

1 taking three to four injections a day of pramlintide.

2 On the three that didn't continue they  
3 wanted to go from the therapy they were on and to  
4 insulin pumps and that was not permitted.

5 When the open-label study was stopped, our  
6 patients were incredibly disappointed and I still get  
7 telephone calls asking when will this drug be  
8 approved. They still don't have the control they had  
9 when they participated in the study.

10 I'm also concerned about how ADA standards  
11 of care for the HbA<sub>1c</sub> has been looked at today. We  
12 struggle with controlling diabetes and even with  
13 everything we know, working with the DCCT, working in  
14 the core trial, we need every tool we have to achieve  
15 the goals we have and still commit to these standards  
16 HbA<sub>1c</sub> over 7 percent. We all want our patients to be  
17 less than 7 percent but we need every tool available  
18 to achieve that.

19 I would never minimize the risk of  
20 hypoglycemia. I worked diligently with it in the DCCT  
21 and I'm working with it now in the core, and I worked  
22 with it in our pramlintide studies.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           But, in fact, within the DCCT a small cadre  
2 of patients accounted for the majority of the  
3 hypoglycemic events. When we worked with those  
4 patients and when we adjusted our protocols throughout  
5 the nine years of the study, we were able to decrease  
6 hypoglycemia.

7           It's a side effect and a risk to every  
8 therapy we use in diabetes and we can do that with  
9 pramlintide. We have done it and it has been  
10 demonstrated today but we need that tool for our  
11 patients.

12           I've also heard pramlintide called a burden  
13 because it needs to be injected three or four times a  
14 day. The reality is diabetes is the burden, not  
15 pramlintide, not the injections. The reasons patients  
16 have concerns about injections, it's not the patients,  
17 it's the providers.

18           I've not met in the 19 years of my practice  
19 any patient that will not take an injection if it will  
20 improve the quality of their life and prevent the  
21 complications of the diabetes. It's how we as  
22 providers perceive that injection and how we present

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 our case to the patient.

2 As a provider diabetes care is an art, not  
3 a science necessarily. It all falls together and we  
4 need every tool available to help patients improve  
5 their outcome and improve their lives. I believe that  
6 pramlintide offers that one more tool that we need in  
7 the cadre of what we have to provide. I urge you to  
8 approve that medication for us today so that we can  
9 continue to improve the lives of people with diabetes.  
10 Thank you.

11 DR. KREISBERG: Are there any additional  
12 people that wish to make a statement? If not, I would  
13 like to thank everybody that took the time to come.

14 It's now 15 minutes to 1:00. We are going  
15 to adjourn for an hour and we'll reconvene at 15 to  
16 2:00. Thank you.

17 (Whereupon, at 12:47 p.m. off the record for  
18 lunch to reconvene at 1:45 p.m.)  
19  
20  
21  
22

A F T E R N O O N   S E S S I O N

1:57 p.m.

DR. KREISBERG: We probably have a long agenda for this afternoon and we're about an hour behind schedule. We don't want to constrain any of the discussion that goes on so we need to be as expeditious as possible.

We have a break scheduled but whether we take it or not, I think, depends upon how we're progressing.

This afternoon will be devoted to an opening statement by Dr. Orloff. Then we are going to proceed with an in depth discussion which will involve the panelists and the company with regard to the data that was presented this morning as well as other pathophysiologic or physiologic issues.

With that, David, I wonder if you would start.

DR. ORLOFF: Thank you. This item on the agenda is called Charge to the Committee. I think traditionally it involves reading the questions to the committee. I don't think I need to do that.

**NEAL R. GROSS**COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 I thought I would take a few minutes to sort  
2 of sum up FDA's concerns and try to set the tone for  
3 the discussion and deliberations surrounding the  
4 questions. Then any clarifications you need as we go  
5 on what we might or might not be referring to in the  
6 questions, we'll be happy to offer from the table  
7 here.

8 I wanted to make sure that everyone  
9 understands that when we approve a drug, it is on the  
10 basis of a determination that we know enough about the  
11 safety and effectiveness of the drug so that we can  
12 label it for safe and effective use by patients across  
13 the populations in which it is indicated.

14 To go into that in a little more specifics,  
15 we need to be able to tell people if they use it  
16 according to the directions what they can expect with  
17 regard to risk and well as benefit.

18 But the start of that phrase was "if used  
19 according to the directions." We also need to know  
20 how to use it. We need to be able to develop  
21 directions for use.

22 I think that a central theme that has come

1 out of the FDA's review of this application, and I  
2 think what has been conveyed in the presentations by  
3 FDA, is that, as I said, we have concerns about  
4 whether the data are adequate, whether the trials were  
5 adequate by their designs to guide physicians and  
6 patients in the safe and effective use of the product.

7 We all agree that on average across both  
8 types of patients there was a small statistically  
9 significant mean reduction in HbA<sub>1c</sub> in association  
10 with pramlintide use when added to insulin.

11 There was definitive demonstration of  
12 efficacy of this drug, albeit on average relatively  
13 small. You saw as presented by the sponsor that this  
14 was attributable to really across the board for all  
15 categories of HbA<sub>1c</sub> response from baseline an  
16 incremental, I guess, population response this from  
17 the cumulative response data that they showed.

18 The question that is -- one of the first  
19 questions that we've come up with is whether the  
20 trials were by their designs adequate to address the  
21 efficacy so that we know about expected benefits of  
22 this drug when patients are treated towards optimum

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 glycemic control goals.

2           Again, the sponsor did show a pulled  
3 subgroup analysis of response among patients who  
4 started out in the lower ranges, I guess, of HbA<sub>1c</sub>s  
5 within their population of Type 1 diabetic patients,  
6 and it looked as though in that subgroup analysis that  
7 the response was similar to that for the overall  
8 cohort.

9           However, I would caution you that there are  
10 lots and lots of subgroups in a database and this may  
11 well be something that needs to be prospectively  
12 investigated.

13           In addition, you heard about our concerns  
14 regarding a safety signal that arose particularly in  
15 the Type 1 patients with regard to an increased risk  
16 of hypoglycemia, particularly, I would say, in the  
17 early phases of treatment but, as expressed in the  
18 safety review, apparently associated with significant  
19 sequelae in a number of instances.

20           I emphasize now that this is a signal. I  
21 think everyone can see that to the extent that no one  
22 ever really knows what the safety parameters are going

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 to be of a drug when it goes into investigations,  
2 admittedly for a diabetes drug, hypoglycemia is  
3 something everybody looks for.

4 To the extent that we don't know the full  
5 spectrum of the safety concerns that are ultimately  
6 going to crop up, we never have complete ascertainment  
7 of all the events of a given type.

8 It is a signal and I'm not really sure how  
9 much of a concern we need to have regarding, if you  
10 will, the integrity of the database to have enumerated  
11 every single event of the types with which we are  
12 concerned. It is safe to say there is a signal there.  
13 Perhaps it bears further investigation.

14 I would also add it is our impression, again  
15 something that may bear further investigation, that  
16 the hypoglycemic risk is not necessarily restricted to  
17 market responders or to patients who entered into the  
18 trials with relatively low HbA<sub>1c</sub>s.

19 Finally, I would reemphasize the fact of the  
20 issue of our concern about whether the trials were  
21 adequate by their designs, again referring back to Dr.  
22 Misbin's comments about the maintenance of insulin

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 dosing as part of the protocols.

2 We question whether the trials are there for  
3 adequate by their designs to shed light on the safe  
4 use of the product under conditions aiming at strict  
5 glycemic control.

6 The questions that you'll get relate to  
7 safety, efficacy, approvability, and any  
8 recommendations for further studies, clinical or  
9 otherwise, that would shed light, or shed further  
10 light on this decision by FDA.

11 Finally, I should have said this at the  
12 beginning, but I do want to thank the sponsor and the  
13 FDA for their clear discussions of the data. I want  
14 to thank the presenters at the open public hearing for  
15 their compelling testimony. We are ready to proceed  
16 and listen to the deliberations as they go. Thank  
17 you.

18 DR. KREISBERG: Thank you, David.

19 Well, as usual, I'm sure that many of the  
20 panelists and the representatives from both sides will  
21 actually have questions. I would like to do this in  
22 an orderly fashion and I wouldn't like any one person

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 to monopolize all of this.

2           What I would like to do is either recognize  
3 you to ask your question and then ask you not to ask  
4 a second question unless it is related to the question  
5 that you previously asked. We will make sure we'll  
6 keep going around the table until everybody has had an  
7 opportunity to have all of their questions asked and  
8 to get full explanations of them.

9           Having said that, I will primarily try to  
10 keep the peace and let people ask the questions that  
11 they want. Why don't I start on my left and we'll  
12 just go around. If you have a question, fine. If you  
13 don't, I'll understand that.

14           There was a question brought up earlier by  
15 the sponsor in response to a question about the  
16 database. I would like to say we do not consider the  
17 database to be an issue in our discussions but if the  
18 sponsor would like to make a very brief statement  
19 regarding the database, I would be glad to receive it.

20           DR. KOLTERMAN: Thank you, Mr. Chairman. On  
21 behalf of the sponsor, I would just like to state that  
22 we unequivocally feel that our safety database is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 reliable for the purpose of making regulatory  
2 decisions.

3 There are three issues that have been called  
4 to your attention in the briefing book that I would  
5 just like to very quickly give you some expanded  
6 details on.

7 First slide, please. One related from an  
8 inspection of a site in study 137-112 related to  
9 patient 2216 who had a single hypoglycemic event that  
10 is represented in the database as nonserious and  
11 severe is possibly related. This event was recorded  
12 as an adverse event but was not recorded by the  
13 subject in the hypoglycemia diary so the event is in  
14 the database and is accounted for.

15 Next slide, please. This was also in study  
16 137-112 related -- that's the same slide. This was in  
17 the extension of study 112 where the subject had a  
18 severe hypoglycemic event and an associated motor  
19 vehicle accident in 1997 involving paramedics.

20 This event was recorded in the database as  
21 hypoglycemia and was classified as serious life  
22 threatening. A narrative was provided on the event.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 This event did not appear as a motor vehicle accident  
2 largely due to an issue with the coding dictionary  
3 that was employed. The WHOART coding dictionary,  
4 which is an industry standard and is accepted by the  
5 agency, does not have a preferred term for motor  
6 vehicle accident.

7 Had the patient had any injury that resulted  
8 from the accident, the injury would have been captured  
9 and would have been coded.

10 Next slide, please. In the last instance to  
11 provide clarification, there's a comment about some  
12 missing records for study participants at a site.  
13 This is a site that was affiliated with the clinical  
14 practice of a clinical endocrinologist who subsequent  
15 to completion of the study closed their practice.

16 The records were removed to storage when we  
17 were notified that the inspection needed to occur.  
18 The sites were brought back to a common area from  
19 storage. In that transfer process it appears that two  
20 records were misplaced and were unaccounted for.

21 Copies of those records exist at Amylin.  
22 They were shared with the site and the data related to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that subjects are accounted for in the database. This  
2 in conjunction with the standard process of auditing  
3 and what have you serves as the basis for my statement  
4 to you. Thank you.

5 DR. MISBIN: Mr. Chairman, may I just make  
6 a brief comment about that? I think one has to  
7 remember whether something is in your database or not,  
8 the question is whether it is accessible to our review  
9 and we try to find those patients when we became aware  
10 of this on the inspections. We were unable to  
11 identify those cases in the electronic submissions  
12 that you gave us.

13 Now, I have to point out so there's no  
14 misunderstanding one of these patients was on  
15 pramlintide, one was on placebo so there is no --  
16 there should be no idea that there was anything  
17 inappropriate about the way the data was collected or  
18 reported.

19 In fact, when the inspectors told us they  
20 could not find these cases, we went and looked at the  
21 submission and we could not find them either. In my  
22 judgement, we are really not sure about how many cases

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 of MVAs there are and how many cases of severe  
2 hypoglycemia there are.

3 DR. DATA: I don't know that we're going to  
4 solve this issue here. I believe it's a discussion  
5 that needs to take place between the sponsors and  
6 ourselves relative to whether actually these patients  
7 are or are not in the database.

