CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-868

STATISTICAL REVIEW(S)

Statistical Consultation for Shelf Life Evaluation

Date of the Consultation Received: November, 2005
NDA: 21-868
Purpose: Shelf life evaluation on insulin powder for oral inhalation
Chemist Reviewers: Prasad Peri and Brian Rogers
Statistical Reviewer: Qian H. Li
Statistical Supervisor: Stella G. Machado

Introduction:

The purpose of this consult is to evaluate shelf life of insulin powder for oral inhalation packed in blisters, which was submitted in NDA 21-868 by Pfizer Inc. seeking approval for marketing for the proposed indication "treatment of adult patients with diabetes mellitus for the control of hyperglycemia". The insulin powder was packed into two strengths in blisters, 1 mg and 3 mg insulin, respectively. The sponsor has determined a shelf life of — months based on — month stability study on clinical batches under condition 30C/60%RH and 25C/60%RH for 30-blister count desiccated foil pouch, using a ——— method which is not insulin specific, and ICH acceptance criteria. Data from stability study for insulin specific information from three production-scale batches suggested faster degradation over time than expected under certain conditions. A formal statistical consult for shelf life evaluation based on the three production-scale batches using insulin specific data under normal condition were therefore requested. The three batches were labeled as Z133B, Z173B and Z193A for 1mg blisters, and Z133A, Z173A, and Z193B for 3mg blisters.

Data Collection:

For this stability evaluation, the insulin particles distribution information was collected using ———. With this method, insulin powder packed in blisters was pumped ——— and insulin power was collected from ——— plates, referred to as Stages — and a filter, with the larger particle size landing on early stages and smaller particle size traveling through the plates landing on later stages. This stability evaluation uses the total collection of insulin particles from Stages ———

Such stability data were collected at Months ——— under various conditions. The data used for this evaluation was collected under the usual room condition of 25°C/60% RH with cavity down for 30-count package. About 6 replicates were repeated at each time point for each batch and strength, except at Month 0 for Batches Z133 and Z173, three replicates were available. For 1mg strength, three 1mg blisters were used in one replicate and one 3mg blister was used in one replicate for 3 mg strength. Data for cavity up at Month 0 under the same condition (25°C/60% RH) are also available for each of the three batches and two strengths. However, this reviewer has noticed that the cavity up data at Month 0 are exactly the same as those for cavity down at Month 0. It is the reviewer's speculation that the cavity up data at Month 0 were not

obtained independently from the cavity down data at Month 0. The chemist reviewers in fact were requesting stability data with cavity up condition. For these reasons, cavity up data are excluded in this stability evaluation.

SAS datasets stgi1_ai and atgi3_ai submitted by the sponsor on 8-19-05 are used for this stability evaluation.

Evaluation acceptance criteria:

According to chemistry review, fine particle dose (FPD) — µm and mass median aerodynamic diameter (MMAD) were used by the sponsor to characterize aerosol performance of the insulin power emitted from inhaler. The target mean values of FPD —, based on the sponsor, were 0.4 mg of insulin and 1.0 mg of insulin for 1 mg and 3 mg blisters, respectively. The range of acceptable values for FPD was established as from — of the target value. The acceptance range of MMAD for 1 mg blister was set to be from — and that for 3 mg blister was from —.

In chemistry review, the sponsor's acceptance criteria was determined as unacceptable for particle size distribution (PSD) evaluation and a set of new release and stability acceptance criteria was proposed for production-scale batches. The new set of acceptance criteria was derived from the stability data up to 6-months for the three production-scale batches. The data of different stages were regrouped based on the distributions of the stability data of the three production-scale batches up to 6 months. The acceptance criteria for the regrouped stages were determined using mean ±3SD (standard deviation) of each regroups. The acceptance criteria are listed in Table 1. Based on this table, this stability evaluation for Stages — uses the ranges — for 1 mg and 3 mg blisters, respectively.

Table 1: Acceptance criteria for insulin specific PSD evaluation

Group	Proposed Acceptance Criteria	
	1 mg	3 mg
	NMT	NMT
	NMT	NMT
	—	—
	NMT	NMT
	NMT	NMT

This statistical reviewer is concerned with the new set of acceptance criteria proposed, as the criteria are solely based on the data distribution from the production-scale batches which have not been tested and trialed in clinical trial settings. It is not clear why such proposed acceptance criteria will guarantee the efficacy and safety of the insulin powder of oral inhalation. Nevertheless, the evaluation performed in this review is based on the proposed acceptance criteria.

Results of shelf life evaluations:

Data from the three production-scale batches were first evaluated for poolability according to FDA guidance. A full model incorporating month, batch, and strength as covariates is used to assess the pooling potential. The analysis result from SAS GLM procedure is presented in the following table (Table 2). As it can be seen from the table, the p-value for testing the sameness of the slopes of the highest order interaction , the batch by strength interaction, is 0.0509, which is less than <0.25. Therefore, it is not appropriate to pool the three batches and two strengths.

For the purpose of understanding the highest order interaction, further analyses suggest that the slopes between the two strengths from Batch Z193 were statistically significantly different (p=0.0068). The slopes between the two strengths from Batches Z133 and Z173 are not statistically significant at the level of 0.05, the p-values are 0.150 and 0.532, respectively for the two batches.

For both strengths, the slopes are statistically significantly different among the three batches. The p-values are 0.0049 and 0.0296 for 1 mg and 3 mg strengths, respectively.

Table 2: Result from poolability assessment.

Source	DF	Type I SS	Mean Square	F Value	Pr > F
MONTH	1	0.26224173	0.26224173	27.01	<.0001
BATCH	2	0.13644048	0.06822024	7.03	0.0012
PSTRNGTH	1	0.69030572	0.69030572	71.09	<.0001
MONTH*BATCH	2	0.12281861	0.06140931	6.32	0.0023
MONTH*PSTRNGTH	1	0.05770069	0.05770069	5.94	0.0159
BATCH*PSTRNGTH	2	0.11807704	0.05903852	6.08	0.0029
MONTH*BATCH*PSTRNGTH	2	0.05894037	0.02947018	3.04	0.0509

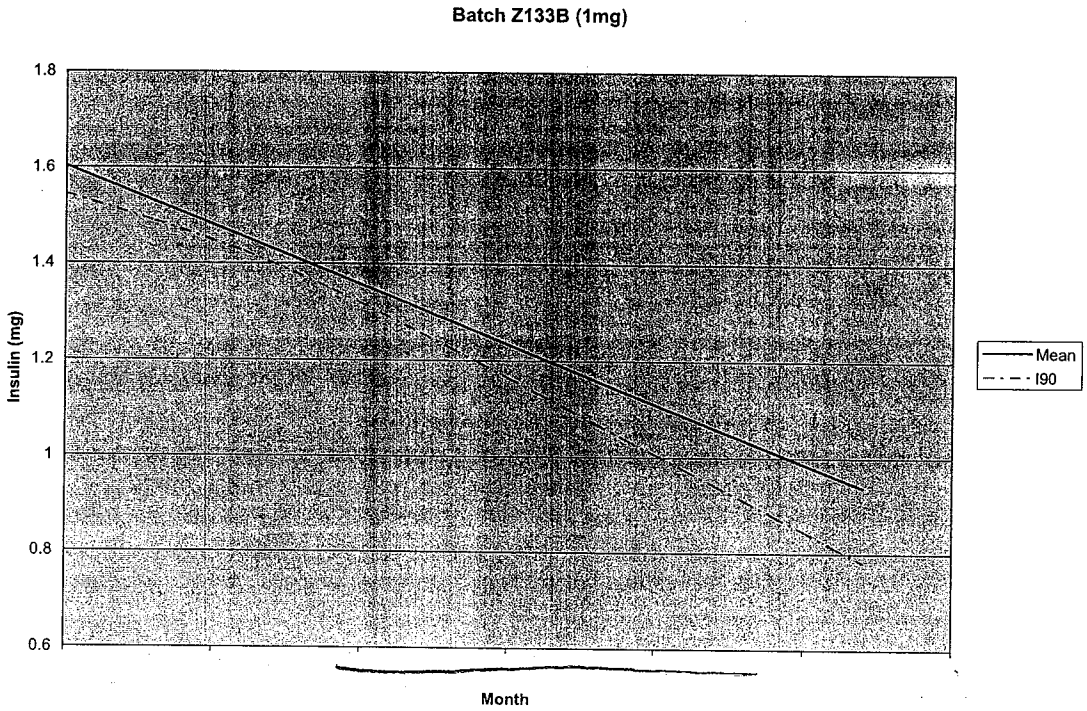
Source	DF	Type III SS	Mean Square	F Value	Pr > F
MONTH	1	0.29211122	0.29211122	30.08	<.0001
BATCH	2	0.23807131	0.11903565	12.26	<.0001
PSTRNGTH	1	0.07792214	0.07792214	8.03	0.0052
MONTH*BATCH	2	0.12281861	0.06140931	6.32	0.0023
MONTH*PSTRNGTH	1	0.04106486	0.04106486	4.23	0.0414
BATCH*PSTRNGTH	2	0.13825549	0.06912774	7.12	0.0011
MONTH*BATCH*PSTRNGTH	2	0.05894037	0.02947018	3.04	0.0509

Stability evaluation for each batch and strength is performed as it is determined that pooling data is inappropriate. A simple linear regression with month as the only covariate is used in this evaluation, as this is the default model for stability evaluation unless the data obviously support non-linear model over time.

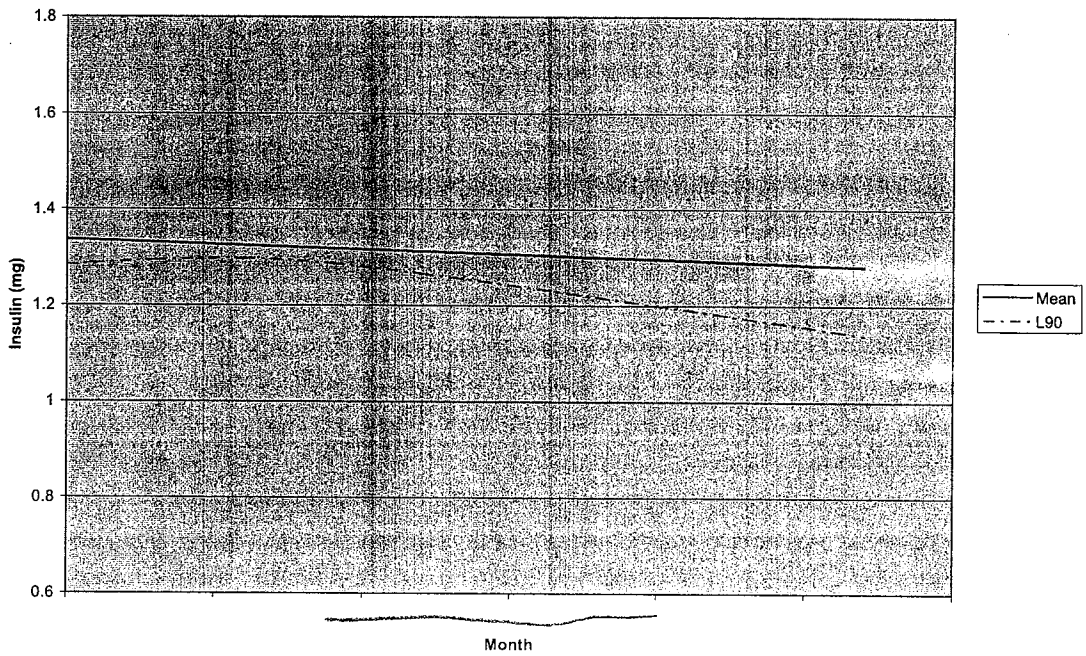
The results of shelf life evaluation are summarized in Table 3. The individual regression lines and the lower bound of the two-sided 90% CIs for each batch and strength are presented in a series of graphs entitled by the batch labels with the same scale. Based on these analyses, Batch Z133B with 1 mg strength showed the shortest shelf life of — months. Thus, the results of these analyses do not support a shelf life of — months for production-scale batches based on the acceptance criteria proposed by the chemist reviewer.

Table 3: Results of shelf life by batches and strengths.

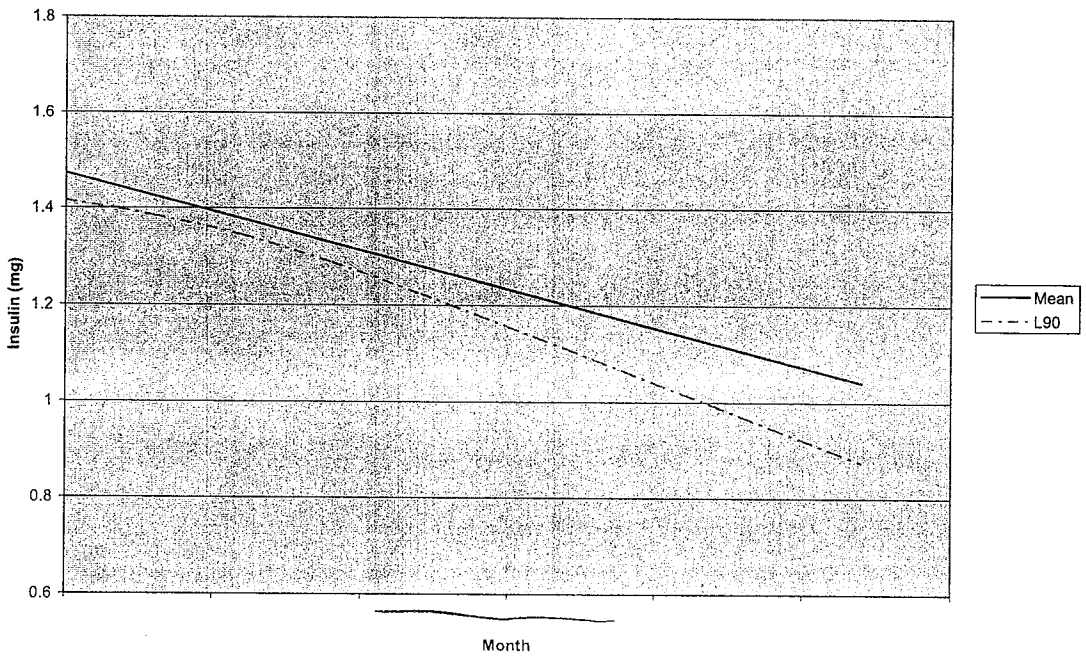
Strength	Batches	Means by Month					Slope	Shelf life
		0	3	6	9	12		(Month)
1 mg	Z133B	1.533	1.563	1.463	1.400	1.280	-0.025	
	Z173B	1.283	1.360	1.287	1.415	1.252	-0.002	
	Z193A	1.523	1.400	1.377	1.207	1.380	-0.016	
3 mg	Z133A	1.660	1.563	1.487	1.585	1.403	-0.015	
	Z173A	1.650	1.525	1.510	1.493	1.533	-0.006	
	Z193B	1.375	1.522	1.535	1.510	1.413	-0.002	



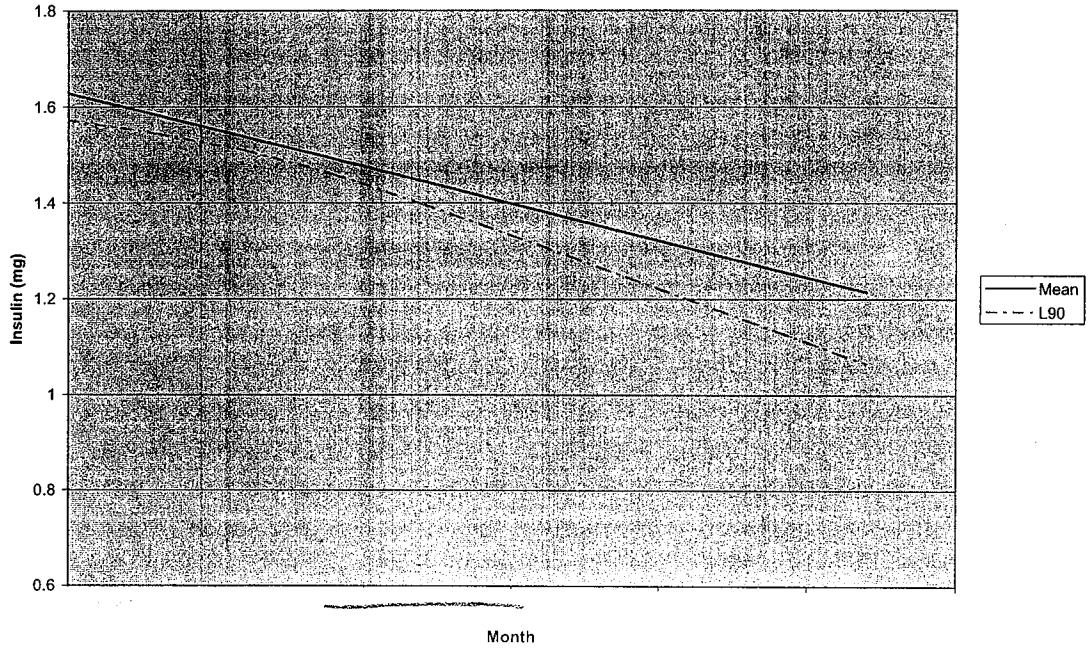
Batch Z173B (1mg)



