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Clinical Review
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1 EXECUTIVE SUMMARY

This Executive Summary contains a brief overview of the clinical review. The complete body of the review is somewhat lengthy, and contains numerous sections and tables. For the reader who wants a more complete summary than that found in the Executive Summary, please refer to Section 9.1, the Conclusions Section, which contains an expanded discussion of most of the findings of the overall review. In Section 9.1, each point of discussion is followed by a section number for the pertinent section of the main body of the review. The reader can refer to the relevant section, if desired, for more complete information regarding the review of that topic.

This document reflects information available to the clinical reviewer as of 12 Sep 05. Reviews from several scientific disciplines are still pending, and may be considered by signatory authorities for regulatory action.

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends approval of Exubera® for the control of hyperglycemia in adult Type 1 and adult Type 2 diabetes, with certain exceptions for patient populations for whom more efficacy and/or safety data are needed. The applicant has provided substantial evidence, through adequate and well-controlled clinical trials, of effectiveness of Exubera® for the treatment of Type 1 diabetes in adults (in combination with a longer-acting insulin), and for the treatment of Type 2 diabetes in adults (as monotherapy, in combination with a longer-acting insulin, or in combination with oral agent[s]). However, inadequate evidence exists to determine whether the drug is likely to be safe for use by patients with underlying lung disease. Further data are also needed to determine if the drug will be likely to be effective and safe for use by patients under age 18 years, and by African Americans. Exubera® exposure is significantly elevated in smokers, and current or recent smokers should not use the drug. Further data are needed regarding the effects of passive smoking on Exubera® pharmacokinetics and pharmacodynamics.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

In addition to routine postmarketing pharmacovigilance activities, the applicant proposes the following risk management activities:

- A large simple trial in 5,000 diabetics with Type 1 or Type 2 diabetes, with 1:1 randomization to either Exubera® or usual care. This trial is to estimate the relative risk of clinically significant (>20%) declines in lung function as measured by pulmonary function tests.

- Completion of Studies 1022 and 1029, in Types 1 and 2 diabetes respectively, to obtain data regarding changes in forced expiratory volume in one second (FEV1) over 5 continuous years of Exubera® exposure.
-
- Completion of Studies 1028 and 1030, in diabetics with mild to moderate asthma and COPD respectively. These studies are to assess change in FEV1 and diffusion capacity for carbon monoxide (DLco), control of diabetes and underlying lung disease, and frequency and severity of exacerbations of underlying lung disease.
- Further pediatric studies.

The clinical reviewer agrees that these proposed investigations will provide useful data regarding outstanding questions about the safety of Exubera®. In addition to the above, the clinical reviewer recommends the following:

- Study of the pulmonary safety of Exubera® in African American diabetics. African Americans have been described to have lower normative values for baseline lung function than those seen in Caucasian Americans and Mexican-Americans.
- Study of the pharmacokinetics and pharmacodynamics of Exubera® in persons chronically exposed to cigarette smoke who are not themselves smokers. This could include workers in bars or restaurants in which smoking is permitted, or family members in households occupied by smokers.
- Implementation of an active education program to reduce the likelihood that smokers will receive the drug.
- Provision of detailed plans for how the applicant will ensure that physicians, allied health care professionals, and patients are educated in proper use of the Exubera® inhaler. A Medication Guide for patients is recommended.

1.2.2 Required Phase 4 Commitments

The clinical reviewer proposes that all of the above risk management activities be included as Phase 4 commitments, except for further pediatric studies, which may be the subject of a future Written Request for Pediatric Study after further adult safety data are obtained.

1.3.2 Efficacy

The applicant seeks the following four indications:

- control of hyperglycemia in Type 1 diabetes (inhaled insulin in combination with a longer-acting insulin)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin monotherapy)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with oral agents)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with longer-acting insulins)

Although the applicant does not seek an indication for the use of Exubera® in children, the clinical reviewer anticipates significant interest in the use of inhaled insulin in children, and therefore efficacy data regarding pediatric use were also considered.

In general, the major Phase 3 trials met the definition of "adequate and well-controlled" studies contained in 21 CFR 314.126. One concern regarding trial design was the method of treatment assignment, which was block allocation within center. However, ordering of block sizes was random, and statistical analyses did not reveal evidence of bias related to this treatment allocation method. All studies were open label, and none used inhaler or injection placebos. Historically, clinical trials of insulin have generally not been blinded trials, due to safety, logistical, and ethical concerns. With few exceptions, exclusion criteria used in Phase 2 and Phase 3 trials were unlikely to limit the general applicability of trial results.

The Exubera® inhaled insulin drug-device combination (referred to hereafter as "inhaled insulin" or "Exubera®") appears to be effective in control of hyperglycemia for the following indications:

- control of hyperglycemia in Type 2 diabetes (inhaled insulin monotherapy)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with oral agents)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with a longer-acting subcutaneous insulin)

On balance, Exubera® also appears to be effective for control of hyperglycemia in Type 1 diabetics (inhaled insulin in combination with a longer-acting subcutaneous insulin), although the average patient might not be expected to achieve "intensive" control.

There is a clear standard for glycemic control of Type 1 diabetes; this standard was established by the findings of the Diabetes Control and Complications Trial (DCCT) of intensive insulin therapy. The applicant submitted Study 107 as an "intensive control" trial in which inhaled insulin as a premeal insulin was compared to regular subcutaneous insulin as a premeal insulin; both regimens included long-acting "basal" subcutaneous insulin. Although inhaled insulin was noninferior to subcutaneous insulin for change in HbA1c in this trial, neither treatment group achieved a mean HbA1c in the range achieved in the DCCT. Only 23% of inhaled insulin group patients achieved a HbA1c <7%; the American Diabetes Association recommends a HbA1c <7%, and the American Association of Clinical Endocrinologists recommends a HbA1c of <6.5%. Upward change in postprandial glucose excursion was greater for the inhaled insulin

group than for the subcutaneous group at end of study. During a meeting of the Endocrine and Metabolic Drugs Advisory Committee (EMDAC), committee members pointed out that it has been very difficult to replicate DCCT-level control, either in clinical trials of other diabetes drug products, or in clinical practice. Thus, it might not be reasonable to expect DCCT-level control out of other diabetes drug products.

By the statistical model used by the applicant, rates of severe hypoglycemia appeared higher in the inhaled insulin group than in the subcutaneous insulin group in Study 107. If an antidiabetic agent is noninferior, but not superior, in efficacy to an active control, rates of severe hypoglycemia should be comparable between groups, but this did not appear to be the case using the applicant's statistical model. However, FDA Biostatistics review indicates that the model selected by Pfizer might not have been the best model to compare rates of hypoglycemia, and it appears by a more appropriate model that rates of severe hypoglycemia actually did not differ between treatment groups for Study 107.

Given the opinion of the EMDAC that DCCT-level control is difficult to achieve for Type 1 diabetics, and may not be a reasonable standard for diabetes drug trials; and also given the fact that rates of severe hypoglycemia for inhaled insulin do not appear to exceed that for subcutaneous insulin, the clinical reviewer concurs that Exubera® exhibits a reasonable degree of efficacy for control of Type 1 diabetes. However, the completed trial results for Type 1 diabetes are less convincing than those for Type 2 diabetes, and it is not clear that the average Type 1 diabetic can expect to be able to achieve optimal glycemic control with Exubera®. Type 1 diabetics who do not achieve optimal control with Exubera® can return to subcutaneous insulin for their premeal insulin needs. In Type 1 diabetes, Exubera® cannot be used as monotherapy, but only as premeal shortacting insulin; all Type 1 diabetics will continue to require injected longacting insulin.

Studies performed in children to date have not demonstrated that the desirable level of glucose control (i.e. that associated with decreased risk for later diabetic complications) can be reliably achieved with inhaled insulin.

1.3.3 Safety

A separate pulmonary safety review is being conducted by the Division of Pulmonary and Allergy Drug Products. This review concerns nonpulmonary safety issues.

For deaths occurring in the development program, no clear differences were demonstrated between inhaled insulin patients and comparator patients for incidence or cause of death.

Nonpulmonary serious adverse events occurred with approximately equal frequency among inhaled insulin patients and comparator patients. Serious hypoglycemia was the most commonly reported serious adverse event, and occurred with similar frequency between inhaled insulin groups and subcutaneous groups for most studies. Adult patients in oral agent comparator groups were less likely to experience serious hypoglycemic adverse events than were patients in either inhaled insulin groups or subcutaneous insulin groups. Diabetic ketoacidosis occurred

with similar frequency among pediatric patients treated with inhaled insulin or subcutaneous insulin. In the controlled Phase 2 and Phase 3 trials, no other serious nonpulmonary adverse event appeared to occur with significantly greater frequency in inhaled insulin group patients than in comparator group patients for either adult or pediatric patients.

Hypoglycemia was evaluated in three ways; as a reported adverse event, as a protocol-defined secondary endpoint measure within individual studies, and as an overall safety measure using a separate definition. Hypoglycemia in general did not occur more frequently in inhaled insulin patients than in subcutaneous comparator patients. Among Type 1 diabetics, inhaled insulin group patients were more likely to experience prebreakfast hypoglycemia, while subcutaneous insulin group patients were more likely to experience prelunch hypoglycemia. The reason for this difference in time-of-day for occurrence of hypoglycemia is unknown; mean daily and evening doses of longacting insulin do not appear to have been higher in inhaled insulin group patients.

Among nonserious common adverse events, hypoglycemia was the most common adverse event for both Type 1 and Type 2 patients, but did not occur with greater frequency among inhaled insulin group patients than among comparator group patients. Common adverse events which had a higher incidence among adult inhaled insulin group patients, and seem likely to be related to inhaled insulin use, include cough, and nasopharyngeal events such as pharyngitis, rhinitis and sinusitis. Adverse events related to the ear, including otitis media, appear likely to be related to inhaled insulin use in pediatric patients.

Rare but potentially serious adverse events which appeared to occur somewhat more frequently numerically in inhaled insulin group patients than in comparator patients per unit of patient-time over all Phase 2/3 trials (controlled and uncontrolled) included the event terms "retinal hemorrhage" and "allergic reaction".

The development of insulin antibodies was common among inhaled insulin group patients. End-of-study titres, change from baseline in titres, and rates of seroconversion (from nonmeasurable to measurable) were all higher for inhaled insulin group patients than for comparators, for both Type 1 and Type 2 patients. Type 1 patients exhibited greater increases than Type 2 patients; children exhibited greater increases than adults; and women exhibited greater increases than men. Despite these laboratory findings, a clinical correlate was not found. Associations were not demonstrated between insulin antibody levels (insulin binding activity) and hypoglycemia, allergic adverse events, or other adverse events. There was no clinical evidence of a neutralizing effect of these antibodies on insulin action, and no associations were found between insulin binding activity and indices of glycemic control. Discontinuation of inhaled insulin resulted in a decline in insulin binding activity.

Declines in pulmonary function tests for forced expiratory volume in one second (FEV1) and diffusion capacity for carbon monoxide (DLco) were more common in inhaled insulin group patients than in comparator group patients, and will be discussed in the pulmonary review.

Discontinuations due to adverse events were more common among inhaled insulin group patients than among comparator group patients. The most common category of adverse events leading to discontinuation was respiratory, and cough was the most common individual adverse event leading to discontinuation. The clinical reviewer noted a concern for possible investigator reporting bias in the assignment of reasons for discontinuation. A large number of discontinuations were listed as being due to "withdrawn consent" or "patient no longer willing to participate". The clinical reviewer requested further information regarding stated reasons for discontinuation among these patients. Some of these reasons appear to have been misclassified, and some were actually due to additional adverse events, lack of efficacy, or device concerns. Misclassification appeared to have been more frequent among discontinuing patients in inhaled insulin groups than in comparator groups. Revision of these reasons for discontinuation led to greater differences between groups for discontinuations due to adverse events (both Type 1 and Type 2 patients), and discontinuations due to insufficient clinical response (Type 1 patients). Subsequent to these review observations, Pfizer provided details of continuing efforts they have made to improve the accuracy of reporting of reasons for discontinuation.

There was no clear difference in routine laboratory results between inhaled insulin group patients and comparator patients.

1.3.4 Dosing Regimen and Administration

In the DOSAGE AND ADMINISTRATION section of the proposed product label, the applicant proposes a similar regimen to that used in clinical trials. Administration 10 minutes prior to meals is proposed. Calculation of initial dosage based on body weight is proposed, with a formula: $\text{body weight (kg)} \times 0.05 \text{ mg}$, rounded down to nearest whole mg, = premeal dose, assuming 3 meals/day. The applicant does not propose instructions for transitioning from subcutaneous premeal insulin to inhaled insulin, based on the patient's current premeal subcutaneous insulin dose. No formula is presented for dosing by carbohydrate exchanges, and there are no recommendations for calculation of bedtime snack doses. The label does not include recommendations for titration increments. Mention is made of the fact that three 1 mg unit dose blisters result in greater insulin exposure than one 3 mg dose blister. The dosage and administration section does not mention a need for close monitoring by the patient and physician during initiation of inhaled insulin.

Dose proportionality and dose equivalence were not demonstrated for Exubera®.

In Study A2171012, a dose proportionality study, approximately 1/3 of all samples for C_{max} and AUC for the 3 mg (1x3 mg) dose group had values below the mean observed for the 2 mg (2x1 mg) dose group. This could create a problem in upward titration of dose, particularly in the lower dosage ranges such as might be used in Type 1 diabetes. This problem would be magnified if the drug is used off-label for the treatment of pediatric Type 1 diabetics, who generally have lower body weights and therefore smaller initial insulin doses.

Dose equivalence was also not demonstrated for three 1 mg blisters and one 3 mg blister. In Study 1006, the AUC₀₋₃₆₀ for 3 inhalations of 1 mg was approximately 40% higher than that for 1

inhalation of 3 mg, and C_{max} was approximately 30% higher. This difference appears to be related in part (but not entirely) to a problem with the inhaler; it is much more efficient in breaking up the powder in blisters of a lower fill mass. In addition to the potential problems noted above with titration, patients must be instructed not to substitute three 1 mg inhalations for one 3 mg inhalation if patients run out of their 3 mg blisters. Such substitution could result in greater insulin exposure and risk for hypoglycemia.

This particular drug-device combination exhibits variability in emitted dose of dry powder insulin; this variability exceeds previously established limits for dry powder pulmonary inhalers. This variability in delivered dose is concerning, because it could theoretically result in an increased risk for hypoglycemia when doses significantly above the mean are delivered. Chemistry review is ongoing, and will address the acceptability of this variability in emitted dose from a manufacturing quality control standpoint.

While variability in delivery of insulin with Exubera® is a concern, it is noteworthy that marked variability in absorbed dose of insulin, and pharmacodynamic response, is also a major concern with subcutaneous insulin, and is well-described in the medical literature. Within this development program, significant variability in pharmacodynamic (glucose) response was seen for both inhaled and subcutaneous insulin, and the variability was comparable in standardized meal studies. There was no evidence of a clinical correlate for the observed variability in emitted dose of inhaled insulin, i.e. patients treated with inhaled insulin were not more likely than patients treated with subcutaneous insulin to have events of hypoglycemia or hyperglycemia.

Of potential concern for Type 1 diabetics is the fact that the lowest available blister strength (1 mg) may not allow for the fine titration that is often used for Type 1 diabetes. A 1 mg blister is roughly pharmacodynamically equivalent to 3 IU of subcutaneously injected shortacting insulin. For Type 1 diabetics, titration is often done in increments of 1 IU, and premeal "sliding scales" are often prescribed in 1 IU increments. However, this lack of fine titration capability does not seem to have had a clinical correlate in the clinical trials, either for glycemic control or hypoglycemia risk.

1.3.5 Drug-Drug Interactions

Study 1005 included pharmacokinetic (PK) data regarding co-administration of inhaled insulin and inhaled albuterol. While overall, inhaled insulin PK did not differ from 30 minutes pre- to 30 minutes post- albuterol, the small subset of emphysema patients (5/12 total COPD patients) had mean insulin exposure that was 46% higher post-albuterol than pre-albuterol.

Smokers have a 2-5 fold higher C_{max}, T_{max} and AUC for inhaled insulin than do nonsmokers. Smoking cessation leads to a decline in insulin exposure within 3 days of abstinence; by 7 days, insulin exposure is near that seen in nonsmokers. Resumption of smoking after abstinence results, within 2-3 days, in increases in exposure to levels similar to that seen prior to smoking cessation. The applicant's proposed product label states that smokers should not use inhaled

insulin. Specific education of providers and patients may be necessary in order to reduce the likelihood that smokers will receive inhaled insulin.

No other drug-drug interaction studies were submitted with the NDA.

1.3.6 Special Populations

A clinical pharmacokinetic and pharmacodynamic study was conducted in gestational and pregestational diabetic pregnant women. This study showed similar relative pharmacokinetics between inhaled insulin and regular subcutaneous insulin to that seen in a separate study in nonpregnant Type 2 diabetics. In the overall development program, women who became pregnant during study were all discontinued from study per protocol. Rates of spontaneous pregnancy loss were not significantly higher in these patients than in pregnant diabetics described in the medical literature. There was one neonatal death (from congestive heart failure) which occurred six months after the mother discontinued inhaled insulin; estimated exposure in utero had been 3-4 weeks.

