

1 DR. KOLTERMAN: Excellent question. I
2 believe that both the glucagon effect and the gastric
3 emptying effect are relevant to patients with Type 1
4 diabetes. The data that you cite related to "an
5 absent glucagon response after five years of Type 1
6 diabetes," refers primarily to the glucagon response
7 in insulin-induced hypoglycemia.

8 There are papers, nicely done studies in the
9 literature that clearly demonstrate that those
10 patients who have lost their glucagon response to
11 hypoglycemia still have postprandial hyperglucagonemia
12 in response to the ingestion of presumably food stuffs
13 that contain a stimulatory amino acids. Even in those
14 patients there is excess glucagon during the
15 postprandial period.

16 DR. GRADY: One important thing about just
17 the quality of randomized trials is whether or not
18 they're blinded. I wonder if there are ways in which
19 the participants or the investigators could know that
20 the participant was taking the active drug. Does it
21 taste different? Certainly it produces a lot more
22 nausea. Do you have any information? Did you ask

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1 participants if they knew what they were taking?

2 DR. KOLTERMAN: Okay. There's no indication
3 that participants knew what they were taking.

4 DR. GELATO: Did you ask them?

5 DR. KOLTERMAN: At some centers they were
6 asked at the end of the trial. That was an ad hoc
7 thing so it's anecdotal information. This is not
8 information that was assessed in a prospective
9 controlled manner.

10 DR. KREISBERG: Dr. Kolterman, with regard
11 to the formulation, I'm curious why there was this
12 mid-stream correction in the ph? Was that because it
13 was not formulated correctly when you started or were
14 you just tinkering with the preparation in order to
15 maximize bioavailability?

16 DR. KOLTERMAN: Okay. The change in
17 formulation, as I understand it, relates to the
18 studies that were done showing an effect of ph upon
19 long-term stability of the product in the formulation.

20 This is not atypical for what happens with
21 various drug formulations during the development
22 program. It so happens at the time that the study

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1 that I identified for you was initiated, the status of
2 the drug supply was ph 4.7 formulation.

3 DR. KREISBERG: Dr. Levitsky.

4 DR. LEVITSKY: The question I have is did
5 you in the course of any of these studies examine
6 nutrient intake? I assume that total calories, total
7 energy was diminished or they wouldn't have been
8 losing weight but did you look to see whether the
9 nausea effect introduced some changes in the quality
10 of the nutrients that were taken in so that perhaps
11 carbohydrate intake was diminished? Could that be
12 clarified a little bit to see whether you could
13 determine why the glyceimic control remained improved
14 with time?

15 DR. KOLTERMAN: Again, we do not have
16 controlled data addressing that in the program. There
17 are anecdotal reports that come primarily from long-
18 term open label safety studies where investigators and
19 trial coordinators have reported to us an impression
20 that they have of the patient changing somewhat the
21 composition of the nutrients that they ingest in terms
22 of moving away from fat-containing foods or foods rich

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1 in fat to those that contain more complex
2 carbohydrates. Understand that is anecdotal reports
3 at this time.

4 DR. TAMBORLANE: Orville, have you tried to
5 break down the incidence of severe hypoglycemia as a
6 function of time of day?

7 DR. KOLTERMAN: We have evaluated that. The
8 data is divided into four segments beginning at 8:00
9 a.m. The period from 8:00 a.m. until about noon time
10 and the period from noon until the evening are roughly
11 the same.

12 There is a clustering of events from like
13 6:00 p.m. or so until 10:00 p.m., 11:00 p.m. Bedtime
14 basically. Then there is certainly no increase of
15 events during the night time and there is actually a
16 trend toward decrease in hypoglycemia over night.

17 DR. GRADY: Do you know what proportion of
18 patients were taking postprandial short-acting
19 insulin?

20 DR. KOLTERMAN: I can give you a ballpark
21 figure for Type 1. For Type 1 patients over 80
22 percent -- I'm sorry, over 90 percent were taking two

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1 injections a day. There were very few patients taking
2 a single injection a day.

3 Of those patients taking two or more
4 injections a day, they almost all were using either a
5 premixed formulation or a self-mixed formulation that
6 gave short-acting and intermediate acting or long-
7 acting insulin in the morning and the evening.

8 There are, if my memory serves me correctly,
9 approximately 35, 40 percent of patients that were
10 using postprandial short-acting insulin at mealtime
11 and/or using insulin pump therapy.

12 Type 2 population was the twice daily means
13 of administering insulin was more common. I don't
14 have the Type 2 numbers in my memory bank, as well as
15 the Type 1 numbers.

16 DR. GRADY: And one more question. There
17 were patients who changed their insulin doses during
18 the trials. Do you have any data concerning whether
19 or not increases in insulin dose were associated with
20 increases of hypoglycemic episodes?

21 DR. KOLTERMAN: We have looked at that and
22 there does not appear to be an increased risk for

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1 hypoglycemia in those patients that increased their
2 insulin.

3 DR. KREISBERG: I think we'll go on with the
4 program now. We have the FDA scheduled to make a
5 presentation. We have allocated one hour for their
6 presentation. Dr. Robert Misbin will lead off.

7 DR. MISBIN: Mr. Chairman, ladies and
8 gentlemen. May I have the first slide, please.

9 The FDA presentation will be in two parts.
10 I will be making the efficacy presentation and then
11 Dr. Dragos Roman will make the safety presentation and
12 will focus primarily on the problem of hypoglycemia.

13 This is a slide that I took directly from
14 the sponsor's briefing document. It shows an overview
15 of the Phase 3 trials in Type 1 diabetes. What is
16 shown here is the placebo subtracted reduction in
17 HbA_{1c}. There were three Phase 3 trials. One had one
18 arm the other two each had three arms.

19 This slide here shows there is no difference
20 from placebo and anything below that line would show
21 a reduction in HbA_{1c} or a benefit of pramlintide.

22 As you can see, not all of the individual

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1 points are statistically significant. But leaving
2 that aside, there is a reproducible decrease in HbA_{1c}
3 across the board of approximately 0.3 percent units.

4 What I've added now is something that was
5 not in the sponsor's briefing document and is the
6 HbA_{1c} values at endpoint that correspond to these
7 reductions. Now, as has been discussed earlier, the
8 American Diabetes has said that the goal of treating
9 Type 1 diabetes is to get the HbA_{1c} down to 7 percent.
10 That is the goal of treatment.

11 As one can see, even despite six months of
12 treatment with pramlintide, all of the HbA_{1c} values
13 here were quite high and would indeed be considered
14 unacceptable by most good clinicians. This, I think,
15 is the major problem that we have with respect to the
16 data that was presented to us.

17 I'm going to discuss one trial in detail.
18 I'm going to discuss the middle trial here. Here.
19 I'm sorry. These three arms from this one trial,
20 trial 117. Later Dr. Roman will present some data
21 briefly on this trial as well.

22 This is sponsor's trial 117. It was in

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1 patients with Type 1 diabetes. They were all on
2 stable metabolic regimen, as you heard earlier. To
3 get into this, the inclusion criterion was a HbA_{1c} of
4 at least 8 percent at screening.

5 The approach in this trial was that patients
6 were to remain on their usual diet, type of insulin,
7 insulin regimen, and exercise regimen and exercise
8 regimen as Dr. Kolterman indicated to you earlier.

9 The mean age of these patients was 38 years.
10 They had a mean duration of diabetes of 16 years.
11 They were not obese. Their mean bmi was 25. HbA_{1c}
12 was 9 percent and they were taking an average of 50
13 units of insulin per day. This, I think, is very
14 reflective of patients with Type 1 diabetes, indeed,
15 reflective of the patients that Dr. Polonsky said we
16 need additional tools to treat.

17 Now, let me remind you -- I believe this was
18 discussed earlier -- what are the recommendations of
19 the American Diabetes Association? The goal of
20 treatment is to get the HbA_{1c} level down to 7 percent
21 or less.

22 At a value of 8 percent or greater the

1 American Diabetes Association says that additional
2 action is suggested, which presumably in patients with
3 Type 1 diabetes would mean further adjustment of their
4 insulin regimen.

5 This is a repeat of the slide I just showed
6 about the patients with Type 1 diabetes in this trial.
7 They were on a stable metabolic regimen. They had an
8 HbA_{1c} of at least 8 percent and they were told to
9 remain on their usual type of diet, type of insulin
10 regimen, and exercise regimen.

11 I think it's fair to say that these
12 instructions are exactly the opposite of what the
13 American Diabetes Association believes is the standard
14 of practice for treating patients with Type 1
15 diabetes. This is really the major problem that the
16 FDA has with accepting the data that we heard earlier.

17 It's our belief that new drugs should be
18 tested in a way which is consistent with the way which
19 those drugs are going to be used. Unless the sponsor
20 believes that these recommendations are wrong, we do
21 not understand why the drugs were tested in this
22 particular matter and, therefore, have difficulty

1 accepting the data as being clinically relevant.

2 This is the data that I'm going to show in
3 this trial. I've plotted the HbA_{1c}. This is not the
4 reduction from baseline from this is the actual values
5 which a clinician would see if he was following a
6 patient.

7 Six percent is the approximate upper limit
8 of the normal range. Seven percent is the goal of
9 treatment by the American Diabetes Association. Eight
10 percent is the value which the American Diabetes
11 Association says something needs to be done. Then 9
12 percent is the starting value in most of these
13 patients.

14 As one can see just looking across, all
15 these values are really quite high. They are much
16 higher than would generally be considered acceptable.

17 I think if one looks at these results, one
18 does see a consistent fall in HbA_{1c}. This is placebo
19 and these are the three treatment arms, 90 micrograms
20 bid, 60 micrograms tid, and 90 micrograms tid.

21 There is a consistent fall in HbA_{1c} at four
22 weeks. The purple is baseline and the dark blue is

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1 four weeks. The light blue is 26 weeks. There is a
2 consistent fall in HbA_{1c} in the treated groups. This
3 is statistically different from the small dip that you
4 see with placebo alone. However, when you go out to
5 26 weeks, you can see really in every case the HbA_{1c}
6 value is going back toward the baseline.

7 At this point I would recall a slide, or
8 perhaps two slides, that you saw earlier from the
9 Phase 2 trials showing that pramlintide is very
10 effective in blunting postprandial hyperglycemia.

11 These data, I think, are very impressive.
12 Looking at this, I could understand the sponsor's
13 enthusiasm when they did those trials many years ago
14 why they were enthusiastic about developing
15 pramlintide. Indeed, if you were to stop the trial
16 just at these dark blue lines and look at the fall in
17 four weeks recognizing that HbA_{1c} is a lagging
18 indicator of glycemic control, you would believe that
19 indeed you had a potentially successful treatment.

20 Unfortunately, diabetes is a long-term
21 disease. The agency requires 26 weeks of efficacy
22 data and control trials and 52 weeks total. One can

1 see here that by 26 weeks one is clearly going back
2 toward the baseline. The efficacy, as we see it, was
3 really not sustained.

4 I would also recall a statement I think Dr.
5 Baron made earlier. I think he said that the way he
6 saw the data, hypoglycemia was a problem early in the
7 trial but then tended to go away. Nausea was a
8 problem early in the trials and then tended to go
9 away. I think we would largely agree with that.

10 I would also point out that the efficacy
11 also tended to go away. From our evaluation, the main
12 problem here is that all of the effects of pramlintide
13 both good and bad seem to be very transient.

14 I need to point out this is an intent-to-
15 treat analysis and this is a very conservative way of
16 looking at data. We recognize there are no other
17 treatments for Type 1 diabetes and it is unreasonable
18 to expect that every patient with Type 1 diabetes
19 would necessarily respond to a new drug in the same
20 way.

21 We are willing to look at subsets to try to
22 determine if there are any specific patients who might

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1 benefit from pramlintide. The subset that I'm going
2 to describe is one that was put forward by the sponsor
3 as a way of identifying patients who based on a four
4 week determination seemed to be responding to the
5 drug.