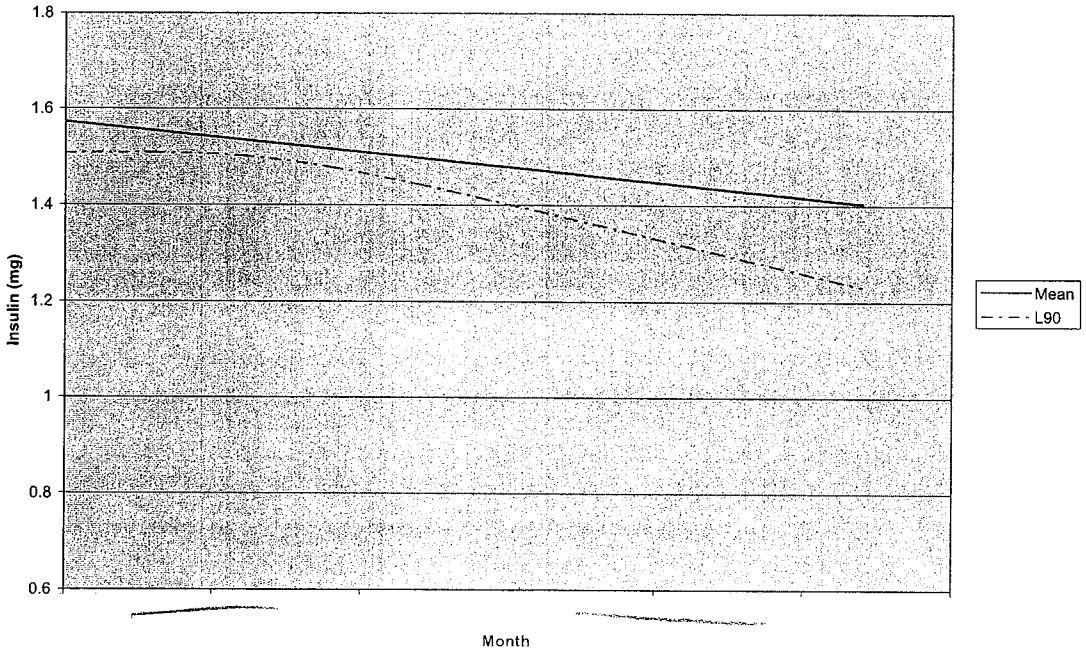
Batch Z193A (1mg)

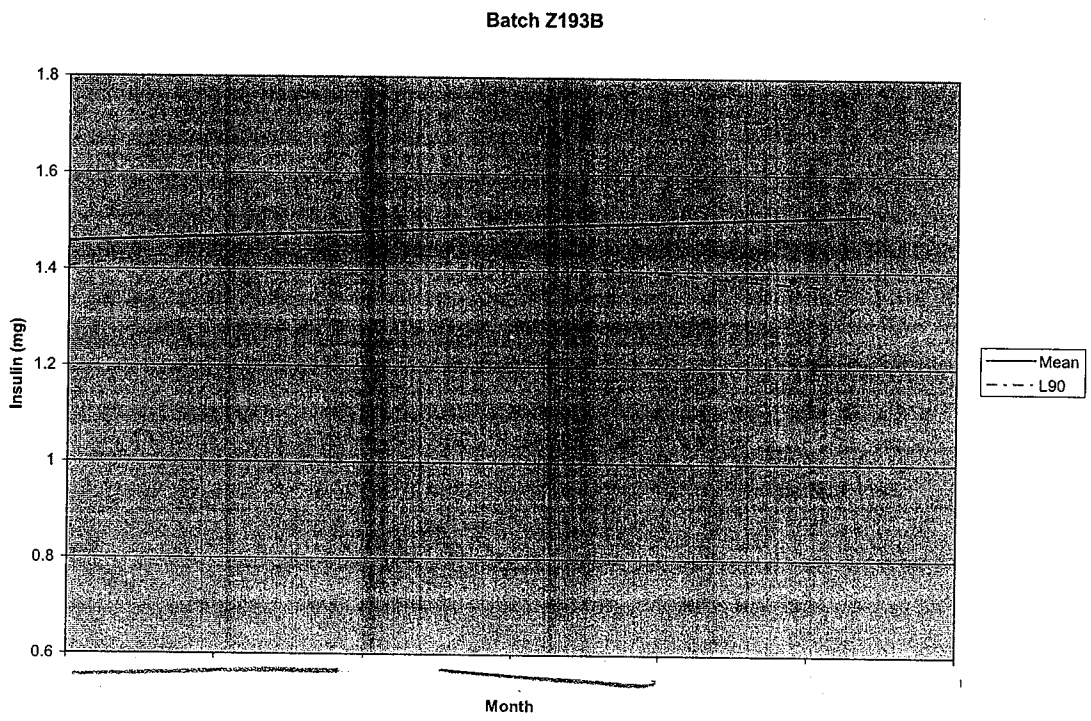


Batch Z133A (3mg)



Batch Z173A (3mg)





Discussion:

This shelf life evaluation is based on stability data collected up to [redacted] months. Therefore the shelf life beyond [redacted] month is extrapolated under the assumption that the degradation of insulin is linear over time following a constant degradation rate. It is not clear if such assumptions are reasonable. If yes, is it OK to use a short period stability data to estimate the constant degradation rate?

According to the chemist reviewers, the sponsor now has stability data beyond [redacted] month for production-scale batches. The graphs provided by the sponsor seem to suggest possibly shorter shelf life than 18 months. Data beyond [redacted] month were not available for this evaluation .

It is this reviewer's opinion that this simple statistical evaluation can only be used to confirm that [redacted] month shelf life is not appropriate, based on the assumption of constant degradation rate. However, caution should be exercised to use the result of such analyses to extrapolate the shelf life beyond the time period ([redacted] month) without data support.

Conclusion:

The shelf life evaluation based on [redacted] month stability data from production scales batches does not support [redacted] month shelf life using cavity down data and the acceptance criteria

provided by the chemistry reviewer. Although the results of the analyses suggest possible 18 month shelf life, this reviewer would advise some caution because the analyses is based on an assumption of constant degradation rate which has not been verified and the estimation is based on the extrapolation beyond the period of available data.

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/s/

Qian Li
1/10/2006 03:27:57 PM
BIOEQUIVALENCE STATISTICIAN

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1/20/2006 03:04:58 PM
BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-868
Drug Name:	EXUBERA (insulin [rDNA origin] powder for oral inhalation)
Indication(s):	Treatment of adult patients with Type 1 or Type 2 diabetes mellitus for the control of hyperglycemia
Applicant:	Pfizer Global Research and Development
Date(s):	Submitted December 27, 2004; Review completed October 17, 2004
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Joy Mele, M.S.
Concurring Reviewers:	Todd Sahlroot, Ph.D. Biometrics Team Leader Ed Nevius, Ph.D. Biometrics Division Director
Medical Division:	Division of Metabolic and Endocrine Drug Products (HFD-510)
Clinical Team:	Karen Mahoney, M.D. Clinical Reviewer David Orloff, M.D. Division Director
Project Manager:	Oluchi Elekwachi

Keywords: Clinical studies, NDA, active control

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

This reviewer has the following comments and conclusions based on the statistical review of the seven Phase 3 trials submitted to demonstrate the efficacy and safety of INH (Exubera). Note that Figures 3.1.3.1 and 3.1.3.2 on page 40 summarize the efficacy data.

- Approximately 85 to 90% of the Type 1 and 2 patients studied were Caucasian; so the races were not adequately represented in the database
- INH was shown to be non-inferior to SC insulin in patients with Type 1 diabetes in two Phase 3 clinical trials, 106 and 107 (see Table 3.1.1.5 and Figures 3.1.3.1 and 3.1.3.2). The HbA1c results are more favorable to INH in Study 107, a study where SC insulin was given TID and the same long-acting insulin was given in both groups. There was no evidence that long-acting insulin was titrated differently in the two groups allaying concerns that the long-acting dosing may have compensated for inadequate treatment on short-acting insulin.
- For Type 1 patients, statistically significant differences in favor of INH over SC were seen for the change from baseline in FPG in both studies. An examination of 24-hour diary records suggest a drop in glucose levels overnight in the INH group may explain the significantly lower FPG. This issue is discussed in the clinical review by the FDA medical reviewer, Dr. Mahoney.
- Across the Type 2 studies, variability in several baseline parameters was seen suggesting some heterogeneity among the patient populations which could improve generalizability of the results.
- For Type 2 patients inadequately treated with metformin or a sulfonlyurea, add-on INH yielded HbA1c lowering comparable to adding either glibenclamide or metformin, respectively (Studies 1001 and 1002, see Table 3.1.2.2.8 and Figure 3.1.2.2.1). For patients inadequately treated with two oral agents, adding INH resulted in highly significant drops in HbA1c (Study 109, see Table 3.1.2.2.6 and Figure 3.1.2.2.1).
- Type 2 patients on SC insulin therapy were able to maintain their HbA1c levels when switched to INH insulin (Study 108, see Table 3.1.2.2.5 and Figure 3.1.2.2.1)
- Naïve Type 2 patients randomized to either rosiglitazone (4 mg BID, the most effective marketed dose) or INH showed statistically significantly more lowering of HbA1c and FPG on INH in Study 110 (Table 3.1.2.2.7) ; however the length of the trial at 12 weeks provided inadequate time for rosiglitazone to show a full effect (Figure 3.1.2.2.1). This reviewer concludes that Study 110 was inadequate by design and the results should not be included in labeling.
- Antibody counts were significantly higher in INH patients than in patients treated with SC insulin or oral agents. This reviewer found no relationship between change in antibody count and change in dose. A crude analysis of antibody count by severity of hypoglycemia suggests that higher levels of antibodies may be associated with more severe levels of hypoglycemia, although antibody level does not appear to be a strong predictor of moderate to severe hypoglycemia in patients treated with INH (see pages 32 to 34 for more details.)
- The hypoglycemic event rates in the Type 1 studies were comparable regardless of the definition of hypoglycemia. The definition suggested by an FDA medical reviewer at the IND stage resulted in counts of events that were a mixture of mild to severe events with about 20% non-symptomatic. These FDA-events were only distinguishable from other hypoglycemic events based on a glucose level of 36 or below. An FDA advisory committee concluded such events may contain too much noise and the most reliable measure of a severe hypoglycemic event should include a measure of neurologic impairment. The latter was included in the

protocol-defined severe hypoglycemia.

1.2 Brief Overview of Clinical Studies

1.2.1 Phase 2/3 clinical trials in patients with Type 1 diabetes

A total of five Phase 2/3 trials plus one long term extension study were conducted in patients with Type 1 diabetes (Table 1.2.1.1). Phase 3 studies 106 and 107 are adequately designed to provide data to support the efficacy of INH compared to SC and are reviewed in detail here. Study 102 is a small Phase 2 study of short duration and was not reviewed.

Table 1.2.1.1 Phase 2/3 Open-Label, Randomized, Parallel-group Completed Clinical Trials

Study (# of centers)	Inhaled Insulin group	SC Insulin group	Duration of treatment
Phase 2 Studies			
102 (10 US) centers also in 106 and 107	Pre-meal TID + bedtime SC Ultralente 35 rand. 100% completed	Usual SC regimen (BID or TID) 37 rand. 95% completed	4 wk run-in: usual SC regimen 12 wks randomized treatment
Phase 3 Studies			
106 (33 US, 8 Can.) scr and base HbA1c 6%-11%	Pre-meal TID + bedtime SC Ultralente 170 rand. 89% completed	SC regular insulin (BID) +NPH ins 165 rand. 92% completed	4 wk run-in: BID SC reg +NPH ins 24 wks randomized treatment
107 (32 US, 8 Can.) scr and base HbA1c 6%-11%	Pre-meal TID + NPH ins AM and bed 163 rand. 94% completed	SC regular insulin (TID) + NPH ins AM and bed 165 rand. 92% completed	4 wk run-in: pre-meal SC reg +BID NPH ins 24 wks randomized treatment
111 LT Safety Extension of 106, 107, 108, 109, 110, 1009	All pts switched to INH 664 Type 1 patients Included pul fn tests	NA	Most pts had more than 18 months of extended trt -- up to 3 yrs
1026 dose-finding, pharmacology	TID INH +BID NPH 24 rand.	TID reg ins +BID NPH 23 rand.	4 wk run-in SC 24 wks post-prandial glucose
1027 (US, Can, Braz) Safety study Pulm. Fn. tests	Pre-meal TID + QD or BID ultralente or NPH, or QD ins glargine 110 rand. 84% complet. 24 wks	BID or TID reg ins + QD or BID ultralente or NPH, or QD ins glargine 116 rand. 84% complet. 24 wks	3 wk run-in SC short-acting ins 12 wk randomized treatment 12 wk follow-up SC short-acting ins Efficacy data was collected

Results from bolded studies are included in the labeling. Sample sizes are total number of patients including both adult and pediatric patients.

Study 1026, a small PD/PK trial, included standardized meal challenges as well as euglycemic clamp studies. The applicant concluded that there was no difference in post-prandial control

between INH and SC. This study is not reviewed here because there is insufficient HbA1c data to draw definitive conclusions on efficacy.

Study 111, a long-term uncontrolled safety study of both Type 1 and Type 2 patients, and Study 1027, a 12 week pulmonary function study, were reviewed by the FDA safety reviewers, Dr. Buenconsejo, Dr. Mahoney and Dr. Seymour.

An additional study (Study 1009) was conducted in children aged 6-11 years with Type 1 diabetes (total of 121 patients; 61 INH and 60 SC). An indication for pediatric patients is not being sought at this time so this study is not reviewed here although the applicant's results from this study are briefly stated in Section 4.2.1 (page 36).

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1.2.2 Phase 2/3 clinical trials in patients with Type 2 diabetes

The applicant has conducted two Phase 2 studies and five Phase 3 studies in patients with Type 2 diabetes (Table 1.2.2.1 on following page). Only the Phase 3 studies (108, 109, 110, 1001 and 1002) are reviewed here because they have adequate size and duration to provide data to establish efficacy. The results of Study 111, the long term safety study, are included in safety analyses performed by this reviewer and by the FDA safety reviewers (Drs. Mahoney, Seymour and Buenconsejo).

Table 1.2.2.1 Phase 2/3 Open-Label, Randomized, Parallel-group Clinical Trials

Study (# of centers)	Inhaled Insulin group	Insulin or oral agent group	Duration of treatment
Phase 2 Studies			
103 (US 10)	pre-meal INH +bedtime ultralente 28 rand. 89% completed	BID or TID SC (dose, not freq., could be adjusted) 28 rand. 93% completed	4 wk run-in SC ins 2-day inpt instructions 12 wk rand. treatment
104 (US 9) add-on trial	INH+oral agent 33 rand. 100% completed	oral agent 36 rand. 100% completed	4 wk run-in usual oral agent (sulf and/or met) 2-day inpt instructions 12 wk rand. treatment
Phase 3 Studies			
108 (US and Canada 49)	pre-meal INH +bedtime ultralente 149 rand. 89% completed	SC BID reg + NPH 150 rand. 93% completed	4 wk run-in SC ins 24 wk rand. treatment
109 (US and Canada 52)	Arm 1= pre-meal INH 105 rand. 92% completed Arm 2= pre-meal INH+2 OA's 102 rand. 97% completed	Arm 3= 2 OA's SU or repaglinide + glitazone or MET 102 rand. 91% completed	4 wk run-in 2 OA's 12 wk rand. treatment
110 (US 40)	pre-meal INH 76 rand. 93% completed	ROSI 4 mg BID 67 rand. 91% completed	4 wk run-in diet+exer 24 wk rand. treatment
1001 (Eur, Scan, UK, Israel, Brazil, S. Africa 73)	pre-meal INH 225 rand. 92% completed	Metformin Add-on to SU 202 rand. 88% completed	4 wk run-in metformin 24 wk rand. treatment
1002 (Eur, Scan, UK, Israel, Brazil, S. Africa 77)	pre-meal INH 243 rand. 90% completed	Glibenclamide Add-on to MET 233 rand. 88% completed	4 wk run-in glib. 24 wk rand. treatment
111 LT safety Extension of 106, 107, 108, 109, 110, 1009	All pts switched to INH 626 Type 2 patients Included pul fn tests	NA	Most pts had more than 18 months of extended trt – up to 3 yrs

Results from bolded studies are included in the labeling.

Each of the five Phase 3 trials has a unique design in terms of comparator arm and the population studied. Based on the results of these trials, the applicant is seeking a broad indication for use in patients with Type 2 diabetes stating that "Exubera can be used as monotherapy or in combination with oral agents or longer-acting insulins."

At the time of the submission of the NDA, several safety studies were ongoing. These trials are listed in a table in Appendix 6.1. Since the focus of this review is primarily efficacy, the ongoing trials are not reviewed here.

