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ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY  
COMMITTEE

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Thursday, July 26, 2001

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The meeting came to order at 8:00 a.m. in the Versailles Room, Holiday Inn Bethesda, 8120 Wisconsin Ave., Bethesda, MD, Robert A. Kreisberg, M.D., Acting Chair, presiding.

PRESENT:

Robert A. Kreisberg, M.D., Acting Chair  
Marie C. Gelato, M.D., Ph.D., Member  
Deborah Grady, M.D., Ph.D., Member  
Lynne L. Levitsky, M.D., Member  
William V. Tamborlane, M.D., Member  
Allan R. Sampson, Ph.D., Member  
Kathleen Reedy, Executive Secretary  
Jose F. Cara, M.D., Consultant  
Wendy W. McBrair, R.N., M.S., C.H.E.S., Consumer Rep.  
Rebecca W. Killion, Patient Representative  
Robert F. Misbin, M.D., FDA  
Dragos G. Roman, M.D., FDA  
John Jenkins, FDA  
David Hobberman, FDA  
David D. Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products

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A-G-E-N-D-A

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P-R-O-C-E-E-D-I-N-G-S

8:08 a.m.

1  
2  
3 DR. KREISBERG: Good morning. This is the  
4 Endocrinologic and Metabolic Drugs Advisory Committee  
5 to discuss the new drug application Symlin submitted  
6 by Amylin Pharmaceuticals. I'm Bob Kreisberg and I am  
7 the Acting Chair of the meeting for today.

8 I would like to ask that each of the members  
9 of the advisory panel introduce themselves. Let me  
10 tell you that you have to click on the microphone and  
11 talk directly into it. The red light will come on and  
12 when you're done, I would appreciate it if you would  
13 turn it off. Do not speak tangentially into the mic  
14 because it will not record the proceedings accurately.

15 Let me start all the way down on my right.

16 MR. JENKINS: Good morning. I'm John  
17 Jenkins. I'm the Director of the Office of Drug  
18 Evaluation II and the Center for Drug Evaluation  
19 Research.

20 DR. ORLOFF: Good morning. I'm Dr. David  
21 Orloff, Director of the Division of Metabolic and  
22 Endocrine Drug Products, Center for Drug Evaluation

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1 and Research.

2 DR. MISBIN: Robert Misbin, Medical Officer.

3 DR. ROMAN: Dragos Roman, Medical Officer.

4 DR. SAMPSON: Allan Sampson, Professor of  
5 Statistics, University of Pittsburgh.

6 DR. GELATO: Marie Gelato, Professor of  
7 Medicine at SUNY Stonybrook.

8 MS. REEDY: Kathleen Reedy, Executive  
9 Secretary of this committee, Food and Drug  
10 Administration.

11 DR. TAMBORLANE: Bill Tamborlane, Chief of  
12 Pediatric Endocrinology and Director of the Pediatric  
13 Pharmacology Research Unit at Yale.

14 DR. LEVITSKY: Lynne Levitsky, Chief of the  
15 Pediatric Endocrine Unit at Mass General.

16 DR. CARA: I'm Jose Cara, Section Head of  
17 Pediatric~~and~~ Endocrinology and Diabetes at Henry Ford  
18 Health Systems in Detroit.

19 MS. MCBRAIR: Wendy McBrair, Director of the  
20 Arthritis and Osteoporosis Center at Virtual Health.

21 DR. GRADY: Hi. I'm Deborah Grady. I'm a  
22 Professor of Medicine and Epidemiology at the

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1 University of California and San Francisco.

2 DR. KREISBERG: At this point I would like  
3 to introduce Dr. Kathleen Reedy, the Executive  
4 Secretary, who will read the meeting statement.

5 MS. REEDY: For the Endocrinologic and  
6 Metabolic Drugs Advisory Committee on July 26, 2001,  
7 the following announcement addresses the issue of  
8 conflict of interest with regard to this meeting and  
9 is made a part of the record to preclude any the  
10 appearance of such at this meeting.

11 Based on the submitted agenda for the  
12 meeting and all financial interest reported by  
13 committee participants, it has been determined that  
14 all interest in firms regulated by the Center for Drug  
15 Evaluation and Research Present no potential for an  
16 appearance of a conflict of interest at this meeting  
17 when evaluated against the agenda with the following  
18 exceptions.

19 Dr. Mark Molitch and Dr. Thomas Aoki are  
20 excluded from participating in the discussions and  
21 vote concerning Symlin. In the event that the  
22 discussions involve any other products or firms not

1 already on the agenda for which an FDA participant has  
2 a financial interest, the participants are aware of  
3 the need to exclude themselves from such involvement  
4 and their exclusion will be noted for the record.

5 With respect to all other participants, we  
6 ask in the interest of fairness that they address any  
7 current or previous financial involvement with any  
8 firm whose products they may wish to comment upon.

9 DR. KREISBERG: Next on the agenda is Dr.  
10 David Orloff.

11 Welcome and Introduction for us, David.

12 DR. ORLOFF: Thank you and good morning  
13 again. I want to extend my own welcome to the  
14 committee and thank them in advance for this service  
15 to the agency and to the drug review and approval  
16 process.

17 As Dr. Kreisberg has said and we'll hear as  
18 the day proceeds, we are convened to discuss the  
19 information on the safety and efficacy of pramlintide,  
20 an analog of endogenous peptide of pancreatic origin  
21 as an adjunct to insulin therapy in the treatment of  
22 Type I and Type II diabetes mellitus.

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1 I have a few remarks I would like to make by  
2 way of introduction. The advisory committee process  
3 is an important aspect of FDA's review and regulatory  
4 oversight function in its decision making with regard  
5 to new drugs affording an opportunity for us, the FDA,  
6 to hear from experts in the field, from members of the  
7 public, as well as from the sponsor on the subject  
8 application.

9 At the outset it should be understood by all  
10 that we the agency enter into this meeting without an  
11 established course of regulatory action. We are here  
12 to engage in a discussion between the committee and  
13 the FDA and the sponsor on the scientific merits of  
14 the investigations, clinical and otherwise, of this  
15 drug and of the ramifications of the resulting data  
16 for a decision regarding marketing of the product for  
17 the proposed indications.

18 Let me remind everyone that the tone and  
19 outcomes of the deliberations today and the opinions  
20 expressed by the committee, as well as those expressed  
21 by the presenters for FDA do not represent final  
22 agency stance on the application.

1 Final regulatory action awaits further  
2 review, internal discussion, and potentially further  
3 discussions with the sponsor and, in this case, will  
4 not come for several months likely.

5 Again, I thank the committee for being here  
6 and I'll have further remarks in my charge to the  
7 committee early this afternoon following the FDA and  
8 the company presentations and prior to the committee  
9 discussion in response to our questions.

10 With that, I'll turn it back over to Dr.  
11 Kreisberg. Thank you.

12 DR. KREISBERG: Next on the agenda is the  
13 presentation by Amylin Pharmaceuticals. I would like  
14 to turn it over to Dr. Data who will introduce her  
15 associates in sequence. This is scheduled to go  
16 approximately an hour and a half and I would like to  
17 ask the panel to restrict any questions to  
18 clarification and not for discussion. I think there  
19 should be time at the end of the presentation to  
20 further question the presentation.

21 DR. DATA: Thank you, Dr. Kreisberg.

22 Good morning, ladies and gentlemen. I am

1 Joann Data and I head Regulatory Affairs and Quality  
2 Assurance at Amylin Pharmaceuticals.

3 On behalf of Amylin I would like to  
4 particularly thank the Endocrine and Metabolism  
5 Division for their guidance through the drug  
6 development process of pramlintide and for their care  
7 and rapid review of our application.

8 Symlin, or pramlintide acetate, as you have  
9 heard, is the synthetic analog of the peptide hormone  
10 amylin and, as such, can be used as replacement  
11 therapy for amylin, the hormone that is deficient in  
12 insulin using patients.

13 Symlin is an injectable product. Our  
14 indication, or proposed indication, is as adjunctive  
15 therapy to insulin to improve glycemic and metabolic  
16 control in Type 1 and Type 2 diabetes. It is to be  
17 administered subcutaneously approximately 15 minutes  
18 prior to a meal. It will be made available in both  
19 vials and cartridges.

20 Our presentation today includes a  
21 presentation by Dr. Kenneth Polonsky. Dr. Polonsky is  
22 Chair of the Department of Medicine at Washington

1 University. He will set the stage for the unmet need  
2 of insulin using patients.

3           Following that Dr. Andrew Young of our  
4 Research Division will present pramlintide's  
5 pharmacology. The clinical program will be provided  
6 by Dr. Orville Kolterman, Senior VP for Clinical  
7 Affairs. The Risk/Benefit/Summary will be prepared  
8 and presented by Dr. Alain Baron. Dr. Polonsky, Dr.  
9 Kolterman, and Dr. Baron are diabetologists.

10           In addition to our presentation today, this  
11 afternoon during the question and answer period, in  
12 addition to Amylin employees answering questions, we  
13 have brought along the following consultants to  
14 provide some additional support to the questions that  
15 you might have.

16           Those people are Dr. Huge Black representing  
17 toxicology; Dr. Wayne Colburn providing some  
18 additional input on pharmacokinetics; Dr. Richard  
19 Dickey to provide the clinical perspective from a  
20 general practitioner's point of view; Dr. Kerry Hafner  
21 talking about the statistics; and Kenneth Polonsky  
22 again will be joining us on the platform.

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1           This morning we look forward to presenting  
2           our clinical findings and to show to you what we feel  
3           that we have that we've demonstrated safety and  
4           efficacy for pramlintide for the use in insulin  
5           requiring patients with diabetes. There is a role for  
6           Symlin. It has a role in terms of both glycemic and  
7           metabolic control.

8           Before moving on to the company's  
9           presentation, I would like to introduce Dr. Kenneth  
10          Polonsky.

11           DR. POLONSKY: Thank you. My goal this  
12          morning is to give a brief overview of where I feel we  
13          are in the therapy of Type 1 and Type 2 diabetes and  
14          what the unmet needs are in terms of current therapy  
15          and the opportunities for advancement.

16           The basic message from my perspective is  
17          that although there have been significant advances in  
18          therapy in recent years, unfortunately we still are  
19          unable to achieve goals of therapy in the vast  
20          majority of patients.

21           I think we all know that in Type 1 diabetes  
22          the mainstay therapy still remains insulin. Although

1 insulin was discovered in the 1920s and although there  
2 have been a number of advances in novel preparations  
3 of insulin that have different pharmacokinetics and  
4 pharmacodynamics this is still really the only therapy  
5 that is available for reducing blood glucose  
6 concentrations in Type 1 diabetes.

7 In Type 2 diabetes, obviously there are a  
8 number of oral hypoglycemic agents that are sometimes  
9 used alone but frequently together with insulin  
10 therapy.

11 As I mentioned, in Type 1 diabetes insulin  
12 treatment is the mainstay of therapy and essentially  
13 all patients with Type 1 still have to be treated with  
14 insulin.

15 In Type 2 diabetes where there is a gradual  
16 destruction of the B-cell frequently we have to resort  
17 to insulin in the end stages to control blood glucose  
18 concentrations.

19 There are a number of important points that  
20 have become evidence as a result of research,  
21 particularly in the last 10 years. The first is that  
22 it's extremely important to achieve tight glucose

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1 control.

2           These are results from two very landmark  
3 studies in the treatment of Type 1 diabetes on the  
4 left, the DCCAT, and Type 2 diabetes on the right, the  
5 UKPDS study. What they both show that as you lower  
6 HbA<sub>1c</sub> an acceptable measure of glucose control from  
7 high levels shown here. This is the vertical axis  
8 HbA<sub>1c</sub> and this is risk of retinopathy. What you can  
9 see is as you lower HbA<sub>1c</sub> from a high-level down to a  
10 lower level, there is a substantial reduction in the  
11 risk of retinopathy.

12           As you can see, the exact reduction of risk  
13 depends on where you are starting in the curve, but  
14 reductions for even relatively small reductions in  
15 HbA<sub>1c</sub> of .5 percent may lead to reductions in risk of  
16 retinopathy of 10 to 20 or even 30 percent. The same  
17 is true in Type 2 diabetes from the UKPDS.

18           The other important point is that we  
19 currently believe there is no threshold effect and  
20 that even when you get down to low levels of HbA<sub>1c</sub>  
21 additional improvements in glucose control have  
22 additional beneficial effects on reducing

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1 complications.