6 This is what the sponsor has called the
7 early glyceimic responders subgroup. In order to get
8 into this subgroup the way it's defined, it's a
9 reduction in HbA_{1c} of at least 5 percent units at four
10 weeks.

11 What I'm going to show now is data, mean
12 data, for this subgroup at both four weeks when it is
13 described and at 26 weeks which is the endpoint of the
14 trial.

15 The first line, I have to orient everybody
16 to this because it might be confusing otherwise. This
17 is placebo and the three arms of the trial. It's not
18 necessary to look at all of these data. Basically the
19 results here are all pretty much the same so I
20 wouldn't concentrate on that.

21 The point is that expressed as a percent of
22 the total intent-to-treat population, 25 percent of

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1 the patients on the placebo were defined as being
2 responders, and roughly 40 to 45 percent of the
3 patients on pramlintide. This, I think, is the
4 efficacy determination in this type of analysis.

5 When I was listening to Dr. Kolterman, I
6 realized something that I had forgotten. This trial
7 117 is one of the three trials that was not
8 statistically significant by the initial prespecified
9 statistical evaluation. This data, I think, the way
10 Dr. Kolterman presented it could be considered a
11 negative trial.

12 Nevertheless, if you look at this subset of
13 population, you would say that the effect of the drug
14 in getting you into a responder group was almost twice
15 as great as placebo. Even though the initial
16 evaluation might be negative, looking at it this way
17 you could see that they might actually be efficacy
18 even in this otherwise negative trial.

19 But that's not the reason I want to show
20 this data. I mean, we'll take it -- the accept the
21 fact that there were more responders on pramlintide
22 than placebo.

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1 The reason I want to show it is something
2 else. That is, I think looking at this gives you a
3 handle to try to differentiate the effects of lower
4 glucose levels either with pramlintide or with insulin
5 alone.

6 To illustrate that point, let me show you
7 that in four weeks when the subgroup was defined, the
8 mean HbA_{1c} across these groups was roughly the same,
9 about .8 percent units in the placebo patients as well
10 as in the HbA_{1c} treated patients. At 26 weeks the
11 HbA_{1c} reduction in the placebo patients as well as the
12 pramlintide treated patients was approximately .5
13 percent units.

14 Since these values are roughly the same, I
15 think it's reasonable to pose the question given a
16 specific level of HbA_{1c} reduction achieved either with
17 placebo or with pramlintide what is the difference in
18 the way one got to that level.

19 This is the mean data at 26 weeks. Again,
20 the measure of efficacy here, 25 percent response in
21 placebo versus 40 to 45 percent on pramlintide. The
22 HbA_{1c} reduction in the placebo group, and I say

1 placebo but this really should be insulin alone. We
2 have to remember that all these patients were taking
3 insulin.

4 Insulin alone reduction across the board,
5 either insulin alone or insulin plus pramlintide you
6 saw the same HbA_{1c} reduction of about .5 percent.

7 Let's look at the placebo group. This .5
8 percent reduction in the placebo group, how was it
9 achieved? It was achieved by giving them a little
10 more insulin. Now, the starting value is around 50
11 units, I think, so this is a very small amount of
12 insulin.

13 Nevertheless, by giving a little more
14 insulin in this group of patients, you achieve this .5
15 percent reduction at HbA_{1c}. But they also achieved a
16 mean body weight gain. This is, I think,
17 characteristic of the treatment of diabetes. If you
18 want to lower glucose levels, you give a little
19 insulin and you find that you gain weight.

20 By contrast, in order to get the same
21 reduction in HbA_{1c} on pramlintide, you could actually
22 give less insulin by in large. It was not totally

1 reproducible but, by in large, you gave less insulin.

2 A very reproducible finding was that there
3 was a very substantial reduction in weight between .4
4 and 2 kilograms which is, I think, quite substantial
5 when you consider that the placebo patients gained a
6 kilogram.

7 If you look at these data, you would say
8 this really isn't bad. You get the same reduction in
9 HbA_{1c} and you lose weight relative to gain weight. If
10 there was nothing else to say about this, I think we
11 would all accept the fact that preventing weight gain
12 is desirable.

13 Unfortunately, there is, however, a price to
14 be paid. The price to be paid is the annual event
15 rates of severe hypoglycemia presented here as events
16 per patient year. It was very low in the placebo
17 patients, 0.2 percent per year, but in the pramlintide
18 treated groups, there was a reproducible five to eight
19 fold increase in the event rate of severe
20 hypoglycemia.

21 Really the question is a small reduction in
22 body weight worth a five or seven or eight fold

1 increase of severe hypoglycemia recognizing, as Dr.
2 Roman will discuss later, that some of these events,
3 these were all severe events as described by the
4 sponsor but some of them had very serious sequelae
5 and, indeed, divesting sequelae.

6 Here I'm showing the rest of the data. This
7 is now at four weeks and, I think, here this is just
8 more of the same. The HbA_{1c} reduction across the
9 board was about .8. Again, you see here a four to 12
10 fold increase in the event rates of severe
11 hypoglycemia here expressed as events per patient
12 year.

13 Again, for the same degree of HbA_{1c}
14 reduction, you get an enormous increase in the
15 reporting of severe hypoglycemia.

16 I do need to point out in the interest of
17 fairness that there is a small flaw in this analysis.
18 The starting value of HbA_{1c} was somewhat higher in the
19 placebo -- in the subgroup anyway was somewhat higher
20 in the placebo patients than in the pramlintide
21 treated patients. To some extent, some of this
22 difference might be accounted for. A small amount

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1 might be accounted for by that baseline imbalance.

2 I would point out that at this high level a
3 small difference in HbA_{1c} would not of itself be
4 expected to cause much of a difference in the
5 hypoglycemia rate and certainly could not account for
6 an eight-fold increase in the event rate expressed per
7 patient year.

8 In leaving that, I would like to remind
9 everybody why we treat diabetes in the first place.
10 This is from the New England Journal of Medicine
11 published in 1993. This is from the DCCT trial which
12 we've heard a lot about but didn't actually see any
13 raw data.

14 Here we have HbA_{1c} here expressed as
15 glycosylated hemoglobin, mean values and the year of
16 study. The starting value here was about 8.8 percent
17 which is virtually identical to what we saw the
18 starting value in the pramlintide treated patients
19 that we heard about today.

20 In the DCCT trial a convention treatment
21 represented one to two injections of insulin per day
22 and intensive treatment with three and more injections

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1 of insulin per day or an insulin pump. The point of
2 this slide is that we shouldn't forget that it is
3 possible to lower HbA_{1c} levels very dramatically with
4 insulin alone and to keep them down there for an
5 extended period of time.

6 Based on this trial, this is the reason that
7 we treat diabetes, the basis for the goals established
8 by the American Diabetes Association. It is also the
9 basis of using glycosylated hemoglobin by the FDA as
10 the surrogate endpoint for approving new drugs to
11 treat diabetes.

12 But what I would like to -- the reason I'm
13 showing it today is to kind of bear this in mind as to
14 what might be considered a reasonable goal post to how
15 diabetic patients should be treated in the community.

16 Now, I completely recognize that it's one
17 thing to set a goal and it's quite another thing to
18 achieve that goal. I also agree with what was said
19 earlier, that we do need additional tools.

20 But in considering today's application, I
21 think the committee should ask itself really given
22 what we know about pramlintide, is that going to help

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1 patients achieve a goal or is it going to make it more
2 difficult, or perhaps it's really going to delay even
3 trying to achieve the goal by some kind of futile
4 effort at a product that may not be very effective.

5 In trying to consider this, I would just
6 pose the following observations. Pramlintide has to
7 be given by three and four -- what is being proposed
8 is it be given by three and four injections per day in
9 addition to insulin.

10 It cannot be mixed with insulin and has to
11 be given by additional injection. Three or four
12 injections of an additional drug over and above the
13 insulin dose that a patient is taking is really quite
14 a substantial burden on a patient.

15 Secondly, by our analysis there is much more
16 severe hypoglycemia with pramlintide than reducing
17 HbA_{1c} with insulin alone. This is by far the most
18 important thing that I think we have to bring to your
19 attention. It is in my judgement the single most
20 important reason that would be preventing the approval
21 of pramlintide.

22 On a more positive note, I would agree with

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1 the sponsor that there is weight loss on pramlintide
2 relative to insulin alone. That clearly is the case
3 and of itself would be considered desirable but would
4 have to be balanced to get all of these other risks
5 and burdens that are imposed by using pramlintide.

6 Now, weight loss is certainly desirable in
7 everyone, or most people anyway, my self included
8 perhaps, but it's more desirable in patients with Type
9 2 diabetes than Type 1 diabetes. You might expect
10 given a drug like pramlintide which causes weight
11 loss, you might expect that pramlintide would be more
12 effective in patients with Type 2 than in Type 1
13 diabetes.

14 The data, however, this is data from Type 2
15 diabetes, and I don't think one could make the
16 statement that it's more effective in Type 2 than in
17 Type 1. The format of this slide is exactly what I
18 showed earlier with Type 1 diabetes. Again, this is
19 taken directly out of the sponsor's briefing document
20 and it shows the three arms from each of their three
21 Phase 3 trials.

22 Again, one sees across the board, again, not

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1 all these points are statistically significant from
2 zero. There are several of them that are not, but
3 we're not going to make anything of that. We're just
4 going to assume that the point estimates are
5 absolutely right and just deal with the proposition
6 that pramlintide lowers HbA_{1c} levels by about .3 or .4
7 percent units.

8 What I'm going to discuss now in detail is,
9 again, the middle trial. Just like I did with Type 1
10 diabetes, the middle trial here for Type 2 diabetes is
11 what I'm going to show now.

12 This is the sponsor's trial 123. Mean data
13 at baseline is what I'm showing here. The patients
14 were 58 years old. Again, mean data, 13 years of
15 diabetes. They were mildly or moderately obese, bmi
16 of 30.6 which again is very typical for patients with
17 Type 2 diabetes.

18 HbA_{1c} of a mean value at baseline was 9.4
19 percent. They were taking an average of 56 units of
20 insulin per day. Again, these, I think, are very
21 typical of the types of patients that indeed need
22 additional treatment.

1 The patients had to have an HbA_{1c} of 8
2 percent or greater at screening. They were to remain
3 on their usual diet and insulin regimen and exercise
4 regimen just like we heard before.

5 This is a direct quote from the protocol and
6 I'll quote now. "Changes in insulin doses were in
7 encouraged in order to limit the impact of alterations
8 in insulin dosing on glycemic control."

9 As Dr. Kolterman said, the purpose of doing
10 this is to isolate to the effects of pramlintide and,
11 indeed, maximize the effects of the drug so one could
12 observe that over and above the effects that might be
13 seen by altering the insulin dose in some way.

14 Despite the efforts to isolate and maximize
15 the effects, I think the effects are really very
16 small. Again, 6 percent is the upper limit of the
17 normal range, 7 percent is the goal set by the
18 American Diabetes Association, 8 percent is the level
19 that the American Diabetes Association says something
20 needs to be done, 9 percent is the starting value.

21 In most of these 9 to 9.5 percent is where
22 we started in most cases. Again, one can see, as

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1 we've seen many times, there is a reduction initially,
2 this time 13 weeks, in HbA_{1c}, but by 26 weeks one is
3 going back toward the baseline here almost 9 percent.

4 Now, Type 2 diabetes is characterized by
5 hyperschloneimia, large insulin dose, obesity, insulin
6 resistance. It is difficult to lower HbA_{1c} levels.
7 One often has to use more insulin and just kind of
8 chase a vicious cycle. I think the sponsor might say,
9 "Maybe this is the best you can do." Furthermore,
10 this is not ordinary practice. This is a clinical
11 trial so we are justified in doing our trials in this
12 way.