1.3 Statistical Issues

The following statistical issues arose during the process of this review:

- Randomization procedures described in the protocols and in the study reports were not the procedures actually carried out. Patients were not assigned using a minimization algorithm but instead were randomized centrally blocking on center (see page 15 for more details).
- All trials in the Exubera submission were open-label trials. The lack of blinding introduces the possibility of bias in several aspects of the trial. The first aspect considered by this reviewer was the enrollment of patients. The lack of blinding can lead to selection bias in that the randomization code could be broken based on the patients already entered in the trial. An investigator may be able to guess the treatment assignment for the next patient. Guessing is more difficult if the randomization is carried out from a central office, if stratification is not done by center and if block sizes are unknown by the investigator (i.e. not mentioned in the protocol). The first and third conditions were in place in the Exubera trials. Stratification was done by center so it is possible that the pattern of treatment assignment could be discerned and that assignment would be predictable for some patients. To test if selection bias was an issue this reviewer performed a test described by Berger and Exner on the data from Study 107 (the most important Type 1 study). Basically this test determines whether the probability of having a good response is related to the probability of being assigned to the test drug; this is essentially testing whether patients with a good prognosis are more likely to have been assigned to Exubera. This reviewer found no evidence of selection bias based on the results of this test.
- The lack of blinding can also bias the measurement of both efficacy and safety measures. HbA1c is an objective measure not likely to affected by knowledge of treatment, particularly since dosing of patients was well-controlled by specific parameters spelled out in the protocols and inspection of the data suggests that dosing was adjusted as would be expected. There is some evidence that safety measures may have been affected by the lack of blinding. More specifically, the medical reviewer, Dr. Karen Mahoney, carefully describes the misclassification of discontinuation reasons as "withdrawn consent" or "subject request" where the data suggests that the reason was "adverse event". She found a larger number of misclassifications in the INH group than in the comparator group suggesting the possibility that knowledge of treatment could have played a role in the naming of the discontinuation reason.
- The 12-week duration of Study 110 was insufficient to provide a fair comparison of rosiglitazone to INH (see page 26).
- Patients who discontinue from therapy due to hypoglycemia may provide HbA1c LOCF data that suggests a beneficial result when in reality the therapy was a failure for that patient. This reviewer examined the data to determine if the LOCF estimates were biased by the use of such dropout data and found no evidence that this was the case.
- Noninferiority trials were powered to rule out a treatment difference for HbA1c change from baseline of 0.5% while 0.4% is the margin usually used by FDA. This, however, was not an issue since the boundary of 0.4% was met in all relevant trials.
- The Type 2 development program consisted of five Phase 3 trials; 3 conducted in North America and 2 conducted in foreign countries. The majority of the investigator sites participated in more than one study. For Studies 1001 and 1002 (foreign studies) and for Studies 108, 109 and 110, about half of the total sites participated in more than 1 study (see page 19 for additional details). Patients were not allowed to participate in more than one study and, in addition, entry criteria differed making patients ineligible for more than one study so this reviewer was not concerned that patients may have been retested. Enrollment dates were overlapping for the studies so investigators would be seeing patients during the same timeframe from the different studies suggesting that experience from participating in one trial would not carryover and affect the conduct of a subsequent trial. Also the sample size of

each site is small and no one site would greatly influence the outcome. Though overlapping sites could affect the independence of the trial results, this reviewer did not feel, for these studies, that independence was comprised for the reasons given.

- The applicant computed risk ratios for hypoglycemia using a recurrent events proportional hazards model that assumes events are independent. This model is not appropriate primarily because it ignores the dependency among events within patients. The model is oversensitive to patients with many events; for example, dropping just one patient from an analysis of Study 107 data changed the estimate of the risk ratio from 2.25 to 1.65. A preferred method of analysis would be a non-parametric analysis (e.g. Wilcoxon rank sum test) of the number of events per patient.
- The applicant summarized the incidence of hypoglycemia as number of events per patient-month. These measures are not appropriate for the data from these studies for two reasons; 1) essentially all patients had the same exposure time in the controlled trials and 2) a few patients had many events such that averaging overestimated the counts generally seen for most patients. Instead, hypoglycemia may be summarized as the median number of events observed per patient or as the number of patients with at least one event.

2. Introduction

2.1 Overview

Exubera is an inhaled insulin product combining a dry powder formulation of a recombinant human insulin with a customized inhalation system. At the time of this application, insulin was only available via subcutaneous (SC) injection. Exubera, then, offers an alternative non-invasive route of administration. Exubera, according to the applicant, is "rapid-acting with a faster onset of action than SC regular insulin" and so it can replace pre-meal insulin. The Phase 1 and 2 studies in the development program used a 20% insulin formulation while the Phase 3 studies and stability studies used a 60% insulin formulation. The inhaler also was modified between the Phase 2 and Phase 3 studies.

The focus of this review is primarily on efficacy in the Phase 3 trials. This reviewer did not perform a full safety review; safety is addressed by three FDA reviewers in their individual reviews (Drs. Mahoney, Seymour and Buenconsejo). Safety issues addressed in Section 3.2 arose from consultations with the clinical reviewer, Dr. Mahoney.

The applicant is seeking an indication in adults only, based on a recommendation from FDA. However, children were included in some of the Phase 3 trials. For those trials, the review is of the adult patients; results for children are briefly summarized in Section 4.2.1 on page 36 of the review.

2.2 Data Sources

The applicant provided a Common Technical Document and datasets electronically. The address for the SAS datasets in the FDA Electronic Document Room is \\Cdsesub1\n21868\N_000\2004-12-27\crt.

Study reports were well-organized and easy to navigate with essentially the same structure used for each report making it easy for the reviewer to quickly find information from several studies. Datasets were also well-organized although some data (such as detailed explanations of why patients discontinued) were not available.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Clinical Trials in Patients with Type 1 Diabetes

3.1.1.1 Studies 106 and 107

Both adult and pediatric patients were enrolled in the studies of Type 1 diabetics. The focus for the review is on adult patients as previously mentioned.

Design

Two phase 3 clinical trials (Studies 106 and 107) were conducted in patients with Type 1 diabetes to assess the efficacy and safety of Exubera (for descriptions of other trials conducted in Type 1 patients see Table 1.2.1.1). Both trials were 6-month, open-label, out-patient trials comparing Exubera to subcutaneous human insulin therapy.

In Study 106, all patients were administered twice daily (BID) regular insulin SC plus BID SC NPH insulin given pre-breakfast and bedtime, during a lead-in period of 4 weeks. Eligible patients were randomized to one of the following treatment groups:

1. pre-meal (TID) inhaled insulin (INH) plus single Ultralente SC injection at bedtime
2. twice daily (BID) regular insulin SC plus BID SC NPH insulin; patients with a different pre-study regimen could receive dosing comparable to their prestudy dosing (e.g. pre-meal insulin)

In Study 107, all patients were administered pre-meal (TID) regular insulin SC plus BID SC NPH insulin given pre-breakfast and bedtime, during a lead-in period of 4 weeks. Eligible patients were randomized to one of the following treatment groups:

1. pre-meal (TID) inhaled insulin (INH) plus BID SC NPH insulin
2. pre-meal (TID) regular insulin SC plus BID SC NPH insulin

Inclusion criteria included the following:

- Diagnosis of Type 1 diabetes for more than one year
- Aged 12 to 65
- 2 months on a stable insulin regimen involving at least 2 daily injections
- Screening (Week -4) and pre-randomization (Week -1) HbA1c of 6% to 11%, inclusive
- Fasting plasma C-peptide≤0.2 pmol/ml
- BMI≤30

Exclusion criteria included the following:

- Use of insulin pump therapy within 2 months of screening
- History of severe hypoglycemia
- Significant respiratory disease
- Smoker within 6 months prior to screening
- Abnormal pulmonary function tests at Week –3
- Significant major organ system disease

HbA1c was measured on therapy at Weeks 6, 12 and 24. The primary efficacy endpoint was

HbA1c change from baseline at Week 24. Baseline was computed as the average of Weeks -1 and 0.

Secondary variables included FPG, % of patients achieving HbA1c below 7% or 8%, body weight, pre and post prandial glucose values, serum lipids and a measure of quality of life (Phase V Quality of Life (QOL) Treatment Satisfaction Questionnaire).

Patient Disposition

In each study, the plan was to enroll 160 patients in each treatment group, including pediatric patients; so the trial was powered with the inclusion of the pediatric patients. About 1/5 of the Study 106 patients and about 1/3 of the Study 107 patients were under aged 18; these patients are excluded from the tables in this review. Neither study then was adequately powered for only adult patients based on the parameters[1] used to estimate sample size.

A total of 273 adult patients were enrolled in Study 106 and a total of 208 in Study 107 (Table 3.1.1.1). Patients in Studies 106 and 107 were recruited at 41 and 40 centers, respectively in the United States and Canada with the majority of the patients (about 78%) in US centers. Sample sizes in each center ranged from 2 to 20 with most centers enrolling 10 or fewer patients.

Table 3.1.1.1 Patient Disposition

	Study 106		Study 107	
	INH	SC	INH	SC
Randomized	137	136	103	105
Never treated	0	1	1	0
Wk 6	134 (98%)	132 (97%)	102 (100%)	103 (98%)
Wk 12	127 (93%)	128 (94%)	102 (100%)	100 (95%)
Completers	120 (88%)	124 (91%)	97 (94%)	96 (91%)

In both studies, more than 90% of the patients completed 24 weeks on study; there is no notable difference between the treatment groups regarding completion rates.

Three INH patients discontinued from Study 106 due to ADE (Table 3.1.1.2); 2 due to severe hypoglycemia (Weeks 4-5) with one patient experiencing a diabetic coma plus one due to mild coughing (Week 9). One SC patient discontinued from Study 106 due to accidental injury (ADE at Week 8). In Study 107, ADE's included one INH patient who discontinued during Week 6 due to pulmonary obstruction and one SC patient who discontinued due to carcinoma.

Table 3.1.1.2 Reasons for discontinuation

	Study 106		Study 107	
	INH (n=137)	SC (n=136)	INH (n=103)	SC (n=105)
ADE	3 (2.2%)	1 (0.7%)	1 (0.9%)	1 (0.9%)
Lack of Eff.	2 (1.5%)	2 (1.5%)	0	0
Lost-to-FU	2 (1.5%)	2 (1.5%)	2 (1.9%)	1 (0.9%)
Pt request	7 (5.1%)	6 (4.4%)	1 (0.9%)	6 (5.7%)
Other	3 (2.2%)	1 (0.7%)	1 (0.9%)	1 (0.9%)
Abn. Lab	0	0	1 (0.9%)	0

The impact of the dropouts on assessment of efficacy when using LOCF was examined. There

1 Sample size was estimated assuming, power of about 90%, no treatment difference, standard deviation of 1.2 to 1.5% for change in HbA1c, 2-sided 95% confidence interval and noninferiority margin of 0.5%.

was only one discontinued patient in the INH group who had a large drop in HbA1c carried forward; the large response was due to hypoglycemia. The impact of this one patient on the results is negligible and this reviewer did not consider alternative analyses to address the problem of carrying-forward what appears to be a beneficial result coupled with an adverse event leading to dropout.

Baseline Demographics and Medical History

The treatment groups were adequately balanced on demographic characteristics (Table 3.1.1.3). The average age of patients was 38 years (patients under 18 are excluded from the table). No patients in either trial were 65 years or older. About 5% of the patients had an BMI>30 although the cutoff for entry was 30. The majority of patients were white and had never smoked.

Table 3.1.1.3 Baseline Demographics

	Study 106		Study 107	
	INH (n=137)	SC (n=136)	INH (n=103)	SC (n=105)
Age				
Mean (SD)	38 (10)	38 (10.5)	38 (11)	38.5 (11)
Range	20-63	20-64	19-65	19-65
% >50	14%	14%	16%	17%
Gender				
% female	49%	47%	48%	44%
Race				
% White	88%	95%	87%	94%
% Hispanic	7%	3%	5%	4%
% Black	3.7%	1.5%	3%	1%
% Asian	1.5%	0	4%	0
% Amer. Ind.	0	0	1%	0
% Other	0	0.7%	0	1%
BMI				
Mean (SD)	26 (3)	26 (3)	25 (3)	26 (3)
Smoker				
Never	76%	75%	65%	70%
Former	23%	25%	35%	30%
Yes	1%	0	0	0
Duration of Diabetes (yrs)				
Mean (SD)	19 (9)	18.5 (11)	17 (11)	19 (11)
Range	1-41	1-49	2-50	1.5-49
Diabetic conditions (N)				
Retinopathy	45	39	39	35
Neuropathy	21	32	24	28
Hypertension (N)	16	20	14	16

This reviewer checked the medication history and found the groups to be well balanced; the most commonly used drugs were drugs to treat rheumatic disease or gout (about 50-60% of the patients), antibacterials and analgesics.

Dosing

During the run-in phase of both trials, all patients were given SC insulin plus NPH insulin. Patients randomized into the control arm continued on their run-in dosing regimen. In Study 106, for the patients randomized to INH, the long acting NPH daily dose was replaced with bedtime Ultralente at approximately 65-75% of the dose of the run-in NPH dose.

Regular home monitoring of glucose was expected and dosing was individualized (goal of 2-hour post-prandial increment <60 mg/dL). For INH patients, one of the following 5 dose levels was to be used prior to meals with the initial dose based on weight as follows:

Body Weight (kg)	INH dose	Equivalent SC dose
30-44	1 inhale 1 mg	3 U
45-59	2 inhales 1 mg	6 U
60-79	1 inhale 3 mg	9 U
80-99	1 inhale 1 mg 1 inhale 3 mg	12 U
>100	2 inhales 3 mg	18U

Extra doses could be given prior to snacks or at bedtime.

Dose titration was performed based on the recommendations shown in the table below.

Time out of target range	Target range		INH insulin dose adjustment		SC insulin dose adjustment	
	Study 106	Study 107	Study 106	Study 107	Study 106	Study 107
Pre-breakfast	80-140	80-120	Bedtime Ultralente	Bedtime NPH	Evening NPH	Bedtime NPH
Pre-lunch	80-140	80-120	Pre-brkfast INH	Pre-brkfast INH	Pre-brkfast reg SC	Pre-brkfast reg SC
Pre-supper	80-140	80-120	Pre-lunch INH	Pre-brkfast +/-pre-lunch INH	Pre-breakfast NPH	Pre-brkfast NPH+/-pre-lunch reg SC
2-hr post-prandial	NA	<180	NA	preceding meal INH	NA	preceding meal reg SC
Bedtime	100-160	100-140	Pre-supper INH	Pre-supper INH	Pre-supper reg SC	Pre-supper reg SC

On the following page is a summary of the mean dose levels for short and long acting insulin. One concern of FDA was that increases in long-acting use may compensate for inadequate treatment on short-acting insulin and then may mask notable treatment differences.

In Study 106, the treatment groups differed in both the type of long-acting insulin and the type of short-acting insulin administered so changes in either cannot be independently compared across the treatment groups. Within the INH group, baseline long-acting was NPH BID and, on-study, bedtime Ultralente was given. Within the SC group, NPH BID was given throughout the trial. So the decreases seen in long acting in the INH group are due to the differing types of long-acting (Table 3.1.14). For both treatment groups, doses of short-acting increase while on randomized treatment from Week 1 to Week 24 with a larger increase seen within the INH group.

Table 3.1.1.4 Insulin Dosing; For INH group, short-acting is measured in mg, all other doses are in units (Medians and distributions are provided for long-acting dose and ratio of doses in Appendices 6.2 and 6.3)

	Study 106		Study 107	
	INH Mean (SD)	SC Mean (SD)	INH Mean (SD)	SC Mean (SD)
Insulin Use Screening	n=132	n=130	n=97	n=101
Short-acting	23.8 (15.0)	26.2 (17.3)	25.9 (19.1)	25.4 (20.7)
Long-acting	34.4 (18.5)	34.6 (20.6)	31.7 (16.8)	35.1 (20.1)
Ratio	2.2 (2.4)	1.8 (1.4)	2.1 (3.0)	2.1 (1.8)
Insulin Use Run-in Wk -3	n=132	n=134	n=101	n=103
Short-acting	18.8 (11.9)	17.6 (8.4)	22.2 (13.9)	22.6 (12.4)
Long-acting	32.4 (15.0)	32.2 (15.4)	29.8 (14)	29.4 (12.4)
Ratio	2.7 (3.8)	2.1 (1.2)	1.8 (1.4)	1.7 (1.1)
Insulin Use Run-in Wk 0[1]	n=137	n=135	n=103	n=105
Short-acting	18.4 (9.2)	18.2 (9.0)	23.7 (12.4)	24 (11)
Long-acting	34.4 (15.0)	35.7 (18.0)	30.8 (14.8)	30.3 (12.6)
Ratio	2.4 (1.8)	2.3 (1.5)	1.6 (1.4)	1.5 (0.8)
Insulin Use by Week on Study				
Week 1	n=136	n=135	n=103	n=105
Short-acting	10.8 (4.0)	18.2 (9.4)	8.0 (4.0)	24.1 (10.6)
Long-acting	23.8 (11.8)	36 (17.8)	30.5 (14)	30.5 (12.7)
Ratio	2.4 (1.4)	2.4 (1.6)	4.7 (3.4)	1.4 (0.7)
Week 6	n=134	n=130	n=103	n=102
Short-acting	11.8 (5.3)	18.2 (10.5)	9.4 (4.5)	24.1 (10.7)
Long-acting	26 (12)	37.6 (18.8)	31.0 (14.8)	31.1 (13.6)
Ratio	2.5 (1.6)	2.6 (1.7)	3.9 (2.5)	1.5 (0.7)
Week 12	n=127	n=125	n=102	n=99
Short-acting	12.4 (5.7)	17.9 (8.9)	10.2 (4.7)	24.2 (11.1)
Long-acting	25.9 (12.5)	37.5 (17.9)	31.1 (15.2)	31.1 (14)
Ratio	2.4 (1.4)	2.7 (2.8)	3.6 (2.4)	1.4 (0.7)
Week 24	n=123	n=124	n=98	n=97
Short-acting	13.4 (5.9)	18.3 (9.6)	10.8 (5)	26.0 (12.7)
Long-acting	26.1 (13)	36.8 (18.3)	31.5 (15.9)	32.5 (14.7)
Ratio	2.3 (1.4)	2.8 (3)	3.4 (2.2)	1.4 (0.7)
Change from Week 0 LOCF Long-acting	-8:8 (11)	+1.4 (10)	+0.7 (7.9)	+2.0 (7.6)
Trt Difference	-10.5 (-13, -8)		-1.3 (-3.4, 0.8)	

In Study 107, the treatment groups are comparable regarding long-acting insulin (NPH BID) and short-acting SC at baseline. All patients continued on their long-acting insulin regimen through the study; an overall small increase in dose is seen in both groups with essentially no difference

1 Week 0 is the last week of the run-in period; the last day of Week 0 is the baseline visit.

between the groups (Table 3.1.1.4). The treatment differences in short-acting doses and the differing ratios are in keeping with what would be expected for INH compared to SC. There is no evidence that long-acting doses are increased over time in either treatment group. The dose of INH increases on average from Week 1 to about Week 12 and then is stable; an inspection of individual patients by this reviewer showed that the dose of INH is generally stable by about Week 10.

