's protected LSD procedure.				

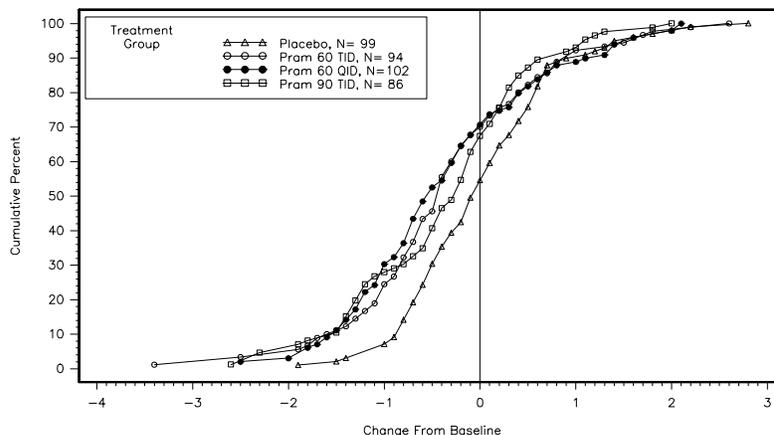
To further characterize the effect size of pramlintide treatment, ANOVA was also performed including baseline HbA_{1c} in the model; the treatment effects in the pramlintide 60 µg TID and 60 µg QID groups confirmed those obtained in the ANOVA without baseline as a covariate in the model, and pairwise comparisons with placebo were statistically significant for both groups. The parametric analysis in the evaluable population approached, but did not achieve, an overall statistically significant difference among the treatment groups (p=0.059). Since the overall treatment comparison in the evaluable population was not statistically significant, the pairwise comparisons could not be declared statistically significant under the planned analyses; however, the pairwise comparison of the pramlintide 60 µg TID group with the placebo group was nominally significant at the $\alpha=0.05$ level (p = 0.019). Results from the stable insulin subgroup analysis were consistent with that of the intent-to-treat

population, and showed a larger magnitude of effect. Secondary efficacy results associated with HbA_{1c} measurements (the proportion of early glyceic responders, the proportion of durable glyceic responders, the absolute change in HbA_{1c} from baseline at Weeks 4, 13, 20, 39, and 52, as well as the average change from baseline for Weeks 4 – 26 and Weeks 4 – 52, and the relative change in HbA_{1c} from baseline to each study visit) were consistent with the primary efficacy parameter. The changes in HbA_{1c} were durable as evidenced by the maintenance of the mean decreases in HbA_{1c} from baseline in the pramlintide groups over the 52-week study period.

The plot below shows cumulative percent of subjects versus change in HbA_{1c} from baseline at Week 52. The points on the curve represent the cumulative percentage of subjects (Y axis) assigned to a particular treatment group who completed 52 weeks of treatment and who achieved a change in HbA_{1c} from baseline at least as large as the HbA_{1c} change value given on the X axis. A negative change from baseline represents improved glucose control; a positive change indicates worsening of glucose control. It is clear that in all three pramlintide treatment groups the curves are shifted to the left of the placebo curve, indicating more improvement in glucose control for subjects treated with pramlintide than for subjects treated with placebo.

As can be determined from the figure below, the cumulative percent of subjects who had a decrease from baseline in HbA_{1c} of $\geq 0.5\%$ at Week 52 was approximately 46%, 53% and 41% in the pramlintide 60 μg TID, 60 μg QID, and 90 μg TID groups, respectively, compared with 30% in the placebo group. The cumulative percent of subjects who had a decrease from baseline in HbA_{1c} of $\geq 1.0\%$ at Week 52 was approximately 24%, 30% and 28% in the pramlintide 60 μg TID, 60 μg QID, and 90 μg TID groups, respectively, compared with 7% in the placebo group.

Week 52 Cumulative Percent of Subjects who Achieve Changes in HbA_{1c} From Baseline



Mean total daily insulin dose appeared to decrease with time in the pramlintide groups compared to small increases in mean total daily insulin dose in the placebo group. Further, the joint outcomes analysis of HbA_{1c} and total daily insulin dose revealed that the mean decrease in HbA_{1c} observed in the pramlintide groups was not associated with any consistent trend in the mean relative change in total daily insulin dose. Total daily insulin dose either remained approximately the same, as in the pramlintide 60 µg TID group, or decreased, as in the pramlintide 60 µg QID and pramlintide 90 µg TID groups. The results indicate that the effect of pramlintide on decreasing HbA_{1c} was accompanied by a decreased insulin dose. A mean decrease in body weight, which persisted throughout the 52 weeks of the study, was observed in all three pramlintide groups, compared with a mean increase in body weight during the same time period in the placebo group. There were no clinically or statistically significant differences among the treatment groups in any of the lipid profile parameters measured.

SAFETY RESULTS:

Adverse Events: A total of 602 of 651 (92.5%) subjects reported at least one treatment-emergent adverse event. The percentage of subjects reporting a treatment-emergent adverse event was similar among the treatment groups. The most frequently reported treatment-emergent adverse event among all treatment groups was nausea (41.9% overall) which was reported by a greater percentage of subjects in each of the pramlintide treatment groups than in the placebo group. Severe nausea was reported in 5.7% of subjects overall: 1.3%, 8.5%, 6.8% and 5.8% of subjects in the placebo, pramlintide 60 µg TID, 60 µg QID, and 90 µg TID treatment groups, respectively. Upper respiratory tract infection, hypoglycemia and inflicted injury were also common but were evenly distributed among all treatment groups. Anorexia, vomiting, and fatigue were reported by subjects in all of the treatment groups but were more common in the pramlintide groups. Of the adverse events reported, 88.6% were mild or moderate in intensity. Nausea, hypoglycemia and anorexia were the most common adverse events considered possibly or probably related to treatment. A higher occurrence of nausea was observed for all of the pramlintide treatment groups as compared with placebo through Week 52 of the study. A higher incidence of withdrawals due to nausea was observed in the intent-to-treat population in each of the pramlintide treatment groups than in the placebo group. The profile of treatment-emergent adverse events leading to withdrawal did not suggest any major safety concerns. Ninety-six subjects (14.7%) had treatment-emergent adverse events leading to withdrawal: 3.9% placebo, 19.5% pramlintide 60 µg TID, 13.0% pramlintide 60 µg QID, and 21.5% pramlintide 90 µg TID. Nausea (10.1% overall) was the most frequently reported treatment-emergent adverse event leading to withdrawal.

Severe Hypoglycemic Events: The event rate per subject-year of observation was similar across treatment groups: 0.7, 1.3, 1.1, and 1.2 in the placebo, pramlintide 60 µg TID, pramlintide 60 µg QID, and pramlintide 90 µg TID treatment groups, respectively.

Deaths: No deaths were reported during the course of the study.

Serious Adverse Events: The incidence of serious treatment-emergent adverse events was similar in the placebo and the pramlintide groups: 14.3% placebo, 17.1% pramlintide 60 µg TID, 19.3% pramlintide 60 µg QID, and 15.7% pramlintide 90 µg TID. The most frequently reported serious treatment-emergent adverse event among all treatment groups was hypoglycemia (11.4% overall) which was evenly distributed among the treatment groups.

Clinical Laboratory Values: Overall, the percentage of potentially clinically important laboratory values was low in all treatment groups, and there did not appear to be any clinically important differences among the treatment groups.

Vital Signs, Physical Examinations and ECGs: Pramlintide treatment appeared to have no clinically important effect on vital signs, physical examinations, and electrocardiogram measurements during the 52-week treatment period.

CONCLUSION: Pramlintide at dosages of 60 µg TID and 60 µg QID is effective as an adjunct to insulin in significantly improving glycemic control in subjects with type 1 diabetes. Pramlintide at dosages of 60 µg TID and 60 µg QID results in a decrease in HbA_{1c} that is not associated with an increase in the mean total daily dose of insulin in subjects with type 1 diabetes. The largest pramlintide treatment effect was observed in the stable insulin subgroup, a subject cohort which allows isolation of the drug effect independent of contributions from changing insulin usage. The drug is also associated with a decrease in weight, and has no adverse effects on lipids. There exists a subgroup of early glycemic responders, defined as those subjects who achieve a decrease of 0.5 percentage points or more in HbA_{1c} by Week 4. A substantial proportion of the population treated with pramlintide also achieve this level of response after Week 4. Pramlintide, at the dosages used in this study, appears to be safe for use as an adjunct to insulin in subjects with type 1 diabetes.

1.3 Short-term Controlled Study in Type 2 Diabetes Using Insulin

There was one short-term study in subjects with type 2 diabetes using insulin [137-114], and a brief summary is provided in the following section.

1.3.1 Study 137-114

Title of Study: Four-Week, Multicenter, Double-Blind, Placebo-Controlled, Dose Frequency Study to Evaluate the Effects of Pramlintide upon Glucose Control as Measured by Fructosamine Concentrations and Plasma Glucose Profiles in Patients with Type II Diabetes Mellitus

Investigators and Study Centers: 20 investigators at 19 centers

Key Publication (Reference):

Thompson RG, Pearson L, Schoenfeld SL, Kolterman OG. Pramlintide, a synthetic analogue of human amylin, improves the metabolic profile of patients with type 2 diabetes using insulin. *Diabetes Care*, 1998; 21:987-993.

Studied Period (Years): 1995-1996

Phase of Development: 2

Objectives: The primary objectives of this study were to:

Determine the effect of three dose frequency regimens of pramlintide versus placebo on changes in fructosamine concentrations obtained at baseline versus fructosamine concentrations obtained after four weeks of study drug;

Determine the safety of three dose frequency regimens of pramlintide versus placebo when administered by subcutaneous injection.

Secondary objectives were to determine the effect of three doses of pramlintide versus placebo on plasma glucose profiles, plasma insulin profiles, postprandial C-peptide concentrations, weight changes, blood pressure changes, changes in lipid concentrations, and the incidence and severity of hypoglycemia meeting the following criteria: (a) hypoglycemia requiring intervention by another individual; (b) clinical symptoms associated with measured glucose concentrations ≤ 80 mg/dL prior to self-administered oral carbohydrates; or clinical symptoms of hypoglycemia when blood glucose was not monitored.

Methodology: This was a multicenter, double-blind, parallel group, placebo-controlled, dose frequency study. Subjects who met all inclusion and no exclusion criteria and successfully completed the screening visit were to begin a three- to ten-day, single-blind, placebo lead-in period which terminated following a 14-hour multiple blood draw for glucose and insulin analyses at Visit 2 (baseline visit). At the end of Visit 2, subjects were to be randomized to one of four treatment groups (placebo, pramlintide 30 μ g QID, pramlintide 60 μ g TID or pramlintide 60 μ g QID) for a four week double-blind treatment period.

Number of Subjects: Two hundred and three subjects were entered into the randomization phase of the study, and constituted the intent-to-treat population. Of these subjects, 50 were in the placebo group, 49 were in the pramlintide 30 µg QID group, 50 were in the pramlintide 60 µg TID group and 54 were in the pramlintide 60 µg QID group.

Diagnosis and Main Criteria for Inclusion: Males and females with a history of type 2 diabetes mellitus requiring treatment with insulin for a minimum of six months at study screen visit were to be included in the study.

Test Product, Dose and Mode of Administration, Batch No.: Pramlintide acetate (pramlintide injection, 0.1 mL subcutaneous): 0.3 mg/mL (30 µg) QID (lot numbers: first packaging - 95-0801GB (AC-0137-F21), second packaging - 95-0902GB (AC-0137-F21), 0.6 mg/mL (60 µg) TID and 0.6 mg/mL QID (lot number: first and second packaging - 95-0501GB (AC-0137-F17); each TID kit contained one vial of placebo for the HS injection.)

Duration of Treatment: Four weeks

Reference Therapy, Dose and Mode of Administration, Batch No: Placebo, 0.1 mL QID (lot number: first and second packaging - 95-0504GE)

Criteria for Evaluation:

Efficacy: The fructosamine concentrations obtained at Visit 2 (baseline) and after four weeks of treatment (Visit 4) were to be used as the primary efficacy parameter to determine the effect of the three dose frequency regimens of pramlintide vs placebo in the intent-to-treat population. Change in HbA_{1c} from baseline at Week 4 was a secondary efficacy parameter used to assess glycemic control. Other secondary efficacy parameters included the changes from baseline at Week 4 and the area under the curves (AUC_(0-14h)) of the 14-hour glucose and insulin profiles, as well as the changes from baseline at Week 4 in C-peptide concentrations. The incidence of severe hypoglycemic events (defined in the Statistical Methods Section as events requiring the assistance of another individual or occasions when the blood glucose concentrations were ≤ 80 mg/dL) was also considered a secondary efficacy parameter.

Safety: Safety was assessed throughout the study period by monitoring adverse events, clinical laboratory tests, vital signs, physical examinations and electrocardiograms.

Statistical Methods:

Efficacy: A two-way analysis of variance (ANOVA) model was used to test for change at treatment end (Visit 4) from baseline in concentrations or measures of fructosamine, HbA_{1c}, weight, C-peptide and lipids. All tests were conducted as two-tailed on the intent-to-treat population. Pairwise comparisons between treatment groups and placebo were carried out

using the Hochberg adjustment to the Bonferonni procedure. Plasma glucose AUC_(0-14h), plasma insulin AUC_(0-14h), and the incidence of severe hypoglycemic events were compared descriptively among the treatment and placebo groups.

Safety: Detailed listings and summaries for the intent-to-treat population presented pretreatment and post-treatment values, as well as change from pretreatment, to provide descriptive comparisons for the treatment groups. Adverse events were tabulated by incidence, severity, whether they led to study withdrawal and attribution to study drug.

SUMMARY – CONCLUSIONS:

EFFICACY RESULTS:

Subjects with type 2 diabetes mellitus using insulin who were treated with pramlintide at doses of 30 µg QID, 60 µg TID, and 60 µg QID subcutaneously for four weeks experienced statistically significant decreases in both fructosamine (primary endpoint) and HbA_{1c} concentrations from baseline at Week 4 compared to placebo as shown in the following table. There was a suggestion that pramlintide was associated with a decrease in weight.

**Fructosamine, HbA_{1c} and Weight Changes from Baseline at Week 4: Parametric Statistical Analysis:
Population: Intent-to-Treat (N=203)**

Analyte		Placebo (N = 50)	Pramlintide		
			30 µg QID (N = 49)	60 µg TID (N = 50)	60 µg QID (N = 54)
Fructosamine µmol/L	LSMean ± SE	-2.56 ± 4.57	-16.22 ± 4.69	-23.43 ± 4.63	-22.22 ± 4.45
	Pairwise p-value		0.0365*	0.0014*	0.0022*
HbA _{1c} %	LSMean ± SE	-0.25 ± 0.08	-0.52 ± 0.08	-0.56 ± 0.08	-0.53 ± 0.07
	Pairwise p-value		0.0145*	0.0039*	0.0087*
Weight kg	LSMean ± SE	-0.07 ± 0.28	-0.37 ± 0.28	-0.94 ± 0.27	-0.72 ± 0.27
	Pairwise p-value		0.4458	0.0246	0.0885

*Pairwise p-values determined for comparisons to placebo which are marked with an asterisk are significant using the Hochberg adjustment to the Bonferroni multiple comparison procedure.

The percent changes in cholesterol values from baseline at Week 4 were: -0.7%, 0.0%, -4.4% and -5.7% in the placebo, pramlintide 30 µg QID, 60 µg TID, and 60 µg QID, respectively. The overall comparison among the groups was statistically significant at Week 4 (p=0.0051). The 60 µg QID group at Week 4 (p=0.0061) reached statistical significance by applying the Hochberg adjustment to the Bonferroni procedure for multiple comparisons.

Mean percent increases from baseline at Week 4 in fasting triglycerides were observed in the placebo (3.3%) and pramlintide 30 µg QID (12.8%) groups compared with mean percent decreases observed in the pramlintide 60 µg TID (-1.3%) and pramlintide 60 µg QID (-2.8%) groups. These comparisons did not achieve statistical significance.

Mean decreases from baseline at Week 4 in the LDL/HDL ratio were observed in all three pramlintide treatment groups as well as in the placebo group, but neither the comparison among the groups nor any of the pairwise comparisons versus placebo were statistically significant.

No statistically significant differences were found between any pramlintide treatment group and placebo in C-peptide determinations.

Not all subjects were valid for assessment of glucose and insulin $AUC_{(0-14h)}$ determinations as originally planned. Accordingly, formal statistical analyses of these data were not performed. Plasma glucose $AUC_{(0-14h)}$ data were, however, consistent with an effect of pramlintide to lower postprandial plasma glucose concentrations; and plasma insulin $AUC_{(0-14h)}$ data were consistent with an ability of pramlintide to reduce the requirements for exogenous insulin.

The number and percent of subjects having a severe hypoglycemic event were similar in the placebo (40.0%), pramlintide 30 µg QID (44.9%), and pramlintide 60 µg TID (40.0%) treatment groups. Compared with the other three groups, a smaller number and percent of subjects in the pramlintide 60 µg QID group reported a severe hypoglycemic event (25.9%).

SAFETY RESULTS:

Adverse Events: A total of 131 (64.5%) subjects reported 280 adverse events. Of these, 91 events for 50 (24.6%) subjects were judged by the Investigators to be possibly or probably related to treatment, including placebo (5 placebo subjects experienced 6 adverse events). Adverse events with an occurrence rate of $\geq 5\%$ were comprised of nausea, upper respiratory infection; and headache. For subjects experiencing headache and upper respiratory infection, the incidence of events was similar among treatment groups. Nausea events were similar among the active treatment groups, with seven (14.3%) subjects in the pramlintide 30 µg QID treatment group reporting eight events, five (10.0%) subjects in the pramlintide 60 µg TID treatment group reporting six events, and seven (13.0%) subjects in the pramlintide 60 µg QID treatment group reporting ten events. No subjects in the placebo group reported nausea as an adverse event. All of the reports of nausea were mild to moderate in intensity. Three subjects withdrew from the study due to adverse events.

Deaths: Approximately two weeks after study completion, one subject in the pramlintide 30 µg QID group died due to myocardial infarction, which was judged by the investigator as probably not related to study medication.

Serious Adverse Events: The incidence of serious treatment-emergent adverse events was 2.0%, 4.1%, 2.0%, and 0.0% in placebo, pramlintide 30 µg QID, 60 µg TID, and 60 µg QID treatment groups, respectively.

Clinical Laboratory Values: There were no clinical laboratory values that appeared to be adversely affected by pramlintide treatment. There were three subjects with abnormally low serum calcium concentrations reported at Week 4, which upon medical review appeared spurious. Changes in mean serum glucose values and in urinary glucose determinations were consistent with improved glycemic control in the pramlintide groups. All active treatment groups had a decrease from baseline to Week 4 in serum glucose that appeared to be dose-related, compared to the increase in serum glucose in the placebo group.

Vital Signs, Physical Examination Findings and ECG Data: Pramlintide appeared to have no clinically important effect on vital signs, physical examinations, or ECGs during the 4-week treatment period.

CONCLUSIONS:

As measured by changes in plasma fructosamine concentrations, pramlintide, self-administered SC at dosages of 30 µg QID, 60 µg TID, and 60 µg QID for four weeks, significantly improves glycemic control in subjects with type 2 diabetes mellitus using insulin.

