DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE

VOLUME I

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8:00 a.m.

Holiday Inn Silver Spring
Kennedy Room
8777 Georgia Avenue
Silver Spring, Maryland

PARTICIPANTS

Paul D. Woolf, M.D., Acting Chair
Cathy Groupe, RN, BSN, Executive Secretary

MEMBERS:

Sonia Caprio, M.D.
Dean Follmann, Ph.D.
Nelson B. Watts, M.D.

CONSULTANTS (VOTING):

William J. Calhoun, M.D.
James K. Stoller, M.D., M.D.
Karen Schell, R.R.T. (Consumer Representative)
Talmadge E. King, Jr., M.D.
Dara P. Schuster, M.D.
Rebecca W. Killion (Patient Representative)

FDA STAFF:

Robert J. Meyer, M.D.
David Orloff, M.D.
Sally Seymour, M.D.
Karen M. Mahoney, M.D.

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. WOOLF: Good morning. I am informed it is eight o'clock and, therefore, it is time to start the meeting. The Endocrine and Metabolic Diseases Advisory Committee is meeting today--as if everybody doesn't know that--to discuss new drug application 21-868, proposed trade name Exubera, insulin recombinant deoxynucleotidyl acid origin powder for oral inhalation, 1 mg and 3 mg powder for inhalation, by Pfizer for the treatment of patients with diabetes mellitus.

I would like the committee members to introduce themselves and also their specialty, and I will start with Dean Follmann.

DR. FOLLMANN: Thanks. I am Dean Follmann and head of biostatistics at NIAID.

DR. WOOLF: Nelson Watts, endocrinology, from the University of Cincinnati.

DR. CAPRIO: I am Sonia Caprio, endocrinology, and my area of expertise is diabetes and childhood obesity.

DR. KING: I am Talmadge King, and I am a pulmonologist from the University of California, San Francisco.

DR. STOLLER: I am James Stoller. I am lung doctor at the Cleveland Clinic.

DR. CALHOUN: Bill Calhoun. I am a pulmonologist at the University of Texas, Galveston.

MS. SCHELL: I am Karen Schell. I am a consumer representative. I am a respiratory therapist.

DR. SCHUSTER: I am Dara Schuster. I am an endocrinologist at Ohio State.

DR. WOOLF: I am Paul Woolf. I am an endocrinologist at Crozer Chester Medical Center in suburban Philadelphia.

LCDR GROUPE: I am Cathy Groupe. I am with FDA's Advisors and Consultants Staff. I am the executive secretary for the committee.

MS. KILLION: I am Rebecca Killion and I am the patient representative.

DR. SEYMOUR: I am Sally Seymour. I am a

medical officer in the Division of Pulmonary and Allergy Drug Products.

DR. MAHONEY: I am Karen Mahoney. I am a medical officer in the Division of Endocrine and Metabolic Drug Products.

DR. ORLOFF: David Orloff, Director of Metabolic and Endocrine Drugs, FDA.

DR. MEYER: Bob Meyer, Director of the Office of Drug Evaluation II at the FDA.

DR. WOOLF: Cathy will now discuss the conflict of interest statement.

Conflict of Interest Statement

LCDR GROUPE: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following

exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), full waivers have been granted to the following participants:

Dr. Dara Schuster for consulting on unrelated matters for the sponsor and a firm that co-developed, co-promotes and co-manufactures the product at issue, for which she receives less than $10,001 per year, per firm; and for being on a speakers bureau on unrelated matters for the sponsor and a firm that co-developed, co-promotes and co-manufactures the product at issue, for which she receives less than $10,001 per year, per firm.

Dr. Talmadge King for being a member of the sponsor's advisory board on unrelated matters for which he receives less than $10,001 per year.

Dr. Paul Woolf for ownership of stock in a sponsor, valued from $25,001 to $50,000. This de minimis financial interest falls under the 5 CFR Part 2640.201 which is covered by a regulatory waiver under 18 U.S.C. 208(b)(2).

In accordance with the 18 U.S.C.

208(b)(3), a limited waiver has been granted to Dr. Nelson Watts for consulting on unrelated matters for a competitor for which he receives less than $10,001 per year; and for speaking on unrelated matters for the sponsor for which he receives between $5,001 to $10,000 a year. Under the terms of this limited waiver, Dr. Watts will be permitted to participate in the committee's discussions of Exubera. He is, however, excluded from voting.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with

any firm whose products they may wish to comment upon. Thank you.

DR. WOOLF: Thank you. The next speaker is David Orloff.

Welcome

DR. ORLOFF: Thank you, Dr. Woolf. Good morning. Let me begin by welcoming the members of the committee, the consultants and the FDA participants and thank them for their presence and their contributions in advance.

I would like to make a few remarks by way of introduction. First, let me begin with a discussion of a few background points. Exubera is native[?] sequence of common human insulin in a drug-device combination product for administration by inhalation. As we begin today's discussion, several basic premises bear highlighting.

First, insulin itself is safe and effective for the treatment of diabetes mellitus, both type 1 and type 2, period. Second, if active insulin can be delivered to the bloodstream then, dosed adequately, it will lower blood glucose and

glycemic exposure in patients with diabetes. Third, essential to the approval of a given insulin product is to establish a method of its optimal integration into diabetes management, and to so label the product for safe and effective use. At the start though, there are no mysteries regarding the pharmacology of Exubera. It is quite simply insulin, though administered by a new route.

Now, with regard to trial design, it is perhaps notable that all trials of Exubera were open-label, active controlled trials. Why is this? Simply stated, it is because the benefit of insulin therapy, that is, glucose lowering, and the principal risk associated with its use, that is hypoglycemia, are one and the same and because fixed dosing is for practical purposes impossible. Therefore, if doctors and patients are blinded to treatment allocation, then patients can be expected either to achieve suboptimal glycemic control or to experience excessive hypoglycemia, or both.

Stated differently, on the one hand, blinding of insulin trials is not necessary for

inference of efficacy of insulin. On the other, blinding would not permit a valid assessment of hypoglycemic risks in real-world use because achievement of glycemic goals and simultaneous avoidance of hypoglycemia require titration which, itself, can only be accomplished in a setting of open-label use.

Lastly, a point of caution. As the committee considers the efficacy and safety information presented here today, as the public attends to the discussion, and as the FDA completes its own decision-making processes regarding Exubera in the coming weeks, it is critical to understand the following: While the drug in the Exubera drug-device combination is highly purified recombinant human insulin, it also contains excipients and is administered utilizing a device unique in its mechanics and, therefore, the characteristics of the insulin cloud, if you will, produces ventilation. As such, conclusions about the dosing, method of use, hypoglycemic risk per glucose lowering and, particularly the pulmonary

effects associated with this product are not generalizable to all inhaled insulin products.

Most importantly perhaps, what we learn about the pulmonary effects associated with Exubera and inhaled insulin must not be ignored as we consider other such products, but we must be careful not to widely extrapolate final conclusions regarding the safety or, for that matter, the efficacy of Exubera to inhaled insulins generally.

Let me turn to a few words about the objectives of the Exubera development program. There were obviously several and they may be broadly described as follows: First, the appropriate dose or doses of Exubera had to be determined initially by comparison of acute kinetics and glucose disposal dynamics to short-acting subcutaneously administered insulins.

Additionally, an extensive biopharmaceutics research program characterized kinetic and dynamic variability with Exubera compared to subcutaneous insulin in relevant patient subgroups. It also explored dose

proportionality and dose of strength equivalence.

Second, because of concerns about the variable kinetics of Exubera related, for example to device function and patient characteristics and performance, an extensive program of clinical trials in type 1 and type 2 diabetes comparing regimens using Exubera versus injected short-acting insulin was undertaken. Specifically, comparisons to subcutaneous insulin as monotherapy as part of basal bolus insulin therapy and in type 2 diabetes in combination with oral hypoglycemic agents of several classes were deemed necessary to characterize a hypoglycemia risk for glucose control of this novel insulin device combination.

Critical to the interpretation of the findings of the trial regarding hypoglycemia was the achievement, trial by trial, of clinically meaningful and comparable reductions in glycemia with Exubera compared to subcutaneous insulin treatment groups. These studies are discussed in detail in the FDA background documents by Drs. Al Habet, Mahoney and Mele who will also present here

today some of the salient FDA review findings pertaining to these points.

Next, and critically, the acute and chronic direct pulmonary risks associated with the large quantities of insulin powder along with the excipient inhaled by patients using Exubera for long-term treatment of their diabetes had to be assessed. In this vein, the risks in patients with existing lung disease also needed to be investigated given the anticipated broad appeal of an inhaled insulin product and the fact that a large population burden clearly not sparing patients with diabetes of pulmonary disease, including chronic bronchitis, chronic obstructive pulmonary disease and reactive airways disease, goes undiagnosed. At a minimum, it was necessary to determine whether there is a significant risk of acute important pulmonary decompensation in such patients who may choose to use Exubera despite labeled recommendations, or who may inappropriately use it because of ignorance as to their existing pulmonary compromise. Dr. Seymour, of FDA's

Division of Pulmonary and Allergy Products, will present the findings of her thorough review of the pulmonary safety information submitted.

Of note, no follow-up studies in the pediatric age group were required to be included in the application. This was due to uncertainties about pulmonary safety prior to having results in adults. A relatively small number of adolescents were, however, included in the program. Only a single trial in patients with type 1 diabetes age 6-11 was conducted which included 61 children treated with inhaled insulin. There were no children under age 6 studied.

So, while the efficacy of inhaled insulin in children prone to compliance and able to manipulate the Exubera device, for example from assembly to activation to inhalation, may not be a particularly critical question at this juncture, direct pulmonary safety experience in the broad pediatric population is needed before use in children can be recommended.

In conclusion, the prospect of being able

to use insulin, while avoiding some for those treated with basal bolus insulin regimens or all for those on short-acting insulin alone, of the injections historically part and parcel of insulin therapy stands to appeal to many patients, family members and physicians. It is, therefore, essential that we and they understand the benefits and risks associated with this novel drug-device combination for pulmonary delivery of human insulin.

As we begin the day's discussion, let me list the salient questions impacting FDA's regulatory decision that is related to potential approval and labeling regarding Exubera. These will be discussed in more detail later as they are reflected in our questions and our list of items for comment and discussion by the committee.

So, they are, pulmonary safety in patients with and without existing pulmonary disease. Two, the utility of Exubera as an alternative short-acting insulin, perhaps particularly in regimens directed at intensive glycemic control.

In this vein, more specifically considerations related to dose titration and insulin switching from subcutaneously administered to inhaled insulin.

Number three, safety regarding hypoglycemia, particularly in patients engaged in intensive insulin therapy regimens. Four, use in populations with underlying acute or chronic pulmonary conditions, for example related to infection or smoking, impacting the kinetics of systemic insulin delivery via the lung. Five, use by young children with type 1 diabetes.

Finally, let me acknowledge at the start the phenomenal work by the FDA reviewers from both the Division of Metabolism and Endocrinology Products and the Division of Pulmonary and Allergy Products and their careful and concerted review of the data submitted with this application. I want to thank them for their efforts in preparation for this meeting. I may also thank Dr. Woolf for agreeing at the last meeting to chair this meeting. With that, let's proceed, Dr. Woolf.

DR. WOOLF: Thank you, Dr. Orloff. Scheduled for the morning will be for the sponsor to speak until roughly 9:45, followed by discussion. There will then be a 15-minute break, followed by discussion by the FDA. The first speaker for the sponsor is Neville Jackson, full development team leader of Exubera, Pfizer.

Sponsor Presentation

Introduction

DR. JACKSON: Dr. Woolf, Dr. Orloff, members of the advisory committee, thank you for our opportunity to present on Exubera today. Exubera, as you have just heard, is human insulin, delivered not by injection but by inhalation. Our thanks additionally go to the over 4,500 patients who were studied in our clinical trials, and to their families who supported them. Finally, we thank the staff and almost 400 investigative centers whose diligent efforts have made this extensive clinical program possible.

My name is Neville Jackson and I am the Exubera development team leader at Pfizer. After

my introduction Dr. Anne Cropp, the Exubera global clinical leader at Pfizer, will give you a comprehensive review of the results from our clinical program.

After this, Dr. William Cefalu, who is an expert in diabetes and has real first-hand experience in using the product in the clinic as an investigator, will show us why it is so important that patients with diabetes have another option to the treatments currently available. I am personally deeply grateful to Dr. Cefalu who, being located in southeast Louisiana, has been himself significantly affected by the recent tragedy but has, nevertheless, chosen to show his commitment to this product by coming here to appear before you today.

I will then summarize what we have shown you and lay out how we intend to ensure that inhaled insulin is used appropriately in the clinic, and how we intend to continue to monitor and manage its safety.

We have a number of subject matter experts

apart, from Dr. Cefalu, here today to help us to answer questions. Most of them have provided substantial advice during the program and some have also been investigators and, therefore, have experience in the use of inhaled insulin as well.

There is an epidemic of diabetes and it is continuing to grow. Over one-third of people born in the year 2000 are likely to develop diabetes in their lifetime. Over 90 percent of those will have type 2 diabetes. This will have a significant impact not only on their life span but also on the length of time that they live with the consequences of chronic sickness unless something is done.

Right now we know that glycemic control is suboptimal in the United States. We know that insulin is the most effective treatment for diabetes, and is mandated for type 1 patients, and 57 percent of type 2 patients are not achieving target glycemic control because not only is insulin therapy often initiated too late in the patients, but also intensive insulin therapy is under-utilized both in type 2 diabetes and in many

patients with type 1 diabetes, and intensive they is frequently necessary to obtain the best glycemic control.

These are some of the reasons that have led us to develop inhaled insulin, which we see as providing an opportunity in particular to reduce barriers of earlier insulinization. The following is a video showing what the delivery system looks like and how it is used.

[Video presentation]

"This is Exubera, the first inhaled insulin. The Exubera system consists of two main components, the foil blisters that contain insulin powder and an inhaler for administering insulin powder to the patient. The inhaler consists of the base unit, the chamber and the insulin release unit. The pump handle operates a piston inside the base. This piston draws in and compresses ambient air. The insulin release unit is the part that pierces the blisters and channels the pressurized air, together with aerosolized insulin powder, into the chamber. From the chamber, this insulin cloud

is promptly inhaled by the patient. To take an Exubera dose, the patient loads an insulin blister into the base; pressurizes by pumping the handle once to draw air into the inhaler; releases the insulin powder and compressed air into the chamber as a visible insulin cloud and then inhales the insulin. The patient takes one deep breath from the inhaler, inhaling slowing over a few seconds until her lungs are full. She then holds her breath for five seconds and then exhales normally. If a patient's dose requires more than one insulin blister she simply repeats these steps for each insulin blister required. When all blisters have been taken the inhaler is closed by collapsing the base back into the chamber."

In our development program we studied a range of treatment situations and proposed that inhaled insulin is indicated for both type 1 and type 2 diabetes, used either in combination with basal insulin or in type 2 patients only in combination with oral agents or as monotherapy.

Here is the essence of the clinical

development program which has been running now for ten years. We have had many interactions with the agency, particularly over the last five years as our knowledge base has developed. Phase 1 has been long and intensive as we optimized the delivery system itself.

Phase 2 explored efficacy in short-term studies and enabled many patients to enter long-term treatment so that now we have data from patients who have taken inhaled insulin for over seven years.

Phase 3 was divided into two groups, group 1 primarily studied efficacy but also measured pulmonary function. It was only when data from hundreds of patients in each of these studies became available that we were able to detect asymptomatic small falls in lung function. These findings led us, in consultation with the agency, to run further really long-term studies in group 2, where we concentrated on measuring primarily pulmonary function both in diabetics with normal lung function as well as in patients with asthma

COPD.

Note that we suspended work in children and adolescents at this time, again in consultation with the agency, until we could better characterize the lung effects. Finally, also note that the Phase 2 and Phase 3 efficacy studies were set up at a time when treatment targets were not as stringent as they are today.

Intensity of the effort to characterize the pulmonary function test changes and to show that they were reversible can be seen by the fact that the NDA submission contains data from over 43,000 PFT measurements performed in over 4,000 adult subjects.

Our conclusions from the program, as Dr. Cropp will show, are that inhaled insulin is efficacious as short-acting subcutaneous insulin. It provides long-term glycemic control, up to two years in controlled studies. More patients prefer it to their previous treatment. And, we have seen it to be well tolerated, with hypoglycemia comparable to injected insulin. We have also seen

it to produce a larger insulin antibody response to the subcutaneous human insulin, and to produce small, around one percent, early, non-progressive, asymptomatic, reversible declines in pulmonary function tests. The mechanism of this is unknown but under continued exploration.

Now I would like to hand over to Dr. Anne Cropp to take us through the results of the clinical program.

Overview of Clinical Program

DR. CROPP: Good morning. Mr. Chairman and committee members, my name is Anne Cropp and I am the global clinical leader for inhaled insulin. I would like to thank the committee and the agency for the opportunity to present the clinical efficacy and safety data for inhaled insulin, or INH.

The presentation will cover four topics, an overview of the clinical development program; highlights from clinical pharmacology; the short- and long-term efficacy; and the safety of INH.

Next slide, please. First I will provide

an overview of the clinical development program.

Next slide. As noted in Dr. Jackson's presentation, the clinical development program for INH was comprehensive. The controlled Phase 2 studies and Phase 3 group 1 studies had a primary focus on efficacy. The Phase 3 group 2 studies had a primary focus on safety, utilizing highly standardized methods of lung function testing.

Next slide. There are three main data sets in reviewing the numbers of individuals participating in the INH program, the clinical pharmacology studies, the controlled Phase 2/3 studies, and the set of controlled and uncontrolled Phase 2/3 studies. In total, 4,613 individuals participated, with 3,274 receiving INH. Of those, 2,498 adult patients received INH in the Phase 2/3 studies.

Next slide. This slide provides the main demographic information for the 2,498 adult patients that received INH in the Phase 2/3 studies. The mean age of patients with type 1 diabetes was 38 years and their BMI was 25. The

mean age for patients with type 2 diabetes was 57 and their mean BMI was 30. Ten percent of type 1 patients and 20 percent of type 2 patients were non-white. These demographics are similar to the comparator population provided in your briefing document.

Next slide. This slide presents the INH exposure for the 2,498 patients whose demographics I just provided, and 1,698 were treated for over one year and 821 were treated for more than two years. The median exposure for type 1 and type 2 patients was approximately 1.7 years.

Next slide. Next I will discuss the clinical pharmacology.

Next slide. A comprehensive set of clinical pharmacology studies has been completed using the Phase 3 INH formulation. I will now highlight the results.

Next slide. The bioavailability of INH is approximately 10 percent relative to subcutaneous regular insulin in patients with type 1 and type 2 diabetes.

Next slide. This figure illustrates the following oral inhalation of INH. Approximately 40 percent reaches the alveolar space, the primary absorption site for insulin. Once absorbed systemically, INH has the same disposition characteristics of recombinant human insulin.

Next slide. INH is absorbed more rapidly than sub-q regular insulin and as rapidly as sub-q insulin lispro.

Next slide. This slide illustrates the pharmacodynamic profile for 6 mg of INH versus 18 units of sub-q insulin lispro and 18 units of sub-q regular insulin in 18 healthy male volunteers. On the Y axis is the mean glucose infusion rate expressed as a percent of maximum. This is the amount of glucose required to maintain a constant blood glucose level and is a measure of insulin pharmacodynamics. The Tmax for INH demonstrates rapid uptake, similar to the onset of action of insulin lispro. The duration of INH is longer than lispro and is comparable to regular insulin.

INH displays dose linear pharmacokinetics

and each increase in dose results in a separable increase in AUC and Cmax when studied over 1-6 mg.

Study 1012 investigated the dose proportionality of INH over the range of 1-6 mg, a range that includes the most commonly used doses. Using 1 mg and 3 mg blisters alone or in combination, there is an increase in AUC with increase in dose. The next slide will show you the AUCs for each patient in this study. On an individual basis, there was a consistent increase in INH exposure with increase in dose.

PK studies have shown that three 1 mg blisters are not equivalent to one 3 mg blister as a function of the intrinsic properties of the delivery system. This was specifically studied in trial 1006, as shown in the next slide.

The overall systemic exposure following inhalation of three 1 mg blisters is 40 percent greater and the Cmax 27 percent greater than that following the inhalation of one 3 mg blister. This is a function of blister fill weight and the aerodynamics of the inhalation device. I would

note that inappropriate substitution of three 1 mg blisters in place of one 3 mg blister was not a clinical problem in over 2,500 patients participating in the development program. The proposed labeling will clearly indicate that three 1 mg blisters cannot be substituted for one 3 mg blister.

Next slide. Studies have also examined the effects of age, gender, race and BMI on PK of INH and have found no effect. Smoking does significantly affect the absorption of INH. Smokers achieved higher total and maximal insulin concentrations than non-smokers. INH should not be used in smokers, and this is in the proposed labeling. Bioavailability tends to be higher in patients with COPD, and in patients with asthma it tended to be lower than in volunteers. The proposed labeling will note these changes.

Next slide. The intra-patient variability with 1 mg and 3 mg doses were comparable to that observed with regular sub-q insulin.

Now I would like to turn to efficacy.

This presentation is going to focus on the primary evidence for efficacy coming from Phase 2 studies and the Phase 3 group 1 studies. Key supportive efficacy data provided by Phase 3 group 2 studies will also be presented. Please refer to Table 2 of the briefing document, on page 30, to assist you as the various study numbers are identified. Highlighted in bold are those protocols that studied INH in type 1 diabetes, studies 102, 106, 107 and 1009. These were efficacy studies where the primary endpoint was change from baseline in hemoglobin A1c. In addition, three Phase 3 group 2 studies provide additional efficacy information in type 1 diabetes, study 1026, a six-month pharmacodynamic study using an intensive insulin regimen; study 1027, a three-month pulmonary safety study; and study 1022, a long-term safety study. The boxed insert lists the studies according to whether the insulin regimen used in the protocol was intensive or standard.

Next one. In bold are those protocols that studied INH in type 2 patients that were

insulin-using at study entry, studies 103 and 108. These were efficacy studies where the primary endpoint was change from baseline in hemoglobin A1c. The long-term safety study, 1029, also enrolled insulin-using patients with type 2 diabetes. The boxed insert notes that all these studies used a regimen of INH plus a basal insulin.

In bold are those protocols that enrolled patients with type 2 diabetes who were on oral agents or diet and exercise alone at study entry, studies 104, 109, 110, 1001 and 1002. These were efficacy studies where the primary endpoint was change from baseline in hemoglobin A1c, with the exception of study 110 in which the primary endpoint was the percent of patients achieving a hemoglobin A1c less than 8 percent at end of study. The boxed insert lists the studies according to whether the INH group received INH alone or INH in combination with an oral agent.

I will now present the results for the efficacy studies and all data will be from the full analysis data set. The next several slides will

show the adjusted mean treatment group differences in hemoglobin A1c change from baseline and their 95 percent confidence intervals. As noted in your briefing document, FDA identified their use of 0.4 percent as the threshold margin for noninferiority. This is represented by the dotted vertical line.

This slide shows the adjusted mean difference in change from baseline hemoglobin A1c in study 102, a Phase 2/3 month exploratory study in patients with type 1 diabetes. There are two Phase 3 studies in type 1 diabetes, studies 106 and 107. Both were six-month noninferiority studies with prespecified noninferiority margin of 0.5. Study 106 used a standard insulin regimen as the comparator and study 107 used a comparator intensive insulin regimen of three times daily regular insulin and twice daily NPH. For both standard and intensive protocols the upper bound of the 95 percent confidence interval did not cross the prespecified noninferiority margin, nor the margin of 0.4. These results indicate that INH was noninferior to sub-q insulin in the treatment of

adult patients with type 1 diabetes.

Study 103 was a Phase 2 three-month exploratory study in type 2 insulin-using patients. Study 108 was a Phase 3 study in insulin-using patients with type 2 diabetes. This was a six-month noninferiority trial with a prespecified noninferiority margin of 0.5. The upper bound of the 95 percent confidence interval did not cross the prespecified noninferiority margin, nor the margin of 0.4. These results indicate that INH was noninferior to sub-q insulin in the treatment of type 2 insulin-using diabetes patients.

The next series of slides will show efficacy data in patients with type 2 diabetes who are non-insulin using. In study 104, a Phase 2 three-month exploratory study, INH demonstrated greater reduction in mean human hemoglobin A1c than in patients on a regimen of oral agents.

This slide highlights Phase 3 superiority studies, 109, 110 and the six-month high strata for studies 1001 and 1002. In study 109 lowering of hemoglobin A1c with INH added to oral agents was

significantly greater than lowering with oral agents alone. In addition, there was significant lowering of hemoglobin A1c by INH alone compared to oral agents.

Efficacy was the primary objective of the six-month time point for studies 1001 and 1002. These protocols stratified patients according to their baseline hemoglobin A1c into high, greater than 9.5-12 percent, and low, less than or equal to 9.5 percent, strata. Superiority was the prespecified goal and was demonstrated for patients in the high strata of both studies. In study 110 the primary endpoint was the percentage of patients achieving a hemoglobin A1c less than 8 percent at end of study. Significantly more INH-treated patients achieved goal than did patients treated with rosaglitazone.

In patients in the low strata, less than or equal to 9.5 percent, of studies 1001 and 1002 noninferiority was demonstrated when INH was added to an oral agent compared to adding a second oral agent.

In summary, results from Phase 2/3 studies indicate that INH is effective in the treatment of adult patients with type 2 diabetes when used alone, in combination with a basal insulin or in combination with an oral agent.

In addition to the three- to six-month trials where efficacy was the primary endpoint, the INH program includes four controlled trials that measure the efficacy of INH over a two-year period. Of note, the earlier slide showed efficacy at six months for studies 1001 and 1002. When the PFT change became evident these trials were extended to treatment of one years and then two years. The timing and logistics of the amendments allowed for approximately one-third of these patients to continue into the extension studies and hemoglobin A1c was collected as a secondary endpoint. These two-year data will be presented.

The other two large trials, study 1022 in patients with type 1 diabetes and study 1029 in patients with type 2 diabetes, were protocols examining pulmonary function as the prespecified

primary endpoint. Change in hemoglobin A1c was also collected and two-year data will be presented.

This slide shows mean hemoglobin A1c data from the two-year analysis of study 1022 in type 1 patients. Hemoglobin A1c control is maintained over two years in both groups. In study 1029, in patients with insulin-using type 2 diabetes, the results are similar with glycemic control maintained over two years.

Shown here are hemoglobin A1c data from patients completing two years in studies 1001 and 1002. Data from other cohorts are similar. These data also support the continued efficacy of INH over two years.

A six-month controlled trial was designed to study the pharmacodynamics of intensive regimens of insulin INH versus sub-q. Hemoglobin A1c is noted at the top of the slide with similar glycemic control in the order of 7 percent in each group. In addition, the postprandial glucose levels remained well controlled throughout the study.

In study 107 satisfaction was assessed

using a validated questionnaire. The mean change from baseline for the treatment satisfaction scales is shown here, with bars to the right showing improved satisfaction. All 12 scales relating to regimen outcomes and net benefit significantly favored INH compared to sub-q insulin. Patients are more satisfied with INH compared to sub-q insulin.

Similarly, in type 2 study 109 statistically significant improvement was observed in the treatment satisfaction scales of efficacy, preference, advocacy and general satisfaction when compared to oral agents.

In summary, the data presented support that INH is as effective as sub-q regular insulin in patients with type 1 and insulin-requiring type 2 diabetes; effective in type 2 diabetes used alone, in combination with basal insulin, and in combination with an oral agent; has sustained efficacy over two years; and is preferred therapy.

The next section will focus on safety. First I will summarize adverse events. This slide

shows adverse events regardless of causality in patients with type 1 diabetes participating in the controlled Phase 2/3 trials.

This slide shows AEs occurring with a frequency of 10 percent or greater in either the INH or sub-q insulin groups. Increased cough was the event occurring noticeably more often in patients receiving INH.

This slide shows adverse events in patients with type 2 diabetes. As in type 1 diabetes, increased cough occurred noticeably more often in patients receiving INH.

This slide presents all serious adverse events that occurred in more than three patients with type 1 diabetes and type 2 diabetes participating in the controlled Phase 2/3 clinical trials. Hypoglycemia was the most common SAE in patients with type 1 diabetes and SAEs related to coronary-artery disease were most common in patients with type 2 diabetes. In both type 1 and type 2 diabetes there is no evidence for an increase in SAEs in INH-treated patients.

As of the safety update, 32 patients died in the clinical development program, and of these 28 patients died during treatment or within 30 days of last receiving study drug. This includes 9 INH patients and 7 comparator patients who participated in the controlled Phase 2/3 studies, with an incident rate, shown in parentheses, of 0.44 per 1,000 subject months for INH and 0.35 for comparator. In the non-controlled extension studies, 12/1,449 INH patients died giving an incidence rate of 0.41, which is very similar to that seen in the controlled studies. There were four deaths occurring more than 30 days following the last dose of study drug, one in INH and three in comparator.

The next several slides will focus on hypoglycemia. The FDA definition of hypoglycemia will be featured defined as blood glucose less than or equal to 36 mg/dL and/or requiring assistance.

This slide presents a pooled analysis of hypoglycemic events in patients in the controlled Phase 2/3 studies. On the Y axis is the event

rate, the number of events per subject month. In patients with type 1 diabetes the event rate was comparable between INH and sub-q treatment groups, at approximately one event per month. In type 2 patients the event rate was lower but comparable between INH and sub-q groups. In non-insulin-using patients the event rate in INH patients was lower still, and the lowest event rate was seen in the group receiving oral agents.