In elderly obese Type 2 patients, inhaled insulin had an earlier insulin T_{max} and a higher C_{max} than regular subcutaneous insulin, but a similar AUC. This pattern is similar to that seen in nonelderly patients, but different dosing regimens did not permit direct comparisons.

Following administration of inhaled insulin, patients with chronic obstructive pulmonary disease (COPD) had a higher C_{max} (by up to 50%) than healthy subjects without COPD. T_{max} was earlier, and AUC was greater, in COPD patients than in healthy subjects.

The applicant did not submit studies of inhaled insulin use in renal or hepatic impairment.

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2 INTRODUCTION AND BACKGROUND

This review was prepared utilizing the current "Center for Drug Evaluation and Research Clinical Review Template" (Jul 04 version), and the "Reviewer Guidance for Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review" (Feb 05 version). This template and guidance seek to provide consistency and ensure completeness in clinical reviews, and to allow subsequent readers to readily locate specific types of information. In certain areas of the review, this uniformity of format may sometimes result in writing that does not flow smoothly, and the reader may need to refer to the Table of Contents for location of a specific type of information. Also, the completeness required for each section under the template may result in some redundancy of information.

Conclusions reached in this review are the result of the clinical reviewer's evaluation of the clinical portions of the New Drug Application; nonclinical and clinical pharmacology portions are also undergoing evaluation by reviewers with expertise in the relevant areas, and these reviews may also affect decisions made by signatory authorities regarding approvability of this application.

2.1 Product Information

Pfizer, Inc. has developed a dry powder formulation of recombinant human insulin designed to be delivered systemically via pulmonary inhalation. This product, under the proposed trade name Exubera®, is to be delivered through a novel pulmonary inhaler developed by Nektar, Inc.; this inhaler was designed specifically for delivery of this insulin product. Because of the novel characteristics of this insulin formulation, and because this is the first inhaled insulin:pulmonary inhaler drug-device combination to be considered for marketing, this is considered to be a new molecular entity.

Pfizer seeks indications for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Pfizer considers the drug comparable to rapid-acting insulin analogs in onset of action; its duration of action is similar to that of regular insulin. For Type 1 diabetics, Exubera® is to be used in combination with a longer-acting injected insulin. For Type 2 diabetics, Pfizer proposes use as monotherapy, or in combination with oral agents or longer-acting insulins.

2.2 Currently Available Treatment for Indications

Type 1 diabetes is currently treated almost exclusively with subcutaneously administered insulin, which is available in a variety of formulations and analogs, with a spectrum of time-action profiles. Because Type 1 diabetics have virtually no residual pancreatic islet beta cell function, these patients have an absolute requirement for administered insulin for survival, and cannot be managed with diet and exercise alone. Patients generally receive one or two subcutaneous injections per day of a relatively long-acting insulin as "basal" insulin, and take a short-acting subcutaneous insulin before each meal. Continuous subcutaneous infusion via insulin pump of

short-acting insulin, with mealtime boluses, is also used. Pramlintide, an amylin analog, was recently approved as the first agent other than insulin for treatment of Type 1 diabetes, but pramlintide is adjunctive to mealtime insulin, rather than substitutable for subcutaneous insulin.

Type 2 diabetics often undergo an initial trial of diet and exercise. If control is inadequate, a variety of oral agents is available. Classes include sulfonylureas; other oral insulin secretagogues (such as repaglinide and nateglinide); the biguanide metformin; thiazolidinediones; α -glucosidase inhibitors; and the amylin analog pramlintide. If adequate blood glucose control is not achieved with oral agents, subcutaneous insulin is often used.

The applicant considers Exubera® comparable in time-action profile to rapid-acting insulin analogs, which have a rapid onset of action (about 15 minutes), a short time to peak action (0.5-1.5 hours), and a short duration of action (2-5 hours). Currently marketed rapid-acting analogs available in the United States include insulin aspart and insulin lispro. Regular soluble crystalline zinc insulin is also used as a premeal insulin; it has an onset of action at 30-45 minutes, peak action between 1.5 and 4 hours, and a duration of action of 5-8 hours.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient used in the production of the inhalation powder is a recombinant human insulin which is not approved for marketing in the United States. Aventis Pharmaceuticals, the manufacturer of the active ingredient insulin, has authorized Pfizer to cross reference the Drug Master File (DMF) for this insulin, and that DMF is under review by the FDA Office of New Drug Chemistry.

2.4 Important Issues With Pharmacologically Related Products

As of 8 Sep 05, no other inhaled insulins are approved in any country. In published research reports in the medical literature, concerns are mostly related to the question of longterm pulmonary safety (Royle 2004).

2.5 Presubmission Regulatory Activity

During the development of Exubera®, there were many meetings and written communications between FDA and the sponsors. The following are highlights of some of those interactions:

31 Aug 93: Investigational New Drug Application (IND) 43313 was submitted to the Division of Metabolic and Endocrine Drug Products (DMEDP) by Inhale Therapeutics, which is now Nektar Therapeutics, the manufacturer of the pulmonary inhaler used in this application.

17 May 95: IND ownership was transferred to Pfizer, Inc.

6 May 96: Meeting with FDA to discuss development plans. FDA placed emphasis on longterm pulmonary safety data and characterization of pharmacokinetics. Concerns were raised regarding the lack of a blinded comparator.

2 Jun 98: Supplier of recombinant human insulin was changed from Lilly to Hoechst Marion Roussel (now Aventis).

3 Jun 98: End-of-Phase-2 Meeting. General agreements reached regarding the proposed Phase 3 clinical program. Concerns regarding longterm pulmonary safety again stressed by FDA.

15 Mar 99: Teleconference regarding pulmonary safety evaluation plans. FDA stated that longterm comparative pulmonary safety trials were needed.

10 Aug 99: Letter to sponsor from FDA stating that Written Request for Pediatric Studies would not be issued at that time.

18 Aug 00: Pulmonary safety meeting. FDA stated that the size of the proposed pulmonary safety database might be inadequate for NDA approval, and requested study of patients with underlying lung disease.

16 Apr 01: Pulmonary safety meeting. FDA pulmonary reviewer stated that 1-year controlled safety data on 200 Type 2 patients from other efficacy studies might not be adequate, due to small patient numbers and short duration of exposure. FDA stated that the proposed overall pulmonary safety database might be inadequate due to lack of adequate longterm controlled pulmonary safety data and lack of adequate efficacy/safety information in patients with concurrent lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Data for pulmonary safety in Type 1 patients also requested. FDA stated that subset analyses from other studies might not be adequate for evaluation of longterm safety in patients with underlying lung disease. FDA requested controlled study, for ≥ 1 year, of patients with COPD ($n \geq 100$), asthma ($n \geq 100$), and Type 1 diabetics with underlying lung disease ($n \geq 100$).

5 Apr 02: Meeting regarding monotherapy studies and pulmonary safety issues. FDA again requested controlled study, for ≥ 1 year, of patients with COPD ($n \geq 100$), asthma ($n \geq 100$), and Type 1 diabetics with underlying lung disease ($n \geq 100$), and stated that this information must be included with the initial NDA application.

29 Jul 02: Letter to sponsor requesting controlled high resolution computerized tomography (HRCT) data and lung biopsies in a subset of patients.

15 Nov 02: Teleconference regarding FDA requests for lung high resolution computerized tomography (HRCT) and lung biopsies for antigen-antibody complexes. FDA expressed concern regarding a decline seen in pulmonary function tests at six months, for forced expiratory volume in 1 second (FEV1) and lung diffusing capacity for carbon monoxide (DLco). FDA requested

HRCT for 50 patients on Exubera® and 50 patients on control at zero and 24 months. FDA requested that ongoing and future protocols include specific indications for pulmonary consultation for patients with the highest titres of circulating anti-insulin immunoglobulin G (IgG). FDA again expressed concern about possible immune complex deposition or other immune processes at the level of the alveolae and interstitium, and requested lung biopsies, with immunostaining, in 5-10 patients.

12 Dec 02: Letter to sponsor stating that, for efficacy and safety studies in Type 1 patients, both the inhaled insulin and subcutaneous (SQ) insulin groups must achieve HbA1cs that demonstrate tight glycemic control. The agency reiterated its previous requests for adequate pulmonary safety data at the time of NDA submission.

8 Dec 03: Letter to sponsor expressing concern about sponsor's proposal to study fewer patients with underlying lung disease. Reiterated previous requests for controlled study, for ≥ 1 year, of patients with COPD ($n \geq 100$), asthma ($n \geq 100$), and Type 1 diabetics with underlying lung disease ($n \geq 100$).

28 Jun 04: Pre-NDA meeting. FDA stated that the proposed efficacy and general safety databases appeared to be adequate to allow for review. The Division of Pulmonary and Allergy Drug Products (DPADP) stated that, for years, DPADP had been giving a clear and consistent message regarding the importance of pulmonary safety in the ultimate review of an Exubera® NDA. DPADP also stated that the duration of exposure and the proposed number of patients for whom data would be submitted in the underlying pulmonary disease protocols were far below that requested by DPADP on multiple occasions in prior meetings. Pfizer proposed submission of additional pulmonary safety data during the review cycle, but DPADP emphasized that the NDA should be complete upon submission.

2.6 Other Relevant Background Information

As of 8 Sep 05, Exubera® is not approved for marketing in any country. The European Agency for the Evaluation of Medicinal Products (EMA) filed the application for review on 4 Apr 04; as of 8 Sep 05, approval had not occurred.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Chemistry and Microbiology reviews are ongoing as of 15 Sep 05. To date, significant concerns

Assessment of the clinical significance of these concerns will follow completion of the CMC review, which is ongoing as of 15 Sep 05.

3.2 Animal Pharmacology/Toxicology

Major preclinical issues were not noted in the Animal Pharmacology and Toxicology review conducted by Dr. Alavi. However, animal studies were performed in nondiabetic animals, resulting in significant limitations of testing due to animal hypoglycemia. Longterm safety data in animals are not available. Animal carcinogenicity and reproductive toxicity studies were not performed.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary sources of clinical data for this review were the clinical trial data submitted by the applicant. The clinical reviewer also conducted an independent literature review. The Division of Pulmonary and Allergy Drug Products is conducting a separate review of the pulmonary safety of the product; this review is ongoing as of 15 Sep 05. The Endocrine and Metabolic Drugs Advisory Committee met on 8 Sep 05 regarding this product.

4.2 Tables of Clinical Studies

The following tables list all clinical studies submitted with the original NDA. They are grouped by diabetes type (1 or 2), and by study type (efficacy and safety, or clinical pharmacology).

Table 4.2.1 Controlled Clinical Efficacy and Safety Studies in Type 1 Diabetics						
Study Number	Study Type	Inhaled Insulin Regimen	Control Grp	n	Duration	Considered "Pivotal" by Applicant?
217-102	R ¹ , OL ² , PG ³ , inh ins vs "conventional" SQ ⁹	TID ⁴ ac ⁵ inh ins + hs ⁶ UL ⁷	subject's usual SQ (BID or TID)	35 inh ins, 37 SQ	3 mo	n
217-106	R, OL, PG, inh ins vs "conventional" SQ	TID ⁴ ac inh ins + hs UL	SQ regular insulin ac brkfst and supper + NPH ⁸ ac brkfst and hs	170 inh ins, 164 SQ	6 mo	y
217-107	R, OL, PG, inh ins vs "intensive" SQ	TID ac inh ins + NPH ac brkfst and hs	SQ regular insulin TID ac + NPH ac brkfst and hs	162 inh ins, 165 SQ	6 mo	y
A2171009	R, OL, PG, children ages 6-11, inh ins vs "conventional" SQ	TID ac inh ins + hs UL or hs NPH or BID UL or BID NPH	SQ regular or lispro insulin ac brkfst and supper + q day or BID UL or NPH (2 nd UL or NPH ac supper or hs)	61 inh ins, 59 SQ	3 mo	n

1 randomized
 2 open-label
 3 parallel group
 4 three times daily
 5 before meals
 6 at bedtime
 7 Ultralente® insulin
 8 neutral protamine Hagedorn insulin
 9 subcutaneous

Table 4.2.2 Ongoing Clinical Efficacy and Safety Studies in Type 1 Diabetics						
Study Number	Study Type	Inh Ins Regimen	Control Grp	n	Duration	Considered "Pivotal" by Applicant?
A2171022	R, OL, PG, general safety and pulmonary safety	titrated premeal inh ins + hs UL, NPH or insulin glargine	SQ premeal lispro, regular or aspart + hs UL, NPH or insulin glargine	randomized 291 inh, 291 SQ; completed 12 months 238 inh, 258 SQ	2 yrs planned	y

Table 4.2.3 Controlled Clinical Efficacy and Safety Studies in Type 2 Diabetics						
Study Number	Study Type	Inhaled Insulin Regimen	Control Group	n	Duration	Considered "Pivotal" by Applicant?
217-103	R, OL, PG; inh ins vs "conventional" SQ in Type 2s already on insulin	TID ac inh ins + hs UL	subject's usual SQ (BID or TID)	28 inh, 28 SQ	3 mo	n
217-104	R, OL, PG; inh ins + OAs ¹ vs OAs in pts not well-controlled on OAs	TID ac inh ins + subject's usual OAs	subject's usual OAs	33 inh + OA, 36 OA	3 mo	n
217-108	R, OL, PG; inh ins vs "conventional" SQ in pts already on stable SQ regimen	TID ⁴ ac inh ins + hs UL	SQ regular and NPH, both BID ac brkfst and supper	149 inh, 149 SQ	6 mo	y
217-109	R, OL, PG; inh ins	TID ac	continued combo	105 inh alone,	3 mo	y

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Study Number	Study Type	Inhaled Insulin Regimen	Control Group	n	Duration	Considered "Pivotal" by Applicant?
	monotherapy vs combo OAs in pts not well-controlled on combo OAs	monotherapy or TID ac + continued combo OA	OA	102 inh + OA, 102 OA		
217-110	R, OL, PG; inh ins vs rosiglitazone	TID ac	rosi ² 4 mg BID ac brkfst and supper	76 inh, 69 rosi	3 mo	y
A2171001	R, OL, PG; inh ins + SU ³ vs met + SU in pts poorly controlled on SU	TID ac + SU	met ⁴ + SU	222 inh + SU, 201 met + SU	6 mo reported of planned 2 yr study	n
A2171002	R, OL, PG; inh ins + met vs SU + met in pts poorly controlled on met	TID ac + met 1 gm BID	glibenclamide (max 5 mg BID) + met 1 gm BID	239 inh + met, 231 glibenclamide + met	6 mo reported of planned 2 yr study	n
A2171001/ A2171002 combined 2 yr final report	R, OL, PG	TID ac + met 1 gm BID or SU	baseline met 1 gm BID or baseline SU + either met or glibenclamide	471 inh, 441 combo OAs	2 yrs	n
A2171027	R, OL, PG; short-term pulmonary safety and PFT study	TID ac x 12 weeks, then SQ x 12 weeks	SQ x 24 wks	110 inh ins then SQ, 116 SQ only	3 mo with comparator, 3 mo followup SQ	n
1 oral diabetic agents 2 rosiglitazone 3 sulfonylurea 4 metformin						

Study Number	Study Type	Inh Ins Regimen	Control Group	n	Duration	Considered "Pivotal" by Applicant?
A2171017	R, OL, PG; inh ins vs rosi as add-on for pts poorly controlled on SU + met	inh ins + met +/- SU	met + rosi	74 randomized	52 wks planned	n
A2171029	R, OL, PG; inh ins vs SQ pulmonary safety study	titrated premeal inh ins + hs UL, NPH or insulin glargine	SQ premeal lispro, regular or aspart + hs UL, NPH or insulin glargine	randomized 316 inh, 314 SQ; completed 12 months = 228 inh, 235 SQ	2 yrs planned	y

Study Number	Study Type	Inh Ins Regimen	Comparator	n	Duration	Considered "Pivotal" by Applicant?
A2171028	R, OL, PG, in pts with asthma	TID ac + hs or BID long-acting insulin ¹ SQ	TID short-acting SQ + hs or BID long-acting SQ	randomized 45 inh, 49 SQ; completed 7 inh, 10 SQ	15 mo planned	n
A2171030	R, OL, PG, in pts with COPD	TID ac + hs or BID long-acting SQ	TID short-acting SQ + hs or BID long-acting SQ	randomized 30 inh, 27 SQ; completed 8 inh, 6 SQ	15 mo planned	n
1 hs UL or glargine; or BID UL or NPH						

Table 4.2.6 Uncontrolled Clinical Studies in Combined Type 1 and Type 2 Diabetics