8 Our understanding is that they are and your  
9 understanding is that they are not but I think we need  
10 to move on.

11 MS. KILLION: All right. Let's move on. I  
12 have a question as it relates to hypoglycemia which,  
13 of course, is a serious issue that we deal with every  
14 day as diabetics.

15 Something that hasn't been clarified to my  
16 liking or understanding is, is there something about  
17 pramlintide or the patients on pramlintide where the  
18 onset of hypoglycemia is very rapid or is there some  
19 kind of impairment of the sensitivity to or the  
20 awareness of oncoming hypoglycemia that we should be  
21 aware of?

22 I mean, I know when I'm becoming

1 hypoglycemic I can feel it but I know that sometimes  
2 that is not the case for all patients. Is there  
3 something about this? I wouldn't get in a car if I  
4 was feeling I had low blood sugar. If I'm in the car  
5 I eat my lifesavers or whatever. What's going on here  
6 that these people are having serious hypoglycemia that  
7 requires intervention by another party?

8 DR. KOLTERMAN: We do not believe that  
9 pramlintide alters an individual's ability to sense  
10 hypoglycemia. That statement is based upon results  
11 from a clinical pharmacology study that was done  
12 evaluating pramlintide treated patients with insulin-  
13 induced hypoglycemic challenge.

14 Neither the counter-regulatory response nor  
15 the ability to sense symptoms were altered in that 14-  
16 day study. We have slides that Dr. David Maggs from  
17 our Medical Affairs group can review with you if you  
18 would like.

19 DR. MAGGS: Good afternoon. Thank you for  
20 the question. We have no evidence that pramlintide  
21 influences the responses to hypoglycemia or the rate  
22 of glucose decent, etc., with regard to responses seen

1 in Type 1 patients.

2 Slide up, please. We have conducted a  
3 series of studies which I'll just quickly touch upon  
4 briefly. The first two studies employ the use of  
5 pramlintide at super pharmacologic doses so I won't  
6 dwell on those two studies for the moment.

7 The third study, 9308, is a 14-day study  
8 that was conducted in Type 1 patients in which they  
9 had a hypoglycemic challenge conducted days prior to  
10 initiating pramlintide therapy. They received  
11 pramlintide at 300 micrograms TID for a 14-day period  
12 at which time they then had a second hypoglycemia  
13 challenge.

14 The net results from these three clinical  
15 trials but in this trial inclusive, or as indicated  
16 here, there was no effect of pramlintide on the  
17 glucose decent, the glucose nadir, or glucose  
18 recovery.

19 No effect of pramlintide on counter-  
20 regulatory hormone responses, metabolic substraights.  
21 Psychomotor testing was also conducted and there was  
22 no effect there. Lastly, no effect on hypoglycemia

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 systems.

2 Next slide, please. This is data taken from  
3 this last study looking at the glucose decent, nadir,  
4 and recovery. What was carried out in this study  
5 during the hypoglycemia challenge was from zero to 100  
6 minutes an insulin infusion was conducted after the  
7 time which the patients had relatively stable glucose  
8 levels.

9 During this period of insulin infusion,  
10 glucose descended. At the time of glucose nadir the  
11 insulin infusion was switched off. A low-dose insulin  
12 infusion was substituted and then you saw glucose  
13 recovery.

14 The 10 plot on each figure indicates the  
15 effective of pramlintide at this dose in each of the  
16 three treatment arms whereas the red plot indicates  
17 the effect in the hypoglycemic challenge prior to the  
18 initiation of pramlintide therapy.

19 Next slide, please. This quickly shows you  
20 the catecholamine responses noted in these studies  
21 where the incremental two-hour area under the curve  
22 for the catecholamine during the hypoglycemia

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 challenge, the catecholamines, of course, being the  
2 key hormones with regard to hypoglycemic counter-  
3 regulation. We saw no difference in the catechol  
4 responses during these hypoglycemia challenges.

5 As Dr. Kolterman indicated, super  
6 pharmacologic doses of pramlintide in healthy subjects  
7 does not induce hypoglycemia. Under these conditions  
8 in Type 1 patients pramlintide does not influence  
9 counter-regulatory or hormonal responses.

10 DR. MISBIN: Mr. Chairman, could we ask the  
11 sponsor to present the data from the two earlier  
12 studies, the five-day studies that they have not  
13 presented yet? The committee really should see the  
14 entire evidence rather than just the one study that we  
15 all agree is negative. If you are unable to find  
16 that, we have brought the data that you supplied to  
17 us.

18 DR. KOLTERMAN: We have the data but I want  
19 to point out to the committee that the reason that we  
20 showed data from the study that Dr. Maggs just showed  
21 is that these studies employed a hypoglycemic  
22 challenge prior to the initiation of pramlintide

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 therapy and on the last day of pramlintide therapy.

2 The other two protocols while using much  
3 higher doses of pramlintide also were five-day  
4 exposure. There is data in the literature that shows  
5 that one hypoglycemia challenge alters the response to  
6 a subsequent hypoglycemic challenge for a period of up  
7 to 10 to 12 days. The data that we just showed was  
8 from a study of 14 days duration which we think is the  
9 most representative data that exist addressing this  
10 important issue.

11 DR. MISBIN: Mr. Chairman, again, we would  
12 like the opportunity to show the data if the sponsor  
13 does not have the data to show.

14 DR. MAGGS: Slide up, please. Again, going  
15 back to these three studies, let me just highlight the  
16 important points in these studies. As Dr. Kolterman  
17 indicated, the hypoglycemic challenges were done just  
18 prior to the initiation of pramlintide therapy and  
19 then days later.

20 What I would draw your attention to is in  
21 the first study pramlintide was administered at 500 to  
22 1,000 micrograms once daily on the days of the study.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 At the completion of the study, hypoglycemic  
2 challenges were conducted at peak or trough levels  
3 and/or placebo.

4 The point being that we are conducting a  
5 hypoglycemic challenge where pramlintide levels are  
6 either at a high level in circulation or at a nadir  
7 the following day.

8 In the second study, 9303, a similar  
9 principal pramlintide administered now QID dosing at  
10 800 micrograms dosing. Again, very super  
11 pharmacological. In both instances you can liken this  
12 to administering five or 10 grams of metformin to a  
13 patient at the time of conducting a hypoglycemic  
14 challenge.

15 If I may have the next slide up. The data  
16 that Dr. Misbin refers to is the hypoglycemic symptom  
17 scores from these two earlier studies that I refer to  
18 and the last study which I drew attention to at the  
19 very end.

20 In the first study we saw subjective  
21 symptoms of hypoglycemia scored at the time of the  
22 hypoglycemia challenge. Remember, these are patients

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 either on placebo or pramlintide either at peak or  
2 trough levels.

3 In the pramlintide treated patients baseline  
4 indicates these hypoglycemia scores in the  
5 pretreatment challenges. The second line indicates  
6 the symptom scores at the time of the pramlintide  
7 challenge.

8 There is no clinically relevant change in  
9 hypoglycemic symptom scores during the course of this  
10 particular clinical trial or, in fact, the second  
11 clinical trial.

12 What I think Dr. Misbin is referring to is  
13 the number here which falls from seven out of 12 to  
14 three out of 12 in the peak study, and in the 9303 the  
15 9303 the score of going from 19 out of 20 in this  
16 instance to 13 out of 20 in this instance, the  
17 pramlintide peak study, the pramlintide treatment arm  
18 for the second study.

19 This raises the question of hypoglycemic  
20 unawareness. Again, I should draw your attention to  
21 the fact these were studies done days after an  
22 original hypoglycemic challenge questioning the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 validity of doing a second challenge only days later.

2 Also, these patients are being studied at a  
3 time when they had had super pharmacologic doses of  
4 pramlintide administered.

5 I should also draw your attention to the  
6 fact that in 9302 this group of patients had a much  
7 lower HbA<sub>1c</sub> at entry compared to the other treatment  
8 arms which, again, confounds the interpretation of  
9 this data.

10 Finally, 9308, which is the most clinically  
11 relevant study, where we are actually administering  
12 doses of pramlintide somewhat nearer to  
13 pharmacologically use. In particular, the 30  
14 microgram arm of the study. You can see that during  
15 the course of these two hypoglycemic challenges  
16 separated by 14 days, the hypoglycemia scores in 30  
17 microgram treatment arm were, in fact, unaffected or,  
18 if anything, slightly increased.

19 In the placebo arm, again, slightly  
20 unaffected or you could argue slightly decreased. The  
21 net message from these three studies is that this last  
22 study bears the most clinical relevance and there

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 doesn't seem to be any impact on hypoglycemic symptom  
2 scores as the studies were designed.

3 MS. MCBRAIR: As the consumer rep, I was  
4 particularly taken by the testimony of the patients  
5 and the caretakers involved. One of the things I  
6 didn't hear anything about was quality of life studies  
7 and wondered if any were done and what their results  
8 were.

9 DR. KOLTERMAN: There have been no formal  
10 quality of life testing done with pramlintide. We are  
11 at the juncture where we feel that we have  
12 demonstrated efficacy, provided an assessment of  
13 safety, and have planned to undertake formal quality  
14 of life studies as part of early post-marketing  
15 studies.

16 DR. CARA: I'd like to clarify a point that  
17 I was trying to get at earlier and make sure that I  
18 understand it. This question is actually for Dr.  
19 Misbin, if I may.

20 I was asking you about looking at adverse  
21 events, specifically hypoglycemia in the "intent-to-  
22 treat population" as a way of getting at possible

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 hypoglycemia in people that had been discontinued from  
2 the study.

3 My understanding is that there really is no  
4 way to do that so that if somebody had dropped from  
5 the study for any reason, that any hypoglycemia that  
6 they had had would not go into the final data  
7 analysis. Is that correct?

8 DR. MISBIN: No, I don't think that's true.  
9 The sponsor could correct me but I think any  
10 hypoglycemic event would have captured in the data  
11 that we have regardless of whether the patient dropped  
12 out.

13 DR. CARA: I thought that was only a  
14 completer analysis?

15 DR. MISBIN: Well, no. The ITT analysis,  
16 and please, the sponsor will correct me if I misstate  
17 this, but that pertains to efficacy. The data I  
18 showed on the ITT for A<sub>1c</sub> reduction, that pertains to  
19 efficacy with the last observation carried forward for  
20 patients who dropped out.

21 But any hypoglycemic event that occurred  
22 anywhere in the trial in anyone would have been

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 captured assuming that we got it in our electronic  
2 submission which, of course, we have already dealt  
3 with.

4 But once anything that was entered into the  
5 database got to FDA regardless of when it was, even a  
6 patient who dropped out, that would have been analyzed  
7 in Dr. Roman's presentation.

8 DR. CARA: Was all of that data included in  
9 the submission?

10 DR. KOLTERMAN: Yes, it was. Perhaps more  
11 importantly is that the analysis of the safety  
12 database that I presented this morning was based on  
13 the intent to treat cohort that included all patients.  
14 If a patient started in the trial, had some sort of an  
15 adverse event and dropped out, that adverse event was  
16 captured and reported in the data that was presented.

17 As it relates to severe hypoglycemia, we  
18 have done some other analyses. If you do the intent  
19 to treat analysis and you compare that with either an  
20 intent to treat observed cases which means that you  
21 just look at the observed values that end up being  
22 entered into the database. You don't try to account

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 for patients dropping out.

2 Or if you limit the analysis to what we  
3 refer to as an invaluable cohort which means patients  
4 that started the study and continued all the way  
5 through the period of observation, you see similar  
6 patterns and you come to the same conclusions.  
7 Neither the safety nor the efficacy conclusions that  
8 we shared with you this morning are adversely impacted  
9 by dropouts.

10 DR. CARA: I'm sorry. You said that you  
11 come to the same conclusions. What conclusions are  
12 those?

13 DR. KOLTERMAN: They are the conclusions  
14 that I presented this morning in terms of severe  
15 hypoglycemia in the Type 1 population. There is an  
16 increase occurrence irregardless of whether you look  
17 at incidence or whether you look at analyzed event  
18 rates during the first four weeks of treatment beyond  
19 the first four weeks of treatment the occurrence of  
20 severe hypoglycemia is similar between pramlintide and  
21 patients treated with insulin alone.