This slide summarizes hemoglobin A1c and hypoglycemic events in studies where the comparator arms included t.i.d. short-acting insulin. Across protocols in type 1 patients using intensive insulin regimens the event rates for FDA-defined hypoglycemia were comparable between the INH and sub-q treatment groups while still achieving a hemoglobin A1c of less than or equal to 7.5 percent.

The bar graph on the right shows severe hypoglycemic events. Note the Y axis in events per 100 subject months. In the pooled analysis, shown in the bars on the far right, severe hypoglycemia

was similar in the INH and sub-q groups. In study 107 INH had a higher rate due primarily to one patient, a college student, who accounted for 12/43 events. Nine of these 12 events occurred during a college break and did not have confirmatory blood glucose measurements. When this patient is removed, as shown in the second blue bar, the rate of severe hypoglycemia is noticeably reduced. Of note, this patient enrolled in the extension study and reported only two events in the ensuing two years of INH treatment. Increases in severe hypoglycemic events in INH treatment arms were not noted overall, nor in the largest study, 1022.

This slide shows that there is a noticeable reduction in hypoglycemic event rates with duration of study therapy in both INH and sub-q insulin patients. Similar patterns are noted in type 2 patients that are insulin using and in those not previously using insulin.

This slide shows the diurnal variation of hypoglycemic events. INH patients tended to have higher event rates in the early morning as compared

to sub-q insulin, while the converse was true for midday. Importantly, lower hypoglycemic event rates at all time points were seen with continued duration of study participation.

The next section will focus on pulmonary safety. Pulmonary safety was a focus during the entire clinical program and a specific focus of Phase 3 group 2 studies. The pulmonary topics that will be presented are PFT results, chest x-rays and HRCT and respiratory adverse events.

Pulmonary function was comprehensively assessed. This included standard spirometric tests, lung volume measurements and assessment of diffusing capacity. This presentation will show FEV1, a standard spirometric endpoint, as it is a robust measurement that is sensitive to changes in both airway function and lung volume. There are also INH-associated changes in DLco. The DLco changes were very similar in magnitude and pattern to FEV1, and a full summary of DLco is presented in the briefing document and will not be shown here.

The next several slides will illustrate

mean adjusted treatment group differences for FEV1 change from baseline. In Phase 2 studies FEV1 changes did not show a consistent signal. Data from most of the Phase 3 studies, however, showed a consistent small INH-associated decrease in FEV1, on the order of 1-1.5 percent change from baseline. Subsequent to identifying this effect, the focus of the Phase 3 group 2 studies was pulmonary safety.

This slide shows the distribution of change from baseline FEV1 in patients with type 1 diabetes in the controlled Phase 2/3 studies at the three-month time point. The INH-associated decrease in FEV1 is due to a shift in the distribution of FEV1 changes, and is not caused by the occurrence of notable outliers. In patients with type 2 diabetes the distribution is very similar.

Shown here is the change from baseline in FEV1 in type 1 patients from study 1022 over two years. The INH-associated decrease in FEV1 was small and fully manifest at the first assessment time point, three months. As illustrated in the

top boxes, annualized change in FEV1 between months 3 and 24 and the corresponding intervals for months 3-12 and 12-24 showed no significant difference.

Similarly, in insulin-using type 2 patients, two year data from study 1029 showed that INH-associated decrease in FEV1 was fully manifest at the first assessment time point, month three, and annualized change in FEV1 was similar beyond three months.

The change from baseline FEV1 in type 2 non-insulin-using patients completing two years of treatment in the extension studies 10001 and 1002 are shown on this slide. In these studies the first assessment time point was month six. The treatment group differences favoring comparator seen after six months did not progress. The results of all three studies establish that INH-associated decreases in FEV1 were fully manifest at the first assessment time point and did not progress in up to two years of treatment.

The next two characteristics that will be presented are time of onset and reversibility.

Study 1027 specifically examined the time of onset and reversibility of INH-associated FEV1 changes in patients with type 1 diabetes. Randomized patients received 12 weeks of INH or Scientific insulin, followed by a 12-week period where all patients received sub-q insulin. The results are shown on the next two slides.

INH was associated with a small, approximately one percent decline from baseline in FEV1 compared to sub-q insulin. The INH decrease occurred as early as 1-2 weeks after initiation of INH and did not get larger with continued INH treatment.

This slide shows the withdrawal phase, shaded in yellow. Within two weeks of INH withdrawal treatment group differences are resolved. It should be noted that although a specific 12-week time point shows an INH decrease slightly less than the average change, INH showed a value less than comparator at six of the seven time points during the treatment phase and a value greater than or equal to comparator at three of the

four time points during the withdrawal phase.

In addition to this data, the resolution of FEV1 changes has been shown in two-year controlled trials in patients with type 2 diabetes and in a randomized withdrawal from an open-label extension trial. This slide was presented earlier and shows the change from baseline FEV1 in the two-year completer cohort from studies 1001 and 1002 in type 2 diabetes. PFTs were performed during the 12-week withdrawal following two years of treatment. The resolution of treatment group differences occurred within six weeks of discontinuation.

Another protocol that was designed to examine pulmonary function in longer-term treatment was study 111. Study 111 was an uncontrolled extension trial available to patients completing one of the specified listed Phase 3 trials. In order to obtain randomized information in patients receiving long-term INH the protocol was amended to study PFTs in patients randomly assigned to either continue INH or withdraw to sub-q insulin or oral

agents. The randomized withdrawal design is particularly robust since it includes an enriched group of patients who are achieving both a favorable response and good toleration, specifically matching patients who are likely to be receiving long-term INH in medical practice.

Following the withdrawal of INH, FEV1 is noted to increase. Shown on the left is the increase in patients with type 1 diabetes, and on the right in patients with type 2 diabetes. FEV1 changes favoring the group discontinuing INH therapy equal in magnitude to the treatment group differences following treatment initiation occur in both the type 1 and type 2 patients, and further support the observation that the effect of FEV1 resolves after up to three years of INH administration.

In summary, INH-associated decreases in FEV1 occur early; are small in magnitude; are not driven by outlier subjects; are non-progressive; and resolve upon discontinuation.

Having characterized pulmonary function

test results, the next pulmonary safety topic is chest x-ray and HRCT. Eight patients in completed and ongoing controlled Phase 2/3 studies had a significant change in their chest x-ray findings from baseline. Of these, 54 were INH patients; 15 sub-q insulin; 11 patients receiving oral agents. Of the 54 INH patients, two were less abnormal and 52 more abnormal.

Abnormalities were localized to one of the four listed areas. Follow-up imaging was performed as part of standard care and of the patients with lung parenchyma abnormalities follow-up imaging was performed in 25 and resolution of the abnormality was seen in 22 of these 25. Of the three without resolution, there was one case of lung cancer, a topic which will be discussed separately. All lung vasculature had abnormalities resolved. The pattern seen in the comparator groups was similar and no consistent pattern of INH-related abnormality was evident.

HRCT was also performed, with the HRCTs interpreted by a radiologist blinded to treatment

assignment at a central reading site. HRCT data came from two sources. First, in the six-month substudies for three controlled Phase 3 studies HRCT results were interpreted as being normal or abnormal at baseline and end of study. Patients whose scans were abnormal at baseline met entry criteria for study participation. Highlighted in bold are the number and proportion of subjects whose scans were normal at baseline and abnormal at end of study, or whose scans were abnormal at baseline and became more abnormal at end of study. The values noted in bold are similar between the INH and sub-q insulin groups. The HRCT results from study 1029 in insulin-using patients with type 2 diabetes show no increase in the INH treatment groups compared with sub-q insulin groups, with nominal increase in the sub-q group.

The database evaluated for INH pulmonary safety comprises 2,498 INH-treated patients, with durations of up to seven years. This slide shows respiratory adverse events, regardless of causality, reported in two or more patients with

type 1 and type 2 diabetes in the controlled Phase 2/3 studies. Three respiratory adverse events occurred at an appreciably greater frequency with INH, increased cough, dyspnea and increased sputum. Cough and dyspnea will be addressed separately.

Increased sputum occurred in 3-4 percent of INH compared to 0.5-1 percent of comparator. As a group, nasopharyngeal adverse events of epistaxis, laryngitis, pharyngitis, rhinitis, sinusitis and altered voice also occurred nominally more often with INH than with comparator, although the difference between groups was less consistent.

Cough occurred with greater frequency in patients receiving INH. INH-associated cough occurred most often during the first month and decreased with continued INH administration. It was mainly mild in severity and one percent of INH-treated subject discontinued due to cough. In studies 1022, 1027 and 1029 a specific cough assessment tool was used. Cough occurred within seconds to minutes after dosing, rarely occurred at night and was rarely productive. In addition,

cough was not associated with decreases in FEV1.

For dyspnea the majority of cases were mild. A formal dyspnea assessment using the BDI/TDI was used in studies 1022, 1027 and 1029. No clinically important mean changes were identified in either treatment with exposures up to two years. There were five SAEs of dyspnea in the controlled database. Of these, four occurred in comparator-treated patients and one in an INH patient.

Overall, the number of respiratory SAEs is low in both the INH and comparator groups. There was one event of bronchospasm in an INH patient and one event of dyspnea and, as mentioned, there were more events of dyspnea among comparator patients. Asthma was reported as an SAE in three INH patients with type 2 diabetes. There were no reports of asthma as an SAE in patients with type 1 diabetes. It should be noted that all serious respiratory adverse events occurred in patients with type 2 diabetes, with the exception of a single case of pneumonitis in a patient with type 1 diabetes

treated with sub-q insulin.

Overall, asthma is reported infrequently and comparably in the INH and sub-q insulin groups, and rarely causes discontinuation. There are, however, more reports of severe asthma and asthma causing discontinuation in patients receiving INH.

There are two additional relevant serious adverse events that are presented in the briefing document. These are pleural effusion and lung neoplasm. These will be discussed in the next two slides.

There were no cases of pleural effusion in the controlled two-year studies. In the Phase 2/3 program pleural effusion was reported in eight INH patients and three sub-q insulin patients. Seven of the eight INH cases occurred in the uncontrolled extension studies and one in COPD trial 1030. The INH patients are listed here. In six of the patients the pleural effusions developed in the setting of medical conditions well-known to cause pleural effusion. In two patients an etiology was not identified, a 58 year-old man with a minute

effusion that resolved continued INH treatment, and a 13 year-old boy with an effusion on day 351. The cause of his pleural effusion was never determined and the case summary is presented in the briefing document.

A review of malignant lung neoplasm cases is included because of a theoretical concern arising from insulin being a very weak ligand for growth factor receptors. In the clinical program there were four cases of malignant lung neoplasm. All four cases were in patients with type 2 diabetes, and two in the INH group were present upon retrospective review of chest x-rays prior to study entry. All patients had a history of smoking. The total number of observed malignant lung neoplasms in the INH group is less than the seven predicted based on modeling from Kaiser Permanente database.

The next three slides will review the use of INH during intercurrent respiratory illness and in patients with mild to moderate underlying lung disease. This slide shows glycemic control and

hypoglycemic events in 394 type 1 and type 2 INH-treated patients during periods with and without intercurrent respiratory illness.

As seen in the top half blue shaded area, there was similar glycemic control during periods with and without intercurrent respiratory illness. As seen in the bottom half, there was no evidence of increase of risk of hypoglycemia in INH-treated patients with intercurrent respiratory illness. Patients with intercurrent respiratory illness rarely discontinued or temporarily interrupted treatment with INH.

In the integrated cohort of 149 patients with mild to moderate asthma glycemic control was maintained and there was no excess hypoglycemia. The pattern of respiratory AEs and the magnitude of FEV1 change was similar to non-asthma patients. INH and comparator reported a similar number of asthma AEs and there was only one SAE in a comparator patient. The number and total of severe asthma exacerbations in the ongoing study 1028 was not remarkably different between groups.

Similar observations are noted in patients with mild to moderate COPD. IN these patients INH achieved comparable glycemic control without excessive hypoglycemia, and had a pattern of respiratory AEs and magnitude of FEV1 change similar to those seen in patients without COPD.

There were four respiratory SAEs in INH patients, two of which were exacerbations of COPD. In study 1030 the number of non-severe COPD exacerbations was higher in the INH group. There was, however, only one severe COPD exacerbation. A summary of the interim reports for studies 1028 and 1030 are appended to the briefing document.

The last safety topic is insulin antibodies. INH-associated antibodies were first observed in the Phase 3 studies using a semi-quantitative RLB assay. A second, more quantitative RLB was developed and used in later studies. INH administration is associated with an increase in insulin antibody levels that have been characterized as IgG. This rise is noted in approximately 75 percent of all INH patients, and

the antibody levels are generally higher among patients with type 1 diabetes and females.

The next several slides illustrate data as box plots, as described in figure 56 of the briefing document. In these box plots the median is shown as the center horizontal line within each bar. The blue solid line joining bars connects the means. The 25th and 75th percentiles, bottom and top edges of the box; whiskers extend from the box to the farthest point within 1.5 times the inter-quartile range. Values beyond that are indicated by an X.

These data from study 1022 in type 1 diabetes show that insulin antibody levels rise within the first several months following the initiation of INH and plateau after approximately 6-12 months of treatment.

In type 2 patients that are insulin-using, INH increases insulin antibody levels in a similar pattern but to a lesser extent. Discontinuation of INH results in a decline in insulin antibody levels and has been demonstrated in two studies. In study

1027 all patients receiving INH were switched to sub-q insulin after week 12. Using the quantitative assay, results show that antibody levels decreased within four weeks of stopping INH.

Study 111 was an earlier trial and used the semi-quantitative assay. The first set of data, labeled baseline, is the point at which patients were randomized either to continue INH therapy or to discontinue INH therapy and use sub-q insulin or oral agents. The antibody levels decreased by more than 50 percent in the initial three months and by more than 60 percent in the following months after long-term INH treatment.

Four separate methods were used to examine the potential calibrator impact of INH-associated insulin antibodies, scatter plots of antibody levels in selected clinical parameters; binary distribution plots of antibody levels in subjects with and without selected clinical findings; time plots of FEV1 decreases and antibody levels; and a specific review of all AEs of an allergic nature.

Data has been extensively examined to

assess a potential correlation of insulin antibody levels to clinical endpoints. No correlation was found with any clinical endpoint, including key parameters of hemoglobin A1c, hypoglycemia, insulin dose or PFTs. There is no discernible difference in the distribution of insulin antibodies in subjects with cough, dyspnea or notable PFT declines.

This is a representative slide showing the scatter plot of insulin antibodies with change from baseline hemoglobin A1c in a two-year subset of patients in study 1022. There was no correlation between hemoglobin A1c and antibody levels.

Overall, the reporting of AEs of an allergic nature was comparable between groups in the controlled Phase 2/3 studies. One patient experienced an apparent hypersensitivity reaction characterized by bronchospasm and eosinophilia one month following initiation of INH therapy. This patient's symptoms resolved promptly after stopping INH and receiving standard treatment.

A specific time plot analysis was also

performed to examine whether there is an association of insulin antibodies with FEV1 decline. This slide shows the change from baseline FEV1 in the INH and sub-q insulin groups in study 1027, along with the level of insulin antibodies in the INH group. While the INH-associated FEV1 decline occurs one to two weeks following INH administration and does not progress, antibodies do not noticeably rise until after the first few weeks.

In summary, INH is associated with higher insulin antibody levels compared to sub-q insulin. Mean antibody levels plateau after 6-12 months. Antibodies are of the IgG class. Insulin antibodies are not associated with changes in hemoglobin A1c, hypoglycemic events, insulin doses or PFTs. And, insulin antibody levels decline after discontinuation of INH.

Now it is our privilege to have Dr. William Cefalu present the medical need for inhaled insulin. Of note, Dr. Cefalu comes to us under difficult circumstances from the Pennington

Biomedical Research Center in Baton Rouge, Louisiana.

Medical Need

DR. CEFALU: I want to thank Dr. Woolf and the committee for giving me the opportunity to discuss medical need. With my brief presentation I really have essentially three goals. First and foremost, I want to make the case that there is a benefit of glycemic control in reducing complications. The majority of our patients in this country fail to achieve glycemic control. I also want to make the case for the benefit of insulin treatment, particularly in type 2, and raise issues that there is resistance for its use in type 2 diabetes. Finally, I would like to discuss that the availability of new innovations, like pulmonary delivery of insulin, offers an alternative and has the potential to greatly improve glycemic control.

I would like to start with this first slide and recap what Dr. Cropp said about the efficacy for the hemoglobin A1c. We have known for

years that improved glycemic control will reduce complications and, clearly, from the diabetes control and complications trial in type 1 diabetes we have seen that.

We have also seen for the UKPDS study in type 2 diabetes that glycemic control reduces complications. So, it has been proven both in type 1 and type 2 that glycemic control, as assessed by an objective marker, the hemoglobin A1c, is related to reduction in complications.

But there is also something interesting about the UKPDS. If we now extrapolate and put the ADA goal on these particular graphs, we begin to appreciate another observation, and that observation is simple that it appears there is no threshold behind which improvement of glycemic control does not reduce complications. I will state that these were not prospective studies but this is kind of an epidemiologic evaluation.

Clearly, another example is the EPIC-Norfolk study where, even in non-diabetic individuals, when we look at the reduction in the

hemoglobin A1c where the relative risk of cardiovascular disease, mortality, is reduced.

So, based on these studies we have been given some guidelines by governing agencies of what is an acceptable level for the hemoglobin A1c. Clearly, we know that the optimal level is a hemoglobin A1c less than 6.5 percent. That is the non-diabetic range. But the American Association for Clinical Endocrinology would suggest a level less than 6.5 percent, as would the European Association for the Study of Diabetes. American Diabetes Association sets a goal of less than 7 percent. Clearly, in clinical medicine we would think that anything greater than 8 percent would be unacceptable. We this background, how well have we done in this particular country?

Well, we can take some of the data from the surveys the NHANES III, conducted between 1998 and 1994, and the NHANES between 1999 and 2000, and clearly it was suggested that with NHANES III approximately 44 percent of our patients were controlled below the ADA goal in the NHANES III.

By the survey from 1999 to 2000 that was about 37 percent.

How well are we doing as far as glycemic control compared to the other risk factors? Well, I think in this particular study we can suggest that maybe hypertension rates have not significantly improved. Here is some good news in the sense that it appears that less of our patients with diabetes have high cholesterol as there are significantly greater diabetics with cholesterols under 200 in this particular study.

Now, nationwide how well are we doing? Well, this is a report from the American Association for Clinical Endocrinology so this schematic represents the percentages of patients in each state above the goal established by the American Association for Clinical Endocrinology. You can see in color here the 11 highest states. The national average is about 67 percent, meaning that two our of three people in this country are above the goal established by this organization.

So, the question is why is it that we have

such lack of adequate control in this country, particularly for type 2? We can suggest that type 2 is a very progressive disorder and keeping up with the progressive nature of this disease is a challenge clinically. We do know with all the pathophysiologic abnormalities with type 2, clearly the one that is ever-changing is the insulin secretion abnormalities. It is diminished at the time of diagnosis. It continues to diminish over time and we need to keep up with treatment to maintain glycemic control. This is shown clearly in the United Kingdom study, again, with the suggestion that at diagnosis approximately 50 percent of beta-cell function is already gone. This continues to decline over time.

So, now for a look at this progressive nature of the disease and now compare that with the current treatment paradigm in this country, many of us agree that by the time you diagnose a non-pharmacologic approach is indicated--diet and exercise. Once that fails, we have choices of monotherapy in many different classes of drugs and

there is efficacy for every one of these agents. When that fails we generally choose a drug from a different class and combination therapy is incredibly effective. When that fails we generally add insulin to the combination and eventually that may fail and we have to go to 24-hour insulin dosing, a physiologic regimen of basal insulin combined with bolus therapy at each meal. But I would argue that the biggest clinical hurdle is taking this step toward insulin initiation, and I am going to show you some data that may suggest this.

If we now go back to the schematic of the UKPDS, I would now suggest that based at diagnosis we can provide a phasic management for our patients. At diagnosis phase one, we can argue, would be monotherapy. But with the continued progressive nature of the insulin secretory abnormalities this is going to progress and the patient will proceed to combination therapy. Eventually that patient may need insulin therapy. It has been estimated today, depending on whom you

read, that 40-50 percent of type 2 diabetics may need insulin currently.

Now, what is the criteria for advancing from one phase to the next? Well, if we look at the current goals of glycemic control, and with the understanding that glycemic control is necessary to prevent complications, we can say, well, if you don't achieve goal with any phase of management we really should go to the next phase of management.

How well are we doing in this country? Well, again, going back from the NHANES III versus the NHANES in 1999 to 2000, we clearly have shown that there is not a great improvement in glycemic control, but what is interesting is that treatment patterns appear to have changed. Those individuals who were treated with non-pharmacologic therapy only have actually decreased. Those individuals treated with oral agent alone have actually increased. I think the good news is the fact that insulin combined with oral agents has actually increased in our population, but use of insulin alone has actually decreased.

When you look at the comparison of NHANES III versus 1999-2000, it suggests that 27 percent of the population is treated with insulin and there is perhaps no significant change over this time interval.

I would also like to share with you and introduce a concept called clinical inertia. By definition, this is just failure to advance therapy based on the need. This was a study that was done by Brown's group.

This is a population of Kaiser Permanente northwest in the United States, Oregon and southwestern Washington, where they went back between the years of 1984-2002. Over 7,000 patients were evaluated. In this situation they looked at the last hemoglobin A1c that was recorded before they was advanced. In this situation, for those individuals on diet and exercise about 2.5 years elapsed before treatment was changed. In this situation the last hemoglobin A1c recorded was about 8.6 percent. Now, this contrasts with the ADA goal of 7 percent. So, anything above 7

percent we are talking about a significant increase in complication rate.

Now, once they failed diet and exercise they were either randomized to sulfonylurea or metformin. Well, with the sulfonylurea about 2.9 years elapsed. With the last treatment HbA1c averaged about 9.1 percent for metformin. About 2.2 years elapsed on metformin therapy and the last HbA1c recorded in this paper was about 8.8 percent. Now, for the combination of the two agents, for these individuals about 2.8 years elapsed, and by the time treatment was abandonment HbA1c was 9.6 percent. I think this study clearly demonstrates the clinical inertia that we were referring to.

How many patients were advanced if the HbA1c was greater than 8 percent? Again Brown's paper suggested that if you failed non-pharmacologic therapy about 66 percent advanced once the A1C was greater than 8 percent as opposed to approximately 35 percent and 44 percent with sulfonylurea and metformin monotherapy. But the patients who probably needed it most, those who

failed combination therapy with the highest HbA1c, only 18 percent advanced.

So, this suggests that is no question that there is a clinical inertial in this country. Now, if you look at this particular study and suggest if a patient was diagnosed and went through each phase of management with the current HbA1c's that were established, that would mean in this particular study a patient would be left with five years with an HbA1c greater than 8 percent and 10 years with an HbA1c greater than 7 percent. So, I don't think there is any question we are not getting aggressive with treatment, as demonstrated with this large managed care group.

So, the barriers do exist. There are patient barriers and I don't think there is any question. I don't think many of us really understand all the concerns of a patient whether it is compliance issues, fears of scarring, some other perception. We also know that there are physician concerns, maybe not time to implement insulin; a lack of resources; other concerns among physicians.

There is no question there are real and perceived adverse events. Among those are weight gain, hypoglycemia. This figures into a patient and physician decision about insulin. We also recognize that in order to get physiologic control you may require multiple daily injections. The only way to give insulin currently is with injection. So, it is these latter two parameters that, with the availability of an alternative means of insulin, may help the patient. I think that has been clear. There is some evidence in the literature to date that suggests that there is some anxiety and concerns among patients either to start insulin or, if they are on insulin, to go to more physiologic regimens.

So, the question I will ask is if inhaled insulin was available what could we expect? Well, this is a study that was presented just this last year by Freemantle's group. In this situation they took individuals that we think most need insulin. In fact, in this particular study about 77 percent of patients actually had a hemoglobin A1c greater

than 10 percent. Now, they were given guidelines, and they were given education regarding the need to advance therapy. In one group they were given essentially conventional guidelines. They were educated on oral agents. They were educated on insulin syringes, the risk to benefit ratio.

On the other hand, another group--there were about 350 in each group--were given education not only on conventional therapy but about the availability of inhaled insulin, again, the benefits and efficacy of inhaled insulin if it was available. Granted, this is a hypothetical study but, once again, it talks about patient attitude.

In this study about 15 percent of patients only given conventional education opted for use of an insulin regimen. However, with the availability of inhaled medicine about 43 percent, almost three times as many individuals, opted for treatment with insulin therapy. Now, I would argue that in this situation this group of patients that most need insulin, the availability of an alternative means of insulin allowed these people, based on

hypothetical grounds, to make a choice.

Actual insulin treatment in this group was actually about 16 percent. This is despite that over half the physicians wanted to implement an insulin regimen. So, clearly the patient preference appeared to be stronger than the physician preference in this particular study.

In conclusion, I just wanted to recap that I think glucose control remains inadequate for the majority of the patients in this country despite significant evidence regarding its benefit. I don't think there is any question for the need and effectiveness of insulin. I mean, it was mentioned here, we have insulin and its use in this country and it is beneficial but there is resistance to use of insulin on clinical grounds. I think this resistance to use insulin is secondary to many, many factors. Finally, I would like to argue that the availability of inhaled insulin can overcome many of these factors and, as such, as great potential to improve glycemic control in many of our patients. Again, I appreciate the opportunity

to provide this update. Thank you.

Benefit and Managing the Risk

DR. JACKSON: Thank you, and it remains to me now to summarize this large and wide-ranging package of data that we have presented. Then I will show you how we plan to manage the safety aspects of inhaled insulin once it become available to the public.

We have shown inhaled insulin to be as efficacious as short-acting subcutaneous regular insulin in patients with both type 1 and type 2 diabetes requiring insulin. It is effective in type 2 diabetes when used alone, in combination with basal insulin and in combination with oral agents. It provides long-term glycemic control in both type 1 and type 2 diabetes. And, most patients preferred inhaled insulin over previous subcutaneous and oral agent treatments. We anticipate this to translate into better acceptance of insulinization and compliance with prescribed insulin treatment. In turn, this should result in earlier and better glycemic control in the diabetic

population outside of clinical trials, with a beneficial impact upon diabetes complications.

The most common adverse event that we saw was hypoglycemia as with, an no more than, subcutaneous insulin. There was an increased antibody response which was not linked to important clinical outcomes. Cough was the most common pulmonary symptom. This was generally mild, mostly post-inhalational and improved with time on treatment. There were small early, non-progressive and reversible asymptomatic declines in pulmonary function. We don't know what causes this; we have an understanding of what doesn't. It doesn't appear to be due to acute bronchoconstriction. It is unlikely to be inflammatory. We have initiated a risk management program to fully explore the mechanism and follow the longer-term effect.

We completely understand that inhaled insulin is a first example of a polypeptide intended for therapeutic delivery via the lung over periods of many years. Therefore, we are committing to an extensive and prolonged risk

management plan. As you can see, this program contains activities to minimize both known and potential risks. It also contains activities to increase our knowledge in areas where information is, understandably at this time, limited. We understand the need to continue to assess the longer-term effects on pulmonary function. We understand that we need to be able to monitor for rare pulmonary events. We understand the interest in this product for children and adolescents and our need to increase our knowledge in this group of patients.

We propose to institute comprehensive and careful education and customer care programs. We will set up enhanced pharmacovigilance procedures to intensify follow-up for rare respiratory adverse events in particular. We will propose labeling that closely follows the conditions of our clinical program.

I want to show you as an example how we intend to ensure that patients use the two different dose strength blisters correctly. First,

let me show you how they used them in our clinical program. We know that 1 mg and 3 mg doses were used safely and effectively. All patients were dispensed 1 mg and 3 mg blisters at treatment initiation. They were instructed to self-titrate up or down by 1 mg increments, dependent upon home glucose monitoring. Instructions were given to them to use as few blisters as possible at each dosing session.

Let's see how the patients actually took blisters in our Phase 3 efficacy studies. You can see here that on average over 80 percent of patients used 1-7 mg doses at mealtimes. That means 80 percent of doses comprised 1-3 blisters, which also means 1-3 puffs per dose. Interestingly, we have calculated that for the entire clinical program patients took over 10 million puffs of inhaled insulin.

In our proposed labeling we will show, as seen here in this table, how different doses are achieved using different blister combinations. This particular table has been generated in

discussion with the European medicines evaluation agency. Note that we also show the approximate equivalence to insulin international units to help understanding by those physicians more familiar with the meaning of such units.

We selective also provide for education of patients to self-titrate by 1 mg increments There will be clear tactile and visual differentiation of the blisters, including coloration differences. There will be education of physicians to closely monitor patients on the initiation of inhaled insulin therapy. We will manage the risk of substitution of one 3 mg blister with three 1 mg blisters by clear labeling, including secondary packaging, and education. Where unavoidable substitution is necessary, specific instructions to use two 1 mg blister in place of one 3 mg blister will be given in labeling, and education materials as well with a recommendation to carefully monitor glucose levels.