Statistical Methods

The protocol and study report stated that patients were assigned to treatment using an algorithm to balance on inclusion/exclusion criteria. Discussions with the applicant revealed that an algorithm was not used and patients were randomized to treatment via a central telephone system. Randomization was blocked within centers in sizes of 2 and 4. The protocol did not mention the block sizes or that blocking was within center so investigators should have been unaware of the blocking scheme. However, even without that knowledge, one might be able to guess the block sizes quite easily particularly since the block sizes are small and the number of patients in each site is small. Given the trials are open-label and blocking was within centers, there is a potential for selection bias. To test for selection bias, this reviewer performed an analysis described by Berger and Exner (Controlled Clinical Trials 20:319-327, 1999). This analysis was only done for Study 107.

The protocol specified that the evaluable population (compliant with a specified minimum amount of treatment) would be the primary analysis set. In addition, an analysis of the intent-to-treat (ITT) population was planned. Missing data were handled by using the last observation carried forward (LOCF) approach; other imputation schemes were also considered. For this reviewer's analysis, the primary analysis population is the ITT population. In addition, analyses of completers was done. Due to the small number of dropouts, there is no expectation that the choice of analysis population will impact on the results.

The primary outcome variable, change from baseline HbA1c, was analyzed using an analysis of covariance model which included baseline HbA1c as a covariate and terms for center (with smaller centers pooled) and treatment. As secondary analyses, the applicant considered other factors as covariates: these factors included age, BMI, baseline C-peptide, gender, race and baseline insulin antibody. This reviewer also considered dosing as a covariate. First order interactions were tested. All randomized patients were analyzed with stratification on age (<18 versus 18 and older). Only the 18 and older patients are presented here. Results for under 18 are included in the subgroup section of this review.

Both trials were powered to rule out a treatment difference of 0.5% in favor of SC over INH based on a 95% confidence on the difference in HbA1c change from baseline at Week 24.

Efficacy Results

Given that the trials are open-label and that randomization was blocked on center, this reviewer was concerned that investigators could have selected patients based on knowledge of the next assignment. For Study 107, the results for a test for selection bias showed that baseline characteristics and outcome were not related to the probability of being assigned to the INH group; therefore this reviewer believes that there is no evidence that there was bias in the selection of patients for Study 107. The analysis was not done for Study 106 since Study 107 was considered the most important of the two studies.

Baseline was computed as the average of Weeks -1 and 0. For each study, the treatment groups were comparable at baseline for HbA1c and FPG (Table 3.1.1.5). Plots of the baseline values can be found in Appendix 6.4.

The confidence intervals for the HbA1c treatment differences (Table 3.1.1.5) indicate no statistically significant difference between the treatment groups. The results in Study 106 are more favorable to SC while the opposite is true for 107 with more favorable results for INH; although the differences are not clinically relevant with confidence limits within the noninferiority margin set by the protocol (0.5) and within a margin of 0.4 which is generally accepted by the FDA .

Table 3.1.1.5 Results for HbA1c and FPG

	Study 106			Study 107		
	INH Mean (SD)	SC Mean (SD)	LSM Diff 95% CI	INH Mean (SD)	SC Mean (SD)	LSM Diff 95% CI
HbA1c	n=136	n=132		n=103	n=103	
Baseline	7.9 (0.9)	8.0 (1.0)		7.8 (0.9)	7.8 (1.0)	
Change from baseline						
Wk 24 Completer	-0.25 (0.8) (n=120)	-0.4 (0.7) (n=123)	+0.1 (-0.1, +0.3)	-0.3 (0.8) (n=97)	-0.2 (0.8) (n=96)	-0.1 (-0.3, +0.1)
Wk 24 LOCF	-0.2 (0.8)	-0.4 (0.8)	+0.1 (-0.04, +0.3)	-0.3 (0.8)	-0.2 (0.8)	-0.1 (-0.3, +0.1)
FPG	n=131	n=129		n=101	n=97	
Baseline	191 (61)	198 (61)		178 (69)	191 (68)	(p=0.18)
Change from baseline						
By week						
12	-31 (99)	-13 (96)	-22 (-42, -0.8)	-30 (89)	-11 (85)	-26 (-50, -3)
24	-31 (91)	-1 (95)	-33 (-54, -12)	-25 (97)	+5 (83)	-38 (-63, -14)
Wk 24 LOCF	-29 (95)	-7 (100)	-27 (-48, -7)	-21 (98)	+5 (89)	-35 (-59, -12)

For the least squares mean difference (LSM), negative values favor INH. Statistical model included treatment, baseline, age as a stratifier (<18 and ≥18) and an interaction term for age and treatment.

The FPG results show significantly larger decreases in FPG for INH than for SC. The decreases in FPG are not correlated with decreases in HbA1c with r^2 values of less than 0.01 for INH and less than 0.1 for SC for each treatment group at Week 24.

Percentages of patients with final HbA1c level below 7% and 8% were named as secondary variables; percentage of patents below 8% at end of study is included in the applicant's proposed labeling. This reviewer has provided these results for all patients and by subgroups defined by baseline values of 8% and 7%. Results by subgroup indicate whether patients were able to maintain baseline levels or improve from baseline. There is no statistically significant difference between the groups in either study for both measures of overall percentages. For the subgroups, the most notable differences are a treatment difference of 38% (p=0.02, Fisher's exact test), in favor of SC in Study 106 for patients with baseline values less than 7% and a treatment difference of 20% (p=0.07, Fisher's exact test) in favor of INH in Study 107 for patients with baseline values greater than or equal to 8%. The inconsistency of the results makes it difficult to draw any conclusions from these analyses. Overall it seems that patients with low values (under 7 or 8) at baseline tend to stay low even when changing treatment regimens. Less than half the patients with values above 8 at baseline are able to achieve HbA1c levels below 8% after 24 weeks of titrated treatment.

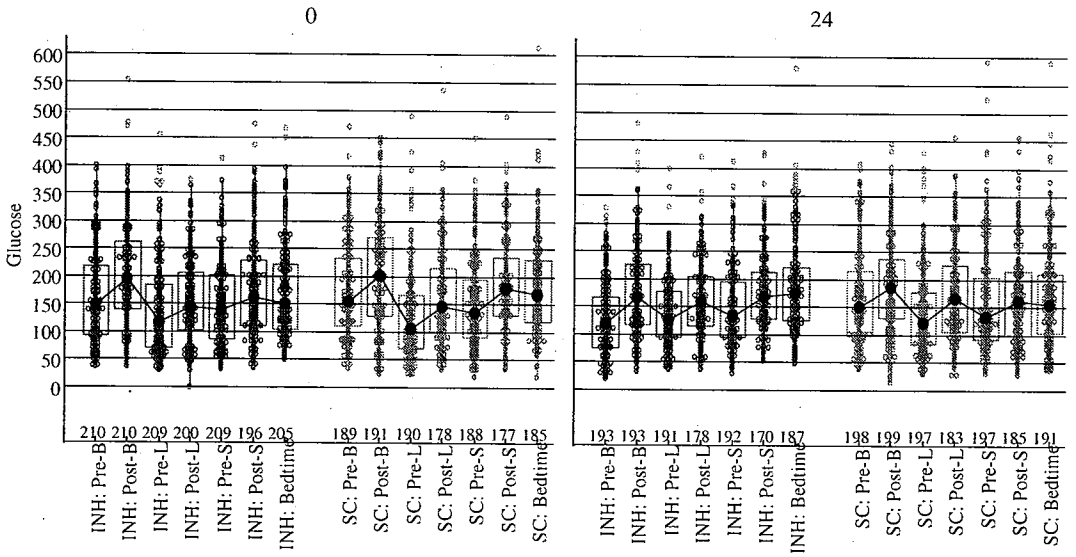
Table 3.1.1.6 Percentage of patients with HbA1c below 8 and below 7 at Week 24 LOCF by study and treatment and by baseline category

	Study 106		Study 107	
	INH (n=136)	SC (n=132)	INH (n=103)	SC (n=103)
% pts w/ last HbA1c <8%	64%	68%	75%	66%
By Subgroup				
Baseline<8%	84% (62/74)	91% (64/70)	92% (55/60)	85% (57/67)
Baseline≥8%	40% (25/62)	42% (26/62)	51% (22/43)	31% (11/36)
% pts w/ last HbA1c <7%	17%	20%	28%	30%
By Subgroup				
Baseline<7%	50% (12/24)	88% (14/16)	63% (12/19)	68% (13/19)
Baseline≥7%	10% (11/112)	10% (12/116)	20% (17/84)	21% (18/84)

The significant treatment effects seen for fasting plasma glucose levels but not for HbA1c changes led this reviewer to look, with the medical reviewer, at changes in glucose levels as recorded in 24-hour diaries over a 3-day period. The results are illustrated in the boxplots on the following page (Figure 3.1.1.1).

At baseline, the groups are comparable with medians varying within a day from about 125 to 200. At Week 24, in the INH group, the pre-breakfast value (median of about 130) is notably lower than the bedtime value (median of about 180) while in the SC group, the pre-breakfast values are similar to bedtime values and baseline values. This difference between the treatment groups in pre-breakfast values is about the same difference seen for FPG as reported in Table 3.1.1.5 on the previous page.

Figure 3.1.1.1 Glucose levels from 24-recordings of 3 days combined at Week 0 and Week 24



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3.1.2 Clinical Trials in Patients with Type 2 Diabetes

For this review, the designs and the descriptions of the patient populations for all five of the Phase 3 trials of Type 2 diabetes are presented in the following section (3.1.2.1) in order to allow the reader to more clearly see the similarities and differences among the five trials. The results are presented in Section 3.1.2.2 with separate sections for each of the studies.

3.1.2.1 Overview of Phase 3 trials in Patients with Type 2 Diabetes

The applicant has conducted five Phase 3 clinical trials in Type 2 diabetics: Studies 108, 109, 110, 1001 and 1002 (see Summary Table 1.2.2.1 on page 7). Study 108 was an active-controlled trial in patients previously treated with SC insulin with the goal being to show that the effect of Exubera was non-inferior to the effect of SC insulin; the design of this trial is similar to the studies in Type 1 diabetics. Study 110, in seemingly naïve patients who were without medication for at least one month prior to screening and during the run-in, compared Exubera to rosiglitazone (4 mg BID, the most effective marketed dose of rosiglitazone). Study 109 was a three arm study of Exubera plus two oral agents (combination therapy), Exubera monotherapy and the combination of two oral agents. Studies 1001 and 1002 were add-on studies where patients inadequately treated with sulfonylureas or metformin, respectively, were randomized to either add-on Exubera or oral agent (metformin or glibenclamide). Studies 109 and 110 were superiority trials and the other three studies were non-inferiority trials.

Three trials (108, 109 and 110) were conducted in North America and two trials (1001 and 1002) were conducted in Europe, South America, the Middle East and Africa (Table 3.1.2.1.1). Three were of 24-week duration and two of 12-week duration; generally FDA recommends 24 to 26-week duration for a trial to assess Type 2 antidiabetic drugs.

Table 3.1.2.1.1 Studies in patients with Type 2 diabetes

Study	Dates	Locations (# centers)	Duration of randomized treatment	Total # of patients randomized
108	9/99 to 12/00	US (38) Canada (11)	24 weeks	299
109	6/99 to 9/00	US (40) Canada (12)	12 weeks	309
110	10/99 to 3/01	US (40)	12 weeks	145
1001	2/00 to 12/01	Europe (43) Scandinavia (13) UK (6) Israel (4) Brazil (4) South Africa (3)	24 weeks	427
1002	3/00 to 5/02	Europe (44) Scandinavia (13) UK (7) Israel (5) Brazil (5) South Africa (3)	24 weeks	476

Studies 108, 109 and 110 were conducted at many of the same sites; Studies 1001 and 1002 were also conducted at many of the same sites. Patients could not enter more than one trial according to all the study protocols so with regard to enrolled patients, the studies would be considered independent. The trials are, however, not independent regarding investigators. Since the trials are overlapping and the patient entry criteria varied based on diabetic treatment experience, it seems unlikely that the collection of data by an investigator would be biased by their prior participation in the trial. Also since a large number of sites participated in each trial, the

number of patients at each site is small. No one site would be expected to have a strong influence on the outcome of the trial; nevertheless, this reviewer did examine data by center, though data by center is not presented in the review.

Patients in all trials were asked to follow the ADA diet, to do moderate exercise 3 times per week (no specific questions regarding diet and exercise were asked) and to monitor home glucose 4 times per day.

Patients enrolled in these five trials had to meet the following entry criteria:

- No significant respiratory disease
- No smoking within 6 months of screening nor on study
- Fasting C-peptide of 0.2 pmol/ml or more
- No more than 1 episode of severe hypoglycemia and no ER or hospital visits for hypoglycemia in the 6 months previous to screening (not a criterion in 1001 and 1002)

Additional entry criteria as well as study design characteristics are summarized below.

Table 3.1.2.1.2 Entry criteria and treatment arms in Phase 3 studies of Type 2 diabetics

Study	HbA1c	Diag Diab	BMI≤	Trt Prior to Screening	4 Week Run-in Trt	Randomized Trt	
						INH	Control
108	6-11% at Wks-4+-1	≥1 year	40	Stable SC for 2 mos+	SC BID reg+NPH	Pre-meal + Ultralente	SC BID reg+NPH
109	8-11% at Wks-4+-1	≥1 year	35	Stable doses of 2 OA's for 2 mos+	2 OA's; SU or repaglinide + glitazone or MET	Mono INH Comb INH+2 OA's	2 OA's SU or repaglinide + glitazone or MET
110	8-11% at Wks-4+-1[1]	≥2 mos	35	No antidiab. drug for 1 month+	diet+exer	Pre-meal	ROSI 4 mg BID
1001	8-12% at Wk -1	≥6 mos	Not in protocol	Poorly controlled on SU for 2 mos+	SU	Pre-meal Add-on to SU	Metformin Add-on to SU
1002	8-12% at Wk -1	≥6 mos	Not in protocol	MET for 2 mos+	MET	Pre-meal Add-on to MET	Glibenclamide Add-on to MET

SU=sulfonylurea MET=metformin

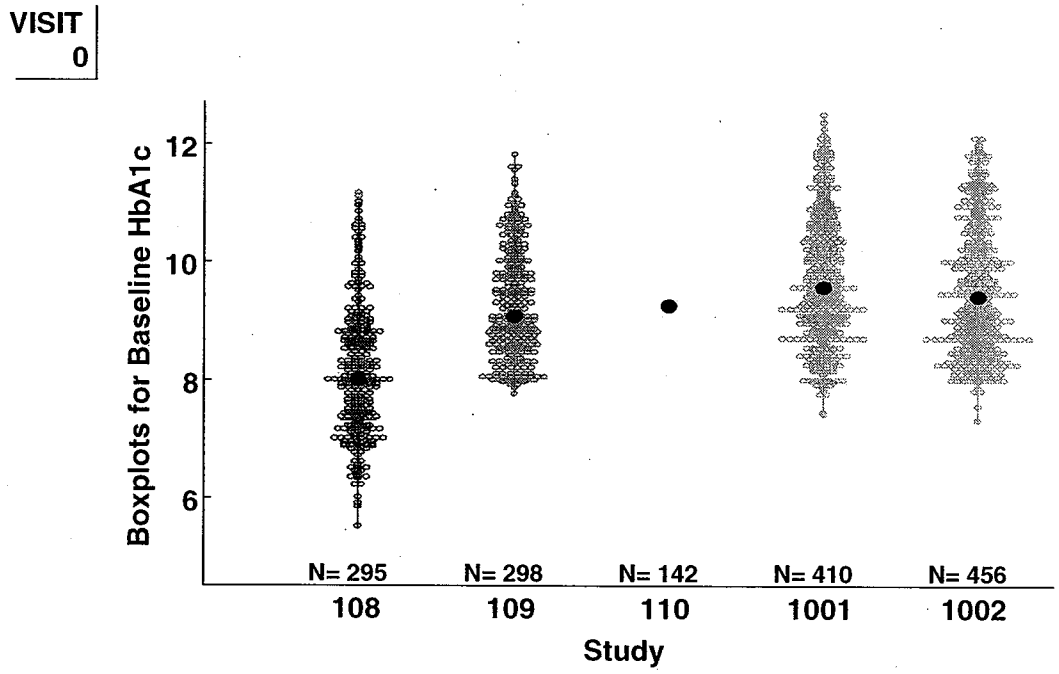
In all studies, the initial dose of INH was based on body weight; titration of the INH dose was based on self-measured premeal glucose levels and a target range of 80-140 mg/dL. A table of the oral antidiabetic medications and doses is provided in Appendix 6.5.

The entry criteria for HbA1c are similar for the studies with the exception of Study 108 where patients could be enrolled with values below 8. For Study 108, patients were not necessarily considered inadequately treated at baseline as they were in the other 4 studies. The distributions of the observed HbA1c baseline data (Figure 3.1.2.1.1 on following page) illustrate the differences among the studies (note that the treatment groups had comparable distributions within each study so data with the groups combined is shown).