22 DR. LEVITSKY: The compelling comments of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the patients and care givers who spoke this morning  
2 compared with some of the data that we were presented  
3 with suggest that there may be categories of patients  
4 for whom this drug may be very much more appropriate  
5 than others because I could not imagine as a care  
6 giver having the degree of intensity and wish for this  
7 drug if I had seen a e or 4 percent drop only in HbA<sub>1c</sub>  
8 in the patients I had in a .3 or .34 percent drop.

9           Clearly there are some patients who do very  
10 much better. Is this related to the frequency of  
11 blood sugar monitoring? We know the frequency of  
12 monitoring can reduce the risk of hypoglycemia to some  
13 extent.

14           Have you looked in anyway to separate out  
15 what types of patients are likely to be the ones who  
16 would stand up and tell us how their life has been  
17 changed compared to the others who clearly just added  
18 to your statistics?

19           DR. KOLTERMAN: Yes, I believe I can. We've  
20 looked -- the short answer is we've looked in detail  
21 for identifying factors that predict who will have a  
22 robust HbA<sub>1c</sub> response. The only parameter that is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 identified, you know, you look at baseline  
2 demographics, insulin types, what have you. The only  
3 thing that was identified as being a major predictor  
4 is that the higher the baseline HbA<sub>1c</sub>, the larger the  
5 reduction in HbA<sub>1c</sub> that is usually seen. That is  
6 consistent with what is seen with other therapies.

7 If you look at the entire population of  
8 patients treated with pramlintide, as I showed you  
9 during the presentation, 70 percent achieve some  
10 reduction in HbA<sub>1c</sub>. Over 90 percent achieve a  
11 reduction in HbA<sub>1c</sub> or improvements in body weight  
12 control or a combination of both.

13 We think as with a number of hormones, given  
14 where the patient is in comparison to other factors  
15 that can impact, you know, glycemic metabolic control,  
16 that the pattern of response that you see is  
17 different.

18 Maybe going forward there will be better  
19 ways to identify people that particularly have a nice  
20 response. At the present time we looked at all of the  
21 data that is available and have not been able to find  
22 the magic bullet that would allow us a priori on

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 clinical grounds to select those patients.

2 DR. TAMBORLANE: I think this sort of  
3 segways into a common two related questions that I  
4 have.

5 Dr. Baron talked about the unique properties  
6 of Symlin and its ability to control postprandial  
7 hyperglycemia. I think one of the messages we were  
8 hearing from the patients was the smoothing effect.  
9 Where you might have more severe events initially,  
10 that there seems to be fewer fluctuations in glucose.

11 That particularly resonates with me because  
12 we have just completed a sensor study involving 56 of  
13 our kids primarily who were on insulin pump and using  
14 Lispro and well controlled with A<sub>1c</sub>s of about 7.7.

15 Despite what we would consider great  
16 control, 90 percent of those youngsters had  
17 postprandial peak glucoses over 180 which would be our  
18 normal target. 50 percent of the kids had glucose  
19 values over 300 milligrams per deciliter peak  
20 postprandial values.

21 Here are my two questions. One is, do you  
22 have any data during either the Phase 2 or Phase 3

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 studies looking at glucose fluctuations in the treated  
2 patients? The second question is are you considering  
3 in your plan any pediatric studies?

4 DR. KOLTERMAN: The answer to both of your  
5 questions is yes in terms of plans for additional  
6 studies to explore those issues.

7 I'm sorry. If I could have the slide that  
8 was on the monitor up, please. There is a limited  
9 amount of data in the Phase 2 program. If I could  
10 have the slide up, please. I think that is consistent  
11 with both what we heard from the patients this morning  
12 as well as the data that you alerted to from your own  
13 group.

14 Here a group of patients were treated for 28  
15 days with 30 micrograms of pramlintide given four  
16 times a day. These patients had 24-hour glucose  
17 profiles done. This was in the presensor area so this  
18 was a more laborious means of bringing patients into  
19 a metabolic ward and doing frequent sampling.

20 You can see with the patients using similar  
21 insulin regimens, controlled meals, that prior to  
22 treatment you see this kind of a glucose pattern.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Whereas with pramlintide on board, there is less  
2 fluctuations of glucoses here in this postprandial  
3 period.

4 In this study we tried looking at the data  
5 in a number of different ways to get some statistical  
6 measure of glucose variability. As you may  
7 understand, that can be a difficult thing to do.

8 There is a slide that we may find here that plots the  
9 variance, just a simple sort of variance, and it is  
10 reduced in the pramlintide treated groups.

11 In terms of pediatric studies, we clearly  
12 understand in terms of Type 1 diabetes that is an  
13 important population to look at and we cannot just  
14 assume that what we have in adults will extrapolate to  
15 that population.

16 In September of 2000 at our pre-NDA meeting  
17 with the agency we actually made a commitment to them  
18 to undertake a pediatric study following approval of  
19 the drug -- a pediatric program.

20 Slide up, please. We did find this one.  
21 You can see here that the variability measures as a  
22 standard deviation of the plasma glucose

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 concentrations is reduced in four different dosage  
2 regimens of pramlintide treatment versus the same  
3 patients treated with insulin alone.

4 DR. GRADY: Would you put that slide back  
5 for just a sec?

6 DR. KOLTERMAN: Sure. Can we have the slide  
7 back?

8 DR. GRADY: I'm sorry. It really looks like  
9 the variability went from, say, 74 down to about 65?

10 DR. KOLTERMAN: That's correct. Slide off.

11 MS. McBRAIR: You may have already answered  
12 this question, I thin, by some of the discussion but  
13 one of the points that Dr. Misbin made, and I guess I  
14 was struck by the same thing, when you showed some of  
15 your earlier data and showed what a dramatic decrease  
16 you got in the postprandial blood sugars, I was struck  
17 that overall the change in glycated hemoglobin was  
18 relatively small it seemed for the dramatic change in  
19 postprandial.

20 The question I had was do you get a waning  
21 effect? Because I know that was one of the things  
22 that Dr. Misbin pointed out. Are there some patients

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 where you do see it and in other subsets where you  
2 don't? Have you looked at the data that way?

3 Again, I think it gets to the question of is  
4 there a population, especially hearing the patients  
5 this morning, who seem to have had such a dramatic  
6 increase in the control of their blood sugar from this  
7 drug that kind of is somewhat discordant with the  
8 overall picture of the data presented in aggregate?

9 DR. KOLTERMAN: I believe you've asked two  
10 questions. Let me address the first one. That is,  
11 the apparent discrepancy between the reductions in  
12 postprandial glucose observed and the eventual results  
13 in reductions in HbA<sub>1c</sub>.

14 The reductions in postprandial glucose were  
15 done as acute studies, single center studies in very  
16 carefully controlled, if you will, metabolic ward  
17 conditions. Those are relatively precise measures  
18 with a lot of the variability that occurs in the day-  
19 to-day control of plasma glucose factored out.

20 If one looks at those reductions in  
21 postprandial realizing that pramlintide does nothing,  
22 appears to do nothing to lower fasting glucose and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 leverage off of data published in the literature, you  
2 would anticipate a reduction maintained long-term of  
3 approximately .7 to .8 percent of HbA<sub>1c</sub>.

4 That, we believe, is the merit of the stable  
5 insulin evaluation. If I could have the slide from  
6 the Type 1 presentation, stable insulin.

7 When you look to that 30 to 40 percent of  
8 patients that for whatever reason did not vary their  
9 total daily dose of insulin by more than plus or minus  
10 10 percent and, therefore, I believe, isolated the  
11 effect of pramlintide.

12 Slide up, please. You, in fact, see a  
13 reduction in HbA<sub>1c</sub> that, in fact, is almost one  
14 percent here from baseline initially during the early  
15 part of the double blind period where, as Dr.  
16 Tamborlane referred to earlier in the morning, there  
17 is still a study effect present where everyone has  
18 sort of had a come-to-Jesus meeting with the  
19 investigator and what have you so there is more  
20 glucose monitoring, more attention, yadda, yadda,  
21 yadda.

22 There is a bit of waning in that group by 26

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 weeks. But if you then look between week 26 and week  
2 52, the line is flat as a table top. Okay? I think  
3 this shows durability of response. It also yields a  
4 reduction in HbA<sub>1c</sub> of .7 percent which is exactly what  
5 you would predict from the reduction seen in  
6 postprandial glucose concentration. That, I think, is  
7 the tie.

8 The other point that I would make relates to  
9 the differences of clinical trial design versus  
10 routine clinical practice. I think it is clear that  
11 there is a reason why the B-cell secretes both insulin  
12 and amylin.

13 The two work together sort of hand in hand.  
14 One works on the input side to the system and the  
15 other works primarily on the output side of the  
16 system. These two need to be used in conjunction with  
17 each other and titrated with each other.

18 Since there has been no other compound like  
19 this for the treatment of diabetes evaluated, the  
20 initial double-blind placebo controlled trials needed  
21 to focus on quantitating drug effect, just what we did  
22 right here, to demonstrate efficacy because if there

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 is not efficacy, one is not justified from an ethical  
2 standpoint to continue to expose patients to this.

3 Now that we have demonstrated efficacy, we  
4 are in a position to consider single-center trials  
5 where things can be explored in considerable detail to  
6 define various protocols for really how to optimize  
7 the interplay between these two pancreatic hormones.

8 Thank you. Slide off.

9 DR. TAMBORLANE: I've been looking at the  
10 data trying to understand the dose response nature  
11 both in Type 1 and Type 2 that allowed you to select  
12 the proposed doses that you have put in your  
13 materials.

14 DR. SAMPSON: I'm wondering have you done  
15 any -- again, I have not seen it -- some sort of  
16 integrated summary of efficacy that would have  
17 addressed the issue of dose response. To the naked  
18 eye it looks fairly flat in both cases, and yet your  
19 choices of doses don't seem to totally reflect that.

20 The specific question is dose response. How  
21 did you come by your choices of doses, your  
22 recommended doses, both for Type 1 and Type 2?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. KOLTERMAN: Right. Okay. The  
2 recommended selection of doses for Type 1 and Type 2  
3 for use in clinical practice is based upon  
4 observations in the long-term controlled trials. The  
5 doses for use in the long-term controlled trials was  
6 covered in part in the presentation this morning.

7 If I could have the slide up, please. It  
8 comes from data similar to what we were just talking  
9 about in terms of a reduction in postprandial glucose  
10 concentration.

11 This is data from Type 1 patients and  
12 plotted as a change from baseline. This is change  
13 from fasting, if you will, in plasma glucose values  
14 over time following the ingestion of a standard  
15 Sustacal meal challenge. There is a dose-dependent  
16 decrease in the degree to which these plasma glucose  
17 concentrations rise.

18 Next slide shows that there is, in fact, a  
19 dose response relationship and this was -- slide up,  
20 please -- tested on the glucose data using an  
21 appropriate statistical test that I cannot describe to  
22 you as a clinician but I have statistical colleagues

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 who can help us out if need be.

2 We also see that there is a dose response  
3 relationship here for the most commonly occurring side  
4 effect, nausea. We think there is evidence in the  
5 Type 1 population of a dose response for both efficacy  
6 and the side effects.

7 The next slide shows a similar approach to  
8 patients with Type 2 diabetes. Here we used a HbA<sub>1c</sub>  
9 endpoint -- slide up, please -- looking at treatment  
10 at the end of 13 weeks where you can see a dose  
11 dependent decrease in HbA<sub>1c</sub> from the range of 30 to  
12 150 micrograms. Again, there is also a dose dependent  
13 increase in the nausea profile.

14 There are similar data at 26 weeks and 52  
15 weeks of exposure that was subjected to, again, one of  
16 your statistical tests to document the presence of a  
17 dose response that was reported in the study report in  
18 the integrated summary of efficacy.

19 Slide up, please. In another study in  
20 patients with Type 2 diabetes, namely study 122, which  
21 I showed you data from this morning, here is the plot  
22 of the statistical function test, the dose response

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 test, done by the statisticians with a statistically  
2 significant p-value here.

3 DR. SAMPSON: Do you have dose response data  
4 for Type 1 patients or does the same question apply to  
5 individuals with Type 1 diabetes?