We also propose specific studies to attain knowledge where our understanding is limited. Note

the length of observation we are proposing, with studies running into the next decade, one not completing until the end. Note also the focus on lung effects with long-term pulmonary function being monitored in strictly standardized studies over five years continuous and seven years cumulative dosing. Note the continued emphasis on understanding effects in asthma and COPD over longer-term exposure. Also, we continue to explore the mechanism of lung function effects with ongoing bronchoalveolar lavage studies and proposals for further preclinical and clinical studies of this mechanism. We intend to restart pediatric studies after consultation with the agency.

This effort is not inconsiderable. Let me leave you with an example of what this really means. In this one study we are proposing to enroll 5,000 patients to assess, amongst other things, whether there are a small number of patients who are unusually sensitive to the lung effects, and whether the product labeling safely manages that.

This study will randomize patients to be observed over five years. This large study emphasizes our determination to manage the introduction of this pioneer treatment with the utmost diligence and the fullest of rigor.

With that, I thank you for your attention and put us at your disposal for questioning.

Committee Discussion

DR. WOOLF: I want to thank the sponsor for a complete and understandable presentation. We will now take questions from the panel. This seems to be a bashful panel so I will start. There are several slides on the same theme, 58, 59 and 60, which show differences in pulmonary function tests, FEV1 between the comparator and INH, using time increments to demonstrate that there was no change over time. I would like to ask whether that is perhaps the most relevant way to do this. Would a trend analysis over time be a better analysis to look at whether there is a difference between groups over the entire time period? I don't know whether that has been looked at, but picking times

can give you all sorts of different results. Has the sponsor looked at alternative methods?

DR. JACKSON: We have looked at alternative methods and I will ask Dr. Richard Riese, who is our internal pulmonary expert, to give you some examples.

DR. RIESE: So, we used the time analysis to sort of provide all the data. You know, what it does is a slope is calculated for each subject over the determined times, and then the data of the slope analysis is the average of the subjects of the slope over the indicated times. So, it actually incorporates all the data we have.

We also have done other methods, other ways of looking at that. Can I have slide P-539, please? What this figure shows is sort of a compilation of all the data we have in our long-term two-year trials. What it shows is the adjusted mean treatment group differences for each time point for each trial, starting at the first post-baseline visit at three months and extending to 24 months.

When I talk about treatment group differences I mean the mean difference at each time point between the INH group and comparator. It is the INH minus the comparator. If the value is negative, it favors comparator. If the value is positive, it favors INH. So, this was plotted over each month. The pink dots refer to study 1029, treatment group differences in 1029. The green dots refer to study 1022 in type 1 diabetics. The dark blue dots refer to study 10001 and 1002, again in type 2 diabetics.

As you can see, there are small but consistent treatment group differences favoring comparator therapy. The important point I want you to notice is that these treatment group differences from months three to months 24 are completely flat. It looks like you can draw a flat line right through those points, that is, there is no progression.

I want to draw your attention to month 24. The treatment group difference for study 1022 was 34 mL. The treatment group difference for study

1029 was 35 mL. The treatment group difference for study 1001 and 1002 was 39 mL--remarkably consistent. In the shaded yellow area is the withdrawal data that is derived from 1001, 1002 type 2 diabetics showing resolution of treatment group differences within six weeks of cessation of therapy after two years of continuous therapy.

DR. WOOLF: Other questions? Yes?

DR. KING: This is a procedural question. I have a number of questions, should we start them now?

DR. WOOLF: If they are related to the sponsor, yes. If it is specifically related to the presentation, yes but we will give you one or two and then we will move around.

DR. KING: So, I will ask just a couple. The first one is there is a proposal to study bronchoalveolar lavage in this population and I wonder if there are preliminary data that have looked at bronchoalveolar lavage to this point.

DR. JACKSON: Preliminary data from our program or from other people's? No, there is no

preliminary data. The studies are ongoing and they are in type 1 and type 2 diabetes patients. The data from that I do not anticipate being available until the end of next year at the earliest. These are quite difficult studies to do. They require a number of lavage assessments for each patient.

DR. KING: I will just ask one other question now. Showing the data for lung function changes the way you have shown it I think is fine, but what is more interesting to me, and maybe you can clarify for me, when you look at the actual number of subjects who had a greater than 10 percent change in a parameter which, as pulmonologists we think is real, we find that there were upwards of 10 percent of the population who had such a change. So, I wonder could you comment on those patients and what happens to them over time.

DR. JACKSON: Yes, we have looked at patients with 15 percent and 20 percent changes. We thought looking at 20 percent ones were probably the best ones to look at to see if there was a

signal particularly in those particular patients, and I will ask Dr. Riese if he could exemplify what we have seen.

DR. RIESE: Could I have slide P-55 in the preview, please? This is the change in FEV1 over time for individual patients, every patient in our Phase 2/3 controlled clinical trial on INH therapy who at any point in the trial had a change in FEV1 of 20 percent or greater. There are 54 persons over time and 54 lines in the spaghetti plot time format.

Interestingly, of these 54, 25 patients recovered their FEV1 spontaneously while on INH to within less than 20 percent change, showing that there is quite a bit or variability in the FEV1 measurements in these people. We picked out three subjects who sort of looked like they were falling out of the group, and 8153 and 6285 were subjects with known cardiac disease, diagnosis CHF and cardiac disease. Patient 2621 is a subject in an ongoing trial, 1029. Interestingly, the reason he/she stops there is because that is when the data

cut-off was. At that point this patient got a pulmonary consult. The pulmonary consultant could find no clinical reason for the FEV1 decline. The patient continued on the study and has subsequently improved to less than five percent decrease from baseline without any change in treatment.

The orange lines are the washout data that we have, the cessation of therapy, data from 1001 and 1002. There are ten subjects there, for nine of these subjects the FEV1 during washout either improved or stabilized. One of the subjects had a variable course, starting at minus 24 percent FEV1, at plus six weeks went to minus 17 percent, and then at plus 12 weeks went to minus 30 percent.

Can I have the next slide, please? I want you to compare this in your mind to what happens in our comparator group. There were 44 subjects in the comparator group who had a decrease and change in FEV1 of greater than 20 percent at any time in our trial. The pattern is quite similar. We see a lot of bouncing around. In fact, of these 44 subjects 25 improved while on INH therapy to less

than 20 percent from baseline. Again, we see about three patients that are falling out of the group, and 1667 was a gentleman who went into heart failure and was withdrawn for a PFT decline. Interestingly, 8114 and 6767 were in the early Phase 3 studies and these patients were elected to enroll in the INH extension studies. So, this is the control; they were not on INH. Following this, they elected to enroll in the INH extension studies and their PFT stabilized thereafter.

Again, we see the discontinuation in the orange, the fallout. There are seven patients there. Of these seven patients, six either stabilized their FEV1 or increased their FEV1 during the washout phase of this study. DR. WOOLF: Thank you.

DR. JACKSON: So, what we see here is that there is really no defect that is fixed after two years; it still seems to improve. And, I think a lot of this is due to variability. I think underlying your question might be can you identify why these particular patients--is there anything

about the patients that had the bigger changes? The answer is there is but it is equivalent in both groups. So, the older patients, those with the bigger FEV1 at baseline, those are the ones that tend to get the bigger changes.

DR. WOOLF: Dr. Stoller and then Dr. Schuster.

DR. STOLLER: I have several questions about the design and structure of 1030 which, I understand, is the prospective population with COPD, which I couldn't elucidate from the various documents. So, let me simply pose those questions. In 1030 specifically, how many centers were involved? It is a relatively small number of patients.

Let me perhaps list the questions because they are serial. The other regards the entry criteria. There is some text on page six of the appendix with regard to the possibility that non-smokers were entered into the COPD population and I am interested in some clarity about the number of eligible participants who would, in fact,

have been non-smokers in the COPD population.

Third, it would be helpful to characterize the baseline FEV1 characteristics of patients enrolled and their FEV1 strata, that is to say to characterize the decline in FEV1 stratified by the baseline FEV1 impairment which is not possible to do from the available documents. Obviously Dr. King's question about categorical analysis, significant drops stratified by baseline impairment would be important to understand. In other words, I think it gets to the comment you made that the bigger FEV1 declines were seen in those patients with larger baseline FEV1, which is what I think I heard you say, but actually seeing that laid out would be quite helpful. Then perhaps I have some follow-on questions as well.

DR. JACKSON: I think you have picked up on some of the very critical points around 1030 that have been vexing us to some extent as well. There is a considerable number of centers in this particular study and Dr. Riese will give us some more information on that.

You picked up the question on smokers. My memory, and I am sure Dr. Riese will correct me if I am wrong, is that all, if not nearly all of these COPD patients enrolled, had been previous smokers but it is critical for this particular product that we do not have patients who are currently smoking. Ex-smokers, fine; current smokers, no because of the variability in absorption that comes as a result of smoking and changing smoking patterns. I think that is a critical thing. That is why it is so difficult to get hold of these patients.

DR. STOLLER: Right, I take that point but my question specifically involves the eligibility for enrollment in the COPD trial among non-smokers, just for clarity.

DR. JACKSON: All right, thank you. I will pick that up as Dr. Riese answers the rest of the question.

DR. RIESE: I have your questions written down, at least three of them; I may have missed the last one. But just to close the last question by Dr. King and then I will address the questions--is

that okay?

Could we have P-41, please? We have defined in our NDA cohort these notable decliners, and we have defined a notable decliner with FEV1 of greater than 15 percent from baseline to the last observation in DLco of greater than 20 percent from baseline to the last observation. In this cohort generally in all our controlled Phase 2 trials we generally see about 30 percent increase in the INH number.

However, I want to draw your attention to our new Phase 3 studies, 1022, 1026, 1027 and 1029. The reason I want to do this is we use very well controlled, rigorous PFT monitoring in these specific studies. What I mean by that is that every patient was measured on the same machine at each site. Each technician who administered the test had to take a two-day course and had to pass a written test and a practical test before they could administer the exam. And every test, within 24 hours, was reviewed by our contractor, Quantom, and feedback was given to the sites if there were

problems with this.

What we noticed when we used in a multi-center strategy these rigorous PFTs is that not only did the number of notable declines fall but the difference between the INH and the subcutaneous, the comparator group, becomes much, much smaller. This was very reassuring to us.

Now moving on to the other questions, could I have slide--

DR. WOOLF: We are over time. It looks like this afternoon is relatively light so we will entertain a few more questions but brevity would be appreciated. So, go ahead.

DR. RIESE: Could I have P-544 in preview, please? Study 1030 has been a very difficult study to enroll despite the very large amount of effort by the investigator community, and between 1028 and 1030 we have 99 investigative centers, just to give you an idea of the effort that the investigator community has put into this. In terms of the entry criteria, I think your question was there is a caveat saying that non-smokers who meet the

criteria, if reviewed by the sponsor, may be admitted. As far as I know, there were no non-smokers in this trial so far.

Your third question referred to baseline FEV1 in 1030 specifically. Let's see, can I have P-504, please? This is a table listing the post-bronchodilator FEV1 for the INH and subcutaneous group of the subjects enrolled in 1030. You can see that for the majority of the subjects the FEV1 was between 50 percent and 80 percent in both groups.

DR. STOLLER: May I ask just a follow-on question? Obviously this speaks to relatively mild COPD in the entry cohort for 1030. The follow-on question was to stratify the changes in FEV1, stratified by the baseline FEV1 in these patients. In other words, as you showed in your outliers, a one liter decline in FEV1 is clearly far more impactful for a patient whose baseline FEV1 is 50 percent predicted than it is in someone whose baseline FEV1 is 80 percent predicted. In understanding the risk profile of INH versus

comparator, it would be important to examine those almost categorical analyses stratified by baseline FEV1. Does that make sense?

DR. JACKSON: Yes, it does. It makes a great deal of sense. The problem for us at the moment is that this is an ongoing study. We have given you an interim analysis. I think we have about 30 patients on inhaled insulin in that particular study. When we have sufficient patients, I take your point and that is a good thing to do.

DR. WOOLF: Dr. Schuster?

DR. SCHUSTER: My question actually has to do with treatment satisfaction because, just given the background that this is a fairly laborious therapy and that it takes a while that gets good at it, efficacy appears to improve and side effects appear to decrease but it looks like it doesn't start leveling out until about six months. So, my question then is, number one, when were the treatment satisfaction scales done? How early in the therapy? Is this an emotional

satisfaction--great, I don't get to take shots?

The second question then is, you know, if we are seven months out into therapy did this combine all your studies? Because in some studies they did more work than others. In some studies they took it three times a day but they didn't take as many injections. So, my question is are the satisfaction subscales then a summary of all the studies that have been done or very specific, really equivalent labor therapies?

DR. JACKSON: We didn't do satisfaction studies in all of the studies that we did. The ones that we showed you were a composite of I think three main studies, the main efficacy studies. Those studies lasted for three to six months, and the satisfaction scales were done at baseline but then at the clinic visits at three months and six months, and they were done before measurements of hemoglobin A1c or anything like that so they were done before the patients really knew what the effect, in objective terms, on their diabetes was.

DR. WOOLF: The committee has warmed up.

Drs. Caprio, Watts, Follmann and Calhoun.

DR. CAPRIO: Yes, I am not a pulmonologist but I am questioning whether we have the proper control here in terms that to understand whether the side effects on the lungs are do to insulin or whatever is in the preparation, I think we need to see whether they have to use the product without the insulin and do PFTs or pulmonary function to see what is happening to the lung.

DR. JACKSON: We haven't done anything with patients who are not diabetic. We have done it in patients who are not taking insulin in a number of those studies, 1001, 1002, where we showed that out to the six-month time point the comparator groups took oral therapy only, no insulin.

DR. CAPRIO: Inhaled?

DR. JACKSON: Inhaled for the treatment group. The comparator group, they did not take insulin. Are you asking whether we should do it with just a placebo?

DR. CAPRIO: Right, for the lung, you

know. In terms of understanding whether it is insulin. It may not be insulin. Insulin may be very friendly.

DR. JACKSON: I accept that and it is one of the things that we have to do in trying to understand the mechanism of its effect, to try to get that excipient powder into lungs. It is very, very difficult. Unfortunately, one of the difficulties--or one of the good things I suppose is that insulin itself gives the powder the characteristics that are needed in order to get into the deep lung and to get the absorption. It is very, very difficult to get a placebo that would actually allow you to get to the deep lung.

DR. WOOLF: Dr. Watts?

DR. WATTS: The old saying is a picture is worth a thousand words. It was nice to see the video of the device in use, but I need to get my hands on one to see what it is like. I am curious about the learning curve for patients; the amount of education and training that is needed; the specific question about the procedure once the

blister had punctured and how long does the patient have to inhale the dose and what happens if they wait too long. And patients who are taking insulin typically have a draw full of syringes and a vial full of needles so if there is device failure there is backup. What about device failure with your device?

DR. JACKSON: All right, I can answer part of that question and then I will turn the rest of it over to our pharmaceutical sciences expert, Mr. Jim Spavins. I am assured that the cloud that is formed needs to be inhaled within about 20 seconds after its formation. So, if you run away to the telephone you need to go through the procedure again.

In terms of training and in terms of device failure, I will ask Mr. Spavins if he will give us some more details.

MR. SPAVINS: There are several parts to you question. First of all from a training point of view, as Dr. Jackson mentioned, there will be a comprehensive training program instituted to ensure

that patients are trained in how to use the device.

I think the second part of your question was what about device reliability in the clinics? The devices performed very robustly in the clinic. We know that by three different analyses. First of all, while the device was in the clinic we would periodically check on its performance to make sure it was performing as expected. We have what we have a planned return program where we prospectively pulled devices back from the clinic to see how the device was doing. Thirdly, there is a large amount of mechanical robotic testing that is done in vitro on the product to demonstrate, through substantial mechanical cycles that equal several times its expected use life, that it performs satisfactorily.

DR. WOOLF: To follow-up on that, do you actually have a device here that we can see in addition to the video? Number two, who will be training? The physician will be training the patient, each patient? The nurse educators? I mean, that is going to require a fairly robust

effort to train millions of potential users.

DR. JACKSON: So, the first question was did we bring any devices with us? No, deliberately so because we thought that people would spend quite a lot of time playing the device and may not necessarily hear what we were saying.

DR. WOOLF: I think you are doing us a disservice. We can play and think at the same time.

[Laughter]

DR. JACKSON: Touche. In terms of education, the intent is to formally train investigators and clinic nurses and healthcare providers who will be, in turn, training the patients. We will give videos or DVDs out, many different forms of training in order to make sure that the patients do use the device properly. Underlying the question is, you know, is there training and the answer is definitely. People have to be trained how to use this and the first few inhalations give a different result to the later inhalations as patients get used to it.

DR. WOOLF: A follow-up to the question that I perhaps I didn't ask as clearly as I might, and that is were there device failures during the course of these studies? If so, what failed and what backup plan was in place?

DR. JACKSON: I think you asked the question very clearly the first time and we forgot to answer it. Mr. Spavins?

MR. SPAVINS: Yes, there were device failures in the clinic. There were two categories. Some were self-inflicted actually. The program I talked about where we would measure the performance actually required some manipulation of the device which actually caused some breakage. We did learn some things during the program with regard to certain device mechanical properties, for example, the pull ring which you say had some mechanical robustness issues which have been resolved.

Another good anecdote, one that sort of demonstrates where robots aren't humans, is that we had a button that cracked during the clinical trials. The reason I mention that is that the

robotic trials that did the cycling didn't have, of course, some finger oils on them so when we repeated it using simulated oils we found that the button could crack, and that was resolved.

DR. WATTS: I still don't have an idea of how often there was a device failure and what, if anything, is a backup. Did they have more than one device?

DR. SPAVINS: Two questions and two answers. In the clinic we reported 2.9 percent failures but after the ones I mentioned had been resolved we have only had 1/600 devices that had an issue so that is the current rate.

With regard to replacements, the call center that Dr. Jackson pointed out will be available for patients that do have an issue with the device during use.

DR. FOLLMANN: Just to clarify on that, the 1/600 is 1/600 devices, not 1/600 uses?

MR. SPAVINS: Correct.

DR. FOLLMANN: Then I would like to ask the question I was thinking about earlier so I

would like a little more discussion of study 111, which was the randomized withdrawal study where you had patients who were happy and successful apparently taking inhaled insulin for various lengths of time, a year or two, and then they were randomized to continuing inhaled insulin or to be withdrawn from that. I wasn't clear about what conclusions you drew from that study, if you did a test of the two groups at the end and I assume you did, and what conclusions you drew.

DR. JACKSON: So, the two groups that we are talking about are those who had been treated for three months to three years and then one group was withdrawn and the other group continued on inhaled insulin therapy. Yes? And the conclusion we drew from that is that essentially both groups at baseline, after their three months to three years therapy, had a reduction in lung function which came on early in their studies. And, the group that stopped taking inhaled insulin had a return of lung function by about approximately the same amount of loss that they had in their initial

studies. Whereas, the group that stayed on inhaled insulin continued to have the same amount of decline. That was the conclusion.

DR. FOLLMANN: So, you did the statistical test for whether the two groups were different at the end of six months and three months?

DR. JACKSON: We didn't do a statistical test and you can see that the confidence intervals--can we have M-67?

DR. FOLLMANN: I just wanted to know whether the difference is due to chance or, you know, was a real difference.

DR. JACKSON: It occurred in both type 1 and type 2 patients and it is exactly what we saw in 1001 and 1002, which were studies where we knew what the patients had been doing throughout in a controlled way.

DR. FOLLMANN: So, I guess a test wasn't done?

DR. CALHOUN: I have one pulmonary question and a couple of immunology questions. In the follow-on pulmonary function data you mentioned

that there was really no difference between inhaled insulin and subcutaneous insulin when the pulmonary function testing was done in a very rigorous fashion, when you had careful control of both the operator and the machine. Am I taking the point--

DR. JACKSON: Looking at outliers? Is that correct?

DR. CALHOUN: Yes.

DR. JACKSON: So, for patients who had large changes there seemed to be no difference really between the groups. That is right.

DR. CALHOUN: So, I just wanted to be sure that you weren't asserting that this was a technical error. There is a real signal there--

DR. JACKSON: There is a signal. In those studies there is a very real signal, a very real change. It is small. The point is when you standardize and you are very rigorous with the methodology and you train people well you don't see the large variations in the measurement.

DR. CALHOUN: Thank you for that. Then on the immunology side, on the antibodies, have you

evaluated the consequences of the IgG class antibodies? Is there any evidence of new complex formation? Is there any immunologic activation of these IgG antibodies?

DR. JACKSON: I understand the question and we have our internal expert on antibodies, Dr. Krasner, who will be able to answer that.

DR. KRASNER: We have not identified a clinical consequence of the antibodies. We have looked at our adverse events for evidence of immune complex disease states and we have found no imbalances with regard to unusual clinical consequences. We have evaluated the antibodies in many ways related to hypoglycemia and glycemic control as well and have not found such clinical consequences.

DR. CALHOUN: I understand that you didn't see reduction in efficacy and you didn't see any increase in the need for inhaled insulin dose, but did you look specifically for circulating immune complexes?

DR. KRASNER: We do not have an assay for

insulin immune complexes. Insulin immune complexes are thought to be very small compared to other larger antigens. I would like to ask Dr. Fineberg to comment further.

DR. FINEBERG: Immune complexes that fix complement are found in increased amounts in people who have diabetes. When it has been looked for it has not been related to insulin immune complexes. It is other complexes that seem to be related primarily to inflammatory disease that is present, primarily vascular disease. It has been looked at in a number of studies over the years, none very recent in fact, but when it has been looked at, complement fixing anti-insulin antibody immune complexes don't seem to be related.

DR. CALHOUN: Along those lines, have you evaluated for antibody formation of classes other than IgG class? That is, specifically have you seen IgA class antibody or IgE?

DR. JACKSON: We have evaluated the others and this is the same IgG and the same pattern that you see with subcutaneous human insulin. So, the

other antibody classes we have looked at and we don't see increases.

DR. CALHOUN: Thank you.

DR. WOOLF: Dr. King?

DR. KING: Thank you. There are a number of inhalational technique questions that need to be addressed and we can wait on that.

DR. WOOLF: I think what we are going to do is basically delay lunch so go ahead.

DR. KING: I am going to come back to that because I want to follow-up on the question related to immune complexes. We have debated, and maybe you can clarify, what does diabetes do to the lung itself? Because the lung is basically a bunch of blood vessels and the microangiopathic process probably occurs in the lung in diabetes. We have not really figured out what happens but we have this view that diabetics develop lung disease from the microangiopathic process. Is that going to be a problem? How are you going to address that?

DR. JACKSON: So, how are we going to address the problem of--

DR. KING: As you continue to use this inhalational therapy, will it increase or will it affect the microangiopathic process in the lung of a diabetic patient?

DR. JACKSON: Well, we are addressing it by continuing to look basically. We have run studies so far with two years continuous exposure. We have some that have gone to three years in an uncontrolled way and they were part of that withdrawal study. We are proposing to continue to run seven-year cumulative dosing studies and five-year continuous dosing studies. These studies are under way at the moment and we will continue to look to see if there is any effect. That is about all I can say in terms of the mechanism. We will look for the effect. We do have other investigations going on to look for mechanism. In terms of diabetic lung, we don't have any specific studies. We would be happy to hear any suggestions on that.

DR. KING: My other question relates to what is an ex-smoker. It sounds simple until you

try to figure it out. Most of us believe that you have to have stopped smoking for more than five years to start to look a never-smoker. You never actually look like a never-smoker but it takes a long time. You have said that you would consider using this agent in never-smokers or ex-smokers so how are you going to define ex-smoker?

DR. JACKSON: We define ex-smokers in our particular studies as those patients who have not smoked for six months. Following those on, looking at cotarine levels in patients during the studies we saw no greater than two percent of patients with increased cotarine levels, some of which, of course, may have been due to passive smoking.

DR. KING: So, my issue is that if you look at the inflammatory component of the disease, it takes about five years for that to disappear.

DR. JACKSON: Yes, and we studied those patients basically and we looked to see whether there was any effect of previous smoking. Forty percent of our patients were previous smokers in our clinical program, and we looked at those to see

if there was any effect on the rate of change of the pulmonary function decline, for instance. The answer was no, there was no difference in those particular patients.

DR. KING: So, I want to go to questions about the technique. The video suggested to me that that was a very good technique. But the question I have is when does a patient start to inhale? This is something that we, pulmonologists, have been trying to figure out for a while. So, do they inhale it from FRC, from RV? When does the technique matter? I am sure it does. And what exactly is the technique?

DR. JACKSON: The technique does matter. I am looking for volunteers to answer the question about the technique--

[Laughter]

DR. KING: So, in pulmonary disease when they use inhalation therapy the patient has two--well, two things happen. When you start to use a bronchodilator therapy, and I assume that will happen here, you cough. So, the concern will

be that with the first treatment they cough but they still have the drug in their pharynx and their trachea and the patient doesn't know will they actually absorb enough from that inhalation that they then have the effect of the drug, or should they take another inhalation so they can do it properly without the cough. What would be their monitor that that was a bad inhalation and you should do another one?

DR. JACKSON: A lot of questions in there. Just one thing, you made an allusion to bronchodilator therapy basically. The mechanism of this product is not quite like that an albuterol inhaler for instance. You get a standing cloud and the patient breathes through that cloud. That cloud goes in very, very quickly very early in the inspiration. Most, if not all, of the cloud is inhaled and then inspiration continues. It is a very passive process; it is not an active process. It is not a coordination of breathing so it is relatively simple for patients to do, but they do have to be told to breathe at the correct rate. We

have tried varying rates of force of inhalation, speed of inhalation, and looked at the differences there. It is pretty constant, the absorption is pretty constant over quite a wide range of inspiration rates. I will ask Mr. Spavins just to update you on some of the other things that I didn't answer.

MR. SPAVINS: I think embedded in your question are several engineering considerations which I will try to answer and then Dr. Heise can tell you how it is instructed to be used in the clinics.

A couple of very important features of the device, it is a standing cloud, as was mentioned earlier, sort of design. The chamber actually is a very important part of the design. The compressed ambient air that aerosolizes it goes into a chamber which is about 200 mL. It is specifically designed for that volume to be only a fraction of what a typical lung capacity would be so that evacuating that volume is guarantied, and by forming the standing cloud first you are assured to get your

dose.

Maybe you are familiar with other dry powder inhalers where a patient's inspiration energy has to do two things, not only inhale the product but that is the energy that disperses the product. That is not the design here.

The other thing is that our formulation is a homogeneous dispersion. It is not a mixture of excipients that can separate out. So, the standing cloud design is very important and was specifically designed for this product to avoid any kind of variations of the kind you are alluding to, particularly 200 mL chamber.

A couple of other points. The product has a check valve and you cannot cough into it. It is only one way. That same check valve also regulates how fast a patient can actually breathe into it. Having said that, those are the engineering features that I can bring to the discussion. Then potentially Dr. Heise can talk about the clinical experience.

DR. HEISE: Thank you. I thought it might

help if I just described how we did it in the clinical studies with the type 1 and type 2 patients. Basically, all the patients received an information leaflet and watched the video first. Then we demonstrated the use to the patients and let them do a few practice inhalations using empty blisters. Usually it took about two to three practice inhalations until they were familiar with that and they did their first real inhalation. We had to do a second training session very often in the elderly type 2 patients but very rarely did we have to repeat the training sessions for these patients. Basically, after one or two training sessions the patients were able to use the device and they, themselves, felt that this was very easy to do.

DR. JACKSON: And I would point out that Dr. Heise was one of our investigators who ran a single study, study 1026, in which patients were able to achieve HbA1c's of less than 7. So, he was able to train them very well.

DR. WOOLF: I am going to ask one brief

question and then we will take a break. It gets back to one of Dr. Watts' points. This looks like a great toy, and what is the robustness of the device in the hands of a three year-old who is playing with their parent's device? Is this something that will withstand when they throw it against the wall, stomp on it and do other things that a three, four and five year-old will do with their toys?

DR. JACKSON: Thank you. It is designed to be very robust but, again, Jim will be able to give us more information on that.

MR. SPAVINS: I think there are a couple of perspectives. Were you asking about child resistance or about general mechanism robustness?

DR. WOOLF: Child resistance.

MR. SPAVINS: The product delivery system, which is both the inhaler and the blisters, as you know, was presented to the Consumer Product Safety Commission which, of course, oversees child resistance packaging. Based on their evaluation of the product, child resistance packaging was not

appropriate.

I will give you some insight from what they said. The oral toxicity of the insulin itself is not active orally and, therefore, the blisters--their rationale was--didn't require it. The inhaler, of course, uses no propellants. It is standard air. So, there is no inherent safety issue with the device.

Having said that, the other point is that we have done, as you should do, standard drop testing, ISTM various testing to make sure that the device can, for the appropriate adult and patient, be very robust.

DR. WOOLF: But it hasn't been child-proofed?

MR. SPAVINS: No. Again, we went to the Consumer Product Safety Commission for that reason.

DR. WOOLF: We will take a 15-minute break. The FDA will have its chance and then we will have lunch at the appropriate time.

[Brief recess]

DR. WOOLF: Can we get started, please?

It is now the FDA's turn. Dr. Mahoney will start.

FDA Presentation

Clinical Efficacy and Non-Pulmonary Safety Review

DR. MAHONEY: Good morning, Dr. Woolf, members of the advisory committee, ladies and gentlemen. My name is Karen Mahoney and I will be discussing some findings of the clinical efficacy review and the non-pulmonary clinical safety review of Exubera. Following my talk you will also hear presentations from FDA biometrics regarding hypoglycemia analyses, biopharmaceutics regarding special populations and dosing concerns, and clinical pulmonology regarding pulmonary safety.