Statistically significant reductions in HbA_{1c} were also observed for all pramlintide groups compared to placebo. In addition, approximately twice as many subjects had an HbA_{1c} reduction of at least 0.5% compared to placebo.

Larger reductions in 14-hour plasma glucose profiles for all pramlintide treatment groups were observed compared to placebo. These reductions in glucose were achieved despite corresponding reductions in plasma insulin in all pramlintide groups. Corresponding plasma insulin concentrations in the placebo group increased.

There is a suggestion that pramlintide, at the dosages used in this study, and particularly at a dosages of 60 µg TID and 60 µg QID, is associated with a decrease in weight in subjects with type 2 diabetes using insulin.

Pramlintide, at the dosages used in this study, has no statistically significant changes in fasting total cholesterol, LDL/HDL ratio, and triglycerides.

Self-administration of pramlintide (30 µg QID, 60 µg TID or 60 µg QID) for four weeks by subjects also taking insulin to treat their type 2 diabetes mellitus does not result in any increase in the incidence of severe hypoglycemic events as defined in this study (i.e., events requiring the assistance of another individual or occasions when the blood glucose concentrations were < 80 mg/dL) when compared to the number of such events in subjects self-administering placebo over the same time frame.

Pramlintide administered SC at dosages of 30 µg TID, 60 µg TID, or 60 µg QID for four weeks as an adjunct to insulin appears to be safe for use in subjects with type 2 diabetes mellitus. Nausea is the most common adverse event associated with the use of the drug at these dosages.

1.4 Long-term Controlled Studies in Type 2 Diabetes Using Insulin

There were three long-term, controlled studies in subjects with type 2 diabetes using insulin. Two of these studies (137-122 and 137-111) were conducted in the United States and Canada (1-year duration) and one (137-123) was conducted in Europe and Canada (6-month duration). A brief summary of each of the three studies is provided in the following sections.

1.4.1 Study 137-111

Title of Study: Fifty-Two Week, Multicenter, Double-Blind, Parallel Group, Placebo Controlled and AC137 Dose Ranging Study to Evaluate Glycated Hemoglobin in Patients With Type II Diabetes Mellitus

Investigators and Study Centers: 39 Investigators at 37 centers in the US

Publication (Reference): Key Publications:

1. Ratner R, Levetan C, Schoenfeld S, Organ K, Kolterman O. Pramlintide therapy in the treatment of insulin-requiring type 2 diabetes: results of a 1-year placebo-controlled trial. *Diabetes* 1998;47 (suppl 1):A88.
2. Whitehouse F, Ratner R, Rosenstock J, Schoenfeld S, Kolterman O. Pramlintide showed positive effects on body weight in type 1 and type 2 diabetes. *Diabetes* 1998;47 (suppl 1):A9.

Studied Period: June 1995 to July 1997

Phase of Development: 3

Objectives:

Primary objectives were to determine:

The effect of three dosages of pramlintide (30 µg TID, 75 µg TID, or 150 µg TID) versus placebo TID on hemoglobin A_{1c} (HbA_{1c}) obtained at randomization (Visit 2) versus HbA_{1c} obtained after thirteen weeks (Visit 6) and end of fifty-two weeks treatment (Visit 10).

The safety of three dosages of pramlintide versus placebo administered by subcutaneous injection.

Key secondary objectives were to determine:

The effect of pramlintide on HbA_{1c} compared to placebo at each visit

The effect of treatment with pramlintide versus placebo on weight change from baseline to 13 weeks (Visit 6) and 52 weeks of treatment (Visit 10).

Methodology: This was a multicenter, double-blind, parallel group, placebo-controlled, dose ranging study comparing three dose regimens of pramlintide versus placebo administered for 52 weeks after a three- to 10-day single-blind placebo lead-in period. The original duration of the study was 13 weeks, which was subsequently increased to 52 weeks by Amendment 2.

Number of Subjects: A total of 538 subjects (57.6% male, 42.4% female) between the ages of 26 and 76 years (mean age, 56.5 years), inclusive, were randomized. A total of 381 (70.8%) subjects completed 52 weeks of treatment: 99 (72.8%), 90 (73.8%), 102 (75.0%), and 90 (62.5%) in the placebo, pramlintide 30 µg TID, pramlintide 75 µg TID, and 150 µg TID groups, respectively. A total of 205 subjects participated in Amendment 1 (glucose and insulin profile subset).

Diagnosis and Main Criteria for Inclusion: Subjects with type 2 diabetes mellitus receiving insulin who met all other protocol inclusion and none of the exclusion criteria were eligible. Females of child-bearing potential practicing appropriate methods of contraception were allowed by protocol amendment.

Test Product, Dose and Mode of Administration, Batch No.: Pramlintide 30 µg TID [0.1 mg/ml AC-0137-F8 (0.3 mL)] subcutaneous injection, Lot Nos. 95-0308CB, 95-0602CB; Pramlintide 75 µg TID [0.25 mg/mL AC-0137-F18 (0.3 mL)] subcutaneous injection, Lot Nos. 95-0307CB, 95-0604CB; Pramlintide 150 µg TID [0.5 mg/mL AC-0137-F19 (0.3 mL)] subcutaneous injection, Lot Nos. 95-0306CB, 95-0601CB.

Duration of Treatment: Three- to 10-day placebo lead-in followed by 52 weeks of randomized treatment.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo TID (0.3 mL) subcutaneous injection, Lot Nos. 95-0305CE and 95-0603CE. Both lots were used for placebo lead-in and also for subjects randomized to placebo.

Criteria for Evaluation:

Efficacy: The protocol as amended stated that HbA_{1c} determinations obtained at Baseline (Visit 2), after four weeks of treatment (Visit 4), after 13 weeks of treatment (Visit 6), after 19 weeks (Visit 7), after 26 weeks (Visit 8), after 39 weeks (Visit 9) and after 52 weeks of treatment (Visit 10) will be used to determine the effect of the pramlintide dosages versus placebo. The Statistical Analysis Plan, finalized prior to breaking the blind, defined the primary efficacy parameter as the relative change in HbA_{1c} from baseline to Week 52. Key secondary efficacy criteria would include the relative change in HbA_{1c} from baseline to Weeks 13 and 26 and the absolute change in HbA_{1c} from baseline to Weeks 13, 26, and 52, and the number and percent of subjects achieving an HbA_{1c} value <8%. Additional secondary efficacy criteria included the change from baseline at Weeks 13, 26, and 52 for body weight and the relative change from baseline at Weeks 13 and 52 for fasting serum lipid concentrations. Episodes of severe hypoglycemia were categorized as secondary efficacy criteria and were evaluated by incidence and event rates. Although not specified in the protocol or the Statistical Analysis Plan the following analyses listed below were performed after breaking of the blind. Analyses of absolute and relative change in HbA_{1c} from baseline

were performed at Weeks 4, 19, and 39, and for the average of Weeks 4-26 and 4-52. In addition to the target of achieving an HbA_{1c} value of <8%, three additional HbA_{1c} targets were added: achieving an HbA_{1c} value <7%, achieving a decrease from baseline in HbA_{1c} of ≥0.5%, and achieving an HbA_{1c} value <8% with a decrease from baseline in HbA_{1c} of ≥0.5%. Survival analyses were also performed on the proportion of subjects achieving target HbA_{1c} values (<7%, <8%, decrease of ≥0.5%, and <8% with a decrease of ≥0.5%). Plots of cumulative percent of subjects versus change in HbA_{1c} from baseline at Weeks 4, 13, 26, and 52 were constructed. A summary of joint outcomes for change in HbA_{1c} from baseline and relative change from baseline for total daily insulin dose was also performed. A subject's joint outcome for HbA_{1c} and insulin was classified at each visit as a drug effect, an indeterminate drug effect, or no drug effect. Finally, consistent with the design of the study, a statistical test of dose response was also performed. For all analyses (those defined before unblinding and those defined after unblinding), a contrast comparing the average of the 3 pramlintide groups with the placebo group was conducted for each visit.

Safety: Safety was assessed throughout the study period by monitoring adverse events, clinical laboratory evaluations, vital signs, physical examinations, and ECGs.

Statistical Methods:

Efficacy: Two-way ANOVA models were used for assessing change from baseline in HbA_{1c}, relative change from baseline in HbA_{1c}, change in weight, and relative change in lipid profile. All tests were conducted as two-tailed with a significance level of 0.05. Pairwise comparisons for the primary endpoint (HbA_{1c}) were done using the Hochberg adjustment. The parametric “linear trend test” was used to assess dose-response. The null hypothesis for this test was that the slope of the dose response curve was equal to zero.

Safety: Detailed listings and summaries were prepared showing pre-treatment and post-treatment values, as well as change from pre-treatment values, to provide descriptive comparisons for the pramlintide treatment regimens and placebo. Adverse events were tabulated by incidence, intensity, and study drug relationship, and compared between treatment regimens.

SUMMARY – CONCLUSIONS:

EFFICACY RESULTS:

HbA_{1c}: Key HbA_{1c} results for the evaluable population, including the primary efficacy parameter (analysis of relative change in HbA_{1c} from baseline to Week 52), are shown in the table that follows. Despite the absence of any statistically significant pairwise comparisons with placebo when tested using the Hochberg adjustment to the Bonferroni multiple comparison procedure, the contrast between the highest pramlintide dosage group (150 µg

TID) and the placebo group in the evaluable population was nominally significant at the alpha 0.05 level and approached statistical significance ($p = 0.0337$ versus a required p -value of 0.0167). Furthermore, there was a significant dose-response ($p = 0.0360$) with increasing dose. In the intent-to-treat population, the treatment effect was -2.22%, -3.26%, and -4.39% in the pramlintide 30 μg TID, 75 μg TID, and 150 μg TID groups, respectively, and the difference between the pramlintide 150 μg group and the placebo group was statistically significant when tested using the Hochberg adjustment to the Bonferroni multiple comparison procedure ($p = 0.0069$). The pramlintide 75 μg TID group was nominally significant at the alpha 0.05 level and approached a statistically significant difference from placebo using the Hochberg adjustment ($p = 0.0414$ versus $p = 0.025$ required by the Hochberg procedure). The dose-response was also statistically significant in the intent-to-treat population ($p = 0.0093$). As further evidence of a dose-response in the intent-to-treat population, the comparison between all three pramlintide groups combined versus placebo was statistically significant ($p = 0.0126$) as was the overall F-test for the comparison among treatments ($p = 0.0467$). Compared with the evaluable and intent-to-treat populations, the stable insulin population had relatively few subjects, making interpretation of these results difficult. Accordingly, the treatment effect in the stable insulin population, +4.50%, -1.19%, and -2.33% in the pramlintide 30 μg TID, 75 μg TID, and 150 μg TID groups, respectively, were not as marked as in the other two populations. Secondary efficacy parameters associated with HbA_{1c} measurements (the absolute change in HbA_{1c} from baseline at Weeks 13, 19, 26, 39, and 52, the relative change in HbA_{1c} from baseline at Weeks 13, 19, 26, and 39, and the number and percent of subjects achieving various HbA_{1c} target values) were all consistent with the primary efficacy parameter.

SUMMARY OF KEY HbA_{1c} VARIABLES

	Placebo	Pramlintide 30 µg TID	Pramlintide 75 µg TID	Pramlintide 150 µg TID	
<u>HbA_{1c} relative change (%) from Baseline at Week 26^[1]</u>					
N	99	90	102	90	
LSMEAN	-4.11	-5.50	-7.78	-7.92	
SE	1.14	1.19	1.10	1.19	
LSM difference		-1.39	-3.67	-3.81	
Pairwise p-value		0.3879	0.0193	0.0198	
<u>HbA_{1c} relative change (%) from Baseline at Week 52^[1]</u>					
N	99	90	102	90	
LSMEAN	-1.91	-3.58	-4.31	-6.17	
SE	1.42	1.46	1.35	1.46	
LSM difference		-1.67	-2.40	-4.26	
Pairwise p-value		0.3968	0.2110	0.0337	
<u>HbA_{1c} absolute change (%) from Baseline at Week 26^[1]</u>					
N	99	90	102	90	
LSMEAN	-0.41	-0.51	-0.77	-0.76	
SE	0.11	0.11	0.11	0.11	
LSM difference		-0.10	-0.36	-0.35	
Pairwise p-value		0.5038	0.0172	0.0265	
<u>HbA_{1c} absolute change (%) from Baseline at Week 52^[1]</u>					
N	99	90	102	90	
LSMEAN	-0.21	-0.34	-0.46	-0.60	
SE	0.13	0.14	0.13	0.14	
LSM difference		-0.13	-0.25	-0.39	
Pairwise p-value		0.4761	0.1650	0.0387	

Early Glycemic Responders (%) ^[2]	47.1	45.9	50.7	55.6	

<u>Kaplan-Meier estimate of proportion of subjects achieving targets by Week 52</u>					
HbA _{1c} <8% ^[3,5]	0.401	0.478	0.528	0.597	p=0.0482
HbA _{1c} <7% ^[3,5]	0.119	0.140	0.155	0.219	p=0.1778
Decrease of ≥0.5% ^[3,6]	0.775	0.806	0.812	0.892	p=0.0327

^[1] Evaluable population; ANOVA with treatment and site as factors in the model

^[2] Intent-to-treat subjects who achieved a reduction in HbA_{1c} of ≥0.5% at Week 4

^[3] Intent-to-treat population without imputation

^[4] Log-rank test for overall comparison of time to first achieving target

^[5] Kaplan-Meier estimate of the proportion of subjects with HbA_{1c} at baseline above target value who achieved target value by Week 52

^[6] Kaplan-Meier estimate of the proportion of subjects who achieved a 0.5% decrease from baseline in HbA_{1c} by Week 52

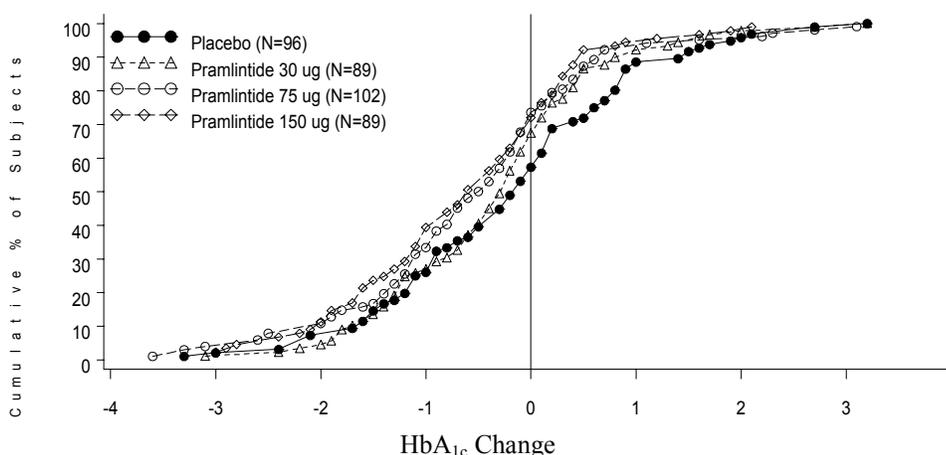
To further characterize the estimate of the pramlintide treatment effect size in terms of the absolute change in HbA_{1c} from baseline at Weeks 4, 13, 19, 39, and 52, as well as the average change from baseline for Weeks 4 – 26 and Weeks 4 – 52, the analysis was also performed including baseline HbA_{1c} as a covariate in the model for all three populations (evaluable, intent-to-treat, and stable insulin). The results of these additional analyses were similar to those without baseline HbA_{1c} as a covariate.

The figure that follows shows cumulative percent of subjects versus change in HbA_{1c} from baseline at Week 52. The points on the curve represent the cumulative percentage of subjects

(Y axis) assigned to a particular treatment group who completed 52 weeks of treatment and who achieved a change in HbA_{1c} from baseline at least as large as the HbA_{1c} change value given on the X axis. A negative change from baseline represents improved glucose control; a positive change indicates worsening of glucose control. The variability of the response is apparent from the fact that the distribution of responses under both pramlintide and placebo treatments range from large negative to large positive values. The curves for the 75 µg TID and 150 µg TID dose pramlintide groups are shifted to the left of the placebo curve, indicating more improvement in glucose control for subjects treated with these two dosage regimens of pramlintide than for subjects treated with placebo. The 30 µg TID pramlintide group was not appreciably shifted relative to the curve for placebo, indicating that this dose was ineffective at improving glycemic control in this population of type 2 diabetics using insulin.

As seen in the figure that follows, the cumulative percent of subjects who had a decrease in HbA_{1c} from baseline of 0.5% or more at Week 52 was 39.6%, 40.4%, 50.0%, and 50.6% in the placebo, pramlintide 30 µg TID, 75 µg TID, and 150 µg TID groups, respectively. The cumulative percent of subjects who had a decrease from baseline in HbA_{1c} of 1.0% or more at Week 52 was 26.0%, 27.0%, 33.3%, and 39.3% in the placebo, pramlintide 30 µg TID, 75 µg TID, and 150 µg TID groups, respectively.

Week 52 Cumulative Percent of Subjects who Achieved Changes in HbA_{1c} from Baseline
Population: Intent-to-Treat -- Observed Values



Weight: All pramlintide treatments were associated with a statistically significant decrease in weight from baseline to Weeks 13, 26, and 52 compared to placebo. Subjects in the pramlintide 30 µg TID, 75 µg TID, and 150 µg TID dose groups showed mean decreases in weight from baseline to Week 52 of 0.49 kg (LSMean), 0.52 kg (LSMean), and 1.49 kg (LSMean), which were all statistically significant (p=0.0100, p=0.0071, and <0.0001, respectively) differences from placebo. Subjects in the placebo group experienced a mean increase in weight from baseline to Week 52 of 1.04 kg (LSMean).

SAFETY RESULTS:

Adverse Events: The overall incidence of treatment-emergent adverse events was similar across treatments. Nausea, which was the most frequent single gastrointestinal symptom, was reported in 16.9%, 14.8%, 26.5%, and 22.9% of subjects receiving placebo, pramlintide 30 µg TID, 75 µg TID, and 150 µg TID, respectively. Adverse events that showed higher incidences in pramlintide-treated subjects and which increased with increasing dose, were those coding to the preferred terms fatigue, constipation, retinal disorder, and abnormal vision. Fatigue, constipation, and retinal disorders occurred with an overall incidence $\geq 5\%$. Retinal disorders were reported in 10.4% of subjects receiving pramlintide 150 µg TID. Based on detailed medical review of individual subject information, it is likely that these retinal disorders reflect pre-existing conditions that were likely present but not documented at screening. Adverse events of hypoglycemia were reported in 70.6%, 67.2%, 67.6%, and 64.6% of subjects receiving placebo, pramlintide 30 µg TID, 75 µg TID, and 150 µg TID, respectively. While subjects enrolled in this study did not maintain hypoglycemic diaries, severe hypoglycemic data were obtained from the record of concomitant medications. Severe hypoglycemic events were defined as those events requiring the administration of glucagon or intravenous glucose. Seven subjects (2 placebo, 2 pramlintide 30 µg TID, 1 pramlintide 75 µg TID, and 2 pramlintide 150 µg TID) reported eight events which fulfilled these criteria, suggesting that there is no difference in the incidence of severe hypoglycemic events between placebo and pramlintide-treated subjects.