2           The other message that has come out of these  
3 studies is that it's not easy to achieve this level of  
4 control that is needed to really lower complications.  
5 You can see from the DCCT on the left again and in the  
6 follow-up study, the EDIC study, the HbA<sub>1c</sub> was 8.8 at  
7 the onset of the study and came down very  
8 significantly and then over time tends to go up again.

9           The same is true in the UKPDS study of Type  
10 2 diabetes where the initial benefits in control tend  
11 to wear off with time. Long-term maintenance of  
12 sustained good glucose control is really quite  
13 difficult. This has been shown in a number of  
14 studies.

15           This is a cross-sectional study from the  
16 University of Wisconsin that followed patients  
17 perspective over time for about 10 years. You can  
18 see that even when patients were taking two or three  
19 or more injections of insulin shown over here in the  
20 blue bars and the green bars, and even when they were  
21 using combinations of insulin with multiple short-  
22 acting forms of insulin in addition to long-acting,

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1 you can see that the HbA<sub>1c</sub> is really disappointingly  
2 high.

3 The American Diabetes Association has  
4 defined that we would really like to achieve levels of  
5 around 7. The normal range is around 6. You can see  
6 that the average values in this study, which I think  
7 is fairly representative of the literature, shows  
8 levels of around 9 percent or so.

9 Additional studies, these are recent ones as  
10 you can see that were just presented at the American  
11 Diabetes Association meetings and some other more  
12 recent studies show that frequently or usually average  
13 HbA<sub>1c</sub>'s in the diabetic population are in the 9  
14 percent range approximately. Again, the ADA  
15 recommended target is down here at 7 percent, the  
16 upper limit of normal being around 6 percent.

17 Why do we have this difficulty? Well, there  
18 are a number of reasons but among them are  
19 hypoglycemia, weight gain, and the difficulty of  
20 controlling the elevation and glucose that occurs  
21 after meal ingestion or postprandial hyperglycemia.  
22 I'll briefly discuss these in the next couple of

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1 minutes.

2 It's been well demonstrated that as you take  
3 patients and you treat them aggressively to try and  
4 achieve the sort of glucose control that we've  
5 outlined, there is a significant increase in the risk  
6 of hypoglycemia.

7 This just shows in patients treated  
8 conventionally or with intensified regimens, as you  
9 attempt to lower the HbA<sub>1c</sub> there is a substantial  
10 increase in risk of hypoglycemia, particularly in the  
11 intensively treated patients but even in those under  
12 conventional therapy.

13 This occurs in patients with Type 1 diabetes  
14 that was on the previous slide, but also in Type 2  
15 diabetes. This is data from the UKPDS study. You can  
16 see a significant increase in hypoglycemia in  
17 intensively treated patients.

18 Even in Type 2 diabetes when we add oral  
19 hypoglycemic agents as an adjunct to insulin with  
20 increasing dose of these agents there is a significant  
21 increase in the risk of hypoglycemia.

22 In addition to that, we also know that as we

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1 treat patients more aggressively with insulin, they  
2 tend to gain weight. These are data from the DCCT  
3 which just shows that if you divide patients up into  
4 the quartile of weight gain, at each level of weight  
5 gain the patient is treated intensively shown here in  
6 yellow gain more weight than the patients on the  
7 conventional regimen.

8 In the upper quartile you can see the gain  
9 in weight is really quite significant. Very  
10 substantial increases in weight gain. The same  
11 principles apply in Type 2 diabetes, although the  
12 absolute amount overall in the study was not as much  
13 as in the highest quartile in the DCCT.

14 Why does this matter? Well, obviously  
15 weight gain per se is not a desirable outcome, but in  
16 addition to that there has been an analysis of these  
17 data to demonstrate that the patients who gain the  
18 most weight also have a disturbing increase in  
19 cardiovascular risk factors.

20 This just demonstrates that if you take the  
21 same patients that I showed you on the previous slide  
22 looking at the quartiles of weight gain and you look

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1 at the effects on systolic blood pressure, diastolic  
2 blood pressure, triglycerides, and total cholesterol.

3 As you can see, as people go into the higher  
4 quartiles of weight gain, there are increases in these  
5 parameters of blood pressure as well as triglycerides  
6 and cholesterol which are obvious risk factors for  
7 cardiovascular disease.

8 The final point that I'd like to just  
9 briefly touch on is this issue of postprandial  
10 hyperglycemia.

11 These are data from a study that we did a  
12 number of years ago which demonstrate that in Type 2  
13 diabetes if you study patients over a 24-hour period  
14 and you give them the three normal meals, breakfast,  
15 lunch, and dinner, and you measure the blood sugars  
16 after meals, the predominate increase in plasma  
17 glucose that occurs over the 24-hour period is a  
18 postprandial one.

19 Available therapies have had a lot of  
20 difficulty in really controlling or normalizing  
21 postprandial hyperglycemia. This has been a  
22 particular challenge.

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1           It occurs in Type 2 diabetes as well. This  
2 is just a study from a single patient who actually  
3 happens to be an endocrinologist who is treated with  
4 a pump who is overall in pretty good control. HbA<sub>1c</sub>  
5 of 7.1. This is a glucose sensor measurement of a  
6 plasma glucose profile over a 24-hour period.

7           What you can see is this patient is treated  
8 with multiple -- he's actually on a pump and he's  
9 treated with multiple bonuses of insulin in addition  
10 to the constant insulin infusion shown here in the  
11 blue triangles. There are frequent finger stick  
12 measurements of glucose, as you can see.

13           Despite these pretty intense efforts of  
14 trying to control the plasma glucose concentration,  
15 what you can see is that when you look very carefully  
16 over the 24-hour period at what the profile looks  
17 like, it's not completely normal. It's not what we  
18 would we would like it to be.

19           There are times when the blood sugar is  
20 higher than ideal and there are times when it is sort  
21 of bordering on the low limit of normal. In fact,  
22 slightly below where we would like it to be. Although

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1 this is a single patient, this is a fairly common  
2 experience of both patients and physicians who take  
3 care of patients with Type 1 diabetes.

4 There is a real unmet need and an  
5 opportunity to develop therapies that will address  
6 these issues. Therapies that might control better  
7 postprandial hypoglycemia, hypoglycemia that would  
8 achieve the levels of glucose control that we've  
9 outlined without excessive weight gain and obviously  
10 without increasing hypoglycemia which is a very  
11 important risk factor and a very important danger.

12 Just a couple of words about the  
13 hypoglycemia. Obviously, particularly in Type 1  
14 diabetes, the patients have to still be maintained on  
15 insulin which is always going to have a risk of  
16 causing hypoglycemia.

17 Any combination of an oral agent together,  
18 or an injectable agent together with insulin if one is  
19 to avoid hypoglycemia, is going to require additional  
20 adjustments to the insulin therapy either perspective  
21 reductions in the insulin dose, frequent home glucose  
22 monitoring, and other maneuvers to try and reduce the

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1 risk of hypoglycemia.

2 I think I'll stop there and thank you for  
3 your attention.

4 DR. YOUNG: Thank you, Dr. Polonsky. My  
5 name is Andrew Young. I'm Vice President of Research  
6 at Amylin Pharmaceuticals. My purpose here today is  
7 to present to you the pharmacologic rationale for  
8 amylin replacement therapy using pramlintide.

9 Doing that, I'm going to compare the amylin  
10 and pramlintide molecules. I'm going to describe  
11 abnormalities of amylin secretion. I'm going to  
12 describe the role that amylin and pramlintide play in  
13 glucose homeostasis. In particular, I'm going to  
14 describe the glucose dependence of those effects, that  
15 they only occur when plasma glucose is normal or  
16 elevated.

17 I'll preface this talk by the remark that  
18 our knowledge of amylin biology is based upon  
19 seventeen hundred scientific communications including  
20 abstracts, papers, and reviews.

21 Amylin is a neuroendocrine hormone. It is  
22 a 37-amino acid peptide. It is located almost

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1 entirely within the pancreatic B-cells where it is co-  
2 secreted with insulin and from which it is co-secreted  
3 with insulin in response to meals as shown in this  
4 panel here.

5 We can see in the orange that the amylin  
6 profile follows the insulin secretory profile and they  
7 are, in fact, secreted in a comparatively fixed molar  
8 ratio.

9 Recently the receptor for amylin has been  
10 characterized and is present in the central nervous  
11 system. In particular, I want to draw your attention  
12 to the area postrema which is a site of dense amylin  
13 receptors. This part of the brain is implicated in  
14 glucoregulatory gut reflexes. It has no blood brain  
15 barrier and is accessible to circulating peptide.

16 Type 1 and insulin-using Type 2 diabetes is  
17 characterized not only by insulin deficiency but also  
18 by amylin deficiency as exemplified in this graph on  
19 the right-hand side. Type 1 diabetic patients have an  
20 almost absolute deficiency of circulating amylin and  
21 Type 2 diabetic patients, although amylin is present,  
22 it does not follow the normal secretory profile.

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1 I will also point out that for the last 30  
2 years diabetes has also been recognized as a condition  
3 characterized by excessive glucagon secretion.

4 Pramlintide is an analog of the human  
5 hormone amylin. When one wishes to replace a human  
6 hormone that is absent, the initial intent may be to  
7 replace it with the human hormone that is missing.  
8 In the case of human amylin, this is not  
9 pharmaceutically practical because the molecule  
10 aggregated and was insoluble and unstable.

11 Instead, by the substitution of prolines at  
12 these three positions in the human amylin molecule, we  
13 produced pramlintide which is non-aggregating,  
14 soluble, and stable. In addition, has the full  
15 spectrum of activity that amylin has. It is equally  
16 potent to it and it has similar pharmacokinetics.

17 There are three fluxes that control plasma  
18 glucose. The efflux of glucose from the plasma is  
19 primarily under the control of insulin. There are two  
20 influxes of glucose into the plasma. One from  
21 endogenous sources, principally the liver, and that is  
22 under the control of the hormone glucagon. Also

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1 uptake from the gut.

2 Amylin by directing affecting nutrient  
3 assimilation from the gut and also indirectly by  
4 affecting glucagon secretion is able to modulate  
5 plasma glucose, particularly in the context of a meal.

6 This is exemplified in this slide where  
7 pramlintide administers prior to the ingestion of a  
8 test meal in Type 1 diabetic human subjects is shown  
9 to have a dose-dependent effect to flatten  
10 postprandial glucose excursions.

11 In describing the glucoregulatory actions of  
12 amylin I'm going to exemplify this by describing those  
13 effects which are well characterized and well  
14 understood in man as well as in animals.

15 I'm going to start with amylin's effects on  
16 the glucagon secretion. The effect of pramlintide to  
17 suppress postprandial glucagon secretion is  
18 exemplified here in Type 1 and Type 2 diabetic  
19 subjects where we can see that in the absence of  
20 pramlintide the postprandial secretion of glucagon is  
21 excessive.

22 Here a prior injection of pramlintide 30

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1 micrograms has essentially normalized postprandial  
2 glucagon. The same effect is observed in Type 2  
3 diabetic subjects where the excessive postprandial  
4 glucagon secretion has been normalized by a  
5 pramlintide infusion.

6           These animal data show an additional aspect  
7 of the glucagon suppression effect. First of all, in  
8 this part of the experiment where plasma glucose is  
9 clamped to glycemic levels, we can see that the co-  
10 infusion of amylin, which occurs throughout the  
11 experiment, has reduced nutrient stimulated glucagon  
12 secretion.

13           However, at this part of the experiment  
14 where glucose infusion was turned off the animal  
15 became hypoglycemic, we can see that the hypoglycemia  
16 induced glucagon secretion has been unaffected by the  
17 presence of high levels of amylin. That is, amylin  
18 has selectively inhibited nutrient stimulated glucagon  
19 secretion.

20           In support of amylin's absence of effect  
21 during hypoglycemia our some clinical data which show  
22 that pramlintide does not suppress the secretion of

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1 the counter-regulatory hormones, glucagon, growth  
2 hormone, cortisol, epinephrine, and norepinephrine.  
3 Further, pramlintide does not impede the glucose  
4 response to exogenous glucagon injection.

5 I will now turn to the effect of amylin to  
6 modulate nutrient uptake from the GI tract. I will  
7 focus on gastric emptying

8 Amylin and pramlintide potently slow gastric  
9 emptying as amplified in this study of human Type 1  
10 diabetic subjects. Here gastric emptying has been  
11 measured scintigraphically and is expressed as the  
12 time to half empty the stomach.