Figure 3.1.2.1.1 HbA1c baseline values for five studies of Type 2 diabetics; each symbol

1 The study report stated that the acceptable range for HbA1c was 6 to 11 while the protocol stated 8 to 11; from the data, it is clear that the study report is incorrect.

represents a patient



Within studies, treatment groups are fairly well balanced with regard to baseline demographics with the only notable exception being gender within Study 110. Across studies, variability in all baseline parameters is seen suggesting some heterogeneity among the patient populations; this being a positive observation which could improve generalizability.

Table 3.1.2.1.3 Baseline demographics in Type 2 studies

	108		109			110		1001		1002	
	INH	SC	INH	INH+ OA's	OA's	INH	ROSI	INH	MET	INH	SU
Age											
Mean	59	56	57	58	56	53	54	61	60	55	55
Range	36-80	23-78	35-77	38-77	33-80	28-76	29-80	37-79	35-79	35-74	36-77
% ≥65	29%	25%	23%	22%	21%	17%	19%	34%	36%	16%	16%
Gender											
% female	32%	34%	29%	36%	36%	36%	55%	45%	49%	44%	42%
Race											
White	77%	74%	79%	78%	82%	77%	70%	96%	95%	93%	95%
Black	12%	10%	8%	9%	5%	9%	15%	2%	2%	3%	2%
Asian	3%	3%	2%	0%	2%	1%	0%	1%	1%	2%	2%
Other	1%	5%	3%	5%	3%	0%	1%	2%	2%	3%	1%
Hispanic	8%	8%	8%	8%	7%	12%	13%	0%	0%	0%	0%
BMI											
Mean	31	30	30	30	30	32	33	29	29	32	31
Range	21-51	21-38	22-39	18-38	18-38	20-44	22-48	20-48	20-57	19-47	22-47
Dur. of Diabetes (yrs)											
Mean	13.8	13.2	9.3	9.8	9.6	4.3	3.1	9.6	8.8	8.4	7.8
Range	.4-59	.9-43	2-25	1-37	1-33	.1-22	.1-18	.7-37	.5-33	.6-36	.3-30

The comparator in Study 110, rosiglitazone, has found to be more effective in women and overweight men in studies previously reviewed by FDA; so the larger number of women in the

rosiglitazone group of Study 110 may favor rosiglitazone over INH. However, gender subgroup analyses of the data from this study showed no gender effect and suggests no bias due to this small imbalance.

This reviewer checked the coding for "other" race and found that a total of 3 patients enrolled in the five studies were Native Americans; clearly this ethnic group is under-represented in the Type 2 database for Exubera.

3.1.2.2 Efficacy Results for Phase 3 trials in Patients with Type 2 Diabetes

In this section, patient disposition and discontinuation reasons are summarized for all five trials in Tables 3.1.2.1.3 and 3.1.2.1.4, respectively. Following these tables, the efficacy results with a brief description of the statistical methods for the five Phase 3 trials are presented separately. This section closes with some graphics summarizing the efficacy results.

Studies 108, 109, 1001 and 1002 all recruited more patients then specified in the protocol with the largest increases in sample sizes seen for Studies 1001 and 1002 where the trials were powered for 180 patients in each group. An inspection by this reviewer of the enrollment dates shows no irregularities; for example, there are no breaks in the dates suggesting that enrollment was stopped and started for a period of time. This reviewer does not think that over-enrollment biases the results.

For Study 110, investigators had difficulties enrolling adequate numbers of patients so the protocol was modified from requiring 150 patients per group to requiring 124 patients per group. This new goal of a total of 248 patients also could not be met and enrollment into the trial was halted at a total of 145 patients. Based on the protocol assumption of a 20% difference in response rates, the trial, as executed, was underpowered; however, a larger difference was observed and the treatment difference on the primary outcome (percent of patients with HbA1c below 8%) was statistically significant.

In all studies, the dropout rates are at most 12% and are generally less than 10% (Table 3.1.2.2.3). These low dropout rates do not impact the interpretation of the outcome data therefore this reviewer did not perform any sensitivity analyses.

Table 3.1.2.2.3 Patient disposition in Type 2 studies

	108		**109**			**110**		**1001**		**1002**	
	INH	SC	INH	INH+ OA's	OA's	INH	ROSI	INH	MET	INH	SU
Rand.	149	150	105	102	102	76	69	225	202	243	233
Never trt.	0	0	1	3	0	1	1	3	1	4	2
Week 6	99%	99%	99%	91%	97%	99%	94%	96%	98%	95%	95%
Week 12	98%	98%	NA	NA	NA	NA	NA	94%	95%	93%	91%
Completer	89%	93%	92%	91%	97%	93%	91%	92%	88%	90%	88%

For studies 1001 and 1002, week 12 in the table above actually refers to Week 14.

The primary reasons for dropout across the studies were adverse event (ADE) and subject request (bolded numbers in Table 3.1.2.2.4). Subject request referred to both lost-to-follow-up and voluntary withdrawal. The most common ADE among Type 2 patients across all controlled studies was increased coughing; in Studies 1001 and 1002, 2 patients out of the 12 discontinuing for an ADE had increased coughing as a reason (one moderate and one severe).

Table 3.1.2.2.4 Reasons for discontinuation in Type 2 studies; Number of patients

	108		**109**			**110**		**1001**		**1002**	
	INH	SC	INH	INH+ OA's	OA's	INH	ROSI	INH	MET	INH	SU
Total SS	149	150	105	102	102	76	69	225	202	243	233
Death	2	0	0	0	0	0	0	0	0	0	3
ADE	**2**	**2**	**1**	**1**	**0**	**1**	**3**	**4**	**7**	**8**	**3**
LOE	1	1	3	0	2	0	1	0	2	0	4
Lab abn.	0	0	0	0	0	0	0	1	0	0	0
Subj req.	**10**	**6**	**2**	**2**	**2**	**2**	**0**	**7**	**5**	**4**	**6**
Oth/pr. viol	2	0	1	1	2	1	1	**3**	**9**	**8**	**10**
Total	17	9	7	4	6	4	5	15	23	20	26

The "other" reason referred to protocol violations (including not satisfying entrance criteria) or to other reasons . In Studies 1001 and 1002, about half the patients in the "other" category were listed as protocol violators.

Statistical Methods

The sponsor performed an analysis of covariance (ANCOVA) of HbA1c change from baseline with baseline HbA1c as a covariate and with terms for treatment and center (small centers pooled). This reviewer did not include center in the model and obtained essentially the same results; all results presented in the efficacy tables and graphs were computed by this reviewer. ITT data with the last observation substituted for missing data (LOCF) was analyzed. For all endpoints, a 95% confidence interval was computed and a difference of 0.4% for HbA1c was considered to be clinically relevant.

Study 108 Efficacy Results

The goal of Study 108 was to show that meal-time INH was comparable to conventional SC insulin given twice daily in patients stable on SC therapy at baseline. This goal was met for HbA1c change from baseline with the confidence interval showing no clinically relevant difference (Table 3.1.2.2.5). The treatment difference on FPG is statistically significant.

Table 3.1.2.2.5 Study 108 Efficacy results at Week 24; means and SD's and LSM difference

	INH (TID) (n=146)	SC (BID) (n=149)	INH-SC diff (95% CI)	p-value
HbA1c				
Baseline	8.1 (1.1)	8.2 (1.1)		
Change	-0.7 (1.2)	-0.6 (1.1)	-0.1 (-0.3,+0.2)	0.45
%<8% at EP	76%	69%	OR 1.4 (0.9, 2.4)	0.19
BSL<8%	92% (65/71)	88% (61/69)		
BSL≥8%	61% (46/75)	53% (42/80)		
FPG				
Baseline	152 (37)	159 (45)		
Change	-20 (55)	-9 (52)	-16 (-26, -5)	0.004

Negative differences favor INH, model with trt and baseline as terms. OR=odds ratio

Study 109 Efficacy Results

For Study 109, patients on oral therapy were randomized either to INH alone (i.e. switching from OA's), to continue on their OA regimen or to add-on INH. The protocol described a step-down procedure to adjust for making two comparisons (the combination versus OA and OA monotherapy versus INH). Usually in combination studies, the combination is expected to beat each component for approval of the combination product. For this study, the combination does beat each component at a <0.0001 nominal level (Table 3.1.2.2.6) for both HbA1c and FPG. In addition to showing that the combination product was effective, the applicant wished to show that switching from oral therapy (in this case two oral therapies) to INH resulted in more effective lowering of HbA1c which they were able to demonstrate (CI's not shown here).

Table 3.1.2.2.6 Study 109 Efficacy results at Week 12; means and SD's and LSM difference

	INH (n=102)	OA (n=96)	INH+OA (n=100)
HbA1c			
Baseline	9.3 (0.9)	9.3 (1.0)	9.2 (1.0)
Change	-1.5 (1.0)	-0.3 (0.9)	-1.9 (0.9)
Trt diff vs INH+OA (95% CI)	-0.5 (-0.7, -0.3)	-1.7 (-1.9, -1.5)	
%<8% at EP	56%	19%	86%
FPG			
Baseline	203 (43)	203 (44)	195 (49)
Change	-26 (58)	-1.7 (41)	-49 (50)
Trt diff vs INH+OA (95% CI)	-28 (-41, -16)	-53 (-65, -40)	

Negative differences favor the combination INH+OA

Study 110 Efficacy Results

Study 110 differed from the other studies in that the percentage of patients with an HbA1c of less than 8% at Week 12 was the primary efficacy variable. A logistic regression analysis was planned to analyze the primary efficacy variable.

The efficacy results showed significant effects on HbA1c for INH compared to rosiglitazone (4 mg BID, highest effective dose) for both the primary measure and change form baseline; the decrease in HbA1c for rosiglitazone is larger than what has been seen in earlier trials in naïve patients where mean decreases are usually less than 1%.

Table 3.1.2.2.7 Study 110 Efficacy results; means and SD's and LSM difference

	INH (n=75)	ROSI (n=67)	INH-ROSI diff (95% CI)	p-value
HbA1c				
Baseline	9.5 (1.1)	9.4 (0.9)		
Change	-2.3 (1.1)	-1.4 (1.2)	-0.9 (-1.2,–0.5)	<0.0001
%<8% at EP	83%	58%	OR 3.4 (1.6, 7.4)	0.0014
FPG				
Baseline	208 (56)	199 (50)		
Change	-64 (57)	-56 (42)	-2.6 (-16, +11)	0.71

Negative differences favor INH. OR=odds ratio

No significant treatment differences are seen for FPG. Due to the differing results for HbA1c and FPG, this reviewer looked at the correlation between the measures both at baseline and change at endpoint. For each treatment group, significant correlation is seen both at baseline and endpoint, as would be expected for these measures of glucose control. It is not clear to this reviewer why no statistical difference is seen for FPG.

Studies 1001 and 1002 Efficacy Results

Patients inadequately treated on a sulfonylurea in Study 1001or on metformin in Study 1002 were randomized to add-on therapy of INH or an OA (metformin in Study 1001 and glibenclamide in Study 1002). For each trial, two objectives were named; to show superiority in patients with baseline HbA1c above 9.5% and to show non-inferiority using all patients. This reviewer is only presenting the results for all patients in the table below. In both studies, no clinically relevant difference was seen between the treatment groups on both HbA1c and FPG .

Table 3.1.2.2.8 Efficacy results for Studies 1001 and 1002; means and SD's and LSM difference

Study 1001				
	INH (n=214)	MET (n=196)	INH-MET diff (95% CI)	p-value
HbA1c				
Baseline	9.7 (1.1)	9.7 (1.2)		
Change	-2.1 (1.1)	-1.9 (1.2)	-0.2 (-0.4, -0.04)	0.02
%<8% at EP	64%	58%	OR 1.3 (0.9, 1.9)	0.22
FPG				
Baseline	220 (55)	219 (55)		
Change	-48 (55)	-50 (55)	+2.4 (-6, +11)	0.56
Study 1002				
	INH (n=234)	GLIB (n=222)	INH-GLIB diff (95% CI)	p-value
HbA1c				
Baseline	9.5 (1.1)	9.6 (1.1)		
Change	-2.1 (1.2)	-2.1 (1.1)	-0.2 (-0.4, +0.01)	0.13
%<8% at EP	77%	73%	OR 0.8 (0.5, 1.2)	0.28
FPG				
Baseline	203 (56)	216 (54)		
Change	-42 (54)	-53 (54)	+2 (-6, +10)	0.59

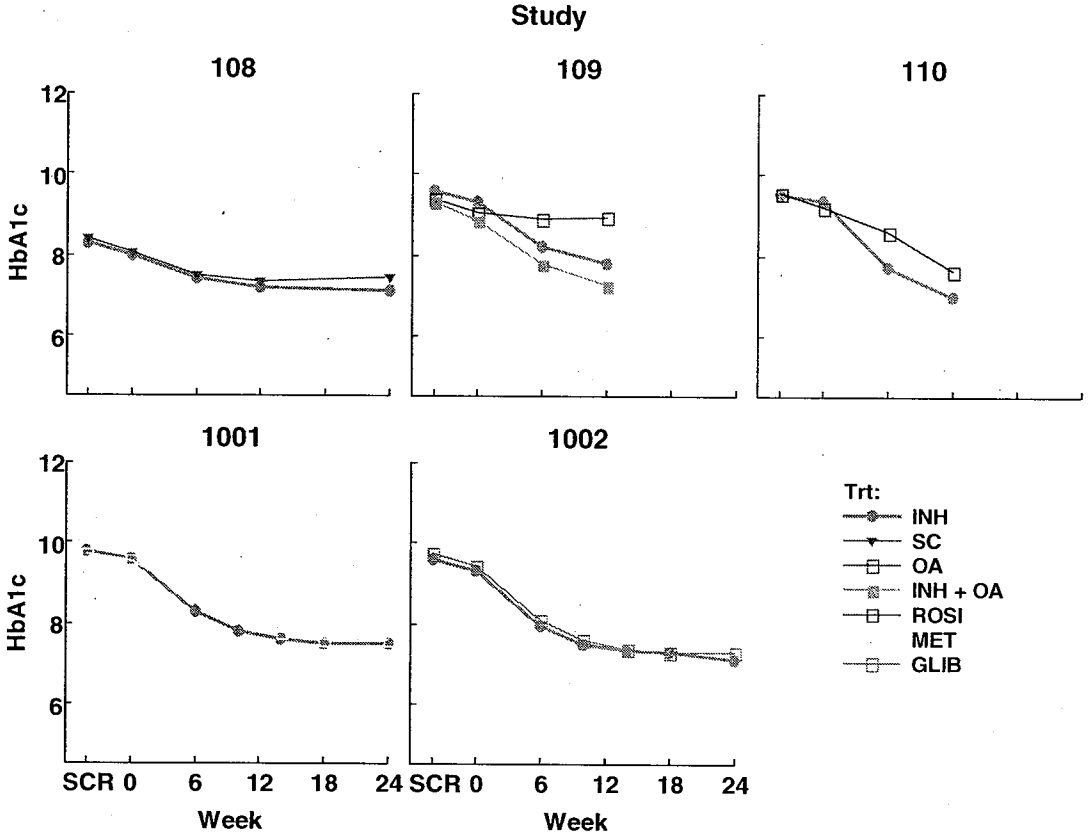
Negative differences favor INH, model with trt and baseline as terms. OR=odds ratio

In patients with baseline HbA1c values above 9.5% (about 100 patients in each group), essentially the same results were seen in each of the studies. The treatment difference was statistically significant with mean differences of –0.38 (CI -0.63, -0.14) in Study 1001 and –0.37 (CI -0.62, -0.12) in Study 1002. Since a difference of about 0.4 is often named as the smallest clinically relevant difference in diabetes trials, it is clear that these results can only be considered marginally favorable to INH. [The treatment difference in the lower stratum is very small being between –0.1 and +0.1.]

Summary Graphs of Efficacy in all 5 studies in Type 2 diabetic patients

Figure 3.1.2.2.1 below shows mean HbA1c overtime in each of the 5 trials in Type 2 diabetics. A slight decrease in mean HbA1c is seen during the run-in period even though patients are maintained on their screening regimen during this period. The solid red line represents treatment with INH. Graphs of FPG are provided in Appendix 6.6.