The number of subjects withdrawing from the study because of adverse events was 11.0%, 7.4%, 10.3%, and 16.7% in the placebo, pramlintide 30 µg TID, 75 µg TID, and 150 µg TID treatment groups, respectively. The highest overall incidence for withdrawal due to adverse event was for events in the gastrointestinal system, primarily nausea. Withdrawal due to nausea was similar across placebo, pramlintide 30 µg TID, and 75 µg TID treatment groups (2.2%, 1.6%, and 2.2%, respectively), and higher (8.3%) in the pramlintide 150 µg TID group.

Deaths: Four deaths occurred during the study, two in subjects randomized to pramlintide. Subject 8116 (placebo), died of a cardiac arrest, and Subject 9035 (placebo) died of cardiac arrhythmia. Subject 9069 (pramlintide 75 µg TID) and Subject 8363 (pramlintide 150 µg TID) died of myocardial infarctions; both had prior histories of underlying cardiovascular disease.

Serious Adverse Events: The incidence of serious adverse events was 18.4%, 11.5%, 11.0%, and 10.4% in placebo, pramlintide 30 µg TID, 75 µg TID, and 150 µg TID treatment groups, respectively. Chest pain had the highest overall incidence rate (2.2%) of all events, and rates were similar across treatments.

Clinical Laboratory Values: There were no clinical laboratory values that appeared to be adversely affected by pramlintide treatment.

Anti-Pramlintide Antibodies: Four placebo subjects and 32 pramlintide subjects who had negative anti-pramlintide antibody results at baseline had a positive antibody assay at some time during the treatment period. Review of individual subject HbA1c listings did not suggest a relationship between development of antibodies and loss of pramlintide clinical activity.

CONCLUSION:

This adequate and well-controlled study supports the following conclusions:

Pramlintide 150 µg TID administered subcutaneously is effective when used as an adjunct to insulin to improve glycemic control in subjects with type 2 diabetes.

Pramlintide, over the dose range used in this study, is associated with a decrease in HbA_{1c} and weight, and exhibits no adverse effect on plasma lipids. The drug does not appear to increase the chances of severe hypoglycemia in this population.

Pramlintide, at the dosages used in this study, appears to be safe for use as an adjunct to insulin in subjects with type 2 diabetes. (4) While approximately 9% of pramlintide TID subjects had a treatment-emergent positive anti-pramlintide antibody assay result at some time during treatment, there is no evidence of a relationship between development of antibodies and loss of pramlintide clinical activity.

1.4.2 Study 137-123

Title of Study: A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC-0137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients with Type II Diabetes Mellitus

Investigators and Study Centers: 78 principal investigators at 78 sites (61 European, 17 Canadian).

Publications (References):

1. Fineman MS, Bahner A, Gottlieb AB, Kolterman OG. Effects of six months' administration of pramlintide as an adjunct to insulin therapy on metabolic control in people with type 2 diabetes. Program and Abstracts of the 81st Annual Meeting of the Endocrine Society, San Diego, CA, 1999; pp 471-2.
2. Gottlieb A, Fineman M, Bahner A, Parker J, Waite G, Kolterman O. Pramlintide therapy in addition to insulin in type 2 diabetes: effect on metabolic control after 6 months. *Diabetologia*. 1999, 42:A232.

Studied Period: 1996 – 1998

Phase of Development: 3

Objectives: The primary objectives were to 1) Determine the effects of three different dosage regimens of pramlintide compared with placebo on glycemic control as determined by change in hemoglobin A_{1c} (HbA_{1c}) from baseline to Week 26 in subjects with type 2 diabetes mellitus treated with insulin and 2) Determine the safety of three different dosage regimens of pramlintide. The secondary objectives included examining the effect of pramlintide on body weight, lipid parameters, insulin dose, and severe hypoglycemic events.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate glycemic control in insulin-treated subjects with type 2 diabetes mellitus on three different dosage regimens of pramlintide. Subjects who met the enrollment criteria and successfully completed screening were to complete 28 to 32 days of single-blind placebo lead-in. Following the stabilization lead-in period, all subjects enrolled in the study were randomized to one of the four treatment regimens (90 µg pramlintide BID, 120 µg pramlintide BID, 90 µg pramlintide TID, or placebo) for a 26-week, double-blind treatment period.

Number of Subjects: A total of 701 subjects entered the placebo lead-in period; 499 subjects between the ages of 23 and 79 were randomized in the 26-week, double-blind treatment period. Of the 499 subjects randomized, 442 (88.6%) completed the study.

Diagnosis and Main Criteria for Inclusion: Male and female subjects with type 2 diabetes mellitus treated with insulin were enrolled. Females were required to use appropriate contraception if they were not post-menopausal or surgically sterilized.

Test Product, Dose and Mode of Administration, Batch No.: Pramlintide 0.45 mg/mL (AC-0137-F27), 0.2 mL (90 µg), subcutaneous administration. Lot Nos. 96-0905JB1, 96-0905JB2, 96-1105JB, and 97-0607JB. Pramlintide 0.6 mg/mL (AC-0137-F22), 0.2 mL (120 µg), subcutaneous administration. Lot Nos. 96-0503JB, 96-0805JB, 96-1104JB, and 97-0401JB.

Duration of Treatment: 26 weeks

Reference Therapy, Dose and Mode of Administration, Batch No: Placebo, 0.2 mL, subcutaneous injection. Lot Nos. 96-0505JE, 96-0302JE, 95-0803GE, 96-1010JE, and 97-0101GE.

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the change in HbA_{1c} values from baseline at Week 26 for the intent-to-treat population. Secondary efficacy variables were the proportion of early glyceemic responders (subjects who achieved a $\geq 0.5\%$ reduction in HbA_{1c} at Week 4), the proportion of durable glyceemic responders (subjects who achieved a $\geq 0.5\%$ reduction from baseline in HbA_{1c} at Weeks 4 and 26), the change in HbA_{1c} from baseline at Weeks 4, 13, 20, and 26 as well as the average change from baseline for Week 4 to 26, the relative change in HbA_{1c} from baseline at each study visit, and the cumulative frequency for change in HbA_{1c} from baseline at Weeks 4, 13, and 26. The proportion of subjects in each treatment group who achieved each of four different HbA_{1c} target values or changes was determined, and a joint outcome analysis of HbA_{1c} and total daily insulin dose was performed. Other secondary efficacy variables were changes in insulin regimen, weight, and fasting lipids, as well as the incidence of severe hypoglycemia.

Safety: Safety was assessed throughout the study period by monitoring adverse events, clinical laboratory data, vital signs, physical examination findings, and ECGs.

Statistical Methods:

Efficacy: Two-way analysis of variance (ANOVA) models were used to assess change in HbA_{1c} from baseline, relative change in HbA_{1c} from baseline, change in weight, and relative change in lipid profile. Pairwise comparisons between each pramlintide group and the placebo group were done by using a step-down procedure for HbA_{1c} variables. In addition, post-hoc ANOVA analysis of change in HbA_{1c} from baseline was performed that included baseline HbA_{1c} as a covariate in the model. The primary analyses of HbA_{1c} were performed

on the intent-to-treat population, and additional analyses were done on the evaluable population and the stable insulin subgroup. Change in HbA_{1c} from baseline was also summarized by gender and by age. A repeated measures analysis was used to evaluate change in HbA_{1c} from baseline values at post-randomization visits in the intent-to-treat population. The proportions of early and durable glyceic responders were analyzed by using the Cochran-Mantel-Haenszel test in the intent-to-treat population. An analysis of the time to first achieving an HbA_{1c} value <8% was performed. A post-hoc analysis of the time to first achieving three additional HbA_{1c} targets was also performed. A log-rank test was performed to compare the time to first achieving each of the four target values among treatment groups. The Kaplan-Meier estimate of the survival function corresponding to the time to first achieving each of the target values was presented for each of the four treatment groups. A dose-response analysis was undertaken for change in HbA_{1c} from baseline to Week 26 in the intent-to-treat population, excluding the 90 µg TID group. An analysis of joint outcomes for change in HbA_{1c} from baseline and relative change from baseline for total daily insulin dose was undertaken at Weeks 4, 13, 20, and 26 in the observed cases dataset for the intent-to-treat population. The mean change in HbA_{1c} from baseline and the mean of relative change from baseline for total daily insulin dose are displayed in a joint graph for the post-randomization visits. At a given visit, only subjects who had observed data for both variables were included in the sample. A subject's joint outcome for HbA_{1c} and insulin was classified at each visit as (1) a drug effect, (2) an indeterminate drug effect, or (3) no drug effect.

At each visit, the frequency of the joint outcome classifications for the four treatment groups is displayed in a histogram. An overall treatment comparison of the ordinal distribution of the joint outcomes was undertaken at each visit by using Van Elteren's test. Change in weight was analyzed in the evaluable population and in evaluable subjects with body mass indices of <27 or ≥27 kg/m². Changes in serum lipid concentrations were analyzed in the evaluable population. The total number of severe hypoglycemic events per subject was analyzed by using Poisson regression. A log-rank test for the time to the first severe hypoglycemic event was performed. All testing was two-tailed. All tests for overall treatment effects were conducted with a significance level of 0.05, with the exception of the log-rank test and Poisson regression for severe hypoglycemia, which were carried out at the 0.10 level.

Safety: Detailed listings and summaries were prepared showing pretreatment and post-randomization values as well as change from pretreatment to provide descriptive comparisons of the pramlintide groups with the placebo group. Adverse events were tabulated by incidence, severity, and causality, and compared between treatment regimens.

SUMMARY - CONCLUSIONS:

EFFICACY RESULTS:

HbA_{1c}: Key HbA_{1c} results for the intent-to-treat population, including the primary efficacy parameter (analysis of change in HbA_{1c} from baseline at Week 26 analyzed without baseline HbA_{1c} in the ANOVA model), are shown in the table below.

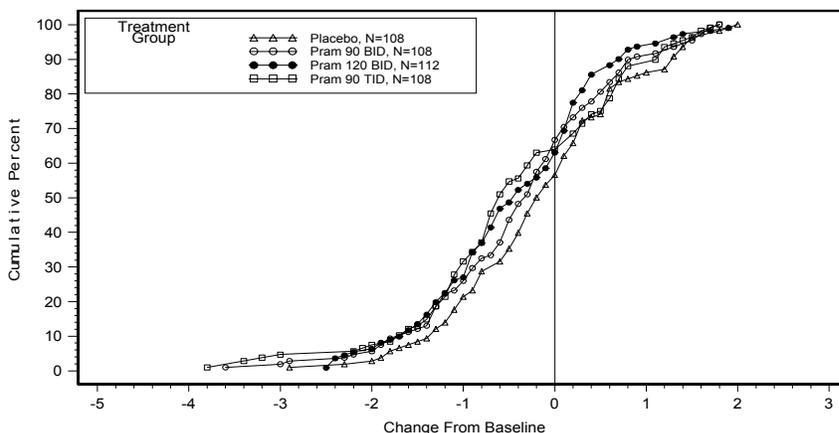
SUMMARY OF EFFICACY RESULTS					
	<u>Placebo</u>	<u>Pramlintide 90 µg BID</u>	<u>Pramlintide 120 µg BID</u>	<u>Pramlintide 90 µg TID</u>	<u>Overall p value</u>
<u>HbA_{1c} change from Baseline at Week 26</u> ^[1]				0.127 ^[2]	0.019 ^[3]
N	123	121	126	129	
LSM	-0.06	-0.30	-0.36	-0.30	
SE	0.10	0.10	0.10	0.10	
LSM difference		-0.24	-0.30	-0.24	
Pairwise p-value		0.075	0.029	0.073	
Early Glycemic Responders (%) ^[4]	31 (26.05)	56 (46.28)	62 (50.00)	65 (51.59)	0.001 ^[6]
Durable Glycemic Responders (%) ^[5]	17 (14.29)	33 (27.27)	40 (32.26)	39 (30.95)	0.006 ^[6]
Kaplan-Meier estimate of proportion of subjects achieving targets by Week 26					
HbA _{1c} <8% ^[7,9]	0.158	0.243	0.279	0.324	0.038 ^[8]
HbA _{1c} <7% ^[7,9]	0.009	0.045	0.081	0.131	0.002 ^[8]
Decrease of >0.5% ^[7,10]	0.500	0.700	0.771	0.798	<0.0001 ^[8]
HbA _{1c} <8% and decrease of >0.5% ^[7,9,10]	0.140	0.233	0.251	0.317	0.029 ^[8]
^[1] Intent-to-treat population with imputation ^[2] F-test for the overall comparison of treatment regimens ^[3] Contrast comparison of pramlintide regimens versus placebo ^[4] Intent-to-treat subjects who achieved a reduction in HbA _{1c} of ≥0.5% at Week 4 ^[5] Intent-to-treat subjects who achieved a reduction in HbA _{1c} of ≥0.5% at Weeks 4 and 26 ^[6] Statistically significant difference among treatment regimens using Cochran-Mantel-Haenszel test ^[7] Intent-to-treat population without imputation ^[8] Log-rank test for the overall comparison of time to first achieving target HbA _{1c} value. ^[9] Kaplan-Meier estimate of the proportion of subjects with HbA _{1c} at baseline above target value who achieved an HbA _{1c} value below the target value by Week 26. ^[10] Kaplan-Meier estimate of the proportion of subjects achieving an 0.5% decrease from baseline in HbA _{1c} by Week 26.					

Absolute change in HbA_{1c} from baseline to Week 26 was also analyzed for the evaluable and the stable insulin populations. Results for all three populations were consistent and indicate

a drug effect for pramlintide. The largest decrease from baseline was observed in the pramlintide 120 µg BID group and the smallest decrease was found in the placebo group. In each of the populations, because the first specified pairwise comparison (pramlintide 90 µg TID versus placebo) was not statistically significant at the 0.05 level, none of the pairwise comparisons at Week 26 was considered statistically significant by the step-down procedure described in the statistical analysis plan. Nonetheless, there was strong evidence that pramlintide 120 µg BID was effective in improving glycemic control as a nominally significant p-value ($p=0.029$) was achieved compared to placebo. Further comparison of pramlintide treatment effect size was achieved by adjusting for the differences in baseline HbA_{1c} observed between treatment groups. When a post-hoc ANOVA was performed that included baseline HbA_{1c} in the model all three doses achieved statistical significance compared to placebo for the intent-to-treat population. Secondary efficacy results associated with HbA_{1c} measurements (the proportion of early glycemic responders, the proportion of durable glycemic responders, the absolute change in HbA_{1c} from baseline at Weeks 4, 13, and 20, as well as the average change from baseline for Weeks 4 – 26, and the relative change in HbA_{1c} from baseline to each study visit) were consistent with the primary efficacy parameter. Intent-to-treat subjects treated with pramlintide were more likely to become early glycemic responders ($p=0.001$) and durable responders ($p=0.006$) than placebo-treated subjects in this population. Also, the Kaplan-Meier estimates of the proportion of subjects achieving various HbA_{1c} target values or changes from baseline consistently showed a significant difference in favor of pramlintide.

The plot below shows cumulative percent of subjects versus change in HbA_{1c} from baseline at Week 26. In all three pramlintide treatment groups the curves are shifted to the left of the placebo curve, indicating more improvement in glucose control for subjects treated with pramlintide than for subjects treated with placebo.

The cumulative percent of subjects who had a decrease from baseline in HbA_{1c} of 0.5% or more at Week 26 was 44%, 49% and 55% in the pramlintide 90 µg BID, 120 µg BID, and 90 µg TID groups, respectively, compared with 35% in the placebo group. Also at Week 26, the cumulative percent of subjects who had a decrease from baseline in HbA_{1c} of 1.0% or more was 26%, 27% and 31% in the pramlintide 90 µg BID, 120 µg BID, and 90 µg TID groups, respectively, compared with 21% in the placebo group.

**Cumulative Percent of Subjects vs Change in HbA_{1c} from Baseline at Week 26
(Population: Intent-to-Treat with no Data Imputation)**

The decreases in HbA_{1c} in all three pramlintide treatment groups were accompanied by decreases in the mean total daily insulin dose, illustrating that the effect of pramlintide on HbA_{1c} was independent of any concomitant increase in insulin dose. In the evaluable population, mean total daily insulin dose tended to increase by almost 3 units from baseline to Week 26 in the placebo group and varied by <1 unit in the pramlintide groups.

Weight: Evaluable subjects treated with pramlintide experienced weight loss between baseline and Week 13 (0.7 to 1.2 kg) and baseline and Week 26 (0.8 to 1.6 kg) while placebo-treated subjects gained weight (0.1 kg) at both time points. All pairwise comparisons were statistically significant (p-values <0.001 to 0.019) and the effect was maintained from Week 13 to Week 26.

Lipids: No consistent effect of pramlintide on lipid concentrations was observed at Weeks 13 and 26 in the evaluable population.

Severe Hypoglycemia: In spite of a statistically significant (p<0.01) difference among treatment groups (subjects treated with pramlintide, especially 120 µg BID, were more likely to have severe hypoglycemic events than placebo-treated subjects), the event rate per subject-year for severe hypoglycemia appeared to be similar across treatment groups and generally was deemed low from a clinical perspective.

SAFETY RESULTS:

Adverse Events: Gastrointestinal adverse events were most frequent and occurred in 37.1% of subjects. Nausea occurred in 8.9% of placebo-treated subjects and in 14.9% to 27.1% of pramlintide-treated subjects, appeared to be dosage-dependent, and decreased in incidence

from Week 2 to Week 26 in all treatment groups. A higher percentage of pramlintide-treated (3.9% to 4.8%) than placebo-treated (2.4%) subjects withdrew from the study due to adverse events. Nausea was the most common adverse event that led to withdrawal.

Deaths: One subject, who received placebo, died seven days after study completion.

Serious Adverse Events: The incidences of serious adverse events were 5.7% in the placebo group, and 9.9%, 3.2%, and 11.6% in the pramlintide 90 µg BID, 120 µg BID, and 90 µg TID groups, respectively. The most frequent serious adverse events were hypoglycemia and inflicted injury (any injury or trauma).

Clinical Laboratory Values: Laboratory values were similar for placebo- and pramlintide-treated subjects throughout the study.

CONCLUSION: Pramlintide is effective as an adjunct to insulin therapy in significantly improving glycemic control in subjects with type 2 diabetes. Pramlintide administration resulted in mean decreases in HbA_{1c} that do not appear to be associated with an increase in mean total daily dose of insulin in subjects with type 2 diabetes. A substantial proportion of the population treated with pramlintide, particularly pramlintide 120 µg BID, achieved a decrease of 0.5 percentage points or more in HbA_{1c} after Week 4. Pramlintide-treated subjects experienced a mean weight loss during the study compared with a mean weight gain in placebo-treated subjects. Pramlintide at dosages of 90 µg BID, 120 µg BID, and 90 µg TID was safe for the treatment of type 2 diabetes mellitus in subjects who use insulin. Pramlintide appeared to transiently increase the incidence of nausea and to increase the incidence of severe hypoglycemia.