13 Well, I don't really see it that way. To
14 illustrate another way of doing a trial, I would show
15 you this data that was published from Annals of
16 Internal Medicine of testing of metformin in patients
17 with Type 2 diabetes, also insulin treated patients
18 with Type 2 diabetes.

19 Again, the axes are exactly the same. I
20 haven't changed them. They are exactly the same as
21 what we saw with pramlintide starting at 6 percent and
22 7 percent is the goal set by the American Diabetes

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1 Association.

2 You can see immediately that the shape of
3 these curves is markedly different from what we've
4 seen before and there is a dramatic reduction in HbA_{1c}
5 during the 24 weeks of the trial. What may not be
6 obvious is that this dramatic reduction was not due to
7 the studied drug metformin. No, this reduction was
8 due to insulin.

9 This trial was done by Phil Raskin at the
10 University of Texas. He and his colleagues treated
11 these experimental subjects as if they were their own
12 private patients. They treated them in such a way
13 that they were able to bring down the HbA_{1c} very
14 dramatically.

15 Under these circumstances of good clinical
16 care, the further reduction that one saw with
17 metformin, this .9 percent here, is, I think,
18 clinically important because it's over and above what
19 one could reasonably be expected to achieve with
20 insulin alone.

21 In other words, if this is good control,
22 then this is better control and metformin really has

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1 added something that would not have been present
2 otherwise.

3 Let's examine something more about these
4 patients. What I showed in the figure is now showed
5 here in the table. Again, they had a starting value
6 of HbA_{1c} of around 9 percent. With insulin alone on
7 placebo the reduction was 1.6 percent. With metformin
8 the reduction was 2.5 percent so the treatment effect
9 due to metformin was a reduction of .9 percent.

10 These patients were taking a lot of insulin.
11 They were taking more insulin than in the pramlintide
12 trials for Type 2 diabetes that we heard today. They
13 were taking almost 100 units. They were also very
14 obese. They had a mean weight of well over 100
15 kilograms.

16 On placebo alone in order to achieve this
17 reduction in HbA_{1c}, they took 23 more units of insulin
18 than what they started with. They gained 3.2 kilos on
19 average. Those things would be considered as
20 undesirable.

21 However, in the presence of metformin in
22 addition to lowering the HbA_{1c}, there was a mean

1 reduction in the insulin dose. Although they gained
2 weight slightly, most of this weight gain was
3 mitigated and there was a mean 2.7 percent kilogram
4 reduction in body weight.

5 I'm not showing this data to make a
6 comparison of pramlintide to metformin. That's not
7 the purpose of showing this slide. The reason I'm
8 showing this slide is to make a comparison to how this
9 trial was done to how the pramlintide trials were
10 done.

11 These data are not just statistically
12 significant. They are clinically meaningful because
13 they were done under circumstances of good medical
14 practice. Therefore, I think we, the agency, as well
15 as clinicians can look at this and be confident of
16 these data.

17 This is not the same as constructing an
18 artificial design and coming up with the statistically
19 significant reduction in any one of these variables
20 that may or may not have any relevance if applied to
21 real patients.

22 This brings us then back to pramlintide.

1 Again, I would point out that although there is this
2 brief reduction at 13 weeks -- yes, it does go down a
3 bit -- at the end of 26 weeks we are well back on our
4 way to where we were.

5 In comparison to the metformin data that I
6 just showed, as well as to the DCC data that we are
7 all familiar with, to me it looks like the real result
8 of being in one of these trials is the perpetuation of
9 the state of hyperglycemia. It is not at all clear to
10 me how these data can be considered relevant to
11 treating real patients with diabetes.

12 That concludes the efficacy presentation by
13 the FDA. I would like to turn to Dr. Roman for the
14 safety presentation.

15 DR. ROMAN: Dr. Kreisberg, committee
16 members, the purpose of this presentation is to
17 discuss solely the major safety issues that are
18 associated with the use of pramlintide in the
19 treatment of patients with Type 1 and Type 2 diabetes.

20 Our review process has covered extensively
21 a vast majority of the safety information submitted
22 with the agency. While a few areas are still under

1 review, the only important safety signal we have come
2 across so far is severe hypoglycemia.

3 Therefore, the focus of this safety review
4 is severe hypoglycemia as it has been observed during
5 the long-term controlled pramlintide studies.

6 In this presentation I will cover the
7 following topics. First, I will briefly describe some
8 of the features of the Phase 3 clinical trials in
9 order to provide an understanding of the clinical
10 context during which severe hypoglycemia occurs.

11 Second, I will discuss aspects of severe
12 hypoglycemia. Assisted hypoglycemia defined as any
13 hypoglycemic event requiring another person's help for
14 treatment and serious adverse events, or SAEs,
15 associated with hypoglycemia in Type 1 diabetes trial.

16 As an extension of the SAE category, I will
17 discuss motor vehicle accidents associated with
18 hypoglycemia and other types of trauma and injuries
19 associated with hypoglycemia as they occur during the
20 Phase 3 Type 1 diabetes trials.

21 Both hypoglycemia and SAEs associated with
22 hypoglycemia will be discussed in the context of the

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1 long-term controlled Phase 3 clinical trials.

2 Among the 51 studies which constitute the
3 pramlintide clinical program, the Phase 3 studies
4 allow the most extensive side-by-side comparison
5 between the pramlintide and placebo treatments both in
6 terms of duration up to one year, and number of
7 patients over 2,000.

8 From the start I would like to make the
9 following clarification. In this presentation
10 pramlintide treatment will always mean pramlintide
11 injection plus insulin injection. Placebo treatment
12 will always mean placebo injection plus insulin
13 injection.

14 Shown here is a cumulative summary of the
15 Phase 3 Type 1 diabetes trials. There were 1,179
16 patients enrolled in the pramlintide group and 538
17 patients in the placebo group. Only 75 of the
18 patients completed the placebo arm and even a lower
19 number, 66 percent, completed the pramlintide arm.

20 Patients who withdrew for all reasons were
21 34 percent in the placebo groups and only 25 percent
22 in the -- I'm sorry, in the pramlintide groups and

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1 only 25 percent in the placebo groups.

2 When one looks at withdrawals due to adverse
3 events, they were 18 percent in the pramlintide group
4 and 6 percent in the placebo group. There was a
5 three-fold difference.

6 Then adverse event with unusually high
7 frequency resulting in early withdrawals in the
8 pramlintide treatment group was nausea.

9 Shown here is the frequency of nausea
10 related to withdrawals during the first month of
11 treatment in the Type 1 diabetes trials. On the Y
12 axis you have percent of patients who withdrew. The
13 yellow bars represent pramlintide group. The blue
14 bars represent placebo group.

15 Individual studies 121, 117, and 112 as well
16 as all studies combined are presented. It is quite
17 striking that nausea related withdrawals occur across
18 all studies many times over placebo. On the average,
19 there is a 17-fold ratio between percent of nausea
20 related withdrawals in the pramlintide group and the
21 placebo group respectively.

22 The net effect of this occurrence is the

1 early preferential loss in the trial of patients
2 sensitive to the effects of pramlintide.

3 Shown here is the cumulative summary of the
4 Phase 3 Type 2 diabetes trials. A similar number of
5 patients were enrolled in these studies, 1,273
6 patients in the pramlintide group and 420 patients in
7 the placebo group.

8 The subject indemnization ratio was the same
9 as in the Type 1 diabetes studies three to one. There
10 was an equal percentage of patients who completed
11 trials and an equal percentage of patients who
12 withdraw from the trials. However, adverse events
13 were slightly higher, 90 percent versus 7 percent in
14 pramlintide compared to placebo.

15 Nausea was also reason for first-month
16 withdrawals during the Type 2 diabetes trials albeit
17 to a lower extent.

18 This slide displays the frequency of nausea-
19 related withdrawals during the first month of the
20 Phase 3 Type 2 diabetes trials. The Y axis represents
21 patients who withdrew due to nausea in the first
22 month. It should be noticed that the values on the Y

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1 axis are smaller than the previous slides shown for
2 the Type 1 diabetes patients, 1.6 percent versus 6
3 percent.

4 The yellow bars represent pramlintide
5 treatment. The blue bars represent placebo treatment.
6 The data are presented for individual studies and all
7 studies combined.

8 Overall, a two-fold difference between
9 pramlintide and placebo in nausea-related withdrawals
10 is present. First month nausea-related withdrawals
11 were four time less frequently than during the Type 1
12 diabetes trials.

13 With this general information in mind about
14 the Phase 3 trials, I would like to move on to discuss
15 one of the aspects of hypoglycemia and assisted
16 hypoglycemia.

17 Assisted hypoglycemia has been defined as
18 any episode of hypoglycemia requiring the help of
19 another individual for treatment be it oral
20 carbohydrates, glucagon injection, or intravenous
21 glucose.

22 This definition of hypoglycemia has been

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1 applied consistently in all three Type 1 diabetes
2 trials and in two of the three Type 2 diabetes trials.
3 Analyses of the time of occurrence of assisted
4 hypoglycemia during the Phase 3 trials has been
5 presented to the agency stratified by two time
6 intervals. Assisted hypoglycemia occurring during the
7 first month of the trial and assisted hypoglycemia
8 following the end of the first month after the
9 completion of the trial.

10 Shown here is the incidence of subjects who
11 experienced assisted hypoglycemia during the first
12 month of pramlintide treatment in Type 1 diabetes. Y
13 axis represents patients with at least one episode of
14 hypoglycemia. Yellow bars represent pramlintide
15 patients, blue bars placebo patients, the data
16 presented for individual studies and for all studies
17 combined.

18 One can observe consistently the two-fold
19 difference between pramlintide and placebo. A
20 different picture emerges after the first month.

21 This slide depicts the incidence of assisted
22 hypoglycemia after the end of the first month and

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1 after the completion of the trial. Again, the Y axis
2 is subject patients with at least one episode of
3 assisted hypoglycemia. The yellow bar represent
4 pramlintide patients. The blue bar represents placebo
5 patients. Data are presented for individual studies
6 and for all studies combined.

7 It should be noticed that the Y carrier
8 values are different than those shown in the previous
9 slide. Therefore, I included the pramlintide to
10 placebo comparison observed during the first month of
11 the trial in pale colors, pramlintide and placebo.

12 In contrast to the first month of treatment,
13 the difference in incidence between pramlintide and
14 placebo is less obvious but still present. It should
15 be noticed that the incidence is cumulative for 11
16 months in the studies 121 and 112 and for five months
17 in study 117.

18 When we contemplate this particular slide,
19 we need to keep in mind two things. First of all, the
20 patient population observed here is not the patient
21 population which started the trial. As shown
22 previously, the first month of pramlintide treatment

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1 is associated with 17-fold high withdrawal ratio in
2 the pramlintide group.

3 Therefore, subjects sensitive to the drug
4 discontinued early. The second point I would like to
5 make is that the occurrence of hypoglycemia has to be
6 looked at in the context of efficacy.

7 Shown here are the HbA_{1c} changes during a
8 representative Type 1 diabetes trial study 137-121.
9 Y axis represents mean changes in HbA_{1c} from baseline.
10 X axis represents time within the trial. The top line
11 represents HbA_{1c} in the placebo arms. The bottom line
12 represents HbA_{1c} during the different pramlintide
13 dosage arms.

14 The two-fold interest in assisted
15 hypoglycemia noticed in the first month of the trial
16 are associated with a drop in HbA_{1c}. The differences
17 in assisted hypoglycemia between the end of the first
18 month of the trial and the end of the trial happen in
19 a context of waning HbA_{1c} reduction.

20 In summary, pramlintide therapy is
21 associated with a two-fold increase in incidence of
22 assisted hypoglycemia when compared to placebo during

1 the first month of the treatment.

2 The difference in incidence of assisted
3 hypoglycemia between pramlintide and placebo groups
4 persist following the first month of the treatment,
5 albeit to a lower extent.

6 The decreasing hypoglycemic events
7 associated with pramlintide takes place in the context
8 of prior nausea related patient withdrawals and waning
9 drug efficacy.