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration	Considered "Pivotal" by Applicant?
217-111	OL extension of multiple Phase 3 trials; later randomized withdrawal to examine PFT effects after withdrawal	T1D inh ins ac + long-acting insulin or OA (continued throughout extension)	T1D inh ins ac + long-acting insulin or OA for up to 36 months; then randomized withdrawal	Prior to randomized withdrawal, 664 Type 1s and 626 Type 2s; after randomized withdrawal, 394 cont inh ins and 415 discontinued inh ins	up to 36 months before randomized withdrawal; 6 months after randomized withdrawal	n
A2171036	OL extension of other extension protocols (102E, 103E and 104E)	inh as short-acting diabetic treatment +/- other long-acting diabetic treatments	no control	62 ongoing	up to 4 years	n

Table 4.2.7 Clinical Pharmacology Studies in Healthy Subjects

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
217-003	R, OL, 3-way X-over ¹ ; examine effect of increased # of inhalations on plasma insulin concentrations	1x1 mg 2x1 mg 3x1 mg	n/a	18	1 day/tx
A2171012	R, OL, 6-period X-over; dose proportionality and PK ² using 1 and 3 mg dose combinations	1, 2, 3, 4 and 6 mg	n/a	25	single dose x 2 days
HA001	OL, self-controlled; compare bioavailability of inh vs SQ	0.32 U/kg, 0.5 U/kg	SQ regular insulin, 0.15 U/kg	24	1 dose q 2 weeks (total 5 wks)
217-001	R, OL, 3-way X-over; compare concentrations for sq regular insulin, and 1 and 3 mg inh ins	3x1 mg 1x3 mg	SQ regular insulin 0.15 U/kg	24	1 day/tx
217-011	R, OL, 3-period, 3-tx X-over; examine effect of change in rate of inhalation	3 mg; inhalation rates of 10, 25, and >35 L/min	n/a	12	1 day/tx
217-002	R, OL, 3-way X-over; examine effect of 3 different breathing regimens	3 mg; "standard" breathing maneuver, breathing preceded by forced exhalation, forced exhalation + 3 maximum inspirations	n/a	14	1 day/tx
217-004	R, OL, 2-tx, 3-period X-over; intrasubject variability in insulin and glucose response, and effect of breath-hold	3 mg on days 1 and 8; 3 mg on day 15 without breath-holding	n/a	20	1 day/tx
217-012	R, OL, 4-period, 4-way X-over; compare closed and open chamber top position with different insulins	P2 inhaler with 3 mg Lilly insulin, P3 inhaler with HMR ¹ insulin and closed chamber top, P3 inhaler with HMR insulin and open chamber top	10 u SQ regular insulin	23	1 day/tx
217-014	R, OL, 3-period, 3-way X-over; compare particle size and breath-holding effects	2 mg as 3.4 µM; 2 mg as 2.2 µm with breath-holding; 2 mg as 2.2 µM without breath-holding	n/a	24	1 day/tx
217-019	R, OL, 3-period, 3-way X-over; effect of controlled inhalation rate and reduced particle size	2 mg, 3.4 µM, inhal rate 25 L/min; 2 mg, 3.4 µM, 10 L/min; 2 mg, 2.2 µM, 10 L/min	n/a	25	1 day/tx
217-015	R, OL, 2-period, 2-way X-	2 mg; fill weights = 1.7 mg	n/a	27	1 day/tx

Table 4.2.7 Clinical Pharmacology Studies in Healthy Subjects					
Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
	over; effect of fill weight	powder/blister (60% insulin) or 5 mg powder/blister (20% insulin)			
A2171006	R, OL, 5-period, X-over; bioavailability of 1 and 3 mg blisters compared to SQ; within subject variability of 1 and 3 mg blisters	3x1 mg 1x3 mg	9 U SQ regular insulin	27	1 dose/ tx period
A2171015	R, OL, 5-period X-over; bioequivalence of Phase 3 and commercial formulations of 1 mg	1 mg Phase 3 formulation; 1 mg commercial formulation	3 U SQ regular insulin	79	inh 1 dose x 2 days; SQ 1 dose x 1 day
A2171014	R, OL, 5-period X-over; bioequivalence of Phase 3 and commercial formulations of 3 mg	3 mg Phase 3 formulation, 3 mg commercial formulation	9 U SQ regular insulin	51	inh 1 dose x 2 days; SQ 1 dose x 1 day
217-008	R, OL, 3-period, 3 tx X-over; effect of change in particle size on site of deposition in lung, and on PK/PD	2 mg of 4 µM; 2 mg of 2 µM; 1 mg of 1 µM	n/a	13	1 day/tx
217-007	R, OL, 2-period, X-over; bioavailability in obese subjects	3 mg	10 u SQ regular insulin	12 obese, 12 nl wt	1 day/tx
217-006	R, OL, 2-period X-over; bioavailability in adolescents ages 12-17 yrs	2x1 mg in subjects < 50 kg body wt; 1x3 mg in subjects >50 kg body wt	0.15 u/kg regular insulin SQ	20 inh; 20 SQ	1 day/tx
217-010	R, OL, 3-period; effect of rhinoviral challenge vs saline on insulin concentrations	3 mg on days 1, 3 and 4	n/a	20 rhinovirus, 4 saline	3 days
A2171016	R, OL, 4-way X-over; PK/PD in healthy Japanese men	1, 3 and 6 mg	12 U regular insulin SQ	16	1 dose/ tx period
217-023	R, OL, 3-period, 3 tx, X-over; Japanese and Caucasian males	1 and 2 mg, Japanese vs Caucasian	6 U regular insulin SQ, Japanese vs Caucasian	12 Japanese, 13 Caucasian	1 dose/tx period
217-005	R, OL, 2-period, 2 tx, X-over; bioavailability in smokers	1 mg	0.15 U/kg regular insulin SQ	24	1 day/tx
217-016	R, OL, PG; effect of cessation of smoking on bioavailability	2 mg, smokers vs nonsmokers	6 U regular insulin SQ	38 smokers, 30 nonsmokers	1 day/tx
A2171020	R, OL; effect of short-term smoking cessation	1 mg; smokers willing to quit for 7 days vs nonsmokers	3 U SQ regular insulin	20 smokers, 10 nonsmokers	2 single doses for nonsmokers; 6 single doses for smokers
217-017	R, OL, 3-period, 3-way X-over; euglycemic clamp to compare PK/PD of inh ins, lispro and regular insulin	2x3 mg	18 U lispro SQ or 18 U regular insulin SQ	18 inh, 17 lispro, 17 regular insulin	1 day/ tx period

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Table 4.2.8 Clinical Pharmacology Studies in Type 1 Diabetics

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
217-021	R, OL, 4-period X-over; compare PK/PD inh ins to SQ	3, 4, or 6 mg	9, 12, or 18 U patient's usual short-acting premeal insulin	22	1 dose/ tx period
217-018	R, OL, 2-period X-over; ages 6-17	1 mg (wt 20-34.9 kg); 2 mg (wt 35-49.9 kg); 3 mg (50-64.9 kg)	SQ 3 U (20-34.9 kg); 6 U (35-49.9 kg); 9 U (50-64.9 kg)	13 pediatric (ages 6-11); 14 adolescent (ages 12-17)	1 day
A2171026	R, OL, PG; examine week 24 change from baseline in postprandial glucose	T1D ac titrated + BID NPH	T1D ac titrated SQ regular insulin + BID NPH	24 inh, 23 SQ	24 weeks

Table 4.2.9 Clinical Pharmacology Studies in Type 2 Diabetics

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
217-101	R, OL, 4-period X-over; compare PK/PD inh ins to SQ	1 mg/18 kg	0.2 U/kg SQ insulin	16	1 dose/ tx period
A2171004	R, OL, 4-way X-over; compare inh vs SQ bioavailability in elderly obese patients	4 mg for pts < 150 kg wt; 6 mg for pts ≥ 150 kg wt	12 U SQ for pts <150 kg wt; 18 U SQ for pts ≥ 150 kg wt	20	2 doses ea tx on separate days
A2171003	R, OL, 4-way X-over; euglycemic clamp, intra- and inter- subject variability in smokers and nonsmokers	6 mg	18 U SQ	15 smokers, 14 nonsmokers	1 day/tx

Table 4.2.10 Clinical Pharmacology Study in Pregnant Diabetics

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
A2171007	R, OL, 2-period X-over; pregnant gestational diabetics and pregnant pregestational Type 2 diabetics	3 mg	9 U SQ	10 gestational, 3 pregestational	1 dose/ tx period

Table 4.2.11 Clinical Pharmacology Studies in Patients with Underlying Lung Disease

Study Number	Study Type	Inh Ins Regimen	Comparator Regimen	n	Duration
217-009	OL, 3-period X-over; bioavailability in mild asthmatics vs healthy nondiabetics	1x1 mg 1x3 mg	0.15 U/kg regular SQ insulin	24 asthma; 12 nl	1 day/tx
A2171005	R, OL, X-over; bioavailability in mild COPD pts vs healthy nondiabetics; examine effect of bronchodilator on bioavailability	1x3 mg; albuterol before and after	9 U SQ regular insulin; albuterol before and after	26 COPD; 12 nl	1 dose/ tx period

4.3 Review Strategy

For the efficacy review, the clinical reviewer emphasized evaluation of the controlled Phase 3 trials. For the safety review, the clinical reviewer emphasized review of the controlled Phase 2 and Phase 3 studies for comparison of rates of events. Safety review was augmented by review of all serious adverse event data from all human trials.

Separate reviews are being conducted by Biostatistics (separate reviewers for safety and efficacy), Animal Pharmacology and Toxicology, Biopharmacology, Chemistry (multiple reviewers), and Microbiology.

4.4 Data Quality and Integrity

The Division of Metabolic and Endocrine Drug Products requested that the Division of Scientific Investigations conduct clinical site audits at the University of Vermont (Principal Investigator Dr. William Cefalu, Study 107 of most interest) and Methodist Hospital San Antonio (Principal Investigator Dr. Sherwyn Schwartz, Study 106 of most interest). Inspection of these sites and audit of source documents revealed only minor findings, and the Division of Scientific Investigations concluded that data from these two sites were acceptable in support of this NDA.

4.5 Compliance with Good Clinical Practices

All subjects in all trials were required to provide informed consent. Review of the consent forms for the Phase 3 studies revealed adequate descriptions of the potential risks of participation. The applicant documented protocol violations when they occurred. Major protocol violations were sometimes cause for discontinuation from study, as further discussed in Section 7.1.3. The Division of Scientific Investigations conducted audits for site-specific issues regarding good clinical practices, and found no significant issues.

In general, the applicant and previous sponsors involved in the development of this product appear to have complied with the principles of good clinical practice.

4.6 Financial Disclosures

The applicant provided financial disclosure in keeping with 21 CFR 54.2. For the 2,336 investigators involved in studies of Exubera[®], the applicant obtained financial disclosure forms from all but 80. The applicant demonstrated due diligence in attempting to obtain forms from these investigators, with at least two written requests and two phone calls for each investigator. A total of 137 investigators had financial information to disclose in the form of equity interest or significant payments of other sorts (SPOOS) exceeding \$25,000. Financial disclosure forms for all these investigators are included in the NDA, Module 1, Section 1.3.6.5. Because of the large number of investigators with significant equity or payments of other sorts, the clinical reviewer limited review to those individual investigators with >\$100,000 in financial disclosures. The following table summarizes those disclosures, and notes the study for which the investigator had the largest financial disclosure, the center number, and the number of patients contributed from that center.

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Table 4.6.1 Financial Disclosure Information for Investigators Disclosing >\$100,000 in Equity Interest or Significant Payments of Other Sorts (SPOOS)

Total Amount Disclosed	Investigator	SPOOS	Equity	Studies ¹	Centers	# Subjects from Center
\$453,000		\$453,000				
\$444,000			\$444,000			
\$397,000			\$397,000			
\$334,000			\$334,000			
\$326,000		\$215,000	\$111,000			
\$264,000			\$264,000			
\$248,000		\$248,000				
\$243,000			\$243,000			
\$221,000			\$221,000			
\$209,000			\$209,000			
\$209,000			\$209,000			
\$175,000			\$175,000			
\$166,000		\$166,000				
\$156,000		\$156,000				
\$152,000		\$152,000				
\$151,000		\$151,000				
\$141,000		\$141,000				
\$140,000			\$140,000			
\$131,000			\$131,000			
\$128,000			\$128,000			
\$125,000		\$125,000				
\$123,000			\$123,000			
\$121,000		\$121,000				
\$120,000		\$120,000				
\$111,000		\$111,000				
\$109,000		\$109,000				

¹ Study for which the investigator had the largest financial disclosure. If the investigator disclosed the same amount for >1 study, all studies with that amount are claimed. Some investigators participated in other studies, but only those studies with the largest financial disclosure are listed.

Dr. Cefalu, —

In order to assess whether the financial interests held by these investigators could have influenced the outcome of any of the affected studies, the following table examines the data by study, center, and total financial interests of investigators disclosing >\$100,000 per investigator.

Table 4.6.2: Financial Interests by Center of Investigators Disclosing >\$100,000

Study	Total Patients in Study	Total Patients in Study Contributed by Centers with Investigators Disclosing >\$100,000 (% of Total Patients in Study)	Center	Total Patients in Center	Total Financial Interest per Center for Investigators Disclosing >\$100,000	Total Financial Interest per Study for Investigators Disclosing >\$100,000
					\$152,000	\$1,107,000
					\$444,000	
					\$248,000	
					\$123,000	
					\$140,000	
					\$366,000	\$1,213,000
					\$453,000	
					\$243,000 + \$151,000	
					\$444,000	\$725,000
					\$125,000	
					\$156,000	
					\$121,000 + \$111,000	\$1,030,000
					\$248,000	
					\$243,000 + \$151,000	
					\$156,000	\$2,552,000
					\$121,000 + \$111,000	
					\$453,000	
					\$152,000	
					\$397,000	
					\$243,000 + \$151,000	
					\$156,000	
					\$131,000	\$926,000
					\$221,000	
					\$141,000	
					\$166,000 + \$109,000	
					\$243,000	
					\$334,000	\$175,000
					\$209,000	
\$140,000						
\$175,000	\$175,000					
\$175,000						
\$243,000	\$1,151,000					
\$264,000						
\$175,000						
\$120,000						
\$140,000						
\$209,000	\$303,000					
\$128,000						
\$175,000						

Of the _____ studies, Study _____ appeared most vulnerable to investigator bias due to financial interests. Study _____
_____. Thusfar _____ nvestigators have disclosed financial interests of >\$100,000 each, and their disclosures to date total \$1,151,000. Their centers have contributed _____ of patients enrolled to date.

The statistical review team (Ms. Mele and Dr. Buenconsejo) reanalyzed the primary efficacy endpoint for Study _____ and the primary safety endpoints for Study _____, excluding the study centers in the above table. For Study _____ results for the primary efficacy endpoint (change in I _____) remained highly statistically significantly in favor of the inhaled insulin group, even when those centers with large investigator financial disclosures were excluded (p value including all centers = <0.0001; p value excluding high financial interest centers = 0.0007). For Study _____, the difference between treatment groups for change in _____ months was nonsignificant when including all centers, and remained nonsignificant when excluding high financial interest centers.

5 CLINICAL PHARMACOLOGY

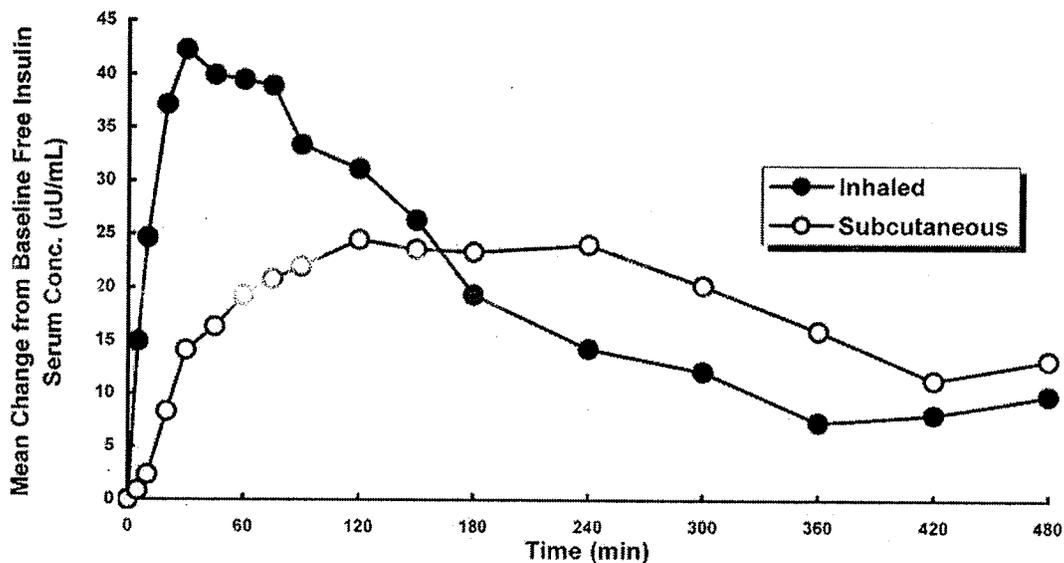
As of 15 Sep 05, the Biopharmacology review of Exubera® is ongoing. The information below is extracted from the applicant's summary information. The clinical reviewer does not have expertise in this area, and the Biopharmacology review should be considered to represent the most accurate FDA interpretation of the NDA findings regarding clinical pharmacology.