13 We can see that compared to the occasion  
14 when placebo was administered, that the administration  
15 of pramlintide has slowed gastric emptying by  
16 approximately one hour. Again, we ask the question  
17 what is the effect of hypoglycemia on this response.

18 This is an animal study and here gastric  
19 emptying has been assessed by measuring the gastric  
20 contents 20 minutes after gavage. In a normal rate  
21 about half of the gastric contents are present 20  
22 minutes later.

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1 Amylin in this case has almost entirely  
2 ceased the emptying of the stomach such that 100  
3 percent of the contents are present 20 minutes later.

4 However, in the presence of insulin-induced  
5 hypoglycemia shown as a progression to the right, we  
6 can see that there is an over-ride of the effect of  
7 amylin to slow gastric emptying. That is hypoglycemia  
8 has opened the emptying of the stomach.

9 The clinical implication of this animal  
10 experiment is that the presence of amylin or  
11 pramlintide will not inhibit the oral rescue from  
12 hypoglycemia.

13 How does this occur? We believe we  
14 understand why this hypoglycemic over-ride occurs.  
15 You will recall that I pointed to the area postrema,  
16 the part of the brain where we believe amylin has its  
17 effects to modulate gastric emptying.

18 This is a recording of a neuron from that  
19 part of the brain. We can see from this spike that  
20 when amylin is applied to that neuron that it is  
21 amylin sensitive. But we also see that when the  
22 glucose concentration surrounding that neuron is

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1 changed, we get an inhibition of its activity.

2 It would be tempting to suggest that the  
3 property of hypoglycemic override resides within the  
4 properties of these neurons that control gastric  
5 emptying.

6 To summarize, amylin and pramlintide exert  
7 their glucoregulatory actions via two broad  
8 mechanisms. Firstly, the inhibition of nutrient  
9 stimulated glucagon secretion. Secondly, the  
10 regulation of nutrient uptake from the gut.  
11 Importantly, both of these mechanisms are over-ridden  
12 during hypoglycemia.

13 It is clear that amylin is meant to be  
14 there. Pramlintide replaces amylin that is absent in  
15 those subjects who do not possess amylin.

16 Pramlintide restores control of glucose  
17 influx and in this way it complements the action of  
18 insulin which controls the efflux of glucose from the  
19 plasma.

20 At this stage, I would like to pass over to  
21 Dr. Kolterman who will present the clinical data.

22 DR. KOLTERMAN: Thank you, Dr. Kreisberg and

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1 members of the committee. My name is Orville  
2 Kolterman. I service as Senior Vice President of  
3 Clinical Affairs at Amylin Pharmaceuticals.

4 This morning I come before you to provide an  
5 overview of the clinical efficacy and safety data  
6 supporting the regulatory approval of pramlintide  
7 acetate.

8 Pramlintide is indicated as adjunctive  
9 therapy to insulin to improve glycemic and metabolic  
10 control in people with Type 1 or Type 2 diabetes.

11 Pramlintide is intended for patients with  
12 significant B-cell dysfunction. Patients with Type 1  
13 diabetes enter the zone of B-cell dysfunction rapidly  
14 due to the autoimmune nature of the disease which  
15 destroys B-cells. They arrive in this zone soon as  
16 the diagnosis of Type 1 diabetes.

17 On the other hand, patients with Type 2  
18 diabetes follow a slower more progressive course to  
19 arrive at the area where they rely upon exogenous  
20 insulin injections to allow them to achieve metabolic  
21 control.

22 It is this collection of patients, those

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1 that have severe impairment of the B-cell function and  
2 are, therefore, deficient in both endogenous insulin  
3 and amylin that pramlintide is intended.

4 These patients essentially have no other  
5 therapeutic options. Since the advent of insulin  
6 therapy, patients with Type 1 diabetes have had no  
7 other choices.

8 Patients with Type 2 diabetes who have  
9 progressed to this region have by in large extracted  
10 the therapeutic benefits available to them of the  
11 other therapeutic agents available.

12 As a principal investigator in the diabetes  
13 control and complications trial, I learned first hand  
14 how difficult it is for patients to achieve the  
15 desired level of metabolic control relying upon  
16 insulin alone.

17 In a center which was successful in the  
18 diabetes controlling complications trial, it took the  
19 significant part of a physician's time, the full-time  
20 efforts of a trial coordinator research nurse, part-  
21 time dietician, and part of a mental health care  
22 professional's time to achieve the target level of

1 glucose control in only 30 to 40 patients pursuing  
2 intensive control.

3 It was that experience that led me to  
4 appreciate a paradox in my professional career.  
5 Namely, as a clinical endocrinologist I was trained  
6 that when we see hormone deficiency, that replacing  
7 the deficient hormone restores reasonable -- not  
8 perfect but reasonably normal physiology.

9 Therefore, I was struck by why if insulin  
10 was the answer that giving insulin back to these  
11 patients, highly motivated intelligent patients, did  
12 not do better and easier in terms of restoring normal  
13 physiology and became attracted to the possibility  
14 that there was something else that was missing.

15 When I learned about amylin it seemed that  
16 the fact that another peptide that came from the B-  
17 cell hormone was also deficient could perhaps be  
18 involved. That is what leads me to be here today to  
19 review the data with you.

20 The presentation will provide a program  
21 overview followed by a pharmacodynamic review. I will  
22 then turn to review of the safety and efficacy data

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1 for first Type 2 diabetes, and subsequently patients  
2 with Type 1 diabetes.

3 As I give this presentation, I will draw  
4 from an extensive database where 4,493 patients with  
5 Type 1 and Type 2 diabetes have been exposed to  
6 pramlintide. The total duration of pramlintide  
7 exposure is 2,727 years. We feel unequivocally that  
8 this database is robust and satisfactory for  
9 regulatory decision making.

10 As I progress through the presentation,  
11 approximately \$1,300 with Type 2 diabetes,  
12 approximately \$1,200 patients with Type 1 diabetes who  
13 participated in the long-term control trials will  
14 serve as the basis for many of the points that I make.

15 The 2,727 of patient exposure is composed as  
16 follows. There were 2,109 patients exposed for six  
17 months or longer. There were 1,350 patients exposed  
18 for one year or longer. And there were 261 patients  
19 who are exposed for an excess of two years.

20 The population demographics of the patients  
21 participating in pramlintide clinical program are  
22 representative of those of the intended populations.

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1 If we look at Type 1 diabetes the mean age of 40  
2 years, the duration of the diabetes of 17 years is  
3 representative of what we see in the clinic when we  
4 treat patients.

5 Baseline HbA<sub>1c</sub> in both Type 1 and Type 2  
6 diabetes is approximately nine years -- I'm sorry, 9  
7 percent. The duration of the diabetes in patients  
8 with Type 2 diabetes that participated was  
9 approximately 12 years.

10 With this duration of diabetes, these  
11 patients had a representative presence of the various  
12 comorbidities which we see in patients with diabetes  
13 and, therefore, were exposed to the relevant  
14 concomitant medications.

15 You can see 56 percent of patients with Type  
16 1 diabetes used concomitant medications. And only  
17 over 80 percent of patients with Type 2 diabetes use  
18 concomitant medications --

19 (Whereupon, off the record.)

20 DR. KOLTERMAN: -- are well represented. Of  
21 particular interest to our considerations today are  
22 patients with Type 2 diabetes where over 20 percent of

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1 patients were using an oral hypoglycemia agent in  
2 addition to the insulin therapy that they employ.

3 This use of oral hypoglycemic agents  
4 consisted primarily of the biguanide used by  
5 approximately 12 percent of patients and various  
6 sulfonylureas used by 13 percent of patients.

7 The data that I will review shows that  
8 pramlintide is adjunctive therapy to insulin results  
9 in further improvement in glycemic control above that  
10 seen with insulin alone. This improvement in glucose  
11 control comes primarily from a reduction in  
12 postprandial hypoglycemia which with chronic therapy  
13 translates into a reduction in HbA<sub>1c</sub>.

14 This improvement in glucose control, as you  
15 will see, is achieved without an increase in insulin  
16 use. Unlike the majority of situations where we  
17 improve glucose control in patients with diabetes, the  
18 improvement in glucose control with pramlintide is  
19 accompanied with weight loss as opposed to weight  
20 gain.

21 Let us now turn to the pharmacodynamic  
22 review. To begin that review, look at the

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1 pharmacokinetic profiles in patients with Type 1  
2 diabetes shown in the left panel, Type 2 diabetes  
3 shown on the right panel.

4 You can see that there is a dose dependent  
5 increase in C-max with increasing doses of pramlintide  
6 both in Type 1 and Type 2 patients.

7 You will also notice that in both patient  
8 types that circulating plasma pramlintide  
9 concentrations are essentially gone from the  
10 circulation by the end of three hours consistent with  
11 a short duration of action.

12 I also point out to you in this slide that  
13 for a given dose of pramlintide administered  
14 subcutaneously, that the plasma concentration  
15 achieved in patients with Type 2 diabetes are somewhat  
16 lower than those achieved in patients with Type 1  
17 diabetes.

18 The addition of pramlintide to regular  
19 insulin results in significant improvement in  
20 postprandial glucose concentrations. These patients  
21 with Type 1 diabetes were studied on two separate days  
22 under identical conditions. The same dose of insulin

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1 administered preprandial prior to the morning meal.  
2 And the same meal, Sustacal meal challenge.

3 You can see from the data of the patients  
4 that received pramlintide, there's a significant  
5 reduction in postprandial glucose concentrations.

6 I call your attention to the plasma  
7 concentration profile engendered by this 30 microgram  
8 dose of pramlintide. These plasma concentrations are  
9 similar to circulating amylin concentrations in  
10 healthy individuals following the ingestion of a  
11 similar meal.

12 Thus, it follows that the addition back of  
13 this amylin affect which is there in normal  
14 individuals, the addition of this effect back in  
15 patients with Type 1 diabetes where it had become  
16 deficient accounts for the reduction in postprandial  
17 glucose concentrations.

18 If one looks at another study in patients  
19 with Type 1 diabetes who were treated for 28 days with  
20 Placebo in a randomized manner and then washed out for  
21 six weeks and crossed over for treatment with the  
22 other agent.

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1           The study ended on the 28th day of therapy  
2 with either placebo or pramlintide and had the same  
3 meals administered for breakfast and for the mid-day  
4 meal and employed the same dose of intermediate and  
5 short-acting insulin.

6           You can see that the addition of pramlintide  
7 resulted in the same reduction in postprandial  
8 hypoglycemia after both the morning and the mid-day  
9 meal. The administration preprandially is important  
10 in terms of getting the effect of the drug.

11           I also call to your attention here the fact  
12 that 28 days of treatment with pramlintide did not  
13 significantly impact the fasting glucose concentration  
14 consistent with pramlintide being a postprandial drug.

15           Studies of this sort demonstrate a dose  
16 response relationship for pramlintide and served as  
17 guidance for selection of dose for study in long-term  
18 trials.

19           Plotted here a change in plasma glucose  
20 concentrations following the administration of a  
21 standardized Sustecal meal challenge. You can see  
22 that there is a dose dependent decrease in the

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1 increase in postprandial glucose concentrations when  
2 we go from 10 micrograms to 300 micrograms.

3 Shown here is the mean incremental area  
4 under the glucose curve from those studies plotted as  
5 a function of dose. You can see there is a nice dose  
6 response relationship and when an appropriate  
7 statistical test is applied, one see statistical  
8 significance.

9 If one superimposes on this, the incidents  
10 of the most frequently encountered side effect from  
11 pramlintide, namely nausea, one sees nausea  
12 increasing in a dose-dependent manner as well. This  
13 data defined the range between 30 and 100 micrograms  
14 as an appropriate dose range for exploration in long-  
15 term studies.

16 In a similar way in patients with Type 2  
17 diabetes, treatment with pramlintide of doses between  
18 30 and 150 micrograms yielded evidence of a dose  
19 response relationship based on evaluation of HbA<sub>1c</sub>  
20 after 13 weeks of treatment.

21 If one superimposes a side-effect profile  
22 here, you again see a dose-dependent increase. I call

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1 to your attention that the incidence of the nausea  
2 side effect is significantly lower in patients with  
3 Type 2 diabetes.