10 Some similarities to the Type 1 diabetes
11 trials are present within Type 2 diabetes Phase 3
12 studies. Shown here is the incidence of subjects who
13 experienced assisted hypoglycemia during the first
14 month of pramlintide treatment in Type 2 diabetes.

15 Y axis represent percent of patients with at
16 least one episode of hypoglycemia. Yellow bars
17 represent pramlintide. Blue bars represent placebo.
18 Data represented for individual studies and for all
19 studies combined.

20 The first month of treatment is associated
21 with a three-fold increase in assisted hypoglycemia in
22 the pramlintide group over placebo. It should be

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1 noticed that the incidence is lower compared to the
2 Type 1 diabetes trials. Only 3 percent compared to 13
3 percent.

4 Shown here is the incidence of assisted
5 hypoglycemia in the Type 2 diabetes trials following
6 the first month of treatment. Again, the Y axis are
7 subjects with at least one episode of hypoglycemia.
8 Yellow bar is pramlintide patients. Blue bar is
9 placebo patients.

10 It should be noticed that the Y scale value
11 is different than the one shown in the previous slide.
12 Therefore, I included the pramlintide to placebo
13 comparison as observed in the first month of the trial
14 in pale colors. This is pramlintide and this is
15 placebo.

16 When one observes assisted hypoglycemia for
17 the rest of the trial duration in Type 2 diabetes the
18 differences in assisted hypoglycemia incidence are
19 minimal and inconsistent between trials. The one-year
20 study, study 137-122, shows almost no difference. The
21 six-month study 137-123 shows approximately two-fold
22 difference. Overall there is a small difference.

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1 One should keep in mind that the incidence
2 is cumulative for 11 months for study 137-122 and five
3 months for study 123.

4 We also need to keep in mind that the first
5 month nausea withdrawals were higher for the
6 pramlintide group and also interpret the hypoglycemia
7 in the context of decreased efficacy. With time it is
8 shown previously by Dr. Misbin.

9 In summary, pramlintide therapy is
10 associated with a three-fold increase in incidence of
11 assisted hypoglycemia when compared to placebo during
12 the first month of treatment.

13 The difference in incidence of assisted
14 hypoglycemia between pramlintide and placebo groups
15 waned following the first month of treatment. This
16 decrease takes place in the context of prior nausea
17 related patient withdrawals, although to a lower
18 extent than in Type 1 diabetes.

19 Finally, we should remember that the
20 incidence of assisted hypoglycemia was higher than the
21 Type 1 and Type 2 diabetes trials when compared to
22 controls during both time intervals analyzed.

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1 Hypoglycemia associated with pramlintide was more
2 common in Type 1 diabetes patients.

3 I would like to move on and discuss serious
4 adverse events, or SAEs, associated with hypoglycemia
5 during Type 1 diabetes. SAEs are defined as adverse
6 events that result in death or life-threatening,
7 result in hospitalization, or disability.

8 We believe there were two deaths which may
9 have been due to hypoglycemia. The first one, which
10 was presented by Dr. Kolterman also, is a 48-year-old
11 male with a 12-year history of Type 1 diabetes
12 mellitus with a prior history of diabetes related
13 seizures who died during a hypoglycemia seizure. The
14 patient was receiving pramlintide 30 micrograms qid.

15 The second patient was a 35-year-old male
16 with a six-year history of Type 1 diabetes mellitus
17 who died in a motor vehicle accident within 24 hours
18 from the beginning of the trial. Food was present in
19 the stomach at the post-mortem examination indicating
20 that the subject had eaten lunch prior to the event.
21 The patient was receiving pramlintide 90 micrograms
22 TID.

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1 We feel that the presence of food in the
2 stomach, and Dr. Levitsky has suggested also
3 previously, is a fact of significant concern because
4 it is one of the major effects of pramlintide such as
5 delayed gastric emptying.

6 In addition to these two patients, there was
7 a 31-year-old patient with not other past medical
8 history except for diabetes who died and who was also
9 in the pramlintide group. Although this death was
10 hypothesized to have been due to an alcohol problem,
11 the evidence was inconsistent and circumstantial.

12 During the review process the observation
13 was made that SAEs associated with hypoglycemia
14 occurred two to three times more frequently during the
15 pramlintide treatment over placebo in the Type 1
16 diabetes trials.

17 In search for a possible explanation, the
18 patient's narratives were reviewed in detail. As a
19 reminder, patient narratives are a brief description
20 of the events and circumstances which led to a
21 subject's withdrawal from the study, the subject's
22 death, or a left-threatening event.

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1 A total of 20 motor vehicle accidents and
2 other driving-related events occurred in conjunction
3 with hypoglycemia were thus identified along with
4 several other injuries.

5 Therefore, the agency has requested an
6 analysis of all MVAs and trauma occurring in
7 association with hypoglycemia during the pramlintide
8 clinical program.

9 These events have been presented to us in
10 the following categories. The first category is MVA
11 related events. This is a self-explanatory category
12 and involves the patient behind the wheel losing
13 control of the car and sustaining a collision.

14 The second category is automobile related
15 adverse events with no motor vehicle accident
16 reported. As this title suggest, this is a less
17 specific category and it may involve a patient behind
18 the wheel who is able to stop in time before a
19 collision occurs, or an event taking place in the car
20 in the parking lot or an event occurring about the
21 time the patient is entering or leaving the car.

22 The third category is other accidents and

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1 injury-related events. This category includes a whole
2 range of non-MVA related trauma such as falls,
3 fractures, and lacerations.

4 Shown here are the MVA and automobile-
5 related adverse events presented for the entire
6 pramlintide clinical program. The MVAs are presented
7 as total numbers and MVAs association with
8 hypoglycemia. The automobile-related events were all
9 presented as associated with hypoglycemia.

10 Before going any further, it should be noted
11 that these events have been collected from the entire
12 clinical program including, for instance, patients in
13 uncontrolled studies and pre-Phase 1 studies.

14 Out of the 2,573 patients in the pramlintide
15 group, 1.8 percent experienced MVAs. Out of the 904
16 patients in the placebo group, .66 percent experienced
17 an MVA. There was a slight predominance of 1.4
18 approximately pramlintide to placebo for total MVAs.

19 .66 percent of patients in the pramlintide
20 group had an MVA associated with hypoglycemia. Only
21 .22 percent of the placebo groups had an MVA
22 associated with hypoglycemia, roughly a three-fold

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1 difference. All automobile-related hypoglycemic
2 events occurred in the pramlintide group, eight versus
3 zero.

4 We feel that both categories represent in
5 essence different facets of the same range of events
6 of hypoglycemia in the context of driving activity and
7 they should be analyzed together. This would give a
8 completely different percentage.

9 I would also like to point out that a
10 balanced analysis of these events should involve the
11 pramlintide to placebo comparison limited to the Phase
12 3 controlled studies.

13 Such an analysis is presented in this slide
14 as driving-related events associated with hypoglycemia
15 in the Phase 3, Type 1 diabetes trials. Out of 1,179
16 patients in the pramlintide group, 1.53 experienced
17 such an event in association with hypoglycemia. Out
18 of the 538 patients in the placebo group, .37 percent
19 experienced such an event.

20 It should be kept in mind that these
21 driving-related events have not been actively
22 ascertained during any of the clinical trials and they

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1 may be grossly underestimated.

2 In summary, pramlintide use in addition to
3 insulin is associated with a four-fold increase in
4 driving related events in Type 1 diabetes patients.

5 Shown here is a summary of the non-MVA or
6 other accidents and injuries which occurred during the
7 Type 1 diabetes pramlintide clinical program. Again,
8 it should be noted that these events have been
9 collected from the entire clinical program including
10 uncontrolled studies and pre-Phase 3 studies.

11 Out of the 2,570 patients in the pramlintide
12 group, 7.65 percent had such events. Out of 904
13 patients in the placebo group, 5.86 percent have such
14 events. There was a predominance of trauma in the
15 pramlintide group.

16 The patients who had trauma associated with
17 hypoglycemia showed a percentage of .39 percent versus
18 .2 percent, also slightly higher. However, I would
19 like to point out that we have identified at least two
20 more patients in the database that fit these category.
21 In study 137-121 patient 5030 sustained a fall
22 associated with hypoglycemia and a facial laceration.

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1 In study 137-117 patient 6303 fell from a
2 tree during a hypoglycemia episode, sustained a broken
3 elbow, and required surgical intervention. Therefore,
4 we believe that this number should actually be 12.

5 In summary, pramlintide use in addition to
6 insulin is associated with a four-fold increase in
7 non-MVA injuries in Type 1 diabetes patients.

8 I would like to finish this presentation
9 with two labeling safety questions. First of all, do
10 we understand how to initiate safely pramlintide
11 treatment and avoid the risk of first month
12 hypoglycemia in both patients with Type 1 and Type 2
13 diabetes.

14 In the briefing document, it has been
15 suggested to initiate treatment with 30 micrograms or
16 60 micrograms of pramlintide per dose in Type 1
17 diabetic patients and 120 micrograms per dose in Type
18 2 diabetic patients. Today we heard the suggestion to
19 go even lower than that.

20 All of the above doses have been shown to be
21 associated with approximately two-fold increased risk
22 of hypoglycemia during the Phase 3 trials.

1 It has also been suggested, and I'm quoting
2 from the briefing document, that in clinical practice
3 it will be prudent to reduce the patient's insulin
4 dose, particularly the short-acting insulin
5 administered postprandially by 10 to 20 percent at the
6 time of initiation of pramlintide therapy.

7 While such an approach seems prudent, it has
8 not been tested in a clinical trial and its potential
9 usefulness remains unknown.

10 Finally, we have to consider this question.
11 How can one prevent the four-fold risk of driving-
12 related events and the four-fold risk of non-MVA
13 injuries associated with hypoglycemia observed in the
14 Type 2 diabetes trials. This is a very difficult
15 question. This is illustrated by this slide.

16 This is time of driving related events
17 versus HbA_{1c} levels and the X axis represents time
18 within the trial. This is a distribution of all
19 driving-related events associated with hypoglycemia
20 during the Phase 3 Type 1 diabetes trials. In yellow
21 are the pramlintide patients who have been involved in
22 MVAs and in red the placebo patient.

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1 The blue horizontal line represents the
2 hemoglobin 7 or the target hemoglobin for treatment
3 suggested by the American Academy of Pediatrics. The
4 vertical orange line represents the first month of the
5 treatment.

6 As you can see, there is a lot of
7 cloistering of MVAs occurring during the first month
8 of treatment, approximately one-third of them.

9 On the other hand, two thirds of all MVAs
10 and MVA related events which occur in the pramlintide
11 group take place during the whole clinical trial. The
12 prediction of which subject will experience such an
13 event, to me, appears impossible at this time based on
14 the information we have.

15 As a final summary, pramlintide therapy
16 results in the small but statistically significant
17 reduction HbA_{1c}. This reduction is associated with a
18 two-fold increase of severe hypoglycemia during the
19 first month of treatment.

20 In addition, a four-fold increase in
21 hypoglycemia associate MVAs and non-MVA trauma was
22 observed in patients in Type 1 diabetes.

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1 DR. KREISBERG: Dr. Hobberman will present
2 one overhead transparency also on behalf of the FDA.

3 MR. HOBBERMAN: I have a couple of
4 transparencies, but I also have three comments about
5 the sponsor's presentation. Following Dr. Roman's
6 talk, I wanted to comment on the sponsor's use of the
7 p-value of .13 to describe the result of an analysis
8 comparing the groups with respect to motor vehicle
9 accidents.

10 We don't think that the use of a p-value is
11 necessarily a good thing in the light of a very
12 serious safety problem. This was not a planned
13 analysis. The purpose of the analysis seems to be to
14 have minimized the concern with respect to motor
15 vehicle accidents to say that it was not a
16 statistically significant difference.