5.1 Pharmacokinetics

In all Pharmacokinetic (PK studies), subcutaneous regular insulin was used as a comparator. Inhaled insulin is more rapidly absorbed than regular SQ insulin (Tmax 38-78 minutes vs Tmax 83-258 minutes). Postprandial Cmax is similar for inhaled insulin and regular SQ insulin, but fasting Cmax for inhaled insulin is higher. The following figure illustrates the concentration-time profile of inhaled insulin and regular SQ insulin.

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Figure 5.1 Mean Change from Baseline in Serum Concentration of Free Insulin in Nonsmoking Patients with Type 2 Diabetes Mellitus Following Administration of 2x3 mg Inhaled Insulin or 18 U SQ Regular Insulin



Source: Module 2.7.2, Figure 2

Bioavailability was evaluated in adults with Type 1 diabetes (Study 021), adults with Type 2 diabetes (Study 1003), children and adolescents with Type 1 diabetes (Study 018), elderly obese patients with Type 2 diabetes (Study 1004), and pregnant gestational/pregestational diabetics (Study 1007). Among these various diabetic populations, mean bioavailability of inhaled insulin relative to SQ insulin was 10% (range 8-11%).

Dose proportionality and dose equivalence could be of clinical concern.

Dose proportionality was not demonstrated over a range of doses in Study A2171012. In this study, dose proportionality of several dose combinations was compared, including doses of 1 mg (1x1 mg), 2 mg (2x1 mg), 3 mg (1x3 mg), 4 mg (1x3 mg + 1x1 mg) and 6 mg (2x3 mg). None of the 90% confidence intervals for any AUC comparison fell within the applicant's predefined bioequivalence boundaries (80-125%).

When examining the actual individual subject data from the trial, one notes that multiple samples obtained for insulin C_{max} and AUC for 3 mg dosing had lower values than the mean seen for 2 mg dosing. For C_{max}, 10/29 samples obtained for C_{max} at the 3 mg dose fell below the mean C_{max} for the 2 mg dose. In this study, each patient generally only received 3 of the 5 dose combinations. A total of 6 patients received both the 2 mg dose and the 3 mg dose (doses given at different times during study). Among these 6 patients (each of whom had 2 C_{max} values recorded for each dose), 4/6 had a C_{max} value for the 3 mg dose that was lower than a C_{max}

value for the 2 mg dose. A total of 6/26 samples for the 6 mg dose had lower Cmax values than the mean for the 4 mg dose, and 2/6 patients who received both the 4 mg dose and the 6 mg dose had a Cmax value for the 6 mg dose that was lower than a Cmax value for the 4 mg dose (Source: Applicant's Table 5.2.1, Study 1012 report).

Similar findings are noted for AUC at each time interval, as illustrated in the following table:

	AUC 0-60	AUC 0-120	AUC 0-360	AUC 0-600
Number and percentage of AUC samples for 3 mg dose with lower AUC than the mean AUC for the 2 mg dose	8/29 (28%)	9/29 (31%)	11/29 (38%)	12/29 (41%)
Number and percentage of AUC samples for 6 mg dose with lower AUC than the mean AUC for the 4 mg dose	6/26 (23%)	4/26 (15%)	6/26 (23%)	7/26 (27%)
Number and percentage of patients who had both a 3 mg and 2 mg dose, who had a lower AUC value at the 3 mg dose than a 2 mg dose AUC ¹	4/6 (67%)	2/6 (33%)	3/6 (50%)	4/6 (67%)
Number and percentage of patients who had both a 6 mg and 4 mg dose, who had a lower AUC value at the 6 mg dose than a 4 mg dose AUC	4/6 (67%)	2/6 (33%)	2/6 (33%)	1/5 (20%)

¹ Each patient had two measurements for each AUC time interval.
 Source: Applicant's Tables 5.2.3, 5.2.4, 5.2.5, 5.2.6, Study 1012 report

This could lead to clinical problems with dose titration; if a clinician advises a patient to increase their dose of inhaled insulin from 2 mg to 3 mg, expecting an increased exposure and/or concentration of insulin, the patient could actually have a paradoxical decrease in exposure and/or concentration. This could be a problem for patients in the lower dosage ranges, e.g. Type 1 diabetics and children. If these patients have high blood sugar levels at 2 mg, and are deemed to need more insulin action, they could actually achieve lower insulin levels with an "increase" to 1x3 mg, and develop paradoxically higher blood sugars. For the brittle Type 1 diabetic, these changes could be significant.

Dose equivalence was also not demonstrated for three 1 mg blisters and one 3 mg blister. In Study 1006, the AUC₀₋₃₆₀ for 3 inhalations of 1 mg was approximately 40% higher than that for 1 inhalation of 3 mg, and Cmax was approximately 30% higher. This difference appears to be related in part (but not entirely) to a problem with the inhaler; it is much more efficient in breaking up the powder in blisters of a lower fill mass. Although the overall emitted mass is fairly similar for 3x1 mg and 1x3 mg, the 1 mg strength emits a higher proportion of particles — which the applicant asserts is the particle size most capable of reaching the deep lung, and the particle size associated with optimal systemic absorption. However, the relative difference in fine particle dose for the 1 mg blister vs the 3 mg blister does not entirely account for the dose nonequivalence, as demonstrated in the following table proposed by the applicant for inclusion in the product label:

Table 5.1.2

Fill Mass (mg powder)	Nominal Dose (mg insulin)	Emitted	Fine Particle Dose ² (mg insulin)
1.7	1.0		0.4
5.1	3.0		1.0

¹ Flow rate of 30 L/min for 2.5 seconds

² Flow rate of 28.3 L/min for 3 seconds

Source: Applicant's Table 1, proposed Exubera® label

The applicant has proposed some dose acceptance criteria using fine particle dose rather than emitted mass. This does not have a precedent within inhaled medicines. However, if further pharmacodynamic studies demonstrated a more consistent relationship between fine particle mass and pharmacodynamic effect, dose titration (and perhaps blister labeling) by fine particle mass might make dose titration less confusing. A crude indication of this was gained in Study 019, in which glucose pharmacodynamics were compared using 3.4 μM and 2.2 μM mean particle sizes. In this study, 2.2 μM particles resulted in higher AUC and C_{max} than did an equivalent mass of 3.4 μM particles. Of possible use would be a comparison of rates of hypoglycemia and mean changes in glucose levels when one uses titration by mg dosing vs fine particle dosing.

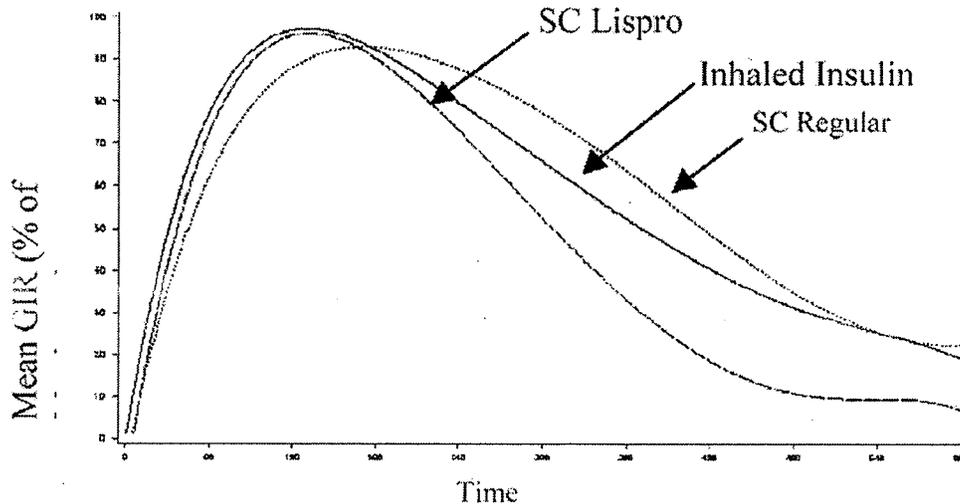
In addition to the potential problems noted above with titration, patients must be instructed not to substitute three 1 mg inhalations for one 3 mg inhalation if they run out of their 3 mg blisters. This could result in greater insulin exposure and risk for hypoglycemia.

As mentioned above, the FDA Biopharmacology review is ongoing as of 15 Sep 05; the material above is based on the clinical reviewer's examination of the NDA materials. However, the FDA Biopharmacology reviewer has the expertise in this area, and that review will represent the most accurate interpretation of the clinical pharmacology data.

5.2 Pharmacodynamics

In healthy subjects, inhaled insulin exhibited a rapid onset of action similar to SQ insulin lispro, and a duration of action similar to SQ regular insulin. This time-action profile is illustrated in the following figure from Study 217-017, a glucose clamp study. In this study, glucose was held nearly constant to a pre-defined level by varying the glucose infusion rate (GIR). An earlier GIR T_{max} was demonstrated for inhaled insulin and SQ lispro than that seen for SQ regular insulin. A longer duration of action was demonstrated for inhaled insulin and SQ regular than for SQ lispro.

Figure 5.2.1 Mean Glucose Infusion Rate Over Time, Glucose Clamp Study 217-017, Healthy Subjects

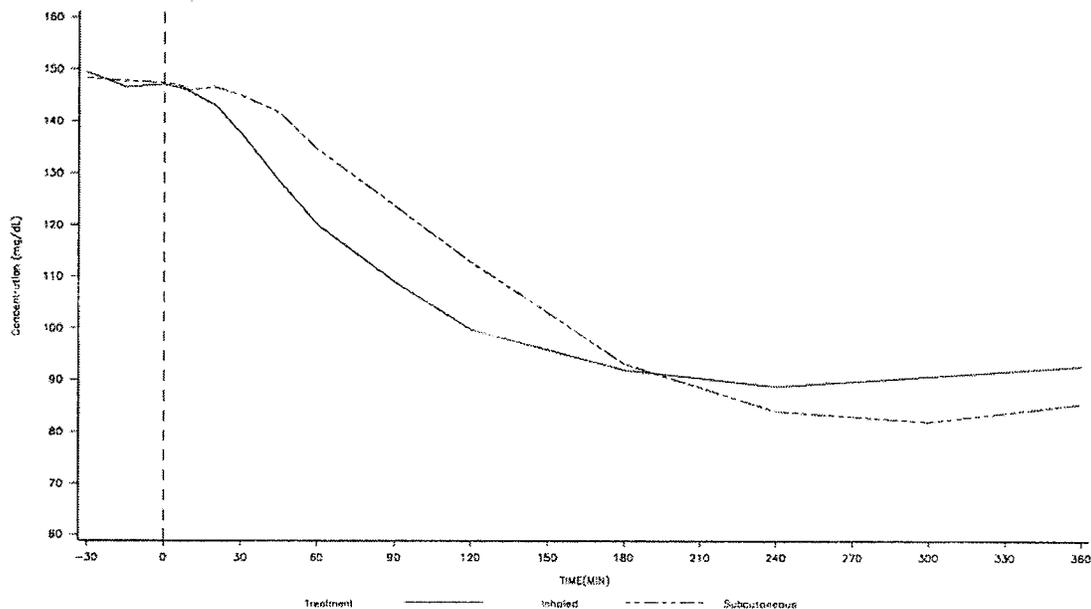


Source: Module 2.7.2, Figure 8

Glucose clamp pharmacodynamics were not compared between insulin lispro and inhaled insulin in diabetic patients. In Study 1004, postprandial glucose declined somewhat more rapidly over the first 120 minutes after inhaled insulin administration than it did after SQ regular insulin administration. Time to peak glucose-lowering activity was not statistically significantly different between the two treatments.

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Figure 5.2.2 Mean Glucose Concentration Following Administration of Inhaled Insulin (4 mg) or SQ Regular Insulin (12 U), Type 2 Diabetics, Study 1004



Source Data: Section 1.3, Table 2.5 Date of Data Extraction: 11MAY2001 Date of Table Generation: 09OCT2001 (14-34)

Source: Applicant's Figure 2.1, Study 1004 report

5.3 Exposure-Response Relationships

The applicant did not provide exposure-response analyses. Exposure-response relationships will be explored by the Biopharmaceutics reviewer.

6 INTEGRATED REVIEW OF EFFICACY

The applicant proposes the following language for the "Indications and Usage" section of the product label:

"EXUBERA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. EXUBERA has an onset of action similar to rapid-acting insulin analogs and has a duration of glucose-lowering activity comparable to subcutaneously administered regular human insulin. In patients with Type 1 diabetes, EXUBERA should be used in regimens that include a longer-acting insulin. In patients with type 2 diabetes, EXUBERA can be used as monotherapy or in combination with oral agents or longer-acting insulins."

Although the basic indication is for control of hyperglycemia in adult diabetics, the clinical reviewer chose to examine the evidence for efficacy for adult Type 1 and adult Type 2 diabetes separately, as these diseases differ in several ways, including etiology, age at onset, expected time from diagnosis to onset of complications, et al. Efficacy in adult Type 1 diabetics is

discussed in Section 6.1, and efficacy for adult Type 2 diabetics is discussed in Sections 6.2-6.4. Because the applicant proposes use in Type 2 diabetics either as monotherapy, or in combination with longer-acting insulins or oral agents, the clinical reviewer considered monotherapy and combination therapy trials separately. Section 6.2 covers inhaled insulin as monotherapy in Type 2 diabetes, Section 6.3 covers combined therapy for Type 2 diabetes with inhaled insulin and longer-acting insulins, and Section 6.4 covers combination therapy with inhaled insulin and oral agents.

Although the applicant does not seek an indication for the treatment of diabetes in pediatric patients, the clinical reviewer anticipates significant interest in the potential efficacy of this product in children, with the potential for widespread off-label use. The clinical reviewer therefore provides a brief review of the limited data regarding pediatric efficacy in Section 6.5.

For each of these indications, the clinical reviewer has provided specific review of the most relevant trial or trials for that indication. When appropriate, summary information for other trials regarding that indication has also been included.

6.1 Indication: Treatment of Hyperglycemia in Adult Type 1 Diabetics; Inhaled Insulin in Combination with a Longer-Acting Insulin

6.1.1 Methods

The clinical reviewer placed emphasis on Studies 217-106 and 217-107 for evaluation of efficacy for Type 1 diabetics. The applicant also designated these trials as "pivotal". Study 217-106 was a trial involving 334 patients, and compared inhaled insulin to "conventional" subcutaneous insulin therapy. Study 217-107 involved 327 patients, and compared inhaled insulin to "intensive" subcutaneous insulin therapy. Because the standard of care for Type 1 diabetics is now intensive insulin therapy, greater emphasis was placed on Study 217-107.

6.1.2 General Discussion of Endpoints

For both Study 217-107 and Study 217-106, the primary efficacy endpoint was the change in HbA1c from baseline to week 24 of treatment. HbA1c is well-accepted as a surrogate endpoint for evidence of glycemic control in diabetes, and is the most commonly used primary endpoint in diabetes efficacy trials submitted to the FDA. Of possible endpoints that are measurable within the limitations of practical clinical trial sample size and duration, HbA1c is at present, the best available surrogate endpoint. However, as with most such markers, HbA1c is an imperfect surrogate. Problems exist with assay variability, biologic variability between individuals, and the question of utility as a predictor of diabetic complications. An ideal trial would use diabetic complications as endpoints, but the trial size and duration needed for use of such endpoints would be very large. There is some controversy about whether HbA1c is truly a good marker of the risk for complications of diabetes. However, the correlation of HbA1c with risk for the development of microvascular disease in Type 1 diabetics is well-established (Jeffcoate 2004), and thus HbA1c is a good surrogate endpoint for the trials of inhaled insulin in Type 1 diabetics.

6.1.3 Study Design

6.1.3.1 General Description of Study Design

The design for Study 217-107 is described in Section 6.1.3.1.1; a brief description of how Study 217-106 differed from 217-107 appears in Section 6.1.3.1.2.

6.1.3.1.1 Design of Study 217-107

Study 217-107 was a 6-month, block-allocated (within center), open-label, parallel group efficacy and safety trial intended to establish noninferiority of inhaled insulin to subcutaneous insulin, with the goal of "intensive" diabetes control in both treatment groups. A total of 162 patients were treated with premeal inhaled insulin and 165 patients were treated with premeal subcutaneous regular insulin. All patients received NPH insulin prebreakfast and pre-bed (hs). The study included male and female Type 1 diabetics, ages 12-65 years, with HbA1cs between 6 and 11% at entry.

The primary efficacy endpoint was change in HbA1c from baseline to week 24 of treatment. A noninferiority margin of 0.5% was specified.