My talk will be limited to the following topics. I will first outline the scope of the development program. I will then give a brief overview of the efficacy evaluation in type 1 diabetes, with a focus on the question of whether Exubera can be used successfully in so-called intensive control regimens, commensurate with the optimum management of type 1 diabetes. The applicant has presented information regarding the

efficacy of Exubera in type 2 diabetes and I will not be presenting further information on that topic. After a general overview of non-pulmonary safety I will introduce some specific safety topics, including issues related to hypoglycemia and insulin antibody formation.

Pfizer undertook an extensive development program for Exubera including over 50 Phase 2 and Phase 3 clinical trials. Almost 5,000 patients were reported in the new drug application, over 3,600 of whom were exposed to inhaled insulin. The patient time exposure was very substantial, with over 47,000 patient-months of inhaled insulin exposure. Over 1,500 patients had more than one year of inhaled insulin exposure, with some patients receiving inhaled insulin for up to seven years in extension studies.

The FDA review to date has been an enormous and complex undertaking, and numerous reviewers in multiple review disciplines deserve credit. Prior to Phase 3, the following are the key findings: The applicant had demonstrated that

after inhalation of Exubera insulin was absorbed from the lung into the blood and that once that insulin got to the blood via the lung, the insulin could lower blood glucose.

Major questions to which FDA wanted answers from Phase 3 included can Exubera be used to effectively manage types 1 and 2 diabetes? Does Exubera have a different risk profile for hypoglycemia or other adverse events than one would see with comparator agents? In order to be able to meaningfully compare rates of hypoglycemia both the inhaled insulin and the control groups needed to achieve comparable hemoglobin A1c's. Given that large volumes of insulin and excipients were going to be delivered chronically to the lung in powder form, the agency also wanted to know what pulmonary risks might be associated with Exubera.

The review team put a great deal of thought into each of the efficacy indications sought by the applicant. After reviewing and carefully auditing data submitted by an applicant, I always ask myself this question, if a patient was

sitting in front of me and asking me does this drug work well for my disease, what would I say knowing what I have learned about the drug?

You have heard the applicant's presentation. For their data regarding type 2 diabetes which I have carefully reviewed and audited for accuracy, I generally agree that it appears that Exubera is effective in type 2 diabetes. Therefore, for a type 2 diabetic sitting across for me I would probably say, yes, I think this drug would probably be effective for your type of diabetes. For a type 1 diabetic, however, I might say I am not sure. I will attempt to present the reasons behind that uncertainty in the next few slides.

This is the first product that has ever been considered for approval by the FDA as a substitute for injected pre-meal insulin for type 1 diabetics. We have tried to carefully consider the evidence that pre-meal inhaled insulin actually can substitute for the subcutaneous administration of pre-meal insulin, which is the only route of

administration that has ever been available previously.

There were several studies conducted in type 1 diabetes but the two major completed efficacy trials were studies 106 and 107. In study 106 the comparator was subcutaneous regular insulin administered in the fashion usually considered conventional control. In study 107 the comparator was subcutaneous regular insulin administered in an intensive fashion, similar to that administered in the landmark Diabetes Control and Complications trial, or DCCT.

The DCCT established the current standard for glycemic control of type 1 diabetes. Therefore, for the review of efficacy in type 1 diabetes emphasis was placed on study 107 because intensive glycemic control has become the standard for optimal management of type 1 diabetes. Study 107 was a six-month, open-label, parallel group study with a noninferiority design. Patients in this study drug group received pre-meal inhaled insulin three times daily. Patients in the active

control group received pre-meal subcutaneous regular insulin three times daily. All patients in both treatment groups received NPH insulin subcutaneously pre-breakfast and pre-bed.

The trial included male and female adults and adolescents with a wide range of hemoglobin A1c's on entry. There were 103 adults in each treatment group. Because the applicant seeks only an adult indication I will present the results for adults in the following tables. Later in the presentation I will touch on the evidence regarding pediatric efficacy.

The primary endpoint in study 107 was mean change in hemoglobin A1c from baseline to 24 weeks. For the adults in the study mean hemoglobin A1c's did not differ between groups at 24 weeks and the change from baseline at 24 weeks was not significantly different between groups. There were hemoglobin A1c declines of 0.3 percent for the inhaled insulin group and 0.2 percent for the subcutaneous group. The Lees square means difference between the groups for the change in

hemoglobin A1c from baseline to 24 weeks was minus 0.1 percent. Inhaled insulin was, therefore, statistically noninferior to subcutaneous insulin for this primary endpoint.

Similar percentages of adult patients in the inhaled insulin and subcutaneous groups achieved hemoglobin A1c's of less than 8 percent and less than 7 percent; 28 percent of inhaled insulin group patients and 30 percent of subcutaneous group patients achieved hemoglobin A1c's of less than 7 percent in 24 weeks. In both treatment groups patients who at study entry had tight control, that is a hemoglobin A1c less than 7 percent, were much more likely to have a hemoglobin A1c of less than 7 percent at 24 weeks.

Fasting plasma glucose was slightly higher in the subcutaneous group than in the inhaled insulin group at study entry. At 24 weeks patients in the inhaled insulin group had a mean fasting plasma glucose that was 21 mg/dL lower than it had been at study entry, while patients in the subcutaneous group had a mean fasting plasma

glucose that was 5 mg/dL higher than it had been at baseline. The reason for this difference between groups is not clear. Logically, one would expect a difference in fasting glucose to be more related to an evening, long-acting insulin than to a pre-meal, short-acting insulin. However, patients in the inhaled insulin group actually had somewhat lower mean evening and total daily doses of long-acting insulin than the patients in the subcutaneous group.

At zero and 24 weeks patients had a standard meal test with measurements of plasma glucose 30 minutes before and two hours after the meal. Patients had similar baseline values for postprandial glucose excursion or the difference between the 30 minute pre-meal value and the two-hour postprandial value. From week zero to week 24 the amount of this postprandial glucose excursion increased by 24 mg/dL in the inhaled insulin group while it decreased by 9 mg/dL in the subcutaneous group, with a mean difference between groups of 24 mg/dL.

Going back to that question that a type 1 diabetic might have, namely, will this drug work well for my disease? I would think about these issues: Inhaled insulin was statistically noninferior to subcutaneous insulin for change from baseline in hemoglobin A1c, but neither treatment group achieved mean hemoglobin A1c as tight as that maintained in the Diabetes Control and Complications Trial which led to the current standard of glycemic control for type 1 diabetes.

The study regimen in 107 was intended as an intensive regimen such as that used in the DCCT. We will discuss DCCT hemoglobin A1c control in a moment. Only 28 percent of adults in the inhaled insulin group achieved a hemoglobin A1c or less than 7 percent. Meal study postprandial glucose excursion actually increased from baseline to 24 weeks with inhaled insulin, while it decreased with subcutaneous insulin.

The Diabetes Control and Complications Trial was a landmark study in type 1 diabetes, which established the current standard of glycemic

control when it showed that an intensive insulin regimen resulted in a significantly lower risk of microvascular complications of diabetes, such as retinopathy, neuropathy and nephropathy. In the DCCT mean hemoglobin A1c, depicted here on the Y axis, remained at or slightly below 7 percent throughout the duration of the trial. Mean hemoglobin A1c of less than 7 percent had been achieved by 6 months of study.

In study 107, which the applicant intended as an intensive control study, mean hemoglobin A1c in the inhaled insulin group at 6 months was 7.5 percent, which is about 0.6 or 0.7 percent above that achieved by that point and subsequently maintained in DCCT. Tight glycemic control was needed in study 107 not only to assess the efficacy of inhaled insulin for intensive type 1 diabetes management but also to push the hemoglobin A1c low enough to be able to compare rates of hypoglycemia, which is the major complication reported in the literature for tight glycemic control.

In clinical practice endocrinologists and

other physicians caring for diabetics are strongly encouraged by the practice standards of their professional organizations to push for tight control for type 1 diabetes. The mean hemoglobin A1c of 7.5 percent found in study 107 falls above the hemoglobin A1c target set forth by the American Diabetes Association and the American Association of Clinical Endocrinologists which recommend hemoglobin A1c targets of less than 7 percent and less than 6.5 percent respectively.

Postprandial glucose control is increasingly a target of intensive diabetes management, in part because postprandial glucose shows an epidemiologic association with risk of cardiovascular disease. Diabetics suffer great morbidity from microvascular complications but they usually die from microvascular complications, specifically cardiovascular disease. The ADA has set a target of less than 180 mg/dL maximum postprandial glucose, and the AACE has set a two-hour postprandial glucose target of less than 140 mg/dL. For the inhaled insulin group in study

107 the two-hour postprandial glucose was 287 mg/dL at 24 weeks, and home blood glucose monitoring results at 24 weeks showed a mean two-hour postprandial glucose of 182 mg/dL.

Again, back to that type 1 diabetic who is sitting across from me and asking me whether Exubera would be likely to be effective for their disease, I might have to say that from this particular study, study 107, which the applicant intended as their intensive control trial, I am not sure whether the average type 1 diabetic patient could expect to achieve DCCT style tight control with Exubera. We will be asking the advisory committee to consider that question today.

Perhaps the committee can also consider whether it is even reasonable to expect DCCT level control out of a clinical drug trial. Twenty-eight percent of inhaled insulin group patients in study 107 did achieve a hemoglobin A1c less than 7 percent at 24 weeks. Is that good enough? Would it be acceptable to try it for a given patient and then go back to subcutaneous insulin if the patient

failed to achieve the desired hemoglobin A1c with inhaled insulin? I look forward to the advisory committee's input regarding these efficacy questions in type 1 diabetes.

Now a few words about pediatric efficacy. Pfizer is not seeking an indication for the use of Exubera in pediatric patients at this time. The FDA wants to establish whether Exubera appears safe and effective for adults before requesting further pediatric study. Care of the child or adolescent diabetic is a complex undertaking, with numerous interactions between disease, developmental issues and family concerns. The agency anticipates significant interest in information regarding the potential for use of Exubera for pediatric patients.

Studies 106 and 107 included both adult and adolescent type 1 diabetics. Between these two studies there were 180 adolescents, 92 of whom received inhaled insulin. Study 1009 was conducted solely in children ages 6-11 years. Out of 119 children in the study, 60 received inhaled insulin.

In all three of these efficacy studies which included children or adolescents the pediatric patients began with mean hemoglobin A1c's over 8 percent and there was little hemoglobin A1c change in either treatment group over study. In study 1009 a slightly higher percentage of children achieved hemoglobin A1c's of less than 8 percent and less than 7 percent with inhaled insulin than with subcutaneous insulin. However, only 18 percent of children in the inhaled insulin group obtained a hemoglobin A1c of less than 7 percent. In study 1009 there was little difference between treatment groups for fasting plasma glucose and postprandial glucose.

The limited data acquired to date do not appear to demonstrate efficacy of Exubera for intensive management of type 1 pediatric diabetics. However, future specific pediatric study of inhaled insulin may provide more definitive information.

Safety is always or prime importance in a review and my review covered non-pulmonary safety issues in great detail. That lengthy review was

included in the pre-meeting document provided to the members of the advisory committee. The following slides will touch on the highlights of that in-depth review. This includes information for both types 1 and type 2 diabetes.

Regarding deaths, there was little difference between treatment groups for incidence of death and the incidence of death was similar to that seen in meta-analyses of large diabetes trials. As occurs in practice and in large diabetes trials, most deaths were from cardiovascular causes. The causes of death did not differ between treatment groups and no pediatric trial participants died.

Before I begin to talk about other adverse events I wanted to spend a few moments talking about a potentially confusing topic, that is, the ways in which hypoglycemia episodes could be identified. Hypoglycemia is an important event to consider in diabetes drug trials. As mentioned earlier, the goal of they for type 1 diabetes is now to achieve as low a hemoglobin A1c as possible.

However, the limiting factor in achieving tight glycemic control is hypoglycemia. As that hemoglobin A1c goes lower, hypoglycemic episodes become more frequent and sometimes more severe for type 1 diabetics.

In the adverse event section of my talk I will be discussing hypoglycemia as a patient-reported adverse event. Ms. Mele, the statistician's talk, she will be talking about hypoglycemia as an outcome variable. As you will see as I explain the differences in how these are defined, it is possible to get different results for comparisons between treatment groups depending on how you are defining hypoglycemic episodes.

In this application there were multiple definitions used to compare rates of hypoglycemic events. But in their major study protocols, the applicant had specific definitions for hypoglycemic episodes and for severe hypoglycemia. Data for these definitions were collected prospectively. There was also a retrospective definition used for analyses after an FDA request. In addition to

these three definitions used for specific analyses, investigators could also report episodes as adverse events.

This is the wording used by the applicant for the protocol-defined prospective definition of hypoglycemic events. This definition was used to capture total hypoglycemic events for analysis as an outcome variable. Patients were considered to have a hypoglycemic event if they had any one of the following: Characteristic symptoms of hypoglycemia with a measured blood glucose of less than or equal to 59 mg/dL; or characteristic symptoms of hypoglycemia with no blood glucose check. In that case, the clinical picture must have included prompt resolution with carbohydrate or glucagon. Or, any glucose measurement of less than or equal to 49 mg/dL with or without symptoms.

A subset of those total hypoglycemic events were considered severe hypoglycemic events and were prospectively defined as an outcome variable for analysis. In order to be considered a severe hypoglycemic event, the event had to meet

all three of the following criteria: The subject had to be unable to self-treat; and the subject had to exhibit at least one specified neurologic symptom; and the subject had to have a measured blood glucose of less than or equal to 49 mg/dL or, if no blood glucose was measured, the subject's clinical manifestations had to be reversed by carbohydrate or glucagon.

A retrospective hypoglycemic event definition was also used. This included the definition of a severe event used in many major clinical trials of diabetes, meaning a hypoglycemic event in which the patient required the assistance of another person. The retrospective definition also specified a very low glucose, less than or equal to 36 mg/dL, which would still count as an event even if the patient did not report requiring the assistance of another person.

In talking about hypoglycemia as a serious adverse event, not an outcome variable, the definition was consistent with the regulatory definition of a serious adverse event.

Specifically, it would be an event which resulted in death, or was life-threatening, or required hospitalization, or resulted in disability or resulted in a birth defect. As you can see, this definition of a serious adverse event of hypoglycemia is quite different from the definition used for a severe hypoglycemic episode for the outcome variable.

In the next few slides about adverse events and the safety review, when I mention hypoglycemia I will be talking about reported adverse events of hypoglycemia. In the next presentation Ms. Mele will discuss hypoglycemia as an outcome variable.

Now on to serious adverse events in general, serious adverse events overall occurred with an approximately equal frequency between adult inhaled insulin groups and adult comparator groups, with serious hypoglycemia being the most commonly reported serious adverse event. The rate of serious hypoglycemic event in inhaled insulin group patients did not exceed that of subcutaneous group

patients. For these serious adverse events of hypoglycemia serious consequences of hypoglycemia did not differ between groups. That is, inhaled insulin patients were not more likely to have accidents or injuries accompany their events than were subcutaneous group patients. The types and incidences of other serious adverse events which were examined in detail did not differ significantly between treatment groups.

Among pediatric patients serious adverse events of hypoglycemia were slightly more frequent among inhaled insulin group patients than among subcutaneous group patients. Pediatric patients also had more frequently reported serious adverse events of hypoglycemia than did adult type 1 diabetics for both inhaled and subcutaneous groups. The rates of diabetic ketoacidosis did not differ between groups. Cerebral edema, which is the most frequent cause of death in pediatric DKA, did not occur in either treatment group. Rates of other serious adverse events also did not differ significantly between groups.

Moving from serious adverse events to common adverse events, for both type 1 and type 2 diabetes non-serious hypoglycemia was again the most commonly reported adverse event. It occurred with approximately equal frequency between inhaled insulin and subcutaneous groups, and with lower frequency in oral agent groups. In the trials which compared inhaled insulin to oral agents hemoglobin A1c control was generally better in the inhaled insulin groups, and one might expect more hypoglycemia with better control. Also, some oral agents such as metformin are not associated with hypoglycemia.

Overall adverse events, such as sinusitis, rhinitis, and pharyngitis, occurred with greater frequency in type 1 inhaled insulin group patients than in subcutaneous group patients. Nasopharyngeal adverse events occurred commonly in trials of inhaled products for other indications. In the Exubera program there was no placebo inhaler, therefore, control patients did not even receive any inhaled excipient. It is, therefore,

unsurprising that inhaled insulin group patients might have a somewhat higher incidence of these events.

For type 1 diabetics there was a lightly higher frequency of the event termed allergic reaction for the inhaled insulin groups than for subcutaneous group patients. There was little difference between groups for adverse events of special interest, such as accidents and malignancies. In general, rates of other events were not higher in the inhaled insulin groups than in comparator groups. Pediatric patients taking inhaled insulin experienced adverse events related to the ear, such as otitis media, for frequently than did subcutaneous group pediatric patients. The reason for this difference is unknown, but it is known that the eustachian tube in children is anatomically different from that of adults.

During development it was noted that greater increases in serum insulin binding activity were occurring for inhaled insulin group patients than for patients in subcutaneous or oral agent

groups. Serum insulin binding activity is a measure of the presence and affinity of antibodies to insulin. This finding led to FDA concerns regarding possible immunologic or other clinical consequences of antibody formation.

Among other questions, FDA had the following major questions about the higher rates of insulin binding activity seen with inhaled insulin. What were the rates of serconversion, that is, going from an undetectable level of insulin binding activity to a detectable level? How did the change from baseline in insulin binding activity compare between treatment groups? What types of patients were more likely to have increases in insulin binding activity with inhaled insulin? What was the qualitative nature of these antibodies? Did patients who increased their insulin binding activity have more adverse events of any kind? Was there evidence that these antibodies could neutralize the action of insulin? And, finally, what happened to insulin binding activity after discontinuation of an inhaled insulin?

The following slides will address these questions. The applicant used two types of insulin antibody assays. This and the following slides include the results primarily from the quantitative assay data. Among type 1 diabetics, 88 percent of inhaled insulin group patients who had undetectable serum insulin binding activity at baseline developed detectable insulin binding during the study. The rate of seroconversion was much lower among subcutaneous group patients, at 23 percent. For type 2 diabetics, 71 percent of inhaled insulin group patients seroconverted, while 6 percent of comparator group patients seroconverted.

We will now look at change from baseline in insulin binding activity. This includes both patients who exhibited insulin binding activity at baseline and patients who did not. In this figure the Y axis depicts change from baseline in insulin binding activity measured in micro units/mL for each of the three paris of columns here. The blue column represents the inhaled insulin group and the red column represents the comparator group. For

each pair of columns baseline values are similar.

For type 1 diabetics at six months of study, mean change from baseline in insulin binding activity for inhaled insulin groups was 161 micro units/mL compared to a mean change of 1 micro units /mL for the subcutaneous only groups. For type 1 diabetics who were insulin-using at baseline, insulin binding activity rose by a mean of 69 micro units/mL in the inhaled insulin group and 4 micro units/mL subcutaneous group at 12 months of study.

For type 2 diabetics who were not insulin-using at baseline, mean change from baseline in insulin binding activity was 16 micro units/mL while the mean change in the oral agent comparator group was zero, again at 12 months of study.

When we compare pediatric type 1 diabetics to adult type 1 diabetics, pediatric patients seroconverted more frequently, had higher mean end-of-study insulin binding activity, and had greater changes from baseline in insulin binding activity. I should note that although this

numerical comparison held across all age group comparisons, standard deviations were wide. For type 2 patients there were no clear age differences.

Type 1 diabetic females had numerically greater end-of-study insulin binding activity and greater changes in baseline than did type 1 diabetic males. For type 2 diabetics there were no clear gender differences. There were too few non-Caucasian patients to compare the incidence among racial or ethnic groups.

The antibody seen with inhaled insulin exposure were mostly IgG, which is the same major class of antibody described to occur with subcutaneous insulin exposure. The applicant examined the binding capacity profile and found these antibodies to be primarily low affinity, high binding capacity, which is again the same profile that is usually seen with subcutaneous exposure.

The data were examined extensively for possible associations of antibody formation with risk of adverse clinical events, and no clear

correlates were found. As mentioned earlier, in the Phase 2 and Phase 3 controlled studies there was a slightly higher incidence of the event terms allergic reaction among type 1 inhaled insulin group patients. However, occurrence of this term or other terms potentially related to allergic events did not correlate with the degree of insulin binding activity and did not occur more frequently among patients with very high binding activity. There was no correlation in degree of insulin binding activity and frequency or severity of hypoglycemic events.

With other therapeutic proteins, development of antibodies to the drug product has sometimes resulted in neutralization of action of the product or even of the action of endogenous proteins. Pfizer reported extensive attempts to develop a neutralizing antibody assay but was unable to do so. Neutralization of the action of insulin might be associated with deteriorating blood sugar control or increasing insulin requirement. However, multiple analyses found no

association between degree of insulin binding activity and hemoglobin A1c, fasting plasma glucose, postprandial glucose, overall insulin requirement, or change in insulin requirement over time.

The applicant examined insulin binding activity after discontinuation of inhaled insulin and found that activity began to decline within about two weeks after discontinuation, and by 12 weeks had declined by about 70 percent. At that point, 12 weeks was the end of the follow-up period and decline to baseline was not documented.

To summarize observations from the review of insulin antibody formation, the inhaled insulin group patients were more likely to seroconvert than comparator patients. Inhaled insulin patients had higher end-of-study insulin binding activity and greater change from baseline in insulin binding activity than did comparator patients.

For type 1 diabetics in the inhaled insulin groups, females and children had numerically higher end-of-study insulin binding

activity and greater numerical change from baseline in insulin binding activity. Although this brisk antibody response is concerning, we found that despite an extensive search no clinical correlate was apparent over the period of observation.

In final summary, the major points of my efficacy presentation were that questions remain about whether adult type 1 diabetics can expect to achieve tight control with Exubera, and pediatric efficacy was not clearly demonstrated and may warrant further study. A pediatric indication is not sought by the applicant.

To summarize non-pulmonary safety, there were no clear differences between treatment groups for deaths and serious adverse events. Hypoglycemia was the most common adverse event. In general it did not appear to occur more frequently with inhaled insulin than with subcutaneous insulin.

Non-serious nasopharyngeal adverse events occurred more frequently with inhaled insulin than with subcutaneous insulin in type 1 diabetics.

Non-serious adverse events related to the ear appeared to occur more frequently in type 1 children taking inhaled insulin than in type 1 children taking subcutaneous insulin only.

Inhaled insulin was associated with a greater incidence of antibody response than comparators, but not clinical correlate has been found over the period of observation.

Many people have contributed to the agency review of Exubera and all deserve recognition for their efforts. The team leaders are listed here in alphabetical order over the final slides. Following these acknowledgments I will give the podium over to Ms. Joy Mele, statistical reviewer in the Division of Metabolic and Endocrine Drug Products, who will present some issues regarding hypoglycemic event analyses.

Statistical Review and Evaluation

MS. MELE: Good morning. My name is Joy Mele. I will start my presentation with a description of the entry criteria that pertain to the patient's history of hypoglycemia. Then I will

show you how hypoglycemic data was collected on the case report forms. Next I will present the results from protocol-defined severe hypoglycemia, with one of my goals being to illustrate some issues regarding measures of hypoglycemic risk. Then I will go on to the results of the post hoc FDA definition of hypoglycemia and I will close with some overall conclusions.

One of the criteria for entry into study 107 was that patients could not have had more than one severe hypoglycemic event, or any hospitalization due to poor glycemic control in the previous six months or during the run-in. So, there was an effort not to enter patients with a propensity for frequent severe events.

The protocol spelled out two definitions of hypoglycemia which Dr. Mahoney just showed you. On the next slide I am going to remind you of the definition of severe. As Dr. Mahoney mentioned, both total and severe hypoglycemia were named as secondary efficacy variables.

Information on all hypoglycemic events was

captured on a single case report form. Events initially reported as adverse events were also recorded on these forms to ensure a full account of all events. Here is a partial list of the data collected on a case report form. Patients were asked if the event was accompanied by the usual symptoms. Glucose was collected from several sources, including the patient's work sheet, lab reports or the patient's glucometer.

Three questions were asked: Was the subject unable to self-treat? Did the subject exhibit CNS symptoms? Was blood glucose 49 or lower? Or, if glucose was not measured, did symptoms reverse with carbohydrates? A "yes" to all three questions defined the event as severe. A response of mild or moderate was at the discretion of the investigator since neither was predefined. So, based on the data on this form, there is a recording of the number of events as well as the characteristics of those events.

These events may be summarized by two measures or risk. We can either compute the

percentage of patients with at least one event, using the patient as our unit of measure; or, we could count the total number of events and divide it by the total exposure in months or perhaps years to come up with a rate, essentially averaging the counts over time.

In a recent publication, an ADA work group recommended using both measures, saying that they provide complementary information. With this NDA, I learned that these two measures were not quite enough and I will illustrate this point with the severe events from study 107.

First let's look at the overall hypoglycemia data from study 107. The graph on the left shows the percentage of patients with at least one of each of the three types of events. Note that all severe events are counted as both FDA and total events and all FDA events are counted as total events. Almost all patients have at least one hypoglycemic event in study 107; 90 percent of the patients have at least one FDA event; and relatively few patients have at least one severe

event, with 17 percent of the inhaled insulin patients having severe events and 13 percent of the subcutaneous patients.

The ratios of these percentages are not significantly different from one. Any analysis counting only one event per patient, such as a time to first event analysis, shows no differences between treatments. I want to point out that there was no prespecified criteria for showing comparability on these measures, which is not unusual for a secondary endpoint.

The graph on the right shows the number of events per patient-month. The risk ratios for this measure tell us a different story from the ones on the left, with inhaled insulin showing less risk for hypoglycemia based on the FDA events and more risk based on the severe events. One way to interpret the severe risk might be that for every subcutaneous patient having one event there would be an inhaled insulin patient having two to three events. But I will show you that that is actually not the case.

Here is the distribution of the data for severe events. Most patients in both groups have no severe events. About another 8-9 percent have only one event. So, the groups look pretty balanced until you get to more than 3 events and you notice there is one patient in particular that stands out, and that is the patient with 12 events. Based on a non-parametric test of the counts, the groups are not significantly different, with a p value of 0.3.

However, in "Diabetes Care" in July these results were reported as a significant doubling of risk of severe hypoglycemia for inhaled insulin compared to subcutaneous based on a recurrent events survival model. The model used by the authors was not appropriate for the data, primarily because it failed to account for repeated events within patients. The estimate was driven largely by the multiple events of a couple of patients. For example, if we drop the patient with 12 events from the analysis the risk ratio drops by almost 30 percent to about 1.6 and becomes non-significant.

Let me just point out that the estimate I am showing here of 2.25 is for adults only, while the one that was reported in the "Diabetes Care" article of 2 was for adults and children combined.

Now to be convinced though that the time-to-event model of recurrent events is not the correct model it helps to learn more about the patients having multiple events. Each graph on this slide shows the events for a single patient, with the patient number shown at the top. The X axis is days on study and the Y axis is just a count of the events. The graphs with red symbols are for patients on inhaled insulin and the one graph with blue symbols is a subcutaneous patient. Notice that for four out of the five inhaled insulin patients the events are clustered. For the patient with 12 events, nine of these events occur in a two-week period. Also notice that most of the events occurred during the first half of the trial. the clustering suggests that an analysis that treats these events as unrelated, independent events and ignores the patient as a unit of measure

is not sensible.

Of course, these patients should be further examined. Dr. Mahoney has carefully examined the records for each of these patients with four or more severe hypoglycemic episodes. For the patient with four events there is no pattern to his events. He completes the trial but only participates in one month of the extension. The woman with five severe events has them all within one week. The insulin is reduced. She adds a bedtime snack and she completes the trial and one year of the extension study with no further severe events. The young woman with 12 events is probably the most interesting case, and the sponsor has already mentioned her. She is a freshman in college, home for winter break, when she experiences nine events in a row. No glucoses accompany those nine events. So, it is on the assistance of her mother, bringing her perhaps OJ in the morning early in the morning, that qualifies her events as severe. She has three more a few weeks later. She completes the trial and continues

into the extension for two years with only two additional severe events. So, the two women with the most severe events in 107 are able to continue on inhaled insulin without experiencing multiple severe events again.

So, I concluded for the severe hypoglycemia that one patient with 12 events overly influences estimates of risk based on survival models of recurrent events. A non-parametric analysis of total severe events shows no significant treatment difference in study 107, and these results are consistent with the other type 1 study, study 106.

Let's now look at the results for the events we are calling FDA-defined. These events were retrospectively identified from the data on the case report forms. Recall that the definition was glucose of 36 or less, or the patient was unable to self-treat and needed assistance.

This is the definition but what other characteristics distinguish these events from the total events? I will address this question in the

next several slides.

First let's look at the results, and 91 patients treated with inhaled insulin had a total of 971 events, and 94 subcutaneous patients had a total of 1,327 events. For both treatment groups most events were identified based on the low glucose, as you can see from the table. So, we see that the FDA-defined events are driven by the glucose values.

Now, to put this into context of all the events, I want to step back from the FDA events for a minute and show you the distribution of glucose overall. Here I am showing you the distribution of glucose for all the recorded hypoglycemic events. I have broken down the distribution by severity and drawn a line at 36 to relate the overall results to the FDA events. It appears that glucose levels related to severity but the correlation is weak and the relationship looks to be the same for both treatment groups.