17 .05 is not a magic number. It's used in
18 efficacy analyses in protocol specified analyses and
19 clinical trials but we don't think that it's a proper
20 interpretation of the data. I think that Dr. Roman
21 has presented clear evidence that this is a signal
22 that needs to be taken very seriously.

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1 My second comment has to do with the use of
2 person time in multiple events when the sponsor
3 reported rates of severe hypoglycemia. I don't think
4 that was the best way to present the data for two
5 reasons. One is that it is subject to the problem of
6 multiple events on a patient and, therefore, can
7 confound the incidence with the total event rate by
8 counting multiple events per person.

9 That may be useful in trials or situations
10 in epidemiology where there is gross inequality of
11 follow-up time. In clinical trials that are well-
12 controlled with a very defined follow-up period, it
13 really shouldn't be necessary.

14 The other reason it's not optimum is that
15 the statistical analysis of multiple event data is
16 very complicated so it's hard to even generate a p-
17 value for that. I think the best way to look at this
18 data is the sponsor did report it in the application
19 which was true incidence timed to first experience of
20 severe hypoglycemia which had plenty of statistically
21 significant results, if you want to work in that
22 realm, in a couple of trials.

1 Also indicated that on the Kaplan-Meier
2 curves they did supply the incidence in their either
3 to three-year -- I'm sorry, half to one-year trials
4 was in the order of 10 to 15 percent on placebo
5 insulin and up to 20 percent or over on pramlintide.
6 That comes from just looking at their Kaplan-Meier
7 curves which they submitted with the MVA.

8 The third point has to do with the overheads
9 that I have. This relates to the issue of the target
10 of 7 percent points of HbA_{1c}. What I did was I took
11 the sponsor's data for those patients who essentially
12 completed the trial.

13 One of the things that I found a little
14 confusing is when the sponsor talked about the number
15 of responders, it wasn't clear to me that this was an
16 ITT data set, i.e., with last observation carried
17 forward, or whether these were numbers that were
18 derived from patients who had actually completed the
19 prescribed trial time.

20 I think it's really meaningful only to take
21 those patients who completed the trial when you're
22 talking about what happens after 26 months or 52

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1 months -- 52 weeks.

2 This overhead is the sponsor's completer
3 data for trial 117 in Type 1 diabetes. I'm trying to
4 illustrate three different values. On the vertical
5 axis we have the change from baseline in HbA_{1c}. On
6 the horizontal axis we have the baseline HbA_{1c}.

7 For the third dimension what I've drawn is
8 these lines. These are not regression lines. These
9 are just plain lines and what they correspond to is
10 constant contours of where a patient ended up, their
11 final HbA_{1c} value.

12 For instance, if you started out at 7 and
13 you did not change at all, that's that point there.
14 So anybody on this line for any patient you can look
15 at their baseline value. You can go up to the symbol,
16 go across here for the change from baseline, and then
17 simply see where they ended up between these lines.
18 This is 7, 8, 9, and then I didn't bother with lines
19 there.

20 What this indicates essentially is that as
21 we all know, the baseline values were somewhere
22 between an average of 8 and 9. Here we have the bulk

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1 of changes from baseline. These squares, by the way,
2 are the drug. The crosses, or the pluses, are the
3 placebo. You can see there are very few observations
4 of people who fell below a target of 7 in this trial.

5 This isn't labeled but this is the trial
6 112. Here we have more drug people on pramlintide
7 than in the previous trial who did fall below 7 at the
8 end of the trial. As you can see, the mass of the
9 data, the density of the data, is anywhere between 7
10 and 10 if you draw that line.

11 The import of this partly is getting back to
12 my question about whether the sponsor used an intent-
13 to-treat analysis which carried last observation
14 forward or used completers.

15 Based on what I found with their completion
16 data, I recall that their slide said 14 percent of the
17 patients in Type 1 diabetes reached a goal of .7. I'm
18 not sure whether the data that I've just shown is
19 consistent with that, or whether they were presenting
20 an over estimate. I'm sure that can be clarified
21 later. Thank you.

22 DR. KREISBERG: Dr. Cara.

1 DR. CARA: There was an allusion earlier to
2 the fact that there were two studies in which the
3 insulin dose was allowed to be varied according to
4 standard medical practice. Was there any difference
5 in the number of hypoglycemic events within those
6 studies compared to those studies in which the insulin
7 dose was not changed?

8 DR. KREISBERG: Does anybody from the FDA
9 want to answer that question or anybody from the
10 sponsor?

11 DR. MISBIN: This is our time but I think I
12 would defer to the sponsor. It's our understanding in
13 the Type 2 -- these were the early studies. In the
14 patients with Type 2 diabetes, the data was really not
15 captured in the systematic way so it was not actually
16 even reported to us.

17 In the Type 1 study the incidence that was
18 reported to us was lower than in the other two
19 studies. The protocol for all the later studies state
20 specifically that patients had a touch one meter and
21 that they were told to keep records. There was a
22 great description of the efforts made to capture that

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1 data.

2 In the earliest Phase I study, however, that
3 description is really absent from the protocol so we
4 have data but it seems to me the criteria used and the
5 intensity of capturing the data is different. There
6 was also a change made in the definition of serious
7 hypoglycemia which was not exactly clear when we
8 reviewed the data.

9 I'm not sure why there is that difference
10 but, in fact, in that trial there is still more in the
11 pramlintide treated patients. The enormous
12 discrepancy we saw in the two later trials was not
13 evident in the first trial.

14 DR. CARA: And in looking at the incidence
15 of hypoglycemic reactions and other adverse events,
16 did you specifically look at the intent to treat? Did
17 you do an intent to treat analysis or did you look at
18 completers?

19 DR. MISBIN: I don't understand how you to
20 an intent-to-treat analysis for a safety evaluation.
21 I mean, we scored all of the events that were reported
22 to us and it was not differentiated.

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1 The analysis that I showed you of the
2 responder analysis, those, of course, were completers
3 so that might answer your question but I don't think
4 it was broken down otherwise by the two populations.

5 I would point out that the completer
6 analysis versus the ITT analysis are really very much
7 the same across all the trials. The differences, in
8 my judgement, are not really worth discussing from an
9 efficacy point of view.

10 DR. CARA: The reason for my question was
11 trying to capture those patients that had dropped out
12 of the trial because of an adverse event such as
13 hypoglycemia.

14 DR. KREISBERG: Dr. Kolterman, do you want
15 to add anything to this discussion?

16 DR. KOLTERMAN: With the Chair's permission,
17 I can show a slide that allows a comparison across the
18 three Type 1 trials during the critical period of zero
19 to four weeks if you think that would be helpful.

20 Slide up, please. These are the data that
21 was just presented by the agency from study 137-117
22 which included two doses that are not being

1 recommended. These are the data from study 137-121.
2 Then here is the data from the lower dose trial where
3 patients were allowed -- where there was no
4 recommendation given in terms of insulin treatment.

5 The hatched area here, I remind you,
6 represents the presence of our century man who had in
7 excess of 100 events recorded during the study.

8 DR. CARA: Do you have a similar slide
9 showing the incidence of hypoglycemia rather than the
10 rate?

11 DR. KOLTERMAN: We do have slides that show
12 incidence. We need just a minute. I'm not sure that
13 the incidence numbers will relate directly to the
14 slide that I just showed you.

15 DR. ROMAN: If I can just make a point. It
16 is my recollection that in the same placebo group,
17 placebo arm which had the outlier with 120 over all
18 events, there was another outlier who had about 42 or
19 so events. There are really two outliers in that
20 placebo arm. I do not know exactly how many of those
21 events actually happened in the first month.

22 To go back to the previous question, if I

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1 understand it correctly, the question was if there was
2 incidence of hypoglycemia different between the trials
3 in which there was a 10 percent decrease versus no
4 adjustment in insulin. If I remember correctly, it
5 was 117.

6 Anyway, between study 117 and 121 actually
7 the incidence of hypoglycemia during the first month
8 was pretty much the same, 14 percent, as shown in one
9 of my slides. There was a lower incidence of about
10 8.5 percent in study 137-112 which employed the lower
11 pramlintide. There was a 30 micrograms of QID. I
12 hope that helps clarify the question.

13 DR. CARA: Well, yes and no in the sense
14 that the real critical issue is whether or not
15 hypoglycemia is more frequent or less frequent
16 depending on whether you can adjust the dose of
17 insulin based on accepted standard practice.

18 That also relates to efficacy in the sense
19 that if when you adjust the insulin, do you also see
20 less efficacy of the drug. I would appreciate some
21 comments from the sponsor on that.

22 DR. KREISBERG: Orville, do you have anymore

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1 data you can share with us?

2 DR. KOLTERMAN: Okay. I do not have the
3 appropriate incidence data on a slide. We can provide
4 that after lunch if the committee would like to see
5 that. We obviously have the data. It's just pulling
6 it together so that we can show it for the same
7 groups.

8 DR. KREISBERG: There will be plenty of
9 opportunity after lunch I'm sure.

10 Bill.

11 DR. TAMBORLANE: This is for Dr. Misbin.
12 Several comments alluded to waning drug effect. My
13 impression was that you have a placebo controlled arm
14 to look at changes in study effect and that you do see
15 changes in outcomes depending on the beginning and end
16 of trial and the extra attention placed to the
17 patient. I would suggest that what you've shown is a
18 waning study effect and that the placebo subtracted
19 difference did not wan.

20 DR. MISBIN: Your point is well taken
21 actually. If you look at the difference from placebo
22 at four weeks and endpoint, it was not very different.

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1 It was around -- in various trials it was around .3,
2 .4, or whatever.

3 What seemed to change, however, was the
4 statistical difference. At four weeks every arm,
5 every trial across the board was highly significant.
6 When one got to endpoint, however, sometimes it was
7 and sometimes it wasn't significant. Your point, I
8 think, is well taken.

9 What was being seen, I think, was that there
10 is clearly a drug effect at the beginning but by the
11 end of the trial, I would say just a random variation
12 that you see in patients with diabetes, is fairly
13 great and that, I think, was kind of overwhelming, the
14 statistical difference that one saw between drug and
15 placebo.

16 DR. GELATO: My question really goes back
17 earlier and I think you were going to try to answer
18 it.

19 I just wondered when we were shown the data
20 about who reached target and who didn't in terms of
21 the goals of the ADA in terms of 7 percent for
22 glycated hemoglobin whether you could separate out

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1 where the insulin levels were able to be adjusted in
2 those patients, in those trials, and where it was kept
3 steady and whether there was a difference in terms of
4 who reached target when you were allowed "to do what
5 good clinical practice is," and that is continue to
6 adjust their insulin.

7 DR. KOLTERMAN: We're checking to see if we
8 have the targets by study.

9 DR. TAMBORLANE: I wonder if I could comment
10 while we're waiting because, you know, ADA targets are
11 targets and taking care of patients are a very
12 different thing. I think there was a comment that I'm
13 not sure if Dr. Kolterman made or not that looked at
14 the EDIC results.

15 I happened to be the PI on the DCCT EDIC at
16 Yale and if you look at the outcomes currently of the
17 formerly intensively treated group in the DCCT who had
18 years of intensive management and training, and now
19 that these patients were returned to the community
20 with, more often, community control when they return
21 to their own clinics, the HbA_{1c} has gone up to 8.2
22 percent. Setting a target is something that we shoot

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1 for. Reality is another thing.

2 DR. KOLTERMAN: Again, we have the data and
3 we'll have it on an appropriate slide for you after
4 lunch.

5 DR. GRADY: I would like to ask the FDA a
6 related question. I think the hypothesis has been
7 laid out that hypoglycemia is an early effect of the
8 drug and that it may wane over time.

9 I wonder if the other possibility isn't that
10 initially patients were on a somewhat higher dose of
11 insulin. They developed hypoglycemia and their
12 insulin was adjusted. Did you look at hypoglycemic
13 episodes among patients who had increases in their
14 insulin dose during the studies?