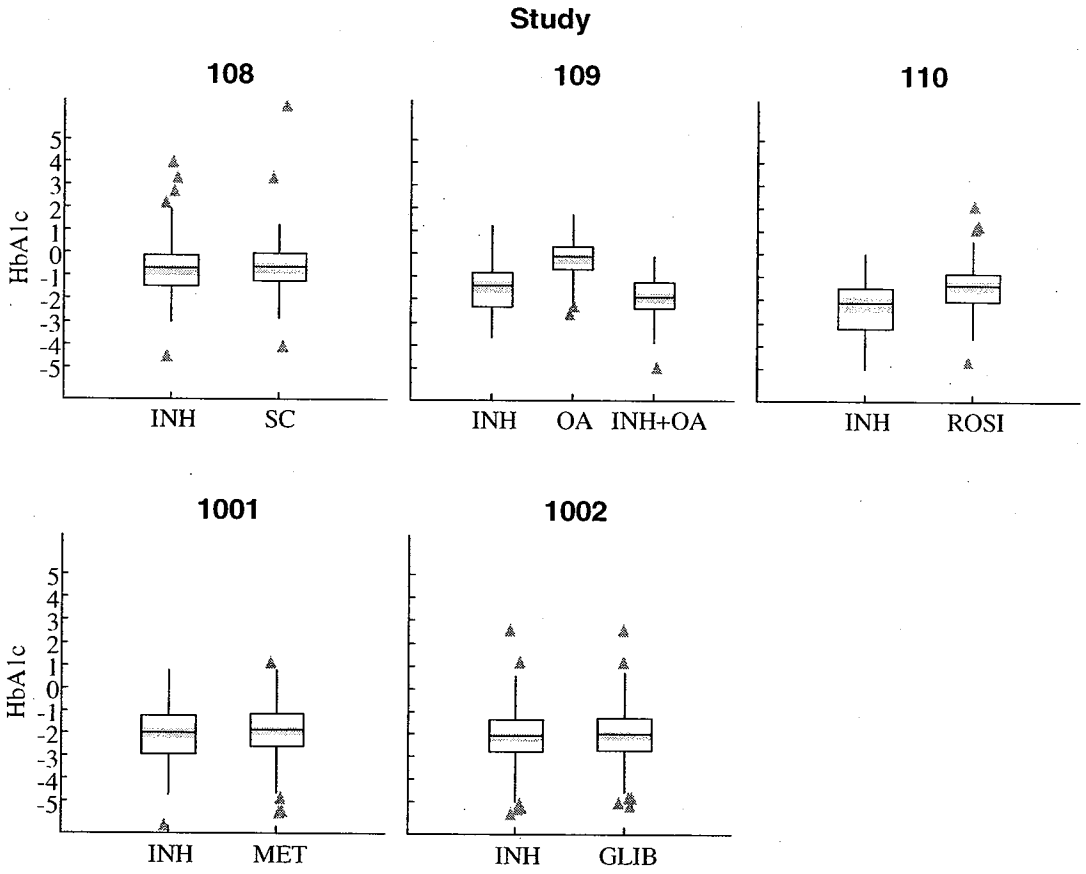
Figure 3.1.2.2.1 Mean HbA1c overtime in Phase 3 studies of Type 2 diabetics



This reviewer had some concern about the length of the trials given that FDA generally recommends at least 24-week trials. From the graphs it is clear that 24 weeks appears to be adequate to obtain a stable response. After 12 weeks of therapy in the 24-week trials, it appears that the maximum mean response is achieved for INH so perhaps in Studies 109 and 110, the INH response at Week 12 is representative of the response we might see with further treatment on INH. This reviewer thinks we can not make this assumption for the rosiglitazone response in Study 110. Previous studies reviewed by this statistician showed more lowering up to about Week 18 in naïve patients on rosiglitazone 4 mg BID. In Study 110, the comparison at Week 12 is unfairly biased against rosiglitazone.

Boxplots of HbA1c change from baseline are shown below in order to illustrate the range and distribution of effects in each of the Phase 3 studies of Type 2 diabetics. The comparability of the distributions is clearly evident in Studies 108, 1001 and 1002 where non-inferiority was demonstrated.

Figure 3.1.2.2.2 Boxplots of HbA1c change from baseline at endpoint for all five Phase 3 studies in Type 2 diabetics



3.2 Evaluation of Safety

Three issues regarding safety were examined by this reviewer: 1) rates of hypoglycemia in Studies 107 and 108, 2) the relationship between insulin antibodies and dose and 3) the relationship between insulin antibodies and the incidence of severe hypoglycemia. Note that full safety reviews were performed by three FDA reviewers; Dr. Buenconsejo (statistical reviewer) and Drs. Mahoney and Seymour (medical reviewers).

Hypoglycemia in Studies 107 and 108

An event was counted as an hypoglycemic event if the patient had symptoms characteristic of hypoglycemia accompanied by a glucose of 59 or lower, or if a glucose reading was missing, symptoms were resolved with carbohydrates OR if the patient had a glucose of 49 or lower with

or without symptoms. A severe hypoglycemic event was defined by 3 additional characteristics listed in Appendix 6.7.

Late in the IND stage of development (after the studies in Type 1 diabetics were complete), an FDA medical reviewer requested that events accompanied by a glucose of 36 or less or events where the patient required assistance also be analyzed. The latter is referred to here as the "FDA" definition. The latter definition was applied retrospectively and so data was not collected specifically for this endpoint. Note that, by definition, FDA events are a subset of the overall protocol-defined hypoglycemic events and that all protocol-defined severe events, also are counted as FDA events.

The applicant has reported risk ratios for hypoglycemia computed using "a counting process approach for recurrent time-to-event data". Based on these estimates, the applicant makes comparative statements about the risk of hypoglycemia. Their model is an Anderson-Gill type proportional hazards model for recurrent events where events are assumed to be independent, i.e. there are no modifications made to the model to account for recurrent events within patient or dependency among events. This reviewer considered an alternative model which calls for a robust sandwich estimate of the covariance matrix (henceforth referred to as the robust variance) to correct for possible correlations. (See Appendix 6.9 for the applicant's and the reviewer's SAS coding and for modifications by this reviewer.) In addition, this reviewer performed Wilcoxon rank sum tests on the count data. So in the latter analysis patient is the unit of measure and the time of the events is not considered.

To summarize the event data, the applicant computed events per patient-months where the total number of events is divided by the total exposure in months. The latter measure essentially averages the number of events over time since the majority of patients had the same exposure. An alternative way would be to compute the percentage of patients with at least one event, using the patient as the unit of measure but only counting one event per patient. In addition, the median number of events in each group was computed as well by this reviewer.

For this review, the hypoglycemic event data for Studies 107 and 108 are examined; two studies of particular interest to the FDA clinical reviewers (see Appendix 6.8 for a summary of events for all Phase 3 studies). For Study 107, the severe hypoglycemic events and FDA-defined events are analyzed while for Study 108 all hypoglycemic events are the focus. Study 107 is a study of Type 1 diabetics so essentially all patients have hypoglycemic events throughout the trial in both groups (average of about 9-10 per month in both groups), so to assess safety, the emphasis is primarily on the severe events. In Study 108, a trial of Type 2 diabetics, there are very few severe hypoglycemic events (a total of 5 in this trial) and so the emphasis in the Type 2 population is on the overall hypoglycemic event rate. The results for Study 107 are described first below, followed by the results of Study 108.

The distribution of severe hypoglycemic events in Study 107 is shown in Table 3.2.1. The median number of events for both groups is zero (p=0.30, Wilcoxon rank sum test). A chi square test comparing 17% versus 13% also yields non-significant results.

Table 3.2.1 Study 107 Tabulation of severe hypoglycemic events

	% (n/N) of pts. with at least 1 event	Number of patients with "n" events							
		0	1	2	3	4	5	6	12
Adults									
INH	17% (18/103)	85	10	3	2	1	1	0	1
SC	13% (13/103)	90	8	4	1	0	0	0	0

This reviewer's results of no treatment difference strongly contrast with the applicant's reporting of a statistically significant doubling of risk of severe hypoglycemia (risk ratio of 2.25 with 95% CI of 1.3 to 3.9; a risk ratio of about 2 for adults and children combined was reported in Diabetes Care 28:1630-1635, 2005) for INH compared to SC (Table 3.2.2). Two additional proportional hazards (PH) analyses (robust variance model and time to first event) performed by this reviewer suggest no difference between the treatments.

Table 3.2.2 Results from different PH models for severe hypoglycemia in Study 107

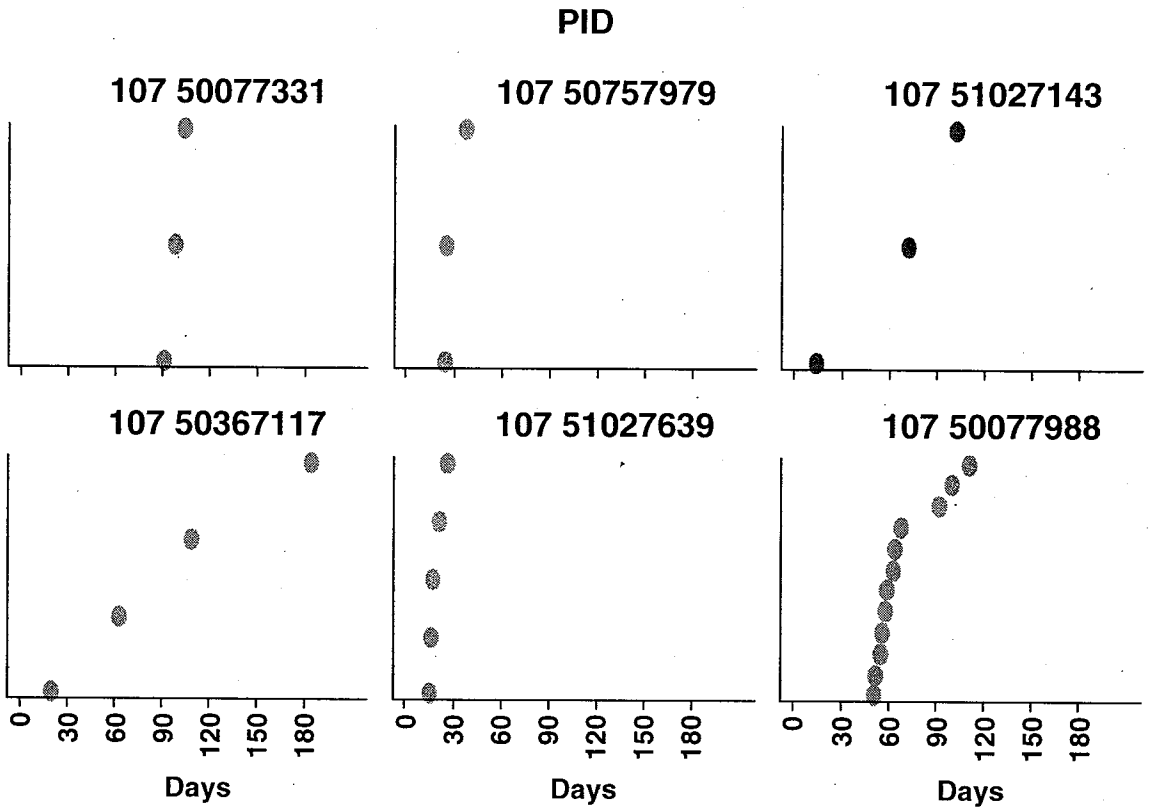
Model	Population	p-value	Risk Ratio (95% CI)
Applicant AG model	Adults	0.003	2.25 (1.3, 3.9)
Reviewer robust variance-AG model	Adults	0.07	2.25 (0.95, 5.3)
Time to first event model	Adults	0.36	1.4 (0.68, 2.85)

A risk ratio below 1 favors INH.

The proportional hazards models suggest higher risk in the INH group while an analysis of counts, ignoring time, suggests no difference between the groups. This reviewer wonders about the importance of time in these studies. To qualify for the studies, patients should not have experienced more than 1 severe hypoglycemic event during run-in and more than 2 in the previous 6 months while on SC insulin therapy. Perhaps, these patients, then, are less likely to experience hypoglycemic events on SC in these trials. On the other hand, patients randomized to INH may need to gain experience with using INH to control their glucose levels and may be more vulnerable to hypoglycemia on the new regimen. Under the latter scenario, INH patients may experience recurrent events in clusters early in therapy and not experience any thereafter.

Generally, this appears to be the case in patients with many recurrent severe events (Figure 3.2.1 on the following page) with the exception of one adult patient who had 4 events spread over the entire trial. Note that none of these patients with 3 or more events dropped out of the trial. Events for patients with only one event or 2 events occur throughout the trial in both groups. It is clear that patients with more than 2 events were most likely to have those events in close proximity and so it seems that these events should not be treated as independent events.

Figure 3.2.1 Study 107; Time of events (x-axis) shown by number of severe hypoglycemic events experienced by the patient. For example, the graph labeled 12 shows the times for the one INH patient experiencing 12 events. Red=INH, Blue=SC



In addition this reviewer ran analyses to determine the impact of the one adult patient with 12 events on the results by leaving this patient out of the analysis. Leaving this one patient out of an analysis using the robust-variance AG model yields non-significant results (p=0.21) with a risk ratio of 1.65. So this one patient has a very large effect on the estimate of risk.

This reviewer thinks that an analysis of time to recurrent events gives too much weight to the few patients experiencing several events particularly when the model assumes the events are independent, as the applicant's model does.

The number of "FDA-defined" events is summarized below for adults only (Table 3.2.3). A chi square test on at least 1 FDA-defined event yields a p-value of 0.49 (odds ratio of 0.73 with 95% CI of 0.29 to 1.8). A Wilcoxon rank-sum test on the number of events observed for each patient yields a p-value of 0.09 (median of 6 events for INH and 8 events for SC). Note that there are four SC patients with a large number of events.

Table 3.2.3 Study 107 Adults Tabulation of FDA-defined hypoglycemic events

	% (n/N) of pts. with at least 1 event	Number of patients with "n" events															
		0	1	2	3	4	5	6-10	11-15	16-20	21-30	31-40	41-50	51	53	56	78
Adults																	
INH	88% (91/103)	12	10	11	8	2	4	22	13	8	8	3	2	0	0	0	0
SC	91% (94/103)	9	5	11	11	2	3	16	15	8	11	7	1	1	1	1	1

Using a survival analysis of recurrent FDA-defined events, the applicant reports a risk ratio of 0.72 with 95% CI of 0.67 to 0.79; a statistically significant reduced risk of hypoglycemia for INH compared to SC. So a conclusion opposite to the one reached for severe hypoglycemia is reached using the FDA definition, according to the sponsor's analysis.

So overall the risk of severe or "FDA" hypoglycemic events for adults in Study 107 appears to be comparable for the treatment groups when the data is analyzed using a non-parametric Wilcoxon test on the ranks. In the analyses of recurrent events using a PH model, it is clear that patients with many events carry considerable weight in the estimate of the risk ratio. Dropping out a single patient with many events has a large effect on the estimate suggesting that the model is too sensitive and may overestimate the risk (in either direction) when there are patients that may be considered outliers.

The applicant reports in their NDA and in their proposed labeling the total number of events divided by the total person years. It is quite obvious that the results of doing so when few patients account for most of the events is that the averaging is not representative of the results. This reviewer strongly recommends that the number of patients having at least one event be reported along with the median number of events in each group; it may also be helpful to report the range of the number of events per patient.

In Study 108 (Type 2 patients), only 5 episodes of severe hypoglycemia were observed; 2 INH patients each experienced one event and 1 INH patient experienced 2 events, only 1 SC patient experienced a severe hypoglycemic event.

A majority of the patients (76% INH vs. 71% SC) experienced at least one protocol-defined hypoglycemic event (Table 3.2.4).

Table 3.2.4 Study 108 Hypoglycemic events

	% (n/N) of pts. with at least 1 event[1]	Number of patients with "n" events							
Protocol-defined all		0	1	2-5	6-10	11-15	16-20	21-25	>25
All pts									
INH	76% (111/146)	35	20	38	16	12	10	3	12
SC	71% (106/149)	43	13	40	15	14	5	4	15

1 This reviewer was not able to replicate the exact numbers reported by the applicant. The applicant reported 109 (76%) events for INH patients and 104 (72%) for SC patients.

For Study 108, the applicant reported a significantly reduced risk of overall hypoglycemia (Table 3.2.5) for patients treated with INH compared to patients treated with SC. A PH model using a robust variance showed no statistically significant difference between the groups (p=0.50). A Wilcoxon rank sum test yielded a p-value of 0.79. Clearly there is no treatment difference regarding hypoglycemia.

Table 3.2.5 Risk ratios for protocol-defined overall hypoglycemic events and for "FDA-defined" events

	Risk ratio (CI)	p-value
Protocol-defined events		
Applicant's AG model	0.89 (0.82, 0.96)	0.003
Reviewer's RV-AG model	0.89 (0.62, 1.3)	0.50

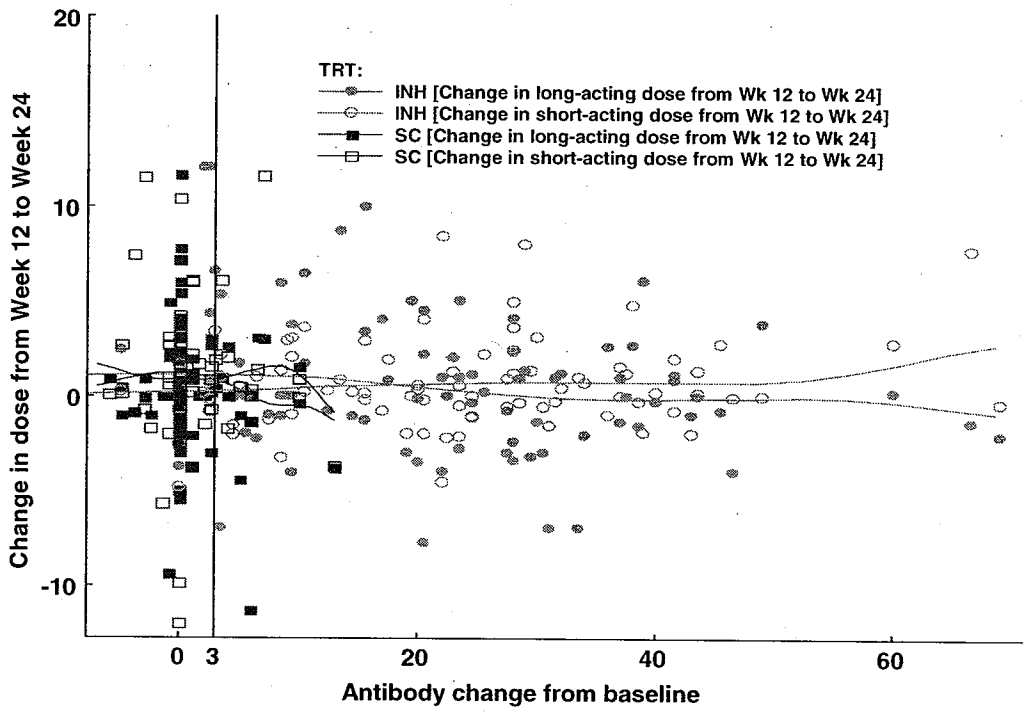
The applicant emphasized the FDA events for all their studies in their summary of hypoglycemia. For a presentation at the AC meeting, this reviewer examined the characteristics of the FDA events. Note that at an earlier AC meeting (late 1990's), panel members did not embrace this FDA definition thinking that the definition may be too all inclusive and include events that would not be considered severe. The latter turned out to be the case. More than half of the FDA events in Study 107 were rated as mild. About ¼ of the events were not accompanied by symptoms. The data in Study 107 suggests that the so-called FDA definition of hypoglycemia is not one that should be used in trials where one wishes to measure primarily severe events.