Also, for the FDA events I computed the mean glucose for each patient and then the overall

group mean, which is about 32 for each group. So, patients with FDA events in the two groups, which is about 90 percent of the patients, experienced comparable mean glucose values.

Before going on to the next slide, I want to point out that what I am presenting is simply descriptive. We would not do statistical analyses on subgroups defined by outcome variables such as severity. My goal though is to show that the event data suggest that the treatment groups are comparable.

This graph shows the breakdown of events by severity for the FDA events on top and for the hypoglycemic events not counted as FDA events on the bottom row. The X axis is on the severity scale shown on the bottom graph but also applies to the graph above. The Y axis is the number of events, and the percentages are noted above each column.

For the FDA events, 52 percent in the inhaled insulin group and 60 percent in the subcutaneous group were rated as mild events,

suggesting a very small treatment difference. But no difference is evident between the groups if we look at the patient mean severity scores, which is 1.5 for each group. As with the previous slide, means are computed for each patient's own mean value based on all their FDA events. So, the unit of measurement for these means is the patient.

These graphs show the number of events accompanied by the usual symptoms of hypoglycemia. The majority of events were symptomatic, as shown in the bars on the left of each graph. A small percentage of the FDA events presented with CNS symptoms, 13 percent in the inhaled insulin group and 9 percent in the subcutaneous group. Patient means are approximately equal, with patients on average experiencing symptoms with about 80 percent of their FDA events.

Here is the distribution of the FDA events. The inhaled insulin group is on top and the subcutaneous group is on the bottom. The X axis is the total number of events per patient and the Y axis is the number of patients. The

distributions look similar, though there are clearly a few more patients in the subcutaneous group that have 40 or more events than in the inhaled insulin group, and that would be those six patients down here, versus two patients in the inhaled insulin group.

These eight patients comprise about 16 percent of the events. There is one subcutaneous patient with 78 events--this patient out here. Overall, he has 182 hypoglycemic events. Nearly all his events are rated as mild and he experiences no severe events, and CNS symptoms accompany only two events. Yet, in a recurring events model this single patient would carry a lot of weight, changing the estimate by about 10 percent.

The medians from the distributions I just showed you are six for the group and eight for the subcutaneous group. Note that if we use the patient-month estimate we would estimate 10 events over six months for the inhaled insulin group and 14 for the subcutaneous group, doubling the difference from two to four. A non-parametric

analysis in the total counts yields a p value of 0.09 which is statistically not significant.

Overall I conclude that the hypoglycemic events are similar in quantity and characteristics between the inhaled insulin-treated group and the subcutaneous-treated group, regardless of the definition of hypoglycemia. These results for study 107 are consistent with results from the other type 1 studies in this application.

Rates of hypoglycemia should not be summarized and analyzed based on total events without carefully examining the distribution of events across patients. As with any assessment of safety, outliers are important to examine but they may grossly skew the risk ratios if estimated from models such as recurrent events survival models which are generally used when patients have few events. Thank you.

Clinical Pharmacology and Biopharmaceutics Review

DR. AL HABET: Good morning. My name is Sayed Al Habet. I am a reviewer in the Office of Clinical Pharmacology and Biopharmaceutics,

co-located in the Division of Pulmonary and Allergy Drug Products.

The focus of my presentation is on the effect of certain conditions on exposure following inhaled insulin. Specifically, the focus of my presentation is summarized in the following leading questions: What is the effect of respiratory condition on the systemic exposure of inhaled insulin, specifically on COPD, effect of asthma and smoking?

The next leading question is related to the interchangeability between one time 3 mg and three times 1 mg blister strength, and what is the variability associated with the inhaled insulin?

I will start with the effect of smoking and insulin exposure following inhalation. The sponsor conducted four studies to investigate the effects of smoking on exposure of inhaled insulin, and one study on the effect of passive smoking, also referred as secondary smoke.

For chronic smoking the study was conducted in healthy subjects who smoked at least

15 cigarettes per day for at least six months. Inhaled insulin was administered at 2 mg doses. That means two times 1 mg blister. Subjects were then asked to quite smoking for 15 weeks. This slide shows that exposure increased in smokers by approximately five-fold compared to non-smokers, as noted in the second bar of each graph.

This increase was consistent for both AUC and Cmax. However, when patients stopped smoking for three weeks the exposure was reduced by approximately half and then stabilized over 15 weeks of the study, as shown in the third and last bars of each chart.

In another study the sponsor investigated the effect of cessation and resumption of smoking on the insulin exposure following inhalation. The data was consistent to the previous study in that the exposure in smokers is higher than non-smokers and stopping smoking for a few days reduces the exposure. The effect of quitting smoking on exposure was not apparent after 12 hours, as shown in the third bar, but was more noticeable on day

three and day seven, as shown in the fourth and fifth bars of each graph.

It is interesting to note that resumption of smoking returns the exposure to the baseline level within two to three days, as shown in the last bar of each graph. This is the resumption, here.

From these data it can be concluded that stopping and resumption of smoking for just a few days produced significant effects on the insulin exposure following Exubera.

It is interesting to note that passive smoking or secondary smoke exhibits an opposite effect compared to chronic smokers. Essentially, the sponsor conducted this study in 28 healthy subjects in a crossover design. The design was as follows, in group A the sponsor administered 3 mg with 2 hours exposure of passive smoke and then in the absence of passive smoke.

From this study, it can fairly be stated that the exposure was reduced by approximately 20-30 percent, rather than increased, as was shown

in the previous slides for chronic smokers. The reason for this discrepancy between the data from chronic smokers and passive smokers is unknown.

According to the sponsor's proposed label, I am going to quote the following statement: Exubera is contraindicated in patients who smoke or who have discontinued smoking less than six months prior starting Exubera. If patients start or resume smoking, Exubera must be discontinued immediately due to the increased risk of hypoglycemia and an alternative treatment must be stabilized, end of quote. Therefore, this statement does not represent occasional smokers and those exposed to secondary smoke.

Now I would like to switch gears to effect on respiratory conditions on disease as COPD and asthma. We will start with the COPD. The sponsor conducted one study to investigate the effect of COPD on exposure from inhaled insulin. The dose administered was 3 mg inhaled 30 minutes before or after two puffs of albuterol. Then, there is another arm of 9 minutes subcutaneous regular

insulin. The study was conducted in healthy subjects, 12 subjects. Also, 12 subjects each for emphysema and bronchitis. During the analysis 6 subjects were excluded. Four subjects were excluded due to high carbohydrate intake which is affecting the insulin baseline. Two outliers--for some reason that we don't understand really, the subcutaneous administration was either incorrect or showed very low subcutaneous exposure. Therefore, the bioavailability of the inhaled insulin was in the number of 600 percent. Therefore, these were excluded.

This slide shows that the exposure from inhaled insulin is higher in COPD patients compared to health patients. The data is consistent for Cmax and AUC. However, for subcutaneous data there was no consistent change in p, as shown for AUC and emphysema patients. I am referring to this bar. The reason for this inconsistency in the subcutaneous data could be due to the high variability in the data, as well as the disease as we will discuss it later.

Overall, it can be concluded that insulin exposure following inhalation increased by approximately 50 percent in COPD patients. Furthermore, the effect is more pronounced for Cmax and AUC. The Cmax is considered an important PK parameter for insulin as it is associated with rapid drop in blood sugar and may result in hypoglycemia.

For those in the back who cannot see, the subcommittee is in brown and the inhalation is in green.

However, the exposure in asthmatic patients is in the reverse order. It is reduced by 20 percent to 30 percent compared to healthy subjects. The data is consistent for both AUC and Cmax. It should be noted, however, that the bigger the dose, the greater the effect of exposure. In other words, the effect was more pronounced after 3 mg than 1 mg, as shown in each of the PK parameters for AUC and Cmax. Just for the people in the back, this is the asthma which is shaded in red and the blue is the normal subjects.

The reason for the observed differences between the effect on COPD and asthma is not clear. The mechanism leading to this discrepancy in exposure observed in COPD and asthmatic patients would be helpful in establishing an optimal titration process in these two respiratory conditions.

The effect of rhinovirus infection was conducted in health subjects after four days. Subjects were inoculated with either the virus or saline. It should be noted that only four subjects received saline and acted as controls in this study. Considering the variability in the data, the effect of rhinovirus infection on the exposure is not apparent. However, there was a small increase in exposure with rhinovirus infection on day three compared to control, as shown in the second set of bars in each chart. I am referring to this second bar. The green is the saline group, which is an N of four, and the virus is the blue and that is about 20 subjects.

The sponsor submitted an additional study

to investigate the effect of two inhalers, fluticasone and albuterol. The study was conducted in four treatment arms in asthmatic patients. Only the albuterol data will be discussed here. Exubera was administered in a 3 mg dose either alone or 30 minutes after inhaled albuterol. Overall, there was a 25 percent and 30 percent increase in exposure with albuterol in mild and moderate asthma respectively. The effect was greater in moderate asthma than mild asthma for both AUC and Cmax, as shown in the last two sets of bars in each graph. I am referring to these two.

It should also be noted that the exposure in mild and moderate asthmatic patients is slightly lower than the healthy subjects. Therefore, the data is consistent with the previous study in asthmatic patients. These are the normals in each graph for Cmax and AUC, and it is slightly lower than the health, and considering the variability in the data as well.

Now we will switch gears to the issue of titration process. We have three issues here.

Number one is switching between strengths. Number two is switching from subcutaneous to inhalation for the first time, and the variability within the patients.

The focus of my presentation will be on number one and number three. For switching between strengths, you can see that some patients may switch from 2 mg, which is two times 1 mg, to 3 mg, which is one 3 mg. So, for 4 mg, for example, you are giving one 1 mg and one of 3 mg to 5 mg, which would be two of 1 mg and one of 3 mg, and continuing like that pattern.

The reason we bring this to your attention is that there is no bioequivalency between the 1 mg strength and the 3 mg strength if you give it at the same dose. And I shall be discussing again the second slide.

This is a bioequivalence study which showed that there is a 30-40 percent increase in exposure when comparing three times 1 mg versus one 3 mg dose. It is always consistent if you give three of 1 mg. It will give you the range of 30-40

percent exposure. In addition to that, this is not bioequivalence. The 90 percent confidence interval--CI stands for confidence interval--is outside the 80-125 percent.

One of several reasons of lack of bioequivalence study between the two dosage form strengths is that there is high variability in the data. This graph is not shown in your package but it is shown in the advisory committee package. This is an additional graph. The study was conducted in replicates at each dose from 1 mg to 6 mg using a combination of 1 mg and 3 mg strengths. In terms of dose exposure responsive, this slide shows a trend for increasing exposure with dose. However, examining the individual data reveals high intra-subject variability in this study. For example, in one subject the AUC at 1 mg dose was 45 and 3,870 micro unit/minute/mL in the first and second dosing period respectively. At the 6 mg dose in another subject the AUC was 934 and 8,020 micro unit/minute/mL in the first and second dosing period respectively.

Therefore, from these observations we can conclude that doubling the dose does not always result in the doubling exposure. In addition, the exposure is not always consistent and predictable within the same subject following the same dose.

I am going back to one slide which I skipped. Overall, you can see the variability that the percent coefficient variation, which is percent CV, is over 100 percent. In almost all the studies that we have reviewed the percent CV is greater than 50 percent. For example, this is the study that we just discussed, 1012. At the 1 mg dose the AUC ranges from 45 to 3,240 micro unit/minute/mL at the dose of 1-6 mg. Within each dose level there is a wide range of exposure. The same trend for the intra-subject variability as seen from the replicate dosing that we just discussed has been observed as well.

Cross study variability analysis is as follows. This slide shows cross study variability in the data for AUC following inhaled and subcutaneous administration. The data is for

coefficient variation from different studies. The figure represents the difference in percent CV for inhaled and subcutaneous insulin. Each data point represents one study. Careful examination of this figure reveals that most of the data points are above zero, as you see here, averaging approximately 30 percent. This indicates that the inter-subject variability in inhaled insulin is higher than subcutaneous. In other words, the coefficient of variation for inhaled insulin is approximately 20-30 percent higher than subcutaneous insulin. This is the difference between inhaled and subcutaneous and each data set represents one study. These are clinical pharmacology studies.

So, the overall summary, the pathology of the lung, as well as other exogenous factors play a critical role in the absorption, delivery and systemic exposure of inhaled insulin. The following conditions affect the exposure to inhaled insulin: Smoking--we have seen that it increases by 2- to 5-fold. The exposure after passive

smoking or secondary smoke decreases by 20-30 percent. For COPD the exposure increases by 50 percent. In asthma it decreases by 20-30 percent. For rhinovirus infection there were little changes in exposure. However, the data should be interpreted carefully as there were only four subjects in the saline group, the control group.

My last slide here is related to the variability and interchangeability. Inhaled insulin can be highly variable. The percent CV or coefficient of variation can be between 50 percent to 100 percent. There is lack of dosage form equivalency between 1 mg and 3 mg. Thank you.

Clinical Pulmonary Safety

DR. SEYMOUR: Good afternoon. My name is Sally Seymour and I am a medical officer in the Division of Pulmonary and Allergy Drug Products. The focus of my presentation this morning--actually, this afternoon now, is the pulmonary safety of Pfizer's human recombinant inhaled insulin, Exubera.

So, why is pulmonary safety a concern?

First, Exubera is administered via inhalation and typically inhalation medications are for the treatment of pulmonary diseases such as asthma or COPD. However, the lungs are an attractive route of administration for non-pulmonary medications, and this proposed drug product contains a drug substance and some excipients which are novel to the inhalation route.

Inhaled insulin is proposed for chronic administration, which raises a concern for the long-term effects of inhaled insulin. Insulin is a polypeptide which has been associated with an immune response and the lungs are immunologically reactive. Both of these issues raise the concern of potential immune response in the lung. Finally, insulin has growth promoting properties which raise the concern for tissue growth, including tumors. Because of these concerns the agency urged the applicant to assess the long-term pulmonary safety of inhaled insulin.

I will begin with an overview of the pulmonary safety database so you have an

understanding of the source of the pulmonary safety data I will describe. The presentation of the safety data will begin with the respiratory adverse events, followed by the effects of inhaled insulin on pulmonary function as measured by pulmonary function tests, specifically the forced expiratory volume in one second, FEV1, and the carbon dioxide defusing capacity, DLco. Next I will present the results for the thoracic imaging, which includes chest x-rays and high resolution computer tomography, or HRCT. Then I will specifically address the pulmonary safety in subjects with underlying lung disease, such as asthma and COPD. Finally, I will summarize my conclusions.

Let me first describe the source of the data I will be presenting. The applicant's controlled Phase 2 and 3 clinical studies were pooled to assess the pulmonary safety of inhaled insulin. We didn't suspect that the pulmonary safety profile on inhaled insulin would be different in type 1 and type 2 diabetes but subjects with type 2 diabetes tend to be older and

have more concomitant disease. Since subjects with type 1 diabetes have less concomitant disease, we thought they may be more sensitive to detect subtle changes in lung function. Thus, the data were analyzed separately for type 1 and type 2 diabetes.

This table displays the six individual studies that contribute to the pulmonary safety data set in subjects with type 1 diabetes. It should be noted that all the studies were open-label in design, which may be associated with potential bias. You will notice that there is one ongoing study, study 1022, in the above table. Ideally, the data utilized for the primary analysis are from completed clinical studies, however, study 1022 is a two-year study that provides information about the long-term safety of inhaled insulin in type 1 diabetes, and without this study the completed studies only provide six-month data. Thus, the data from study 1022 were included in the analysis of pulmonary safety. Note that in the pooled data set there are approximately 700 subjects in each treatment group.

These are the studies which contribute to the pulmonary safety database in subjects with type 2 diabetes. The comparative groups in the type 2 studies could include subcutaneous insulin or oral agents. Again you should notice that one ongoing study, study 1029, contributes to the pulmonary safety database in type 2 diabetes. Study 1029 is important because it provides two-year HRCT data.

Unlike the type 1 diabetes pulmonary safety database, the type 2 diabetes pulmonary safety database includes a completed two-year study, study 101-102. In the pooled data set there are over 1,000 total subjects in each treatment group.

Now let's begin with the respiratory adverse events. Before reviewing the respiratory serious adverse events I would like to note that there were no deaths due to respiratory adverse events. This table displays the respiratory serious adverse events, or SAEs. This table is for type 2 diabetes only. There was only one respiratory serious adverse event in type 1

diabetes which was reported in an interim report for ongoing study 1022. The SAE was for pneumonitis and was reported in the comparator group.

You will notice that there were more respiratory serious adverse events in the inhaled insulin group than in the comparator groups, 18 in the inhaled insulin group versus 12 in the comparator groups. Most of the SAEs were reported only once. Asthma and the related term bronchospasm are highlighted in blue, while bronchitis terms are in pink. These terms were highlighted because these serious adverse events were reported more than once, and were reported more frequently in the inhaled insulin group than in the comparator groups.

This figure displays the respiratory adverse events reported in greater than one percent of the subjects with type 1 diabetes. Overall, the most common respiratory adverse event was respiratory tract infection which was reported in a similar percentage of subjects. The respiratory

adverse event with the biggest difference subject groups was cough. In type 1 diabetes cough adverse events were reported in 28 percent of subjects versus 8 percent of the comparator group.

You will notice that there are other respiratory adverse events which were more common in the inhaled insulin group, such as pharyngitis, rhinitis, sinusitis and dyspnea. In general these respiratory adverse event reports were similar for type 2 diabetes, and the data and figure for that information is in your briefing package. It should be noted that the database is reasonable to assess common adverse events associated with inhaled insulin use, but the database is not likely sufficient to assess uncommon adverse events.

There were few respiratory adverse events associated with discontinuation but almost all of them were in the inhaled insulin group. Cough, followed by dyspnea and asthma were the most common respiratory adverse events that were associated with discontinuation.

As I mentioned earlier, cough was the

respiratory adverse event which was more common in the inhaled insulin group and, to further assess cough, the applicant collected additional information and utilized a cough questionnaire in several of the recent studies. The cough data suggests the majority of the cough adverse events were mild in severity. The duration of cough was longer in the inhaled insulin group than in the comparator group, with the mean duration of cough of 5.4 to 7.7 weeks in the inhaled insulin group and 3.4 to 5.1 weeks in the comparator group.

A cough questionnaire, consisting of six questions, was administered in several of the most recent clinical studies. The cough questionnaire data suggest that in general the cough was non-productive and mild in severity. In addition, cough was frequently noted within seconds to minutes of study medication administration. However, up to a third of subjects reported no relationship of cough to inhaled insulin dosing.

The data I present to you today come from the controlled Phase 2 and 3 clinical studies.

However, a review of all of the clinical studies, including the uncontrolled extension studies, found several respiratory adverse events worth noting. Remember that insulin is associated with growth factor properties and there is a concern about tumor formation.

There were five lung neoplasms noted in the applicant's clinical studies, four of which were malignant. Three of the malignant lung neoplasms were noted in the controlled studies, while one case was noted in an extension study. Of the three malignant lung neoplasms noted in the controlled studies, two were in the inhaled insulin group and one was in the comparator group. In one of the cases in the inhaled insulin group the subject had a preexisting nodule which enlarged and was later identified as adenocarcinoma. So, based upon the available data there does not appear to be a definitive signal for lung cancer.

Recall that insulin is a polypeptide and associated with immune response so other respiratory adverse events, such as pulmonary

fibrosis, pleural effusion and sarcoidosis, were of interest. There were three cases of pulmonary fibrosis reported. However, the diagnosis was not clear in two of the cases. Although there were many cases of pleural effusion noted, most cases were confounded by other potential causes. Finally, two cases of sarcoidosis were noted in the inhaled insulin group in the extension studies. Overall, it is difficult to draw definitive conclusions about any of these adverse events since many of these cases were reported in the uncontrolled extension studies.

Now let's discuss the effect of inhaled insulin on pulmonary function. The applicant performed pulmonary function tests in each of the controlled Phase 2 and 3 studies. Pulmonary function tests were typically performed at baseline and end-of-study and at various intervals during the studies. Pulmonary function test measurements included spirometry, lung volumes and diffusing capacity.

The pulmonary function tests in each of

the controlled Phase 2 and 3 studies were reviewed individually. Typically, for efficacy we review the individual studies for independent substantiation. For safety we often look at the pooled data, and the PFT data I will discuss come from the pooled controlled Phase 2 and 3 data sets which I described earlier.

The applicant obtained pulmonary function tests following withdrawal of inhaled insulin in a few studies to attempt to assess the reversal of the effects of inhaled insulin, and I will briefly describe that data. Finally, the applicant has conducted long-term extension studies in which some subjects received inhaled insulin up to seven years. These studies were not controlled and I will not present the results. However, the pulmonary function tests in the extension studies are addressed in the briefing package.

I will focus my presentation on the effect of inhaled insulin on FEV1 and DLco. The FEV1 is a measure of airflow obstruction and is used clinically to diagnose and monitor diseases such as

asthma and COPD. The DLco is used clinically to assess gas exchange and the integrity of the pulmonary capillary bed. DLco can be helpful to diagnose diseases that alter gas exchange, such as interstitial lung disease and emphysema. Additional pulmonary function tests were analyzed and the results are included in the briefing package.

This figure displays the mean change from baseline FEV1 in type 1 diabetes for up to two years of exposure, and of all the slides I will show you this is one of the most important slides. The blue solid line is the inhaled insulin group, while the pink dotted line is the comparator group. Recall that ongoing study 1022 provided the only data for exposure to study medication beyond 24 weeks in type 1 diabetes.

As you can see, both treatment groups demonstrated a decline from baseline FEV1 throughout the treatment period. However, the inhaled insulin group consistently had a numerically greater decline than the comparator

group. The decline was noted at 12 weeks, which was the first on-treatment pulmonary function test measurement in most of the studies. Note that the treatment difference between groups does not progress after the first year of treatment.

At two years of exposure we have pulmonary function test available for approximately 200 subjects in each treatment group, and at two years the inhaled insulin group had approximately a 40 mL numerically greater decline from baseline than the comparator group. You may wonder if the treatment group difference of 40 mL is clinically significant. Epidemiologic studies show that healthy adult, non-smoking subjects typically have a decline in FEV1 anywhere from 15-30 mL per year. Assuming no further progression, a one time treatment group difference of 40 mL seems unlikely to be clinically significant. For type 2 diabetes the results for FEV1 are similar and the figure is not going to be presented here today. However, the information is in the briefing package.

The applicant has attempted to assess if

there is reversal of this effect on FEV1 after discontinuation of inhaled insulin in type 1 diabetes. The applicant proposes that two studies support that the effect of inhaled insulin on FEV1 is reversible, study 1027 and study 111. Study 1027 was a controlled study of 12 weeks on inhaled insulin, followed by 12 weeks off inhaled insulin, during which pulmonary function tests were measured in both periods. A limitation of the study is that the subjects only had 12 weeks of exposure to study medication and the question of reversibility following longer exposure is not addressed by this study. In addition, the results of study 1027, which I will show you on the next slide, are not convincing.

Study 111 was an uncontrolled extension study which was later amended to include a randomized segment during which inhaled insulin was withdrawn or continued. The problem with study 111 is that the population in the extension study is self-selected and not truly a random population. In addition, subjects had varying lengths of

exposure to inhaled insulin prior to withdrawal. Thus, the available data are not conclusive about the reversal of the effects of inhaled insulin on FEV1 in type 1 diabetes.

These are the results for the mean change from baseline FEV1 in study 1027. On the left half of the slide is the 12-week on-treatment period and on the right half of the slide is the discontinuation phase data. Recall from the previous figure that for the pooled FEV1 data an effect was first noted at 12 weeks. Notice that in this study a difference between treatment groups is noted within the first few weeks of exposure. However, the treatment group difference fluctuates during the first 12 weeks and by the end of the 12-week treatment period there is very little difference between the treatment groups. Following discontinuation the FEV1 in the inhaled insulin group increases, however, this is not sustained and by the end of the discontinuation phase there is little treatment group difference. Essentially, the results are not much different at the end of

the two phases so it is difficult to argue a reversal of an effect when there was very little effect noted at 12 weeks. The data from study 1027 are not convincing regarding the reversal of the effect of inhaled insulin on FEV1 in type 1 diabetes.

Recall that the effect of inhaled insulin on FEV1 was similar in type 1 and type 2 diabetes. We just discussed the reversal of the effect in type 1 diabetes in which the available data are not conclusive. What about reversal of the effect in type 2 diabetes?

In type 2 diabetes the applicant proposes that two studies support that the effect of inhaled insulin on FEV1 is reversible, study 101-102 and study 111. Study 111 was described earlier and design issues limit the utility of that data. Study 101-102 was originally two 24-week studies that were extended to a 104-week treatment period and combined. Pulmonary function tests were performed throughout the treatment period, as well as at six and 12 weeks following discontinuation of

inhaled insulin. This study provides data for type 2 diabetes after long term or two years of exposure. As I will show you on the next slide, the data suggests some reversal of the effect of inhaled insulin on FEV1.

This figure displays the results for the mean change from baseline FEV1 in study 101-102 in which 104 weeks of treatment are followed by 12 weeks off inhaled insulin. The period off inhaled insulin is indicated on the horizontal axis by plus 6 and plus 12. At week 104 the inhaled insulin group had a numerically greater decline than the comparator group by about 40 mL. During the discontinuation phase the change from baseline for each treatment group becomes similar. At 6-12 weeks of discontinuation the treatment groups have a similar decline from baseline FEV1, suggesting that there is a potential reversal of the effect of inhaled insulin on FEV1. Unlike type 1 diabetes and type 2 diabetes, we have data after long-term exposure to inhaled insulin which suggests reversal of the effect of inhaled insulin on FEV1.

So to summarize, inhaled insulin is associated with a numerically greater decline from baseline FEV1 than comparator. The effect of inhaled insulin on FEV1 appears to occur within the first few weeks of exposure. The treatment group difference of approximately 40 mL does not appear to progress out to two years. The data regarding the reversal of the effect of inhaled insulin on FEV1 is not conclusive in type 1 diabetes. However, the data from one study suggest that there is some reversal of effect of inhaled insulin on FEV1 in type 2 diabetes after two years of exposure.

Now let's discuss the effect of inhaled insulin on the DLco. This figure displays the mean change from baseline DLco in type 1 diabetes for up to two years of exposure. This is another one of the important figures that I will show you. Recall that ongoing study 1022 provides the only data beyond 24 weeks. As you can see, both treatment groups had a decline from baseline DLco throughout the treatment period. However, the inhaled insulin

group consistently had a numerically greater decline than the comparator group. The decline was noted at 12 weeks. Note that the difference between treatment groups does not appear to progress after the first six months of treatment. After two years the inhaled insulin group had approximately 0.5-0.6 mL/min/mmHg greater decline from baseline DLco than the comparator group.

You may wonder if the treatment group difference of 0.5-0.6 mL/min/mmHg is clinically significant. There is less epidemiologic data about natural decline of DLco with time. The mean baseline DLco was 27 mL/min/mmHg. Thus, a difference of 0.5-0.6 is approximately a difference of two percent. Assuming no further progression, a one time treatment group difference of two percent seems unlikely to be clinically significant.

When we discussed the FEV1 for the pooled data I only presented the data for type 1 diabetes because the results were similar between type 1 and type 2. For DLco the story is a little different for type 1 and type 2 diabetes. This figure

displays the mean change from baseline DLco in type 2 diabetes for up to two years of exposure. Notice that although the difference between the treatment groups fluctuates throughout the treatment period, at the end of the two years there is essentially no difference between the treatment groups. The largest numerical unadjusted difference between treatment groups occurred at wee 65, in which the difference was approximately 0.5 mL/min/mmHg.

As mentioned earlier, we did not expect a difference in effect in type 1 and type 2 diabetes, however, there is a difference for DLco. In type 1 there is a 0.5-0.6 difference between treatment groups at two years and in type 2 there is some effect during the treatment period but no difference was noted at two years. It may be that subjects with type 1 diabetes have less concomitant disease and may be more sensitive to the subtle changes in lung function.

In terms of the reversal of the effect of inhaled insulin on DLco, the studies to assess the reversal of effect were described earlier. Study

1027 provides controlled pulmonary function test data for 12 weeks on inhaled insulin and 12 weeks off inhaled insulin in type 1 diabetes.

This figure displays the mean change from baseline DLco in study 1027 and, as before, on the left top of the slide is the 12-week on-treatment period and on the right side of the slide is the discontinuation phase data. I showed you on the previous figure for the pooled DLco data that an effect was first noted at 12 weeks. Notice in this study a difference between treatment groups is noted within the first few weeks of exposure. At the end of the 12-week treatment period the inhaled insulin group had a larger decline from baseline DLco than comparator group, and the difference between treatment groups at week 12 is approximately 0.6 mL/min/mmHg.

Following discontinuation of inhaled insulin the difference between treatment groups decreases, suggesting that there is a reversal of the effect of inhaled insulin on DLco. However, it should be noted that study 1027 provides data after

only 12 weeks of exposure and the question of the reversal of effect on DLco following longer exposure in type 1 diabetes is not addressed by this study.

Although the pulmonary function test data in type 2 diabetes did not show a treatment group difference after two years of exposure, data regarding the reversal of the effect of inhaled insulin on DLco in type 2 diabetes is still of interest, primarily because there were treatment group differences favoring the comparator at different time points during the study.