Secondary efficacy endpoints included (full list pg 31 of study report):

- percentage of patients achieving acceptable glycemic control (HbA1c <7% and <8%) at 24 weeks
- change in fasting plasma glucose
- two-hour postprandial glucose and insulin increments following a standardized meal (baseline and week 24)
- body weight
- fasting lipids

In addition to routine safety monitoring and laboratory, special safety assessments included:

- incidence and severity of hypoglycemic events
- chest X-ray at screening and week 24
- insulin antibodies at screening and week 24
- spirometry at baseline, week 12 and week 24
- lung volume, diffusion capacity and oxygen saturation at baseline and week 24
- thoracic high resolution computerized tomography (HRCT) in a subset of patients at baseline and week 24

6.1.3.1.2 Design Differences between Studies 107 and 106

Study 106 design differed from Study 107 design in the following ways:

- The control in 106 was "conventional" subcutaneous insulin administration, meaning that patients received only two shots per day, a mixture of NPH and regular insulin administered before breakfast and supper.

- Secondary endpoints included the percentage of patients achieving a HbA1c <8%, but not the percentage achieving <7%.

6.1.3.2 Adequacy of Study Design with Reference to Code of Federal Regulations Description of "Adequate and Well-controlled Studies"

The characteristics of "adequate and well-controlled" studies are described in 21 CFR 314.126; an abbreviated description includes the following:

- There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results.
- The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. A placebo concurrent control is the first acceptable type of control recognized in the regulation; other types of controls are possible in certain circumstances.
- The method of selection of subjects provides adequate assurance that they have the disease or condition being studied.
- The method of assigning patients to treatment and control groups minimizes bias and is intended to assure the comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease and use of drugs or therapy other than the test drug.
- Adequate measures are taken to minimize bias on the part of the subjects, observers and analysts of the data.
- The methods of assessment of subjects' response are well-defined and reliable.
- There is an analysis of the results of the study adequate to assess the effects of the drug.

In general, the designs of Studies 106 and 107 are consistent with "adequate and well-controlled trials". One concern regarding trial design was the method of treatment assignment, which was block allocation within center. However, ordering of block sizes was random, and statistical analyses did not reveal evidence of bias related to this treatment allocation method. The statistical review will include further explanation of the allocation procedure, and its implications.

All studies were open label, and none used inhaler or injection placebos. Historically, clinical trials of insulin have generally not been blinded trials, due to safety, logistical, and ethical concerns. In the case of Exubera®, the use of a "double dummy" technique, where all patients had both an inhaler and injections (with only one of the two methods delivering active study drug or active control), would have been logistically very difficult and cumbersome. Placebo injections pose ethical issues, and Institutional Review Boards responsible for approval of initiation of trials often will not agree to allow studies to include placebo injections. Overall, the clinical reviewer generally did not note evidence of problems related to lack of blinding in Studies 106 and 107, or to lack of blinding in other Phase 2 and Phase 3 trials. However, please refer to Section 7.1.3 for a discussion of a concern for apparent misclassification of reasons for discontinuation. Apparent misclassification occurred more frequently among inhaled insulin

group patients than among comparator patients. This discrepancy is unexplained, but may be attributable to investigator reporting bias in favor of open-label inhaled insulin.

6.1.4 Efficacy Findings

6.1.4.1 Demographics

Demographic characteristics for Studies 106 and 107 are included in the following table:

Characteristic	Inh Ins	SQ
Study 107 Male:Female	54:49	59:46
Study 106 Male:Female	70:67	71:64
Study 107 Mean Age, years	38.1	38.6
Study 106 Mean Age, years	38.2	38.2
Study 107 Mean BMI (with range), Male	26.1 (19-32)	26.3 (20-35)
Study 106 Mean BMI (with range), Male	26.4 (21-36)	25.8 (19-32)
Study 107 Mean BMI (with range), Female	24.7 (18-32)	24.9 (17-31)
Study 106 Mean BMI (with range), Female	25.1 (19-34)	25.2 (18-33)
Study 107 Race (White/Black/Asian/Hispanic/Other)	90/3/4/5/1	99/0/0/4/2
Study 106 Race (White/Black/Asian/Hispanic/Other)	121/5/2/9/0	128/2/0/3/2
Study 107 Mean Baseline HbA1c	8.12	8.16
Study 106 Mean Baseline HbA1c	8.23	8.24
Study 107 Mean Duration of Diabetes (range)	17.1 (2.2-50.0)	19.4 (1.5-49.0)
Study 106 Mean Duration of Diabetes (range)	19.0 (1.0-41.0)	18.5 (1.0-49.0)

Source: Applicant's Tables 7.1.1, 7.1.2, 7.2.1, 7.2.2, 7.4.1, 7.4.2, Module 2.7.3

Little difference was noted between groups for these demographic characteristics; few non-white patients participated.

6.1.4.2 Primary Endpoint

In both Studies 107 and 106, the inhaled insulin regimen was noninferior to the subcutaneous control regimen for the percent change in HbA1c from baseline to Week 24 of treatment. These results for Study 107 are illustrated in the following table:

	Inh Ins (n = 162)		SQ (n = 165)	
	Mean	SD ¹	Mean	SD ¹
Baseline HbA1c	8.0	0.9	8	1.0
Week 24 (LOCF) ²	7.7	1.0	7.8	1.2
Unadjusted change from baseline	-0.3	0.8	-0.1	0.9
Adjusted change from baseline ³	-0.3	0.1	-0.1	0.1

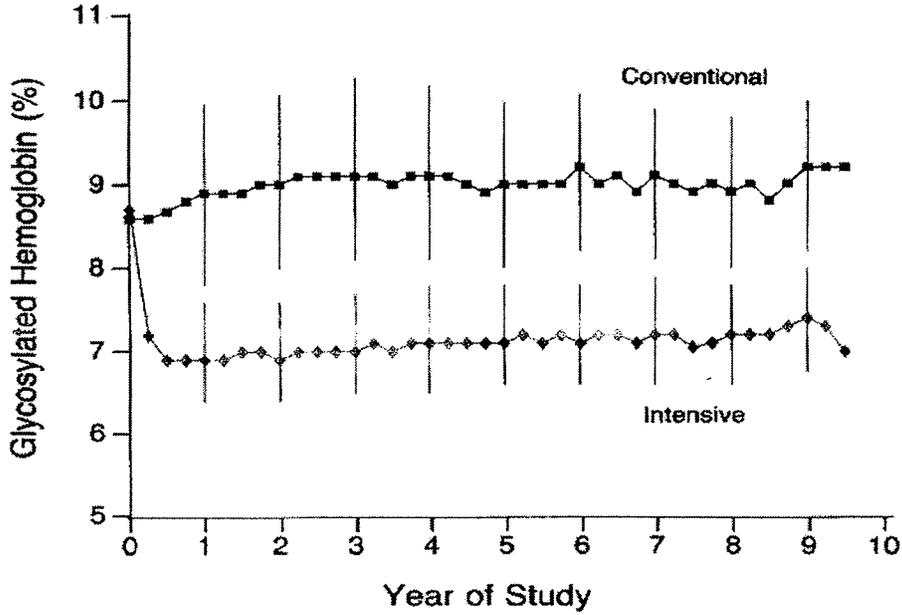
¹ SE used instead of SD for adjusted change from baseline
² Last observation carried forward
³ Least Squares Means
 Source: Applicant's Table 5.2.1, Study 107 Report, pg 139

For the treatment comparison, the difference between the adjusted mean changes from baseline for inhaled insulin vs SQ was - 0.17 (SE 0.09; 95% CI limits -0.34, 0.01).

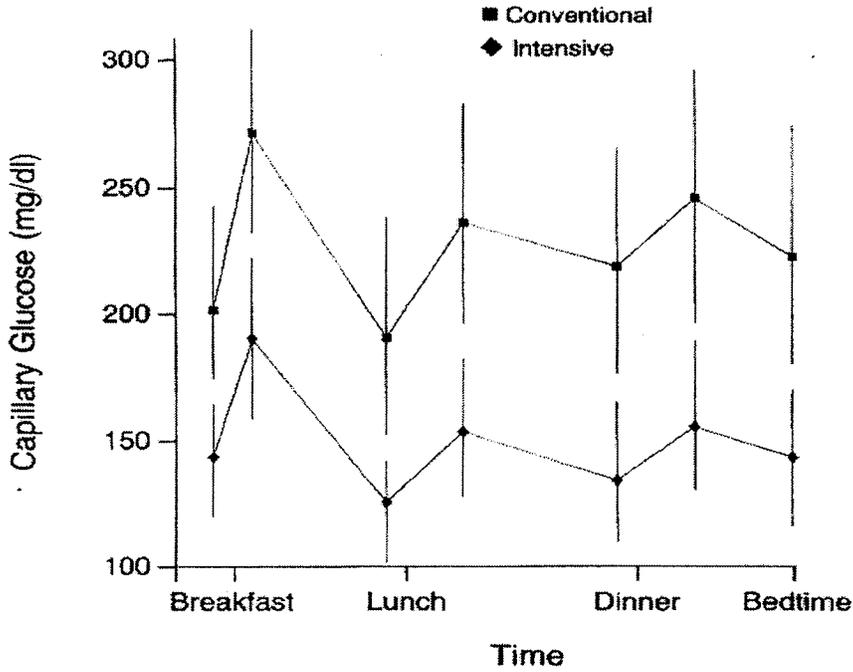
During the development of Exubera®, DMEDP had communicated to the sponsor that, in their intensive control study, it was important that the subcutaneous control group actually achieve intensive control. Mean HbA1c in the DCCT at two years was slightly below 7% in the intensive control arm, and slightly below 9% in the conventional control arm, as illustrated in the following figure:

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Figure 6.1.4.2 Mean HbA1c over Time in the Diabetes Control and Complications Trial



A



B

Source: DCCT Research Group 1993 (see reference section)

The following table displays the changes in HbA1c seen in Study 106. As in Study 107, inhaled insulin was noninferior to subcutaneous insulin for change in HbA1c.

Table 6.1.4.2.2 Mean Percent Change from Baseline in HbA1c to Week 24, Intention to Treat (ITT) Population, Study 106 (Control = "Conventional" SQ)				
	Inh Ins (n = 169)		SQ (n = 161)	
	Mean	SD¹	Mean	SD¹
Baseline HbA1c	8.1	1.0	8.1	1.0
Week 24 (LOCF) ²	7.9	1.1	7.7	0.9
Unadjusted change from baseline	-0.2	0.9	-0.4	0.7
Adjusted change from baseline ³	-0.2	0.1	-0.4	0.1
¹ SE used instead of SD for adjusted change from baseline ² Last observation carried forward ³ Least Squares Means Source: Applicant's Table 5.2.1, Study 106 Report, pg 122				

For the treatment comparison, the difference between the adjusted mean changes from baseline for inhaled insulin vs SQ was 0.16 (SE 0.08; 95% CI limits 0.08, 0.33).

6.1.4.3 Important Secondary Endpoints

The applicant used only their "evaluable" ("per protocol") patient population (i.e. not the "Intent to Treat" population) for the applicant's secondary efficacy analyses. The per protocol population included patients who did not have a major violation of the inclusion or exclusion criteria, received at least half the protocol-required duration of treatment (12 out of 24 weeks for both Studies 107 and 106), and had at least one "evaluable" post-baseline HbA1c. An evaluable HbA1c was defined as having been preceded by a treatment duration of 75% or more of the elapsed time since the previous assessment.

6.1.4.3.1 Treatment to Goal

In Study 107, the percentages of patients achieving HbA1cs <8% and <7% were comparable between the inhaled and SQ insulin groups at Week 24.

Table 6.1.4.3.1.1 Percentages of Patients Achieving <8% or <7% HbA1c at Week 24, Applicant's "Evaluable"¹ Population, Study 107				
End-of-Study HbA1c	Inh Ins (n = 159) % of Patients	SQ (n = 159) % of Patients	Odds Ratio²	95% CI for Odds Ratio
<8%	64.2	60.4	1.44	0.77, 2.69
<7%	23.3	22.0	1.53	0.75, 3.14
¹ Defined as patients who did not have a major violation of the inclusion or exclusion criteria, received at least half the protocol-required duration of treatment (12 out of 24 weeks for both Studies 107 and 106), and had at least one "evaluable" post-baseline HbA1c. An evaluable HbA1c was defined as having been preceded by a treatment duration of 75% or more of the elapsed time since the previous assessment. ² Inhaled/SQ adjusted odds ratio. Crude odds of reaching vs not reaching specified HbA1c with inhaled/ Crude odds of reaching vs not reaching specified HbA1c with SQ Source: Applicant's Tables 5.3.1.2 and 5.3.2.2, p 141, Study 107 report				

In Study 106, the percentages of patients achieving HbA1cs <8% and <7% were again comparable between the inhaled and SQ groups at Week 24. A lower percentage of patients in both groups achieved a HbA1c <7% in Study 106 than in Study 107; this is expected with the less intensive regimen used in Study 106.

Table 6.1.4.3.1.2 Percentages of Patients Achieving <8% or <7% HbA1c at Week 24, Applicant's "Evaluable"¹ Population, Study 106				
End-of-Study HbA1c	Inh Ins (n = 157) % of Patients	SQ (n = 155) % of Patients	Odds Ratio²	95% CI for Odds Ratio
<8%	58.0	61.9	0.71	0.39, 1.28
<7%	15.9	15.5	0.92	0.40, 2.10

1 Defined as patients who did not have a major violation of the inclusion or exclusion criteria, received at least half the protocol-required duration of treatment (12 out of 24 weeks for both Studies 107 and 106), and had at least one "evaluable" post-baseline HbA1c. An evaluable HbA1c was defined as having been preceded by a treatment duration of 75% or more of the elapsed time since the previous assessment.

2 Inhaled/SQ adjusted odds ratio. Crude odds of reaching vs not reaching specified HbA1c with inhaled/ Crude odds of reaching vs not reaching specified HbA1c with SQ

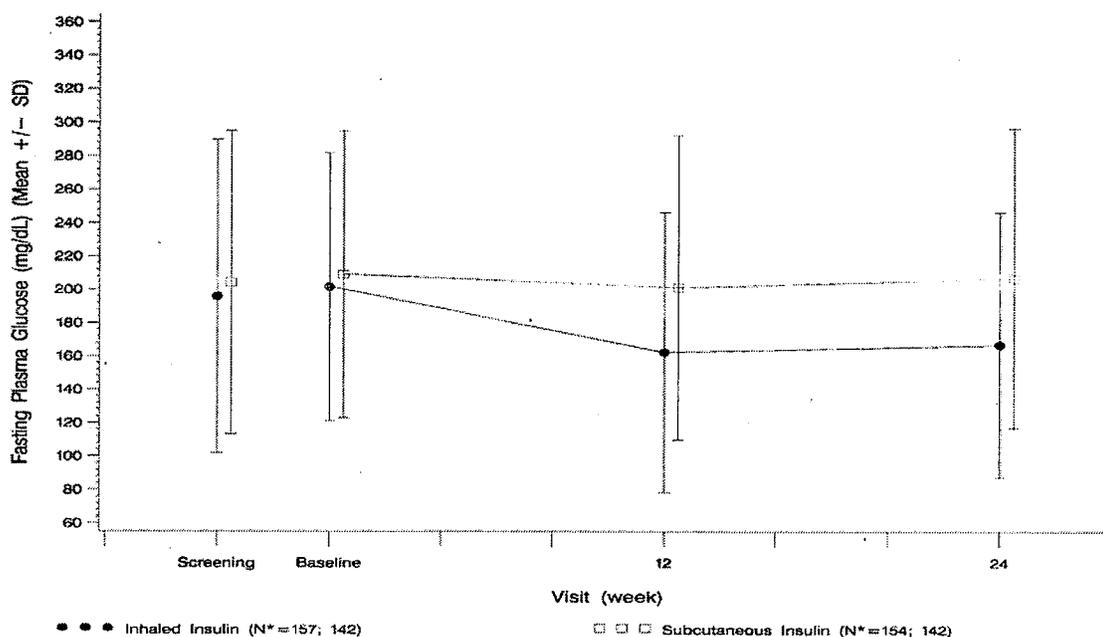
Source: Applicant's Tables 5.3.1.2 and 5.3.2.2, p 124, Study 106 report

6.1.4.3.2 Fasting Plasma Glucose

In Study 107, mean fasting plasma glucose concentrations were similar at baseline, but were significantly lower in inhaled insulin group patients than in SQ group patients at both week 12 and week 24. At week 24, inhaled insulin group patients had a mean decrease from baseline in fasting plasma glucose of 35 mg/dL, while patients in the SQ group had a mean increase of 4 mg/dL. The limits of the 95% confidence interval for the difference between groups were -57.50 and -21.56. This difference is illustrated in the following figure:

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Figure 6.1.4.3.2.1 Fasting Plasma Glucose Over Time, Study 107, Per Protocol Population

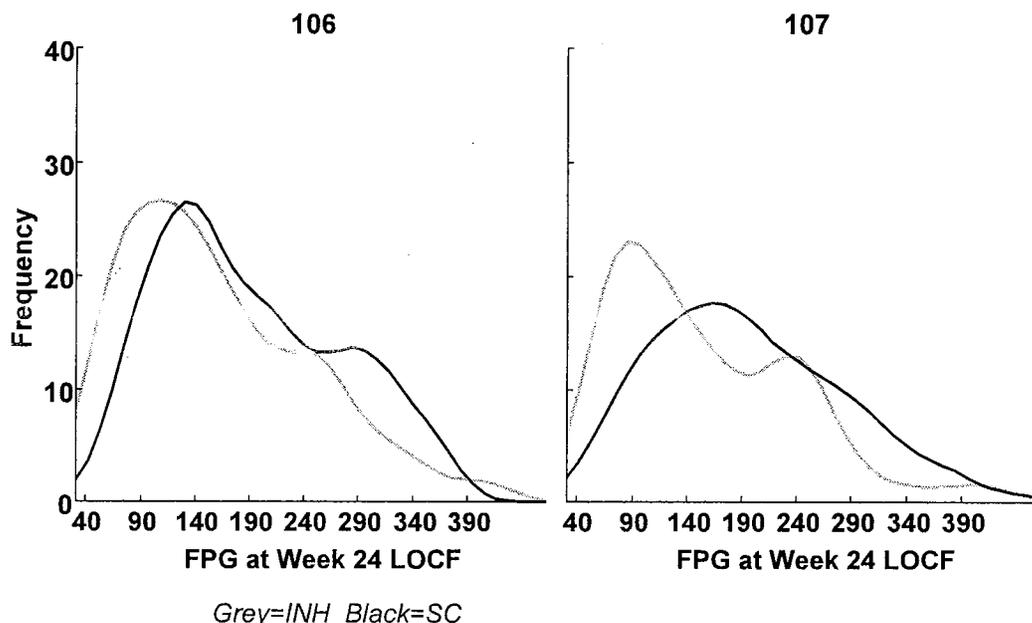


N* = Number of subjects at baseline; Number of subjects at Week 24.
 Source Data: Section 11, Item 11, Table 5 Date of Data Extraction: 09APR2001 Date of Table Generation: 09APR2001 (23:30)

Mean fasting plasma glucose in the SQ group did not fall in the desired range (<140 mg/dL after DCCT, 70 to <110 mg/dL by current standards of American Association of Clinical Endocrinologists). Frequency distribution for FPG values is illustrated in the following figures for Studies 106 and 107.