Antibody levels and dosing

Higher insulin antibody levels were seen for patients treated with INH, particularly Type 1 patients, compared to patients treated with SC or OA's (see Appendix 6.10 for a boxplot of antibody data from combined studies). The applicant examined the impact of antibody production on dose requirements, glycemic control and adverse clinical outcomes and concluded that there was no association between level of antibodies and the aforementioned outcomes.

Under the guidance of Dr. Mahoney, this reviewer examined further the relationship of antibody level to dosing and to hypoglycemia. For dosing, we restricted our review to Study 107, a study in Type 1 patients, because the largest effect on antibodies is seen in Type 1 patients and Study 107 had two treatment arms that only differed in type of short-acting insulin used (INH versus SC). Since increases in antibodies usually occur after a few months of therapy, we looked at the association of change in dose for both long and short-acting insulin between Weeks 12 and 24 with the endpoint antibody count. We saw no indication that either long or short-acting doses were increased to compensate for increased antibody production; the smoothed lines in Figure 3.2.2 illustrate the lack of relationship between dose change and antibody change. The applicant combined all Phase 2 and 3 studies and also reported no association between dose and antibody level.

Figure 3.2.2 Change in short and long-acting insulin doses from Week 12 to Week 24 versus change in antibodies at endpoint in Study 107 (Type 1 patients)

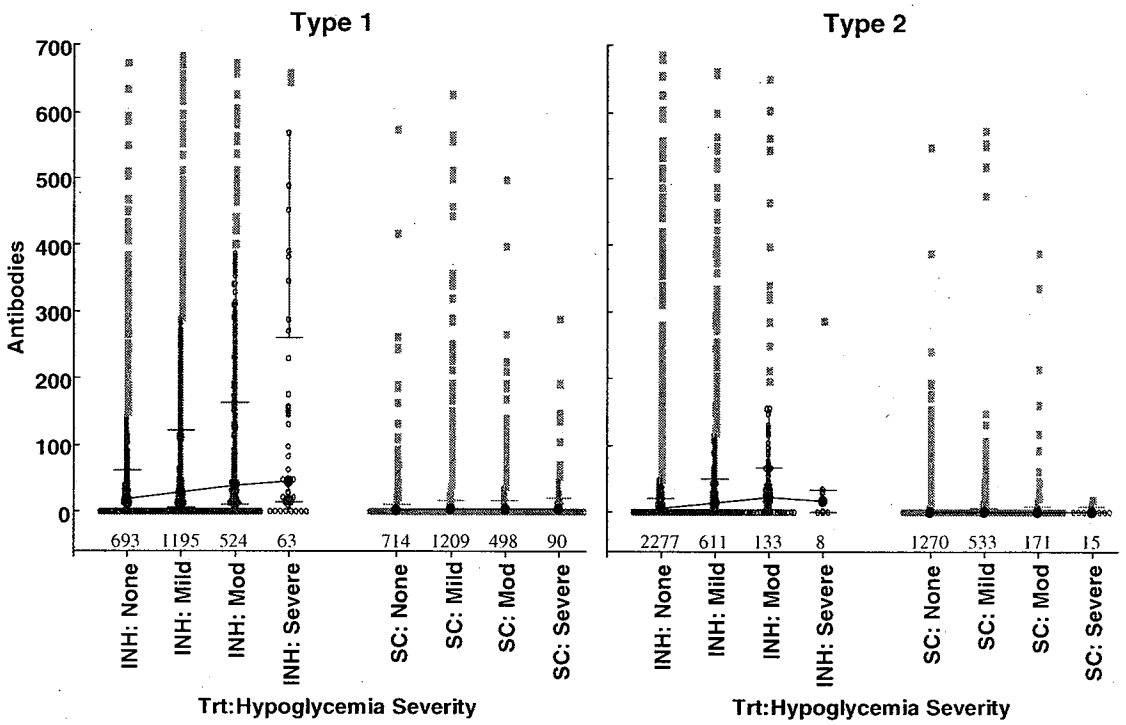


Antibody levels and hypoglycemia

This reviewer also looked at the relationship between hypoglycemia and antibody levels. For the applicant's examination of this issue, a more stringent definition of hypoglycemia (see Appendix 6.9 for the protocol definition) was used with glucose level at 36 or less OR patient required assistance. The applicant looked at monthly incidence of hypoglycemia versus end-of-study antibodies and reported no association.

For our FDA analysis, we looked at the antibody count versus the level of hypoglycemia (0=no hypoglycemia to 3=severe hypoglycemia) in the combined Phase 2/3 studies containing antibody data; antibody data was matched to hypoglycemia event by date (only data on treatment was considered). The distributions of antibodies for Type 1 and Type 2 patients are shown in the boxplots below; essentially no antibodies are seen for patients treated with oral agents. This is a rather crude depiction of the data in that there is no regard for multiple observations per patient; however further examination of the data by time and by patient for patients with multiple severe events indicated that the overall impression from this graph is reasonable.

Figure 3.2.3 Boxplots of antibody levels by observed hypoglycemia severity for INH and SC patients (the graphs are truncated such that outliers ranging from 700 to over 5,000 are not visible, outlier ranges were unrelated to hypoglycemic severity) RED=OUTLIER



It is clear that higher levels of severity of hypoglycemia are associated with higher levels of antibodies. The relationship between an increase in antibody level and the chance of developing moderate or severe hypoglycemia is statistically significant in patients treated with INH[1] but the risk is not appreciable. For example, increases in antibody levels as high as 500 do not even result in a doubling of the risk (odds ratio of about 1.4 for all patients, 1.2 for Type 1 patients

1 Results based on a logistic regression model. Note that change in antibody level is not predictive of moderate or severe hypoglycemia in patients treated with SC (p>0.15).

only). So though there appears to be a relationship between the two measures, antibody level does not appear to be a strong predictor of moderate to severe hypoglycemia in patients treated with INH.

4. Findings in Special/Subgroup Populations

The Phase 3 trials in the Exubera development program each utilized a unique trial design, so studies should not be pooled to examine subgroups. This reviewer checked subgroups in each study and will report here only notable interactions of subgroup and treatment for HbA1c change from baseline.

4.1 Gender, Race and Age

For Type 1 patients, there was no difference in treatment effects due to age with elderly defined as 50 or more (there are no patients over 65, see Table 3.1.1.3) or due to gender. The vast majority of patients were Caucasian so effects by race could not be assessed.

For Type 2 patients, there was no difference in treatment effects due to age with elderly defined as 65 or more or due to gender. As for the Type 1 patients, the vast majority of patients were Caucasian so effects by race could not be assessed.

4.2 Other Special/Subgroup Populations

4.2.1 Children

The applicant is not seeking an indication in children, however data from children was provided in Type 1 Studies 106, 107 and 1009. The results for Studies 106 and 107 show essentially no difference between INH and SC in patients under 18 years.

Table 4.2.1.1 HBA1c results for children in Studies 106 and 107

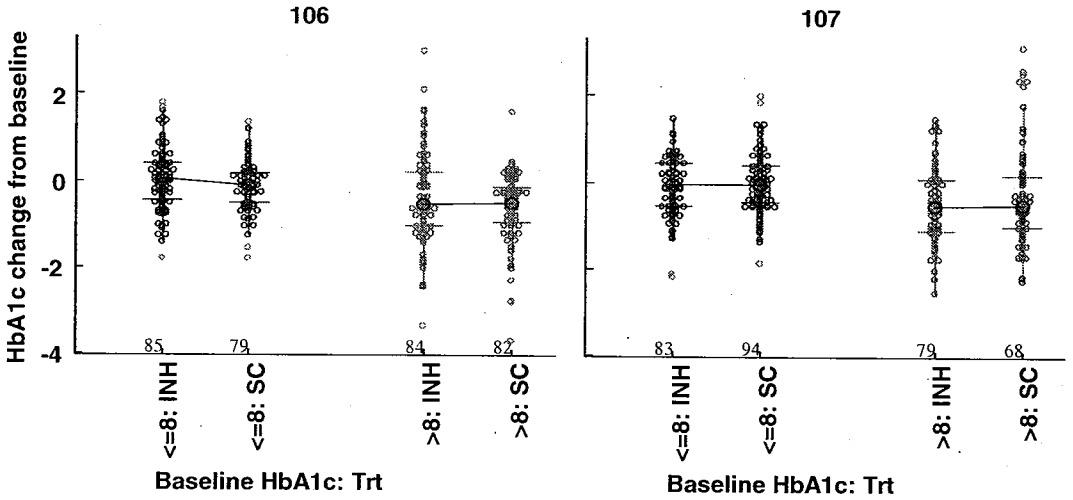
	Study 106			Study 107		
	INH Mean (SD)	SC Mean (SD)	LSM Diff 95% CI	INH Mean (SD)	SC Mean (SD)	LSM Diff 95% CI
HbA1c	n=33	n=29		n=59	n=59	
Baseline	8.6 (1.0)	8.5 (0.8)		8.3 (0.9)	8.3 (0.9)	
Change from baseline Wk 24 LOCF	0 (1.2)	-0.3 (0.7)	+0.3 (-0.09, 0.7)	-0.2 (0.8)	0 (1.1)	-0.2 (-0.5, 0.1)

Results from a 12-week study of children aged 6-11 (Study 1009) showed results similar to Study 107 with a treatment difference of –0.2 and 95% CI of –0.5 to 0.03.

4.2.2 Baseline HbA1c

In Type 1 patients, more lowering of HbA1c is seen for larger baseline values regardless of treatment as can be seen in the boxplots of Figure 4.2.2.1. Tests for interaction yielded p-values greater than 0.30.

Figure 4.2.2.1 Boxplots of Week 24 HbA1c change from baseline by median baseline HbA1c for Studies 106 and 107



In all five Phase 3 trials of Type 2 patients, changes in HbA1c are baseline-related with p-values for the interaction of HbA1c change and baseline ranging from 0.001 to 0.05 in the individual studies. This reviewer looked at the treatment effects by tertiles (tertiles are defined within study) and found no statistically significant interaction in Studies 1001 and 1002 while, for the other 3 studies, the interaction remained significant (Figure 4.2.2.2 on the following page).

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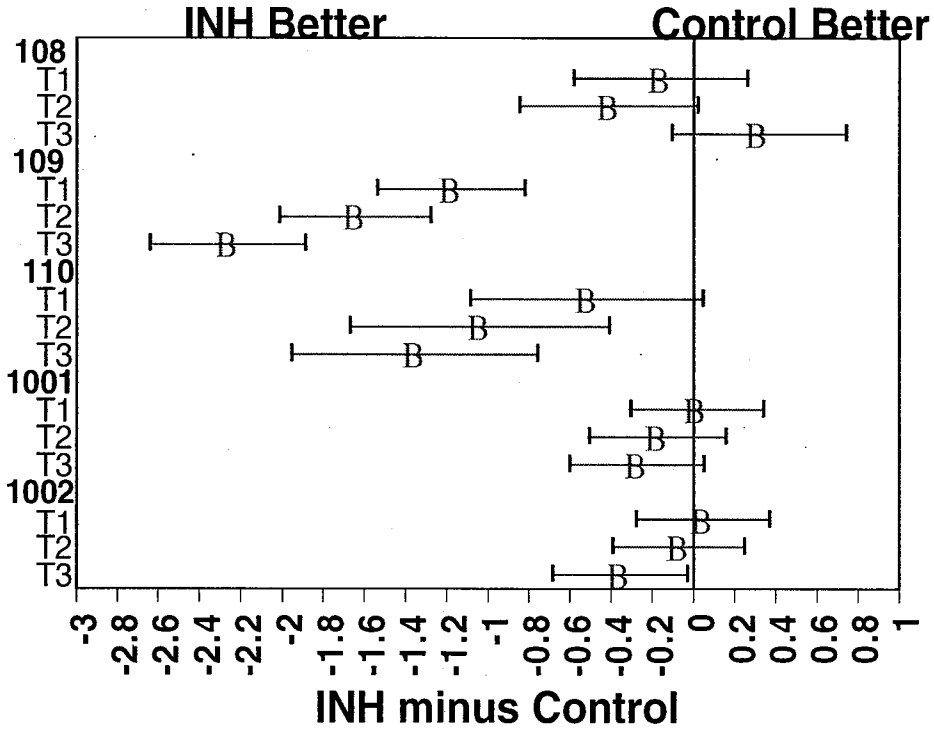
Figure 4.2.2.2 Treatment difference and 95% CI by baseline study and baseline tertiles.



With increasing baseline, the treatment effects appear to favor INH over comparator, with the exception of Study 108 where the comparator is SC insulin. It is worth recalling that in Studies 109 and 110, the comparators are fixed doses of oral agents so it is not surprising that INH (a titrated drug) would appear more efficacious as baseline increased. This analysis suggests that against titrated medications, INH appears to be "equally" efficacious and offers no significant advantage over SC insulin or titrated oral agents (metformin and glibenclamide).

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5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The following statistical issues[1] arose during the process of this review:

- Randomization procedures described in the protocols and in the study reports were not the procedures actually carried out. Patients were not assigned using a minimization algorithm but instead were randomized centrally blocking on center (see page 15 for more details).
- All trials in the Exubera submission were open-label trials. The lack of blinding introduces the possibility of bias in several aspects of the trial. The first aspect considered by this reviewer was the enrollment of patients. The lack of blinding can lead to selection bias in that the randomization code could be broken based on the patients already entered in the trial. An investigator may be able to guess the treatment assignment for the next patient. Guessing is more difficult if the randomization is carried out from a central office, if stratification is not done by center and if block sizes are unknown by the investigator (i.e. not mentioned in the protocol). The first and third conditions were in place in the Exubera trials. Stratification was done by center so it is possible that the pattern of treatment assignment could be discerned and that assignment would be predictable for some patients. To test if selection bias was an issue this reviewer performed a test described by Berger and Exner on the data from Study 107 (the most important Type 1 study). Basically this test determines whether the probability of having a good response is related to the probability of being assigned to the test drug; this is essentially testing whether patients with a good prognosis are more likely to have been assigned to Exubera. This reviewer found no evidence of selection bias based on the results of this test.
- The lack of blinding can also bias the measurement of both efficacy and safety measures. HbA1c is an objective measure not likely to affected by knowledge of treatment, particularly since dosing of patients was well-controlled by specific parameters spelled out in the protocols and inspection of the data suggests that dosing was adjusted as would be expected. There is some evidence that safety measures may have been affected by the lack of blinding. More specifically, the medical reviewer, Dr. Karen Mahoney, carefully describes the misclassification of discontinuation reasons as "withdrawn consent" or "subject request" where the data suggests that the reason was "adverse event". She found a larger number of misclassifications in the INH group than in the comparator group suggesting the possibility that knowledge of treatment could have played a role in the naming of the discontinuation reason.
- The 12-week duration of Study 110 was insufficient to provide a fair comparison of rosiglitazone to INH (see page 26).
- Patients who discontinue from therapy due to hypoglycemia may provide HbA1c LOCF data that suggests a beneficial result when in reality the therapy was a failure for that patient. This reviewer examined the data to determine if the LOCF estimates were biased by the use of such dropout data and found no evidence that this was the case.
- Noninferiority trials were powered to rule out a treatment difference for HbA1c change from baseline of 0.5% while 0.4% is the margin usually used by FDA. This, however, was not an issue since the boundary of 0.4% was met in all relevant trials.
- The Type 2 development program consisted of five Phase 3 trials; 3 conducted in North America and 2 conducted in foreign countries. The majority of the investigator sites participated in more than one study. For Studies 1001 and 1002 (foreign studies) and for Studies 108, 109 and 110, about half of the total sites participated in more than 1 study (see

1 The statistical issues listed here are identical in wording to the list provided in Section 1.3 of this review.

page 19 for additional details). Patients were not allowed to participate in more than one study and, in addition, entry criteria differed making patients ineligible for more than one study so this reviewer was not concerned that patients may have been retested. Enrollment dates were overlapping for the studies so investigators would be seeing patients during the same timeframe from the different studies suggesting that experience from participating in one trial would not carryover and affect the conduct of a subsequent trial. Also the sample size of each site is small and no one site would greatly influence the outcome. Though overlapping sites could affect the independence of the trial results, this reviewer did not feel, for these studies, that independence was comprised for the reasons given.

- The applicant computed risk ratios for hypoglycemia using a recurrent events proportional hazards model that assumes events are independent. This model is not appropriate primarily because it ignores the dependency among events within patients. The model is oversensitive to patients with many events; for example, dropping just one patient from an analysis of Study 107 data changed the estimate of the risk ratio from 2.25 to 1.65. A preferred method of analysis would be a non-parametric analysis (e.g. Wilcoxon rank sum test) of the number of events per patient.
- The applicant summarized the incidence of hypoglycemia as number of events per patient-month. These measures are not appropriate for the data from these studies for two reasons; 1) essentially all patients had the same exposure time in the controlled trials and 2) a few patients had many events such that averaging overestimated the counts generally seen for most patients. Instead, hypoglycemia may be summarized as the median number of events observed per patient or as the number of patients with at least one event.