Study 101-102 provides data following discontinuation of inhaled insulin after two years of treatment. This figure displays the results for the mean change from baseline DLco in study 101-102. At week 104 there was essentially no difference between treatment groups, and after 6-12 weeks of discontinuation both treatment groups demonstrated a slight increase in DLco.

So to summarize the effects of inhaled insulin on DLco, type 1 diabetes, inhaled insulin

is associated with a greater decline from baseline DLco than the comparator. An effect of inhaled insulin was noted within the first few weeks of exposure and the treatment group difference of approximately 0.5-0.6 mL/min/mmHg did not progress out to two years of exposure. Data from one study suggests reversal of the effect of inhaled insulin on DLco after short-term, 12-week exposure.

In type 2 diabetes both treatment groups demonstrated a similar decline from baseline DLco at two years. The maximum unadjusted treatment group difference was approximately 0.5 mL/min/mmHg during the treatment period.

Now that we have addressed the pulmonary function tests, briefly let me mention the results of the thoracic imaging. Chest x-rays were performed at screening and in study in most of the applicant's clinical studies. Chest x-rays were performed and read locally at radiology departments available to the clinical sites, and there were no specific measures to blind the radiologists to the treatment group. Changes from baseline were

reported and more significant changes from baseline were noted in the inhaled insulin group than in the comparator group.

Notable changes on chest x-ray are listed on this slide, and the applicant has provided follow-up information in subjects with these changes. In general, the follow-up information for the imaging was negative.

To assess the effects of inhaled insulin on the lung parenchyma the agency requested two-year HRCT data for 50 subjects on inhaled insulin and 50 subjects on comparator. The applicant obtained HRCT scans on a subset of patients in ongoing study 1029 at baseline, one year and two years. The HRCT scans were performed at local sites using a standardized algorithm, and subsequently interpreted at a central reading site by a third-party radiologist blinded to the treatment group. The two-year HRCT data on approximately 70 subjects in each treatment group did not suggest an increased abnormal HRCT finding associated with the inhaled insulin group.

The effects of inhaled insulin in subjects with underlying lung disease, such as asthma or COPD, are of particular interest for several reasons. First, the diseases are quite common and it is likely that many patients with asthma or COPD could receive inhaled insulin. Second, patients with asthma or COPD typically have pulmonary symptoms and abnormal pulmonary function. Thus, the pulmonary safety of inhaled insulin in subjects with asthma of COPD should be established. Finally, the variability in pulmonary function associated with asthma or COPD raises the concern that the presence of these diseases could affect the pharmacokinetics and pharmacodynamics and, thus, the efficacy and safety of inhaled insulin.

The pulmonary safety data I discussed up to this point are from the applicant's pooled Phase 2/3 studies in which subjects with a history of underlying lung diseases, such as asthma or COPD, could have enrolled. However, in these studies the diagnostic criteria for asthma and COPD were not prospectively specified. Thus, the agency

requested the applicant conduct prospectively designed studies to assess the safety and efficacy of inhaled insulin in subjects with asthma and COPD.

The applicant's two prospectively designed studies, study 1028 and study 1030, are ongoing studies to assess the safety and efficacy of inhaled insulin in subjects with prospectively defined asthma or COPD. Study 1028 is an ongoing 12-month study in 250 subjects with asthma, and 139 subjects have been randomized and 52-week pulmonary function test data is available for 27 subjects, 10 in the inhaled group and 17 in the comparator group.

Study 1030 is an ongoing 12-month study in 250 subjects with COPD, and 67 subjects have been randomized and 52-week pulmonary function test data is available for only 30 subjects, 15 in each treatment group. I will present the pulmonary safety data from the interim study reports for both of these studies.

In study 1028 139 subjects have been

treated out of a goal of 250. In general, cough and response tract infection were more common in the inhaled insulin group. Three discontinuations due to respiratory adverse events were noted, all in the inhaled insulin group, two for asthma exacerbation and one for respiratory disorder. Investigator-reported asthma adverse events were common in the comparator group. However, protocol-defined non-severe asthma exacerbation and severe asthma exacerbation were more common in the inhaled insulin group.

The asthma control questionnaire is a six-question patient-reported outcome instrument designed to assess asthma control. The questions are on a scale of 0-6, with higher scores reflecting poor control. At 52 weeks in the inhaled insulin group there was a slight increase, a mean of 0.17 in the overall score, suggesting a slight worsening of control. In the comparator group there was a slight decrease, mean of 0.48, in the overall score, suggesting a slight improvement in asthma control. Again note that there is a

limited amount of data at 52 weeks.

This figure displays the interim results for the mean change in baseline in post-bronchodilator FEV1 in study 1028. Again note that PFT data is only available for 27 subjects at 52 weeks. Notice that after week 29 there is a separation in the treatment groups. At week 52 the inhaled insulin group had approximately 160 mL numerically greater decline from baseline FEV1 than the comparator group. You should note that this scale is different compared to the previous figures, and this is a much larger difference between treatment groups than what was seen in the pooled data in type 1 and type 2 diabetes.

For DLco, after week 39 there is a separation in the treatment groups. At week 52 the inhaled insulin group had approximately 1.2 mL/min/mmHg greater decline from baseline DLco than the comparator group and, as with the previous figure, you should note that this scale is different for this figure and there is a much greater difference between the treatment groups

than what was seen in the pooled data in type 1 and type 2 diabetes.

For study 1030, which is the study in subjects with COPD, the interim results show the following: Cough and dyspnea were more common in the inhaled insulin group. There has been one discontinuation due to a respiratory adverse event which occurred in the inhaled insulin group, and that was a COPD exacerbation. The protocol-defined non-severe and severe COPD exacerbations were more common in the inhaled insulin group.

This figure displays the interim results for the mean change from baseline in post-bronchodilator FEV1 in study 1030. Again note that PFT data are available for only 30 subjects at 52 weeks, 15 in each treatment group. Similar to the figures for study 1028, the scale is different from earlier figures and at 52 weeks the change from baseline FEV1 is approximately 30 mL numerically greater in the inhaled insulin group than in the comparator.

This figure displays the interim results

for the mean change from baseline in post-bronchodilator DLco in study 1030. The data shows that at 52 weeks the inhaled insulin group actually increases from baseline, and this is difficult to interpret.

So to summarize the control data in subjects with underlying lung disease, there is limited controlled pulmonary function test data and PFT data is available for only 30 subjects with COPD out to 52 weeks, and 27 subjects with asthma out to 52 weeks. The PFT data in study 1028 shows a separation of treatment groups for FEV1 and DLco after week 39 favoring the comparator. The PFT data in study 1030 suggests a 30 mL greater decline in post-bronchodilator FEV1 in the inhaled insulin group at 52 weeks, and inhaled insulin increase in post-bronchodilator DLco at 52 weeks, which is inconsistent and difficult to interpret.

I have shown you that we have two-year pulmonary safety data from controlled studies and the data show the following: Inhaled insulin is associated with an increase in respiratory adverse

events, particularly cough. Other respiratory adverse events more common with inhaled insulin include rhinitis, pharyngitis, sinusitis, dyspnea and respiratory disorder.

The pulmonary function test data shows that inhaled insulin is associated with a greater decline from baseline FEV1 and DLco than the comparator and the effect appears to occur within the first few weeks of exposure, and the data suggest that the effect is not progressive out to two years. There is some evidence of reversal of the effect but this is not conclusive in type 1 diabetes. There is no increase in abnormal HRCT findings out to two years of treatment. Finally, there is limited control data in asthma and COPD.

With that in mind, I have presented an overview of the pulmonary safety data and would pose the following questions which we will discuss this afternoon.

DR. WOOLF: Thank you very much. In view of the time, there is going to be a slight rearrangement in the schedule. We are going to

break for lunch. We will then have the public discussion at 1:30--open public hearing, excuse me, at 1:30. Then we will follow that with the questions to the FDA and then discuss the questions that have been proposed to the committee. For those of us who are sitting at the table, we have had reserved a long table in the back of the restaurant for us to have lunch. We will be back here promptly at 1:30, please.

[Whereupon, at 12:30 p.m., the proceedings were recessed for lunch, to reconvene at 1:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

Open Public Hearing

DR. WOOLF: Will everybody take their seats, please? This is the open public hearing portion of these proceedings. For the record, both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your oral or written statement to advise the committee of any financial relationship that you may have with the sponsor, its products and, if known, its direct competitor. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the

beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Our first speaker is Marc Sandberg. Will you come to a microphone, please?

DR. SANDBERG: Good afternoon, and thank you for allowing me to address the committee. My name is Marc Sandberg and I am an endocrinologist and I serve as the medical director for the Diabetes Health Center at Hunterdon Medical Center in New Jersey. I would like to disclose to the committee that I have no current financial relationship with the drug sponsor and I am here presenting my own comments at my own expense. I do have experience working on the early clinical studies of Exubera when I was a staff physician at the Ochsner Clinic in New Orleans from 1996 to 2001.

The following are considerations that

should be examined as the committee considers providing guidance to the FDA on the approval of Exubera. My perspective is based on ten years of experience as a clinical endocrinologist and, as I noted, my early involvement in the clinical trials.

Inhaled insulin will need to be given for many years, and we do not know the long-term effects on lung tissue. People with major organ system disease, a history of epilepsy, asthma and other respiratory diseases, as well as smokers, were excluded from the main Exubera studies. These patients are included in a large segment of our diabetic population who may be considered for inhaled insulin. Some Exubera studies have shown that there are changes in lung function. Further, we know that diseases, for example asthma, respiratory infections, smoking and chronic obstructive pulmonary disease, may change lung function. How will this affect inhaled insulin absorption and will there be related variations in absorption across patient types based on their baseline lung function?

Inhaled insulin device requires a very different administration technique than syringes. Many patients may be excluded because of this, especially since, unlike syringes, another person cannot administer the inhaled insulin for the patient. The administration needs to be exact, and we need to be sure that the patients are getting the right dose. When we give eight units of insulin to a patient injected subcutaneously we have good confidence in what dose we are delivering.

For an individual dose, patients have to give themselves on shot of insulin with the appropriate number of insulin units injected. Inhaled insulin may have a limited dose selection and may require multiple administrations to achieve different dose selections. This is a paradigm change in how patients administer insulin from both a mechanism as well as a dose perspective.

We also know that inhaled insulin only addresses the bolus insulin, not the basal insulin. Quite possibly patients will be adding inhaled

insulin to continued use of syringes. Many patients will not be able to throw away their insulin needles. Conversely, we may see patients who are currently managed by one shot of a long-acting insulin per day moving to multiple puffs on inhaled insulin per day.

Finally, the consideration of a new form for the delivery of insulin needs to be fully evaluated so that the diabetes community is able to best determine the right patients that might benefit from inhaled insulin. We will also need the resources to provide education and guidance to ensure that our patients are able to use this new tool correctly. Thank you for your consideration.

Committee Discussion

DR. WOOLF: Thank you. Is there anyone else who would like to come forward and make a statement? Seeing none, I think we will return to the FDA's presentation and questions from the committee for members of the FDA.

Karen, you alluded to the fact that this form of insulin administration failed to deliver

the kind of control that was present in the DCCT. Outside of DCCT, have there ever been clinical trials that have been able to replicate that kind of experience in a more typical physician or clinic setting? In other words, is that a standard that is impossible to reach in clinical practice?

DR. MAHONEY: It has been difficult to replicate those kinds of results in general clinical trials of diabetes drug products.

DR. WATTS: Along those same lines, I think that the climate has changed since DCCT and what you show us may be an unrealistic expectation for other reasons. Patients who are well controlled may be reluctant to give up their control and participate in a clinical trial, so there may be a selection bias if patients, for good reasons, are not able to reach goal, and goal is simply that; it is goal. Not everyone is able to reach goal.

So, I think that while getting everybody to go below an HbA1c of less than 7 is great, in DCCT that was the average value. Presumably the

data were normally distributed so half the patients in the DCCT were above 7.

DR. FOLLMANN: I would just like to amplify on that. I mean, to me, 107 is a fine study and the idea that they should be held to this higher standard of achieving DCCT targets--you know, if you designed such a study where you had a substantial fraction achieving DCCT targets you might question whether the study is generalizable if, in fact, you have to undergo, you know, tremendous effort to achieve that tight control. It might not be so practical when it is used widely. So, you know, the other side of that is that maybe it wouldn't be as generalizable. So, I don't have that concern about the 107.

DR. STOLLER: I have a question for Dr. Seymour. In reviewing the conversations between the agency and the sponsor with regard to criteria for studies in COPD and asthma, conversations about a 100 patient sample in each as I have noted in conversations over time, my question actually regards the rare events, for example lung cancer,

in which, as you pointed out, there were five neoplasms, one hematoma, four malignancies, and I think we heard from the sponsor two that predated initiation of drug--there is some discordance there. My question is, from the agency's point of view, have you given thought to what kind of study sizes would be necessary to discriminate reasonably? We also heard of Kaiser data modeled on incidence of lung cancer over time and that this signal did not exceed the expected rate in the population, given the prevalence of smoking, etc. So, my question is do you have some sense of the kinds of studies that would be necessary to elucidate lung cancer risk going forward, and what would be the power, if you will, and the size of those studies? Because, you know, the sense is that there is a little bit of a signal. There are conflicting data as to how potent that signal is and what it means, and it would be helpful to know what homework has gone on around that fact.

DR. SEYMOUR: We haven't done any formal power calculations to determine how many subjects

they may need to determine a signal for lung cancer. I don't know if there are any other comments from the committee but we haven't done any formal power calculation for it.

DR. FOLLMANN: I would think it would require huge studies to try and detect an effect on lung cancer so, you know, realistically I don't see how we would see it unless we get many years of experience with it.

DR. WOOLF: Nelson?

DR. WATTS: I have two questions fro Sam. One was on the issue of passive smoking. I believe you presented that data. If I remember right, it was volunteers who were exposed to two hours of passive smoke. Do you know if there are data on more prolonged or more chronic passive smoke exposure? I am thinking not in relation to diabetes but I saw a patient recently who doesn't smoke but her job, as a server, exposes her to second-hand smoke six or seven hours a day, five or six days a week.

DR. AL HABET: I can't remember exactly

how the study was designed but the sponsor can maybe answer that. But I know that the subjects involved were non-smokers. I can't exactly remember what is the definition of a non-smoker but my understanding from the overall program is that non-smokers are defined as subjects who are not smoking for at least six months. The sponsor is welcome to address that question as well.

DR. WOOLF: Can one of the sponsor's people address the issue?

DR. JACKSON: I will ask Dr. Fontain if he can tell us the conditions in that study. Just to go back to one of the previous questions where we were talking about the size of study that might be needed to follow-up the potential for lung cancer, we can answer that following Dr. Fontain's presentation, if you would like us to do so, Chairman.

DR. FONTAIN: We did conduct a study to examine the effects of passive cigarette smoke exposure on the pharmacokinetics of inhaled insulin. The study was designed in non-smokers, as

has been summarized. The way we set up the study is that subjects were exposed for two hours at a level of smoke that we measured using atmospheric nicotine concentrations. Then we administered the inhaled insulin dose and measured pharmacokinetic data out to six hours post dose. We did not conduct a study to examine the effects of chronic passive cigarette smoke exposure, but you could expect that for a drug that is titrated it would just titrate to any alterations to availability that might be related to long-term chronic effects, and it would just be part of the day-to-day titration.

DR. WATTS: I am not sure that really answers the question. That may be the data you have but it seems to me that there are a lot of people who are exposed to passive smoke for longer periods than two hours, and exposed repeatedly, and it sounds as though we don't know whether there are changes in pharmacokinetics there or not.

DR. JACKSON: We haven't done that. We have done one single experiment but, as I

understand it--I wasn't actually in the smoke chamber myself but it was a very hefty dose of smoke that was in there that was sufficient to make at least Dr. Fontain cough when he went in. But certainly not for seven hours and certainly not every day a week. This was an initial attempt to explore one particular phenomenon, and we did that and I think we did it quite successfully.

DR. STOLLER: You had some information about the cancer?

DR. JACKSON: yes, I would like simply to get Dr. Reynolds, who will explain. I showed in my opening slide set a particular study which is a 12-year cohort study. Dr. Reynolds is an expert in this area.

DR. ORLOFF: Can I just make a comment, please, Paul?

DR. WOOLF: Yes.

DR. ORLOFF: On the smoking issue to follow-up Dr. Watts, I think to the extent that the effects of smoke, be it active or passive--active smoking versus passive smoking were exactly in the

opposite direction with regard to the impacts on pharmacokinetic bioavailability of the drug. I would think that the real question is at what point does passive smoke exposure become like smoking. So, Dr. Watts, I think, is asking at what point are you exposed to so much passive smoke that you need to actually worry about the potential for overexposure to inhaled insulin? I know you don't know the answer but I wanted to clarify the question.

DR. REYNOLDS: May I have risk management 24, please? This is a proposed study, a 12-year study to look at lung cancer mortality between inhaled insulin-treated and non-inhaled insulin-treated patients. We plan to use the THIN data set which is a prospective medical records data set in the United Kingdom. It currently includes about 57,000 patients with diabetes, and it routinely collects information on demographics, drug exposure, diagnoses and links to vital status.

In addition to the routinely collected data, we are proposing to add an electronic module

which will collect smoking information. Current smoking, obviously, is routinely recorded but we would like to have past history, pack-years smoked, etc. So, that will be added to this electronic database.

We have evaluated more than 15 databases in the U.S. and Europe and this is the only one where we will be able to collect sufficient smoking data to look at the issue of lung cancer. Based on 57,000 patients, we calculate that we should be able to detect a relative risk of 1.5.

DR. FOLLMANN: So you are going to compare the 57,000 patients to the handful who have received inhaled insulin and look at the difference in rates there? That is the basic design of the study?

DR. REYNOLDS: Over the course of the 12 years, it is to compare those exposed to inhaled insulin to those not exposed. We expect that over 12 years of exposure we would have sufficient INH exposure to look at this.

DR. FOLLMANN: Right, but you would have

more smokers, obviously, in the patients who aren't getting INH.

DR. REYNOLDS: Yes, and we would adjust for that. We would stratify and adjust for it in multivariate models.

DR. WOOLF: Dr. Schuster?

DR. SCHUSTER: My question is for Dr. Al Habet. The big issue I have is this coefficient of variation and the variability of the inhaled insulin versus the subcutaneous. Can you just comment, because it looked like an overall kind of generalized statement that the variability is 20-30 percent greater with the inhaled insulin than with the subcutaneous. Is that value arrived at by taking the mean, or was that kind of looking at the completion of the study? I guess the point I am trying to get at is that is one of the downsides of subcutaneous, that there is so much intra-patient variability. Is this inhaled insulin actually by the time the person is really good at using it? Are we able to diminish that variability?

DR. AL HABET: We don't have really data

to say that if the patient continued using it, it would show a lower variability. The sponsor, however, conducted a study. It is called self-administration study, and it trained the patients very well at least two days before and continued even twice before administration of the actual medication, and this showed very good data that when you train the patient very well the coefficient of variation is similar to subcutaneous. That is in our review. The sponsor is welcome to address that.

DR. JACKSON: Yes, thank you. I believe I heard you say that patient variability is the key and I think we completely agree with that with a titrated drug. Particularly with a relatively low therapeutic ratio, it is within patient variability that actually tells us about what is going to happen in the clinic. Bear in mind that over 3,500 patients took inhaled insulin in our clinical program and we showed equivalence in terms of HbA1c control and, critically hypoglycemia, and hypoglycemia I think is where people are most

concerned.

I would just like to ask Dr. Fontain if he could explain a little bit more about the variability and put it in context because we do have data that shows that variability does improve even in our experimental situation. Bear in mind that what we are comparing in our experimental situation and our clinical pharmacology is a completely new entity against subcutaneous insulin that is being injected by people who know how to do it, and have known how to do it for a very long time.

DR. FONTAIN: So, it is important to recognize exactly which variability parameter you are referring to, and for a product like inhaled insulin that is meant to be titrated within an individual, the intra-subject variability is the most important parameter to look at.

What I would like to do is show you a slide that has already been shown in the main presentation, slide 16, please. This is from our dose proportionality study. This shows each and

every value for the 21 subjects that were enrolled in this particular study.

Just to remind you, this was an incomplete block design. Each subject received three of five possible dose levels. So, what you see is the area under the curve value for each subject at each dose that they received. You will notice that for some doses there appears to be just a single value. This is where we have overlapping area under the curve value--so good reproducibility or good intra-subject variability. What you see for each and every subject is that with an increase in dose you do see an increase in exposure. You will note that there are a couple of subjects that appear to have a lower exposure at a higher dose.

Also of interest in this particular study is that these are fairly small dose increments compared to what you will see in the published literature using subcutaneous insulin. Typically in a dose proportionality study, first of all, they won't have a replicate design and then, secondly, they will have larger dose increments or doubling

of dose, 6, 12, 24 units, something to that extent. So, even with the very fine increment that we have here, especially going from 1, 2 and 3 mg, we see that we have this increasing exposure.

Can I have slide CP-124, please? What we have done here is we have taken the mean of the replicate values in each subject. Again, what you see is that each subject can expect to see an increase in exposure with increase in dose. I have highlighted a couple of subjects, six subjects, with orange boxes. These are subjects that received 2 mg and 3 mg doses. This is the finest increment in this particular study. You will see that in each of these cases subjects do see, and can expect to see an increase in the area under the curve with each increase in dose, even at this fine increment.

So, this study does a couple of things for us. It tells us that we have good reproducibility within a subject, and also that we can titrate effectively with dose.

DR. AL HABET: Let me follow-up on this,

please. I do not have the privilege to provide individual data, but I have to quote two subjects as examples for this same study, which is 1012, the dose proportionality study. Look at the replicates, as I already stated in my presentation. For example, in one subject the AUC at the 1 mg dose was 45 and 3,870 macro unit/min/mL in the first and second dosing period respectively. At the 6 mg dose in another subject the AUC was 934 and 6,2020 micro unit/min/mL in the first and second dosing period respectively. This is an example of the replicate study, and there are quite a few replicate dosing in other studies as well showing the same trend. That is just for the record.

DR. WATTS: I wanted to follow-up on that with the other question that I had for Dr. Al Habet, and the sponsor may be able to answer this. In this study of intra-individual variability how much training and how long had the subjects used the drug? And, it is unbelievable to me that that much variability would be biology or pharmacology,

but more on the downside errors in delivery that the patient didn't use it correctly one of those times.

DR. AL HABET: I don't remember if in this particular study they had training but I suspect the patients already had training in this particular dose proportionality study. But the study that I referred to, called self-administration study, they had extensive training, but this is not one of them.

DR. WATTS: I think it is important to know where the learning curve peaks out, and how much of this variability is due to learning and how much is due to the intrinsic nature of the drug and the delivery system, to get some sense of when we start playing with doses for individual patients where are we really using the drug and where are we just dealing with a patient who is learning how to take it.

DR. WOOLF: Can the sponsor answer that? Where in the learning process were these studies done?

DR. JACKSON: I can get Dr. Heise to answer as he was part of this study.

DR. HEISE: Yes, the subjects in this study were trained as already described this morning. So, they had two training sessions with empty blisters and then they participated in the study with the real insulin.

DR. WATTS: So, they were not regular users of the drug at the time the study was done, which is probably not relevant at all to the variability that we would expect to see, but what is the learning curve? Is it two weeks? Four weeks? Two months?

DR. HEISE: Let me make just one comment to the figures for the individual data. I mean, in this study only inhaled insulin was employed but I did studies with the variability of subcutaneous insulin preparations and I can tell you that on an individual basis you see a broad variability which is well within the range you quoted.

DR. FOLLMANN: I guess what I am struggling with is that the point was made that

there was maybe a 20 percent difference between injected insulin and inhaled insulin in coefficient of variation. We would like to know does that really matter. In terms of the HbA1c and hypoglycemic episodes it doesn't really seem to matter. Would it matter in terms of something less far downstream than HbA1c? So, I was wondering if people have looked at between group comparisons, say, of fasting plasma glucose, not the average value but the variability, and does inhaled insulin have more variability for that parameter than injected insulin.

DR. WOOLF: Do you have an answer?

DR. AL HABET: I defer this question to the clinical team.

DR. WOOLF: Does the sponsor have anybody who might be able to answer that using other markers of diabetes control, other than HbA1c?

DR. JACKSON: We have not looked at the variability of fasting plasma glucose. All we can say is that we have looked at something which is pretty close downstream, which is hypoglycemia, and

we don't see a difference between the reporting of that and the reporting on subcutaneous insulin control.

DR. WOOLF: Dr. Caprio?

DR. CAPRIO: I just want to remind you that subcutaneous insulin is not better. The absorption and variability is huge with subcutaneous injection and varies by sites. So, it is very important to keep that in mind.

DR. AL HABET: I agree.

DR. WOOLF: Dr. Watts?

DR. WATTS: A question for Dr. Seymour about cough, my guess is that the first dose or two of inhaled anything is going to provoke a cough response, and knowing clinical trials, any time something happens that gets carried over and counted at the end of the trial. Also, if someone is inhaling something, my guess is they are more likely to report or be queried about cough and respiratory symptoms than someone who is not using the inhaler. As the data have been presented and analyzed by you, is there any way to dissect out

not only how much of the cough difference between the inhaled and subcutaneous insulin groups is related to the actual inhalation of the dose? Is there sort of a learning curve for avoiding the cough? Do they cough as much after six months of use as they did during the first week?

DR. SEYMOUR: I will answer your question and then the sponsor can jump in if they have additional information. In a few of the studies the sponsor utilized a cough questionnaire which is really, in my opinion, the better data for the cough. It was administered to subjects who reported cough as adverse events in whom another alternative explanation for the cough was not assigned to the cough. In that data it does look as if time goes on there is less reporting of cough. So, it may be associated early on with the initial use of it and as time goes on there is less report of it.

DR. CAPRIO: How intense is the cough? Would it subside by drinking water?

DR. SEYMOUR: I don't know if we have

information about water but the severity of the cough was, for the most part, mild in terms of the grading of the severity. There were some moderate; very few severe. But in terms of the cough questionnaire data, the majority of the cough was graded as mild.

DR. WOOLF: Can I ask the sponsor was there, in essence, a learning curve for cough? As patients got more used to administration, did the rate of cough or the severity of cough diminish?

DR. JACKSON: It certainly did diminish; the reporting diminished. I think Table 78 in the briefing document indicates that. It has been pointed out to me by the person who actually ran the studies with the questionnaire that much of the cough that was reported, or classified as cough, is essentially throat clearing.

DR. WOOLF: Dr. Schuster?

DR. SCHUSTER: I have a question for Dr. Seymour. Really it is just a point of clarification for my knowledge. You showed two slides towards the end of your discussion on the change from

baseline DLco in type 1. It is labeled the pooled Phase 2 and Phase 3 studies, and the following one was in type 2 for DLco. When I go back and I look at the briefing document the data looks a little bit different than these two slides. I am assuming it was just a different cohort. I am particularly referring to pages 167 and 169. The reason I ask this is because the DLco appears to continue to decline, whereas in the two slides you showed it really levels off.

DR. SEYMOUR: Pages 167 and 169 of my briefing document?

DR. SCHUSTER: Of whatever briefing document I have.

DR. SEYMOUR: I think that is the sponsor's briefing package so they may be able to answer that. I am not sure what data they have on that page, but I can tell you that the data we have is from pooled controlled Phase 2/3 data sets and it may be slightly different, depending on what the sponsor has in their package.

DR. SCHUSTER: I mean, the only reason I

think it is a point of discussion is that this levels off so nicely very quickly into therapy, and this stuff in the briefing document appears to kind of continue to decline.

DR. SEYMOUR: On page 167 in the briefing document for the sponsor? They can jump in but on page 167 it is actually for an extension study for DLco so that is actually an uncontrolled extension of some of their earlier Phase 2 studies, and it is definitely a different data set from what I showed you. This is for an extension period in which there was no control arm and what I showed you was all data for the controlled studies. Does that help?

DR. SCHUSTER: Yes, it helps.

DR. SEYMOUR: It is a different data set.

DR. WOOLF: It was pointed out to me that perhaps the sponsor didn't have enough time to answer the coefficient of variability question. Do you feel that you need to have more information, or are you satisfied?

DR. FONTAIN: I would just like to refer

you to Table 23 on page 53 in your briefing document. This gets to the point that you were making about the training. In any studies where we did have replicate administration of the drug over time, with more than three replicates we were able to peal away earlier treatments and then assess variability in the earlier treatment periods versus the later treatment periods. Our best example, again from the 1027, we see variability decreases pretty nicely over time, and that is within six doses. That trends down very close to what we see historically for subcutaneous.

DR. WOOLF: Dr. King?

DR. KING: I want to change the conversation a little. I want to go to the inhalation technique issues again. One of the things that concerned me, mainly I guess because I am biased by a prior bias which is that the alveolar space availability seems incredible. I wonder what data actually support that 40 percent of the inhaled drug actually gets to the alveolar space.

A corollary to that is the question about if you switched and swallowed this agent, does it alter your blood glucose?

DR. WOOLF: Clearly that is a question for the sponsor and not the FDA.

DR. JACKSON: I will ask Dr. Finch to attempt to answer that.