6 DR. KOLTERMAN: Okay. We --

7 DR. SAMPSON: At least, I think, the data in  
8 the Type 2 patients is different from the data that  
9 you see in the Type 1 patients in the sense that in  
10 Type 2 patients you need to use higher doses and there  
11 is more of a dose response relationship.

12 I don't get a sense that there is a clear  
13 dose response relationship in the studies that you did  
14 with individuals with Type 1 diabetes.

15 DR. KOLTERMAN: Okay. If we could have the  
16 slide up, please. Let me try something. This looks  
17 across a range of doses. Admittedly, this is not  
18 HbA<sub>1c</sub> data. I've went through the argument with you  
19 how the postprandial glucose data correlates with the  
20 HbA<sub>1c</sub> data. This goes from a range of --

21 DR. SAMPSON: Sorry, but I didn't get a  
22 sense that you did for Type 1 diabetes.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. KOLTERMAN: I'm sorry?

2 DR. SAMPSON: I didn't get a sense that you  
3 did, in fact, talk about dose response data in  
4 relationship to HbA<sub>1c</sub> data for Type 1 diabetes and  
5 that was what my question was about.

6 DR. KOLTERMAN: Okay. I cannot show you  
7 dose response data for HbA<sub>1c</sub>. If I can have the slide  
8 up, I can show you an intermediate marker of glycemic  
9 control, namely fractosomine. This is from a 28-day  
10 treatment protocol in patients with Type 1 diabetes.

11 Plotted here is the change in fractosomine  
12 from baseline for patients treated with insulin alone  
13 versus patients treated with 30 micrograms four times  
14 a day, 60 micrograms given three times a day, and 60  
15 micrograms given twice a day. I believe that you can  
16 appreciate a dose response in terms of fractosomine  
17 response here.

18 I call your attention that the doses that we  
19 are recommending are 30 and 60 micrograms in the Type  
20 1 population. We did work at 90 micrograms. It's not  
21 being recommended because it's clearly not a well-  
22 tolerated dose.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. CARA: Can you show your curve for  
2 efficacy as related to blood glucose concentrations in  
3 Type 1 diabetic again?

4 DR. KOLTERMAN: The dose response?

5 DR. CARA: The dose response. I want to see  
6 how the 30 and the 60 --

7 DR. KOLTERMAN: Sure. That's a very fair  
8 point. Can we have the slide back, please? Slide up,  
9 please. This is data from the 30 microgram dose here,  
10 60 microgram dose here. I'm sorry. This is 10, this  
11 is 30 versus 60 here. This is 100 micrograms.

12 DR. CARA: So it's quite surprising to me  
13 that, on the one hand, you are really dealing with  
14 sort of the lower minimal doses when it comes to  
15 glucose effects and, yet, in terms of lycohemoglobin  
16 levels. You are sort of not really testing, at least  
17 from this data, what I would consider to be adequate  
18 doses.

19 DR. KOLTERMAN: If we could have the summary  
20 bar chart of HbA<sub>1c</sub> intent-to-treat analysis from the  
21 presentation, please.

22 I apologize, Mr. Chairman. We're having

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 some technical difficulties over here with the  
2 computer.

3 Slide up, please. This is the summary  
4 change in HbA<sub>1c</sub> from baseline to 26 weeks across the  
5 three studies in Type 1 diabetes that was in the  
6 presentation this morning. This data here is  
7 essentially data from a 30-microgram dose compared to  
8 doses with 60 micrograms across here. In terms of  
9 magnitude of effect, there is little difference here  
10 which suggest that in Type 1 patients that 30  
11 micrograms may be close to the top end of the dose  
12 response curve.

13 If we look at weight data from patients with  
14 Type 1 diabetes, there is some added benefit in terms  
15 of body weight in terms of going to the 60 microgram  
16 dose.

17 DR. CARA: But, again, I'm not convinced  
18 that there is truly a dose response relationship. If  
19 you look at the 30, 60, and 90 microgram doses, there  
20 is not a linear dose response relationship in terms of  
21 the correlation of that dose response relationship  
22 that you are pointing out here in terms of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 glycosylated hemoglobin with the glucose-lowering  
2 effect, the postprandial glucose-lowering effect of  
3 the drug.

4 DR. GRADY: Could I ask people, you know, if  
5 you look at the third slide from Dr. Misbin, it shows  
6 exactly what -- I mean, it really shows the data on  
7 this issue. There's just no -- it's pretty much flat.  
8 The effect on HbA<sub>1c</sub> with different doses of the drug  
9 is just flat.

10 DR. KOLTERMAN: You are correct. In the  
11 presentation I also pointed out that 30 micrograms  
12 yielded plasma concentrations that are similar to  
13 circulating amylin concentrations during postprandial  
14 period in non-diabetic individuals.

15 The effects in terms of glucose -- a good  
16 part of the effect, a major part of the effect of  
17 glucose lowering in patients with Type 1 diabetes may  
18 already have been achieved by the time one reaches a  
19 30-microgram dose.

20 That is part of our consideration in  
21 conjunction with patient safety for the recommendation  
22 of 30 micrograms as the initial dose for patients with

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Type 1 diabetes.

2 The place where there is a difference  
3 between 30 and 60 micrograms is in terms of the  
4 effects upon body weight. Slide up, please.

5 This is the corresponding data for body  
6 weight to that for HbA<sub>1c</sub>. Here you see that in study  
7 112 the 30 microgram dose has a somewhat smaller  
8 effect on body weight than what the 60 or 90 microgram  
9 dose does in either study 117 or study 121. Slide  
10 off, please.

11 DR. CARA: If I were to then compare that to  
12 your dose response relationship into what you've just  
13 told me, I would say that the mechanism -- I would  
14 conclude that the mechanism of action of the drug then  
15 is primarily anorectic effect.

16 DR. KOLTERMAN: Okay. I don't believe that  
17 is a correct conclusion because when you look at the  
18 inter-relationship between the reduction in HbA<sub>1c</sub> and  
19 the reduction in body weight, reductions in HbA<sub>1c</sub> are  
20 similar. If you divide patients into those that lose  
21 weight and those that do not lose weight, the  
22 reduction in HbA<sub>1c</sub> is similar in the two cohorts.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Have I stated that clearly?

2 DR. TAMBORLANE: I think I want to direct  
3 this to the FDA and I apologize.

4 DR. KREISBERG: Wait. I thought it was  
5 related to --

6 DR. TAMBORLANE: No, I have a different  
7 question.

8 DR. KREISBERG: Deborah.

9 DR. GRADY: When I think about your drug, it  
10 seems like an attractive drug for Type 1 diabetics  
11 mainly because there just aren't good options. Also  
12 because those are the patients at very high risk for  
13 complications.

14 As an internist I primarily take care of  
15 Type 2 diabetics. When I think about it with regard  
16 to Type 2 diabetics, the main concern I have is that  
17 its actions are very similar to those of metformin in  
18 that it reduces HbA<sub>1c</sub>, tends to reduce weight or  
19 prevent weight gain. However, it is much less strong  
20 in producing those outcomes.

21 It seems clear to me that the first drug  
22 that ought to be chosen in Type 2 diabetics would be

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 metformin. Then the real issue is what additional  
2 benefit might your drug have when added in Type 2  
3 diabetics to metformin. I wonder if you have any  
4 information on that question?

5 DR. KOLTERMAN: Yes, we do. I may take us  
6 a minute to find the slide. If you remember from the  
7 presentation this morning, 20 percent of patients in  
8 the Type 2 studies were using either a sulfonylurea or  
9 metformin.

10 If you subset out those patients that were  
11 concomitantly treated with either sulfonylurea or  
12 metformin, you see a beneficial response in those  
13 patients that appears to be above and beyond what  
14 metformin or the sulfonylurea is bringing to the  
15 patient.

16 While we are looking for that slide, if we  
17 could have the slide up, please.

18 This is looking across the studies of the  
19 patients treated with biguanides and without  
20 biguanides compared to the placebo. You can see that  
21 the patients treated with biguanides are showing the  
22 same response that the patients who are treated

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 without biguanides.

2 As I teed this up in the presentation this  
3 morning, I think that pramlintide has the potential to  
4 bring benefit to patients with Type 2 diabetes after  
5 they have extracted the benefits, if you will, from  
6 the presently available agents.

7 DR. GRADY: Do you know what the effect is  
8 on weight in that same group, the ones taking  
9 biguanides?

10 DR. KOLTERMAN: Okay. I don't believe we  
11 have that on a slide but the weight effect is not  
12 dissimilar to that seen in the entire cohort. My  
13 memory is not good enough to quote it precisely as to  
14 whether it's identical or not. I do now that  
15 evaluation of this cohort does show that there is a  
16 weight loss in the metformin treated patients.

17 DR. MAGGS: I'm Dr. David Maggs. Just a  
18 follow-up comment. There is no reason why pramlintide  
19 and metformin can't coexist in the treatment of Type  
20 2 diabetes. As Dr. Kolterman has pointed out, about  
21 12 percent of our Type 2 diabetes cohort were already  
22 on metformin when pramlintide was added as he has

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 shown.

2 We should also bear in mind that not all  
3 Type 2 patients can tolerate or take metformin through  
4 gastro and internal side effects or lactic acidoses  
5 counter indication.

6 The last piece that I should also point out  
7 is although there are similar effects on HbA<sub>1c</sub> and  
8 body weight, weight control or weight loss, they have  
9 two very different mechanisms of action. Metformin  
10 working glucose production and fasting glucose.  
11 Meanwhile pramlintide having an effect on controlling  
12 glucose in the mealtime period. There is no reason  
13 why these two compounds can't coexist in the treatment  
14 of Type 2 diabetes.

15 DR. KREISBERG: Orville, I wonder if you or  
16 one of your colleagues could address the issue of both  
17 weight loss and hypoglycemic responsiveness because I  
18 think the discussion was going in a direction that  
19 suggest that just interfering with the rate of gastric  
20 emptying is not likely to cause weight loss.

21 I mean, if you use glucoside ACE inhibitors  
22 as an example, they slow but they don't actually

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 produce malabsorption. I would believe that if the  
2 diet were held constant, then there should be no  
3 weight loss.

4 I wonder if hypoglycemic awareness and  
5 responsiveness are normal, then it seems to me that  
6 the issue here is that they have changed their diet  
7 and they are not consuming the same amount of energy  
8 as they were consuming. I wonder if you have any  
9 trial data that is controlled enough to look at what  
10 the impact of this would be on the consumption of  
11 calories.

12 DR. KOLTERMAN: We do not yet have clinical  
13 trial data that provide quantitative assessments of  
14 that or look at change in the composition of the food  
15 selected.

16 There is, however, a considerable literature  
17 in preclinical studies indicating an effect upon  
18 amylin itself as a satigenic agent. One of my  
19 colleagues can share some of that data with the panel  
20 if you would like.

21 DR. KREISBERG: I would just think for  
22 additional studies that you might consider to get at

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the issue of hypoglycemia as to, (1) the nausea itself  
2 may, in fact, be anorexigenic. But if there are other  
3 more centrally derived properties of the drug, that a  
4 problem that is contributing to the side effect  
5 profile in this is that people have voluntarily  
6 restricted their intake.

7 I think that would be important to know that  
8 from future studies and it would seem to me it  
9 wouldn't take a lot of patients in order to determine  
10 what the effect was on energy consumption.

11 DR. KOLTERMAN: Okay. That is an area that  
12 we are interested in pursuing. I think it has  
13 actually potential significant clinical benefit to  
14 better understand that.

15 I make the point that patients that never  
16 experience nausea -- never experience nausea show  
17 weight loss similar to that seen in the patients who  
18 do experience nausea.

19 Again, the nausea, as I showed you this  
20 morning, or tried to communicate in my presentation  
21 with some clarity, is a short protracted side effect.  
22 It occurs primarily during the first four weeks and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 then dissipates. The weight affect is persisting over  
2 26 to 52 weeks.

3 I think the nausea piece comes out of it,  
4 but I think the human data by inference as it now  
5 stands indicates that an amylin-like effect exist in  
6 man similar to that demonstrated in animal studies  
7 that decreases food intake. It appears to be a  
8 satiety effect as opposed to a food aversion effect.