15 DR. MISBIN: The change in insulin was very
16 minimal. I think I show that in the responder group.
17 In the placebo patients who responded that were
18 classified as responded, there was an increase of 1.9
19 percent which is one unit of mean change.

20 We didn't even discuss changes in insulin
21 very much because they were very, very small. Nothing
22 was statistically significant. They were just so

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1 small that I don't think that would add much to the
2 analysis.

3 DR. GRADY: (Off microphone.)

4 DR. MISBIN: Oh, yes. There are some
5 patients that do. We did not do a specific analysis
6 on those patients that had a large change in insulin
7 versus hypoglycemia.

8 I mean, that is certainly possible. The
9 mean changes in insulin across all the placebo groups
10 were very, very small, very small increases which was
11 by design. In pramlintide, of course, because of
12 safety issues there was a small mean reduction.

13 DR. SAMPSON: Dr. Roman, I would like to
14 follow up just one of your slides in terms of the
15 reduction of hypoglycemia after the first four weeks.
16 You indicated this took place in the context of prior
17 nausea related patient withdrawals. Was that
18 statement -- one would almost draw an inference from
19 that. Was there some data behind that that you were
20 trying to project with that statement?

21 DR. ROMAN: What I was trying to refer to
22 was the fact that the previous slide which showed that

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1 during the first month of pramlintide treatment if you
2 look at the present of patients who due to the nausea
3 in pramlintide groups compared to placebo groups,
4 there was almost a 17-fold difference in all studies
5 combined.

6 You lose about 7 percent of patients in
7 study 121 to nausea in the first month and about 6.5
8 in study 117, and roughly about 5.2 in study 112. The
9 sense I'm getting from that is that the initial
10 structure and internal organization of the group is
11 changing a little bit because you lose patients and
12 you don't lose them to a nonspecific reason. You lose
13 to a symptom that is directly related to the drug.

14 Nausea, as you know and has been presented
15 before, is the major adverse event in terms of
16 frequency of pramlintide which results in quite wide
17 discrepancies between the pramlintide and placebo
18 group. I made the comment in the context that you
19 lose some patients which are sensitive to the drug.

20 DR. SAMPSON: Was there any way of looking
21 at hypoglycemia in these patients that withdrew early
22 for nausea and comparing that to those that remained?

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1 DR. ROMAN: We don't have that analysis. I
2 do not believe I came across about occurrence of
3 hypoglycemia in those subjects. I don't know if Dr.
4 Kolterman has more information on that.

5 DR. KREISBERG: Can you answer that?

6 DR. KOLTERMAN: I can comment on two things.
7 The point that is on the table now is if you look at
8 patients that did not experience nausea, you do not
9 see the increase in hypoglycemia. If you look amongst
10 patients experiencing severe hypoglycemia, it's
11 roughly a 50/50 split. Half experience nausea and
12 half do not experience nausea.

13 With regards to the changes in insulin use
14 patterns and the occurrence of hypoglycemia, I have a
15 slide that focuses on patients who increased their
16 total daily insulin dose by 10 percent or more during
17 the conduct of the trial that has hypoglycemia on it.

18 This issue about stable insulin, as I
19 outlined in my presentation, the goal of that was to
20 come up with a group of patients that limited the
21 variability of insulin as a confounding factor in the
22 HbA_{1c} analysis.

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1 It turns out that only at best 40 percent of
2 patients were able to do that during the duration of
3 one of these long-term controlled trials. That means
4 that 60 percent of patients varied their insulin.

5 For patients in the type one program treated
6 with the recommended dose, there are 122 patients that
7 increase their insulin by more than -- no, this is
8 increase. I'm sorry. We have the wrong slide. There
9 is a similar slide. It's roughly the same number of
10 patients who will have increased their insulin by more
11 than 10 percent.

12 Sorry, I was misled. We do not have that
13 slide. Again, I think we can have that for you after
14 lunch.

15 DR. KREISBERG: What I would like to do now,
16 unless there are any other compelling --

17 Dr. Levitsky.

18 DR. LEVITSKY: I've been trying for a while.
19 My question for you, Dr. Misbin, would be in the FDA
20 briefing document, and it was alluded to briefly here,
21 there were some concerns over the correlation between
22 the data summarized and supplied by the company and

1 the data when you went in and reviewed them. Is this
2 still a concern for you?

3 DR. MISBIN: Are you talking about the
4 inspections?

5 DR. LEVITSKY: Yes.

6 DR. MISBIN: Yes, it is a concern. I don't
7 know if we are supposed to discuss this.

8 DR. LEVITSKY: Can we talk about it? It was
9 in the briefing document I got.

10 DR. MISBIN: We need to hear a judgement
11 from the Chairman whether this can be discussed.

12 DR. KREISBERG: The Chairman? Let me
13 consult with the FDA.

14 DR. TAMBORLANE: I have another
15 informational question in the meantime.

16 DR. ORLOFF: Dr. Kreisberg, might I suggest
17 that if this is going to come up, it could come up in
18 the discussion after lunch. The sponsor, I believe,
19 would be happy to address the integrity of their
20 database at that time.

21 DR. KREISBERG: Okay.

22 DR. TAMBORLANE: I have another

1 informational question about the hypoglycemia and
2 accidents. I apologize because there were a lot of
3 data in a short period of time. My impression was
4 that you were throwing in the results from all of the
5 exposures to pramlintide. Have you looked at the data
6 with respect to the recommended doses as well? Did I
7 miss that or did you present that?

8 DR. ROMAN: I looked at the doses and
9 practically almost all patients were -- let me make
10 two points. One point is that if you look at all the
11 MVAs, as I said, they were not captured perspective.
12 That being said, some studies had more driving-related
13 events than others. Of course, the data is going to
14 be skewed toward those studies and those doses using
15 those studies.

16 Now, to answer your question, study 121 all
17 patients had 60 micrograms, 90 micrograms, 60, 60, 60.
18 It seemed to be occurring maybe in the 60 range and
19 one in the 90 range. In study 117 they had the 90
20 microgram range of pramlintide.

21 In study 112 they occurred as low as 30 but
22 there were only two of them which were captured in

1 that study. In study 121 it's really not a clear
2 trend that higher dose is associated with events to
3 me. It's very limited data, though.

4 DR. TAMBORLANE: Could the company come up
5 with data related to that? You showed some issues
6 with that at the lower doses. At least the
7 hypoglycemia rate seemed less at what you're
8 recommending. Do you have other safety issues?

9 DR. KOLTERMAN: Yes. I have a slide that
10 will address this issue so we have the slide up. This
11 is a listing of the motor vehicle accidents associated
12 with hypoglycemia.

13 Now, associated with hypoglycemia means that
14 hypoglycemia was recorded by the patient on the same
15 day within the same 24 hour period of the motor
16 vehicle accident. You can see that the accidents that
17 occurred during the initial four weeks by our analysis
18 of the data occurred only at the higher doses.

19 The same is true of weeks four to 12 in that
20 the accidents that did occur on the lower dose of 30
21 micrograms four times a day occurred after 12 weeks of
22 therapy. These accidents here by 112(e) accidents are

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1 accidents that occurred into the second and sometimes
2 the third year of exposure to the compound.

3 If you limit the 30 microgram analysis to
4 just those that occurred during the double blind
5 placebo control period, you have two events right
6 here.

7 DR. MISBIN: It should be pointed out, I
8 think, that 30 micrograms was only used in one trial.
9 Isn't that right?

10 DR. KOLTERMAN: That is correct. It was
11 used in one placebo controlled trial.

12 DR. MISBIN: Of the Phase 3 trials that we
13 are considering, there was one trial in which it was
14 given 30 micrograms QID. The other two trials we have
15 no data on 30 microgram dosing.

16 DR. KOLTERMAN: That's true but as was on
17 the slide, the data related to 30 micrograms is
18 supplemented by data from two open-label safety
19 studies that provide extra additional exposure at that
20 dose.

21 DR. KREISBERG: I'm going to cut off this
22 type of questioning at the present time. We should

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1 have enough time this afternoon to cover this and all
2 other questions for discussion. We are approximately
3 45 minutes behind schedule and I would like to move to
4 the open public hearing.

5 I would like to ask each of the speakers to
6 come to the microphone at the front of the center isle
7 and disclose any financial conflicts that you might
8 have and limit your comments to three minutes.

9 DR. LEVETAN: Good morning. I am Claresa
10 Levetan. I am a endocrinologist who practices in
11 Washington, D.C., at MedStar Clinical Research Center,
12 which is affiliated with Georgetown Medical School.
13 I have been a clinical investigator and a consultant
14 for Amylin Pharmaceuticals since 1995.

15 I am here this morning for one reason and
16 one reason only. My patients have told me that
17 pramlintide has given them back their life. In Type
18 1 patients, in Type 2 patients, in patients on pumps,
19 in patients with A_{1c} of 7 percent, and in patients
20 with A_{1c} of 11 percent.

21 I have had 60 patients receive pramlintide
22 through the clinical trials. My patients travel from

1 as far as London to continue their participation in
2 the open-label pramlintide trial.

3 The comment I hear most consistently from my
4 patients is that pramlintide reduces the glucose
5 fluctuations and swings. Yes, both Type 1 patients
6 and Type 2 patients did experience hypoglycemia during
7 the initial stages of some of the randomized trials,
8 but this only occurred in my patients during the time
9 period when the protocol mandated that their insulin
10 dosages go unchanged.

11 I found that many of my patients actually
12 had sizable reductions in their insulin dosages by
13 study end. During the open-label trial, unlike the
14 randomized trials, we reduced insulin dosages at the
15 time pramlintide was initiated, and avoided all of the
16 serious hypoglycemia previously seen during the first
17 weeks of therapy during the randomized trials.

18 In my practice, I use the continuous glucose
19 monitoring system which measures interstitial glucose
20 every five minutes and records 288 glucose readings
21 per day.

22 To further evaluate the potential benefits

1 of pramlintide that have been described by my
2 patients, I utilized the continuous glucose monitoring
3 on a patient who entered the open-label trial shortly
4 after this monitoring system became available.

5 I have attached the sensor data of this
6 patient who is a Type 1 patient who was one of the
7 patients who fortunately did achieve an A_{1c} of 6.6
8 percent which was the goal, below 7 percent as was
9 mentioned this morning. This patient does also use an
10 insulin pump.

11 Despite the A_{1c} of 6.6 percent, he
12 experienced wide swings in glucose fluctuations and
13 hypoglycemia. By day 27 on pramlintide his insulin
14 requirement before meals was reduced by 18 percent and
15 he had a 54 percent reduction in both the high and low
16 glucose excursions from the mean compared to baseline
17 levels before pramlintide.

18 Currently the most serious and potentially
19 life-threatening limitation to patients with diabetes
20 is hypoglycemia. I believe that amylin plays its
21 greatest role in ameliorating both hypoglycemia and
22 hyperglycemia via different mechanisms of action that

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1 insulin as evidenced by the different structure and
2 locations of the amylin receptors compared to that of
3 the insulin receptors.

4 Far beyond pramlintide's ability to lower
5 HbA_{1c}, I believe that this hormone plays its greatest
6 role as the fine tuner of glucose regulation.
7 Pramlintide's benefits include the inhibition of
8 glucagon which reduces both postprandial hyperglycemia
9 and enhances the liver's stores of glycogen which is
10 reduced in patients with diabetes.

11 Thus, pramlintide's benefit may result from
12 diminishing both the high and the low swings seen
13 among patients with tightly -- that are seen even in
14 tightly controlled diabetes patients.

15 These benefits would not be evident by
16 looking at average blood glucose values, nor reflected
17 in HbA_{1c}. The DCCT demonstrated the benefit of
18 reducing high and low glucose excursions independently
19 of a change in HbA_{1c} on reductions in diabetes related
20 complications and I have attached that data.