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Figure 6.1.4.3.2.2 Distribution of Fasting Plasma Glucose Values, Studies 106 and 107



Source: Ms. Joy Mele, Statistical Reviewer, FDA Biometrics

A higher percentage of Study 107 patients in the inhaled insulin group had a fasting blood sugar in the desired range than did patients in the SQ group. However, a higher percentage of patients in the inhaled insulin group also had fasting blood sugars below 70 mg/dL, which may be undesirably low. These differences are illustrated in the following table.

Table 6.1.4.3.2.1 Frequency of Fasting Plasma Glucose Below, Within, and Above the Desired Range, Week 24, Study 107			
	<70 mg/dL # pts (%)	70-110 mg/dL # pts (%)	>110 mg/dL # pts (%)
Inhaled Insulin	10 (9.9)	29 (28.7)	62 (61.4)
SQ	4 (4.1)	12 (12.4)	81 (83.5)
Cochran-Mantel-Haenszel general association value 12.0078, p 0.0025 Source: analysis by Ms. Mele, FDA Biostatistics			

The reason for the difference between groups for Study 107 is not clear. Concern exists for a lower intensity of management of SQ patients compared to inhaled insulin patients, which could limit the usefulness of Study 107 in determining whether inhaled insulin is noninferior to intensive SQ management. However, rules for titration of long-acting insulin were the same for both groups, and mean doses of both total daily and evening long-acting insulin were not higher for inhaled insulin patients than for SQ patients between groups; in fact, they were slightly higher for SQ group patients. Mean HbA1cs did not differ. As discussed in Section 7.1.3, hypoglycemia tended to occur more frequently in the prebreakfast time period than at other times of day for Type 1 inhaled insulin group patients. Logically, one would expect this finding, and that of lower fasting plasma glucoses in general, to be related to long-acting rather than short-

acting insulin, but mean doses of long-acting insulin were not higher for inhaled insulin group patients. The possibility was considered that subcutaneous group patients actually had more early morning hypoglycemia, with release of counterregulatory hormones and subsequent prebreakfast hyperglycemia (the "Somogyi effect"). However, routine early morning (0200 or 0300) blood sugars were not obtained during Study 107, and therefore this possibility could not be evaluated for this study. In Study 1026, the only study in which 0200 blood sugars were routinely monitored, hypoglycemia at 0200 was more common among inhaled insulin group patients than among SQ group patients. The clinical reviewer considered the possibility of an effect of inhaled insulin on reduction of nighttime hepatic glucose production, but was unable to examine this possibility with the data provided.

In Study 106, as in Study 107, a higher percentage of patients in the inhaled insulin group had fasting plasma glucoses <70 mg/dL at week 24 than did patients in the SQ group [17/131 (12.98%) for inh ins vs 1/129 (0.8%) for SQ]. End-of-study FPG was also lower in the inhaled insulin group than in the SQ group (adjusted difference -26.58; 95% CI -47.13, -6.02).

6.1.4.3.3 Postprandial Glucose Excursion

In Study 107, postprandial glucose excursion after a standard meal was greater at Week 24 for inhaled insulin patients than for SQ patients, as illustrated in the following table:

Table 6.1.4.3.3 Meal Study Postprandial Glucose Increment ¹ , Study 107, Per Protocol Set		
	Inh Ins (n = 130) Mean Plasma Glucose mg/dL (SD) ²	SQ (n = 125) Mean Plasma Glucose mg/dL (SD) ²
Baseline	107 (96)	100 (95)
Week 24 (LOCF)	123 (100)	97 (101)
Unadjusted change from baseline	15 (107)	-3 (95)
Adjusted change from baseline ³	17 (8)	-7 (8)
Treatment Comparison for Inhaled-Subcutaneous:		
Difference Between Adjusted Mean Change = 24.04; SE 11.18; 95% CI limits for difference 2.02, 46.07		
1 2-hour postprandial plasma glucose concentration minus preprandial (-30 min) value		
2 SE used for adjusted change from baseline estimates		
3 Least Squares Means based on primary model with terms for baseline, treatment and center		

In Study 107, inhaled insulin was somewhat less effective than SQ insulin in controlling postprandial glucose excursion. This difference likely contributes to the finding of similar HbA1cs between groups despite lower FPG with inhaled insulin. There is considerable debate in the medical literature about the relative importance of fasting vs postprandial glucose as targets of diabetes therapy. Randomized trials have not answered this question. In epidemiologic studies, postprandial glucose appears to be an independent risk factor for cardiovascular disease, and postprandial glucose may be a stronger risk factor for cardiovascular disease than FPG or HbA1c (Beisswenger 2004).

In Study 106, there was little difference between groups for postprandial glucose excursion.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

In Study 107, a trial in Type 1 diabetics comparing management with preprandial inhaled insulin to management with subcutaneous insulin in an "intensive" manner, inhaled insulin was noninferior to subcutaneous insulin with regard to the primary endpoint, change from baseline in HbA1c. Inhaled insulin was associated with significantly lower fasting plasma glucose at end-of-study than was subcutaneous insulin, but more patients on inhaled insulin had undesirably low fasting plasma glucoses, also. This observation was not due to differences in evening longacting insulin doses. Postprandial glucose excursion was moderately numerically and statistically significantly greater in inhaled insulin group patients than in subcutaneous group patients, which is undesirable due to an epidemiologic association of postprandial glucose levels with cardiovascular risk. Indices of intensive control in Study 107 in the subcutaneous group were somewhat less "tight" than those seen in the "intensive" group in the Diabetes Control and Complications Trial, but were "tighter" than those for the "conventional" arm of the DCCT. Noninferiority of the inhaled insulin regimen to the subcutaneous regimen in this trial does not necessarily indicate noninferiority of this inhaled regimen to the intensive subcutaneous regimen used in the DCCT. However, 23% of patients in the inhaled insulin group were able to achieve a HbA1c of <7%, indicating that it is possible for tight control to be achieved in some patients using this inhaled insulin regimen.

By the best-validated surrogate endpoint available (HbA1c), intensive control of Type 1 diabetes appears possible for some patients with inhaled insulin. Special attention may be needed to ensure control of postprandial glucose excursion, and to avoid fasting hypoglycemia.

6.2 Indication: Treatment of Hyperglycemia in Adult Type 2 Diabetics, Inhaled Insulin as Monotherapy

6.2.1 Methods

Two major trials in Type 2 diabetics included an inhaled insulin monotherapy arm compared to oral agent(s). Study 109 enrolled patients who were poorly controlled on combination oral agent therapy, and randomized patients to one of three arms: premeal inhaled insulin monotherapy, premeal inhaled insulin plus the patient's baseline oral agents, or continued combination oral agents. Study 110 compared premeal inhaled insulin monotherapy to rosiglitazone treatment.

6.2.2 General Discussion of Endpoints

For Study 109, the primary efficacy endpoint was the change in HbA1c from baseline at week 12. For Study 110, the primary efficacy endpoint was the percentage of patients achieving a HbA1c <8% by the end-of-study or discontinuation.

As discussed in Section 6.1.2, the correlation of HbA1c with the development of microvascular disease in Type 1 diabetics is well-established, and thus HbA1c is a good surrogate endpoint for the trials of inhaled insulin in Type 1 diabetics. However, the evidence that monitoring of HbA1c is of value in predicting or preventing macrovascular disease in Type 2 patients is less strong than that for microvascular disease in Type 1 diabetics (Jeffcoate 2004). HbA1c remains, however, the best-validated surrogate endpoint for diabetes trials in Type 2 patients.

6.2.3 Study Design

6.2.3.1 Design of Study 109

Study 109 was a 3-month, block-allocated, open-label, parallel group study done in patients who were already receiving combination oral antidiabetic agents, and who had entry HbA1cs $\geq 8\%$ to $\leq 11\%$. All patients were on an insulin secretagogue (sulfonylurea or repaglinide) and another agent (either metformin or a glitazone). Patients were assigned to one of three treatment groups: continued oral therapy alone, premeal inhaled insulin monotherapy, or premeal inhaled insulin plus continued oral therapy. The objective was to see if inhaled insulin as monotherapy or in combination with continued oral agents would significantly improve HbA1c when compared to continued oral agent therapy alone. In this section regarding the applicant's proposed monotherapy indication, the monotherapy arm's effect relative to the "oral agent alone" arm will be considered. A total of 104 patients were treated with inhaled insulin monotherapy, while 99 continued oral agent therapy alone. The patient population included men and women ages 35-80 years who had been on a stable oral agent regimen (as described above) for at least two months.

The primary efficacy endpoint was the change in HbA1c from baseline at week 12.

Secondary efficacy endpoints included (full list p 25 study report):

- change in fasting plasma glucose
- percentage of patients with HbA1c $<8\%$ and $<7\%$
- two-hour postprandial glucose and insulin increments following a standardized meal
- body weight
- fasting lipids

In addition to routine safety monitoring and laboratory, special safety assessments included:

- spirometry, lung volume, diffusion capacity and oxygen saturation at baseline and week 12
- incidence and severity of hypoglycemic events
- insulin antibodies at baseline and week 12

6.2.3.2 Design of Study 110

Study 110 was a 3-month, block-allocated, open-label, parallel group efficacy and safety study intended to establish superiority of premeal inhaled insulin monotherapy over rosiglitazone for the treatment of Type 2 diabetes. The population included Type 2 diabetics, ages 35-80

inclusive, who had not previously been on insulin, and who had HbA1cs ranging from 6-11%. A total of 75 patients were treated with inhaled insulin, and 68 were treated with rosiglitazone.

The primary efficacy endpoint was the percentage of patients achieving HbA1c <8% by the end of study or discontinuation.

Secondary efficacy endpoints included (full list pg 23 of study report):

- change from baseline to week 12 in HbA1c
- percentage of patients reaching HbA1c <7%
- change in fasting plasma glucose
- two-hour postprandial glucose increment after a standardized meal
- fasting lipids

Routine and special safety monitoring was the same as that used in Study 109.

6.2.3.3 Adequacy of Study Design

Please see Section 6.1.3.2 for a description of the regulatory definition of "adequate and well-controlled studies". Studies 109 and 110 have the same issues as Studies 106 and 107 with regard to blinding and randomization.

6.2.4 Efficacy Findings

6.2.4.1 Demographics

Demographic characteristics of patients in Studies 109 and 110 are included in the following table:

Characteristic	Inh Ins	OA
Study 109 Male:Female	75:30	62:37
Study 110 Male:Female	48:27	31:37
Study 109 Mean Age, years	57.4	56.4
Study 110 Mean Age, years	53.0	54.4
Study 109 Mean BMI (with range), Male	30.5 (22-39)	29.3 (23-38)
Study 110 Mean BMI (with range), Male	31.7 (24-43)	32.6 (24-46)
Study 109 Mean BMI (with range), Female	29.3 (24-39)	31.2 (18-37)
Study 110 Mean BMI (with range), Female	32.2 (20-44)	32.8 (22-48)
Study 109 Race (White/Black/Asian/Hispanic/Other)	83/8/2/8/4	82/5/2/7/3
Study 110 Race (White/Black/Asian/Hispanic/Other)	58/7/1/9/0	48/10/0/9/1
Study 109 Mean Baseline HbA1c	9.58	9.56
Study 110 Mean Baseline HbA1c	9.76	9.64
Study 109 Mean Duration of Diabetes (range)	9.3 (1.8-25.0)	9.6 (1.3-32.8)
Study 110 Mean Duration of Diabetes (range)	4.3 (0.08-22.0)	3.1 (0.01-18.0)

Source: Applicant's Tables 9 and 11, Section 2.7.3.3.1.2

6.2.4.2 Study 109

6.2.4.2.1 Primary Endpoint

Inhaled insulin monotherapy was superior to continued oral agent therapy for change in HbA1c at Week 12, for this population that was failing oral agent therapy at baseline. HbA1c data are summarized in the following table:

Table 6.2.4.2.1 Mean Change from Baseline in HbA1c, Study 109, ITT Population							
Group	N	BL	Wk 12	Adjusted Change ^a	Difference (Inh Grp vs OA)	95% CI Limits for Difference between Grps	p-Value
Inh Ins Monotherapy	102	9.3	7.9	-1.4	-1.18 ^b	-1.41, -0.95	<0.0001 ^b
Inh Ins + OA	100	9.2	7.3	-1.9	-1.67 ^c	-1.90, -1.44	<0.0001 ^c
OA	96	9.3	9.1	-0.2			

^a Least Squares Means based on the primary model with terms for baseline, treatment and center
^b Comparison of inh ins monotherapy to OA
^c Comparison of inh ins + OA to OA
 Source: Applicant's Table 5.2.1, p 42, Study 109 report

6.2.4.2.2 Secondary Endpoints

6.2.4.2.2.1 Treatment to Goal

Inhaled insulin monotherapy was superior to continued oral agent therapy for achievement of HbA1c <8% and <7%, for this population that was failing oral agent therapy at baseline.

Table 6.2.4.2.2.1 Percentage of Patients Achieving HbA1c <8% and <7%, Study 109, ITT Population					
	N	Baseline # pts (%)	End-of-Study # pts (%)	Odds Ratio (Inh Ins Grp vs OA Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins Monotherapy	102	3 (2.9)	57 (55.9)	7.5	3.6, 15.5
Inh Ins + OA	100	5 (5.0)	86 (86.0)	40.5	17.0, 96.9
OA	96	3 (3.1)	18 (18.8)		
<7%					
Inh Ins Monotherapy	102	0	17 (16.7)	19.0	2.5, 145.8
Inh + OA	100	0	32 (32.0)	44.7	6.0, 335.2
OA	96	0	1 (1.0)		

Source: Applicant's Tables 5.3.1.1 and 5.3.2.1, Study 109 report

6.2.4.2.2.2 Fasting and Postprandial Glucose

Inhaled insulin monotherapy was superior to continued oral agent therapy in reduction of fasting plasma glucose and postprandial glucose excursion in this population that was failing oral agent therapy.

Table 6.2.4.2.2.2 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 109, Per Protocol Population

	n	BL	Wk 12 Change	Difference between Inh Ins Grp and OA Grp	95% CI Limits for Difference between Grps
FPG					
Inh Ins Monotherapy	95	203	-23	-24	-36, -11
Inh Ins + OA	96	195	-53	-53	-66, -41
OA	89	203	1		
Two-hour Postprandial Glucose Change (from Preprandial Value)					
Inh Ins Monotherapy	91	98	-43	-41	-56, -25
Inh Ins + OA	91	95	-24	-22	-37, -7
OA	79	95	-2		

Source: Applicant's Tables 5.6.1 and 5.6.3, Study 109 report

6.2.4.3 Study 110

6.2.4.3.1 Primary Endpoint- Treatment to Goal

Inhaled insulin monotherapy was superior to rosiglitazone for the primary endpoint, percentage of patients achieving a HbA1c <8%. A higher percentage of patients in the inhaled insulin group also achieved a HbA1c <7%.