9 DR. CARA: I was just looking at the number  
10 of subjects experiencing treatment-emergent adverse  
11 events. I am impressed by the number who are actually  
12 complaining of anorexia relative to placebo.

13 I can understand that you haven't quite  
14 established what that is due to, whether it's gastric  
15 filling or delayed gastric emptying versus a central  
16 effect. Again, I just think that needs to be looked  
17 at.

18 DR. KOLTERMAN: Not to cut you off but there  
19 is another issue lurking in that term in that that is  
20 the preferred term in the coding dictionary to which  
21 some rather interesting things collapse. A good  
22 number of the things that collapse and are reported in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that term, you and I would probably view as beneficial  
2 attributes to have in a drug treating patients with  
3 diabetes in terms of feeling less hungry, not wanting  
4 to eat as much, what have you.

5 It's anecdotal information but a comment  
6 that you heard from some of the patients in the public  
7 comment session this morning, you know, believe me,  
8 when we had to stop the open-label extension studies,  
9 I took a number of fairly irate phone calls and the  
10 patients were saying a very common theme is that for  
11 the first time since I've had diabetes while using  
12 this compound I don't feel like I need to eat all the  
13 time.

14 DR. TAMBORLANE: Again, this is for the FDA.  
15 I'm kind of proud of being part of the DCCT that  
16 established the A<sub>1c</sub> as a marker for efficacy in  
17 treatment of Type 1 diabetes.

18 It seems to me that has facilitated studies  
19 of efficacy with oral agents in Type 2 diabetes. I  
20 apologize if I don't get all the details right. In  
21 that case, you can withdraw a patient from their oral  
22 therapy.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           You can allow their A<sub>1c</sub> to go up, and then  
2           you come in with a placebo controlled study which then  
3           may actually return their A<sub>1c</sub> back to where they were  
4           before they started. But compared to placebo or no  
5           treatment you have demonstrated efficacy.

6           It seems to me that the agency is holding a  
7           higher standard for a now unique study which the  
8           company pointed out that these kind of studies of  
9           glucose lowering agents in Type 1 diabetics or  
10          insulin-requiring diabetics, particularly Type 1  
11          diabetic patients, is a different kettle of fish.

12          It seems to me also that you're holding them  
13          to a higher standard for efficacy by suggesting that  
14          the only way to demonstrate efficacy is in the context  
15          of a treat the goal and intensive diabetes regimen.  
16          I assume you make guidance to industries. Have you  
17          thought about this further and how are you going to  
18          deal with this in the future as well?

19                 DR. MISBIN: Well, actually, I think, Dr.  
20          Tamborlane, it's really up to you to set the standard.  
21          There is no official documents as far as what the  
22          standards are. I think --

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. TAMBORLANE: Me personally? I'm happy  
2 to try.

3 DR. MISBIN: You will have to vote at the  
4 end so that is, in fact, something that you will  
5 personally have to decide. I think it depends on,  
6 yes, that is one way of looking at it, they are being  
7 held to a higher standard but one could say why do we  
8 have a situation with patients with Type 2 diabetes  
9 when in the past we have allowed patients to be taken  
10 off of active treatment and, indeed, in some protocols  
11 allowed their glucoses to go up to 400.

12 I think there are clearly many people at  
13 industry who believe that informed consent in the  
14 general sense covers that issue. It's my personal  
15 belief that patients should not be required to accept  
16 a substandard treatment simply by virtue of being part  
17 of a clinical trial. Furthermore, the relevance of  
18 such data, I think, is very much open to question.

19 We have evaluated three new molecular  
20 entities with respect to insulin. Three new insulin  
21 analogs. Clearly we didn't do placebo control trials  
22 but these were all evaluated in patients that were in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 reasonably good control.

2 Patients had HbA<sub>1c</sub>s of roughly 7.5 to 8 and  
3 we just said let's take any one of them, Lispro,  
4 Asbart, or Lantis. We basically told doctors to treat  
5 how they would treat in ordinary practice and just at  
6 the end of the day see if there was a difference  
7 between the experimental drug and the standard drug.

8 I've already presented the metformin data so  
9 I don't see any reason why we cannot hold companies to  
10 a standard that they evaluate their drugs under  
11 circumstances which they expect that the drugs will be  
12 used.

13 Now, what kind of label is right for  
14 pramlintide? If you use literally the patients that  
15 were studied, you would have to say these are patients  
16 in whom A<sub>1c</sub> levels are high and you are saying not to  
17 adjust their insulin dose.

18 That is clearly not the way the patients  
19 will be treated. As soon as you allow insulin to be  
20 varied, it may or may not be effective. It may or may  
21 not be safe. We really don't even have the data to  
22 answer that question.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. TAMBORLANE: Just to respond to that, I  
2 was trying to be very specific with my language, and  
3 that is showing efficacy versus safety. The problem  
4 I envision is that the sponsors are caught in a box  
5 when it's a different entity, not another kind of  
6 insulin in which I assume the FDA is willing to accept  
7 noninferiority as a criteria for acceptance where you  
8 have to show efficacy that they get caught in the box  
9 because the harder you work to adjust the insulin  
10 dose, it's a confounder.

11 My impression, only from limited experience  
12 with the FDA, is that other endpoints such as  
13 decreased variability and some of the quality of life  
14 and things like that are not hard endpoints. I assume  
15 that when these protocols are devised, that the agency  
16 provides guidance to the sponsor as far as what they  
17 might be looking for. That is just sort of an  
18 information question.

19 DR. ORLOFF: I think -- I don't think there  
20 is any disagreement as to whether or not the principle  
21 has been proven that this is not placebo in either  
22 Type 1 or Type 2 diabetes. Depending upon the disease

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 target and the nature of the drug and its safety and  
2 efficacy profile, a proof of principle,  
3 notwithstanding any relationship to actual use, may be  
4 sufficient for approval.

5 What we are asking you actually is whether  
6 proof of principle in this instance is sufficient  
7 information for you to go ahead and recommend approval  
8 because you believe that we ought to be able to label  
9 this drug for safe and effective use and that  
10 physicians and patients alike ought to be able to use  
11 it across the board safely and effectively. We're not  
12 holding anybody hostage. It's a question of proof of  
13 principle versus how do you use the drug.

14 DR. MANIGOSKI: I'm Dr. Manigoski. I will  
15 second the opinion of Dr. Orloff. I think we don't  
16 disagree that this drug works and we have stated this  
17 time and time again. The point is whether to prove a  
18 principle you need to treat 2,000 patients. Maybe 100  
19 patients will do to show that this works.

20 Then you have to study a population such  
21 that represents the general population and allow you  
22 to treat across HbA<sub>1c</sub>. What we have learned from the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 studies that have been conducted is that if you start  
2 at 9 you can go low to .3. What happens at 8, at 7 we  
3 don't have the slightest idea.

4 Of course, we can cut among the studies or  
5 the patients that were incorporated in the study in  
6 trying to answer this question but this is not the way  
7 we see that we have to look at the data.

8 We would like to see patients treated in the  
9 way in which you treat your patients in addition to  
10 these to see what happens. We have not seen that and  
11 we are looking into that. We have not forced the  
12 company to do the studies in this manner. They have  
13 chosen to do the studies in this manner.

14 DR. TAMBORLANE: Let me ask -- let's make a  
15 hypothetical. Let's say that we started with patients  
16 who had a HbA<sub>1c</sub> of 6.8 and they did a study to look at  
17 Symlin versus placebo with insulin and it showed that  
18 A<sub>1c</sub> did not change but that the peak postprandial  
19 glucoses were substantially reduced on a seven sample  
20 glucose profile. Would that be a sufficient endpoint  
21 for the agency to say that they have shown a benefit  
22 assuming that there was no difference in safety

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 issues?

2 DR. MANIGOSKI: Assuming that there are not  
3 safety issues, we have to look at the issue of what --  
4 okay, how relevant is postprandial glucose. I am not  
5 a diabetitologist. Three years ago when I became  
6 involved in this project when I went to the  
7 conferences and I learned about postprandial glucose,  
8 it makes a lot of sense. I say the money is there.  
9 If you diminish the postprandial glucose, you have a  
10 winner.

11 I think it makes sense to think in this  
12 manner. However, since then we have evaluated rapid  
13 active insulins and other compounds that act in the  
14 early phase. Although, as you have seen here, you  
15 have dramatic changes in the postprandial, at the end  
16 the HbA<sub>1c</sub> changes at a .3.

17 We still are debating whether what is the  
18 role of postprandial. The literature showing that if  
19 you correct for this, you may prevent cardiovascular  
20 disease. This is open to discussion. I will argue  
21 that the quality of these papers are not very good.

22 I think that the company has stated

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 something also that is extremely important. They  
2 stated that this beautiful data and their conditions  
3 of clinical research meaning that these beautiful  
4 curves -- when I saw the curves I was really impressed  
5 -- is what happens when you bring the patient to the  
6 clinic, you fast the patient, you give them Sustecal,  
7 you give the injection at the time you want, etc.,  
8 etc. When you leave that condition and you conduct a  
9 clinical trial, you see completely different outcomes  
10 and this is what we have seen.

11 There is one more step. You will be the  
12 first to recognize that when you have patients and  
13 their clinical trials, probably this is the best of  
14 care. The question is whether this level, .3, will  
15 remain once you have this in clinical practice.

16 Let me also add that I think clearly the  
17 company has shown, and we have shown, that you don't  
18 have a dose response relationship. Therefore, it is  
19 open to discussion. I argue very hardily that 30 is  
20 safer than 60 or 90. I have not seen the data to make  
21 that judgement.

22 I think we have hypoglycemia with 30, with

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 60, with 90, and under 20. We agree full heartedly  
2 with the company that it seems that during the first  
3 months you have more hypoglycemia. However, you have  
4 motor vehicle accidents that are attributed to  
5 hypoglycemia during the 12 months. We don't have a  
6 mechanism to discriminate who is going to have it, how  
7 he's going to have it, what dose, etc., etc.

8 DR. TAMBORLANE: I just want to follow up on  
9 one point about this clinical research, that it's a  
10 different situation. It certainly is. One thing as  
11 somebody who is actually trying to do some of these  
12 clinical investigations now, Davida Kruger talked  
13 about the art and experience that is involved in  
14 taking care of particularly Type 1 diabetes.

15 We look at the one month hypoglycemia data  
16 and say that this might be expected because whenever  
17 we change a regimen in a patient with Type 1 diabetes,  
18 we might see more hypoglycemia, but nobody has  
19 mentioned the fact that the clinicians who are caring  
20 for these patients, they are naive to this therapy as  
21 well.

22 They don't know perhaps what to expect

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 either. Personally I would take some of the issues  
2 with the hypoglycemia reflecting a change in therapy  
3 in the patients and also a learning curve for the  
4 clinicians.

5 DR. KOLTERMAN: Mr. Chairman, if I could  
6 just interject a comment here. This has been a very  
7 nice conversation and the thing that I would like to  
8 add is that the experience with Lispro insulin is that  
9 it looks much better in the controlled setting of a  
10 metabolic unit than what the results with Lispro have  
11 been in the general clinical setting.

12 Also, in terms of the very real question  
13 that the panel needs to wrestle with this afternoon is  
14 do we know enough to provide reasonable instructions,  
15 reasonable informed instructions to clinicians as to  
16 how to use pramlintide therapy.

17 I would like to call upon Dr. Richard Dickey  
18 who has been a clinical consultant to us who is an  
19 endocrinologist in private practice in North Carolina  
20 who has some experience with pramlintide and also  
21 treats patients on a regular basis and have him  
22 comment upon the introduction of this into clinical

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 use.

2 DR. KREISBERG: Richard, how much time are  
3 you going to take?

4 DR. DICKEY: How much time do you want me to  
5 take, Bob?

6 DR. KREISBERG: Well, not a whole lot.

7 MR. DICKEY: Couple of minutes. Thank you  
8 for inviting me to speak and thanks to Amylin for  
9 inviting me to sit on their team today.