21 In summary, as a clinician whose practice
22 focuses on patients with brittle diabetes, I strongly

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1 urge this panel to approve the usage of this hormone
2 in patients with Type 1 and Type 2 diabetes because
3 pramlintide is the first and only adjunctive therapy
4 which addresses many of the shortcomings in insulin
5 therapy today.

6 In my patients, pramlintide resulted in
7 sustained reductions in the hypoglycemic event rate
8 after insulin dosages were reduced beginning at four
9 weeks.

10 Secondly, it resulted in a sustained
11 reduction in hyperglycemia. It also resulted in a
12 sustained reduction in insulin requirements. And also
13 in enhanced glucose control without weight gain and a
14 sustained weight loss that occurred after the
15 reduction of insulin.

16 I request that all of the data that was
17 presented this morning and hypoglycemic event rates be
18 analyzed after four weeks of therapy. My strong
19 feeling is that you will see the clinically important
20 endpoints which my patients have seen. I thank you
21 very much for your time and consideration.

22 DR. KREISBERG: Thank you.

1 Can we have the next speaker, please.

2 DR. WUERTENBERG: Good afternoon.

3 DR. KREISBERG: Good afternoon. You have
4 three minutes.

5 DR. WUERTENBERG: Okay. My name is Anna
6 Wuertenberg and I am a patient of Dr. Levetan's and a
7 participant in the current open-label trial on
8 pramlintide acetate, trial number 137-140, at the
9 MedStar Research Center.

10 I not only didn't withdraw from the study,
11 I went out about a week after I joined it and bought
12 100 shares of stock. I very much appreciate having
13 this opportunity to speak with the committee about my
14 experience with pramlintide.

15 I have been a Type 1 diabetic for 26 years
16 and for 26 years I have been unable to get control of
17 my diabetes.

18 I won't give you all the gory details but I
19 will tell you that except for the new "basal"
20 insulins, I've tried every insulin and every
21 combination of insulins on the market. I've tried
22 them up to five shots a day. I've used a pump since

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1 1993.

2 I test regularly. I actually test
3 religiously. I exercise almost as religiously. I
4 follow my meal plan. Five years ago I had to start
5 working at home four days a week because I could no
6 longer go into work.

7 Despite all my efforts, despite all the
8 efforts of a number of caring and competent doctors
9 and certified diabetes educators, things have gotten
10 worse, not better and I have been unable to control my
11 diabetes.

12 I'm very emotional because hearing what I've
13 heard in the last hour as made me very angry because
14 it just hasn't been my experience with pramlintide.
15 Even with the pump before pramlintide I had to take a
16 comparatively large amount of insulin with every meal.

17 I had to use very low basal rates for the
18 rest of the time. This was totally ineffective and I
19 had lots of severe hypoglycemia, especially at night.
20 I was never able to find a more effective balance. I
21 just couldn't get there.

22 I can't overstate how debilitating this was.

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1 By the time I began the trial, my blood sugars still
2 ranged within a range of about 300 points every day
3 with the most severe lows at night. I was unable to
4 exercise. I was working only an hour to two hours per
5 day and sitting in sort of a semi-static sense for the
6 rest of the day. This was my last ditch effort before
7 disability retirement.

8 Since starting pramlintide at the end of
9 January 2001, my blood sugars have grown progressively
10 more stable. I currently take an injection of
11 pramlintide three times a day. Doing this on top of
12 using a pump is kind of a bore and it's not always
13 convenient to take a shot and then eat immediately
14 afterwards. Let me tell you, it's worth the trouble.

15 My last A_{1c} is 6.4 but I want to reemphasize
16 what Dr. Levetan said. It's not just the score, it's
17 the fact that it's happening in a range that is much
18 smaller. Before it was truly an average of the very
19 high and the very low.

20 My insulin dosages at meal have been reduced
21 a little more than Dr. Levetan indicated. My dinner
22 insulin dose has gone down 70 percent. My bolus at

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1 breakfast is 30 percent and it's somewhere in between
2 for lunch. I've had very good luck that way.

3 I've also been able to reduce my overall
4 dose of insulin despite being able to raise my basals
5 a little bit without having hypoglycemia. I am now
6 able to sleep through the night.

7 I've increased my workload and my turnaround
8 times at work so dramatically that I'm now working a
9 50-hour week. If you want to include a warning on
10 this drug, tell them it may make you too productive
11 for your own good. I get lectured about it now when
12 I go in.

13 My life on pramlintide isn't perfect but I'm
14 getting closer to achieving the holy grail of control
15 all the time. I now have several good days in a row
16 and the bad days are fewer and fewer and they are much
17 less bad than they ever were before.

18 I can't believe how much better I feel. I
19 not only encourage you to approve pramlintide, I beg
20 you to do it. This could change a lot of lives and we
21 diabetics have been waiting since Banting and Best for
22 something that will.

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1 DR. KREISBERG: Thank you very much.

2 Can we have the next speaker, please.

3 MS. BENESH: Thank you for allowing me to
4 have the opportunity today to speak in behalf of
5 Symlin generically known as pramlintide produced by
6 Amylin.

7 My name is Susan Benesh. I am 53 years old,
8 and I have managed my Type 1 juvenile diabetes
9 mellitus for 38 years. This chronic illness was very
10 traumatic for me and affected my entire family. It
11 meant a complete change in lifestyle for all of us.

12 Although insulin was being used to treat
13 diabetes at the onset of my diabetes, it was still
14 tricky to keep glucose levels under control. Many
15 factors such as diet, physical activity, stress, and
16 hormonal changes make it difficult to control blood
17 sugar levels.

18 Because of continued research and
19 developments since my diagnosis, new products have
20 come on the market to help control glucose levels.
21 Research and development is essential to find a cure
22 for this dreadful disease.

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1 More and more people of all age groups are
2 being diagnosed everyday with diabetes. In order to
3 aid in glucose control and avoid daily multiple
4 injections, I began an insulin pump user. When the
5 pramlintide study was initiated and my physician
6 approached me because she felt I was a good candidate
7 for the study, I agreed to participate because I was
8 excited about the possibility that this new drug would
9 enhance and perhaps prolong my life.

10 The insulin pump has helped me considerably
11 and I was more than willing to take the pramlintide
12 injections because of the success I was experiencing
13 in the pramlintide study.

14 Pramlintide not only helped with my glucose
15 control, it lowered my cholesterol and enabled me to
16 stabilize my weight. I participated in three
17 pramlintide clinical trials.

18 The second trial conducted was terminated by
19 Amylin Pharmecuticals because of funding issues. It
20 took less than 30 days for me to notice a tremendous
21 negative difference in my health without pramlintide.

22 Although I was able to maintain my HbA_{1c}

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1 below 7, I easily gained 20 pounds, my total
2 cholesterol level increased, hypoglycemia became
3 frequent again, and my HbA_{1c} rose at each subsequent
4 testing.

5 Prior to participating in the study, my
6 HbA_{1c} was in the double digit range despite my hard
7 work to keep my glucose levels under the best of
8 control. During the study my HbA_{1c} was a low as 5.9
9 and not higher than 6.9. It was very disheartening
10 and depressing to be denied use of pramlintide.

11 For a year following the termination of the
12 study and much pleading by me and other study
13 patients, my physician was able to obtain pramlintide
14 once again for only a few study patients on an open-
15 label trial basis. I was very, very fortunate to be
16 one of those patients. I am presently using open-
17 label pramlintide.

18 Pramlintide as been responsible for
19 controlling my glucose levels, smoothing glucose
20 levels to a point of experiencing much less frequent
21 insulin reactions or high blood sugars, and aiding in
22 the reduction of insulin intake for optimum control.

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1 In closing, I am one diabetic patient among
2 millions of diagnosed, and yet to be diagnosed,
3 diabetics who has greatly benefitted from using
4 pramlintide.

5 I hope that the information I have provided
6 in addition to the overall study results of
7 pramlintide will convince this advisory committee, as
8 it has me, that even though I have to deal daily with
9 diabetes, there is an opportunity that I will have a
10 better quality of life with pramlintide. Thank you.

11 MS. ASHCRAFT: My name is Rose Ashcraft. I
12 have been an attorney for about 20 years. I was
13 diagnosed with diabetes at age 34 in September of
14 1987. I am a Type 1 diabetic. I participated in
15 clinical trials for pramlintide at MedStar Research
16 Institute. I am now taking pramlintide on a open-
17 label trial.

18 I have heard several comments today about
19 why pramlintide is not good enough. While I am here
20 to tell you that many medical regimens for diabetes
21 are not good enough, insulin is not good enough but
22 it's the best that we have and we're glad that we have

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1 it.

2 I have two major problems with managing my
3 blood glucose levels and they are reflected in my
4 HbA_{1c}s. The first problem is the dawn phenomenon.
5 None of the insulins that we currently have on the
6 market are adequate with the dawn phenomenon.

7 I began insulin pump therapy in January of
8 this year in order to attempt to get a handle on that
9 problem. The second problem I have with my blood
10 sugar management is after-meal spikes and
11 hypoglycemia. Actually, there are three problems.

12 The pramlintide has made a very significant
13 impact on my after-meal spikes and upon my
14 hypoglycemic incidents.

15 Pramlintide has effectively eliminated
16 after-meal spikes in my blood glucose levels. Without
17 the drug, during the first hour and a half subsequent
18 to meals even with Lispro and the insulin pump, my
19 blood sugars tend to rise rapidly and do not return to
20 normal levels until the Lispro is fully absorbed
21 approximately two and a half to three hours after the
22 meal.

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1 Use of pramlintide with my insulin regimen
2 eliminates the after-meal spike in blood sugars that
3 was consistent for me before I began using the
4 pramlintide.

5 Secondly, I no longer have severe
6 hypoglycemia, and I even have fewer mild hypoglycemic
7 incidents. Despite my best attempts to use insulin to
8 the best of my ability prior to the combined use of
9 pramlintide with insulin, I routinely experienced
10 hypoglycemia.

11 Prevention of hypoglycemia enables me to
12 regularly consume fewer calories which, in turn, helps
13 present unwanted weight gain. Maintaining an ideal
14 weight is important to me for two reasons. First,
15 gaining weight because I am diabetic is a real downer
16 and it does not help me in my overall control.
17 Secondly, being overweight puts me at risk for long-
18 term complications.

19 When I went off pramlintide after the open-
20 label extension ended in 1998, I gained 10 pounds in
21 less than a year but lost it when I began consistently
22 taking the medication again. I attributed this weight

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1 loss in large part to the fact that I was not eating
2 extra carbohydrate.

3 I have continued with pramlintide even with
4 my insulin pump therapy because of the benefits it
5 provides me. The combination of pump therapy with
6 Lispro which ensures a low-fasting blood sugar in the
7 morning and increases flexibility in my routine with
8 pramlintide which evens out mealtime readings and
9 prevents hypoglycemia are giving me freedom and
10 security that I have not had since before I was
11 diagnosed.

12 It is my hope that pramlintide will be
13 approved by the FDA because I think it's benefits are
14 important to all diabetics who want to maintain good
15 glucose control and live a life free of long-term
16 complications. Thank you.

17 MR. BROWN: Good afternoon. My name is
18 Chris Brown. I'm a Type 1 diabetic, a disease that
19 runs in my family. Since being diagnosed in 1996 I
20 have given myself at least four daily injections of
21 insulin. Since June of 1998 when I enrolled in a
22 Phase 3 clinical trial and afterwards on a

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1 compassionate use basis, I also inject 60 micrograms
2 of pramlintide at mealtime.

3 The result is something I never thought
4 possible. My blood sugar control is very nearly
5 perfect. In fact, I now think of myself as a
6 fundamentally healthy person who just happens to be a
7 diabetic.

8 Unless I specifically mentioned it, nothing
9 about my health would give a doctor reason to believe
10 I am a diabetic. I owe this entirely to pramlintide.
11 Assuming pramlintide is approved, I do not expect ever
12 to develop the complications associated with
13 diabetics.