1.4.3 Study 137-122

Title of Study: A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Subjects with Type 2 Diabetes Mellitus

Investigators and Study Centers: Multicenter: 78 centers with randomized subjects, 77 in the United States and 1 in Canada

Publication (Reference):

Fineman M, Gottlieb A, Skare S, Kolterman O. Pramlintide as an adjunct to insulin therapy improved glycemic and weight control in people with type 2 diabetes during treatment for 52 weeks. *Diabetes* 2000;49(suppl 1):A106 (abstract 428 P).

Studied Period (Years): 1996 - 1999

Phase of Development: 3

Objectives: The primary objectives of the study were: (1) to determine the effect of several different dose regimens of pramlintide when compared to placebo, on glycemic control as determined by change in hemoglobin A_{1c} (HbA_{1c}) obtained at baseline (Week 0) and Week 26 in subjects with type 2 diabetes mellitus treated with insulin; and (2) to determine the safety of several different dose regimens of pramlintide.

Methodology: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate glycemic control in subjects with type 2 diabetes mellitus who are using insulin. Subjects were to be randomized to one of four treatment regimens (pramlintide 60 µg TID, 90 µg BID, or 120 µg BID, or placebo) after a three-month subject stabilization period (two months of documented insulin stability followed by one month of placebo lead-in medication). Subjects continued with their usual diabetes regimen that may have included diet, exercise, and oral hypoglycemic agents, in addition to insulin. Subjects were to be treated with double-blind study medication for a 52-week treatment period. The HbA_{1c} measurements were to be blinded to the investigator, subject, and medical monitor during the trial. However, investigators were to be notified if a subject's HbA_{1c} during the trial increased two or more percentage points from baseline (e.g. increased from 9.2% to 11.2%).

Number of Subjects: Six hundred fifty-six subjects aged 18 years or older (mean age, 57.3 years) were randomized into this study. Approximately equal numbers of female (49.2%) and male (50.8%) subjects were enrolled. A total of 466 (71%) subjects completed 52 weeks of treatment: 113 (70.2%), 122 (71.3%), 118 (74.7%), and 113 (68.1%) in the placebo,

pramlintide 90 µg BID, pramlintide 60 µg TID, and pramlintide 120 µg BID groups, respectively.

Diagnosis and Main Criteria for Inclusion: Male and female subjects with a history of type 2 diabetes mellitus (no past history of diabetic ketoacidosis), requiring treatment with insulin for a minimum of six months at study screen visit.

Test Product, Dose and Mode of Administration, Batch No.: Pramlintide 60 µg TID [0.3 mg/mL AC-0137-F21 (0.2 mL)] subcutaneous injection, Lot Nos. 96-0504JB, 96-0601JB; Pramlintide 90 µg BID [0.45 mg/mL AC-0137-F27 (0.2 mL)] subcutaneous injection, Lot Nos. 96-0905JB1, 96-1105JB ; Pramlintide 120 µg BID [0.6 mg/mL AC-0137-F22 (0.2 mL)] subcutaneous injection, Lot Nos. 96-0503JB, 96-1103JB.

Duration of Treatment: 52 weeks

Reference Therapy, Dose and Mode of Administration, Batch No: Placebo TID (0.2 mL) subcutaneous injection, Lot Nos. 96-0505JE, 96-1009JE, and 97-0101GE.

Criteria for Evaluation:

Efficacy: The primary criterion was the change in HbA_{1c} from baseline (Week 0) at Week 26 in the intent-to-treat population. Secondary efficacy parameters associated with HbA_{1c} measurements included the proportion of early glycemic responders (i.e., subjects who achieved a 0.5% reduction in HbA_{1c} at Week 4), the proportion of durable glycemic responders (i.e., subjects who had a 0.5% reduction from baseline in HbA_{1c} at Week 4 and at Week 26), the change in HbA_{1c} from baseline at Weeks 4, 13, 20, 39 and 52 as well the average change from baseline for Weeks 4–26 and Weeks 4–52, and the relative change in HbA_{1c} from baseline to each study visit. The proportion of subjects in each treatment group that achieved each of four different HbA_{1c} target values or changes was determined and a joint outcome analysis of HbA_{1c} and total daily insulin was performed. Other secondary efficacy parameters included changes in insulin regimen, weight, and fasting lipids, as well as the incidence of severe hypoglycemia.

Safety: Safety was assessed throughout the study period by monitoring adverse events, clinical laboratory data, vital signs, physical examination findings and ECGs.

Statistical Methods:

Efficacy: In accordance with a statistical analysis plan finalized before the blind was broken and the results known, all inferential testing excluded the pramlintide 60 µg TID group. Two way ANOVA models were used for assessing change from baseline in HbA_{1c}, relative change from baseline in HbA_{1c}, change in weight, and relative change in lipid profile.

Pairwise comparisons between each pramlintide group and the placebo group were done using Fisher's protected LSD procedure for HbA_{1c} variables. In addition, post-hoc ANOVA analysis of HbA_{1c} change from baseline that included baseline HbA_{1c} as a covariate in the model was performed. The primary analyses of HbA_{1c} were performed on the intent-to-treat population, and additional analyses were done on the evaluable population and the stable insulin and treatment-compliant subgroups. Change from baseline in HbA_{1c} was also summarized by gender and by age. An analysis of joint outcomes for HbA_{1c} change from baseline and relative change from baseline for total daily insulin was undertaken at Weeks 4, 13, 20, 26, 39, and 52 in the observed cases dataset for the intent-to-treat population. A subject's joint outcome for HbA_{1c} and insulin was classified at each visit as a (1) drug effect, (2) an indeterminate drug effect, or (3) no drug effect. The total number of severe hypoglycemic events per subject was analyzed by using Poisson regression. All testing was two-tailed. All tests for overall treatment effects were conducted with a significance level of 0.05, with the exception of the log-rank test and Poisson regression for severe hypoglycemia, which were carried out at the 0.10 level.

Safety: Detailed listings and summaries were prepared showing pre-treatment and post-treatment values, as well as change from pre-treatment values, to provide descriptive comparisons for the pramlintide treatment regimens and placebo. Adverse events were tabulated by incidence, severity, and study drug attributability, and compared between treatment regimens.

SUMMARY - CONCLUSIONS:

EFFICACY RESULTS:

Key HbA_{1c} results for the intent-to-treat population, including the primary efficacy parameter (analysis of change from baseline in HbA_{1c} at Week 26 analyzed without baseline HbA_{1c} in the ANOVA model), are shown in the table below.

SUMMARY OF EFFICACY RESULTS				
	<u>Placebo</u>	<u>Pramlintide 90 µg BID</u>	<u>Pramlintide 120 µg BID</u>	<u>Overall p value</u>
<u>HbA_{1c} change from Baseline at Week 26^[1]</u>				0.008*
N	161	171	166	
LSMEAN	-0.32	-0.53	-0.66	
SE	0.09	0.08	0.08	
LSM difference		-0.21	-0.34	
Pairwise p-value		0.053	0.002*	
Early Glycemic Responders (%) ^[2]	22.64	37.65	40.85	0.004 ^[4]
Durable Glycemic Responders (%) ^[3]	10.06	26.47	26.22	0.001 ^[4]
Kaplan-Meier estimate of proportion of subjects achieving targets by Week 26				
HbA _{1c} <8% ^[5,7]	0.261	0.397	0.415	0.010 ^[6]
HbA _{1c} <7% ^[5,7]	0.032	0.079	0.086	0.046 ^[6]
Decrease of ≥0.5% ^[5,8]	0.573	0.735	0.819	<0.0001 ^[6]
^[1] Intent-to-treat population with imputation ^[2] Intent-to-treat subjects who achieved a reduction in HbA _{1c} of ≥0.5% at Week 4 ^[3] Intent-to-treat subjects who achieved a reduction in HbA _{1c} of ≥0.5% at Weeks 4 and 26 ^[4] Statistically significant difference among treatment regimens using Cochran-Mantel-Haenszel test ^[5] Intent-to-treat population without imputation ^[6] Log-rank test for the overall comparison of time to first achieving target HbA _{1c} value. ^[7] Kaplan-Meier estimate of the proportion of subjects with HbA _{1c} at baseline above target value who achieved an HbA _{1c} value below the target value by Week 26. ^[8] Kaplan-Meier estimate of the proportion of subjects achieving an 0.5% decrease from baseline in HbA _{1c} by Week 26. * Statistically significant difference using Fisher's protected LSD procedure.				

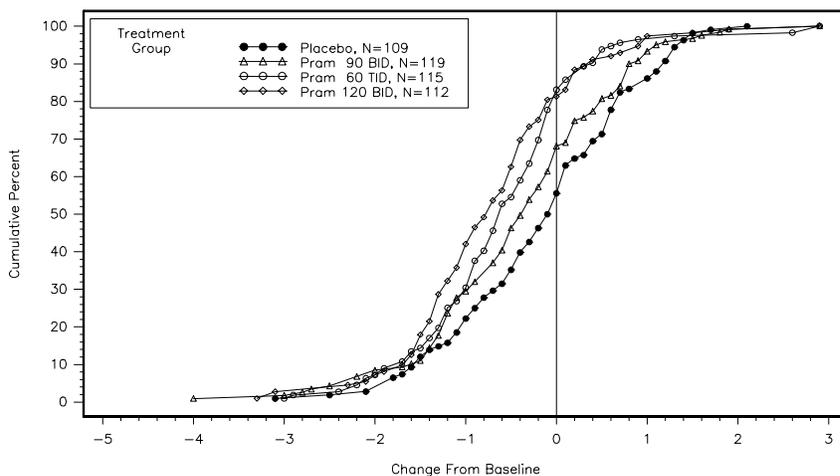
To further characterize the effect size of pramlintide treatment, the ANOVA was also performed including baseline HbA_{1c} in the model; the resulting treatment effects in the pramlintide 90 µg BID and 120 µg BID groups increased to -0.3 and -0.4 percentage points, respectively, and pairwise comparisons with placebo were statistically significant for both groups. Results from analyses in the evaluable population were consistent with those in the intent-to-treat population, as were the results of the analysis of the stable insulin subgroup when site was not included in the ANOVA model. Secondary efficacy results associated with HbA_{1c} measurements (the proportion of early glycemic responders, the proportion of durable glycemic responders, the absolute change in HbA_{1c} from baseline at Weeks 4, 13, 20, 39, and 52, as well as the average change from baseline for Weeks 4-26 and Weeks 4-52, and the relative change in HbA_{1c} from baseline to each study visit) were consistent with the primary efficacy parameter. The changes in HbA_{1c} were durable, particularly with

pramlintide 120 µg BID, as evidenced by the maintenance of the mean decreases in HbA_{1c} from baseline in the pramlintide groups over the 52-week study period.

The plot below shows cumulative percent of subjects vs. change in HbA_{1c} from baseline at Week 52. The points on the curve represent the cumulative percentage of subjects (Y axis) assigned to a particular treatment group who completed 52 weeks of treatment and who achieved a change in HbA_{1c} from baseline at least as large as the HbA_{1c} change value given on the X axis. A negative change from baseline represents improved glucose control; a positive change indicates worsening of glucose control. It is clear that in all three pramlintide treatment groups the curves are shifted to the left of the placebo curve, indicating more improvement in glucose control for subjects treated with pramlintide than for subjects treated with placebo. There was also evidence of a dose response, with the greatest HbA_{1c} response evident in the pramlintide 120 µg BID group.

As can be determined from the figure below, the cumulative percent of subjects who had a decrease from baseline in HbA_{1c} of 0.5% or more at Week 52 was 46%, 54% and 63% in the pramlintide 90 µg BID, 60 µg TID, and 120 µg BID groups, respectively, compared with 35% in the placebo group. The cumulative percent of subjects who had a decrease from baseline in HbA_{1c} of 1.0% or more at Week 52 was 29%, 30% and 42% in the pramlintide 90 µg BID, 60 µg TID, and 120 µg BID groups, respectively, compared with 22% in the placebo group.

Week 52 Cumulative Percent of Subjects who Achieve Changes in HbA_{1c} From Baseline



A decrease from baseline at Week 26 in the mean total daily dose of insulin was observed in the pramlintide 120 µg BID group, compared with a mean increase in insulin dose for the placebo group. However, the joint outcomes analysis of HbA_{1c} and total daily insulin dose revealed that the mean decrease in HbA_{1c} observed in the pramlintide groups was not associated with any consistent trend in the mean relative change in total daily insulin dose, suggesting that the effect of pramlintide on HbA_{1c} was independent of any concomitant

changes in insulin dose. A mean decrease in body weight which persisted throughout the 52 weeks of the study was observed in all three pramlintide groups, compared with a mean increase in body weight during the same time period in the placebo group. The incidence rate of severe hypoglycemia events was slightly higher during the first four weeks of therapy with pramlintide 120 µg BID compared with therapy with placebo, but over time the difference between these two treatment groups diminished and was not considered clinically significant. When analyzed over the entire 52-week course of the study, the incidence of severe hypoglycemic events for each of the three pramlintide groups was either the same or lower than in the placebo group. There were no clinically or statistically significant differences among the treatment groups in any of the lipid profile parameters measured.

SAFETY RESULTS:

Adverse Events: A total of 610 of 656 (93.0%) subjects reported at least one treatment-emergent adverse event and the percentage of subjects reporting a treatment-emergent adverse event was similar among the treatment groups. The most frequently reported treatment-emergent adverse event among all treatment groups was upper respiratory tract infection (32%) which was reported by a similar percentage of subjects in all of the treatment groups. Nausea, vomiting and anorexia were reported by subjects in all of the treatment groups but were more common in the pramlintide groups. Severe nausea was reported in 2.3% of subjects overall: 1.2%, 4.1%, 1.3% and 2.4% of subjects in the placebo, pramlintide 90 µg BID, 60 µg TID, and 120 µg BID treatment groups, respectively. Inflicted injury (13.9%) (including but not limited to lacerations, wounds, sprains, injuries, strains, scratches, broken bones, bruising, contusions, abrasions, cuts, falls, and scrapes) was also common but was evenly distributed among all treatment groups. Headache, fatigue, dizziness, and anxiety were each reported by a greater percentage of subjects in each of the pramlintide groups than in the placebo group. Sinusitis, back pain, urinary tract infection, and constipation were each reported in a greater percentage of subjects in the placebo group than in any of the pramlintide groups. Of the adverse events reported, 93% were mild or moderate in intensity. Nausea, hypoglycemia, injection site reaction and anorexia were the most common adverse events considered possibly or probably related to treatment. A higher occurrence of nausea was observed in all of the pramlintide treatment groups as compared with placebo through Week 13 of the study. After Week 13, the percentage of nausea in the placebo group was at least as great as the lowest percentage in any of the pramlintide groups. The profile of treatment-emergent adverse events leading to withdrawal did not suggest any major safety concerns. Sixty-two of 656 subjects (9.5%) had treatment-emergent adverse events leading to withdrawal: 8.1% placebo, 10.5% pramlintide 90 µg BID, 7.6% pramlintide 60 µg TID, and 11.4% pramlintide 120 µg BID. Nausea (2.4% overall) was the most frequently reported treatment-emergent adverse event leading to withdrawal. A higher incidence of withdrawals due to nausea was observed in the pramlintide 90 µg BID and 120 µg BID groups than in the placebo or pramlintide 60 µg TID groups.

Deaths: Three subjects died during the course of the study, two in the placebo group and one in the pramlintide 120 µg BID group. One subject in the placebo group died on Study Day 119 due to coronary artery disorder that was considered possibly treatment related. The subject had a history of peripheral vascular disease and coronary artery disorder. Another subject in the placebo group died on Study Day 187 due to an acute myocardial infarction that was considered probably not related to study treatment. One pramlintide 120 µg BID treated subject died on Study Day 363 due to a right cerebrovascular stroke and respiratory arrest, both of which were considered probably not related to study treatment.

Serious Adverse Events: Serious treatment-emergent adverse events were reported by 127 of 656 (19.4%) subjects: 29 (18.0%) in the placebo group, 30 (17.5%) in the pramlintide 90 µg BID group, 33 (20.9%) in the pramlintide 60 µg TID group, and 35 (21.1%) in the pramlintide 120 µg BID group. The most frequently reported serious treatment-emergent adverse events among all treatment groups were hypoglycemia (2.6%), coronary artery disorder (2.7%), and myocardial infarction (2.0%).

Clinical Laboratory Values: Overall, the percentage of potentially clinically important abnormal laboratory values was low in all treatment groups, and there did not appear to be any clinically important differences among the treatment groups.

Vital Signs, Physical Examinations and ECGs: Pramlintide treatment appeared to have no clinically important effect on vital signs, physical examinations, and electrocardiogram measurements during the 52-week treatment period.

CONCLUSION: Pramlintide at a dosage of 120 µg BID is effective as an adjunct to insulin in significantly improving glycemic control in subjects with type 2 diabetes. There is also evidence that pramlintide 90 µg BID is effective for this purpose, although the data are not as robust and suggest that the effectiveness of the 90 µg BID dose may not persist past Week 26. The drug is associated with a decrease in HbA_{1c} and weight, and has no adverse effects on lipids. The drug does not appear to increase the long-term risk for severe hypoglycemia. However, initiation of pramlintide therapy, as any perturbation that improves glucose control, may increase the short-term risk for hypoglycemia until appropriate adjustments are made to the insulin regimen. There exists a subgroup of early glycemic responders, subjects who achieve a decrease of 0.5 percentage points or more in HbA_{1c} by Week 4. A substantial proportion of the population treated with pramlintide, particularly 120 µg BID, achieve this level of response after Week 4. Pramlintide, at the dosages used in this study, appears to be safe for use as an adjunct to insulin in subjects with type 2 diabetes.