Table 6.2.4.3.1 Percentage of Patients Achieving HbA1cs <8% and <7%, Study 110, ITT Population

	N	End-of Study Patients to HbA1c Goal # pts (%)	Odds Ratio (Inh Ins Grp vs Rosi Grp)	95% CI Limits for Odds Ratio	p Value
<8%					
Inh Ins Monotherapy	75	62 (82.7)	7.14	2.48, 20.58	0.0003
Rosi	67	39 (58.2)			
<7%					
Inh Ins Monotherapy	75	33 (44.0)	4.43	1.94, 10.12	
Rosi	67	12 (17.9)			

Source: Applicant's Tables 5.3.1.1 and 5.3.2.1, Study 110 report

6.2.4.3.2 Secondary Endpoints

6.2.4.3.2.1 Change from Baseline in HbA1c

Inhaled insulin treatment resulted in a greater decline in HbA1c than that seen with rosiglitazone.

Table 6.2.4.3.2.1 Mean Change from Baseline in HbA1c, Study 110, ITT Population

Group	N	BL HbA1c (SD)	Wk 12 HbA1c (SD)	Adjusted Change ^a	Difference (Inh Grp vs Rosi)	95% CI Limits for Difference between Grps
Inh Ins Monotherapy	75	9.5 (1.1)	7.2 (1.0)	-2.3 (1.2)	-0.89	-1.23, -0.55
Rosi	67	9.4 (0.9)	8.0 (1.3)	-1.4 (1.2)		

Source: Applicant's Table 5.2.1, Study 110 report
 a Least Squares Means based on the primary model with terms for baseline, treatment and center

6.2.4.3.2.2 Fasting and Postprandial Plasma Glucose

The difference between groups was not significant for change from baseline in FPG and postprandial glucose excursion.

Table 6.2.4.3.2.2 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 110, Per Protocol Population

	n	BL (SD)	Wk 12 Change (SD)	Difference between Inh Ins Grp and OA Grp	95% CI Limits for Difference between Grps
FPG					
Inh Ins Monotherapy	68	208 (56)	-64 (57)	-4.26	-17.66, 9.13
Rosi	57	199 (50)	-56 (42)		
Two-hour Postprandial Glucose Change (from Preprandial Value)					
Inh Ins Monotherapy	63	86 (49)	-27 (48)	14.12	-4.25, 32.49
Rosi	54	82 (56)	-38 (60)		

Source: Applicant's Table 5.6.3, Study 110 report

6.2.5 Clinical Microbiology

Not applicable.

6.2.6 Efficacy Conclusions

From Study 109, it appears that inhaled insulin monotherapy is effective in achieving better glucose control (by HbA1c) for Type 2 patients who are failing combination oral agent therapy. From Study 110, inhaled insulin monotherapy appears superior to rosiglitazone in achieving HbA1c goals in Type 2 patients not previously exposed to injected insulin.

6.3 Indication: Treatment of Hyperglycemia in Adult Type 2 Diabetics, Inhaled Insulin in Combination with Longer-acting Insulins

6.3.1 Methods

Study 108 was the major completed trial utilizing inhaled insulin in combination with a longer-acting insulin for Type 2 diabetics, and review focused on this study.

6.3.2 General Discussion of Endpoints

The primary efficacy endpoint was the change in HbA1c from baseline to week 24 of treatment. Please see Sections 6.1.2 and 6.2.2 for a discussion of the value of HbA1c as an endpoint in trials in Type 1 and Type 2 diabetes.

6.3.3 Study Design

Study 108 was a 6 month, block-allocated, open-label, parallel group study done in Type 2 patients who had been on a stable regimen of SQ insulin for at least 2 months prior to study entry, and who had entry HbA1cs between 6 and 11%. Patients were assigned to receive either TID premeal inhaled insulin plus bedtime Ultralente® (UL), or BID mixed SQ NPH and regular insulin. The objective was to determine if inhaled insulin administered in this regimen was at least as effective (in control of HbA1c) as BID mixed SQ insulin. Each arm contained 149 treated patients.

The primary efficacy endpoint was change in HbA1c from baseline to week 24. Secondary endpoints and special safety assessments were similar to those described previously for Study 109.

Please see Section 6.1.3.2 for a discussion of the regulatory characteristics of "adequate and well-controlled" studies. The clinical reviewer had some concern regarding the lower intensity of management in the SQ group (two insulin doses per day) compared to the inhaled insulin group (four insulin doses per day). The increased attention to self-care required for a four time per day intervention might in itself result in a greater decrease in HbA1c than one could achieve with a twice daily intervention. However, a twice daily injected insulin regimen is commonly used in Type 2 diabetes, and thus permits comparison to "usual care". Likely clinical scenarios of use for inhaled insulin in Type 2 diabetics would be either one in which the patient is on a mixed BID regimen and wishes to take fewer injections per day, or one in which the clinician or patient desires tighter control, but wishes to spare the patient a four shot per day regimen. In these cases, substitution of a TID premeal inhaled insulin plus a q day basal SQ injection would be likely. It will be important in this scenario to know if one would be putting the patient at risk of more hypoglycemic episodes in general, or of more serious hypoglycemic episodes. This trial design permits exploration both of the efficacy of this premeal inhaled + q day basal SQ regimen, and of the safety of the regimen with regard to the possibility of increased hypoglycemia. Furthermore, it appears that the likely efficacy of the inhaled insulin portion of this regimen is not in question, because in Study 109 (see Section 6.2.4), inhaled insulin monotherapy was effective in improving glycemic control in Type 2 diabetics who were failing dual oral agent therapy.

6.3.4 Efficacy Findings

6.3.4.1 Demographics

Characteristic	Inh Ins	OA
Male:Female	99:50	99:50
Mean Age, years	58.7	56.2
Mean BMI (with range), Male	29.9 (21-38)	29.5 (21-38)
Mean BMI (with range), Female	31.7 (22-51)	31.1 (22-38)
Race (White/Black/Asian/Hispanic/Other)	116/17/4/11/1	110/15/5/12/17
Mean Baseline HbA1c	8.48	8.47 (0.4-59.0)
Mean Duration of Diabetes (range)	13.8	13.2 (0.9-43.4)

Source: Applicant's Tables 9 and 11, Section 2.7.3.3.1.2

Little difference was noted between groups for these characteristics.

6.3.4.2 Primary Endpoint

For change from baseline in HbA1c, the inhaled insulin plus hs UL regimen was noninferior to the BID mixed SQ regimen.

Group	N	BL (SD)	Wk 24 (SD)	Adjusted Change ^a (SD)	Difference (Inh Grp vs SQ)	95% CI Limits for Difference between Grps	p-Value
T1D premeal Inh Ins + hs UL	146	8.1 (1.1)	7.4 (1.5)	-0.7 (1.2)	-0.07	-0.31, 0.17	NS
BID SQ mixed NPH and regular insulin	149	8.2 (1.1)	7.6 (1.1)	-0.6 (1.1)			

^a Least Squares Means based on the primary model with terms for baseline, treatment and center
 Source: Applicant's Table 5.2.1, Study 108 report

6.3.4.3 Secondary Efficacy Endpoints

6.3.4.3.1 Treatment to Goal

A slightly higher percentage of patients in the inhaled insulin + basal SQ group achieved HbA1cs of <8% and <7% than did patients in the BID SQ group.

Table 6.3.4.3.1 Percentage of Patients Achieving HbA1c <8% and <7%, Study 108, ITT Population					
	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins Grp vs OA Grp)	95% CI Limits for Odds Ratio
<8%					
TID premeal Inh Ins + hs UL	146	70 (47.9%)	111 (76.0%)	1.58	0.82, 3.06
BID SQ mixed NPH and regular insulin	149	68 (45.6%)	103 (69.1%)		
<7%					
TID premeal Inh Ins + hs UL	146	25 (17.5%)	66 (45.2)	1.92	1.07, 3.44
BID SQ mixed NPH and regular insulin	149	17 (11.7%)	48 (32.2)		

Source: Applicant's Table 22, NDA Section 2.7.3.3.2.2.2; Tables 5.3.1.2 and 5.3.2.2, Study 108 report

6.3.4.3.2 Fasting and Postprandial Plasma Glucose

Fasting plasma glucose declined more in inhaled insulin group patients; there was no significant difference between groups in the change in postprandial glucose increment.

Table 6.3.4.3.2 Mean Fasting Plasma Glucose and Mean Postprandial Glucose Excursion, Study 108, ITT Population					
	n	BL (SD)	Wk 24 Change (SD)	Difference between Inh Ins Grp and SQ Grp	95% CI Limits for Difference between Grps
FPG					
TID premeal Inh Ins + hs UL	144	152 (37)	-20 (55)	-16.36	-27.09, -5.63
BID SQ mixed NPH and regular insulin	144	159 (45)	-9 (52)		
Two-hour Postprandial Glucose Change (from Preprandial Value)					
TID premeal Inh Ins + hs UL	115	89 (47)	3 (6)	6.58	-8.79, 21.94
BID SQ mixed NPH and regular insulin	116	94 (83)	-4 (6)		

Source: Applicant's Tables 5.6.3, 5.6.1, Study 108 report

6.3.5 Clinical Microbiology

Not applicable.

6.3.6 Efficacy Conclusions

In Study 108, a regimen of TID premeal inhaled insulin plus bedtime UL was noninferior to a low-intensity regimen of BID SQ mixed regular and NPH insulin, for the control of HbA1c in Type 2 diabetics. It appears that Type 2 diabetics who have been on a subcutaneous insulin regimen can switch to a regimen of premeal inhaled insulin plus basal injected insulin, and achieve at least noninferior glycemic control without undue risk of increased or worsening hypoglycemia (see Section 7.1.3.3.1 for details regarding hypoglycemia rates).

Addendum: The applicant provided an interim analysis of an ongoing study, Study 1029. In this study, patients in the inhaled insulin group are receiving TID premeal inhaled insulin plus hs intermediate to long-acting insulin (UL, NPH or glargine), and patients in the SQ group are receiving TID premeal insulin (regular, aspart or lispro) and hs intermediate to long-acting insulin (UL, NPH or glargine). A one-year interim analysis of this study indicates noninferiority of the inhaled regimen(s) to the SQ regimen(s), with changes from baseline in HbA1c of -0.53 (SE 0.05) for the inhaled insulin group and -0.60 (SE 0.05) for the SQ group. The final results of this study will allow comparison of similar intensity regimens of inhaled and SQ premeal insulins in combination with basal SQ insulin.

6.4 Indication: Treatment of Hyperglycemia in Adult Type 2 Diabetics, Inhaled Insulin in Combination with Oral Agents

6.4.1 Methods

The applicant submitted the results of two major controlled trials in Type 2 diabetics in which inhaled insulin was administered in combination with an oral agent. Study 109, discussed above in Section 6.2, included an arm with TID premeal insulin plus continued combination oral hypoglycemic agents (insulin secretagogue, plus glitazone or metformin). Studies 1001 and 1002 began as separate trials, but were later combined. Study 1001 combined inhaled insulin with a sulfonylurea, and Study 1002 combined inhaled insulin with metformin.

6.4.2 General Discussion of Endpoints

For both Study 1001, and 1002, the primary endpoint was change from baseline in HbA1c. As discussed above in Section 6.1.2, the value of HbA1c as a surrogate for the risk of development of macrovascular disease in Type 2 diabetics is less well-established than the value of HbA1c as a surrogate for the risk of development of microvascular disease in Type 1 diabetics. However, at this time, HbA1c remains the best-validated surrogate for evaluation of the glucose-lowering efficacy of antidiabetic agents.

6.4.3 Study Designs

Both Study 1001 and Study 1002 were designed as 104 week studies, but at 24 weeks, the two studies were combined, and changes in design were included at that point. Therefore, only the data to 24 weeks are used in this efficacy evaluation.

Study 1001 was a block-allocated, open-label, parallel group study done in patients who were already poorly controlled on sulfonylurea therapy and had HbA1cs between 8 and 12%. HbA1c strata included 8-9.5%, and >9.5-12%. Patients were assigned to one of two groups: TID premeal inhaled insulin + continued SU, or metformin (1 gm BID) + continued SU. The objective was to demonstrate superiority of the inhaled insulin regimen over the metformin regimen for change in HbA1c for the high HbA1c stratum. A total of 222 patients were treated with inhaled insulin and 201 were treated with metformin.

Study 1002 was a block-allocated, open-label, parallel group study done in patients who were already poorly controlled on metformin (1 gm BID) and had HbA1cs between 8 and 12%. HbA1c strata included 8-9.5%, and >9.5-12%. Patients were assigned to one of two groups: TID premeal inhaled insulin + continued metformin, or glibenclamide (maximum dose 5 mg BID) + continued metformin. The objective was to demonstrate superiority of the inhaled insulin regimen over the glibenclamide regimen for change in HbA1c for the high HbA1c stratum. A total of 235 patients received inhaled insulin and 229 received glibenclamide.

The primary efficacy endpoint for both studies was change from baseline in HbA1c, and both had similar secondary endpoints and special safety evaluations.

6.4.4 Efficacy Findings

6.4.4.1 Demographics

The following table lists baseline demographics and characteristics for the two studies.

Characteristic	Inh Ins + Continued SU (Study 1001) or Inh Ins + Continued Met (Study 1002)	Met + Continued SU (Study 1001) or Glibenclamide + Continued Met (Study 1002)
Study 1001 Male:Female (HbA1c 8-9.5)	52:53	49:44
Study 1001 Male:Female (HbA1c >9.5-12)	70:47	53:55
Study 1002 Male:Female (HbA1c 8-9.5)	74:56	79:47
Study 1002 Male:Female (HbA1c >9.5-12)	62:47	53:52
Study 1001 Mean Age (HbA1c 8-9.5)	60.5	60.2
Study 1001 Mean Age (HbA1c >9.5-12)	61.0	59.8
Study 1002 Mean Age (HbA1c 8-9.5)	56.2	56.3
Study 1002 Mean Age (HbA1c >9.5-12)	54.6	54.4
Study 1001 Mean BMI (with range), Male (HbA1c 8-9.5)	27.4 (20-34)	28.6 (21-44)
Study 1001 Mean BMI (with range), Male (HbA1c >9.5-12)	27.9 (22-41)	28.3 (20-37)
Study 1002 Mean BMI (with range), Male (HbA1c 8-9.5)	30.7 (19-51)	30.7 (24-44)
Study 1002 Mean BMI (with range), Male (HbA1c >9.5-12)	30.9 (22-47)	30.4 (23-38)
Study 1001 Mean BMI (with range), Female (HbA1c 8-9.5)	29.6 (23-40)	30.3 (21-42)
Study 1001 Mean BMI (with range), Female (HbA1c >9.5-12)	29.4 (22-48)	29.3 (21-57)
Study 1002 Mean BMI (with range), Female (HbA1c 8-9.5)	33.3 (21-47)	31.9 (22-45)
Study 1002 Mean BMI (with range), Female (HbA1c >9.5-12)	32.8 (23-43)	31.9 (22-47)
Study 1001 Race (White/Black/Asian/Other) (HbA1c 8-9.5)	102/3/0/0	91/1/0/1
Study 1001 Race (White/Black/Asian/Other) (HbA1c >9.5-12)	109/1/3/4	101/2/3/2
Study 1002 Race (White/Black/Asian/Other) (HbA1c 8-9.5)	123/1/5/1	120/2/3/1

Characteristic	Inh Ins + Continued SU (Study 1001) or Inh Ins + Continued Met (Study 1002)	Met + Continued SU (Study 1001) or Glibenclamide + Continued Met (Study 1002)
Study 1002 Race (White/Black/Asian/Other) (HbA1c >9.5-12)	99/5/0/5	100/2/1/2
Study 1001 Mean Baseline HbA1c (HbA1c 8-9.5)	9.04	8.95
Study 1001 Mean Baseline HbA1c (HbA1c >9.5-12)	10.66	10.66
Study 1002 Mean Baseline HbA1c (HbA1c 8-9.5)	8.90	9.00
Study 1002 Mean Baseline HbA1c (HbA1c >9.5-12)	10.73	10.94
Study 1001 Mean Duration of Diabetes, years (range) (HbA1c 8-9.5)	9.1 (0.7-28.3)	8.2 (0.5-20.7)
Study 1001 Mean Duration of Diabetes, years (range) (HbA1c >9.5-12)	10.1 (0.8-37.3)	9.2 (1.1-33.0)
Study 1002 Mean Duration of Diabetes, years (range) (HbA1c 8-9.5)	7.7 (0.6-30.3)	7.4 (0.3-27.5)
Study 1002 Mean Duration of Diabetes, years (range) (HbA1c >9.5-12)	9.2 (0.6-35.6)	8.4 (0.5-29.5)

Source: Applicant's Tables 9 and 11, Section 2.7.3.3.1.2

No clear differences in demographic characteristics exist between groups.

6.4.4.2 Primary Endpoints

For Study 1001, for change from baseline in HbA1c, inhaled insulin + SU was not superior to metformin + SU for patients with baseline HbA1cs between 8 and 9.5%. For patients with HbA1cs between >9.5 and 12%, inhaled insulin +SU was statistically superior to metformin + SU. However, the HbA1c difference between groups (-0.38%; 95% CI -.63, -.014) is of uncertain clinical significance for the treatment of Type 2 diabetes. The addition of inhaled insulin to failed sulfonylurea therapy does not appear to be inferior to the addition of metformin to failed sulfonylurea therapy for reduction in HbA1c.