14 Beyond balancing my insulin with my
15 carbohydrate consumption, I pay my diet no special
16 attention. But what's most remarkable is that with
17 pramlintide, my diabetes requires almost no effort to
18 manage.

19 Of course, tight blood sugar control is
20 possible without pramlintide but non-diabetics can
21 scarcely comprehend how much effort is required.
22 Taking insulin together with pramlintide means I

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1 simply stop worrying about my blood sugar readings.

2 Although I continue to test myself four time
3 a day, I know expect my readings to fall well within
4 a normal range. With daily injections of pramlintide,
5 I am as surprised by abnormally high or low blood
6 sugar readings as a non-diabetic would be.

7 I go weeks at a time with pre-breakfast
8 blood sugar readings in the low 90s. Two hours after
9 a meal my blood sugars are anywhere from 110 to 135.
10 I have achieved these results while reducing my
11 insulin requirements to about one-half to two-thirds
12 of what they were before using the pramlintide.

13 I have a much easier time keep my weight
14 down. IN fact, within two months of starting the
15 pramlintide in the summer of 1998, I lost thirteen
16 pounds that I gained trying to maintain tight blood
17 sugar control without it. My HbA_{1c} readings now hover
18 around 5.8.

19 Pramlintide is as close to a miracle cure
20 for diabetes as I can ever hope to see in my lifetime.
21 I know that, strictly speaking, it is not a cure but
22 I consider myself if not perfectly normal, then at

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1 least perfectly healthy again. With pramlintide I no
2 longer think of myself as suffering from a chronic
3 disease.

4 Of course, I do. Pramlintide has not
5 altered the basic fact that my pancreas does not work.
6 Nevertheless, pramlintide has changed how I think
7 about myself. I am once again a healthy person who
8 just happens to have a metabolic disorder.

9 Pramlintide has improved my life to a degree
10 non-diabetics cannot begin to comprehend. To me, it
11 represents the biggest improvement in the lives of
12 diabetics since the development of human insulin some
13 twenty years ago.

14 Pramlintide needs to become a routine
15 element in the treatment of diabetes. Insulin to keep
16 us alive, pramlintide to stave off the diabetic-
17 related complications. The two together should go a
18 long way to making this disease less of a killer.

19 I cannot imagine ever going back to worrying
20 about my blood sugars. Pramlintide allows me to lead
21 a normal life. I hope that eventually all diabetics
22 will be similarly fortunate. For that reason, I ask

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1 that you recommend its approval. Thank you.

2 DR. KREISBERG: Thank you.

3 MS. WANT: Good afternoon. My name is Laura
4 Want. I'm a certified diabetes educator and certified
5 clinical research coordinator at MedStar Research
6 Institute in Washington. I have over twenty years
7 experience in diabetes education, management, and
8 research. I have served as a coordinator for Amylin
9 Pharmaceutical trials at MedStar since 1995. I'm a
10 member of their CDE Advisory Committee and I own some
11 Amylin stock.

12 The DCCT results proved the benefits of
13 tight control to the point that many of our patients
14 will endure severe hypoglycemia in the desperate quest
15 to avoid the long-term complications.

16 The limitations of diabetes management
17 continue to frustrate physicians and educators as well
18 as patients. No matter how hard we try, it seems
19 impossible to maintain near-normal HbA_{1c} without the
20 complications of weight gain and the frequent
21 hypoglycemia.

22 Like the four previous speakers whose A_{1c}s

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1 have remained below 7 since entering the open-label
2 trial, pramlintide has allowed our patients to
3 maintain type control with these miserable side
4 effects.

5 Over the past six years I've coordinated
6 Phase 3 pramlintide trials with 60 patients with
7 diabetes. Before the studies most of these patients
8 paid meticulous attention to balancing diet, exercise,
9 and medication to keep the HbA_{1c} as low as possible
10 but struggling with weight gain and suffering frequent
11 hypoglycemia.

12 Because the earlier trials called for fixed
13 pramlintide and insulin doses, patients reported more
14 nausea and hypoglycemia, especially in the first
15 months of pramlintide therapy. The current open-label
16 trial has allowed us more flexibility. We have found
17 that lowering insulin doses and titrating up to the
18 recommended pramlintide doses has virtually eliminated
19 the problems with hypoglycemia and nausea.

20 Patients on pramlintide have had improvement
21 in HbA_{1c} levels but that does not fully reflect the
22 benefits of pramlintide. Patients have had less

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1 frequent and less severe hypoglycemia.

2 Self-monitoring records showed reduced
3 postprandial glucose rises as well as lower standard
4 deviation from mean glucose indicating more consistent
5 blood glucoses.

6 Patients reported increased well-being and
7 energy. A woman whose pre-pramlintide severe
8 hypoglycemia interfered with her daily activities
9 reported she had fewer and milder hypoglycemic
10 episodes on pramlintide.

11 Patients found it was easier to lose weight
12 without compromising tight diabetes control. Even
13 though the trial requires additional injections,
14 patients felt that the pramlintide therapy
15 dramatically improved their diabetes control and
16 quality of life.

17 According to our patients, insulin made
18 their diabetes survivable but adding pramlintide makes
19 diabetes much more livable. Thank you.

20 DR. WOLFE: I'm Sidney Wolfe. I'm an
21 internist and director of Public Citizen's Health
22 Research Group. About 40 years ago it was possible to

1 approve a drug based on testimonials by physicians, by
2 patients such as the ones you've heard. I have no
3 reason to doubt anything anyone has said but a little
4 less than four years ago the law was changed to
5 require the results of randomized control trials. You
6 hear the good news stories. Again, I have no reason
7 to doubt them but you don't hear people who have had
8 some of the serious problems that have been described
9 in the clinical trials coming forth.

10 As endocrinologists or primary care
11 physicians based on results of the randomized control
12 trials, which is what we are really here to consider,
13 what we recommend for our insulin requiring diabetic
14 patients a drug that had the following benefits and
15 risks, benefits as pointed out compared with placebo
16 lowering of HbA_{1c} of only .3 percent in the four
17 fixed-dose studies.

18 Increased severe hypoglycemia with
19 automobile driving related adverse offense which if
20 this drug were ever approved be in the thousands if
21 not more as opposed to the dozens that were reported
22 in these trials including crashes and confusion while

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1 driving. Most people required paramedic intervention,
2 E.R. visits, and IV glucose administration and one
3 death, as pointed out.

4 Something not discussed, although in the
5 data provided by the FDA, 11 out of 1,179 patients
6 given pramlintide but none out of 538 given the
7 placebo had nervous system problems. Of these 11 four
8 of the patients had convulsions, three had coma, and
9 one each with ataxia headache, vertigo, and migraines.

10 You've heard discussion of the gastro
11 intestinal problems in the Type 1 diabetics. It was
12 51 percent nausea in the pramlintide group versus 17
13 percent in the placebo. Anorexia, again not discussed
14 very much, a serious problem which can contribute to
15 the hypoglycemia, 18 percent in the pramlintide group,
16 and 2 percent in the placebo group.

17 Although the company seemed to want to
18 trivialize it, there was an increase in diabetic
19 retinopathy in one of the studies, an increase of 19
20 percent in the group taking the drug, and 8 percent in
21 the group taking the placebo.

22 The need for more injections goes without

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1 saying. It is an additional burden on people. If the
2 answer for our own patients about recommending the
3 drug is no because the risk so clearly outweigh the
4 benefits, the answer to the question about whether the
5 FDA should approve the drug must also be no.

6 Beyond the question of FDA approval,
7 however, is the issue of any further clinical trials
8 involving new patients such as those proposed by the
9 FDA based on existing knowledge about serious risk
10 caused by pramlintide.

11 It would be unethical to do a study to pin
12 down more firmly the causal relationship of this drug
13 to hypoglycemia on awareness to further study efficacy
14 or to expose new patients for any other purpose.

15 One can only imagine what the informed
16 consent sheets for such studies would now have to look
17 like. This drug deserves to be put out of its misery
18 before any more patients are injured or killed in any
19 further clinical trials.

20 DR. PULLMAN: My name is John Pullman. I've
21 come from Butte, Montana, where I practice as a
22 general internist and I have practiced there for 19

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1 years. I have several hundred patients that are
2 insulin controlled diabetics and I've been an
3 investigator in the Amylin 102, 111, 111(e), 121, 137,
4 140 extension open-label trials.

5 DR. KREISBERG: We're having a little
6 trouble hearing you. Could you just speak a little
7 bit closer to the mic, please.

8 DR. PULLMAN: Surely. My reason for coming
9 here today is to transmit to you the enthusiasm, the
10 30 or more patients that I have enrolled in these
11 trials have transmitted to me, and the enthusiasm I've
12 felt in my ability to improve their glycemic control.

13 The open-label trial has probably been the
14 best form since we've been blinded on the others. 17
15 patients have elected to continue in the open-label
16 trial. Their experience has been remarkable to me
17 after 15 years of frustration up until four years ago.

18 Weight loss, which can be trivialized to a
19 percent of five to 10 percent, can mean a lot when you
20 weigh 180 pounds and you go down to 162 pounds.
21 People would kill for those things.

22 The enthusiasm I've seen in Type 1 diabetics

1 who are totally controlled on pumps includes the
2 improvement they have and those terrible instructions
3 we have to give people which is plan your
4 carbohydrates, count a unit of Lispro for every 15
5 grams you're going to eat.

6 If you take four units of Lispro, you can't
7 eat more. That is the problem they face. What has
8 happened with pramlintide is the satiety effect has
9 actually allowed them to limit the intake to what they
10 had planned which, for many of us who are fortunate
11 enough not to have diabetes, is a near impossible
12 task.

13 I think the behavioral aspects in terms of
14 diet are remarkable. I think the improvement in
15 glycemic control are remarkable and I strongly urge
16 the committee to consider approving this drug.

17 I would like to finish on an ironic note.
18 I know hypoglycemia is a very serious side effect but
19 I find it ironic with the release of Lantis, my
20 clinical experience again just as a practicing
21 internist has been somewhat startling.

22 I know it came out with the approval that

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1 the dose of Lantis as a once-a-day agent be 70 percent
2 of the basal insulin over 24 hours. I don't know a
3 clinician in the area where I practice that dares to
4 use more than 50 percent because of the severe
5 hypoglycemia we see in post-marketing and I find it
6 ironic that it got out with the 70 percent
7 recommendation but I don't think it's anybody's fault.

8 I think the disease continues to humble us
9 in these post-marketing studies. I think it will
10 continue to humble us for a long time unless we start
11 looking for more unique solutions than we have to
12 date. Thank you very much.

13 DR. KREISBERG: Thank you. Thank everybody
14 else who took the time to come.

15 Oh, do we have one more? I'm sorry. Two
16 more.

17 MS. KRUGER: My name is Davida Kruger. I am
18 a certified nurse practitioner at Henry Ford Health
19 Systems in Detroit, Michigan. I have done clinical
20 research for Amylin for the past five years. I've
21 been a speak for them and I do own some stock.

22 I've also been an investigator for the

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1 diabetes control and complications trial, EDIC trial,
2 and presently for the accord trials, all of which look
3 at intensifying tight control for people with Type 1
4 and Type 2 diabetes.

5 Over the past five years I have enrolled
6 more than 60 patients in the four pramlintide trials
7 that I have been involved in. Despite, nausea,
8 increased number of injections, none of our patients
9 have withdrawn from any of our clinical trials. Why?
10 Primarily because pramlintide has provided an improved
11 quality of life, something that I haven't heard this
12 panel talk much about today.

13 With decreased swings in their blood sugars,
14 decreased postprandial rises, less insulin needed,
15 less hypoglycemia, and weight loss. They generally
16 feel better, something that is very important to
17 people's lives with diabetes.

18 When we had an opportunity to offer open-
19 label in the Type 1 study, we had enrolled 21
20 volunteers and 18 of those 21 volunteers chose to
21 continue despite the fact that they were on seven or
22 eight injections a day or they were on an insulin pump

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