APPENDIX 5: ADVERSE EVENTS AND PATIENT DEATHS DURING PRAMLINTIDE CLINICAL TRIALS

Appendix 5 – Part A

Incidence of Treatment-Emergent Adverse Events for All Completed Clinical Studies

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies)

Body System Preferred Term	Type 1												Type 2 Using Insulin				Other	
	Clinical Pharmacology		Controlled				Uncontrolled		Controlled		Uncontrolled		Controlled		Uncontrolled			
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Short-term Pbo (n=43)	Long-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=758)	Short-term Pbo (n=153)	Long-term Pram (n=50)	Long-term Pbo (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Short-term Pram (n=206)	Long-term Pbo (n=100)				
Number (%) with AE	476 (59)	140 (40)	165 (96)	41 (95)	1065 (90)	468 (87)	691 (91)	104 (68)	27 (54)	1119 (88)	363 (86)	315 (92)	124 (60)	45 (45)				
APPLICATION SITE	37 (5)	5 (1)	5 (3)	3 (7)	78 (7)	50 (9)	66 (9)	10 (7)	0 (0)	82 (6)	28 (7)	13 (4)	12 (6)	7 (7)				
INJECTION SITE REACTION	37 (5)	5 (1)	5 (3)	3 (7)	78 (7)	50 (9)	65 (9)	10 (7)	0 (0)	78 (6)	28 (7)	12 (4)	11 (5)	7 (7)				
IMPLANTATION COMPLICATION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)				
SKIN NECROSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)				
INJECTION SITE PAIN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)				
TYMPANIC MEMBRANE PERFORATION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)				
FIBROUS NODULE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)				
BODY AS A WHOLE	69 (9)	21 (6)	23 (13)	4 (9)	402 (34)	193 (36)	256 (34)	25 (16)	8 (16)	511 (40)	160 (38)	139 (41)	17 (8)	6 (6)				
INFLUENZA-LIKE SYMPTOMS	1 (<1)	1 (<1)	2 (1)	1 (2)	120 (10)	65 (12)	82 (11)	6 (4)	0 (0)	113 (9)	39 (9)	36 (11)	1 (<1)	0 (0)				
FATIGUE	17 (2)	5 (1)	4 (2)	0 (0)	80 (7)	22 (4)	42 (6)	2 (1)	1 (2)	83 (7)	17 (4)	18 (5)	5 (2)	1 (1)				
BACK PAIN	2 (<1)	5 (1)	2 (1)	0 (0)	45 (4)	33 (6)	35 (5)	4 (3)	1 (2)	96 (8)	38 (9)	23 (7)	3 (1)	1 (1)				
ALLERGIC REACTION	0 (0)	0 (0)	3 (2)	1 (2)	59 (5)	28 (5)	49 (6)	2 (1)	2 (4)	65 (5)	18 (4)	25 (7)	1 (<1)	0 (0)				
PAIN	7 (1)	3 (1)	0 (0)	0 (0)	47 (4)	33 (6)	32 (4)	2 (1)	0 (0)	83 (7)	30 (7)	25 (7)	1 (<1)	0 (0)				
OEDEMA PERIPHERAL	0 (0)	0 (0)	2 (1)	0 (0)	32 (3)	19 (4)	14 (2)	2 (1)	2 (4)	67 (5)	20 (5)	21 (6)	0 (0)	1 (1)				
FEVER	5 (1)	4 (1)	3 (2)	0 (0)	35 (3)	20 (4)	29 (4)	4 (3)	0 (0)	46 (4)	11 (3)	7 (2)	2 (1)	0 (0)				
CHEST PAIN	5 (1)	0 (0)	0 (0)	0 (0)	18 (2)	13 (2)	17 (2)	0 (0)	1 (2)	58 (5)	16 (4)	14 (4)	0 (0)	0 (0)				
LEG PAIN	2 (<1)	0 (0)	1 (1)	1 (2)	12 (1)	6 (1)	13 (2)	0 (0)	0 (0)	26 (2)	5 (1)	6 (2)	0 (0)	0 (0)				
OEDEMA	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	7 (1)	4 (1)	2 (1)	1 (2)	37 (3)	8 (2)	4 (1)	0 (0)	1 (1)				
SYNCOPE	2 (<1)	1 (<1)	1 (1)	0 (0)	18 (2)	5 (1)	5 (1)	0 (0)	0 (0)	19 (1)	3 (1)	3 (1)	1 (<1)	2 (2)				
ASTHENIA	15 (2)	2 (1)	1 (1)	0 (0)	11 (1)	4 (1)	4 (1)	0 (0)	0 (0)	12 (1)	3 (1)	4 (1)	1 (<1)	0 (0)				
CARPAL TUNNEL SYNDROME	0 (0)	0 (0)	0 (0)	0 (0)	8 (1)	11 (2)	7 (1)	0 (0)	0 (0)	12 (1)	7 (2)	10 (3)	0 (0)	0 (0)				
MALAISE	1 (<1)	0 (0)	2 (1)	1 (2)	10 (1)	3 (1)	8 (1)	0 (0)	0 (0)	8 (1)	3 (1)	2 (1)	1 (<1)	0 (0)				
TEMPERATURE CHANGED SENSATION	9 (1)	1 (<1)	2 (1)	0 (0)	3 (<1)	2 (<1)	10 (1)	0 (0)	0 (0)	4 (<1)	0 (0)	3 (1)	0 (0)	0 (0)				
HERNIA NOS	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	0 (0)	3 (<1)	0 (0)	0 (0)	11 (1)	4 (1)	5 (1)	0 (0)	0 (0)				
RIGORS	6 (1)	1 (<1)	0 (0)	0 (0)	2 (<1)	1 (<1)	5 (1)	2 (1)	0 (0)	3 (<1)	1 (<1)	0 (0)	1 (<1)	0 (0)				
HOT FLUSHES	3 (<1)	0 (0)	0 (0)	1 (2)	7 (1)	4 (1)	3 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)				
ABDOMEN ENLARGED	1 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	2 (<1)	2 (<1)	0 (0)	0 (0)	2 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)				
PALLOR	6 (1)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)				
SCAR	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	3 (1)	1 (<1)	0 (0)	0 (0)	1 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)				
CHOKING	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)				
HALITOSIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)				
NASAL POLYP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)				
CHEST PAIN SUBSTERNAL	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)				
SARCOIDOSIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)				
ACCIDENTAL TRAUMA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)				