4 These data allowed us to define the dose  
5 range of 30 to 150 micrograms as appropriate for  
6 exploration in patients with Type 2 diabetes. Thus,  
7 the long-term studies in Type 2 diabetes examine doses  
8 of 30 to 150 micrograms and those in Type 1 diabetes  
9 examine doses of 30 to 90 micrograms.

10 In terms of the Phase 3 trials, they served  
11 three purposes, need to demonstrate efficacy, assess  
12 safety, and provide a basis for some guidance for  
13 clinical use.

14 Study design considerations that were taken  
15 into account in the area of 1995 to 1996 when this  
16 program was designed and put in place included the  
17 following. At that point in time there was no  
18 precedent at all for the evaluation of another drug in  
19 insulin-treated patients.

20 In fact, in patients with Type 1 diabetes  
21 there has been no successful evaluation of another  
22 drug to lower glucose concentrations. At that point

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1 in time the results of the diabetes control and  
2 complications trial had just become available  
3 validating HbA<sub>1c</sub> as a surrogate endpoint for glycemic  
4 control.

5 There remained, however, an ongoing debate  
6 regarding whether or not there was a threshold effect  
7 for HbA<sub>1c</sub>; namely, was there a degree of glucose  
8 lowering that was required in order to see definite  
9 benefit. Today, as Dr. Polonsky has indicated, there  
10 is a consensus that the answer to that question is no,  
11 there is no threshold effect. That was not known in  
12 1995 to 1996.

13 Also, at that point in time the value of the  
14 ancillary metabolic effects, such as changes in lipid  
15 profiles, changes in body weight, changes in insulin  
16 use, were not as fully appreciated as having value as  
17 they are today.

18 The following approaches were taken to the  
19 program. All subjects needed to be treated with  
20 insulin because that was the target population.  
21 Therefore, all studies employed an add-on design  
22 meaning that either pramlintide or placebo was added

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1 to existing therapies.

2 Oral hypoglycemic agents if used by patients  
3 with Type 2 diabetes who came to the studies were  
4 allowed to be continued but the dose was required to  
5 remain constant throughout the participation. As I  
6 have shown you, this included sulfonylurea compounds  
7 and metformin.

8 Approaches to insulin management deserve  
9 special particular consideration because we have a  
10 tension here between clinical trial design and  
11 clinical practice. In the clinical trial setting  
12 insulin should ideally remain constant in order to  
13 isolate the magnitude of effect of the add-on drug.  
14 Changes in insulin doses during the study period  
15 confound data interpretation.

16 On the other hand, in the clinical practice  
17 setting, patients with diabetes change their insulin  
18 doses on a frequent basis. This is needed for  
19 considerations of patient safety in terms of limiting  
20 the risk for hypoglycemia and also to facilitate the  
21 patient's pursuit of glycemic targets. Within this  
22 program it is necessary to balance these competing

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1 demands.

2           Outlined here are the ways that we chose to  
3 do this after assessing the various clinical  
4 ramifications. In four of the long-term studies  
5 consistent insulin dosing was encouraged but not  
6 mandated.

7           Two studies placed no constraints whatsoever  
8 upon insulin dosing. Patients were always allowed to  
9 change insulin doses for patient safety purposes. To  
10 do otherwise would have been unethical. Very  
11 importantly, patients were not discontinued from the  
12 study if they changed insulin by more than what was  
13 desirable for study purposes.

14           To address the issue or to provide insight  
15 into the confounding nature of changes in insulin, the  
16 analysis plans predefined a stable insulin subgroup  
17 cohort defined by patients who from baseline to study  
18 completion did not change their total daily dose of  
19 insulin by more than plus or minus 10 percent. We  
20 feel that this isolates the true drug effect and  
21 allows it to be quantitated.

22           The general overview of the Phase 3 studies

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1 themselves, they were multicenter, randomized,  
2 placebo-controlled studies. The primary endpoint was  
3 change in HbA<sub>1c</sub> from baseline to either 26 or 52  
4 weeks.

5 Secondary endpoints included changes in body  
6 weight, changes in insulin use and, of course, the  
7 important safety parameters.

8 Let us now turn to consideration of the  
9 efficacy data for patients with Type 2 diabetes. This  
10 data comes from three studies. First study, 137-111  
11 employed a short placebo lead-in period after which  
12 time the patients were randomized to either placebo or  
13 three-dose regimens of pramlintide.

14 The body of the slide, the numbers and the  
15 arrows, indicate the times at which the endpoint  
16 assessments were made. I call to your attention that  
17 in this study, which was done earlier in the program,  
18 the formulation of pramlintide was at a high pH than  
19 that intended for market use.

20 With that formulation there is lower  
21 bioavailability such that 150 microgram dose here  
22 yields plasma concentrations similar to 120 micrograms

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1 in the subsequent studies.

2 The other two studies in Type 2 diabetes are  
3 identical in design with the exception that study 123  
4 is six months in duration whereas study 122 is 123  
5 months in duration or 52 weeks.

6 These studies encouraged investigators to  
7 identify patients that they felt were appropriate for  
8 participation in the clinical trials to make indicated  
9 changes in their management regimens. Having made  
10 those changes, to have the patients in a period of  
11 metabolic stability for two months prior to entering  
12 a one-month placebo lead-in period.

13 These measures were taken to have patients  
14 in appropriate states of control for entry into the  
15 study and to facilitate the acquiring of stable  
16 baseline HbA<sub>1c</sub> measurements. You can see that in each  
17 of the studies patients were randomized to placebo or  
18 one of three treatment regimens of pramlintide.

19 As we turn to evaluate the data, let me come  
20 up front and provide you an overview of what I'm going  
21 to show you. Shown here is a plot of HbA<sub>1c</sub> over time  
22 for patients completing 52 weeks of observation.

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1           You can see that the HbA<sub>1c</sub> in the patients  
2 receiving insulin alone decreased somewhat but that  
3 there are significantly larger reductions in HbA<sub>1c</sub> in  
4 the pramlintide treated patients.

5           The bottom panels show the two significant  
6 side effects that we need to deal with when we  
7 consider pramlintide; namely, overall nausea and  
8 severe hypoglycemia.

9           Both of these show a slight increase in the  
10 first four weeks of therapy and with chronic therapy  
11 after four weeks one sees little difference between  
12 pramlintide treated patients and placebo patients.

13           We look at the HbA<sub>1c</sub> data from the  
14 individual studies. We'll begin with a summary  
15 showing you the data for the intent-to-treat analysis  
16 following 26 weeks of therapy. The data plotted is  
17 changed from baseline.

18           We begin with data from study 137-111 where  
19 data for the 75 and the 150 micrograms achieve  
20 statistical significance versus placebo in a  
21 predefined analysis.

22           The data from study 137-123 provides

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1 supporting data with the 120 microgram dose given  
2 twice a day achieving a nominal p-value. A similar  
3 pattern is seen in study 137-122 where the 120  
4 microgram twice a day dose again achieved statistical  
5 significance by predefined analysis plan.

6 We have two studies that confirm in  
7 predefined analysis the superiority of pramlintide  
8 added to insulin versus insulin alone in terms of  
9 HbA<sub>1c</sub>. We have supportive data for the 120 microgram  
10 dose from study 137-117. These data serve as the  
11 basis for the recommendation for Type 2 diabetes of a  
12 dose of 120 micrograms administers two or three times  
13 a day.

14 We now draw from study 137-122 for data to  
15 look at in more detail to better understand the  
16 effects of pramlintide. The left panel plots the  
17 intent-to-treat analysis over 52 weeks for patients  
18 treated with insulin alone shown in tan, versus  
19 patients treated with pramlintide plus insulin, 120  
20 micrograms a day of pramlintide, the orange line.

21 You can see that both groups evidence a  
22 reduction in HbA<sub>1c</sub> across the 52 weeks but that the

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1 reduction in pramlintide treated patients is  
2 significantly greater than that treated in patients  
3 receiving insulin alone. The results are  
4 statistically significant at both 26 and 52 weeks.

5 The right panel shows data from the stable  
6 insulin cohort. Again, this is the analysis that we  
7 feel best isolates the true pramlintide effect. You  
8 can see that both groups have a reduction in HbA<sub>1c</sub>  
9 across the 52-week period of the trial.

10 The pramlintide treated patients the  
11 reduction is similar in magnitude to that seen within  
12 the entire group consistent with the insulin  
13 resistance that is a component of the Type 2 disease.  
14 Therefore, modest changes in insulin do not have much  
15 of an impact in their response.

16 I call your attention to the fact that the  
17 isolated effect of pramlintide here is sustained in  
18 magnitude across the second six months of the study  
19 contrasted with the decay and glucose control observed  
20 in the patients treated with insulin alone.

21 To date we've looked at mean data which is  
22 required for statistical analysis, but is not

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1 particularly helpful in terms of understanding how  
2 individual patients are performed.

3 I would now like to draw curves for you that  
4 show the data for all patients treated with the  
5 recommended dose of pramlintide, 120 micrograms given  
6 twice a day contrasted with patients receiving insulin  
7 alone. We are going to plot the percent of patients  
8 achieving a given HbA<sub>1c</sub> response shown across the X  
9 axis here.

10 The white vertical line at zero divides the  
11 field into a left panel which represents improvement  
12 in glucose control, versus a right panel representing  
13 worsening of glucose control. If we look first at  
14 patients treated with insulin alone, they come across  
15 the spectrum as such.

16 Approximately 55 percent of patients have  
17 shown improvement in glucose control and 45 percent of  
18 patients show some worsening of glucose control.

19 We now add the pramlintide treated patients.  
20 The most important point on this slide is that the  
21 blind for the pramlintide treated patients across the  
22 spectrum of HbA<sub>1c</sub> responses lives to the left meaning

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1 that for any particular parameter or any particular  
2 target that you want to evaluate, pramlintide added to  
3 insulin is adding benefit.

4 To quantify that more specifically, this  
5 line allows us to see that approximately 70 percent of  
6 patients receiving pramlintide have some improvement  
7 in glucose control with only approximately 30 percent  
8 having some worsening of glucose control.

9 If we look at patients who achieved a .5  
10 percent reduction or greater in HbA<sub>1c</sub>, you can see  
11 that is achieved in 35 percent of patients receiving  
12 insulin alone compared to 55 percent of patients  
13 receiving pramlintide.

14 If we look for patients who achieved a 1  
15 percent or greater reduction in HbA<sub>1c</sub>, you see that  
16 that happened in 20 percent of patients receiving  
17 insulin alone, whereas it occurred in approximately 35  
18 percent of patients treated with pramlintide plus  
19 insulin.

20 Thus, the addition of pramlintide to the  
21 patient's regimen has allowed one out of three  
22 patients to achieve a reduction in HbA<sub>1c</sub> of 1 percent

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1 or greater, a highly relevant beneficial clinical  
2 response.

3 Another way of looking at this is to look at  
4 the percent of patients achieving the ADA targets. If  
5 we look at patients achieving 8 percent or less, you  
6 can see that 21 percent treated with insulin alone,  
7 whereas a larger proportion, 35 percent, receiving  
8 insulin plus pramlintide.

9 If we look at patients achieving the desired  
10 target of 7 percent or less, it happened in only 2  
11 percent of patients treated with insulin alone. This  
12 number is increased four fold in pramlintide treated  
13 patients, 8 percent of patients.

14 Pramlintide is unique by the data I'm going  
15 to show you in this slide in that in conjunction with  
16 this improvement in glucose control, instead of  
17 increasing body weight, pramlintide allows patients to  
18 decrease their body weight.

19 This is data from study 137-111. You see a  
20 reduction in body weight in all treatment arms. This  
21 is a highly reproducible effect seen across all  
22 treatment arms in all studies so the beneficial

1 effects of reduction of HbA<sub>1c</sub> without weight gain.

2 This slide portrays for you the profile of  
3 pramlintide. This is looking at all patients treated  
4 with the recommended doses. We have approximately 300  
5 patients receiving pramlintide represented here.  
6 Baseline HbA<sub>1c</sub> for patients receiving insulin alone  
7 was 9.3 percent compared to 9.1 percent for the  
8 pramlintide treated patients.

9 We are going to look at changes in HbA<sub>1c</sub>,  
10 change in insulin use, change in body weight. You can  
11 see on the left panel that there is a significantly  
12 greater reduction in HbA<sub>1c</sub> in the pramlintide treated  
13 patients.