10 I practice clinical endocrinology in  
11 Hickory, North Carolina, and I did a 121 study with 10  
12 Type 1 diabetes patients. The results of the study  
13 were not dissimilar from the results that have been  
14 summarized today.

15 The importance of the study is that it was  
16 in the clinical practice with patients that I've been  
17 treating for some time who had not achieved optimal  
18 glycemic control to prevent complications. These  
19 patients were offered to participate in the study  
20 because of that.

21 80 percent of the 10 patients in the study  
22 had their insulin doses changed in violation of the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 protocol recommendations but the protocol did not  
2 restrict us from doing that. The clinical practice  
3 was consistent with what I thought was wise, fair, and  
4 appropriate.

5 The results of the study were similar to  
6 those that have been presented. One patient dropped  
7 out at two weeks because of nausea. He was on the  
8 highest dose. Two other patients dropped out because  
9 of the rigorous requirements of the protocol.

10 Not because of the drug but because of the  
11 frequent monitoring, the diary keeping, and because of  
12 travel. Some of these patients, as Claresa Levetan  
13 pointed out this morning, traveled 100 or 150 miles  
14 one way to participate in this study.

15 The results of the study, and I think this  
16 is important because when you do a study to try to  
17 obtain approval for a drug, you are looking at means.  
18 These are not means. These are 10 individual patients  
19 who participated in a study and whose drops in HbA<sub>1c</sub>  
20 were .5 to .8 at the end of the study for half of the  
21 patients in my study.

22 That is a significant improvement. Those

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 patients were mad when I did not offer them to  
2 participate in the open-label extension which was  
3 offered to me and which I declined. They are still  
4 waiting for approval of the drug, as has been  
5 mentioned by some earlier today.

6 I was quite excited about this replacement  
7 for a natural hormone and participated actively in the  
8 study and have continued to follow this product in its  
9 development. I am happy to say that two weeks ago I  
10 found out about this hearing and asked to participate  
11 in the public comment session and instead was invited  
12 by the company to sit here as a practicing clinician.

13 I hope that these findings in my particular  
14 study, which mirror the findings and some of the  
15 statements that were made by some of the individual  
16 patients, will convince you that there are people, in  
17 the case of my study, half of the patients that  
18 participated, who uniquely benefitted by this drug.

19 We did have three patients with hypoglycemic  
20 events. None of them serious or compromising the  
21 patients or resulting in any significant injury but  
22 reported as appropriate by the protocol. All of those

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 patients continued in the study to completion. Thank  
2 you.

3 DR. KREISBERG: So we can do this in some  
4 order, I'm going to go back to Lynne because we  
5 skipped over here. Then I'm going to go to Marie and  
6 around and I'll come back to everybody.

7 DR. LEVITSKY: Okay. I will make one  
8 comment but I need to ask Dr. Dickey a question first.

9 You had 10 patients, three of whom dropped  
10 out, and half of the seven that were left had a  
11 response and the other half did not. Is that correct?

12 MR. DICKEY: There were 10 patients in the  
13 study. There were three who did not complete the  
14 study. One dropped out at 44 weeks because he  
15 developed sarcoidosis and had to go on prednisone  
16 which was in violation of the protocol.

17 DR. LEVITSKY: Okay.

18 MR. DICKEY: One who dropped out at two  
19 weeks because of nausea. He was on the highest dose.  
20 One other who dropped out because of distance, travel,  
21 and the rigors of the protocol. What I said was five  
22 patients out of the 10 achieved reductions in A<sub>1c</sub> of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 .5 to .8.

2 DR. LEVITSKY: Okay. Thank you.

3 The comment which I guess I want to address  
4 to the FDA, I'm getting a fuzzy memory but I seem to  
5 recall that after the approval of human insulin, there  
6 was a big human cry about the fact that much more  
7 hypoglycemia was seen with human insulin than with  
8 beef or pork insulin.

9 There was real concern and worry about this  
10 which you guys had to deal with. It turns out it was  
11 probably just the doctors didn't know how to use it  
12 yet. When we learned how to use it, this wasn't an  
13 issue at all. Could you tell me how you went about  
14 sorting that out? It would be interesting because I  
15 hear something like that happening here, I think.

16 DR. MISBIN: None of us were here during the  
17 approval of human insulin. This is an extremely  
18 contentious area. I will tell you in advance that I  
19 am going to sound very evasive.

20 DR. KREISBERG: You weren't here but you're  
21 going to go into some detail about this? Is that what  
22 you're going to tell us?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. MISBIN: I'll just tell you things that  
2 I think would not be controversial. I think it's fair  
3 to say there are many people that feel very strongly  
4 that there is more hypoglycemia with human insulin  
5 than with animal insulins and they are very eager to  
6 convince the FDA of their position and we certainly  
7 listen to them.

8 They are very vocal and I don't trivialize  
9 this at all. They have diabetes and I don't. It's  
10 not up to me to say that they would do better on one  
11 product than another.

12 On the other hand, when one looks at the  
13 clinical trials, and this has been done, there is no  
14 difference with respect to these events. What is a  
15 regulatory agency supposed to do? We really cannot  
16 address public policy based on the perceptions of  
17 individual cases. We have this responsibility and we  
18 take it very seriously.

19 Now, otherwise the issue of beef and pork  
20 insulin and human insulin is something which we really  
21 cannot go into. The point that you're asking is very  
22 relevant and I wish you would ask it in another way so

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 I would be able to respond.

2 DR. LEVITSKY: Tell me how I should ask it.

3 DR. MANIGOSKI: I will try to address that  
4 issue. I think it is very important. The point is  
5 that we have randomized placebo control studies. Even  
6 one arm of the study -- I don't know why because they  
7 are blinded -- you have four times more hypoglycemia  
8 than in the other. I don't know. Maybe it is placebo  
9 and maybe it's the drug. That is the way in which we  
10 address the issue.

11 We would love to know what the mechanism is  
12 as the company would like to know whether the  
13 mechanism is for hypoglycemia. There are many  
14 interesting and world-wide hypotheses but we don't  
15 know.

16 What we do is we look at the data and we see  
17 that there is a disbalance, a disproportionate number.  
18 The explanation is that maybe people don't know how to  
19 use the product. Therefore, the company has to do the  
20 studies to show us how to use the product and not  
21 allow a product that may induce very life-threatening  
22 conditions to be in the market to let physicians to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 figure out whether these things do happen or not.

2 The same with the motor vehicle accidents.  
3 This was a finding we never expected this to happen  
4 but suddenly when you look at the data, you or 11 or  
5 12 or 14 -- I don't know how many -- on one arm and  
6 one or two on the other.

7 The patients were randomized and this  
8 happened in one arm and the other. If this would have  
9 happened the other way around, we would say placebo is  
10 very dangerous and may lead you to have a motor  
11 vehicle accident. Unfortunately, I think, the results  
12 were different.

13 DR. KOLTERMAN: Mr. Chairman, I would like  
14 to show a couple pieces of data what was asked for  
15 earlier that I think helps address this concern about  
16 hypoglycemia and in the Type 1 population.

17 The first slide -- slide up, please -- is  
18 one that was included in the presentation that look  
19 sat the event rates of hypoglycemia over time during  
20 the first four weeks of therapy where you see a dose  
21 dependent rise with increasing doses. Again, I call  
22 your attention as I did this morning to the data for

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the 30 microgram dose where there is much less of an  
2 increase in hypoglycemia.

3 If we now look at how patients did with that  
4 dose over time -- next slide, please. Slide up -- you  
5 see the data here that on the previous slide and you  
6 can see that there is really a very -- any increase in  
7 severe hypoglycemia needs to be taken seriously.

8 Nothing that I say is intended to downplay  
9 this but there is a significantly less increase in  
10 severe hypoglycemia here with the 30 microgram dose  
11 which leads us to the recommendation that the primary  
12 focus for patients with Type 1 diabetes be on the 30  
13 microgram dose and in some situations one might want  
14 to initiate therapy even at a lower dose.

15 DR. MANIGOSKI: Excuse me. These are  
16 events, not patients. Am I correct? Events not  
17 patients?

18 DR. KOLTERMAN: You are correct, Dr.  
19 Manigoski. These are events and not patients. We  
20 continue to feel as was done in the DCCT that this is  
21 the most meaningful way to look at the data. We have  
22 incidence data. We can pull up incidence data for the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 study.

2 DR. SAMPSON: Could we see the incidence  
3 data? Could we actually see the incidence data?  
4 Would you put that up, please?

5 DR. KOLTERMAN: Yes.

6 DR. CARA: Could I make a comment in the  
7 meantime? Yes, it is. If I'm not mistaken, it  
8 wouldn't surprise me that in this study you did not  
9 see hypoglycemia over time because this is one of the  
10 studies where patients were actually able to adjust  
11 their insulin.

12 DR. KOLTERMAN: Right. They also were able  
13 to adjust their insulin during the first four weeks  
14 during the period of initiation. Basically our recipe  
15 for addressing the issue is to initiate therapy with  
16 a lower dose and to decrease insulin with the  
17 initiation of therapy as I had mentioned in the  
18 presentation this morning.

19 Slide up, please. This is the incidence  
20 data for severe hypoglycemia during the first four  
21 weeks in the three Type 1 studies. I believe this  
22 pattern is similar to that that was seen with the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 annual event rate data.

2 The advantage of the annual event rate data,  
3 we believe does it really apply to this issue because  
4 the amount of patient exposure is pretty much constant  
5 across the different treatment groups.

6 When you look at longer periods of time, the  
7 annual event rate becomes useful to compensate for  
8 differences in exposure. Also the fact that single  
9 patients may have more than one event. Thank you.

10 DR. GELATO: I want to go back to a comment  
11 that you just sort of alluded to when you said that  
12 based on the data that you just showed us that you  
13 might want to start with 30 or perhaps lower.

14 Have you looked at lower doses because, as  
15 was pointed out before, there doesn't seem to be a  
16 dose response when you look at glycated hemoglobin.  
17 I wonder could you start with a lower dose? I mean,  
18 has that been looked at? Would that change your  
19 incidence events with hypoglycemia? Then slowly  
20 titrate patients up.

21 I think one of the things we are all  
22 concerned about is how do you do this. I'm getting

1 the sense that maybe you could go with a lower dose  
2 and maybe that would help this event or the  
3 hypoglycemic problem. Do you have data for that?

4 DR. KOLTERMAN: There are two pieces of data  
5 that go in that direction. In an early clinical  
6 pharmacology study patients were dosed with a dose of  
7 10 micrograms for 14 days. With the 10 microgram dose  
8 it's probably too low for the efficacy.

9 There was evidence of efficacy but it did  
10 not in the small number of patients achieve  
11 statistical significance. With the 10 microgram dose,  
12 there was little nausea and there was not an issue  
13 with hypoglycemia. That is one piece of data.

14 The other piece of data is that for business  
15 reasons the long-term open-label extension studies  
16 that we had under way in 1998 had to be canceled for  
17 financial considerations. There was, as you heard  
18 this morning, or heard allusions to this morning, an  
19 outcry amongst a good number of the participants and  
20 they felt they had something that was valuable to them  
21 being removed.

22 As it became available we offered to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 investigators, who had sizable numbers of those  
2 patients, the opportunity for another open label sort  
3 of extension, if you will, an interrupted extension  
4 study with a period in between.

5 That is the means by which the patients who  
6 spoke this morning appear to be gaining access to the  
7 drug. In that protocol, a number of investigators  
8 have chosen to initiate therapy with 15 micrograms for  
9 a period of one to two weeks and then escalate to 30  
10 micrograms.

11 This, in many ways, is not different from  
12 the experience that we are familiar with as clinicians  
13 in terms of dealing with insulin in this patient  
14 population.

15 DR. GRADY: Well, I'm going to dispense with  
16 the question. Do you have something else?

17 DR. KOLTERMAN: Dr. Baron would like to add  
18 a comment to the last point we were making.

19 DR. BARON: I would like to make a comment  
20 as an endocrinologist. One of the observations that  
21 I made looking at this program was that the patients  
22 with Type 2 diabetes were given a higher dose, yet had

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 a much lower incidence of nausea.