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin						Other	
			Controlled		Uncon- trolled		Controlled		Uncon- trolled					
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Long-term Pbo (n=43)	Short-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=153)	Long-term Pbo (n=50)	Short-term Pram (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Long-term Pbo (n=206)	Short-term Pram (n=100)	Long-term Pbo (n=100)
ASCITES	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
BEZOAR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
BLOOD ALCOHOL EXCESSIVE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BODY ODOUR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DEATH	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HYPOTHERMIA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HYPOVOLAEMIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
OEDEMA GENITAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
OEDEMA MOUTH	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TOLERANCE DECREASED	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
WITHDRAWAL SYNDROME	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
WOUND DRAINAGE INCREASED	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
SUDDEN DEATH	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
CARDIOVASCULAR	8 (1)	4 (1)	1 (1)	0 (0)	60 (5)	33 (6)	42 (6)	5 (3)	1 (2)	177 (14)	63 (15)	53 (16)	3 (1)	2 (2)
HYPERTENSION	1 (<1)	3 (1)	0 (0)	0 (0)	28 (2)	19 (4)	25 (3)	1 (1)	0 (0)	75 (6)	24 (6)	25 (7)	1 (<1)	0 (0)
OEDEMA DEPENDENT	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	6 (1)	3 (<1)	2 (1)	1 (2)	28 (2)	5 (1)	10 (3)	0 (0)	0 (0)
HYPERTENSION AGGRAVATED	0 (0)	0 (0)	0 (0)	0 (0)	6 (1)	0 (0)	0 (0)	0 (0)	0 (0)	26 (2)	11 (3)	1 (<1)	0 (0)	0 (0)
ECG ABNORMAL	3 (<1)	1 (<1)	1 (1)	0 (0)	1 (<1)	2 (<1)	4 (1)	0 (0)	0 (0)	17 (1)	8 (2)	5 (1)	1 (<1)	1 (1)
HEART MURMUR	1 (<1)	0 (0)	0 (0)	0 (0)	8 (1)	4 (1)	2 (<1)	1 (1)	0 (0)	12 (1)	6 (1)	7 (2)	0 (0)	0 (0)
HYPOTENSION POSTURAL	1 (<1)	0 (0)	0 (0)	0 (0)	7 (1)	0 (0)	6 (1)	0 (0)	0 (0)	7 (1)	2 (<1)	1 (<1)	0 (0)	0 (0)
CARDIAC FAILURE	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	3 (1)	1 (<1)	0 (0)	0 (0)	12 (1)	10 (2)	3 (1)	0 (0)	0 (0)
HYPOTENSION	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	8 (1)	3 (1)	2 (1)	1 (<1)	1 (1)
CARDIOMEGALY	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	7 (1)	2 (<1)	0 (0)	0 (0)	0 (0)
HEART DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	1 (1)	0 (0)	3 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)
CYANOSIS	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
ANEURYSM	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
BLOOD PRESSURE FLUCTUATION	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HYPERTENSION PULMONARY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
CENTR & PERIPH NERVOUS	168 (21)	43 (12)	34 (20)	11 (26)	280 (24)	134 (25)	174 (23)	13 (9)	9 (18)	362 (28)	108 (26)	97 (28)	24 (12)	7 (7)
HEADACHE	100 (12)	20 (6)	29 (17)	10 (23)	145 (12)	84 (16)	86 (11)	9 (6)	5 (10)	154 (12)	37 (9)	31 (9)	14 (7)	4 (4)
DIZZINESS	60 (7)	15 (4)	4 (2)	1 (2)	44 (4)	21 (4)	24 (3)	0 (0)	1 (2)	71 (6)	17 (4)	9 (3)	5 (2)	1 (1)
HYPOAESTHESIA	2 (<1)	5 (1)	0 (0)	0 (0)	17 (1)	14 (3)	17 (2)	0 (0)	0 (0)	37 (3)	13 (3)	18 (5)	1 (<1)	0 (0)
PARAESTHESIA	8 (1)	1 (<1)	1 (1)	0 (0)	21 (2)	10 (2)	10 (1)	1 (1)	0 (0)	31 (2)	11 (3)	8 (2)	0 (0)	0 (0)
NEUROPATHY	0 (0)	0 (0)	0 (0)	0 (0)	11 (1)	3 (1)	11 (1)	0 (0)	1 (2)	34 (3)	6 (1)	13 (4)	1 (<1)	0 (0)
HYPERTONIA	5 (1)	1 (<1)	2 (1)	0 (0)	9 (1)	4 (1)	6 (1)	0 (0)	1 (2)	25 (2)	9 (2)	2 (1)	0 (0)	0 (0)
HYPOREFLEXIA	5 (1)	2 (1)	0 (0)	0 (0)	10 (1)	1 (<1)	5 (1)	2 (1)	1 (2)	15 (1)	10 (2)	9 (3)	2 (1)	1 (1)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin						Other	
			Controlled		Uncon- trolled		Controlled		Uncon- trolled					
	Pram (n=805)	Pbo (n=353)	Short-term	Long-term	Short-term	Long-term	Short-term	Long-term	Short-term	Long-term	Short-term	Long-term	Short-term	Long-term
COLLAGEN	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
ARTHRITIS RHEUMATOID	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
DID NOT CODE	8 (1)	7 (2)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DID NOT CODE	8 (1)	7 (2)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ENDOCRINE	0 (0)	1 (<1)	0 (0)	0 (0)	21 (2)	12 (2)	9 (1)	0 (0)	0 (0)	18 (1)	3 (1)	5 (1)	0 (0)	0 (0)
GOITRE	0 (0)	1 (<1)	0 (0)	0 (0)	14 (1)	7 (1)	3 (<1)	0 (0)	0 (0)	12 (1)	3 (1)	3 (1)	0 (0)	0 (0)
HYPOTHYROIDISM	0 (0)	0 (0)	0 (0)	0 (0)	4 (<1)	5 (1)	4 (1)	0 (0)	0 (0)	5 (<1)	0 (0)	2 (1)	0 (0)	0 (0)
FAT ATROPHY	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
GYNAECOMASTIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
HYPERTHYROIDISM	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
THYROIDITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
THYROID DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
FOETAL	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	2 (<1)	0 (0)	0 (0)	3 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
ABORTION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
OSTEOCHONDROSIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BRAIN DAMAGE CONGENITAL	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DEATH FOETAL	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SYNDACTYLY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
UROGENITAL MALFORMATION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
GASTRO-INTESTINAL	294 (37)	37 (10)	61 (35)	9 (21)	785 (67)	212 (39)	466 (61)	41 (27)	5 (10)	608 (48)	153 (36)	131 (38)	79 (38)	14 (14)
NAUSEA	243 (30)	20 (6)	43 (25)	2 (5)	601 (51)	92 (17)	298 (39)	19 (12)	0 (0)	308 (24)	57 (14)	37 (11)	50 (24)	7 (7)
ANOREXIA	55 (7)	0 (0)	12 (7)	0 (0)	209 (18)	12 (2)	119 (16)	6 (4)	0 (0)	98 (8)	13 (3)	11 (3)	24 (12)	0 (0)
VOMITING	58 (7)	2 (1)	5 (3)	1 (2)	154 (13)	36 (7)	73 (10)	5 (3)	0 (0)	85 (7)	23 (5)	11 (3)	12 (6)	2 (2)
DIARRHOEA	27 (3)	6 (2)	6 (3)	1 (2)	107 (9)	62 (12)	78 (10)	9 (6)	1 (2)	118 (9)	42 (10)	24 (7)	12 (6)	3 (3)
ABDOMINAL PAIN	25 (3)	6 (2)	7 (4)	3 (7)	89 (8)	36 (7)	48 (6)	1 (1)	2 (4)	97 (8)	27 (6)	22 (6)	2 (1)	0 (0)
DYSPEPSIA	26 (3)	0 (0)	6 (3)	0 (0)	42 (4)	17 (3)	36 (5)	4 (3)	0 (0)	76 (6)	12 (3)	22 (6)	9 (4)	1 (1)
GASTROENTERITIS	0 (0)	0 (0)	2 (1)	0 (0)	47 (4)	41 (8)	51 (7)	1 (1)	0 (0)	47 (4)	10 (2)	17 (5)	1 (<1)	2 (2)
FLATULENCE/ABDOMINAL FULLNESS	1 (<1)	0 (0)	0 (0)	0 (0)	63 (5)	23 (4)	43 (6)	0 (0)	0 (0)	42 (3)	9 (2)	9 (3)	0 (0)	0 (0)
CONSTIPATION	5 (1)	0 (0)	1 (1)	0 (0)	25 (2)	14 (3)	25 (3)	3 (2)	2 (4)	50 (4)	18 (4)	11 (3)	3 (1)	0 (0)
TOOTH DISORDER	0 (0)	0 (0)	0 (0)	1 (2)	29 (2)	17 (3)	12 (2)	0 (0)	0 (0)	14 (1)	7 (2)	4 (1)	0 (0)	1 (1)
TOOTH ACHE	2 (<1)	0 (0)	1 (1)	1 (2)	14 (1)	12 (2)	15 (2)	0 (0)	0 (0)	21 (2)	6 (1)	5 (1)	0 (0)	0 (0)
GASTROESOPHAGEAL REFLUX	1 (<1)	0 (0)	0 (0)	0 (0)	12 (1)	3 (1)	7 (1)	0 (0)	0 (0)	19 (1)	8 (2)	4 (1)	1 (<1)	0 (0)
MOUTH DRY	7 (1)	0 (0)	0 (0)	0 (0)	10 (1)	6 (1)	2 (<1)	0 (0)	0 (0)	13 (1)	2 (<1)	1 (<1)	3 (1)	1 (1)
ERUCTATION	4 (1)	1 (<1)	2 (1)	0 (0)	8 (1)	2 (<1)	8 (1)	2 (1)	0 (0)	6 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin						Other	
			Controlled		Uncon- trolled		Controlled		Uncon- trolled					
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Long-term Pbo (n=43)	Short-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=153)	Long-term Pbo (n=50)	Short-term Pram (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Long-term Pbo (n=342)	Short-term Pram (n=206)	Long-term Pbo (n=100)
FLATULENCE	13 (2)	2 (1)	4 (2)	2 (5)	0 (0)	0 (0)	0 (0)	10 (7)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2)	1 (1)
HAEMORRHOIDS	0 (0)	0 (0)	0 (0)	0 (0)	6 (1)	3 (1)	5 (1)	0 (0)	0 (0)	8 (1)	0 (0)	6 (2)	0 (0)	0 (0)
GINGIVITIS	0 (0)	0 (0)	0 (0)	0 (0)	13 (1)	4 (1)	4 (1)	0 (0)	0 (0)	6 (<1)	2 (<1)	0 (0)	1 (<1)	0 (0)
GASTRITIS	0 (0)	0 (0)	0 (0)	0 (0)	9 (1)	3 (1)	1 (<1)	0 (0)	0 (0)	8 (1)	3 (1)	2 (1)	0 (0)	0 (0)
DIVERTICULITIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	12 (1)	1 (<1)	5 (1)	0 (0)	0 (0)
APPETITE INCREASED	4 (1)	2 (1)	0 (0)	0 (0)	1 (<1)	2 (<1)	3 (<1)	0 (0)	0 (0)	7 (1)	3 (1)	1 (<1)	1 (<1)	0 (0)
TOOTH CARIES	1 (<1)	0 (0)	1 (1)	0 (0)	3 (<1)	2 (<1)	2 (<1)	0 (0)	0 (0)	7 (1)	3 (1)	1 (<1)	0 (0)	0 (0)
GI NEOPLASM BENIGN	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	2 (<1)	2 (1)	0 (0)	0 (0)
STOMATITIS ULCERATIVE	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	0 (0)	2 (<1)	0 (0)	1 (2)	2 (<1)	1 (<1)	2 (1)	0 (0)	0 (0)
GASTRIC DILATATION	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	5 (1)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
DYSPHAGIA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	3 (<1)	0 (0)	0 (0)	4 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
FAECAL ABNORMALITY NOS	0 (0)	1 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)	3 (<1)	0 (0)	0 (0)	4 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
GASTRO-INTESTINAL DISORDER NOS	4 (1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	4 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
HAEMORRHAGE RECTUM	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	2 (1)	0 (0)	0 (0)
OESOPHAGITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	2 (<1)	1 (1)	0 (0)	4 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
PERIODONTAL DESTRUCTION	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	2 (<1)	0 (0)	0 (0)	3 (<1)	4 (1)	2 (1)	0 (0)	0 (0)
COLITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	3 (<1)	1 (<1)	2 (1)	0 (0)	0 (0)
MELAENA	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	2 (<1)	5 (1)	1 (<1)	1 (<1)	0 (0)
CHANGE IN BOWEL HABITS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	3 (1)	2 (<1)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	1 (<1)	0 (0)
PANCREATITIS	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
DUODENAL ULCER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
GASTRIC ULCER	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
GI HAEMORRHAGE	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
INTESTINAL OBSTRUCTION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	2 (1)	0 (0)	0 (0)
STOMATITIS	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
ENTERITIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	3 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
ILEUS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
IRRITABLE BOWEL SYNDROME	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)
PEPTIC ULCER	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
FAECES DISCOLOURED	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
GINGIVAL RESSION	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
OESOPHAGEAL STRICTURE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
ABDOMINAL ADHESIONS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
ANAL FISSURE	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
APPENDICITIS	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
COLITIS ULCERATIVE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DUODENITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
LEUKOPLAKIA ORAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin						Other	
			Controlled		Uncon- trolled		Controlled		Uncon- trolled		Controlled		Uncon- trolled	
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Long-term Pbo (n=43)	Short-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=153)	Long-term Pbo (n=50)	Short-term Pram (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Long-term Pbo (n=206)	Short-term Pram (n=206)	Long-term Pbo (n=100)
MUCOSITIS NOS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
OESOPHAGEAL ULCERATION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
OESOPHAGEAL VARICES	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
RECTAL DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
SALIVARY DUCT OBSTRUCTION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
TEETH-GRINDING	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
TENESMUS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)
TONGUE DISCOLOURATION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
TONGUE OEDEMA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
SALIVA INCREASED	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)
SALIVARY GLAND ENLARGEMENT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
TONGUE DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
HEARING AND VESTIBULAR EAR DISORDER NOS	1 (<1)	1 (<1)	0 (0)	0 (0)	23 (2)	16 (3)	20 (3)	3 (2)	0 (0)	45 (4)	8 (2)	11 (3)	0 (0)	0 (0)
EAR ACHE	0 (0)	0 (0)	0 (0)	0 (0)	6 (1)	3 (1)	10 (1)	1 (1)	0 (0)	21 (2)	5 (1)	7 (2)	0 (0)	0 (0)
TINNITUS	0 (0)	0 (0)	0 (0)	0 (0)	9 (1)	10 (2)	7 (1)	0 (0)	0 (0)	16 (1)	3 (1)	2 (1)	0 (0)	0 (0)
HEARING DECREASED	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	5 (1)	2 (<1)	1 (1)	0 (0)	6 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
MOTION SICKNESS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (1)	0 (0)	6 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
HYPERACUSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
OTOTOXICITY	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
VESTIBULAR DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HEART RATE AND RHYTHM	9 (1)	6 (2)	1 (1)	0 (0)	18 (2)	15 (3)	18 (2)	2 (1)	0 (0)	58 (5)	16 (4)	17 (5)	5 (2)	1 (1)
TACHYCARDIA	4 (1)	5 (1)	1 (1)	0 (0)	8 (1)	7 (1)	5 (1)	0 (0)	0 (0)	17 (1)	2 (<1)	2 (1)	0 (0)	0 (0)
PALPITATION	3 (<1)	1 (<1)	0 (0)	0 (0)	5 (<1)	2 (<1)	5 (1)	1 (1)	0 (0)	11 (1)	3 (1)	0 (0)	0 (0)	0 (0)
EXTRASYSTOLES	1 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	1 (1)	0 (0)	11 (1)	1 (<1)	2 (1)	1 (<1)	0 (0)
ARRHYTHMIA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	2 (<1)	0 (0)	0 (0)	6 (<1)	5 (1)	3 (1)	0 (0)	1 (1)
BRADYCARDIA	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (<1)	3 (1)	3 (1)	3 (1)	1 (1)
FIBRILLATION ATRIAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	6 (<1)	1 (<1)	3 (1)	0 (0)	0 (0)
AV BLOCK	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	4 (1)	0 (0)	0 (0)	3 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)
BUNDLE BRANCH BLOCK	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
HEART BLOCK	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	3 (1)	1 (<1)	0 (0)
TACHYCARDIA SUPRAVENTRICULAR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
TACHYCARDIA VENTRICULAR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
ARRHYTHMIA ATRIAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
CARDIAC ARREST	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)
FIBRILLATION CARDIAC	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin				Other			
			Controlled		Uncon- trolled		Controlled		Uncon- trolled					
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Long-term Pbo (n=43)	Short-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=153)	Long-term Pbo (n=50)	Short-term Pram (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Long-term Pbo (n=206)	Short-term Pram (n=100)	Long-term Pbo (n=100)
LIVER AND BILIARY	5 (1)	2 (1)	0 (0)	1 (2)	11 (1)	10 (2)	11 (1)	0 (0)	0 (0)	20 (2)	7 (2)	8 (2)	2 (1)	0 (0)
HEPATIC FUNCTION ABNORMAL	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	2 (<1)	3 (<1)	0 (0)	0 (0)	6 (<1)	2 (<1)	4 (1)	0 (0)	0 (0)
CHOLELITHIASIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	3 (1)	1 (<1)	0 (0)	0 (0)	6 (<1)	3 (1)	4 (1)	0 (0)	0 (0)
SGPT INCREASED	1 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	3 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
HEPATOMEGALY	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	2 (<1)	1 (<1)	1 (<1)	1 (<1)	0 (0)
SGOT INCREASED	1 (<1)	1 (<1)	0 (0)	0 (0)	2 (<1)	1 (<1)	2 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
CHOLECYSTITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0 (0)
BILIRUBINAEMIA	3 (<1)	1 (<1)	0 (0)	1 (2)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LIVER FATTY	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
HEPATIC ENZYMES INCREASED	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
HEPATITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
JAUNDICE	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
GAMMA-GT INCREASED	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
HEPATITIS VIRAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BILIARY PAIN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
HEPATIC CIRRHOSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
HEPATIC PAIN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
METABOLIC & NUTRITIONAL	208 (26)	67 (19)	159 (92)	40 (93)	397 (34)	144 (27)	204 (27)	9 (6)	4 (8)	424 (33)	141 (34)	171 (50)	29 (14)	21 (21)
HYPOGLYCAEMIA	176 (22)	53 (15)	158 (92)	40 (93)	323 (27)	101 (19)	139 (18)	6 (4)	4 (8)	355 (28)	115 (27)	163 (48)	27 (13)	21 (21)
HYPERGLYCAEMIA	12 (1)	4 (1)	2 (1)	0 (0)	15 (1)	4 (1)	19 (3)	0 (0)	0 (0)	12 (1)	6 (1)	2 (1)	2 (1)	3 (3)
WEIGHT DECREASE	3 (<1)	0 (0)	0 (0)	0 (0)	22 (2)	4 (1)	15 (2)	0 (0)	0 (0)	9 (1)	2 (<1)	3 (1)	0 (0)	0 (0)
KETOSIS	0 (0)	0 (0)	1 (1)	0 (0)	12 (1)	9 (2)	22 (3)	0 (0)	0 (0)	1 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
OBESITY	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	8 (1)	13 (2)	0 (0)	0 (0)	5 (<1)	1 (<1)	2 (1)	0 (0)	0 (0)
POLYDIPSIA	1 (<1)	0 (0)	0 (0)	0 (0)	9 (1)	5 (1)	0 (0)	0 (0)	0 (0)	9 (1)	2 (<1)	1 (<1)	0 (0)	0 (0)
HYPERLIPAEMIA	0 (0)	0 (0)	0 (0)	0 (0)	4 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)	10 (1)	7 (2)	4 (1)	0 (0)	0 (0)
THIRST	0 (0)	0 (0)	0 (0)	1 (2)	13 (1)	6 (1)	0 (0)	0 (0)	0 (0)	5 (<1)	2 (<1)	0 (0)	1 (<1)	0 (0)
HYPOCHOLESTEROLAEMIA	17 (2)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DEHYDRATION	0 (0)	0 (0)	0 (0)	0 (0)	9 (1)	7 (1)	5 (1)	0 (0)	0 (0)	1 (<1)	4 (1)	1 (<1)	0 (0)	0 (0)
HYPERCHOLESTEROLAEMIA	0 (0)	0 (0)	1 (1)	0 (0)	6 (1)	3 (1)	0 (0)	0 (0)	0 (0)	8 (1)	2 (<1)	1 (<1)	0 (0)	0 (0)
HYPOKALAEMIA	1 (<1)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	9 (1)	2 (<1)	2 (1)	0 (0)	0 (0)
HYPOCALCAEMIA	10 (1)	6 (2)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	3 (2)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
HYPOPROTEINAEMIA	15 (2)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ACIDOSIS	12 (1)	5 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CREATINE PHOSPHOKINASE INCREASED	6 (1)	3 (1)	0 (0)	0 (0)	2 (<1)	1 (<1)	3 (<1)	0 (0)	0 (0)	2 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
OEDEMA GENERALISED	0 (0)	0 (0)	1 (1)	0 (0)	4 (<1)	2 (<1)	2 (<1)	0 (0)	0 (0)	6 (<1)	3 (1)	0 (0)	0 (0)	0 (0)
WEIGHT INCREASE	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	4 (1)	2 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
HYPERTRIGLYCERIDAEMIA	2 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	2 (1)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin						Other	
			Controlled		Uncon- trolled		Controlled		Uncon- trolled					
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Long-term Pbo (n=43)	Short-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=153)	Long-term Pbo (n=50)	Short-term Pram (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Long-term Pbo (n=206)	Short-term Pram (n=100)	Long-term Pbo (n=100)
HYPERURICAEMIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
GOUT	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
HYPERKALAEMIA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	2 (<1)	0 (0)	0 (0)	3 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
HYPERPHOSPHATAEMIA	4 (1)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
PHOSPHATASE ALKALINE INCREASED	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
BUN INCREASED	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
HYPONATRAEMIA	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
NPN INCREASED	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
DIABETES MELLITUS AGGRAVATED	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LIPODYSTROPHY	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HYPERCALCAEMIA	1 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HYPOPHOSPHATAEMIA	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
OEDEMA PERIORBITAL	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
XEROPHTHALMIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
COMA DIABETIC	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DIABETES MELLITUS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
GLYCOSURIA	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HYPERCHLORAEMIA	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HYPOCHLORAEMIA	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LACTOSE INTOLERANCE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
VITAMIN D DEFICIENCY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
GLUCOSE TOLERANCE ABNORMAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HYPOGLYCEMIA	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LIPID METABOLISM DISORDER NOS	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MUSCULO-SKELETAL	13 (2)	0 (0)	4 (2)	2 (5)	158 (13)	83 (15)	130 (17)	8 (5)	2 (4)	244 (19)	88 (21)	76 (22)	4 (2)	1 (1)
ARTHRALGIA	6 (1)	0 (0)	0 (0)	0 (0)	71 (6)	27 (5)	37 (5)	2 (1)	0 (0)	100 (8)	37 (9)	29 (8)	2 (1)	0 (0)
MYALGIA	4 (1)	0 (0)	3 (2)	2 (5)	31 (3)	12 (2)	33 (4)	2 (1)	0 (0)	33 (3)	11 (3)	14 (4)	1 (<1)	0 (0)
ARTHRITIS	0 (0)	0 (0)	0 (0)	0 (0)	10 (1)	4 (1)	9 (1)	0 (0)	1 (2)	50 (4)	17 (4)	16 (5)	0 (0)	0 (0)
ARTHROPATHY	1 (<1)	0 (0)	1 (1)	0 (0)	20 (2)	18 (3)	23 (3)	1 (1)	0 (0)	28 (2)	12 (3)	10 (3)	1 (<1)	0 (0)
TENDON DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	13 (1)	9 (2)	10 (1)	0 (0)	1 (2)	16 (1)	6 (1)	8 (2)	0 (0)	0 (0)
BONE DISORDER	1 (<1)	0 (0)	0 (0)	0 (0)	7 (1)	2 (<1)	10 (1)	0 (0)	0 (0)	18 (1)	7 (2)	2 (1)	0 (0)	0 (0)
ARTHRITIS AGGRAVATED	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	2 (<1)	0 (0)	0 (0)	20 (2)	2 (<1)	2 (1)	0 (0)	0 (0)
BURSITIS	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	8 (1)	3 (<1)	1 (1)	0 (0)	7 (1)	3 (1)	3 (1)	0 (0)	0 (0)
MUSCLE WEAKNESS	1 (<1)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	6 (1)	0 (0)	0 (0)	7 (1)	3 (1)	2 (1)	0 (0)	0 (0)
ARTHROSIS	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	3 (1)	8 (1)	0 (0)	0 (0)	6 (<1)	2 (<1)	2 (1)	0 (0)	1 (1)
SKELETAL PAIN	0 (0)	0 (0)	0 (0)	0 (0)	4 (<1)	4 (1)	4 (1)	1 (1)	0 (0)	5 (<1)	6 (1)	2 (1)	0 (0)	0 (0)
FASCITIS PLANTAR	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	3 (<1)	0 (0)	0 (0)	2 (<1)	3 (1)	4 (1)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin						Other	
	Pram (n=805)	Pbo (n=353)	Controlled		Uncon- trolled (n=758)	Controlled		Pbo (n=50)	Uncon- trolled (n=1273)		Pbo (n=420)	Pram (n=206)	Pbo (n=100)	
			Short-term (n=172)	Long-term (n=43)		Short-term (n=1179)	Long-term (n=538)		Short-term (n=153)	Long-term (n=342)				
MYOPATHY	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	4 (1)	0 (0)	0 (0)	5 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
OSTEOMYELITIS	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	2 (<1)	4 (1)	0 (0)	0 (0)
DUPUYTREN'S CONTRACTURE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (1)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
OSTEOPOROSIS	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	3 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
SYNOVITIS	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	2 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
COSTOCHONDRITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	1 (1)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
TENOSYNOVITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)
POLYMYALGIA RHEUMATICA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	2 (1)	0 (0)	0 (0)
FASCIITIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
MUSCLE ATROPHY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)
CARTILAGE DAMAGE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
FASCIITIS NECROTISING	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MUSCLE HYPERTROPHY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MYOSITIS	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
SPONDYLITIS ANKYLOSING	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ISCHIAL NEURALGIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MYO ENDO PERICARDIAL & VALVE	0 (0)	0 (0)	0 (0)	0 (0)	13 (1)	3 (1)	11 (1)	1 (1)	0 (0)	60 (5)	25 (6)	16 (5)	2 (1)	0 (0)
ANGINA PECTORIS	0 (0)	0 (0)	0 (0)	0 (0)	8 (1)	0 (0)	3 (<1)	0 (0)	0 (0)	24 (2)	8 (2)	9 (3)	1 (<1)	0 (0)
CORONARY ARTERY DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	3 (<1)	0 (0)	0 (0)	26 (2)	11 (3)	7 (2)	0 (0)	0 (0)
MYOCARDIAL INFARCTION	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	2 (<1)	5 (1)	1 (1)	0 (0)	19 (1)	6 (1)	3 (1)	1 (<1)	0 (0)
MYOCARDIAL ISCHAEMIA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
CARDIOMYOPATHY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (1)	0 (0)	0 (0)
THROMBOSIS CORONARY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
MITRAL INSUFFICIENCY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
MYOCARDIAL RUPTURE (POST INFARCT)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
PERICARDITIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
NEOPLASM	0 (0)	0 (0)	0 (0)	0 (0)	25 (2)	19 (4)	21 (3)	1 (1)	1 (2)	33 (3)	11 (3)	15 (4)	0 (0)	0 (0)
NEOPLASM NOS	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	3 (1)	7 (1)	0 (0)	0 (0)	6 (<1)	2 (<1)	3 (1)	0 (0)	0 (0)
BREAST NEOPLASM FEMALE	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	4 (1)	2 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)	4 (1)	0 (0)	0 (0)
BREAST NEOPLASM BENIGN FEMALE	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)	5 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
BASAL CELL CARCINOMA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	3 (1)	1 (<1)	1 (1)	0 (0)	4 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