14 This reduction in HbA<sub>1c</sub> is achieved without  
15 an increase in insulin use. Contrast to get this  
16 smaller reduction in HbA<sub>1c</sub> patients treated with  
17 insulin alone are progressively increasing their total  
18 daily dose of insulin.

19 This reduction in HbA<sub>1c</sub> is accompanied again  
20 by a reduction in body weight contrasted with the  
21 increase of body weight of patients receiving insulin  
22 alone. An improvement in HbA<sub>1c</sub> above and beyond that

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1 achieved with insulin alone without an increase in  
2 insulin use accompanied by a reduction in body weight.

3 Having summarized the efficacy data for  
4 patients with Type 2 diabetes treated with  
5 pramlintide, let us now turn to the safety review.

6 This total will be pulled from 1,512  
7 patients receiving pramlintide and influenced, as I  
8 have pointed out previously, the 1,273 patients  
9 participating in the long-term control trials.

10 Given that pramlintide was a new chemical  
11 entity, the first in the class of a new set of  
12 therapeutic compounds for patients with diabetes, it  
13 was incumbent upon us to do a safe, careful rigorous  
14 safety evaluation. That was done at the individual  
15 study levels.

16 As the application to the agency was  
17 prepared, the data from the individual studies was  
18 rolled up into an integrated safety summary database  
19 where additional analyses were done across the whole  
20 database in a very systematic programmatic way.

21 In addition, serious adverse events were  
22 collected and reviewed in a contemporaneous manner

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1 throughout the conduct of the program. As the Chief  
2 Safety Officer for the company, I personally reviewed  
3 all serious adverse events including the severe  
4 hypoglycemic events.

5 There was no increase in mortality in the  
6 Type 2 population observed with pramlintide. There  
7 were 10 deaths which occurred in the approximately  
8 2,200 patients. None of these were classified as drug  
9 related. The incidents of death in pramlintide  
10 treated patients was lower than that seen in placebo  
11 treated patients. The same is true for cardiac  
12 related mortality.

13 If we look at the event profile for  
14 treatment-emergent and adverse events defined as those  
15 events that had an overall incidence greater than 5  
16 percent excluding hypoglycemia where the incidence was  
17 greater in patients receiving pramlintide, the terms  
18 listed here come to the table.

19 The one where there is the largest imbalance  
20 is nausea which occurred in 24 percent of patients  
21 treated with pramlintide. But importantly only 2  
22 percent of the nausea complaints were categorized by

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1 the trial coordinators and the investigators as severe  
2 in intensity.

3 In study 137-111 there was an apparent  
4 increase in the appearance of retinal disorders in  
5 patients receiving the highest dose, 150 micrograms.  
6 Careful review of this at the study level indicated  
7 that this appeared to be related to a failure to  
8 properly document the presence of existing retinopathy  
9 at baseline.

10 That observation led to some improvements in  
11 data capture techniques for subsequent studies. In  
12 those studies where 120 micrograms which produced  
13 similar plasma concentrations to the 150 microgram  
14 dose were evaluated, there was no evidence of increase  
15 in retinopathy -- retinal disorders. I'm sorry.

16 Similarly, the 75 microgram three times a  
17 day dose in the same study showed no signal and there  
18 was no signal observed in any of the Type 1 studies.  
19 Therefore, we conclude that this is not a safety  
20 concern for patients treated with pramlintide.

21 Shown here is the profile of serious  
22 treatment-emergent adverse events. As you can see,

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1 the profile is similar in pramlintide treated patients  
2 compared to those with insulin alone.

3 Anytime one adds another glucose lowering  
4 agent to insulin regimes in patients treated with  
5 insulin, there is a risk for an increase in  
6 hypoglycemia.

7 Therefore, we put in place at the outset of  
8 the studies a tracking mechanism which employed a  
9 definition of severe hypoglycemia to provide an  
10 objective quantifiable assessment of this risk. We  
11 used a definition similar to the DCCT -- we used the  
12 DCCT definition for this purpose.

13 You can see that in the Type 2 population  
14 there is an increase in the incidence of severe  
15 events, but when one corrects -- when one evaluates  
16 the data in terms of annual event rates which corrects  
17 for the appearance of multiple events within the same  
18 individual and corrects for the duration of drug  
19 exposure, one sees that the event rates are nearly  
20 identical.

21 The events in pramlintide treated patients  
22 tend to occur a bit earlier in that there is some

1 increase during the first four weeks of treatment, .5  
2 versus .2. In the later months of follow up, there is  
3 no increase in the pramlintide treated patients and  
4 perhaps a decrease during the second six months of  
5 treatment.

6 In terms of other safety observations in  
7 patients with Type 2 diabetes, there is no evidence of  
8 serious events that are unusual in the absence of drug  
9 therapy. There is no evidence of cardiac, renal, or  
10 hepatic toxicity.

11 Equally important, there's no increased  
12 frequency of clinically significant changes in lipid  
13 profiles, electrocardiograms, diastolic or systolic  
14 blood pressure, or the various safety laboratory  
15 parameters monitored. This leads us to a conclusion  
16 that pramlintide is efficacious and safe in patients  
17 with Type 2 diabetes.

18 I've shown you an improvement in glycemic  
19 control without an increase in insulin use with weight  
20 loss as opposed to weight gain, no safety issues of  
21 concern, though there is a slight increase in severe  
22 hypoglycemia during the first four weeks of therapy

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1 which is manageable as we will talk about in greater  
2 detail in the Type 1 review. We have a dosage  
3 recommendation of 120 micrograms given two to three  
4 times per day before meals.

5 That concludes the presentation related to  
6 Type 2 diabetes. Let us now move on and review  
7 similar data for patients with Type 1 diabetes.  
8 Again, we begin with the efficacy review.

9 I will move through this a bit more quickly  
10 because the layout of the presentation is identical to  
11 that that you've seen for Type 2.

12 Again, there were three trials. The first  
13 trial had a short lead-in period followed by  
14 randomization to placebo or 30 micrograms four times  
15 a day. This trial was somewhat unique in that at week  
16 20 based upon changes in HbA<sub>1c</sub> at week 13, patients  
17 who had not achieved a reduction of HbA<sub>1c</sub> of 1 percent  
18 or greater were rerandomized to either remain on 30  
19 micrograms or escalate to 60 micrograms.

20 That imbedded rerandomization lead to no  
21 increase in reduction in HbA<sub>1c</sub>. Thus, for the purpose  
22 of the presentation, the patients are treated -- the

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1 pramlintide treated patients are handled as a single  
2 group.

3 The other two studies in Type 1 employed the  
4 study design similar to that that we described for the  
5 Type 2 patients. Here patients were randomized to  
6 either placebo or one of three treatment arms, one of  
7 three pramlintide treatment regimens. The endpoint  
8 assessments again were drawn at the same points as  
9 those for the Type 2 program.

10 Again, allow me to show you the profile  
11 before we actually look at the data. Again, you can  
12 see that there is a significantly greater reduction in  
13 HbA<sub>1c</sub> that is maintained across the entire 52-week  
14 period for patients treated for 12 months.

15 The two side effect issues of concern,  
16 overall nausea and severe hypoglycemia, both increased  
17 during the first four weeks of therapy, but between  
18 weeks four and 26 and 26 to 52 have rates for both  
19 nausea and severe hypoglycemia that are similar to  
20 those seen in patients receiving insulin alone.

21 This slide summarizes the intent-to-treat  
22 analysis for changes in HbA<sub>1c</sub> for baseline six months

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1 of treatment. Study 137-112, the 30/60 microgram QUID  
2 regimen achieved statistical significance and a  
3 predefined analysis.

4 In study 137-117 there is supporting data  
5 coming from 60 micrograms given three times a day  
6 compared to placebo. And in study 137-121 both 60  
7 micrograms given both three times a day and four times  
8 a day achieved statistical significance in a  
9 predefined analysis plan.

10 Again, we have two studies by predefined  
11 analysis plan demonstrating statistical significance  
12 and supporting data from study 137-117.

13 The orange bars, again, highlight the  
14 recommended doses for going forward; namely, we  
15 propose initiating therapy with 30 micrograms or less  
16 given three to four times a day with maintenance  
17 therapy of 30 to 60 micrograms given three to four  
18 times per day.

19 Shown here is the intent-to-treat analysis  
20 for change in HbA<sub>1c</sub> for baseline over the entire 52  
21 weeks for patients treated with insulin alone  
22 contrasted with pramlintide 60 micrograms three times

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1 a day or four times a day this data being drawn from  
2 study 137-121.

3 Again, you see a pattern where all arms have  
4 a reduction in HbA<sub>1c</sub> from baseline throughout the 52  
5 weeks. The reduction in pramlintide treated patients  
6 is significantly larger, statistically significant at  
7 week 26 and at week 52 and is maintained between week  
8 26 and week 52.

9 The right panel now becomes relevant because  
10 we are dealing with patients with Type 1 diabetes.  
11 This is the predefined stable insulin cohort where  
12 patients did not change their insulin by more than  
13 plus or minus 10 percent during the period of  
14 observation.

15 When one looks at the data, one sees that  
16 the patients receiving insulin alone decreased HbA<sub>1c</sub>  
17 initially but during the second six months of the  
18 study, there is a deterioration in glucose control.

19 In contrast, patients receiving pramlintide  
20 plus a stable dose of insulin have a significantly  
21 larger reduction in HbA<sub>1c</sub> that is well maintained over  
22 the 52 week period of treatment.

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1           The difference between placebo and  
2 pramlintide treated patients is .7 percent, exactly  
3 what we predicted based upon the changes in the  
4 postprandial glucose profiles that I showed you at the  
5 outset of this presentation.

6           We feel that this isolates the pramlintide  
7 drug affect and allows one to quantitate the true HbA<sub>1c</sub>  
8 lower properties of the compound.

9           Again, we look at the response pattern seen  
10 in all patients receiving recommended doses. Again,  
11 patients receiving insulin alone are shown by the tan  
12 line. If we look at that group of patients, just over  
13 55 percent have some reduction in HbA<sub>1c</sub>. Just under  
14 45, 42, 43 percent show worsening of glucose control.

15           If we look at the recommended doses for  
16 pramlintide, the 30 and 60 microgram treatment arm in  
17 the various studies, one sees that over 70 percent of  
18 patients -- over 70 percent of patients show  
19 improvement in glucose control contrasted with only 25  
20 percent showing a worsening of glucose control.

21           If we look at patients achieving a HbA<sub>1c</sub>  
22 reduction of .5 percent or greater, one sees that it

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1 happens in 25 percent of patients receiving insulin  
2 alone versus 45 percent of patients treated with  
3 pramlintide.

4 Look at 1 percent target. There's about 12  
5 percent of patients receiving insulin alone versus 25  
6 percent patients treated with pramlintide. In the  
7 Type 1 population the addition of pramlintide yields  
8 a 1 percent or greater reduction in HbA<sub>1c</sub> in  
9 approximately one out of four patients.

10 If we look at the ADA targets for those a  
11 achieving less than 8 percent, it's 28 percent for  
12 insulin alone, significantly larger number of patients  
13 than the pramlintide treated arms.

14 Those achieving the important ADA target of  
15 7 percent or less occurs in 7 percent of patients  
16 receiving insulin alone is doubled in the pramlintide  
17 treated patients at 14 percent.

18 As we saw in the Type 2 population,  
19 pramlintide therapy improves glucose control without  
20 leading to an increase in body weight. You can see  
21 the same reproducible reduction in body weight across  
22 all treatment arms, all studies. Very similar and

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1 consistent with what I showed you in the Type 2  
2 population.

3 We now look at the slide that shows the  
4 pramlintide profile. Again, the data from all  
5 patients treated with the recommended doses of 30 and  
6 60 microgram in the Type 1 program, 716 patients  
7 receiving pramlintide.

8 The same three panels you saw before, change  
9 in HbA<sub>1c</sub>, change in insulin, change in body weight.  
10 Again, a significantly greater reduction in HbA<sub>1c</sub>  
11 compared to patients receiving insulin alone.

12 This larger reduction in HbA<sub>1c</sub> is achieved  
13 with minimal change in total daily insulin use  
14 contrasted with patients treated with placebo who are  
15 constantly increasing their insulin dose through the  
16 period of observation.

17 This change in HbA<sub>1c</sub> with this pattern of  
18 insulin use is accompanied very importantly by a  
19 reduction in body weight contrasted with the increase  
20 in body weight patients treated with insulin alone.  
21 Thus, pramlintide allows improvement in glucose  
22 control without an increase in insulin use and without

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1 an increase in body weight.