2 One has to wonder why even at lower doses  
3 patients with Type 1 diabetes had much more nausea.  
4 We don't really know the answer to that but one of the  
5 things that occurred to me was that patients with Type  
6 1 diabetes have absolute amylin deficiency and, in  
7 this case, on average 19 years.

8 It's not uncommon, at least in  
9 endocrinology, that when we place a hormone there is  
10 hypersensitivity initially. Clearly in patients who  
11 are hypothyroid, for example, and elderly, we are very  
12 careful to introduce the hormone back slowly. The  
13 Type 2 patients are relatively amylin deficient but  
14 not completely amylin deficient. While there is  
15 absolutely no proof to what I say, I think to me that  
16 makes sense, again, as an endocrinologist.

17 DR. GRADY: Thanks. Well, I just want to  
18 compliment everybody on the display of data. I think  
19 it has really been very clear and very helpful. I  
20 think where I am now is maybe more in the discussion  
21 phase. If I could just voice my concerns, that is, it  
22 seems to me this drug does have efficacy. We are not

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 arguing about that, but the efficacy is rather small.

2 I could probably get the same efficacy  
3 relatively easily by increasing insulin doses. But  
4 the advantage your drug has there in contradistinction  
5 to insulin, decreases weight and may decrease insulin  
6 levels. Both of those may be good but maybe  
7 marginally good. What we are trading off against  
8 those potential benefits are, of course, the dangers  
9 of hypoglycemia.

10 The three things that really worry me about  
11 what we understand about hypoglycemia with this drug  
12 are, (1) I am still really worried that there is lots  
13 of nausea associated with this drug, nausea and  
14 anorexia.

15 I'm worried that those two things are  
16 associated with the mechanism of hypoglycemia because  
17 many of the patients with nausea and anorexia dropped  
18 out early in the study and may subsequently have  
19 developed hypoglycemic episodes that we would not have  
20 captured because they were dropped from the study.

21 (2) It may be that physicians will get more  
22 experience using your drug over time, but it could

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 also be that once patients get outside of the  
2 carefully controlled situation of a clinical trial  
3 that we will see yet more hypoglycemia.

4 Thirdly, and maybe most importantly, I  
5 haven't seen any evidence, at least, that your  
6 approach of decreasing insulin levels early on when  
7 you start your drug will really reduce the incidence  
8 of hypoglycemia. Maybe that will work. I don't know.

9 It could also be that once insulin levels  
10 are subsequently increased later in the use of your  
11 drug, that we will again see hypoglycemia. I think  
12 those are sort of the three real concerns about  
13 worries that hypoglycemia is going to be even more  
14 prevalent and more severe than it was in the clinical  
15 trial setting.

16 DR. KOLTERMAN: The primary consideration in  
17 that regard, I think, is that the -- I'll make an  
18 observation, cite some data, and then Dr. Dickey would  
19 like to add a comment to this.

20 The observation is that hypoglycemia  
21 occurred in the setting of a double-blind clinical  
22 trial where patients were being encouraged to maintain

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 their insulin regimens constant. That's not the way  
2 any of us would practice in a patient initiating  
3 therapy.

4 We would know that the patient was getting  
5 the drug. The patient would know that they were  
6 getting active drug. We now know what the side effect  
7 profile is and you could take appropriate actions.

8 I mentioned earlier in my comments that  
9 there were two long-term open-label safety studies  
10 done with the 30 microgram dose. In the open-label  
11 setting it appears that hypoglycemia was significantly  
12 less of an issue than what it was in the 30 microgram  
13 dose treated in a double-blind manner.

14 The reason that I cannot pull that data for  
15 you is that I would be comparing apples to oranges and  
16 that the capture of hypoglycemia data in those open-  
17 label studies were not comparable to what was done in  
18 the double-blind study.

19 Now I would like to ask Dr. Dickey to make  
20 his comment.

21 MR. DICKEY: Thank you. I just wanted to  
22 share the concern that I have with hypoglycemia in any

1 patient irrespective of pramlintide. You mentioned  
2 that you could improve the control of the patient by  
3 increasing insulin.

4 My experience in trying to do that, and I  
5 mentioned that in the patients that I entered into the  
6 trial, I think that I had done the best I could with  
7 the tools available for the treatment of those Type 1  
8 patients, namely, insulin, diet, education, and I  
9 still was not able to achieve my goal. That is why  
10 they met the criteria for the protocol of over 8  
11 percent.

12 In trying to increase the insulin in the  
13 patient to improve control, I believe that you are  
14 likely to increase the risk of hypoglycemia. It is a  
15 special concern of mine and I have published and I  
16 have currently an article in review about that very  
17 risk. Not about new drugs but about the risk of  
18 hypoglycemia as we become more aggressive in our  
19 treatment, namely with insulin.

20 A recent article in Diabetes Care pointed  
21 out that the -- this is no news to you, I'm sure, that  
22 the peaking of insulin, for example, of NPH, and I

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 believe it's going to turn out to be true of Lantis as  
2 well, is not as predictable as we would like.

3 My concern is that in treating these  
4 patients, I can smooth the curve, as some of the  
5 patients alluded to earlier, smooth the curve, reduce  
6 the standard deviation, something that we all want to  
7 do. Reduce hypoglycemia, reduce hyperglycemia with  
8 the use of this drug.

9 That is one of the main reasons I'm excited  
10 about the drug. It reminds me that when I was  
11 thinking about beginning using insulin pump therapy as  
12 a solo practitioner, I was very concerned about not  
13 having another endocrinologist within 60 miles and  
14 doing insulin pumps.

15 I went to two or three meetings sponsored by  
16 an insulin pump maker and heard patients repeatedly  
17 say from the podium that their hypoglycemia was less  
18 on an insulin pump even though their A<sub>1c</sub> was lower.  
19 That impressed me. I believe the same thing can  
20 happen with pramlintide. That's another reason I'm  
21 excited about it.

22 I would beg you to consider that if we've

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 done the best we can with other means of therapy for  
2 the Type 1 patient, namely insulin, education, and  
3 diet, and exercise, then I'm not sure that you can do  
4 enough to do better than this drug can do even though  
5 the magnitude of the reduction in A<sub>1c</sub> is relatively  
6 smaller than you would like to see. Thank you.

7 DR. KOLTERMAN: Mr. Chairman, if I could  
8 just remind the panel that we did present a  
9 recommendation for the initiation of therapy in the  
10 presentation this morning.

11 Slide up, please. This was to choose an  
12 initial dose. The 120 microgram dose appears to be  
13 appropriate for patients with Type 2 diabetes. We  
14 chose the words well or carefully, 30 micrograms or  
15 lower in patients with Type 1 diabetes.

16 Dose frequency determined by the patient's  
17 meal pattern. Some patients only eat two meals a day,  
18 if that is the patient's lifestyle, dosing twice a  
19 day, three times a day, or the patient eats three  
20 meals. Type 1 patient three meals and a snack, four  
21 times a day.

22 The drug is given 15 minutes before a meal.

1 Insulin reduction with initiation of therapy 10 to 20  
2 percent of the postprandial short-acting insulin dose,  
3 not dissimilar to the recommendations in the labels of  
4 other compounds that are approved for use as add-on  
5 therapy to insulin.

6 Next slide, please. This fits into, we  
7 think, allowing the physician the patient to  
8 compensate for both the nausea and the satiety effect  
9 based upon things that most patients and physicians  
10 are already familiar with, namely blood glucose  
11 monitoring and using this data to judge appropriate  
12 modifications to the patient's insulin regimen.

13 With chronic therapy this part of the loop  
14 continues, the blood glucose monitoring and  
15 appropriate adjustments of insulin to facilitate the  
16 patient's going to target. Thank you.

17 DR. CARA: I want to throw out a comment in  
18 response to your questions and maybe get your thoughts  
19 on it and see what you think and sort of have you tell  
20 me whether this is totally off base or not.

21 I think there is a way that I've struggled  
22 in trying to see this medication specifically as a

1 diabetic medication or as a diabetes related drug. I  
2 don't think it is. I think the bottom line is this is  
3 an anorectic agent that works either through essential  
4 mechanism or perhaps through delayed gastric emptying.

5 It's primary efficacy is in decreased food  
6 intake with some weight reduction. I think a  
7 secondary effect is actually reduction of glycosylated  
8 hemoglobin as a result of better compliance with meal  
9 plans.

10 As a result, there is a direct dosage  
11 response between the anorectic effect and the drug  
12 dose. The side effects are related directly to the  
13 biological activity of the medication; hypoglycemia,  
14 anorexia, and nausea.

15 As a result, the dose has to be tapered  
16 individually based on side effects and the clinical  
17 response of the patient. If you think of it in those  
18 terms, and you think of it in terms of that paradigm,  
19 I think it tends to work better. Does that make  
20 sense?

21 DR. KREISBERG: Let me tell everybody what  
22 I would like to do since I'm the Chair. It's 20

1 minutes to 4:00 and we have seven questions to address  
2 with subsets of each question.

3 What I would like to do is invite the  
4 panelists to -- I'm just going to go around the table  
5 -- to make a concise statement about your feelings  
6 about the drug, studies that you might think would  
7 shed more light on the mechanism of action.

8 We are going to move around. Hopefully that  
9 will be in 25 words or less. We'll then begin to vote  
10 and that will be associated with more discussion.

11 Having said that, can I start with you.

12 MS. KILLION: 25 words. Okay. That's four  
13 to five right there. Diabetics are always struggling  
14 for balance and I think that's the theme of this drug,  
15 balancing risks and benefits. Interestingly enough,  
16 I think the parallels are really high. Hypoglycemia  
17 happens. It happens to all of us, some more than  
18 others.

19 My concern is what can you do to minimize  
20 the risk of hypoglycemia in its severe instances in  
21 the four-week window where that risk seems to be most  
22 amplified. I really haven't heard anything. They

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 said, well, reduce your insulin but we don't know what  
2 that effect is so we need to see something on that.  
3 Maybe that will work and wouldn't that be great but we  
4 don't know and that's a scary thing.

5 It's a very seductive drug for diabetics.  
6 To have a new option for Type 1 is very inspiring  
7 since we haven't had -- we've had different kinds of  
8 insulins but not anything that acts in a different way  
9 or in conjunction with.

10 And to have weight loss instead of weight  
11 gain, that's manna from heaven. I guess in addition  
12 to even a small reduction in your HbA<sub>1c</sub> anything that  
13 is going down is good. To have your weight loss, to  
14 use a forbidden phrase, that is icing on the cake.

15 But my concerns are still how do you get  
16 safely through that high risk period if you accept the  
17 notion that it does go down over time? Two, many  
18 patients -- this is a high-level concern for me, this  
19 second one. Many patients, probably most patients, do  
20 not have the level of care, the exquisite level of  
21 care that you get in a clinical study.

22 They are going to people who are not

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 diabetic specialist and they are saying, "Here's a  
2 drug." You get all kinds of responses to that. I  
3 worry about that risk of hypoglycemia being amplified  
4 in a much broader population. Those are my comments.

5 MS. McBRAIR: I agree with everything that  
6 Rebecca has said and I think she's making some  
7 interesting comments. I certainly think that the  
8 patients themselves have the right to decide if they  
9 want to live with the increased number of injections,  
10 if they can handle the nausea side effects.

11 I, too, am concerned about the hypoglycemic  
12 events. I think we could study that more. I think we  
13 can help education patients and physicians that that  
14 could happen and to be more aware to make sure that  
15 they have effective monitoring in place, that they are  
16 staying on top of it now that we know that's an issue.

17 I still think we should be looking at  
18 quality of life and if, at least, the anecdotal  
19 reports that the physicians and the patients have  
20 reported here on quality of life is true, then it's  
21 another reason to approve this drug and look to make  
22 sure we know what the indications are for some of the

1 folks.

2 DR. CARA: I've already told you what I  
3 thought to a large extent but I think, too, that there  
4 are still a number of questions that need to be  
5 resolved. I'm just going to add a couple to what  
6 other people have already commented on.

7 I think issues related to really  
8 establishing the characteristics of the patients that  
9 are likely to respond to this medication and that  
10 might best benefit from this medication still needs to  
11 be established. I still think that we need to learn  
12 more about its dose response characteristics and its  
13 true efficacy.