OVARIAN CYST	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	2 (<1)	2 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
LIPOMA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
BREAST NEOPLASM MALIGNANT FEMALE	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
CARCINOMA SQUAMOUS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
UTERINE FIBROID	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin						Other	
			Controlled		Uncon- trolled		Controlled		Uncon- trolled					
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Long-term Pbo (n=43)	Short-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=153)	Long-term Pbo (n=50)	Short-term Pram (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Long-term Pbo (n=206)	Short-term Pram (n=206)	Long-term Pbo (n=100)
BREAST FIBROADENOSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
CARCINOMA	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	1 (<1)	0 (0)	0 (0)
SKIN NEOPLASM MALIGNANT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (2)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
BREAST NEOPLASM MALE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
CERVICAL SMEAR TEST POSITIVE	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CERVIX CARCINOMA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
COLON CARCINOMA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
LEUKAEMIA LYMPHOCTIC	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
NEUROMA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
POLYCYTHAEMIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
THYROID NEOPLASM MALIGNANT	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
UTERINE CARCINOMA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)
ADENOCARCINOMA NOS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
BRAIN NEOPLASM BENIGN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
CERVICAL UTERINE POLYP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PANCREAS CYST	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
RENAL CARCINOMA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SKIN HYPERTROPHY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
UTERINE NEOPLASM	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BLADDER CARCINOMA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
GASTRIC CARCINOMA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
LYMPHOMA MALIGNANT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TERATOMA BENIGN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
THROMBOCYTHAEMIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
VAGINAL NEOPLASM BENIGN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
PLATELET, BLEEDING & CLOTTING	4 (1)	0 (0)	6 (3)	1 (2)	57 (5)	25 (5)	29 (4)	2 (1)	2 (4)	70 (6)	27 (6)	16 (5)	4 (2)	0 (0)
PURPURA	4 (1)	0 (0)	4 (2)	0 (0)	40 (3)	21 (4)	22 (3)	2 (1)	2 (4)	48 (4)	15 (4)	11 (3)	3 (1)	0 (0)
HAEMATOMA	0 (0)	0 (0)	1 (1)	1 (2)	8 (1)	1 (<1)	2 (<1)	0 (0)	0 (0)	5 (<1)	3 (1)	1 (<1)	0 (0)	0 (0)
EPISTAXIS	0 (0)	0 (0)	1 (1)	0 (0)	4 (<1)	2 (<1)	2 (<1)	0 (0)	0 (0)	7 (1)	6 (1)	1 (<1)	1 (<1)	0 (0)
VITREOUS HAEMORRHAGE	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	6 (<1)	4 (1)	3 (1)	0 (0)	0 (0)
HAEMORRHAGE NOS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
EMBOLISM PULMONARY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
GINGIVAL BLEEDING	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
THROMBOCYTOPENIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
COAGULATION DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
HAEMOPERITONEUM	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Type 1						Type 2 Using Insulin						Other	
	Clinical Pharmacology		Controlled		Uncon- trolled	Uncon- trolled	Controlled		Uncon- trolled	Uncon- trolled	Uncon- trolled	Uncon- trolled	Uncon- trolled	Uncon- trolled
	Pram (n=805)	Pbo (n=353)	Short-term	Long-term			Short-term	Long-term						
POISON SPECIFIC TERMS	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	3 (1)	0 (0)	0 (0)	0 (0)	6 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
STING	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	4 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
CHEMICAL BURN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
FLASHBACKS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PSYCHIATRIC	39 (5)	11 (3)	4 (2)	0 (0)	122 (10)	64 (12)	99 (13)	3 (2)	0 (0)	173 (14)	36 (9)	37 (11)	2 (1)	0 (0)
ANXIETY	6 (1)	2 (1)	0 (0)	0 (0)	32 (3)	20 (4)	34 (4)	0 (0)	0 (0)	53 (4)	9 (2)	12 (4)	0 (0)	0 (0)
DEPRESSION	1 (<1)	0 (0)	0 (0)	0 (0)	34 (3)	15 (3)	36 (5)	1 (1)	0 (0)	48 (4)	12 (3)	11 (3)	1 (<1)	0 (0)
SOMNOLENCE	23 (3)	4 (1)	2 (1)	0 (0)	24 (2)	2 (<1)	13 (2)	1 (1)	0 (0)	23 (2)	3 (1)	2 (1)	0 (0)	0 (0)
INSOMNIA	0 (0)	0 (0)	0 (0)	0 (0)	22 (2)	15 (3)	15 (2)	0 (0)	0 (0)	39 (3)	9 (2)	7 (2)	1 (<1)	0 (0)
NERVOUSNESS	1 (<1)	1 (<1)	1 (1)	0 (0)	9 (1)	8 (1)	2 (<1)	0 (0)	0 (0)	10 (1)	0 (0)	2 (1)	0 (0)	0 (0)
IMPOTENCE	1 (<1)	0 (0)	0 (0)	0 (0)	3 (<1)	4 (1)	3 (<1)	0 (0)	0 (0)	12 (1)	3 (1)	4 (1)	0 (0)	0 (0)
CONFUSION	6 (1)	1 (<1)	0 (0)	0 (0)	2 (<1)	2 (<1)	2 (<1)	1 (1)	0 (0)	7 (1)	1 (<1)	1 (<1)	0 (0)	0 (0)
LIBIDO DECREASED	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	2 (<1)	0 (0)	0 (0)	7 (1)	0 (0)	1 (<1)	0 (0)	0 (0)
AGITATION	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	2 (<1)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
AMNESIA	1 (<1)	1 (<1)	0 (0)	0 (0)	5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)
DEPERSONALIZATION	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
EMOTIONAL LABILITY	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
AGGRESSIVE REACTION	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
THINKING ABNORMAL	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CONCENTRATION IMPAIRED	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
NEUROSIS	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
PARONIRIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PERSONALITY DISORDER	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PSYCHOSIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SUICIDE ATTEMPT	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
APATHY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
DREAMING ABNORMAL	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
EUPHORIA	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HALLUCINATION	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
LIBIDO INCREASED	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SNORING	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
SOMNAMBULISM	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
RED BLOOD CELL	21 (3)	7 (2)	0 (0)	0 (0)	8 (1)	6 (1)	12 (2)	0 (0)	0 (0)	19 (1)	9 (2)	2 (1)	1 (<1)	0 (0)
ANAEMIA	16 (2)	4 (1)	0 (0)	0 (0)	8 (1)	6 (1)	11 (1)	0 (0)	0 (0)	17 (1)	8 (2)	2 (1)	1 (<1)	0 (0)
ANAEMIA MACROCYTIC	10 (1)	5 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HYPERHAEMOGLOBINAEMIA	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin				Other		
	Pram (n=805)	Pbo (n=353)	Controlled		Uncon- trolled (n=758)	Controlled		Uncon- trolled (n=153)	Controlled		Uncon- trolled (n=342)	Pram (n=206)	Pbo (n=100)
			Short-term (n=172)	Long-term (n=43)		Short-term (n=50)	Long-term (n=1273)		Long-term (n=420)				
ERYTHROCYTES ABNORMAL	2 (<1)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SPLEEN DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
REPRODUCTIVE, FEMALE													
VAGINITIS	1 (<1)	0 (0)	5 (3)	0 (0)	43 (4)	23 (4)	39 (5)	1 (1)	0 (0)	30 (2)	9 (2)	6 (2)	0 (0)
DYSMENORRHOEA	0 (0)	0 (0)	0 (0)	0 (0)	11 (1)	4 (1)	12 (2)	1 (1)	0 (0)	5 (<1)	4 (1)	2 (1)	0 (0)
MENSTRUAL DISORDER	1 (<1)	0 (0)	5 (3)	0 (0)	10 (1)	8 (1)	8 (1)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)
MENORRHAGIA	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	5 (1)	6 (1)	0 (0)	0 (0)	4 (<1)	1 (<1)	3 (1)	0 (0)
LEUKORRHOEA	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	6 (1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)
UTERINE HAEMORRHAGE	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	4 (1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)
POST-MENOPAUSAL BLEEDING	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	5 (<1)	1 (<1)	0 (0)	0 (0)
MASTITIS	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
MENOPAUSAL SYMPTOMS	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	2 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)
ENDOMETRIOSIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
VAGINAL DISCOMFORT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)
VAGINAL HAEMORRHAGE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	1 (<1)	0 (0)
CERVICITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)
PREGNANCY UNINTENDED	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AMENORRHOEA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)
CERVICAL DYSPLASIA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
ENDOMETRIAL DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
VAGINITIS ATROPHIC	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)
BREAST ATROPHY	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BREAST ENGORGEMENT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BREAST ENLARGEMENT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BREAST PAIN FEMALE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
ENDOMETRIAL HYPERPLASIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
INTERMENSTRUAL BLEEDING	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
OVARIAN DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PREMENSTRUAL TENSION	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
UTERINE DISORDER NOS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
UTERINE INFLAMMATION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
UTEROVAGINAL PROLAPSE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
VULVA DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LACTATION NONPUERPERAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
REPRODUCTIVE, MALE													
PROSTATIC DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	6 (1)	5 (1)	7 (1)	1 (1)	0 (0)	20 (2)	5 (1)	5 (1)	1 (<1)
	0 (0)	0 (0)	0 (0)	0 (0)	4 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	15 (1)	3 (1)	3 (1)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin						Other	
			Controlled		Uncon- trolled		Controlled		Uncon- trolled					
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Long-term Pbo (n=43)	Short-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=153)	Long-term Pbo (n=50)	Short-term Pram (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Long-term Pbo (n=100)	Other Pram (n=206)	Other Pbo (n=100)
TESTIS DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	3 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
HERNIA INGUINAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	3 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)
PENIS DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BALANOPOSTHITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
EPIDIDYMITIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)
ORCHITIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
EJACULATION DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SEMEN ABNORMAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
TESTICULAR PAIN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
RESISTANCE MECHANISM	6 (1)	0 (0)	3 (2)	2 (5)	160 (14)	80 (15)	114 (15)	7 (5)	0 (0)	180 (14)	55 (13)	65 (19)	7 (3)	0 (0)
INFECTION	2 (<1)	0 (0)	0 (0)	1 (2)	51 (4)	33 (6)	44 (6)	1 (1)	0 (0)	91 (7)	24 (6)	25 (7)	2 (1)	0 (0)
ABSCESS	1 (<1)	0 (0)	0 (0)	0 (0)	30 (3)	13 (2)	17 (2)	0 (0)	0 (0)	27 (2)	10 (2)	7 (2)	1 (<1)	0 (0)
INFECTION VIRAL	0 (0)	0 (0)	1 (1)	0 (0)	26 (2)	13 (2)	22 (3)	1 (1)	0 (0)	17 (1)	2 (<1)	5 (1)	3 (1)	0 (0)
MONILIASIS GENITAL	0 (0)	0 (0)	0 (0)	0 (0)	18 (2)	10 (2)	11 (1)	2 (1)	0 (0)	9 (1)	4 (1)	2 (1)	1 (<1)	0 (0)
OTITIS MEDIA	1 (<1)	0 (0)	1 (1)	0 (0)	11 (1)	3 (1)	5 (1)	0 (0)	0 (0)	14 (1)	3 (1)	9 (3)	0 (0)	0 (0)
MONILIASIS	1 (<1)	0 (0)	0 (0)	0 (0)	14 (1)	5 (1)	7 (1)	0 (0)	0 (0)	15 (1)	8 (2)	3 (1)	0 (0)	0 (0)
INFECTION BACTERIAL	0 (0)	0 (0)	0 (0)	1 (2)	9 (1)	5 (1)	8 (1)	1 (1)	0 (0)	11 (1)	3 (1)	4 (1)	0 (0)	0 (0)
HERPES SIMPLEX	1 (<1)	0 (0)	0 (0)	0 (0)	13 (1)	5 (1)	3 (<1)	1 (1)	0 (0)	6 (<1)	3 (1)	5 (1)	0 (0)	0 (0)
HERPES ZOSTER	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	3 (<1)	0 (0)	0 (0)	7 (1)	2 (<1)	6 (2)	0 (0)	0 (0)
INFECTION FUNGAL	0 (0)	0 (0)	1 (1)	0 (0)	5 (<1)	1 (<1)	5 (1)	0 (0)	0 (0)	3 (<1)	3 (1)	4 (1)	0 (0)	0 (0)
INFECTION PARASITIC	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	4 (1)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
SEPSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	0 (0)	0 (0)	1 (<1)	2 (<1)	3 (1)	0 (0)	0 (0)
SJOGREN'S SYNDROME	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
HEALING IMPAIRED	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
WOUND DEHISCENCE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
RESPIRATORY	37 (5)	15 (4)	38 (22)	9 (21)	498 (42)	248 (46)	333 (44)	25 (16)	4 (8)	527 (41)	183 (44)	170 (50)	15 (7)	6 (6)
UPPER RESP TRACT INFECTION	17 (2)	7 (2)	16 (9)	2 (5)	316 (27)	158 (29)	226 (30)	13 (9)	2 (4)	310 (24)	122 (29)	102 (30)	12 (6)	5 (5)
SINUSITIS	7 (1)	1 (<1)	7 (4)	2 (5)	103 (9)	59 (11)	82 (11)	2 (1)	0 (0)	107 (8)	35 (8)	36 (11)	1 (<1)	0 (0)
PHARYNGITIS	5 (1)	3 (1)	13 (8)	1 (2)	89 (8)	48 (9)	48 (6)	2 (1)	1 (2)	76 (6)	19 (5)	11 (3)	2 (1)	1 (1)
COUGHING	2 (<1)	2 (1)	3 (2)	1 (2)	48 (4)	25 (5)	26 (3)	2 (1)	0 (0)	71 (6)	25 (6)	14 (4)	2 (1)	0 (0)
BRONCHITIS	0 (0)	0 (0)	0 (0)	0 (0)	44 (4)	22 (4)	37 (5)	1 (1)	0 (0)	59 (5)	20 (5)	24 (7)	0 (0)	0 (0)
RHINITIS	7 (1)	1 (<1)	4 (2)	3 (7)	54 (5)	28 (5)	28 (4)	4 (3)	1 (2)	50 (4)	14 (3)	14 (4)	0 (0)	0 (0)
DYSPNOEA	3 (<1)	0 (0)	0 (0)	0 (0)	15 (1)	9 (2)	4 (1)	0 (0)	0 (0)	29 (2)	10 (2)	7 (2)	0 (0)	0 (0)
PNEUMONIA	1 (<1)	0 (0)	0 (0)	0 (0)	12 (1)	8 (1)	8 (1)	1 (1)	0 (0)	23 (2)	11 (3)	4 (1)	0 (0)	0 (0)
ASTHMA	0 (0)	1 (<1)	0 (0)	0 (0)	8 (1)	3 (1)	7 (1)	0 (0)	0 (0)	14 (1)	2 (<1)	4 (1)	0 (0)	0 (0)
BRONCHOSPASM	0 (0)	0 (0)	0 (0)	0 (0)	6 (1)	1 (<1)	3 (<1)	2 (1)	0 (0)	13 (1)	5 (1)	2 (1)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin				Other			
			Controlled		Uncon- trolled		Controlled		Uncon- trolled					
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Long-term Pbo (n=43)	Short-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=153)	Long-term Pbo (n=50)	Short-term Pram (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Long-term Pbo (n=206)	Short-term Pram (n=100)	Long-term Pbo (n=100)
LARYNGITIS	1(<1)	0(0)	0(0)	0(0)	6(1)	6(1)	4(1)	0(0)	0(0)	8(1)	2(<1)	3(1)	0(0)	0(0)
PULMONARY CONGESTION	0(0)	0(0)	0(0)	0(0)	2(<1)	4(1)	1(<1)	0(0)	0(0)	10(1)	3(1)	1(<1)	0(0)	0(0)
RESPIRATORY DISORDER	0(0)	1(<1)	1(1)	0(0)	2(<1)	1(<1)	3(<1)	1(1)	0(0)	1(<1)	0(0)	1(<1)	0(0)	0(0)
SLEEP APNOEA	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	1(<1)	0(0)	0(0)	5(<1)	0(0)	2(1)	0(0)	0(0)
ATELECTASIS	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	1(<1)	0(0)	0(0)	3(<1)	0(0)	1(<1)	0(0)	0(0)
PLEURAL EFFUSION	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	2(<1)	0(0)	0(0)	2(<1)	1(<1)	1(<1)	0(0)	0(0)
PULMONARY OEDEMA	0(0)	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	0(0)	0(0)	3(<1)	2(<1)	3(1)	0(0)	0(0)
CHRONIC OBSTRUCT AIRWAYS DISEASE	0(0)	0(0)	0(0)	0(0)	1(<1)	1(<1)	0(0)	0(0)	0(0)	1(<1)	0(0)	2(1)	0(0)	0(0)
PNEUMONITIS	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(<1)	2(<1)	2(1)	0(0)	0(0)
PLEURISY	0(0)	0(0)	0(0)	0(0)	1(<1)	1(<1)	0(0)	0(0)	0(0)	2(<1)	0(0)	0(0)	0(0)	0(0)
HYPOXIA	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(<1)	0(0)	0(0)	0(0)	0(0)
PULMONARY INFILTRATION	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(<1)	1(<1)	1(<1)	0(0)	0(0)
SPUTUM INCREASED	0(0)	0(0)	0(0)	0(0)	0(0)	2(<1)	2(<1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
TRACHEITIS	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	0(0)	0(0)	0(0)	1(<1)	1(<1)	0(0)	0(0)	0(0)
BREATH SOUNDS DECREASED	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	0(0)	0(0)	0(0)
EMPHYSEMA	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(<1)	1(<1)	0(0)	0(0)	0(0)
HYPERPNOEA	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	0(0)	0(0)	0(0)
HYPERVENTILATION	1(<1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
PULMONARY GRANULOMA	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
RESPIRATORY DEPRESSION	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	0(0)	0(0)	0(0)
RESPIRATORY INSUFFICIENCY	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	0(0)	0(0)	1(<1)	0(0)	0(0)	0(0)
SECONDARY TERMS	3(<1)	5(1)	2(1)	1(2)	222(19)	90(17)	112(15)	6(4)	2(4)	221(17)	73(17)	78(23)	1(<1)	1(1)
INFLECTED INJURY	1(<1)	2(1)	1(1)	1(2)	127(11)	55(10)	70(9)	4(3)	1(2)	136(11)	52(12)	53(16)	1(<1)	1(1)
ABRASION NOS	1(<1)	3(1)	0(0)	0(0)	27(2)	11(2)	11(1)	1(1)	0(0)	20(2)	5(1)	7(2)	0(0)	0(0)
POST-OPERATIVE PAIN	0(0)	0(0)	0(0)	0(0)	18(2)	8(1)	6(1)	0(0)	0(0)	23(2)	8(2)	6(2)	0(0)	0(0)
FALL	1(<1)	0(0)	0(0)	0(0)	8(1)	1(<1)	7(1)	0(0)	0(0)	17(1)	5(1)	6(2)	0(0)	0(0)
CYST NOS	0(0)	0(0)	0(0)	0(0)	11(1)	5(1)	10(1)	0(0)	1(2)	10(1)	4(1)	5(1)	0(0)	0(0)
BURN	0(0)	0(0)	0(0)	0(0)	18(2)	6(1)	4(1)	1(1)	0(0)	8(1)	3(1)	2(1)	0(0)	0(0)
FOOT CALLUS	0(0)	0(0)	0(0)	0(0)	16(1)	7(1)	2(<1)	0(0)	0(0)	11(1)	2(<1)	2(1)	0(0)	0(0)
BITE	0(0)	0(0)	0(0)	0(0)	10(1)	6(1)	5(1)	0(0)	0(0)	12(1)	3(1)	3(1)	0(0)	0(0)
FOOD POISONING	0(0)	0(0)	1(1)	0(0)	7(1)	2(<1)	5(1)	0(0)	0(0)	8(1)	1(<1)	1(<1)	0(0)	0(0)
SURGICAL INTERVENTION	0(0)	0(0)	0(0)	0(0)	7(1)	4(1)	2(<1)	0(0)	0(0)	3(<1)	1(<1)	1(<1)	0(0)	0(0)
HEAT INTOLERANCE	0(0)	0(0)	0(0)	0(0)	3(<1)	0(0)	2(<1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
MEDICATION ERROR	0(0)	0(0)	0(0)	0(0)	0(0)	2(<1)	1(<1)	0(0)	0(0)	1(<1)	1(<1)	1(<1)	0(0)	0(0)
ALCOHOL PROBLEM	0(0)	1(<1)	0(0)	0(0)	2(<1)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
NASAL SEPTUM DEVIATION	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(1)	0(0)	0(0)
VARICELLA	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	0(0)	0(0)	0(0)	1(<1)	0(0)	0(0)	0(0)	0(0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Type 1						Type 2 Using Insulin						Other	
	Clinical Pharmacology		Controlled Short-term		Controlled Long-term		Uncontrolled	Controlled Short-term		Controlled Long-term		Uncontrolled	Pram	Pbo
	Pram (n=805)	Pbo (n=353)	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)	Pram (n=206)	Pbo (n=100)
CARBOHYDRATE CRAVING	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
JOINT DISLOCATION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
POST-OPERATIVE HAEMORRHAGE	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PROCEDURAL SITE REACTION	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ROUTINE DIAGNOSTIC TEST	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
SCOLIOSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BREAST COSMETIC SURGERY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
FAMILY STRESS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HEAT STROKE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
RENAL ARTERY STENOSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
SKIN AND APPENDAGES	30 (4)	9 (3)	5 (3)	1 (2)	191 (16)	115 (21)	158 (21)	7 (5)	2 (4)	307 (24)	99 (24)	92 (27)	5 (2)	4 (4)
SKIN DISORDER	2 (<1)	1 (<1)	0 (0)	0 (0)	33 (3)	15 (3)	28 (4)	1 (1)	0 (0)	54 (4)	25 (6)	13 (4)	1 (<1)	0 (0)
RASH	2 (<1)	1 (<1)	1 (1)	0 (0)	28 (2)	24 (4)	24 (3)	4 (3)	1 (2)	41 (3)	15 (4)	4 (1)	1 (<1)	2 (2)
DERMATITIS FUNGAL	0 (0)	0 (0)	0 (0)	0 (0)	26 (2)	16 (3)	23 (3)	0 (0)	0 (0)	33 (3)	7 (2)	7 (2)	0 (0)	0 (0)
SKIN ULCERATION	0 (0)	0 (0)	0 (0)	0 (0)	13 (1)	5 (1)	7 (1)	0 (0)	0 (0)	34 (3)	7 (2)	13 (4)	0 (0)	0 (0)
SKIN DRY	1 (<1)	0 (0)	0 (0)	0 (0)	14 (1)	12 (2)	11 (1)	0 (0)	0 (0)	22 (2)	4 (1)	9 (3)	1 (<1)	1 (1)
CELLULITIS	0 (0)	0 (0)	0 (0)	0 (0)	10 (1)	4 (1)	4 (1)	0 (0)	0 (0)	33 (3)	5 (1)	10 (3)	0 (0)	0 (0)
ONYCHOMYCOSIS	1 (<1)	0 (0)	0 (0)	0 (0)	10 (1)	13 (2)	8 (1)	0 (0)	0 (0)	19 (1)	11 (3)	11 (3)	1 (<1)	0 (0)
BULLOUS ERUPTION	1 (<1)	0 (0)	0 (0)	0 (0)	10 (1)	7 (1)	9 (1)	0 (0)	0 (0)	22 (2)	7 (2)	7 (2)	0 (0)	0 (0)
NAIL DISORDER	0 (0)	0 (0)	0 (0)	1 (2)	8 (1)	5 (1)	7 (1)	0 (0)	0 (0)	25 (2)	3 (1)	9 (3)	0 (0)	0 (0)
SWEATING INCREASED	15 (2)	3 (1)	2 (1)	0 (0)	9 (1)	4 (1)	2 (<1)	1 (1)	0 (0)	18 (1)	2 (<1)	2 (1)	0 (0)	1 (1)
PRURITUS	2 (<1)	0 (0)	0 (0)	0 (0)	8 (1)	4 (1)	7 (1)	0 (0)	1 (2)	15 (1)	8 (2)	3 (1)	1 (<1)	0 (0)
RASH ERYTHEMATOUS	4 (1)	0 (0)	0 (0)	0 (0)	9 (1)	7 (1)	8 (1)	0 (0)	0 (0)	12 (1)	4 (1)	3 (1)	0 (0)	0 (0)
URTICARIA	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	1 (<1)	7 (1)	1 (1)	0 (0)	13 (1)	1 (<1)	2 (1)	0 (0)	0 (0)
DERMATITIS	0 (0)	0 (0)	0 (0)	0 (0)	4 (<1)	2 (<1)	5 (1)	0 (0)	0 (0)	11 (1)	2 (<1)	7 (2)	0 (0)	0 (0)
ACNE	1 (<1)	1 (<1)	1 (1)	0 (0)	13 (1)	4 (1)	5 (1)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
FURUNCULOSIS	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	3 (1)	1 (<1)	0 (0)	0 (0)	12 (1)	0 (0)	3 (1)	0 (0)	0 (0)
VERRUCA	0 (0)	0 (0)	0 (0)	0 (0)	12 (1)	3 (1)	4 (1)	0 (0)	0 (0)	2 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)
ECZEMA	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	2 (<1)	5 (1)	0 (0)	0 (0)	6 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)
DERMATITIS CONTACT	0 (0)	1 (<1)	0 (0)	0 (0)	3 (<1)	4 (1)	5 (1)	0 (0)	0 (0)	5 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
HYPERKERATOSIS	0 (0)	0 (0)	0 (0)	0 (0)	4 (<1)	6 (1)	3 (<1)	0 (0)	0 (0)	6 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
NAEVUS	0 (0)	1 (<1)	0 (0)	0 (0)	5 (<1)	2 (<1)	4 (1)	0 (0)	0 (0)	4 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
ALOPECIA	0 (0)	0 (0)	0 (0)	0 (0)	4 (<1)	3 (1)	6 (1)	0 (0)	0 (0)	1 (<1)	3 (1)	0 (0)	0 (0)	0 (0)
PSORIASIS	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	2 (<1)	0 (0)	0 (0)	7 (1)	2 (<1)	1 (<1)	0 (0)	0 (0)
FOLLICULITIS	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	3 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	2 (1)	0 (0)	0 (0)
PARONYCHIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	3 (<1)	0 (0)	0 (0)	5 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
RASH MACULO-PAPULAR	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	2 (<1)	2 (<1)	0 (0)	0 (0)	2 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin				Other			
			Controlled		Uncon- trolled		Controlled		Uncon- trolled					
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Long-term Pbo (n=43)	Short-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=153)	Long-term Pbo (n=50)	Short-term Pram (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Long-term Pbo (n=206)	Other Pbo (n=100)	
PRURITUS GENITAL	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	3 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
SKIN DISCOLOURATION	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
HAIR DISORDER NOS	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	2 (<1)	1 (1)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
NAIL DISCOLOURATION	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	3 (1)	0 (0)	0 (0)
HYPERTRICHOSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PHOTOSENSITIVITY REACTION	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SEBORRHOEA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
SKIN EXFOLIATION	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DERMATITIS LICHENOID	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
EPIDERMAL NECROLYSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
PAPILLOMA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
PILONIDAL CYST	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ROSACEA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SKIN COLD CLAMMY	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
ACANTHOSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ERYTHEMA MULTIFORME	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
HAIR TEXTURE ABNORMAL	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ONYCHOLYSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
PILOERECTOR	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PITYRIASIS ROSEA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PRURITUS ANI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
RASH PURPURIC	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
RASH PUSTULAR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
SKIN ATROPHY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
VITILIGO	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ERYTHEMA NODOSUM	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SKIN ODOR ABNORMAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SPECIAL SENSES OTHER	6 (1)	1 (<1)	1 (1)	0 (0)	7 (1)	1 (<1)	4 (1)	0 (0)	0 (0)	3 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
TASTE PERVERSION	6 (1)	1 (<1)	1 (1)	0 (0)	7 (1)	1 (<1)	4 (1)	0 (0)	0 (0)	3 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
PAROSMIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
URINARY	11 (1)	1 (<1)	2 (1)	1 (2)	102 (9)	46 (9)	67 (9)	5 (3)	0 (0)	128 (10)	43 (10)	39 (11)	0 (0)	0 (0)
URINARY TRACT INFECTION	1 (<1)	1 (<1)	0 (0)	0 (0)	48 (4)	17 (3)	29 (4)	4 (3)	0 (0)	53 (4)	28 (7)	18 (5)	0 (0)	0 (0)
HAEMATURIA	6 (1)	0 (0)	0 (0)	0 (0)	7 (1)	5 (1)	5 (1)	1 (1)	0 (0)	12 (1)	4 (1)	6 (2)	0 (0)	0 (0)
CYSTITIS	0 (0)	0 (0)	0 (0)	0 (0)	11 (1)	5 (1)	9 (1)	0 (0)	0 (0)	11 (1)	1 (<1)	2 (1)	0 (0)	0 (0)
ALBUMINURIA	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	6 (1)	6 (1)	0 (0)	0 (0)	9 (1)	1 (<1)	4 (1)	0 (0)	0 (0)
MICTURITION FREQUENCY	1 (<1)	0 (0)	1 (1)	0 (0)	5 (<1)	2 (<1)	6 (1)	0 (0)	0 (0)	9 (1)	2 (<1)	0 (0)	0 (0)	0 (0)