DR. FINCH: Yes, put that on the screen, please. This is a slide that Dr. Cropp showed during her presentation this morning. It shows how we have apportioned the deposition of inhaled insulin following the bolus inhalation. What she has described here is that approximately 30 percent of the blister content is contained in the blister and/or device upon actuation. Then, data from an early gamma scintigraphy study that was conducted with an early exploratory version of the powder, but in the relevant particle size, demonstrated that there was approximately 20 percent of the blister contents deposited in the oral pharynx. That table is contained within your briefing document. Thus, the remainder which is, as you can

see, 50 percent passes the oral pharynx. The number is for 10 percent tracheal/bronchial and 40 percent alveolar spaces are just approximations. We do not have any data that shows specifically what the deposition fractions are in those two compartments. But that is based on what we expect from the literature in terms of deposition of particles of that size.

DR. KING: I thought it was just the opposite so that 40 percent would be deposited in the tracheal/bronchial region and 10 percent in the alveolar space.

DR. FINCH: Those are based on approximate values that are obtained for dry powder, aerosol particles of the size. Perhaps I could ask Dr. Joe Brain to comment further on particle deposition.

DR. BRAIN: I think one thing to keep in mind is the particular breathing pattern that is used, and I think you are absolutely right. For particles of this size for sort of normal breathing, without a breath hold, you might experience greater deposition centrally but, again,

the instructions to the patient are for a slow inspiration from FRC, followed by this 5-second breath hold, and that is a pattern which is in the direction of improving deposition in the deep lung.

I agree with what Dr. Finch has said. We don't know that it is all in the alveoli. Some may be in very small airways. Those distances are very small. We do know, for example, for aerosols, like tobacco smoke that are less than one micron, deep lung deposition can be as high as 60 percent or 70 percent with a deep, slow breath hold. So, I think the pattern of anatomic deposition depends on the breathing pattern that is used, and this device, this particle and this breathing pattern have been designed to optimize deep lung deposition.

DR. WOOLF: Before we open this to general discussion I would like to make sure that the panel has no further questions of the FDA at the moment. So, does anybody have any more questions of the FDA? Otherwise, we have time for an open discussion.

MS. SCHELL: My question is in regards to

the delivery device as well. I am assuming that all the people that were involved in the study were able to take a deep breath. Was there any measurement done? As we have seen with inhalers, some people don't inspire deep enough to even take an inhaler. Were there any measurements done to see if they, first of all, could take a deep enough breath to get the air into their lungs?

DR. JACKSON: All patients, prior to going into the clinical studies, were required to undergo lung function testing and only those who passed the criteria that we set were able to go in.

MS. SCHELL: Further to that question then, with the labeling are there going to be instructions to have that test done prior to see if that person can take a deep breath, or are you just going to take the practitioner's word that they can take a deep breath?

DR. JACKSON: We certainly would anticipate trying to make as much as we can in the label with what we did in the clinical program. What we did in the clinical program is to do

spirometry before patients took a dose.

DR. STOLLER: My question is a follow-on to Dr. King's and Dr. Brain's conversation. Given what we would expect to be variability and what we understand to be variability in the alveolar deposition as a function of inspiratory pattern, can you comment on the impact of inspiratory pattern on both the pharmacodynamics, pharmacokinetics and postprandial glucose values? Obviously, it is ideal to breathe from FRC and we would all aspire to that for our patients using bronchodilators of various sorts, but we all recognize in the effectiveness arena that there is tremendous variability within patients in their use of inhalers. Recognizing that metered-dose inhalers are not what is being proposed here, nonetheless, extrapolating that experience predicts that there would be variability within individuals of their technique in using an inhaler with insulin cloud. I would imagine that you have accrued data that speaks to that and it would be important to know.

DR. JACKSON: Well, we have data from the clinical program, of course, and the variability doesn't seem to be different from subcutaneous insulin in terms of diabetic control and hypoglycemia. We have some data from inspiratory rate studies and Dr. Fontain can give you that.

DR. FONTAIN: Can I have CP-57, please? We did conduct two studies that examined the effects of inhalation rate on pharmacokinetics of inhaled insulin. In general, what we saw was that with decreases in inhalation rate you see a decrease in both AUC and Cmax, and when you decrease inhalation rate you cause an increase in AUC and Cmax.

I will show you the approximately values that we had. So, we conducted our 217/011 study. The target inhalation rates are in the second column from the left. They were 10, 25 and greater than 35 L/min. We measured the actual inhalation rates. They were 14.5, 29.3 and 40.3. The 25 L/min is what we approximate to be our standard inhalation maneuver. It is a normal inhalation.

Again, what you see with the lower inhalation rate is an increase in AUC and Cmax and with the faster inhalation rates you see a decrease in AUC and Cmax. With more moderate changes in inhalation rate that we saw in the 019 study, going from 14.1 L/min to 8.8 L/min you see very little change.

This is essentially a design characteristic of the product. The product has a flow restriction that prevents extremely high rates of inhalation and, because of the range of particle sizes in the product, it is relatively insensitive to modest changes in inhalation rate. We defined our standard inhalation maneuver which is that the subject exhales normally; fires the device; inhales with a full inspiration; holds their breath for 5 seconds and then exhales normally. This is a maneuver that we specified for all of our clinical pharmacology studies, and that was emphasized in instructions in our Phase 3 studies. Again, typical reproducibility in our clin. pharm. is very good relative to sub-q, and we don't see any differences in either hypoglycemic episodes or

efficacy in our Phase 3 studies.

DR. JACKSON: You are right, the key is to make sure the patients are well trained and do the same inhalation move each time.

DR. WOOLF: Would it be incorrect to say that consistency is more important than the magnitude of the inspiration? As long as you are relatively constant you can titrate the dose to that person's effort?

DR. JACKSON: Absolutely.

DR. WOOLF: Nelson?

DR. WATTS: A follow-up to Ms. Schell's question about the pre-enrollment screening, do you know how many subjects who might have otherwise qualified for the trial were excluded because of the spirometry results or other problems in being able to use the device?

DR. JACKSON: Yes, we have looked at that. Dr. Riese?

DR. RIESE: In terms of lung function screening, screening fail rate for all causes, and it varied between studies, was between 30-40

percent. Again, the screening fail rate--the percentage of people who screened and failed because of PFT abnormalities was, on average--there was variability was about a quarter of that. So, our estimation is approximately 10 percent of patients screen-failed because of PFTs.

DR. WOOLF: As I hear this discussion go on, it has become clear to me that perhaps the most important thing of the implementation of this program is training of the patient--first screening the patient and then training the patient. I am really not clear from what I heard this morning how this is going to be carried out effectively in a primary care physician's office when they are seeing patients every 10-15 minutes. Are you going to limit this only to endocrinologists and diabetologists, which obviously limits the market?

DR. JACKSON: Well, screening would be the usual examination one would expect for a patient with diabetes but, in addition, the spirometry in order to ascertain the lung function and then, as with any patient who goes on to insulin, training

has to be given with it is subcutaneous insulin or whether it is inhaled insulin. I don't personally know whether it takes any longer to be trained to take inhaled insulin than it takes to be trained to inject. I wouldn't imagine it is very much different.

DR. WOOLF: Well, I am not necessarily sure how many diabetologists would do routine spirometry; certainly some primary care docs. would. But it is a whole different paradigm. In point of fact, many patients get their training at a centralized site of the diabetes center or with diabetes nurse practitioners and not in the individual practitioner's office. Most of us have been trained in the use of sub-q insulin since time immemorial, but those of us who are out for 40 years have not been trained in this technique. So, when a patient calls and says I have a problem with my device and you have never used that device, and if you say, "well, call the diabetes educator whom you saw," it is not going to work very well.

DR. JACKSON: We have a call center to

deal with problems with the devices and that operates 24 hours a day, or will do.

DR. WOOLF: Dr. King?

DR. KING: My question relates to the device. How do you care for this device? How do you clean it? What do you do with it? I assume all the cloud of stuff is going to collect in the device. What do you do?

DR. JACKSON: Yes, there are procedures that patients have to undertake, and they will be trained in those. Mr. Spavins will be able to give us some of those details.

MR. SPAVINS: May I preview 166 please? Put that on the main, please. I would like to put a picture up of the device and try to go through it by component to answer your questions with regard to care.

As indicated, there is a base unit that generates the ambient compressed air; the blister which is inserted, as you saw in the video this morning. Again, this is taken apart, of course. That little unit in the middle called the insulin

release unit, that is the aerosolization part of the device. Basically, the compressed air generates a venturi that then makes a standing cloud. I am just giving a little background to get to your point with regard to cleaning.

As I mentioned this morning, the chamber, of course, of 200 mL is designed for a fraction of a typical inhalation. There is the mouthpiece, which is where the patient inspires. The patients do have cleaning instructions. The cleaning instructions are to clean the chamber once a week. We will supply two chambers so that if one is waiting to be cleaned there is still another chamber there. We have done extensive cleaning studies, and in the misuse case we have data that supports much longer studies than the one week, but the one week will be the instructed cleaning technique. It is basically mild soap and water and air dried. We have checked out many variations of the types of soaps and different types of cleaning issues along with that.

The insulin release unit is the one unit

that does need to be replaced every two weeks. Its life is limited by the environmental conditions that might be present. We have extensive studies of a variety of temperatures and humidity that support the release unit to a minimum of two weeks. The patient is instructed to change that out.

Are there other types of questions I could answer? Basically, it is clean once a week and change out the insulin release unit every two weeks.

DR. AL HABET: I have a quick question as a follow-up on this cleaning situation. In the replicate design did the patient clean the device or did they use a new device. The observation in the PK study is that it seems to me very consistent that the first dose is lower in exposure than the second dose. Can you answer that, please?

DR. FONTAIN: In all the clinical pharmacology studies, since it was only, you know, six doses or so that were administered, we never cleaned the chamber between doses.

DR. AL HABET: So, this may explain why

the second dose has higher exposure in the same patient.

DR. JACKSON: No. No, that wouldn't explain it at all. We do repetitive in vitro testing of our devices and we would see if there was a fall-off in the important constituents, like AD or FPD, over that period of time. Because there isn't, that is why we allow for the chamber to be cleaned once a week at minimum and for the injector to be replaced every two weeks. I don't know if you wanted to add anything to that, James.

MR. SPAVINS: Just very quickly, we have checked for so-called priming effects that you may be alluding to. The device has no priming effects.

DR. WOOLF: Dr. Calhoun?

DR. CALHOUN: My question is for Dr. Seymour and perhaps for the sponsor as well. Were you able to ascertain in your analysis of the data whether there were any other special populations in the unspecified lung disease that might also have altered pharmacokinetics or pharmacodynamics or altered safety profile? Then I have a follow-on to

this.

DR. SEYMOUR: No, we did look at the change in pulmonary function, FEV1 and DLco, and looked at the standard subgroups which are race and age and sex, and we didn't see any clear pattern for that.

DR. CALHOUN: It is curious that the area under the curve goes in different directions in two different common obstructive lung diseases, COPD and asthma. And, the concern that I have with respect to asthma is that it is not just an obstructive disease but it is a variable obstructive disease. So, the degree to which variation in lung function may alter absorption could actually play a big role in the glucose control of patients who have concomitant asthma and diabetes.

DR. SEYMOUR: I think we share the same concern about variations in lung function with asthma, and that is one of the reasons we asked the sponsor to do a dedicated study in that population, and also to look at efficacy in that population to

see if variation in lung function is going to affect that.

DR. CALHOUN: Were there enough patients with other unspecified underlying lung diseases in the data set for any of the FDA people to sort out particular signals that we should be paying attention to in terms of concomitant disease?

DR. SEYMOUR: I didn't look at other concomitant diseases. Maybe the sponsor has looked at subgroups of patients with other concomitant lung diseases in the overall safety database.

DR. JACKSON: No, we didn't allow patients with significant lung disease, apart from the defined asthma and COPD that you know about, to go into our studies.

I would just like to go back to asthma because we do have a database. We have two databases as described by Dr. Seymour, one prospective and one retrospective, and we have been able to look at those to see, well, what is the difference between the subcutaneous insulin and inhaled insulin in terms of diabetic control, and

the HbA1c between the two groups doesn't look different. Well, what is the difference between the two groups in terms of hypoglycemia? It doesn't look different. We know with asthma, that when subjects have lower FEV1's they have lower exposure to inhaled insulin. When we increase the FEV1 with albuterol the exposure increases. In fact, it is normalized. We can show you that data if you want to see it.

DR. CALHOUN: Well, the issue is that asthma is an episodic disease and one might not expect to see that variation in glucose control manifest in alteration of hemoglobin A1c which is fairly far downstream.

DR. JACKSON: Hypoglycemia, I would think, would readily show itself if--

DR. CALHOUN: On the rebound side as you are increasing insulin.

DR. JACKSON: We instructed all the patients in our studies who were taking inhalers or albuterol or bronchodilators to take the bronchodilators prior to taking inhaled insulin,

and that is something that I believe they should continue to do.

DR. WOOLF: Dr. Caprio?

DR. CAPRIO: Yes, I wonder if there is any data on glucose profiling and what is the peak of postprandial glucose during the inhaled insulin.

DR. JACKSON: I will ask Dr. Krasner to show us some of that data.

DR. KRASNER: We measured postprandial glucose in two ways. If I could preview slide E-161, please? This is data from study 107 that you heard about earlier. This is home monitored glucose profile data obtained from patients in the last week of the study. You will see mean postprandial glucose levels after each meal of the day pictured here. We do not see significant differences between inhaled and subcutaneous treatment groups.

We also designed this study to look specifically at postprandial glucose control. If we could go to main-37, please? This is data we saw this morning in Dr. Cropp's presentation. This

was a prospective pharmacodynamic study in which postprandial glucose was measured in inhaled-treated versus subcutaneous insulin-treated patients for six months. This was done doing a solid standard test meal under controlled conditions. As you can see, over time there is no difference in postprandial glucose control from baseline in either treatment group, and the treatment groups are quite comparable over time as well.

DR. WATTS: I would like to get back to the device question I raised this morning that has not been answered to my satisfaction, and that is about device failure. I have written it down so if the answer comes I will be able to understand it. So, if someone uses this device three times a day for a year, how many, if any, device failures would be expected? Would the device failures be obvious at the time so they could take an alternate dose? And, are they encouraged--and I don't know the price of the device and whether it would be affordable for patients to be encouraged to have a

backup device?

DR. JACKSON: I will ask James Spavins to try and answer that.

MR. SPAVINS: Hopefully, I can be more responsive to the question. There are a couple of questions there. The device itself is designed and engineered so that for one year it will perform as expected. It has a one-year use life. This morning you were asking about have we seen sort of unexpected failures in the clinic, and I did mention that that was the case, and that is part of the learning curve of development. I did mention that since we have seen that, as I mentioned, we have exactly 1/600 devices that we have seen an additional problem with in the last set of devices that went out. So, that would be the expected failure rate, and that would be over the clinical trials running now for at least a year. So, that is our current knowledge of what the failure rate would be at this stage. There was a second question?

DR. WATTS: Was the device failure obvious

to the patient?

MR. SPAVINS: Again, the design allows a cloud visualization so that any kind of failure--certainly the patient would not be able to see the cloud and would certainly have an inkling. Of course, the call centers would be there for any kind of questions they would have with regard to any differences they may detect, whatever they may be. We use that planned return program to generate the types of questions and the types of inquiries that patients have had about the device, not failures but the usual questions about how to work with it; what if I didn't change my transjector out, and that sort of thing.

DR. WATTS: The last question was about backup. It sounds like if it is not going to fail you don't need a backup. What is likely to be the cost of the device? Is it nominal? Is it large? And, are patients going to be encouraged to have a backup device?

DR. JACKSON: I am not aware of the exact intentions as regards providing more than one

device. I am aware that there should be at least one spare chamber and spare devices that are used to puncture the blister. Another backup system that would definitely be there is the 24-hour call system so that a patient whose device has failed can get one very, very quickly. I am not aware in our clinical program that any device failure led to any problem with any patient.

DR. WATTS: For a drug that is being dosed three times a day, 24 hours later to get a replacement is going to miss three doses.

DR. JACKSON: It is a 24-hour call center.

DR. WOOLF: Dr. Stoller?

DR. STOLLER: My question concerns the substantial burden of undiagnosed COPD in the population and the impact of some of the studies, in particular 1022, on understanding with regard to that population. Dr. Riese commented, if I understood it, I gather that spirometry was an entry criterion and that given that screen failure on spirometric criteria, there were no patients with abnormal lung function participating in 1022.

So, the results of that speak to really normal lungs as opposed to 1030 and 1028 which were asthma and COPD respectively. Is that correct? In other words, there is no insight from 1022 on the effectiveness, if you will, of using inhaled insulin in a population with unsuspected but present chronic obstructive pulmonary disease. Is that correct?

DR. JACKSON: Patients in study 1022, like in all our studies, were unable to go into the study with an FEV1 of 70 percent, or down to 70 percent of predicted. I will ask Dr. Riese if there is anything else he wants to add.

DR. RIESE: Sure. As part of our analysis of the effect of inhaled insulin in patients with underlying lung disease, we did retrospectively examine our controlled Phase 2/3 database looking for patients with a history of asthma and who met the Gold criteria for mild and moderate COPD.

Could I have P-468, please? So, in our controlled Phase 2/3 database we identified what we are calling the integrated underlying lung disease

cohort. What this accounted for, in the first line are the number of subjects that were enrolled at the time of this data collection, which was before the interim analysis so the number of subjects enrolled in 1028 and 1030 are a bit less than what Dr. Seymour showed this afternoon. We combined those with subjects we found in our controlled Phase 2/3 database with a history of asthma and who met the Gold criteria for mild to moderate COPD. So, we have an integrated cohort of subjects with asthma, 70 and 79 with INH and comparator respectively, and 80 and 78 INH and comparator in COPD. I would be happy to review any of this data if the committee thought it would be useful in terms of hemoglobin A1c, hypoglycemic event rates, changes in lung function. We do have this cohort that hasn't been presented yet.

DR. STOLLER: Let me make sure I understand what you mean by retrospectively defined COPD. Clarify that for me because I think a lot of the value of this information has to do with what you mean by that.

DR. RIESE: What we mean by that is they were retrospectively identified by the Gold criteria so they had to have an FEV1 over FVC of less than 70 percent and then they were mild. If the FEV1 was greater than 80 percent and moderate; if it was between 50-80--

DR. STOLLER: I understand the Gold criteria. The question is was this a baseline measurement that was retrospectively identified--

DR. RIESE: Correct.

DR. STOLLER: --or was it a downstream spirometric measure at some point during the course of therapy?

DR. RIESE: This was baseline measurements.

DR. STOLLER: Then I think it would be perhaps relevant to see the data about changing FEV1 in what you identified as the integrated data set, yes.

DR. RIESE: Sure. Could we have P-480, please? This is our integrated cohort combined with the retrospective diagnosis of asthma, as well

as the number of people enrolled in 1028. As you can see, the pattern of change in this integrated cohort is very similar to what we see in the normal population. That is, we have small early treatment group differences in FEV1, fully apparent at the first baseline visit at week 12, whereupon they plateau out for the remainder of the treatment phase.

I will note that in 109 and 112 in this integrated cohort the number of subjects is quite small because most of the Phase 2/3 database was based on three- to six-month studies.

Could we have the next slide, please, looking at the COPD cohort? We see a very similar pattern with the COPD cohort in this integrated underlying disease patient population. Small treatment group differences, fully manifest at the first post-baseline visit and then a plateau for the remainder phase. One advantage to using this cohort is that we have a cohort from our controlled Phase 2/3 trials that had neither disorder.

Could we have P-482, please? Again, this

is neither disorder and we see a very similar pattern of change. Obviously, the number of patients is much larger. Small treatment group differences, early onset, plateau after that.

DR. WOOLF: Dr. Schuster?

DR. SCHUSTER: My question actually goes back to the postprandial glucose data that you presented. I guess my question has to do with the noninferiority claim and why you weren't looking for superiority given the profile of how insulin levels go up and how blood glucose lowers, and the difference between the inhaled insulin versus the subcutaneous. Wouldn't you have anticipated actually better postprandial blood glucoses with the inhaled insulin versus the subcutaneous based on its relative quicker onset?

Just a second part of that question is, you know, how were you titrating these levels up? Were we less aggressive than we should have been, and what were our goals given that that data was shown in the intensively controlled group?

DR. JACKSON: For the noninferiority

question, we set up our studies based on noninferiority to insulin in terms of HbA1c control.

DR. SCHUSTER: Okay.

DR. JACKSON: The postprandial glucose question, yes, we would expect to see good control of postprandial glucose and I will ask Dr. Krasner if he can show us the data that we do have on that.

DR. ORLOFF: Dr. Woolf, while they are preparing to answer--sponsor, I am going to let you give you answer; I just want to add a point of clarification from the FDA standpoint. The effects on postprandial glucose profiles of one or another, we will say, prandial insulin may well be relative clinically in the choice of a particular insulin for a particular patient, and that may certainly be on the basis of the judgment of the doctor or of the patient or both. However, the Food and Drug Administration, Division of Metabolic and Endocrine Drug Products doesn't label drugs with regard to specific claims of efficacy related to effects on postprandial glucose. The valid surrogate for

diabetes control and efficacy of hypoglycemic agents that we accept is hemoglobin A1c. But please show the data.

[Laughter]

DR. KRASNER: E-157, please. This is data from a liquid meal challenge test from three of our studies, two are in type 1 diabetes and the third is in insulin-treated type 2 diabetes. What we are looking at here are two-hour postprandial glucose concentrations performed as part of these liquid meal challenge tests. Across these three studies you will see that postprandial glucose concentration is comparable between inhaled and subcutaneous insulin groups.

The study I showed you earlier was a prospective pharmacodynamic study where the various variables which can affect postprandial glucose control, such as baseline glucose levels, were controlled and standardized. Furthermore, as you can see from these postprandial concentrations, these doses were not optimized for this liquid challenge test. In the study I showed you earlier

the doses were assigned to patients based on a dose-finding study in which it was documented that those doses were appropriate for the test meal.

So, regardless of how we look at it, we do not see excessive postprandial glycemia in patients with inhaled insulin.

DR. SCHUSTER: I guess the reason I even asked that question is we are going to be asked in a question how we feel this drug will do with intensive therapy, and one of the markers we would use as a clinician would actually be the postprandial blood glucose reading in terms of titration. Your point is well taken.

DR. WOOLF: Sort of following up a little bit on this, and I am sure it is similar in the six inches of material that is in front of me, but how often were patients in any of these trials titrated in terms of dose in both arms of the study, the sub-q and inhaled insulin? And, what were the guidelines to the clinician to titrate?

DR. KRASNER: Doses were titrated at study visits by the physician. Also, the patients were

allowed to self-titrate in 1 mg increments based on pre-prandial home glucose readings. The targets in the protocols for the studies were pre-prandial glucose readings within standard target ranges.

DR. WOOLF: I would like to shift gears for just a second. Someone showed us a slide earlier this morning on patient preferences, sub-q versus the device, which overwhelmingly favored the device. I would submit that is probably a biased sample since these were people who were already in the trial and wanted to participate in the trial or they would have dropped out. Have you had a chance to take device-naive diabetics who might be candidates for this, describe the device and ask them whether they would prefer to switch to the device or continue taking their insulin as they have been?

DR. JACKSON: I am not sure if I fully understand the question.

DR. WOOLF: You told us that the patients overwhelmingly preferred the device.

DR. JACKSON: Yes.

DR. WOOLF: These are people who were participating in the clinical trial--

DR. JACKSON: Correct.

DR. WOOLF: --and may not be representative of the population as a whole. So, have you taken a device-naive group of people who have not seen this device, described its benefits and said given the potential benefits, would you be willing to diminish the use of your needles and move on to the device?

DR. JACKSON: We haven't done that specific study. The study nearest to it is the one that was shown to you by Dr. Cefalu, the Freemantle study, asking patients whether they would accept insulin inhalation and more of them said they would if they had an inhaler than if they had an injection. We haven't asked ones who have been injecting and not used an inhaler.

MS. KILLION: As a patient representative, I think I might have some insight on that particular point. I think the use of insulin without a needle--the siren call of that is almost

irresistible, aside from the question of practicality, efficacy, etc. It is huge. My concern, following up on Dr. King's and Dr. Watts' questions, has to do more with the practicality side of it as somebody who would be using the device. I guess my first comment would be that I think it is highly regrettable that you didn't bring a device with you that we could actually see because I think that would have been very helpful. So, that is just thrown out there.

But I guess my concern is I would like to know how big the device is as far as its portability for use every day. I will follow-up later after you answer that.

DR. JACKSON: It is about this big, and then you pull it out and it is about this big.

MS. KILLION: Is it about as big as that?

DR. JACKSON: No, no, it is much smaller than that.

MS. KILLION: It is smaller in diameter perhaps?

DR. JACKSON: About like that.

MS. KILLION: Because it is a little easier to carry a pen than a device.

DR. JACKSON: It is bigger than a pen.

MS. KILLION: But smaller than a bread box! I guess my other question--I mean, the concerns I have about size are that, you know, it might be easy for me as someone who carries a purse to carry a device around with me every day; a little more difficult for male patients who don't carry such things around, but whatever.

As far as the failure of the device, I have four meters. I mean, people living with this disease, they are not going to have one device so I would encourage you in your pricing of the device, if this were to be approved, to consider that people would be getting multiple devices because that is only reasonable.

My biggest concern goes back to a training issue because this is truly novel, and it is my experience dealing with other diabetics throughout the country that the level of training that they receive, regardless of whatever their regimen is,

varies dramatically, from non-existent to intense, and their follow-up with their doctors and their doctors being knowledgeable enough to make adjustments to help them learn how to make adjustments also varies dramatically. So, the training commitment for this kind of regimen, especially at the outset, would be enormous. I know you are saying, well, we are going to train but I just would like to have a little bit more of a sense of what you are doing to jump-start this because I think the training, especially in the initial run, would be an intense commitment on the sponsor's part.

DR. JACKSON: So, we are working on training materials at the moment. Our intent is to really train the healthcare givers. As a pharmaceutical company it is very difficult for us to train patients.

MS. KILLION: I realize the stratification in there but that is the commitment I am talking about, the people who will be training the actual patients.

DR. JACKSON: Absolutely, and in our clinical programs we took people off and gave them training sessions. It wasn't just somebody visiting for a short while--I am talking about the healthcare givers, taking them for intensive training prior to them giving the drug to individual patients. I would anticipate that is the sort of thing that we would need to do, from what you are saying.

DR. WOOLF: Have you thought about training the pharmacist?

DR. JACKSON: The pharmacist would be trained as part of the normal process of introducing a product like this.

DR. WOOLF: Dr. Calhoun?

DR. CALHOUN: Thank you. Are there preclinical or animal data on the effects of inhaled insulin, obviously a biologically active peptide, on airway epithelium, cell biology, inflammatory markers? I understand you have a human program in process and you are not prepared to talk about what results you may or may not have

at this time, but do you have any preclinical data that might give us some sense of where the effects might be leading us?

DR. JACKSON: Bearing in mind this is insulin given by the respiratory route, by inhalation, yes, that was our primary focus preclinically. I will ask Dr. Finch if he will come and show us some very pretty slides on that. Interestingly, two of the main species were rat and monkey. Rat is an obligate nose breather so we do have very good data on what happens with powder that is actually deposited in the nasal cavities as well.

DR. FINCH: Yes, as Dr. Jackson mentioned, we did conduct inhalation toxicology studies in two species, in rats and in monkeys. We conducted studies for up to six months in duration and they were multiple dose studies. The maximum doses that we delivered to the animals were based on the induction of hypoglycemia with, of course, human insulin being biologically active in the animals as well.

We conducted post-exposure measurements of insulin and glucose levels to confirm that we were, in fact, delivering biologically active insulin to the systemic distribution and, thus, since absorption is most probably predominant in the alveolar spaces, we were delivering to the entire respiratory tract.

If I could have NC-23 up on the main screen, please, what I would like to do is to talk with you a little bit about how we did the studies and what the results were, using this slide in which we schematically illustrate, on the upper left, the rat respiratory tract, and then some pairs of representative photo micrographs. In each case in the photo micrographs we have control animals depicted at the left and high dose insulin-exposed animals at the right.

Again as I mentioned, the animals were exposed for a period of six months, up to six months in the longest-term study. That is about a quarter of the rat's life span and that is a sufficient duration of time to detect histological

changes to inhalation exposures that are known to be pulmonary toxicants.

The other thing I will mention is that we also did some respiratory function tests, both looking at respiration parameters and also some functional parameters, in both the rat and monkey studies. I will further comment that although I am showing you rat here, we did a very comparable sampling strategy for the monkeys as well.

So, beginning with the nasal cavity, as you can see illustrated there, we took four sections through the nose from near the tip back towards the oral pharynx. At bottom left you can see essentially four rows of the pairs of photo micrographs for levels 1, 2, 3 and 4. What you can see is the very delicate structure there of the nasal turbinates and there was no effect of inhalation exposure of inhaled insulin or the excipients alone in this particular anatomic location and, as Dr. Jackson mentioned, with the rate being an obligate nose breather we would expect there was relatively high deposition of the

inhaled aerosol in this particular anatomic compartment of the animals.

Proceeding on down, we took sections from the larynx. Those are depicted at the lower right, again control on the left and high dose on the right. Again, there was no effect of exposure on any structural change and, in particular, there were no changes in the epithelium as a result of exposure.

Then, getting on to the lung, as you can see at right--I will note that we did also sample trachea but I am not showing that here. We also sampled bronchial lymph nodes and I am not showing that here either, but in both of those tissue spaces there was no effect of exposure.