2           There is one other important cohort to look  
3 at in the Type 1 population; namely, patients who are  
4 approaching the optimal target for glycemic control,  
5 7 percent. These patients represent the lower  
6 quartile of patients treated with pramlintide.

7           We took the entire cohort, rank ordered them  
8 based on baseline HbA<sub>1c</sub> and took the lower third of  
9 the patients for evaluation. These patients had entry  
10 HbA<sub>1c</sub>'s of less than 8.3 percent. The mean for the  
11 cohort was approximately 7.7 percent.

12           In this group of patients who have mean  
13 HbA<sub>1c</sub>'s below the target for intervention proposed by  
14 the American Diabetes Association, these patients  
15 treated with pramlintide show a beneficial effect  
16 compared to the patients receiving insulin alone.

17           There is a larger reduction in HbA<sub>1c</sub> that is  
18 maintained compared to the patients receiving insulin  
19 alone across the entire period of observation.

20           Look at insulin use and we see the same  
21 pattern that we've seen elsewhere. This improvement  
22 in HbA<sub>1c</sub> is coming without an increase in insulin use.

1 Importantly for these patients, it is accompanied by  
2 a reduction in body weight.

3           Having presented the efficacy data for  
4 patients with Type 1 diabetes, let us now turn to the  
5 safety review for patients with Type 1 diabetes.  
6 Again, we will use a similar format to that in the  
7 Type 2 presentation. Here we are drawing on 1,970  
8 patients, Type 1 diabetes treated with pramlintide.  
9 Of those, 1,179 participated in the long-term control  
10 trials.

11           When we look at mortality in the Type 1  
12 patient population, again there is no increase in  
13 mortality. There were seven deaths which occurred  
14 among 3,477 unique subjects. Again, when we look at  
15 the overall incidence of death, there is no increase  
16 in pramlintide treated patients and the incidence of  
17 cardiac death is somewhat larger in pramlintide  
18 treated patients.

19           There was one death in the pramlintide  
20 treated patient that was classified as possibly drug  
21 related. This is a male patient approximately 44  
22 years old who appears to have had a hypoglycemic

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1 seizure at approximately 4:00 a.m.

2           During the seizure he entered cardiac arrest  
3 and it was not possible to resuscitate the individual.  
4 At autopsy a 70 percent lesion was found in the right  
5 coronary artery and the cause of death as described by  
6 the coroner was coronary arterial sclerosis.

7           There was a second patient that I believe  
8 you have seen mentioned in the briefing materials from  
9 the agency, a patient that died in a motor vehicle  
10 accident during the first day of therapy.

11           That patient also underwent autopsy and at  
12 autopsy food was found in the stomach and cerebral  
13 spinal fluid collected at the time of autopsy had a  
14 glucose concentration that argues against that patient  
15 being hypoglycemic at the time of death.

16           We have prepared as backup slides the  
17 details of each of the deaths that occurred in the  
18 pramlintide program and would be happy to review any  
19 of those aspects with you that are of interest during  
20 the question and answer period.

21           Because, as you will see, there is an  
22 increase in hypoglycemia in pramlintide treated

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1 patients in the Type 1 cohort, concern was raised  
2 about the possible increased risk of motor vehicle  
3 accidents and injury associated with motor vehicle  
4 accidents.

5 The data for this are summarized on this  
6 slide for all motor vehicle accidents in the left  
7 panel and hypoglycemia related motor vehicle accidents  
8 in the right panel. The data are plotted as annual  
9 event rate for patient year of exposure.

10 Before we look at that data, I want to call  
11 to your attention that there are more events that  
12 occur in pramlintide treated patients than in placebo  
13 patients in both categories here, but there are also  
14 significantly more patients exposed to pramlintide  
15 than there are exposed to placebo.

16 Therefore, we felt that evaluating this as  
17 an annual event rate where we looked across the entire  
18 safety database looking at all such events that  
19 occurred was the most appropriate way to address this.

20 When we do that, we come with the annual  
21 event rates that are plotted here with the  
22 corresponding confidence intervals. You can see that

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1 on both sides the ledger here that the confidence  
2 intervals overlap and that the p-values do not  
3 approach statistical significance.

4 A similar evaluation was done of other  
5 accident and injury, so-called non-motor vehicle  
6 accidents, for all hypoglycemia shown on the left  
7 panel and all hypoglycemic related accidents and  
8 injuries on the right panel. Again, one comes to a  
9 similar conclusion. Rates are similar, confidence  
10 intervals overlap, and the p-values do not approach  
11 statistical significance.

12 Moving onto the treatment-emergent adverse  
13 event profile, it is similar to that that we saw in  
14 patients with Type 2 diabetes. However, the incidence  
15 of nausea is higher as I alluded back on the dose  
16 response slide, occurs in approximately 50 percent of  
17 patients with Type 1 diabetes treated with  
18 pramlintide. Only 7 percent of this is rated as  
19 severe in intensity by the investigators and the trial  
20 coordinators.

21 To look at this in more detail, 49 percent  
22 of the patients during 52 weeks of observation never

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1 register a nausea complaint. This nausea is  
2 nonspecific so events related to nausea associated  
3 with other medications, viral gastroenteritis, etc.,  
4 are all captured here.

5 The nausea in the pramlintide treated  
6 patients, 44 percent is classified as mild to  
7 moderate. Only 7 percent is rated as severe. This  
8 nausea side effect is dose dependent, as you saw  
9 previously, increasing as one goes from 30 to 60 to 90  
10 microgram doses.

11 This nausea is also transient in nature. It  
12 occurs quickly with the initiation of therapy if it  
13 occurs and it dissipates essentially during the first  
14 four weeks of therapy. If one looks beyond four weeks  
15 of therapy, the rates are similar between pramlintide  
16 and patients treated with insulin alone.

17 Serious treatment-emergent adverse profile  
18 again is similar between pramlintide and patients  
19 treated with insulin alone.

20 I call your attention that in the Type 1  
21 population the metabolic and nutritional category body  
22 system has the most events having an incidence of 6

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1 percent in placebo contrasted with 10 percent with  
2 pramlintide. This captures hypoglycemia and is a  
3 signal that there is an increase in hypoglycemia that  
4 needs to be evaluated.

5 As I indicated earlier in the presentation,  
6 we were diligent in this evaluation. It was  
7 established at the start of the program that this was  
8 something that needed to be looked at and we employed  
9 a procedure, a process, similar to that that I  
10 participated as a member of the safety monitoring  
11 board in a diabetes control and complications trial.

12 The objective endpoints employed were those  
13 of the DCCT looking at patients who required the  
14 assistance of another individual including aid in the  
15 adjustment of oral carbohydrate or requiring the  
16 administration of glucagon or the injection of  
17 intravenous glucose.

18 It was the sponsor's intent to have severe  
19 hypoglycemia reported as a serious adverse event to  
20 ensure the timely and complete collection of data.

21 When one looks at the entire data set, one  
22 sees that there is no overall increase in the annual

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1 event rate of severe hypoglycemia.

2 Let me remind you that I am using annual  
3 event rate data because it captures, it compensates,  
4 deals with, addresses the issue of multiple events in  
5 a single individual and also accounts for differences  
6 in exposure of subjects. The overall rate is  
7 identical. However, given the importance of this, it  
8 needs to be looked at in greater detail.

9 The first thing to call out is within the  
10 placebo treated patients. We have an individual that  
11 we refer to as our century man who reported in excess  
12 of 100 events. If that patient is excluded as an  
13 outlier, you have an annual event rate of .8 versus  
14 1.1 percent in the pramlintide treated patients.

15 One looks at this over time and one sees  
16 that there is a clear -- there is a clear increase in  
17 the incidence of severe -- I'm sorry, in the annual  
18 event rate for severe hypoglycemia during the first  
19 four weeks of treatment.

20 As one progresses through time, this  
21 difference goes away. If one looks beyond four weeks,  
22 one does not see it. This is looking at all patients

1 in the Type 1 indication who received pramlintide.

2 We focus on what is now defined as a  
3 critical period based on the data of zero to four  
4 weeks. There is a clear dose response relationship  
5 for the hypoglycemia risk. You can see as it is  
6 increased from 30 to 90 micrograms the risk rises.

7 Thirty micrograms is not too dissimilar from  
8 that seen in patients treated with insulin alone.  
9 This starts to serve as a basis for a recommendation  
10 as to how this is addressed.

11 This presents the risk for hypoglycemia as  
12 a hazard function as suggested by Dr. Robert O'Neill  
13 with the Biometrics Group of the FDA as a reasonable  
14 way of looking at serious adverse event data such as  
15 this.

16 You can see that when the hazard function is  
17 evaluated that during the first four to six weeks of  
18 therapy there is clearly an increased risk and the  
19 patients receiving pramlintide there is no difference.  
20 There is no difference in the risk as assessed by the  
21 hazard function.

22 I now call your attention to the rate in the

1 placebo treated patients here, the risk of about .03.  
2 This slide is a similar analysis for pramlintide  
3 treated patients receiving 30 micrograms four times a  
4 day in study 137-112. There is a slight difference in  
5 the placebo data here because this is looking for a  
6 realistic or fair comparison at only the placebo  
7 patients in study 137-112 where the 30 microgram dose  
8 was employed.

9 You can see that while there is a bit more  
10 bounce here, that there is little difference in the  
11 hazard function for patients treated with pramlintide  
12 compared to those treated with insulin alone, again,  
13 starting to build an approach to this.

14 Before we talk about that approach, however,  
15 there is an important question. Does pramlintide  
16 itself cause hypoglycemia or does this hypoglycemia  
17 represent insulin induced hypoglycemia?

18 We have data to indicate that pramlintide  
19 alone does not cause hypoglycemia. In the initial  
20 dose rising study, healthy volunteers were dosed with  
21 10,000 micrograms of pramlintide. They had a bit of  
22 nausea but there was no signs of hypoglycemia. That

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1 is 80 times the maximum recommended dose.

2 Pramlintide also does not inhibit the  
3 counter regulatory response to hypoglycemia. Both the  
4 time to counter regulatory hormone release and the  
5 time to glucose recovery are unaffected. There is  
6 also no impact on hypoglycemia awareness in a  
7 controlled setting as evidenced by no change in  
8 catecholamine responses and no change in the  
9 perception of symptoms.

10 This provides us the information that we  
11 need, I think, to make a prudent, rationale, clinical  
12 recommendation for the management of this hypoglycemic  
13 risk. We are dealing with insulin-induced  
14 hypoglycemia.

15 Insulin induced hypoglycemia occurs whenever  
16 the insulin effect, insulin action exceeds nutrient  
17 availability. My diagram here shows food intake going  
18 to the plasma glucose moving on out of the compartment  
19 into tissues.

20 I've just reviewed data with you to show  
21 that there is increased incidence of nausea in  
22 pramlintide treated patients with the initiation of

1 therapy. The body weight data that we have reviewed  
2 indicates that pramlintide increases satiety. Both of  
3 these lead to a decrease in food intake. Therefore,  
4 if one does not alter the insulin dose, you can  
5 readily see how an imbalance could occur.

6 That provides a recommendation. Education  
7 for patients, physicians, and health care providers.  
8 That education focuses on using self blood glucose  
9 monitoring to make rationale changes in insulin dose  
10 just as we do routinely in clinical practice.

11 To provide an additional margin of safety it  
12 will be our recommendation that with the initiation of  
13 therapy that pramlintide insulin doses be reduced by  
14 10 to 20 percent until therapy has been successfully  
15 initiated and insulin can then be titrated based upon  
16 self blood glucose monitoring.

17 Also for the Type 1 population we recommend  
18 that the initiating dose of pramlintide be 30  
19 micrograms or less to limit the nausea side effect.

20 Having reviewed the hypoglycemia data, I  
21 would now like to return to the patients that were  
22 approaching ideal targets of seven percent here. In

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1 proven HbA<sub>1c</sub> no increase in insulin use and no  
2 increase in body weight.

3 We now look at the hypoglycemia data. You  
4 can see there is little increase during the first four  
5 weeks and with follow-on therapy four to 26 and 26 to  
6 52 there is actually some reduction in the risk for  
7 hypoglycemia. As patients approach target, the risk  
8 for hypoglycemia does not increase.

9 In terms of the other safety observations,  
10 they are the same in the Type 1 population as they  
11 were in Type 2 and I'll move on in the interest of  
12 time.