14 I think there is a fine line between  
15 biological effect and adverse effect that still needs  
16 to be teased out. I would also like to know more  
17 about what type of insulin regimens might work best  
18 with this sort of medication. I think the other issue  
19 is trying to get at sort of more concrete evidence of  
20 intolerance to the medication other than just nausea  
21 or anorexia which are very subjective terms would be  
22 very helpful.

1 DR. LEVITSKY: I think the company has set  
2 the background for a drug that could very well be  
3 quite important in the management of Type 1 and Type  
4 2 diabetes and their evidence for efficacy is good.

5 What I would like to see is a study which  
6 evaluated quality of life, nutritional aspects  
7 including quality and quantity of nutritional intake  
8 and change during the course. I would like to see  
9 something that looked in a chronic kind of way at  
10 maximum amplitude of glucose excursions so that you  
11 could see the effects that the patients anecdotally  
12 reported.

13 I would like to examine a dose which perhaps  
14 was slightly lower in the patients with Type 1  
15 diabetes. I think it could be done in a double blind  
16 way with flexible insulin dosing without hurting the  
17 patients. It's possible that it would take a dose  
18 slightly lower than the 30 micrograms to pick this up.  
19 I think if that were done, that there could be really  
20 powerful evidence as to how to use this drug and also  
21 its safety characteristics.

22 DR. TAMBORLANE: I'd like to thank everybody

1 for a very interesting day, actually, and also join in  
2 both the FDA and the company. I agree that efficacy  
3 has been demonstrated. There are the obvious concerns  
4 about safety.

5 However, it's my feeling that these safety  
6 issues related to hypoglycemia, although incredibly  
7 important were also predictable and potentially  
8 manageable. I think ultimately the drug is  
9 approvable. The issue has to do, like everybody else  
10 said, this first month of therapy.

11 It seems to me that would be a very easy and  
12 relatively quick study that could be done that would  
13 just focus in the first four weeks that you could test  
14 placebo versus drug and cut the insulin dose by 20 or  
15 10 percent and have some sort of answer within a few  
16 weeks.

17 DR. GELATO: There are just two things that  
18 I like about this drug very much. One is in the Type  
19 2 patients you get weight loss. I think that is  
20 important. The other thing that I like about it is in  
21 the Type 1 patients if you can truly smooth out their  
22 glucoses, I think that is important because I think

1 that is a problem.

2 I think this drug has a lot of promise. I  
3 think other people have already stated some of the  
4 feelings that I have. I would like to see a lower  
5 dose tried first where you actually do titrate their  
6 own insulin and hopefully get around the problem of  
7 the hypoglycemia because I think the drug really does  
8 have a lot of promise.

9 As many people have said, for Type 1 there  
10 really isn't anything else out there. I certainly  
11 would like to see more done with it and feel, too,  
12 that it should be a drug that should get approved.

13 DR. SAMPSON: I would agree with the  
14 agency's analysis that efficacy has been established.  
15 It seems to me it's worthwhile. Just reiterating what  
16 I said earlier, it would be nice to see a true  
17 clinical dose response group including lower doses.

18 The safety differences were noted in the  
19 first four weeks. I thought I heard the agency also  
20 argue that differences, though they are less, still  
21 exist beyond four weeks.

22 It seems to me that one would like to see

1 perhaps a placebo controlled dose response study in  
2 maybe a setting that is more compliant with the ADA  
3 recommendations.

4 But also you have provided a strategy, I  
5 think, for handling hypoglycemia in the first four  
6 weeks. That certainly could be tested in a clinical  
7 trial to see if it reduced the incidence or made the  
8 comparison to placebo in terms of hypoglycemic events  
9 disappear or get very small in the first four weeks.

10 DR. GRADY: I think it is also a very  
11 exciting drug. I find it a little hard to think about  
12 it in terms of Type 1 and Type 2 diabetes. I think  
13 for Type 1 diabetes it's an exciting drug and we are  
14 worried that the benefits may not exceed the risks.

15 I think all of us have this idea that  
16 somewhat more study of minimizing the risks would be  
17 use. I think particularly a randomized control trial  
18 in which insulin doses were decreased to begin with  
19 and allow to vary as they normally clinically would  
20 with very careful measurement of hypoglycemic  
21 episodes, quality of life, and glucose excursions.  
22 Those are the main things that we've heard today that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 are really the big benefit of the drug.

2 I agree while I know that you can't rip out  
3 and do that in a couple of weeks, I think it could be  
4 a fairly short-term trial perhaps.

5 Secondly, when I think about Type 2  
6 diabetics it is a somewhat different situation because  
7 there I think the efficacy that you demonstrated was  
8 pretty much the same and there was very little risk.  
9 The risk benefit there is much better.

10 However, we have many more options for Type  
11 2 diabetics. The idea that many of our Type 2  
12 diabetics are going to use three or four injections a  
13 day I guess I find -- I mean, I doubt that is going to  
14 happen. Of course, we should let them make that  
15 decision.

16 I guess I would like to bring the committee  
17 back to it seems like everyone was talking about Type  
18 1 diabetics and I would like to -- we are also charged  
19 with the question of what to do about approving a drug  
20 for Type 2 diabetics. I would just like to see what  
21 other folks have to say about that.

22 DR. KREISBERG: The Chair can --

1 DR. KOLTERMAN: I just wanted to make one  
2 comment, Dr. Kreisberg. That is, that the sponsor  
3 sees value in a study evaluating changes in insulin  
4 with the initiation of therapy.

5 Also exploring lower doses and had planned  
6 to do that and feel it would be an appropriate study  
7 to be done very soon. We would hope that it can be  
8 seen prudent to approve the drug with the  
9 understanding that that study would be done.

10 DR. MISBIN: Dr. Kreisberg, may I make a  
11 brief statement also? Very briefly. I think several  
12 people have alluded to the fact that this is America  
13 and people have a choice as to whether they want to  
14 take several injections and whether they will tolerate  
15 nausea or not. We completely agree with that.

16 I just want to point out that if you take  
17 the motor vehicle accident incidence serious as we do,  
18 that there is a four-fold risk in patients on  
19 pramlintide, then not all the adverse events would be  
20 in patients.

21 I think I need to remind people that in the  
22 DCCT there were three patients who died of motor

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 vehicle accidents, one on conventional treatment, one  
2 on intensive treatment, but there was also one person  
3 who was not a patient who died as a result of an  
4 automobile accident that was attributed to  
5 hypoglycemia in the driver who was in the intensive  
6 group.

7 I think, yes, patients have a choice but  
8 some of the adverse events will be in people who do  
9 not have a choice and are not going to be amenable to  
10 black boxes or anything else that patients ordinarily  
11 would have the availability of.

12 DR. KREISBERG: Well, I would like to say  
13 that I think the idea that you could improve the  
14 effectiveness of insulin without increasing the dose  
15 is very attractive. It's a promising concept that I  
16 think needs to be pursued. I think the drug that you  
17 are investigating has a unique mode of action,  
18 although I'm not exactly sure what that mode of action  
19 is, but it clearly is different.

20 I think the efficacy is clear. I think it's  
21 small but that may be an understatement of its value.  
22 I think that the agency really needs to get into

1 explaining -- I'm sorry, the sponsor needs to get into  
2 explaining the discrepancy between the public  
3 testimony and the lack of any information like that  
4 provided to us by you because I can see value in a  
5 drug that perhaps had a modest effect on the HbA<sub>1c</sub> if  
6 it did, in fact, smooth out the curve as Dr. Levitsky  
7 suggested that it might.

8 If it made the quality of life better for  
9 the patient, it would be a valuable drug. I think  
10 that this drug has that potential if we could  
11 understand it somewhat better than we do.

12 I don't want to trivialize hypoglycemia  
13 because I think it's very important but Dr. Tamborlane  
14 pointed out that hypoglycemia was a very common  
15 complication in the DCCT and I think whenever you  
16 strive to get the very best control that you can in  
17 diabetic patients, that's always one of the  
18 considerations that you have to deal with.

19 If I recall, close to 30 or 35 percent of  
20 the patients in the DCCT actually did have significant  
21 hypoglycemic reactions. Many of those were severe  
22 occurring in the early morning hours, as I recall.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           On the other hand, I took some numbers out  
2 of your data and Dr. Grady can correct me because she  
3 knows this area much better than I. In your Type 2  
4 diabetic patients you need to treat six or seven to  
5 get a one percent decrease in the HbA<sub>1c</sub> and you need  
6 to treat 100 to harm a patient. That's what I came up  
7 with in calculating.

8           I just wonder if you would take another look  
9 at your data to see whether you couldn't display it in  
10 some way that showed the relative risk benefit of  
11 that. For the Type 1 diabetics, it turned out that  
12 you had to treat eight to get 1 percent improvement in  
13 HbA<sub>1c</sub> and you had to treat 25 in order to harm a  
14 patient.

15           We have to decide what the risk benefit  
16 ratio is, I think, in order to determine whether the  
17 benefit is worth the risk. I think there are perhaps  
18 some more creative ways you can look at your data to  
19 see if you can cast it in more of a risk benefit type  
20 of effect.

21           I think there's some fine tuning that has to  
22 be done and I would heartedly endorse a study that was

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 more real life, and that is the use of the drug with  
2 intensive management of the insulin alongside of it  
3 because that's the way in which we would hope it would  
4 be utilized in the community so that we can see  
5 whether we have to back pedal on some patients or go  
6 up on other patients.

7 I agree with everybody else that the initial  
8 four week period of time appears to be crucial in  
9 somehow identifying patients who might be withdrawn  
10 from the study subsequently because they show  
11 unusually unpredictable reductions in their glucose  
12 concentration.

13 I think it's as likely that we have missed  
14 some of the hypoglycemia because of the early  
15 dropouts. I also think it's theoretically possible  
16 that you've underestimated the benefit of the drug if  
17 you could have kept some of them in the study because  
18 there may be some relationship between the drop out  
19 and the ability to reduce the glucose concentration.

20 I think there's lots of things that need to  
21 be done to better understand how we could select a  
22 subgroup of patients who might get the most benefit

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 from the use of the medication.

2 Does anybody else want to make a comment?

3 DR. CARA: I just want to add one more area  
4 that I think would be interesting for you to look at  
5 that might be a little bit different from what other  
6 individuals have said, and that is that I would really  
7 encourage you to look at the efficacy of the drug  
8 alone in patients with Type 2 diabetes. That is, non-  
9 insulin requiring individuals with Type 2 diabetes.

10 DR. KREISBERG: If there's no further  
11 discussion, I would like to begin to ask the  
12 questions. I will read them and then we would like to  
13 go around the table. I'm told that each person who  
14 votes has to say what their name is and what their  
15 vote is.

16 The first question deals with efficacy and  
17 it reads, "Based on the information presented by the  
18 sponsor in the NDA, are the data adequate to establish  
19 the efficacy of pramlintide in combination with  
20 insulin for the treatment of patients with (a) Type 1  
21 diabetes, and (b) Type 2 diabetes." Let's do Type 1  
22 diabetes first and we'll start on my left.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 MS. KILLION: Rebecca Killion. Type 1, yes.

2 MS. McBRAIR: Wendy McBair. Type 1, yes.

3 Type 2, questionable.

4 DR. CARA: Jose Cara. Type 1, questionable.

5 DR. LEVITSKY: Lynne Levitsky. Type 1, yes.

6 DR. TAMBORLANE: Bill Tamborlane. Type 1,

7 yes. Type 2, yes.

8 DR. GELATO: Marie Gelato. Type 1, yes.

9 Type 2, yes.

10 DR. SAMPSON: Allan Sampson. Type 1, yes.

11 Type 2, yes.

12 DR. GRADY: Deborah Grady. Type 1, yes.

13 Type 2, yes. I only hesitate because there were only

14 150 people in all of these studies as far as I can

15 tell who were also taking metformin.

16 DR. KREISBERG: Bob Kreisberg. Yes for Type

17 1 and yes for Type 2, and I'm going to come back

18 around.

19 MS. KILLION: Okay. Type 2, yes. Rebecca

20 Killion.

21 DR. KREISBERG: Jose, we've got to get you

22 to commit yourself.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701