On the lung slide, on top is a relatively low magnification, a medium magnification down below that. You can see the terminal bronchioles branching out into alveolar ducts and then out into the alveolar spaces of the lung. There was no effect of exposure. There was no evidence of any inflammatory changes. There were no degenerative

changes. There were no proliferative changes. In fact, we also did on lung sections from both rat and monkey at six-month exposure a quantitative cell proliferation staining technique, in which we were able to count proliferating cells and calculate cell proliferation indices. There was no effect of exposure versus control animals in that.

I think the other thing I will say is that our inhaled insulin powder, as you have heard, contains recombinant human insulin and it contains excipients as well. Those are excipients that are freely soluble in water. They are of a relatively low molecular weight and, thus, as we expected, we did not see any evidence for any accumulation of any of the material either in the lung or anywhere within the respiratory tract.

DR. WOOLF: Dr. King?

DR. KING: If you look at the two bottom higher magnification ones, maybe this is an aging effect but it looks like there is a loss of alveoli in the high dose compared to control.

DR. FINCH: It is difficult to tell

looking at a single section without being able to be at the microscope. I think we are looking certainly at a terminal bronchiole that is branching. There might be some additional alveolar ducts branching there. I will note that the pathologist in his or her evaluation of the study will, of course, look over the course of the entire lung sections that have been taken. I will remind you again of the sampling strategy that was done. In this case all of the lobes are sampled so that they are able to see everything out to the parenchyma, and they will go through magnifications so that they will be able to get a sense for whether there are any changes in thickening or loss of air space. So, this representative photo micrograph I don't think really gives you a sense of how the evaluation was performed.

DR. KING: If you have loss of alveolar [not at microphone; inaudible].

DR. FINCH: Yes, we did not perform any quantitative morphometric--the types of things that you can do with the quantitative morphometric

techniques but, again, that would not seem to have been indicated since there was no apparent effect of exposure, as noted in the H&E evaluation.

DR. WOOLF: Dr. Calhoun?

DR. CALHOUN: I just had one other follow-on to this inflammation theme, talking about the cells and histology. If I recall correctly, when you showed us the data on pulmonary infiltrates and abnormalities of chest radiographs, in those who had normal chest radiographs at the outset there was a higher frequency of those who had abnormal chest radiographs in the inhaled insulin group compared to the subcutaneous insulin group. Yet, when you did the high resolution CT scans, which I think most of us pulmonary physicians would view to be a more sensitive test, there was no difference. Do you have any insights as to why there was that discrepancy in the data?

DR. JACKSON: I don't have insights but Dr. Riese might.

DR. RIESE: Well, I think it is true that when we took our controlled Phase 2/3 database and

looked at the changes in x-rays, there are more changes in the INH group than the subcutaneous and oral agent group. We carefully looked through that database to see if we could find any pattern that would be recurring and we couldn't. We were also assured by the fact that most of these resolve spontaneously while on INH.

Could I have slide main-79? For example, we saw 29 abnormalities in lung parenchyma. Of those, we had follow-up imaging of 25 and 22 of those patients resolved on follow-up imaging, and what was reassuring to us is that 18/22 resolved while still on INH. I don't have the exact answer for you but I will say that our high resolution CT scan tomographies were done with a standardized algorithm and read at a central reading site by a radiologist blinded to treatment. So, you know, as you mentioned, it is a more sensitive and specific technique that was also reassuring to us.

DR. CALHOUN: [Not at microphone; inaudible].

DR. RIESE: The way it worked is the

radiologists were not blinded at the time because they had to compare it to baseline.

DR. CALHOUN: [Not at microphone; inaudible].

DR. JACKSON: Except there was a control group.

DR. CALHOUN: No, what I mean is if you are doing pre and post, they should not know which is pre and which is post. They should just read the film.

DR. WOOLF: Was it done that way or not?

DR. JACKSON: No, it wasn't done that way, not blinded to time.

DR. WOOLF: Dr. Watts?

DR. WATTS: I have what should be a real quick question and a real quick question but then I would like to follow-up with a little bit more and you may want to wait on the answer until after the break.

The quick question is insulin needs to be kept cool when it comes in a glass vial for injection. What about the stability of this

product?

DR. JACKSON: In fact, it should not be put in a refrigerator. It should be kept at room temperature.

DR. WATTS: The thing I want to raise that has been on my mind since I received the briefing document is that your material is measured in milligrams where doctors and patients using insulin think in terms of units. Your preparation is in a minimum of three unit equivalent adjustments, whereas patients may want to adjust in one or two unit increments and, as has been pointed out, three blisters of 1 mg is more than one blister of 3 mg. It seems to me, in my naivete, that if you have unit equivalents you should be able to package it both in units and milligrams and clinicians and patients could be thinking in familiar terms. It seems to me you could also make adjustments in the packets so that you could make them so that three of the 1 mg was equal to one of the other, even though it might not be a 1 mg and a 3 mg packet. It would be based on the delivery dose. If you had

7 mg, which would be roughly two units and something that would be four units and eight units, that would give a lot more flexibility. There may not be time enough before the break to get into those questions but I think they are incredibly important practical issues for clinicians and for patients.

DR. WOOLF: Let me point out that after the break we are into questions so if there is an easy answer to this, fine. Otherwise, no.

DR. JACKSON: It is not an easy answer. We can get the answer.

DR. WOOLF: Briefly, please.

DR. JACKSON: I will ask Mr. Spavins to briefly give the answer to that because it is about can you change the relationship between the blister dosing and the delivery device, which actually has been optimized to do exactly what it does. I will ask Mr. Spavins if he can very briefly address that.

MR. SPAVINS: So two comments. First of all, Dr. Jackson showed a table this morning that

would give some equivalency between milligrams and units. So, that is one answer to your question. We have looked at various options to change this ratio on the 1 and 3. Very briefly--we can to into more detail if you would like, if you try to over-fill or under-fill, it is a non-linear process so you still wind up with a label and content that is non-linear. We certainly can go through some numbers if that would be helpful. When it comes to the labeling proposal that Dr. Jackson mentioned this morning, we would certainly put in this precaution with regard to the substitution issue as well on the label.

DR. WOOLF: Dr. Follmann:

DR. FOLLMANN: Thank you. In the last hour or so there have been several questions related I guess to what you could call robustness of the device--does it fail very often; is there need for a backup, etc. I was wondering if in the trial you have conducted you collected statistics on the number of times people wanted to use the device and the number of times they were

successful. So, basically attempted use failure rate and then what were the reasons for the failure--they didn't have drug; the device malfunctioned; maybe they had a respiratory infection. Some statistics like that I think would allay some concerns about whether this is a robust device in practice.

DR. JACKSON: I am not aware of any statistics about that but if you will give us the break we may be able to delve down into our database and see if we can get anything out--may be able to.

DR. WOOLF: If we can get the number, that is great but not the discussion of the number. Dr. Stoller?

DR. STOLLER: I just wanted again to revisit the issue of co-morbid lung illnesses. Of course, the other lung disease and, of course, the prevalence may be lower than asthma or COPD is interstitial lung disease. I gather there has been no cohort in which the use of this drug has been examined in such a patient population. If the

answer to that is there has not been any investigation, is there any intent to do that in the Phase 4 assessments? I didn't hear you comment on that.

DR. JACKSON: We have not examined those patients and currently there is no proposal to examine those patients, but we take the point.

DR. STOLLER: One other question, just to close--I want to revisit the comment Dr. Orloff had. I am befuddled by the difference between passive and active smoking and I wonder if you have any thoughts to explain that difference on the PK, PT, PD dimensions of this. I am really at a loss.

DR. JACKSON: Well, I think it is a difference between irritation and inflammation but let's see what Dr. Fontain has to say.

DR. FONTAIN: I think it is a bit of a mystery and I can't completely explain it, but I would point out that it does seem to be consistent with what we know about other materials and their rate of removal from the alveolar space to the blood, such as radio-labeled DTPA. So, that and

other proteins such as albumin show a similar increase in chronic smokers. Presumably there is increased leakage of fluid out of blood vessels into alveolar spaces and a corresponding increase in the rate of absorption. So, this seems to be a common phenomenon for chronic smokers.

There is less data on the effects of passive smoking but, again, there are a couple of studies with DTPA showing a change in the direction that has been seen for insulin but it is a little hard to completely explain.

DR. WOOLF: Thank you. This part of the session is closed. I have 3:05. We will reconvene at 3:20 for discussion of the questions and our answers.

[Brief recess]

DR. WOOLF: We have people who need to make some connections and flights and I would like to be able to get them to vote. Are we ready? There is going to be a simple response from the sponsor. They were going to dig through their database for the answer. Do you have the answer to

the question? And, I am having a "senior moment" and I can't remember what that was but I know there was an outstanding answer. Do you have it?

DR. RIESE: Yes, thank you very much for the time. The one device I was talking about represented 6,900 patient-months of experience, that cohort. By our calculation that would be about 120,000 actuations. So, the expectation is the device would fail a patient once in every 20 years.

DR. WOOLF: That is impressive. David?

Committee Discussion and Questions

DR. ORLOFF: Thank you. I just want to take a couple of minutes and walk you through the questions so that we can move, I hope, expeditiously through them. The way I have set these up, as you will see, is that under four separate numbers there are actual yes or no questions. The fifth item prior to the ultimate question is a chance for more discussion, which I think at this point, given time constraints and given the fact that we have had a lot of discussion

before, I would encourage people to be selective in what they choose to bring up.

So, to begin, let me just say that the first question on efficacy I think is self-explanatory. The second question reads: Has the efficacy of Exubera been adequately assessed in patients with type 2 diabetes? I guess another way of phrasing this would be to say has adequate evidence of efficacy of Exubera in type 2 diabetes been provided?

I am just skipping four because there are no other real issues for explanation on the rest of the four items. Under item five, a number of these have come up before. I guess, for my own purposes, I am curious for the pulmonary specialists to comment on the data or their thoughts on the evidence or reversibility of the FEV1 decrement seen with inhaled insulin and on the reversibility of the DLco effect.

In addition, what I did not put in here but I think is worth making a comment about is the pediatric use issue. Again, the sponsor isn't

proposing it but I think for the record it would be nice to hear from the company [sic] any thoughts they have on that issue.

I guess there is still this outstanding issue that Dr. Watts raised related to the interchangeability between insulin international units and the dosage in milligrams for this product. I guess if that comes up again we will be interested to hear further comments from sponsor and from the committee. Thank you. I will turn it back over to you.

DR. WOOLF: The way this is going to work is I will read the question. We will alternate starting positions and Dean Follmann will be first and Rebecca Killion will start on the alternate question and we will go back and forth around the room. Dr. Watts is not permitted to vote so we have nine possible votes.

The first question, efficacy in type 1 diabetes: Is there sufficient clinical trial evidence that Exubera can be effectively applied as an "intensive" glycemic control agent? Dean

Follmann?

DR. FOLLMANN: I think it is pretty convincing. The two major studies, 106 and 107, both showed noninferiority. That is what they were designed to show.

DR. CAPRIO: I would like to see more studies in type 1. Even though they are not applying for use in pediatrics, I know that some folks out there are going to use it so I am concerned about the hypoglycemic episodes. So, I need more studies in type 1.

DR. WOOLF: So, is that no?

DR. CAPRIO: No.

DR. KING: I think that the studies are adequate.

DR. STOLLER: Yes.

DR. CALHOUN: Yes.

MS. SCHELL: Yes.

DR. SCHUSTER: Yes.

DR. WOOLF: Yes.

MS. KILLION: Yes.

DR. WOOLF: If I tally right, eight for

and one nay. Is that correct? Question two, efficacy in type 2 diabetes: Has the efficacy of Exubera been adequately assessed in patients with type 2 diabetes? We will start on my right.

MS. KILLION: Yes.

DR. WOOLF: Yes.

DR. SCHUSTER: Yes.

MS. SCHELL: Yes.

DR. CALHOUN: Yes.

DR. STOLLER: Yes.

DR. KING: Yes.

DR. CAPRIO: Yes.

DR. FOLLMANN: Yes.

DR. WOOLF: Nine yes and zero no. Number three, hypoglycemia: Has the safety of Exubera regarding hypoglycemia been adequately assessed in (a) type 1 diabetes in "intensive" control regimens? Starting on my left?

DR. FOLLMANN: Yes to both.

DR. WOOLF: No, we are going to take then individually, please.

DR. FOLLMANN: Yes to the first.

DR. CAPRIO: No to the first.

DR. KING: Yes.

DR. STOLLER: Yes.

DR. CALHOUN: Yes.

MS. SCHELL: Yes.

DR. SCHUSTER: No.

DR. WOOLF: Yes.

MS. KILLION: Yes.

DR. WOOLF: If I am counting correctly, that is seven yes and two no. Is that correct? Turning to type 2 diabetes, on my right?

MS. KILLION: Yes.

DR. WOOLF: Yes.

DR. SCHUSTER: Yes.

MS. SCHELL: Yes.

DR. CALHOUN: Yes.

DR. STOLLER: Yes.

DR. KING: Yes.

DR. CAPRIO: Yes.

DR. FOLLMANN: Yes.

DR. WOOLF: We are unanimous.

Question four, pulmonary effects: Are

there sufficient data to assess the pulmonary safety of Exubera in patients without underlying lung disease? To my left?

DR. FOLLMANN: Yes again.

DR. CAPRIO: Yes.

DR. KING: Yes.

DR. STOLLER: Yes.

MS. SCHELL: Yes.

DR. CALHOUN: Yes.

DR. SCHUSTER: Yes.

DR. WOOLF: Yes.

MS. KILLION: Yes.

DR. WOOLF: Again unanimous. Therefore, we do not have to answer 4(a)(ii). Question 4(b), are there sufficient data to assess the pulmonary safety of Exubera in patients with underlying lung disease? If yes, do the data suggest an acceptable pulmonary safety profile in patients with underlying lung disease? On my right?

MS. KILLION: I have some concerns about this but I will say on balance yes.

DR. WOOLF: I second your yes and your

concerns.

DR. SCHUSTER: No.

MS. SCHELL: No.

DR. CALHOUN: Yes.

DR. STOLLER: No.

DR. KING: No.

DR. CAPRIO: Yes.

DR. FOLLMANN: No. I would like to wait until 1028 and 1030 are finished.

DR. WOOLF: I have lost track. What is the tally? Five no and four yes, a split vote. For those who said no, you are being punished--if no, what additional information is needed besides Dean Follmann who indicated he wanted completion of those two studies and I am not sure when that will be.

DR. SCHUSTER: I would just want a bigger N. So, I think I would concur with what he says.

MS. SCHELL: A long-term study on interstitial lung disease.

DR. WOOLF: Who is next?

DR. STOLLER: I think there needs to be a

substantially larger study in patients with chronic obstructive pulmonary disease over a spectrum of chronic obstructive pulmonary disease that reflects the population that will likely be using this drug, which is clearly not excluded to the few patients with goal stage 2 that were evaluated. I think that in those analyses there needs to be very close attention to categorical analysis of those patients who experience large drops both in their diffusing capacity and FEV1, stratified by their baseline lung function which is, of course, much more of a threat to patients who start out with impaired lung function than those who are normal to start.

DR. WOOLF: Well said. Who was the next no?

DR. KING: I was. I agree. I am very concerned about patients with diseases other than asthma and COPD, particularly those with diffused lung disease. I agree with James' comment.

DR. FOLLMANN: I just wanted to add something. With 1028 and 1030, I don't know if it is designed at the end of follow-up to have a

withdraw period or not, but I think consideration should be given to having a withdrawal period for those to look at reversibility of the effects on lung function tests.

DR. WOOLF: I think it is safe to say that the pulmonologists are more concerned than the endocrinologists at the moment. I think that is a pretty fair statement. That is not at all surprising.

Question five, comments--in these areas please make them brief, number one and, number two, we have discussed them before. If somebody has had a light bulb go off, that is fine. Comments: 5(a), comment on clinical concerns and recommendations about the use of Exubera in the setting of pulmonary pathology or exogenous factors affecting pulmonary function in viral upper respiratory infection, asthma, COPD and smoking. Members of the panel?

Well, I, for one, am concerned about respiratory infection. I don't think there has been anywhere near enough data. I think that the

clinical trial was a bit synthetic and doesn't necessarily mirror real life. There were many patients who, in fact, got colds during the study but I would like a broader experience because I think that is going to affect a lot of people with the effect of influenza which, you know, was clearly unstudied.

DR. CALHOUN: Yes, viral upper respiratory tract infection has only been studied in the context of rhinovirus and not others. In terms of asthma, I have already expressed my concern that we don't have a good sense of how the pharmacokinetics and pharmacodynamics and absorption characteristics vary with what might be very variable lung function. The question of dose response to smoking, particularly passive smoking, has not been addressed. So, that is probably something that would add value were that information to be available.

DR. STOLLER: I would concur. I think there needs to be a much more ambitious study of passive smoking since this will not be something

that can be explicitly avoided by patients in their use of these agents and, therefore, poses, if you will, a threat to the effectiveness of this drug not withstanding the efficacy issues.

And the same comment, although perhaps not subsumed within the four categories but, you know, one of the other issues that I think would bear more attention is the real, if you will, world use of this device, let's just say, in patients not subjected to the ideal study conditions of intensive treatment who are likely to use this device under the conditions of its being dispensed from an endocrinologist's office, albeit with diabetic teaching, I think should be considered. You know, one of the underlying concerns is the difference between efficacy and effectiveness and I think that is one of the real issues about a novel device that is used by clinicians for whom this route of delivery is not routinely within their practice expertise.

DR. FOLLMANN: Just a comment about passive smoking, if the sponsor did collect data on

whether members of the household smoked they could do some analyses based on that and sort of get, in a non-laboratory setting, at the passive smoking.

DR. WOOLF: Dr. King?

DR. KING: My comments relate to asthma and COPD. One of the problems that we have in dealing with these patients is acute exacerbations of these diseases for multiple reasons. Often in the care of patients during an acute exacerbation, even the medications that are supposed to work to help them are often not used appropriately. I just have concerns that we haven't addressed what will happen in those settings for those patients where they have acute exacerbations, and what will be the effect of the acute exacerbation on subsequent restarting of use of inhaled insulin, for example.

DR. WOOLF: Yes, the whole question of either systemic or pulmonary steroids--we know that systemic steroids are going to make patients insulin resistant. This is an insulin delivery device so one can titrate that, but what are inhaled steroids going to do to absorption? We

didn't hear any data today on that at all. Other issues related to 5(a)?

MS. SCHELL: I just have a concern on the actual baseline spirometry, the performance by a qualified person that can do spirometry in the office. It is very patient dependent, also upon the practitioner doing it, the skills necessary to do the baseline to actually do the test. So, those are my concerns.

DR. WOOLF: Thank you. Number 5(b), comment on clinical concerns and recommendations regarding dose adjustment (titration) and switching from inhaled and subcutaneous insulin--something that Dr. Watts commented on before the break. We were told that the package is a package, is a package; the device is a device, is a device. But I am not quite sure why the sponsor chose milligrams instead of units when we have been using units since 1920-something or other. Other comments? Yes?

MS. KILLION: I would like to see the sponsor do the calculations rather than the patient

do the calculations because I think that is going to end up probably more exact. My primary concern is with the dosage--in a population that is used to sub-q, they are very wedded to the idea of units and that is a hard transition to make. For a population that has not yet been injecting, they are kind of a clean slate and perhaps you can educate them but I think what we need is to be aware that, as we all know, in the real world the plan is the first casualty and it is going to be used very differently, especially when you rely on a population where patients actually have to make those adjustments themselves without calling up their doctor every time they take a dose. So, my concerns are about the dosage; about the equivalence; what is a milligram; how does it relate to unit; why is three 1's not equal to one 3--those are serious issues for patients in a real-world setting.

DR. SCHUSTER: I agree. The only other comment I would have would be in terms of education. Patients need to understand that when

they are titrating and when they are changing over from a sub-q to an inhaled they need to do more frequent blood glucose monitoring. So, just to educate the patient in terms of frequency of blood glucose monitoring with any changes.

DR. WOOLF: Dr. King?

DR. KING: My other concern relates--I don't think it is isolated to the environment that I work in, but I work in a public hospital and one of the things that we find extremely difficult is healthcare literacy and now people understand how to use various things that we prescribe for them. One of the things I am very concerned about is that patients now have a very difficult time--well, physicians have a very difficult time instructing patients in the proper use of an inhaled agent. We know that to be a big problem and we not figured out a very good way to resolve it even for the diseases where the inhaled agent is working for that disease and makes that disease better. So, I am very worried about how we are going to educate patients about this because I think doctors now do

an inadequate job and we haven't substantially improved that, despite a lot of concern about it and efforts nationally and internationally.

The other thing is, that said, when it works best, the education of the patient so they take proper care of themselves, it usually means taking the doctor out of the middle of it. So, what that often means is that we have patient educators who do it, and the problem we find is that nobody pays for it. So, what I am worried about is that we now have a new product, a new way of doing something and I think it requires repeated education. I can tell you that in the care of a patient with asthma where the bronchodilator is what they need to improve their disease, I have to teach them every single visit. I can't depend on the fact that they know from visit to visit how to use the metered-dose inhaler. I think this is easier because it is in a chamber and the breathing is not as critical, but I think that this is going to be a substantial educational problem and we haven't heard much about how they are going to

address this and how clinicians will be helped to implement it.

DR. STOLLER: I have one other comment that falls perhaps under 5(c). We have heard actually of a very laudable, ambitious plan to look for rare events, namely cancer, postmarketing, and I suppose it is a procedural question both to the agency and the sponsor. It would be reassuring I suppose to have some very explicit plan about what the signal is in these postmarketing events that trigger some postmarketing review of these events. It is perhaps difficult to articulate those in advance but I think it would be important to have that explicitly articulated. You know, at what incidence of excess lung cancer does one say there is potential causality and this needs to be seriously reexamined?

DR. WOOLF: Other questions about 5(b)? 5(c), other issues? I would like to turn to training. Despite several of my questions, I am not at all convinced that the company has adequately thought out the training program for the

initiation of patients who are either insulin naive or have been taking insulin. It is a very ambitious project to train literally millions of people, and I don't know what resources will be available to train those people. A 24-hour hotline is find for a question now and then but it doesn't replace some real live person, hands on--no, that is not the way to do it. To have to screen people with spirometry probably won't happen half the time. I am real concerned about that, and I would like to see the sponsor actually demonstrate that they have a successful training program that mirrors real life and I haven't heard anything about that.

The other thing that we have not discussed at all in type 1 diabetics is that this does not mean that the diabetic can throw away their needle and syringe. This is bolus insulin. They are still going to need some long-acting insulin. While we have heard a little bit about it, it certainly has not been emphasized. I think there were three letters to the agency making this point.

Those are people who didn't come today but wrote compelling letters that patients who are type 1 and potentially type 2 are going to need to take a long-acting insulin, be it 24 hours or intermediate acting but something. And, having people rush to this product, saying I can throw away my insulin and syringes is absolutely an incorrect message and that needs to be emphasized more.

DR. KING: I want to go back to the issue of the device. I think that the device is a problem because of the reasons that we have expressed before. That is, it is hard for us to get our asthma patients to take their devices with them. Basically, this is a chamber with an actuator on it so it is actually a fairly large device. I am not in this group but I understand that metrosexuals are carrying purses and they do things like that now--

[Laughter]

--so it is a lot easier for them maybe. As Rebecca said, it won't be a gender issue. But I think it is still a big problem, that people will

not carry this with them and they will leave it.

The other problem that I have experienced with patients is that their employers won't let them do certain things with certain devices, carry things around. These are things we need to think about, the implications of that.

MS. KILLION: Well, that is why God made lawyers! I would like to reiterate your point and my previous point about sort of the practicality of it. It cannot be overemphasized because one of the problems that you have with compliance is practicality. It has to be easy. You know, there is still a stigma about using your medication in public and you have to use your medication in public if you are going to eat out, if you are going to be at work, and that is something. So, to haul out a device of some size, or whatever, calls attention to you and that affects patient compliance. It is just something that I think is sometimes lost when you are looking at it clinically and not practically.

The training issue, I agree with Dr.

Woolf. To me, that is your Mt. Everest if you are going to get this off the ground because I can tell you patients don't want to take a shot if they don't have to. I take four shots a day and the fourth one is always the hardest one because I am tired of it by the time I get to the fourth one. So, if I could get myself down to one, I would be happy; I would be thrilled. A lot of people will not take insulin--they resist it because they are afraid of the needles. Even though it is not that big a deal, to some people it is really an insurmountable barrier. So, you need to be thinking about a patient perspective and not just a clinical perspective on how this is going to be used and how to make it not only attractive in theory but in practice to a patient.

DR. WOOLF: Other questions before we get to the heart of the matter?

DR. CAPRIO: Can I have a comment? As a pediatric, we are using a great deal of pump insulin and there is a large training that goes into it, and 50 percent of our population are using

it. So, that is not undoable. I think we can learn how to deal with this. You have to train the patient and that is feasible.

DR. WOOLF: I forget who goes next, but question six, should Exubera be approved for the proposed indications in, (a) type 1 diabetes? Dean?

DR. FOLLMANN: Yes.

DR. CAPRIO: Yes.

DR. WOOLF: Dr. King?

DR. KING: Yes.

DR. STOLLER: No. Let me qualify that. It is based on concerns about the need for additional data. No.

DR. CALHOUN: I guess yes, with the need for additional data.

DR. WOOLF: Well, if you approve it--that is almost an oxymoron.

DR. CALHOUN: No, it is not an oxymoron. I think yes but there is definitely need for additional data.

MS. SCHELL: Yes.

DR. SCHUSTER: Yes.

DR. WOOLF: No because of the issue of training.

MS. KILLION: I would say yes, but training and also I think this will work for some people under the right circumstances. It just has to be looked at very carefully. But I would say yes.

DR. WOOLF: That is seven yes and two no. Part (b), type 2 diabetes as monotherapy, in combination with basal insulin, in combination with oral agents. Rebecca?

MS. KILLION: Yes.

DR. WOOLF: No for the same reason.

DR. SCHUSTER: Yes.

MS. SCHELL: Yes.

DR. CALHOUN: Yes.

DR. STOLLER: No for the same reasons that I articulated before.

DR. KING: Yes.

DR. CAPRIO: Yes.

DR. FOLLMANN: Yes.

DR. WOOLF: Seven yes and 2 nays. Last question, additional investigations: What, if any, recommendations does the committee have for additional investigations of Exubera? We have talked a lot about this. Are there any new insights for additional investigations?

DR. KING: Without repeating anything we have said already, right?

DR. WOOLF: I think, because we have captured that.

MS. KILLION: I would just like to say there could be sort of a development of a training program so you could see how this would be implemented. I would like to see that.

DR. KING: This may not be a need for investigation but I need my colleagues to help me with a question that didn't get answered. So, the antibodies go up with the use of this agent. When I was training, in ancient days, we worried a lot about insulin resistance and thought it was related to antibodies. Then things improved and the antibodies problem went away. Is this bringing the

antibody problem back? Will there be issues related to it long term? The studies haven't gone long enough for us to understand that this will result in "insulin resistance."

DR. WOOLF: I believe the sponsor showed us data that the doses didn't change as the antibody titers went up. I think that is what they said.

DR. ORLOFF: Can I offer a comment? The point that the studies are limited in duration, certainly compared to life-long use, is well taken. The data to this point, just to recap, is that although there is a very high incidence event of insulin antibodies among patients on inhaled insulin, much, much higher than is seen in subcutaneously treated patients, setting aside immunologic consequences, there appear not to be any consequences metabolically, that is to say with regard to the control of their diabetes or the doses of insulin they require or, for that matter, the hypoglycemic effects of insulin.

So, to this date, the data are what they

are. And, I guess I would ask anybody from the sponsor or Dr. Caprio who has had a lot of experience in treating diabetes to give their own thoughts.

DR. CAPRIO: I would say that is not a concern.

DR. WOOLF: Any other comments?

DR. FEINBERG: Yes, what you have to do is think about in parallel. Pre-1980s insulins which contained over 3,000 ppm of proinsulin and many other non-insulin peptides resulted in average circulating antibody levels in most patients treated in the range of 1-2 million/L, 1,000-2,000 micro units/mL. So, that was a common event. Even in those days when we had insulins which were not nearly as pure as they are now and not as well defined, the incidence of severe complications was less than one-tenth of one percent, and that includes provable hypoglycemia, insulin resistance, systemic allergy, and so on. The levels that we are seeing now, even though they are higher than injected human insulin, are not nearly in those

levels. So, I think that the concern should be relatively minimal.

DR. KING: One additional concern I have is that I think the total population included less than one percent of African Americans, and the African American lung function is different than Caucasian American lung function. So, we don't really have any idea whether African Americans will react differently to this agent than others, and I think we need to consider that before it is used in that population, probably for the same reason we are thinking about the pediatric population.

DR. WOOLF: Good point.

DR. CAPRIO: Yes, I agree.

DR. WOOLF: Any other comments?

DR. STOLLER: One other comment. One other general comment would be to try to gain better mechanistic understanding of the reasons for these declines in FEV1 and diffusing capacity, albeit relatively minor. But I heard discussion of pulmonary data and lavage data, and there was an allusion in the briefing document to methacholine

challenge but obviously not brought forward. I would think that in additional studies that are germane to assuaging concerns about the mechanisms of these accelerated rates of decline of lung function one would want to have a better understanding of these mechanisms, number one, and, for example, of the paradoxic effect of passive versus active smoking which I think will potentially plague the review of this until those concerns are assuaged.

DR. WOOLF: Anything else? If not, the committee stands adjourned.

[Whereupon, at 3:55 p.m., the proceedings were adjourned.]

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