13 Pramlintide in Type 1 diabetes as in Type 2  
14 is efficacious in improving glucose control. It's  
15 accompanied with weight loss. There is an increase in  
16 insulin induced hypoglycemia but only during the  
17 initiation of therapy.

18 There's no increase with long-term therapy.  
19 There are no other safety issues that have been  
20 identified. The dosage recommendation is 30  
21 micrograms or less three to four times a day for  
22 initiation and 30 or 60 micrograms for maintenance

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1 therapy.

2 I would like to conclude with some very  
3 brief guidelines for use of this compound in the  
4 clinic. The initial dose for Type 2 is 120 micrograms  
5 a day. For Type 1 it's 30 micrograms or lower. Dose  
6 frequency is determined by the patient's meal pattern  
7 and the drug administered within 15 minutes before the  
8 meal. Insulin reduction with initiation and 10 to 20  
9 percent reduction in postprandial short-acting insulin  
10 dose.

11 For maintenance therapy, 120 micrograms for  
12 Type 2, 30 or 60 micrograms for patients with Type 1  
13 diabetes and the insulin dose adjusted according to  
14 standard clinical practice based upon self blood  
15 glucose monitoring techniques to allow patients to  
16 optimize their glycemic control.

17 My presentation has provided you with the  
18 data that indicates that pramlintide is safe and  
19 efficacious for both patients with Type 1 and Type 2  
20 diabetes. I have just reviewed the recommended dose  
21 administrations.

22 With that, I would like to conclude and

1 thank the committee for your kind attention and  
2 introduce Dr. Alain Baron who is the Vice President  
3 for Clinical Research at Amylin to provide a risk  
4 benefit assessment.

5 DR. BARON: Thank you, Dr. Kolterman.

6 Dr. Kreisberg, members of the panel, I speak  
7 to you today as a physician scientist, as a  
8 dimatologist, but much more importantly as the brother  
9 of a patient who has had Type 1 diabetes for 39 years.

10 I would like to begin by reviewing with you  
11 some of the comments made by Dr. Polonsky regarding  
12 the risks of insulin therapy. These are well known to  
13 us.

14 First and foremost, the most worrisome,  
15 hypoglycemia, a very vexing issue. As we approach  
16 glycemc goals with insulin therapy, this barrier to  
17 insulin therapy rises. Often we encounter  
18 hypoglycemia in an attempt to control postprandial  
19 hyperglycemia. As Dr. Polonsky indicated, this is a  
20 major problem in patients with both Type 1 and Type 2  
21 diabetes.

22 Typically we increase the insulin dose to

1       normalize the postprandial glucose profile. In doing  
2       so we increase the risk of late postprandial  
3       hypoglycemia. This sets in motion a series of  
4       glycemic swings or oscillations which are very  
5       uncomfortable for patients with Type 1 and Type 2  
6       diabetes. That's because they are unpredictable and  
7       this causes patients much anxiety.

8               Thirdly, weight gain. We now know that  
9       weight gain is part and parcel of insulin therapy and  
10      is particularly vexing with intensive insulin therapy.  
11      Not only in Type 2 diabetic patients who are  
12      overweight to begin with but we now know that is also  
13      true in patients with Type 1 diabetes.

14             We now have novel delivery and monitoring  
15      devices and insulin analogs. These have been valuable  
16      therapeutic advances. However, they still fall short  
17      of overcoming and pushing back those barriers to  
18      insulin therapy. We definitely need more tools.

19             Allow me if you will to show you a schematic  
20      here representing schematically, if you will, the  
21      risks of current insulin therapy. Shown on the Y axis  
22      is reduction in HbA<sub>1c</sub>. On the X axis is a package of

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1 events, namely change in insulin dose, change in  
2 hypoglycemia risk, and weight gain.

3 Let's take a patient who begins here with  
4 HbA<sub>1c</sub> and let's say we want to effect a reduction in  
5 HbA<sub>1c</sub> using insulin alone. This is what happens. We  
6 definitely reduce HbA<sub>1c</sub> but we have to increase the  
7 insulin dose, increase the risk of hypoglycemia, and  
8 increase the risk of weight gain.

9 If one wants to effect a further reduction  
10 in HbA<sub>1c</sub> with insulin, clearly the arrow will go lower  
11 but further to the right indicating that we increase  
12 the risk and meet up with greater barriers. Clearly  
13 therapies that can push back on these barriers are  
14 extremely valuable to patients who are treated with  
15 insulin.

16 Let's examine then the risk benefit analysis  
17 for both Type 2 and Type 1 diabetes in that sequence.  
18 With respect to Type 2 diabetes pramlintide offers  
19 clear benefits. This was clearly demonstrated by the  
20 presentation by Dr. Kolterman. These benefits  
21 outweigh expected and well-recognized risks. These  
22 risks are also manageable.

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1           Let's examine the risks. They are  
2 relatively few with pramlintide therapy. In patients  
3 with Type 2 diabetes the most common adverse event was  
4 nausea. This was mostly mild, infrequent, and  
5 importantly, transient. After the first four weeks,  
6 essentially there was very little nausea.

7           Of concern to any patient treated with  
8 insulin, in particular a patient treated with insulin  
9 in whom we add another anti-hypoglycemic agent is  
10 hypoglycemia.

11           We saw that in patients with Type 2 diabetes  
12 treated with pramlintide there was no overall risk of  
13 increased severe adverse event risk of severe  
14 hypoglycemia. However, this has to be taken very  
15 seriously. As suggested by Dr. Kolterman, judicious  
16 adjustment of the insulin dose particularly focusing  
17 in prandial insulin is important to avoid hypoglycemia  
18 in this population.

19           Let's examine how pramlintide might push  
20 back or overcome, if you will, some of the barriers of  
21 insulin therapy. We see that pramlintide reduces  
22 postprandial glucose excursions. This is very

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1 difficult to do even with the rapid acting analogs  
2 that we currently have today.

3 Pramlintide causes weight loss in the face  
4 of a further reduction in HbA<sub>1c</sub> that one can achieve  
5 with insulin alone. We saw no overall risk of  
6 hypoglycemia.

7 In patients with Type 2 diabetes who are  
8 insulin resistant, one often needs heroic levels of  
9 insulin doses to achieve glycemic if one can achieve  
10 glycemic control at all. This creates  
11 hyperinsulinemia.

12 Many epidemiological studies have suggested  
13 that hyperinsulinemia is not desirable as it possibly  
14 increases the risk of microvascular disease.

15 Pramlintide in addition to insulin allows further  
16 reduction in HbA<sub>1c</sub> with reduction of the insulin dose.

17 Let's now turn to Type 1 diabetes. Again,  
18 Dr. Kolterman presented compelling data showing that  
19 pramlintide offers clear benefits and these benefits  
20 also outweigh expected, well recognized, and  
21 manageable risks.

22 What are the risks? Again, they are

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1 relatively few but they are serious and we need to pay  
2 special attention to them. The most common is nausea.  
3 This was mild and moderate for the most part in this  
4 patient population but it was also severe in the  
5 patient population with Type 1 diabetes treated with  
6 pramlintide.

7           Importantly, however, it is dose dependent  
8 and transient so the management for it is very clear.  
9 One starts with therapy at a low dose, 30 micrograms  
10 or less.

11           Let's dwell a little bit more on severe  
12 hypoglycemia. There was a clear increased risk upon  
13 initiation of therapy with pramlintide when added to  
14 insulin in patients with Type 1 diabetes in the  
15 clinical trial setting which I remind you is double  
16 blind.

17           This increased risk is understandable. It  
18 is explicable and it's manageable. Let's explain it.  
19 Clearly anytime one adds a anti-hyperglycemic agent  
20 such as pramlintide to existing therapy with a  
21 hypoglycemic agent such as insulin, one increases the  
22 risk of hypoglycemia if one doesn't adjust the insulin

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1 dose.

2 If metformin, for example, worked in Type 1  
3 diabetes, which it doesn't, we would expect the same  
4 risk. Moreover, pramlintide causes nausea and some  
5 anorexia. If one doesn't eat the usual meals and  
6 quantity or in timing, clearly if one is treated with  
7 insulin, there's an increased risk of hypoglycemia.

8 Importantly, both nausea and hypoglycemia,  
9 as shown by Dr. Kolterman, is a dose dependent related  
10 phenomenon. The path forward for management is very  
11 clear. We start once again at a low dose, 3  
12 micrograms or less.

13 Again, as recommended by Dr. Kolterman, one  
14 begins initiation of pramlintide after education and  
15 the same recommendations that one would have upon  
16 initiation of insulin therapy in a patient newly  
17 diagnosed who is insulin naive, or in a patient who is  
18 currently treated with insulin in whom we wish to  
19 intensify insulin therapy.

20 What barriers does pramlintide push back on  
21 when added to insulin in patients with Type 1  
22 diabetes? In fact, there is no overall increased risk

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1 of hypoglycemia despite that fact that we achieve  
2 further glycemc control beyond that achieved with  
3 insulin alone.

4 Recall that in the first four weeks the  
5 event rate of hypoglycemia is higher. However,  
6 overall over the 52 weeks, it is not higher. That  
7 means that post initiation of therapy, and the data  
8 indicate this, there is actually possibly a reduction  
9 in risk of hypoglycemia.

10 With respect to weight gain, we see weight  
11 loss in patients with Type 1 diabetes whose HbA<sub>1c</sub> has  
12 improved and this reduction in weight occurs  
13 particularly in patients with Type 1 diabetes who are  
14 overweight to begin with and we'll be happy to share  
15 that data with you in the question and answer period.

16 Finally, because of the unique mechanism of  
17 action of pramlintide, pramlintide is able to reduce  
18 postprandial glycemc excursions in a fashion that is  
19 not possible with insulin therapy alone.

20 Let's ask the important question. Is a  
21 reduction in HbA<sub>1c</sub> obtained with pramlintide  
22 worthwhile? Well, we saw average reductions in HbA<sub>1c</sub>

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1 in the pramlintide trial program of .3 to .7 percent  
2 in the stable insulin population versus placebo or  
3 insulin alone, if you will, and .5 to 1 percent versus  
4 baseline.

5 Clearly these reductions in HbA<sub>1c</sub> are  
6 worthwhile. In fact, according to DCCT data a .5  
7 percent reduction in HbA<sub>1c</sub> as applied to this patient  
8 population that was treated with pramlintide would be  
9 expected to result in approximately a 30 percent  
10 reduction in the risk of microvascular disease,  
11 particularly retinopathy.

12 Why use pramlintide? Well, I think we know  
13 by now, to further reduce HbA<sub>1c</sub> and obtain glycemic  
14 goals beyond that achievable with insulin alone. To  
15 control postprandial hyperglycemia and limit the  
16 associated glycemic swings. And, importantly, to  
17 minimize the weight gain which is part and parcel of  
18 insulin therapy.

19 How do we achieve these benefits with  
20 pramlintide? This is due to its unique mode of  
21 action. Pramlintide limits postprandial glycemic  
22 excursions by two unique mechanisms. Suppression of

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1 the inappropriate secretion of glucagon in the post-  
2 meal period. Parenthetically this is not achievable  
3 with exogenous insulin therapy currently in use.  
4 Moreover, it regulates the nutrient delivery rate to  
5 the small intestine.

6 Both of these effects together, suppression  
7 of glucagon secretion, modulation of nutrient  
8 delivery, are complementary and additive to insulin in  
9 controlling postprandial hyperglycemia.

10 Let's reexamine the schema again. Remember,  
11 if we want to reduce HbA<sub>1c</sub> with insulin alone, one  
12 goes in this direction. We increase the insulin dose,  
13 increase hypoglycemia risk, and increase risk gain.

14 With pramlintide the data suggest the  
15 following. Because of its unique mechanism added to  
16 insulin, we go in a different direction. We achieve  
17 the same HbA<sub>1c</sub> reduction. However, without an  
18 increase in insulin dose, without no net increase in  
19 overall hypoglycemic risk, and no weight gain, or  
20 perhaps weight loss.

21 No manipulation of insulin therapy alone,  
22 not in the types of insulin, the regimens applied can

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1 move this arrow to here so pramlintide offers unique  
2 benefits.

3 The complementary actions of insulin and  
4 pramlintide form a potent binary therapeutic tool to  
5 control postprandial glycemc excursions. You need  
6 both insulin and pramlintide as the B-cell intended to  
7 leverage the effects of insulin to lower glucose  
8 further than can be achieved with insulin alone  
9 without the increased risk of weight gain and having  
10 to increase the insulin dose.