Number (%) of Subjects with Treatment-Emergent Adverse Events (Completed Studies) - continued

Body System Preferred Term	Clinical Pharmacology		Type 1				Type 2 Using Insulin				Other			
			Controlled		Uncon- trolled		Controlled		Uncon- trolled					
	Pram (n=805)	Pbo (n=353)	Short-term Pram (n=172)	Long-term Pbo (n=43)	Short-term Pram (n=1179)	Long-term Pbo (n=538)	Short-term Pram (n=153)	Long-term Pbo (n=50)	Short-term Pram (n=1273)	Long-term Pbo (n=420)	Short-term Pram (n=342)	Long-term Pbo (n=206)	Other Pram (n=100)	
DYSURIA	1 (<1)	1 (<1)	1 (1)	0 (0)	8 (1)	1 (<1)	3 (<1)	0 (0)	0 (0)	5 (<1)	2 (<1)	2 (1)	0 (0)	0 (0)
NOCTURIA	0 (0)	0 (0)	0 (0)	0 (0)	5 (<1)	3 (1)	1 (<1)	0 (0)	0 (0)	11 (1)	2 (<1)	1 (<1)	0 (0)	0 (0)
POLYURIA	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	3 (1)	0 (0)	0 (0)	0 (0)	10 (1)	1 (<1)	4 (1)	0 (0)	0 (0)
RENAL CALCULUS	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	4 (1)	0 (0)	0 (0)	4 (<1)	3 (1)	1 (<1)	0 (0)	0 (0)
NEPHRITIS	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	4 (1)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
RENAL FUNCTION ABNORMAL	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	2 (<1)	0 (0)	0 (0)	4 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
URINARY INCONTINENCE	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	3 (1)	0 (0)	0 (0)
URINE ABNORMAL	2 (<1)	0 (0)	0 (0)	1 (2)	4 (<1)	2 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
NEPHROPATHY TOXIC	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	4 (1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
PYELONEPHRITIS	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	2 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
MICTURITION DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
URINARY RETENTION	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
RENAL PAIN	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
RENAL FAILURE ACUTE	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
URETHRAL DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
NEPHROSIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
URETHRITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BLADDER CALCULUS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
BLADDER DISCOMFORT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
GLOMERULONEPHRITIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
NEPHROCALCINOSIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
OLIGURIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
STRANGURY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
CYSTITIS HAEMORRHAGIC	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
VASCULAR (EXTRACARDIAC)	16 (2)	3 (1)	0 (0)	0 (0)	36 (3)	15 (3)	24 (3)	1 (1)	0 (0)	79 (6)	23 (5)	18 (5)	1 (<1)	0 (0)
VASCULAR DISORDER	1 (<1)	0 (0)	0 (0)	0 (0)	18 (2)	8 (1)	9 (1)	0 (0)	0 (0)	33 (3)	12 (3)	11 (3)	0 (0)	0 (0)
FLUSHING	13 (2)	1 (<1)	0 (0)	0 (0)	7 (1)	1 (<1)	5 (1)	0 (0)	0 (0)	5 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
OCULAR HAEMORRHAGE	1 (<1)	0 (0)	0 (0)	0 (0)	8 (1)	4 (1)	1 (<1)	0 (0)	0 (0)	13 (1)	3 (1)	4 (1)	0 (0)	0 (0)
CEREBROVASCULAR DISORDER	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	12 (1)	2 (<1)	0 (0)	0 (0)	0 (0)
PERIPHERAL ISCHAEMIA	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	5 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
VEIN DISTENDED	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	0 (0)	0 (0)	0 (0)	0 (0)
VEIN VARICOSE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1)	0 (0)	0 (0)	1 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
TRANSIENT ISCHAEMIC ATTACK	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	3 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
CLAUDICATION INTERMITTENT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	2 (<1)	1 (<1)	0 (0)	0 (0)
THROMBOPHLEBITIS	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
ATHEROSCLEROSIS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
PHLEBITIS	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)

Appendix 5 – Part B

**Brief Narrative Summaries for all Patient Deaths During the Pramlintide Clinical
Development Program**

Pramlintide-treated Patients

Subject 137-112-02804 (30 µg pramlintide QID) died as a result of convulsions, coronary artery disorder, and hypoglycemia, which is consistent with the increased risk of cardiovascular disease with diabetes. Coronary artery disorder was considered probably not treatment related whereas convulsions and hypoglycemia were considered possibly treatment related by the investigator.

Subject 137-117-03501 (90 µg pramlintide TID) died from a motor vehicle accident that was considered probably not treatment related by the investigator.

Subject 137-117-07010 (90 µg pramlintide BID) died as a result of suspected alcohol abuse during the study that was considered probably not treatment related by the investigator.

Subject 137-112E-00907 (30 µg pramlintide QID) died as a result of myocardial infarction that was considered probably not related to treatment by the investigator. At the time of his death the subject was receiving 60 µg pramlintide QID. The subject's medical history included hypertension and smoking.

Subject 137-116-2008 (30 µg pramlintide QID) died due to multi-organ failure following an extended, complicated hospitalization for presumed pulmonary embolus. The death was considered probably not treatment related by the investigator.

Subject 137-114-00103 (30 µg pramlintide QID) died due to myocardial infarction. Death occurred two weeks after the subject completed the study. The event was considered by the investigator to be probably not related to study medication.

Subject 137-122-03003 (120 µg pramlintide BID) died on Study Day 363 due to cerebrovascular disorder and respiratory depression, both of which were considered probably not related to study treatment by the investigator.

Subject 137-111-01441 (150 µg pramlintide TID) died due to myocardial rupture (post infarct) which was considered probably not related to study treatment by the investigator.

Subject 137-111-01512 (75 µg pramlintide TID) died due to myocardial infarction, which was considered probably not related by the investigator.

Subject 137-111E-01911 (30 µg pramlintide TID) on placebo in the original study (137-111), died as a result of cardiac arrest after 254 days of open-label pramlintide treatment. The subject had a history of cardiovascular disease and a previous myocardial infarction. The death was considered by the investigator to be probably not related to study drug.

Placebo-treated Patients

Subject 137-112-01917 (placebo) died as a result of cardiac arrest during hospitalization for pneumonia following an elective hernia repair. The pneumonia was felt to be consistent with aspiration pneumonia. The event cardiac arrest was considered probably not treatment related by the investigator

Subject 137-117-03823 (placebo) died of a myocardial infarction that was considered probably not related treatment by the investigator.

Subject 137-111-01510 (placebo) died due to cardiac arrest that was considered probably not related by the investigator.

Subject 137-123-6270 (placebo) was a 70-year-old male with a 15-year history of type 2 diabetes and Parkinson's disease at study entry. The subject died suddenly approximately 189 days after starting double-blind therapy with no cause of death identified. No autopsy was performed and the family requested that no further requests for information be made of them

Subject 137-122-03829 (placebo) died on Study Day 187 due to an acute myocardial infarction that was considered probably not related to study treatment by the investigator.

Subject 137-111-00604 (placebo) died due to cardiac arrhythmia that was considered probably not related by the investigator.

Subject 137-122-03608 (placebo) died on Study Day 119 due to coronary artery disorder that was considered possibly treatment related by the investigator. The subject had a history of peripheral vascular disease and coronary artery disorder at study entry.

No deaths were reported during the conduct of the clinical pharmacology studies. However, information is available about two subjects who died after conclusion of the study. These two subjects are not included among the 17 deaths described above, as they occurred well beyond having received their final dose of study medication.

Study AP93-08 Subject 00424 (placebo) was a 34-year-old male with a 10-year history of type 1 diabetes mellitus. His past medical history and physical examination were recorded as normal at the screening visit. He was randomized to placebo and on the day of his randomization he had a near syncopal episode (time of onset and duration not available). The investigator assessed this as mild and probably not related to the study medication. The subject received study drug for 2 days and on the third day, he was hospitalized for multiple episodes of headache and dizziness that were severe in intensity, after involvement in a motor vehicle accident. Other adverse events reported on this day were numbness of the right side of the head, acute alcohol intoxication, blurry vision, memory loss, abdominal discomfort, and a bump on the right side of his head. He experienced a single episode of unsteady gait of moderate severity and conjunctival congestion of moderate severity. The duration of these adverse events was not specified other than they were resolved on the same day. In fact, all the adverse events mentioned above, (other than the single syncopal episode) were recorded as resolved at study withdrawal and all were assessed by the investigator as not study drug related. It was not recorded whether concomitant medications were given for these adverse events. The motor vehicle accident was given as the reason for the early study withdrawal. Approximately 1½ months after his last dose of study medication, the subject died due to a self-inflicted gunshot wound to the head.

Study 137-120 Subject 1024 (pramlintide and placebo) died approximately 1 month after discontinuation of study medication. The subject was found to be “fit and healthy” at the follow-up visit. A post mortem was performed, and the cause of death was determined to be a myocardial infarction with evidence of ischemic disease, which is consistent with an increased risk of cardiovascular disease with diabetes. Since a role for study medication could not be ruled out, this death was assessed as possibly related to study medication.

APPENDIX 6: PRAMLINTIDE NONCLINICAL TOXICOLOGY

Pramlintide has been tested in a series of toxicity studies in mice, rats and dogs by both SC and IV injections over periods ranging from a single injection (acute) to daily injections for 52 weeks (repeated-dose) to daily injections for 2 years (carcinogenicity). Pramlintide was well tolerated in all species tested.

Pramlintide was evaluated for reproductive toxicity in the rat and the rabbit. Special toxicity tests compared pramlintide made by different manufacturers and determined the potential for pramlintide to induce delayed-type hypersensitivity. Pramlintide was evaluated for genotoxicity potential in a battery of mutagenicity assays.

A lack of acute toxicity was demonstrated in the rat and dog. No mortality occurred that was attributable to pramlintide. The LD₅₀ for rats and dogs, respectively, was shown to be >500 mg/kg (rat) and >2 mg/kg (dog) (SC) and >10 mg/kg (IV) in both species. Clinical signs in the acute studies included vasodilation of the ears, forepaws and hindpaws; diarrhea; decreased activity; and abnormal stance/gait. They usually occurred shortly after dosing and disappeared within 30 minutes to four hours.

In the repeat dose toxicity studies, the main clinical sign observed in mice, rats and dogs was cellulitis and irritation of the subcutaneous injection site. They occurred in both control and treated animals and were attributed to the process of injection rather than to pramlintide per se. Vasculitis and perivasculitis observed in dogs given pramlintide IV suggested a mild irritant effect of pramlintide. Other observations at the injection sites (hemorrhage, myositis, necrosis, cellulitis, fibrosis) were more equally observed in both the vehicle control and pramlintide-treated dogs and were considered related to the volume of vehicle administered and mechanics of dosing. Other clinical signs that appeared in one or more species included vasodilation of the extremities, loose stools, diarrhea, emesis, quivering, abnormal stance and gait, reduced activity, and salivation.

Changes in clinical chemistry in one/more studies included higher erythrocyte counts and hemoglobin and hematocrit values (rats, 2.0 mg/kg), higher serum phosphorus values (rats, 2.0 mg/kg) and lower serum glucose (rats, ≥ 0.2 mg/kg), lactate (rats, 2.0 mg/kg), total protein (rat, ≥ 0.5 mg/kg), total albumin (rats, ≥ 1.2 mg/kg) and serum calcium levels (male rat, ≥ 0.5 mg/kg; female rat, 1.2 mg/kg), and shorter prothrombin times (dog, ≥ 0.5 mg/kg).

Food consumption was less than control in rats (males, 26 weeks, 1.2 mg/kg) and dogs (7 days, 2.0 mg/kg; 26 weeks, ≥ 0.2 mg/kg). Body weight gains were lower than control in rats (males, 26 weeks, ≥ 0.2 mg/kg) and dogs (26 weeks, ≥ 0.5 mg/kg).

At necropsy, irritation/sores occurred at the injection sites of both treated and control animals and were attributed to the injection process.

Mean heart weights were lower than control values in male rats that received 1.2 mg/kg pramlintide for 28 days. However, there were no microscopic changes in the heart. A similar change was not found in other 28-day studies or studies of longer duration in the rat, mouse or dog.

Microscopically, injection site irritation was characterized by cellulitis and/or hemorrhage. Vasculitis and perivasculitis was observed in pramlintide-dosed animals only, indicating a slight local tissue response to pramlintide. Other injection site observations included myositis, necrosis, and fibrosis.

Irritation induced at the injection site was similar for lots of bulk pramlintide manufactured by three different companies. In a special toxicity study a single SC injection of one of four formulations of pramlintide was given to rabbits. There was no significant difference in the irritation induced by the four formulations. In another special toxicity study, pramlintide did not induce a delayed-type hypersensitivity response in the mouse.

The mutagenic and clastogenic potentials of pramlintide were evaluated in six *in vitro* and *in vivo* studies. Pramlintide was not mutagenic, with or without metabolic activation in two bacterial reverse mutation assays and was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes, the AS52/XPRT mammalian cell forward mutation assay or the *in vivo* micronucleus test.

The carcinogenic potential of pramlintide was evaluated in 2-year studies in the rat and the mouse. Pramlintide was not carcinogenic at any dose in either sex of either species.

The reproductive toxicity studies with pramlintide demonstrated the compound had no effect upon the fertility or reproductive performance of the adult rat of either sex. The no effect dose for the neonates was 1.0 mg/kg. Pramlintide was not embryotoxic or teratogenic at doses up to 3 mg/kg in the teratology study in the rat. Pramlintide was not teratogenic or embryotoxic in the rabbit when administered at doses up to 3.0 mg/kg. In the perinatal/postnatal studies in the rat pramlintide had no effect on the physical or neurodevelopment or reproductive performance of the F₁ generation and had no effect on the F₂ fetuses. Pramlintide did not cross the placental barrier in pregnant rats.

In conclusion the toxicology program for pramlintide was adequate and the results support the chronic daily subcutaneous administration of pramlintide in humans.