Group	N	BL (SD)	Wk 24 (SD)	Adjusted Change^a (SD)	Difference (Inh + Continued SU vs Met + Continued SU)	95% CI Limits for Difference between Grps	p- Value
Inh + Continued SU, Baseline HbA1c 8- 9.5%	101	8.8 (0.5)	7.4 (0.8)	-1.4 (0.8)	-0.07	-0.33, 0.19	0.610
Met + Continued SU, Baseline HbA1c 8- 9.5%	93	8.8 (0.5)	7.4 (0.8)	-1.4 (0.9)			
Inh + Continued SU, Baseline HbA1c >9.5-12%	113	10.5 (0.7)	7.9 (1.0)	-2.7 (1.1)	-0.38	-0.63, -0.14	0.002
Met + Continued SU, Baseline HbA1c >9.5-12%	103	10.6 (0.9)	8.3 (1.2)	-2.4 (1.2)			

^a Least Squares Means based on the primary model with terms for baseline, treatment and center
 Source: Applicant's Tables 5.2.1.2 and 5.2.1.3, Study 1001 report

For Study 1002, for change from baseline in HbA1c, inhaled insulin + continued metformin was not superior to glibenclamide + continued metformin for patients with baseline HbA1cs between 8 and 9.5%. For patients with HbA1cs between >9.5 and 12, inhaled insulin + continued metformin was statistically superior to glibenclamide + continued metformin. However, the HbA1c difference between groups (-0.37%; 95% CI -.62, -.12) is of uncertain clinical significance for the treatment of Type 2 diabetes. The addition of inhaled insulin to failed metformin therapy does not appear to be inferior to the addition of glibenclamide to failed metformin therapy for reduction in HbA1c.

Table 6.4.4.2.2 Mean Change from Baseline in HbA1c (%) at 6 Months, Study 1002, ITT Population

Group	N	BL (SD)	Wk 24 (SD)	Adjusted Change ^a (SD)	Difference (Inh + Continued Met vs Glibenclamide + Continued Met)	95% CI Limits for Difference between Grps	p-Value
Inh + Continued Met, Baseline HbA1c 8-9.5	125	8.6 (0.5)	7.2 (0.8)	-1.4 (0.8)			
Glibenclamide + Continued Met, Baseline HbA1c 8-9.5	119	8.7 (0.5)	7.1 (0.9)	-1.6 (0.9)	0.04	-0.19, 0.27	0.733
Inh + Continued Met, Baseline HbA1c >9.5-12	109	10.4 (0.7)	7.5 (1.1)	-2.9 (1.2)	-0.37	-0.62, -0.12	0.004
Glibenclamide + Continued Met, Baseline HbA1c >9.5-12	103	10.6 (0.7)	8.0 (1.2)	-2.6 (1.2)			

^a Least Squares Means based on the primary model with terms for baseline, treatment and center
 Source: Applicant's Tables 5.2.1.2 and 5.2.1.3, Study 1002 report

Please see Table 6.2.4.2.1 for change from baseline in HbA1c for Study 109. In that study, inhaled insulin plus continued failed oral agent therapy was superior to continued failed oral agent therapy for change in HbA1c. As discussed in Section 6.2.4.2.1, inhaled insulin monotherapy was also superior to continued failed oral agent therapy; inhaled insulin plus failed oral agent therapy resulted in a greater mean decline in HbA1c than inhaled insulin monotherapy (-1.9% vs -1.4%).

6.4.4.3 Secondary Endpoints

6.4.4.3.1 Treatment to Goal

In Study 1001, for patients with baseline HbA1cs 8-9.5%, a numerically higher percentage of patients in the inhaled insulin + continued SU group achieved HbA1cs of <8%; there was no difference between groups for the percentage of patients who achieved HbA1cs <7%.

Table 6.4.4.3.1.1 Percentage of Patients Achieving HbA1c <8% and <7%, Study 1001, ITT Population, Baseline HbA1c 8-9.5%

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins +Continued SU Grp vs Metformin + Continued SU Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins + Continued SU	101	6 (5.9)	82 (81.2)	1.78	0.86, 3.69
Met + Continued SU	93	8 (8.6)	68 (73.1)		
<7%					
Inh Ins + Continued SU	101	0	31 (30.7)	0.96	0.51, 1.79
Met + Continued SU	93	0	30 (32.3)		

Source: Applicant's Table 22, NDA Section 2.7.3.3.2.2.2; Tables 5.3.1.1.2, 5.3.1.1.3, and 5.3.2.1.2, Study 1001 report

In Study 1001, for patients with baseline HbA1cs >9.5-12%, a slightly larger percentage of patients in the inhaled insulin add-on group achieved HbA1cs <8% than did patients in the metformin add-on group. For patients with baseline HbA1cs >9.5-12%, few patients achieved HbA1c <7% in either group, but a larger percentage of patients in the inhaled insulin add-on group achieved this goal than did patients in the metformin add-on group.

Table 6.4.4.3.1.2 Percentage of Patients Achieving HbA1c <8% and <7%, Study 1001, ITT Population, Baseline HbA1c >9.5-12%

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins +Continued SU Grp vs Metformin + Continued SU Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins + Continued SU	113	0	55 (48.7)	1.11	0.64, 1.93
Met + Continued SU	103	0	46 (44.7)		
<7%					
Inh Ins + Continued SU	113	0	23 (20.4)	1.45	0.69, 3.01
Met + Continued SU	103	0	15 (14.6)		

Source: Applicant's Table 22, NDA Section 2.7.3.3.2.2.2; Tables 5.3.1.1.2, 5.3.1.1.3, and 5.3.2.1.2, Study 1001 report

In Study 1002, for patients with baseline HbA1cs 8-9.5%, addition of the comparator agent (glibenclamide) was slightly superior to addition of inhaled insulin to failed metformin therapy, for percentage of patients achieving HbA1cs <8% and <7%.

Table 6.4.4.3.1.3 Percentage of Patients Achieving HbA1c <8% and <7%, Study 1002, ITT Population, Baseline HbA1c 8-9.5%

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins +Continued Met Grp vs Glibenclamide + Continued Met Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins + Continued Met	125		101 (80.8)		
Glibenclamide + Continued Met	119		103 (86.6)	0.49	0.23, 1.06
<7%					
Inh Ins + Continued Met	125		50 (40.0)		
Glibenclamide + Continued Met	119		51 (42.9)	0.85	0.49, 1.46

Source: Applicant's Table 22, NDA Section 2.7.3.3.2.2.2; Tables 5.3.1.1.2, 5.3.1.1.3, and 5.3.2.1.2, Study 1002 report

In Study 1002, for patients on failed metformin therapy with baseline HbA1cs >9.5-12%, addition of inhaled insulin appeared superior to addition of glibenclamide for percentage of patients achieving HbA1cs of <8% and <7%.

Table 6.4.4.3.1.4 Percentage of Patients Achieving HbA1c <8% and <7%, Study 1002, ITT Population, Baseline HbA1c >9.5-12%

	N	BL # pts (%)	End-of Study # pts (%)	Odds Ratio (Inh Ins +Continued Met Grp vs Glibenclamide + Continued Met Grp)	95% CI Limits for Odds Ratio
<8%					
Inh Ins + Continued Met	109	0	79 (72.5)	1.91	1.02, 3.55
Glibenclamide + Continued Met	103	0	58 (56.3)		
<7%					
Inh Ins + Continued Met	109	0	37 (33.9)	2.54	1.27, 5.08
Glibenclamide + Continued Met	103	0	18 (17.5)		

Source: Applicant's Table 22, NDA Section 2.7.3.3.2.2.2; Tables 5.3.1.1.2, 5.3.1.1.3, and 5.3.2.1.2, Study 1002 report

Please see Table 6.2.4.2.2.1 for treatment to goal data for Study 109. In that study, inhaled insulin plus continued failed oral agent treatment was superior to continued failed oral agent treatment alone for the percentage of patients attaining HbA1cs of <8% and <7%. A higher percentage of patients achieved these goals with inhaled insulin plus continued failed oral agent treatment than with inhaled insulin monotherapy, which was in turn superior to continued failed oral agent therapy alone (<8% HbA1c= 86% vs 56% vs 19% respectively; HbA1c <7% = 32% vs 17% vs 1% respectively).

6.4.4.3.2 Fasting and Postprandial Plasma Glucose

For both Studies 1001 and 1002, the change in fasting plasma glucose was similar between treatment groups for both HbA1c strata. For both Studies 1001 and 1002, the change in PPG was similar between treatment groups for patients with baseline HbA1cs between 8 and 9.5%.

For both Studies 1001 and 1002, addition of inhaled insulin to either failed SU or failed metformin therapy resulted in a greater favorable change in PPG than did addition of comparator.

Table 6.4.4.3.2.1 Mean Fasting Plasma Glucose (mg/dL) and Mean Postprandial Glucose Excursion (mg/dL), Study 1001, ITT Population, Baseline HbA1c 8-9.5%						
		n	BL (SD)	End-of-study Change (SD)	Difference between Inh Ins + Continued SU Grp and Metformin + Continued SU Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins + Continued SU	97	197 (45)	-33 (51)	4.27	-7.67, 16.20
	Metformin + Continued SU	90	198 (49)	-38 (52)		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins + Continued SU	70	219 (39)	-57 (39)	-5.62	-15.96, 4.71
	Metformin + Continued SU	76	211 (38)	-46 (42)		

Source: Applicant's Tables 5.5.3.2, 5.5.3.3, 5.6.2, 5.6.3, Studies 1001 and 1002 reports

Table 6.4.4.3.2.2 Mean Fasting Plasma Glucose (mg/dL) and Mean Postprandial Glucose Excursion (mg/dL), Study 1001, ITT Population, Baseline HbA1c >9.5-12						
		n	BL (SD)	End-of-study Change (SD)	Difference between Inh Ins + Continued SU Grp and Metformin + Continued SU Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins + Continued SU	107	241 (54)	-63 (55)	0.51	-10.75, 11.78
	Metformin + Continued SU	102	237 (53)	-60 (56)		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins + Continued SU	83	255 (48)	-91 (52)	-17.17	-27.35, -6.98
	Metformin + Continued SU	67	253 (48)	-73 (48)		

Source: Applicant's Tables 5.5.3.2, 5.5.3.3, 5.6.2, 5.6.3, Studies 1001 and 1002 reports

Table 6.4.4.3.2.3 Mean Fasting Plasma Glucose (mg/dL) and Mean Postprandial Glucose Excursion (mg/dL), Study 1002, ITT Population, Baseline HbA1c 8-9.5

		n	BL (SD)	End-of-study Change (SD)	Difference between Inh Ins + Continued Met Grp and Glibenclamide + Continued Met Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins + Continued Met	118	187 (46)	-32 (49)	3.82	-6.90, 14.54
	Glibenclamide + Continued Met	110	196 (42)	-43 (46)		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins + Continued Met	101	200 (43)	-46 (46)	-3.65	-13.73, 6.44
	Glibenclamide + Continued Met	86	206 (36)	-48 (44)		

Source: Applicant's Tables 5.5.3.2, 5.5.3.3, 5.6.2, 5.6.3, Studies 1001 and 1002 reports

Table 6.4.4.3.2.4 Mean Fasting Plasma Glucose (mg/dL) and Mean Postprandial Glucose Excursion (mg/dL), Study 1002, ITT Population, Baseline HbA1c >9.5-12

		n	BL (SD)	End-of-study Change (SD)	Difference between Inh Ins + Continued Met Grp and Glibenclamide + Continued Met Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins + Continued Met	93	223 (61)	-55 (58)	-1.85	-14.00, 10.30
	Glibenclamide + Continued Met	87	243 (58)	-65 (60)		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins + Continued Met	86	236 (50)	-78 (51)	-18.51	-29.04, -7.97
	Glibenclamide + Continued Met	84	250 (49)	-70 (50)		

Source: Applicant's Tables 5.5.3.2, 5.5.3.3, 5.6.2, 5.6.3, Studies 1001 and 1002 reports

Please see Table 6.2.4.2.2.2 for fasting and postprandial glucose data for Study 109. In that study, inhaled insulin plus continued failed oral agent therapy was superior to continued failed oral agent therapy alone for reduction of fasting plasma glucose and postprandial glucose excursion. Reductions in these parameters were greater with inhaled insulin plus continued failed oral agent therapy than with inhaled insulin monotherapy; inhaled insulin monotherapy was also superior to continued failed oral agent therapy.

6.4.5 Clinical Microbiology

Not applicable.

6.4.6 Efficacy Conclusions

For Study 1001, for the primary efficacy endpoint of change from baseline in HbA1c, the 6-month data did not support superiority of the addition of inhaled insulin over the addition of sulfonylurea to failed metformin therapy. For Study 1002, for the primary efficacy endpoint of change from baseline in HbA1c, the 6-month data did not support superiority of the addition of inhaled insulin over the addition of metformin to failed sulfonylurea therapy. However, for both studies, the addition of inhaled insulin appeared noninferior to the addition of the comparator oral agent. In Study 109, the addition of inhaled insulin to continued failed combined oral agent therapy appeared superior to continued failed combined oral agent therapy alone for change from baseline in HbA1c at 3 months.

For both Studies 1001 and 1002, the addition of inhaled insulin resulted in a greater percentage of patients achieving HbA1cs <8% than did addition of the comparator agent. Patients with higher HbA1cs at baseline (>9.5-12%) were more likely to achieve a HbA1c <7% with the addition of inhaled insulin than with the addition of the comparator, although the percentage of patients in either treatment group who achieved a HbA1c <7% was small. In Study 109, the addition of inhaled insulin to continued failed combined oral agent therapy appeared superior to continued failed combined oral agent therapy alone for achievement of HbA1cs <8% and <7%.

Overall, the addition of inhaled insulin to a failed oral agent appears at least noninferior to the addition of a second oral agent for the control of Type 2 diabetes. Addition of inhaled insulin to failed combined oral agent therapy appears superior to continued failed oral agent therapy alone. The combination of inhaled insulin and failed combined oral agent therapy resulted in greater favorable changes in measures of glucose control in Type 2 diabetes than did inhaled insulin monotherapy, which in turn was also superior to continued failed combined oral agent therapy alone.

6.5 Potential Off-label Use: Treatment of Hyperglycemia in Pediatric Patients with Type 1 Diabetes, Inhaled Insulin in Combination with Longer-acting Insulins

6.5.1 Methods

The applicant is not seeking an indication for pediatric use for Exubera®. However, the clinical reviewer anticipates significant interest in the use of the product for children, with the potential for off-label use. Studies 106 and 107 included adolescents ages 12-17 years, and Study 1009 included children ages 6-11 years. No children ages 5 and under were studied.

6.5.2 General Discussion of Endpoints

For all three studies, the primary endpoint was change from baseline in HbA1c. HbA1c is likely a valid surrogate for the risk for development of microvascular complications in Type 1 diabetes, as discussed in Section 6.1.2.

6.5.3 Study Design

Please see Section 6.1.3 for a description of the design of Studies 106 and 107. Study 1009 was a 3-month, open-label, block-allocated, parallel group efficacy and safety study conducted in Type 1 diabetic children ages 6-11 years. A total of 120 children were treated with either an inhaled insulin regimen (TID premeal inhaled insulin + hs or BID UL or NPH) or a SQ regimen (BID lispro or regular + q day or BID UL or NPH). Secondary endpoints and special safety evaluations were similar to those in Studies 106 and 107.

6.5.4 Efficacy Findings

6.5.4.1 Primary Endpoint

There was little difference between treatment groups for change from baseline in HbA1c in Studies 106, 107 and 1009. Neither treatment group attained "tight" control of mean HbA1c in any of these studies. Inhaled insulin patients had little change from baseline in HbA1c.

Study	Group	N	BL (SD)	Change from Baseline (SD)	LSM Difference between Treatment Groups	95% CI Limits for Difference between Groups	p-Value
106	Inh Ins	33	8.6 (1.0)	0 (1.2)	+ 0.3	-0.09, 0.7	NS
	SQ	29	8.5 (0.8)	-0.3 (0.7)			
107	Inh Ins	59	8.3 (0.9)	-0.2 (0.8)	-0.2	-0.5, 0.1	NS
	SQ	59	8.3 (0.9)	0 (1.1)			
1009	Inh Ins	60	8.1 (0.7)	-0.3 (0.1)	-0.2	-0.5, 0.03	NS
	SQ	59	8.1 (0.8)	0 (0.1)			

¹ Studies 106 and 107 analyses at 6 months, patients ages 11-17 yrs; Study 1009 analysis at 3 months, patients ages 6-11 years
 Source: Analyses for Studies 106 and 107 by Dr. Mele, Biostatistics; Table 5.2.1, Study 1009 report

6.5.4.2 Secondary Endpoints

6.5.4.2.1 Treatment to Goal

Analyses of secondary endpoints were not provided for adolescents in Studies 106 and 107.

In Study 1009, a slightly larger percentage of children ages 6-11 years achieved HbA1cs <8% and <7% in the inhaled insulin group than did children in the SQ group.