11 This is not an either/or proposition. The  
12 two together make insulin work better and facilitates  
13 the attainment of glycemc goals.

14 Amylin replacement with pramlintide  
15 represents a novel. In fact, in Type 1 diabetes this  
16 is the only novel drug in 80 years for patients with  
17 Type 1 diabetes. It also represents a unique  
18 therapeutic tool. Why? Because it has a unique mode  
19 of action. As such, it represents an important  
20 therapeutic advance that fulfills a need for patients  
21 with diabetes treated with insulin.

22 I look forward to being able to use

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1 pramlintide to better the lives of patients with  
2 diabetes. Thank you very much for your attention.

3 DR. KREISBERG: I'd like to thank Amylin  
4 Pharmaceuticals for their on-time presentation.  
5 Appreciate that.

6 We're scheduled in a couple of minutes to  
7 take a break for 15 minutes, but I would like to ask  
8 the panel if they would like to ask some short  
9 questions to clarify any of the material that was  
10 presented, again reserving questions requiring  
11 extensive discussion for later.

12 DR. TAMBORLANE: I had a question for Dr.  
13 Kolterman. You made a comment that the 30 microgram  
14 dose in the Type 1 simulated the increase in amylin  
15 that you would see with a meal in a nondiabetic.

16 DR. KOLTERMAN: That is correct.

17 DR. TAMBORLANE: How does the 120 microgram  
18 dose in the Type 2 compare to the nondiabetic  
19 excursion?

20 DR. KOLTERMAN: The peak concentrations are  
21 somewhat higher but by maybe only 15 per ml. It's not  
22 out of the ballpark. I mean, we're not doubling or

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1 tripling the concentration as seen in patients with  
2 Type 2 diabetes.

3           What do you compare that to? Do you compare  
4 it to a normal nondiabetic individual or do you  
5 compare it to that individual as they have evolved  
6 into the state where we actually implement treatment?  
7 Those individuals clearly go through a period of time  
8 where they are hyperamylinemic just like they are  
9 hyperinsulinemic.

10           DR. TAMBORLANE: I mean, you could compare  
11 it to age and weight match control, older more  
12 overweight individuals. You made a very persuasive  
13 and eloquent argument about replacing normal  
14 physiology and that was the issue that I was curious  
15 about.

16           DR. KOLTERMAN: If you compare the  
17 concentration to those individuals you just described,  
18 age matched and weight matched, the 120 microgram dose  
19 is right in the ballpark.

20  
21           DR. TAMBORLANE: I had one more just  
22 informational thing. Those change that you presented

1 was percent change in dose?

2 DR. KOLTERMAN: You're referring to insulin  
3 dose?

4 DR. TAMBORLANE: Yes, insulin dose.

5 DR. KOLTERMAN: That's correct.

6 DR. TAMBORLANE: We're talking about 4 or 5  
7 percent which for most Type 1's, I assume in absolute  
8 terms, was one or two units. Is that probably  
9 correct?

10 DR. KOLTERMAN: It's more on the order of  
11 probably four to five or six units of insulin.

12 DR. TAMBORLANE: They were receiving 100  
13 units to start?

14 DR. KOLTERMAN: No, the mean insulin dose at  
15 baseline, I believe if my memory serves me correctly,  
16 was about 60.

17 DR. TAMBORLANE: So it was 2.5 to 5 percent  
18 so it's like 3. Okay.

19 DR. LEVITSKY: This is a question on  
20 physiology. I think I'm being terminally naive about  
21 this but diminished gastric emptying has always been  
22 felt by me to be a disorder which occurs as a result

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1 of long-term poor diabetes control.

2 It is usually something which interferes  
3 with our ability to control people with diabetes  
4 because you never quite know when you're going to get  
5 your hypoglycemia or your peaks. I'm not exactly sure  
6 how a drug which leads to decreased gastric emptying  
7 is causing a physiologic change. I'm mystified by  
8 this.

9 DR. KOLTERMAN: Okay. Let me make an  
10 attempt to shed some light on this. As we typically  
11 treat hyperglycemia in diabetic patients with insulin,  
12 we are working only on the output side of the system  
13 to stimulate the output or we are working  
14 predominately on the output side to stimulate the  
15 removal of glucose from the circulation.

16 Something that affected the rate of delivery  
17 of nutrients to the small intestine for absorption  
18 will work on the input side so there is a more gradual  
19 delivery or a lower rate of delivery of the nutrients  
20 to the circulation.

21 In terms of the issue I think you're  
22 struggling with, to state it a different way, are we

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1 creating gastroparesis in these patients. Pramlintide  
2 does not induce gastroparesis. What pramlintide does  
3 is slows or retards the rate of gastric emptying.

4 We have some gastric emptying data that  
5 we'll be happy to share with you during the question  
6 and answer period this afternoon. What you see, and  
7 I think Dr. Young showed one slide of that, is that it  
8 prolongs the time of emptying by approximately an hour  
9 or so. We're not arresting it.

10 If you remember the PK profiles that I  
11 showed, I tried to emphasize that plasma  
12 concentrations were gone by the end of three hours.  
13 Typical time between meals is on the order of four to  
14 five hours, so we actually have gastric emptying data  
15 to show that the dose given before the morning meal  
16 lowers postprandial glucoses and it delays gastric  
17 emptying after the morning meal.

18 If you look at gastric emptying after the  
19 midday meal, if you don't give another dose of  
20 pramlintide. What I'm doing is an experimental  
21 paradigm where you are looking at the effects of a  
22 morning administration of pramlintide on gastric

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1 emptying after the mid-day meal you see absolutely no  
2 effect on the gastric emptying after the mid-day meal.

3 DR. LEVITSKY: A practical question. Would  
4 you anticipate then that people taking this drug would  
5 take a very short-acting insulin like Lispro and then  
6 another dose of pramlintide at the same time with each  
7 meal to achieve optimal control, that they would need  
8 to take the two injections?

9 DR. KOLTERMAN: I think to achieve optimal  
10 control based on the information that we have now,  
11 that would probably be the case. The addition of  
12 pramlintide to that regimen would allow patients to  
13 use less of the short-acting analog prior to the meal.  
14 The addition of pramlintide will also blunt the early  
15 postprandial rise in glucose that you still see with  
16 most situations with the use of the short-acting  
17 analog.

18 Also by virtue of the mechanism of action  
19 that we just talked about by having more of the  
20 nutrient load available later in the postprandial  
21 period will provide a buffer against the late  
22 postprandial hyperglycemia.

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1 I'm sorry. I misspoke there. The late  
2 postprandial hypoglycemia.

3 DR. KREISBERG: Dr. Grady.

4 DR. GRADY: Do you have any idea what the  
5 mechanism of the nausea is?

6 DR. KOLTERMAN: I have no direct evidence to  
7 mechanisms there. As Dr. Young reviewed, there are  
8 high density -- there is a high density of amylin  
9 binding sites in the area postrema. The area postrema  
10 is a region of the brain that the gastrointestinal  
11 physiologist tell us is intimately involved in the  
12 regulation of gastrointestinal functions.

13 Other areas that appear to hit the area  
14 postrema also sometimes induce nausea. It's  
15 consistent with the mechanism of action through the  
16 area postrema. Exactly what it is that probably  
17 happens in the area postrema that leads to the  
18 perception of nausea I don't believe we can tell you  
19 today.

20 DR. GRADY: Can I ask one more question? Do  
21 you know what the effect of the drug is on HDL and LDL  
22 cholesterol? You presented in your slides only total

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1 cholesterol.

2 DR. KOLTERMAN: We have data from each of  
3 the six long-term studies looking at changes in the  
4 fasting plasma lipid profile meaning total  
5 cholesterol, triglycerides, HDL and LDL cholesterol.  
6 The overall pattern is that of no change.

7 There is one study, the initial study in  
8 Type 1 diabetes, study 137-112, where there was a  
9 beneficial reduction in LDL and some increase in HDL  
10 cholesterol. That has not been clearly observed in  
11 the other studies.

12 DR. KREISBERG: I now have 7 minutes after  
13 10:00 by my watch and we're going to break for 15  
14 minutes and whatever time that is. 22 after is when  
15 we're getting back.

16 (Whereupon, at 10:08 a.m. off the record  
17 until 10:27 a.m.)

18 DR. KREISBERG: Can I ask everybody to  
19 please sit down so we can begin. After we completed  
20 the brief question and answer session, several other  
21 panelist indicated to me that they had some questions  
22 that needed further clarification so I would like to

1 ask the Amylin people to respond to these.

2 Dr. Sampson.

3 DR. SAMPSON: Dr. Kolterman, I had just two  
4 small technical questions. First of all, I was  
5 wondering if you could say a little bit more about the  
6 difference in formulation in study 111? You indicated  
7 lower bioavailability. I'm just wondering how to  
8 interpret the results of 111 in the context of your  
9 statement.

10 DR. KOLTERMAN: Sure. The only difference  
11 in the formulation was a ph difference. It was ph 4.7  
12 versus 4.0. The relative bioavailability was  
13 decreased by approximately 30 percent.

14 DR. SAMPSON: Was that measured in a common  
15 study that compared the bioavailability or were those  
16 in separate studies?

17 DR. KOLTERMAN: The comment about the  
18 decreased bioavailability comes from study 137-126 or  
19 125 where the two formulations were compared in the  
20 same subjects in the same protocol.

21 DR. SAMPSON: Thank you for that. The other  
22 one is a more technical question. That is, in study

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1 123 there is an indication in the statistics that the  
2 inference was going to be done because of the multiple  
3 doses. As you are aware, there is a question of the  
4 simultaneity of the inference and what is an  
5 appropriate critical p-value. I don't have access,  
6 unfortunately, to your protocol. Otherwise, I could  
7 answer this myself.

8 The synopsis I have says a step-down  
9 procedure was used to assess inference there. I'm  
10 wondering what was the -- and the treatments. What  
11 were the treatment step-downs and in what order?  
12 There 120 bid and 90 tid. I'm wondering which was the  
13 first one supposed to be tested in that step-down  
14 procedure?

15 DR. KOLTERMAN: I believe that the initial  
16 dose arm that was to be tested was the 90 microgram  
17 three times a day arm. That prespecified endpoint was  
18 not met. The p-value that was on the slide for the  
19 123 study represents a nominal p-value comparing the  
20 120 bid arm versus placebo.

21 DR. SAMPSON: Thank you. I understand that.

22 DR. GELATO: I wanted to go back to the

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1       gastroparesis issue for just a moment and just ask you  
2       because nausea is certainly a symptom of gastroparesis  
3       in patients, I just wondered if in the patients if you  
4       saw any correlation between those who may have had  
5       gastroparesis and when they were put on the drug,  
6       maybe that was the group that had the most severe  
7       gastroparesis or whether you even looked at the data  
8       in that way.

9                The concern would be if you had a patient  
10       with gastroparesis, would you feel comfortable using  
11       this drug?    From what I understood before, I'm  
12       gathering your answer to that is that, yes, you would.  
13       I wonder --

14               DR. KOLTERMAN:  There are several points to  
15       be made.  First is, is that patients with diabetes who  
16       have bona fide dense gastroparesis have very dense  
17       vagal neuropathy in terms of intervention of the  
18       gastrointestinal tract.    We have data from  
19       preclinical studies that suggest that an intact vagus  
20       nerve is required for the effect upon gastric  
21       emptying.                Should pramlintide be given to a  
22       patient with true gastroparesis, I don't think that

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1 anything untoward would happen to the patient which  
2 would be our primary concern. Whether there would be  
3 benefits in terms of reduction in postprandial glucose  
4 is a different question.

5 We attempted to do a study to look at that  
6 directly. The problem that we had is in spite of  
7 going to three institutions that publish frequently  
8 about the incidence of gastroparesis in diabetes, we  
9 failed to identify an adequate number of studies to  
10 complete the protocol.

11 DR. GELATO: If I could ask another  
12 question. This may be a point that maybe you can  
13 clarify for me. My understanding was that in Type 1  
14 diabetes after about five years or so into the  
15 disease, that glucagon is really not a component of a  
16 problem with that disease and may not even be  
17 relevant.

18 I wonder then if the mechanism you're  
19 looking at is really in Type 1 a glucagon mediated  
20 mechanism or one that has solely to do with just the  
21 effects on gastric emptying and slowing of the  
22 intensity.

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