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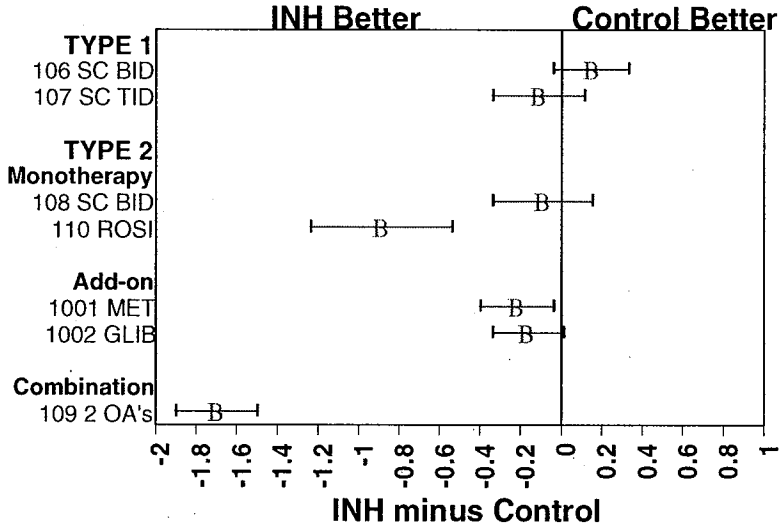
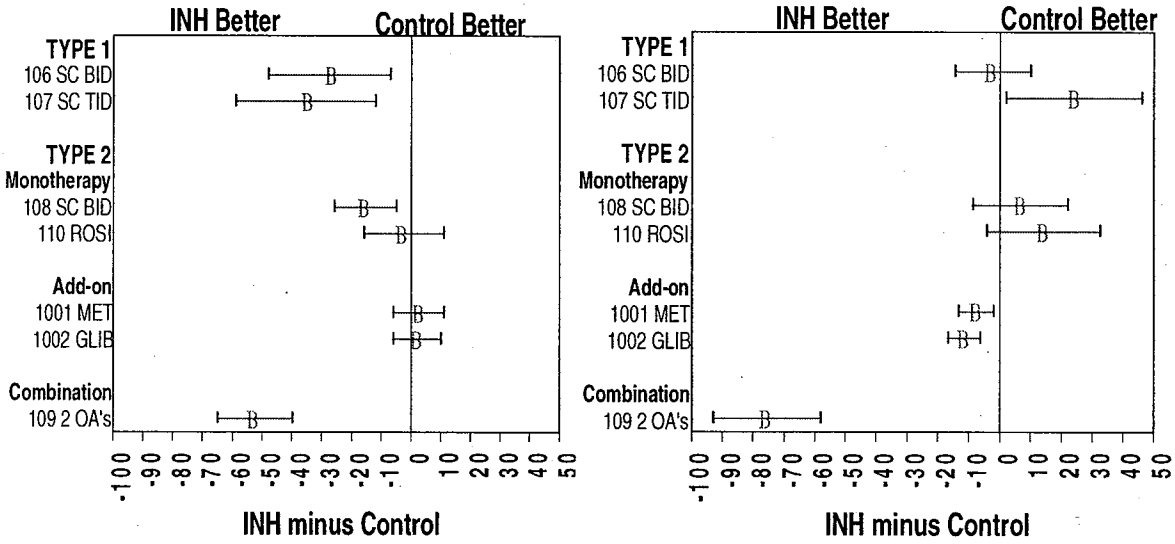
The collective evidence of efficacy from the seven Phase 3 trials in patients with Type 1 and Type 2 diabetes is summarized by the mean treatment difference for HbA1c change from baseline shown in Figure 3.1.3.1 below. The left edge of the graph shows the study number with the control group. For more details regarding these results see Section 3.1.2.2 of this review. A discussion of conclusions drawn from these results follows in Section 5.2.

Figure 3.1.3.1 HbA1c Week 24 change from baseline; LS mean treatment difference with 95% confidence interval



The results for FPG and post-prandial increment, two important secondary endpoints, are summarized in the figures below.

Figure 3.1.3.2 FPG (left graph) and Post-prandial increment (right graph)
Week 24 change from baseline; LS mean treatment difference with 95% confidence interval



5.2 Conclusions and Recommendations

This reviewer has the following comments and conclusions[1] based on the statistical review of the seven Phase 3 trials submitted to demonstrate the efficacy and safety of INH (Exubera). Note that Figures 3.1.3.1 and 3.1.3.2 on page 40 summarize the efficacy data.

- Approximately 85 to 90% of the Type 1 and 2 patients studied were Caucasian; so the races were not adequately represented in the database
- INH was shown to be non-inferior to SC insulin in patients with Type 1 diabetes in two Phase 3 clinical trials, 106 and 107 (see Table 3.1.1.5 and Figures 3.1.3.1 and 3.1.3.2). The HbA1c results are more favorable to INH in Study 107, a study where SC insulin was given TID and the same long-acting insulin was given in both groups. There was no evidence that long-acting insulin was titrated differently in the two groups allaying concerns that the long-acting dosing may have compensated for inadequate treatment on short-acting insulin.
- For Type 1 patients, statistically significant differences in favor of INH over SC were seen for the change from baseline in FPG in both studies. An examination of 24-hour diary records suggest a drop in glucose levels overnight in the INH group may explain the significantly lower FPG. This issue is discussed in the clinical review by the FDA medical reviewer, Dr. Mahoney.
- Across the Type 2 studies, variability in several baseline parameters was seen suggesting some heterogeneity among the patient populations which could improve generalizability of the results.
- For Type 2 patients inadequately treated with metformin or a sulfonlyurea, add-on INH yielded HbA1c lowering comparable to adding either glibenclamide or metformin, respectively (Studies 1001 and 1002, see Table 3.1.2.2.8 and Figure 3.1.2.2.1). For patients inadequately treated with two oral agents, adding INH resulted in highly significant drops in HbA1c (Study 109, see Table 3.1.2.2.6 and Figure 3.1.2.2.1).
- Type 2 patients on SC insulin therapy were able to maintain their HbA1c levels when switched to INH insulin (Study 108, see Table 3.1.2.2.5 and Figure 3.1.2.2.1)
- Naïve Type 2 patients randomized to either rosiglitazone (4 mg BID, the most effective marketed dose) or INH showed statistically significantly more lowering of HbA1c and FPG on INH in Study 110 (Table 3.1.2.2.7) ; however the length of the trial at 12 weeks provided inadequate time for rosiglitazone to show a full effect (Figure 3.1.2.2.1). This reviewer concludes that Study 110 was inadequate by design and the results should not be included in labeling.
- Antibody counts were significantly higher in INH patients than in patients treated with SC insulin or oral agents. This reviewer found no relationship between change in antibody count and change in dose. A crude analysis of antibody count by severity of hypoglycemia suggests that higher levels of antibodies may be associated with more severe levels of hypoglycemia, although antibody level does not appear to be a strong predictor of moderate to severe hypoglycemia in patients treated with INH (see pages 35 to 36 for more details.)
- The hypoglycemic event rates in the Type 1 studies were comparable regardless of the definition of hypoglycemia. The definition suggested by an FDA medical reviewer at the IND stage resulted in counts of events that were a mixture of mild to severe events with about 20% non-symptomatic. These FDA-events were only distinguishable from other hypoglycemic events based on a glucose level of 36 or below. An FDA advisory committee concluded such events may contain too much noise and the most reliable measure of a severe hypoglycemic event should include a measure of neurologic impairment. The latter was included in the

1 This section is identical to Section 1.1 of this review.

protocol-defined severe hypoglycemia.

From a statistical viewpoint and based on the data in this review, this reviewer would recommend approval.

6.0 Appendices

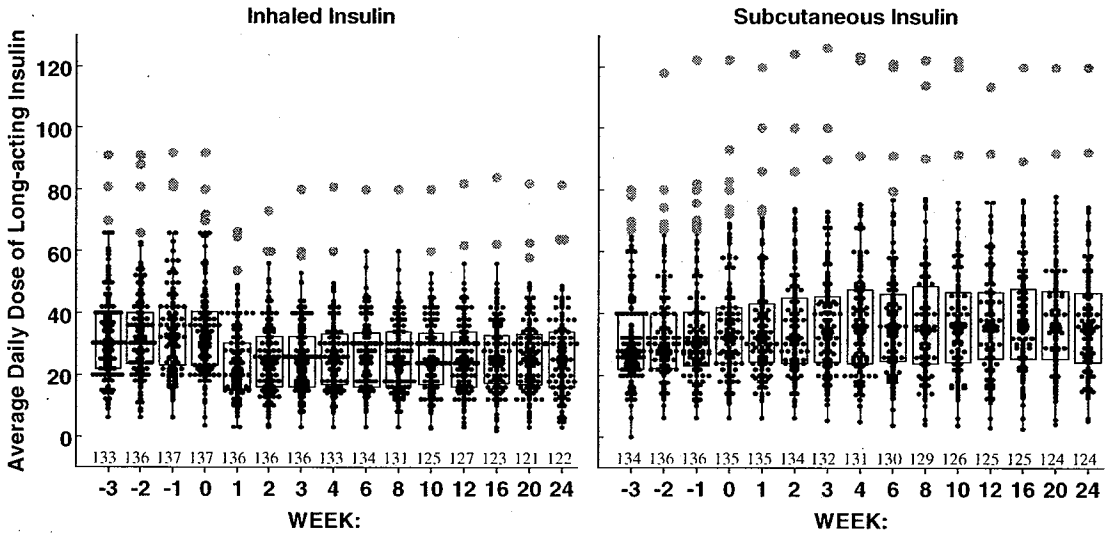
6.1 Ongoing safety studies

Clinical safety studies ongoing at the time of the NDA submission

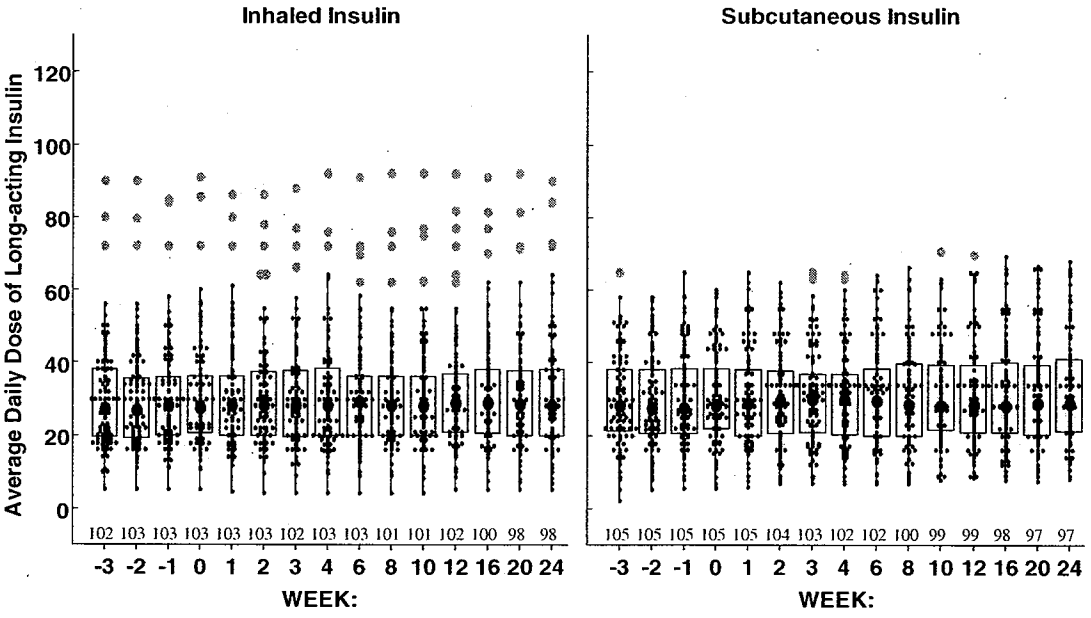
Study (# of centers)	Inhaled Insulin group	Comparator	Duration of treatment
1017 Type 2 *(US)* primarily an efficacy study	add-on INH to MET+SU INH + MET (switch from SU to INH)	add-on ROSI to MET+SU Total of 74 pts. rand. in all 3 arms	1 year started 4/03 completion expected 11/06
1022 Type 1 *(US, Can, Arg., Brazil, Mexico)* Safety study Pulm. Fn. tests	INH regimen not described 290 rand. Enrollment is complete Synopsis, no report	SC regimen not described 290 rand.	4 wk run-in on SC 2 year Median Dur 456 days ~75% > 1 yr exposure
1028 Type 1+2 (US, Can, Ger., Braz., Mex., Costa Rico) Chronic asthma Safety Study	Pre-meal TID + QD or BID ultralente or NPH, or QD ins glargine 46 rand. Enrollment ongoing	BID or TID reg ins + QD or BID ultralente or NPH, or QD ins glargine 49 rand.	3 wk run-in SC short-acting ins 1 year randomized treatment 6 wk runout on SC
1029 Type 2 *(US, Can, PR, Brazil)*	INH 291 rand.	SC 291 rand.	3 year extended treatment period completion expected 5/09
1030 Type 1+2 (US, Can, Ger., Braz., Mex., Costa Rico) Chronic obs. pul. dis. Safety Study	Pre-meal TID + QD or BID ultralente or NPH, OR QD ins glargine OR Oral antidiabetic agent 30 rand. Enrollment is complete	BID or TID reg ins + QD or BID ultralente or NPH, OR QD ins glargine OR Oral antidiabetic agent 27 rand.	3 wk run-in SC short-acting ins 1 year randomized treatment 6 wk runout on SC
1036 Type 1+2 Extension of 102, 103, 104 Pulm. Fn tests	All pts on INH regimen 173 rand. in orig prot 62 ongoing	NA	4 year extension study

6.2 Average daily dose of long-acting insulin by study, treatment and week for Type 1 studies 106 and 107

Study 106

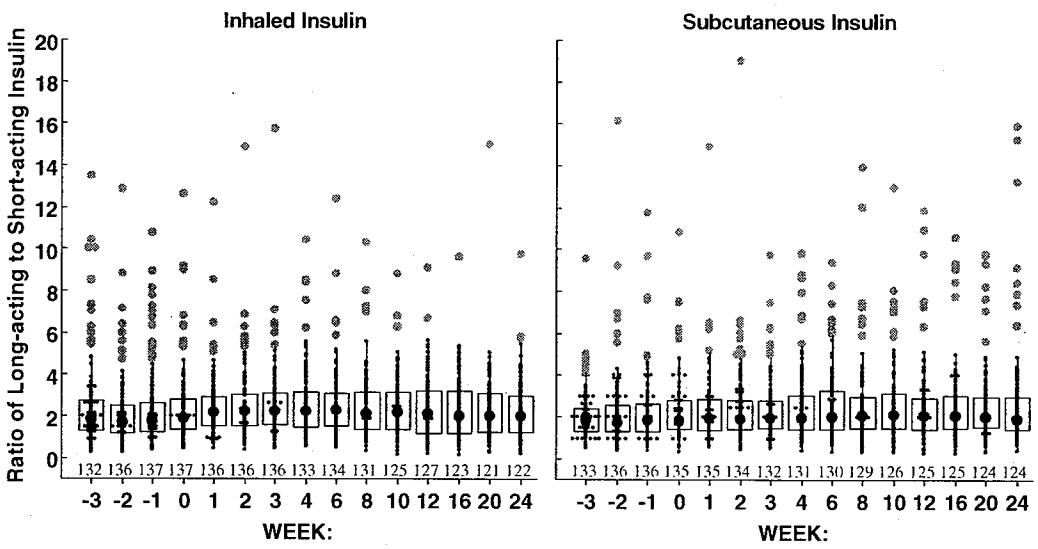


Study 107

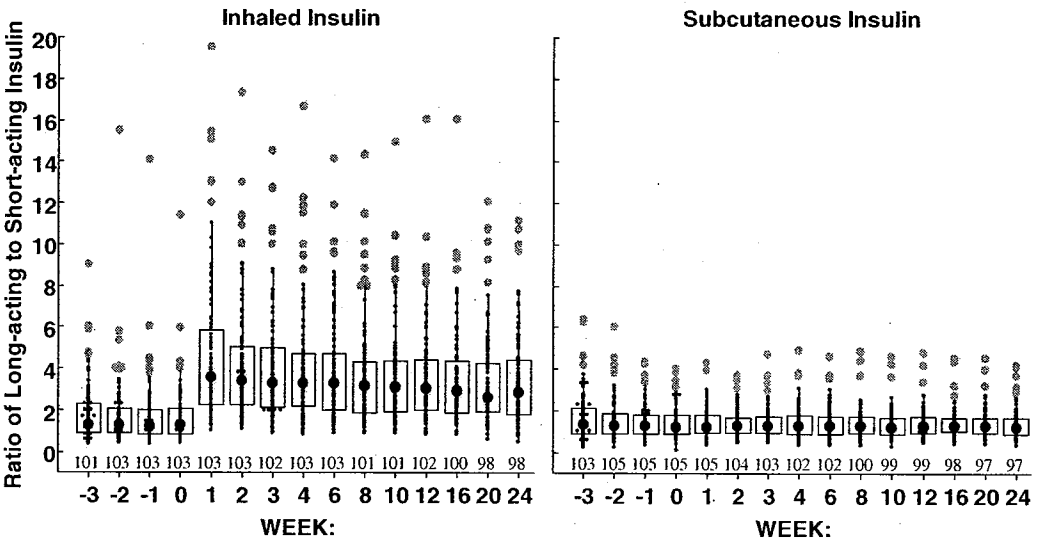


6.3 Average daily ratio of long-acting to short-acting insulin by study, treatment and week for Type 1 studies 106 and 107

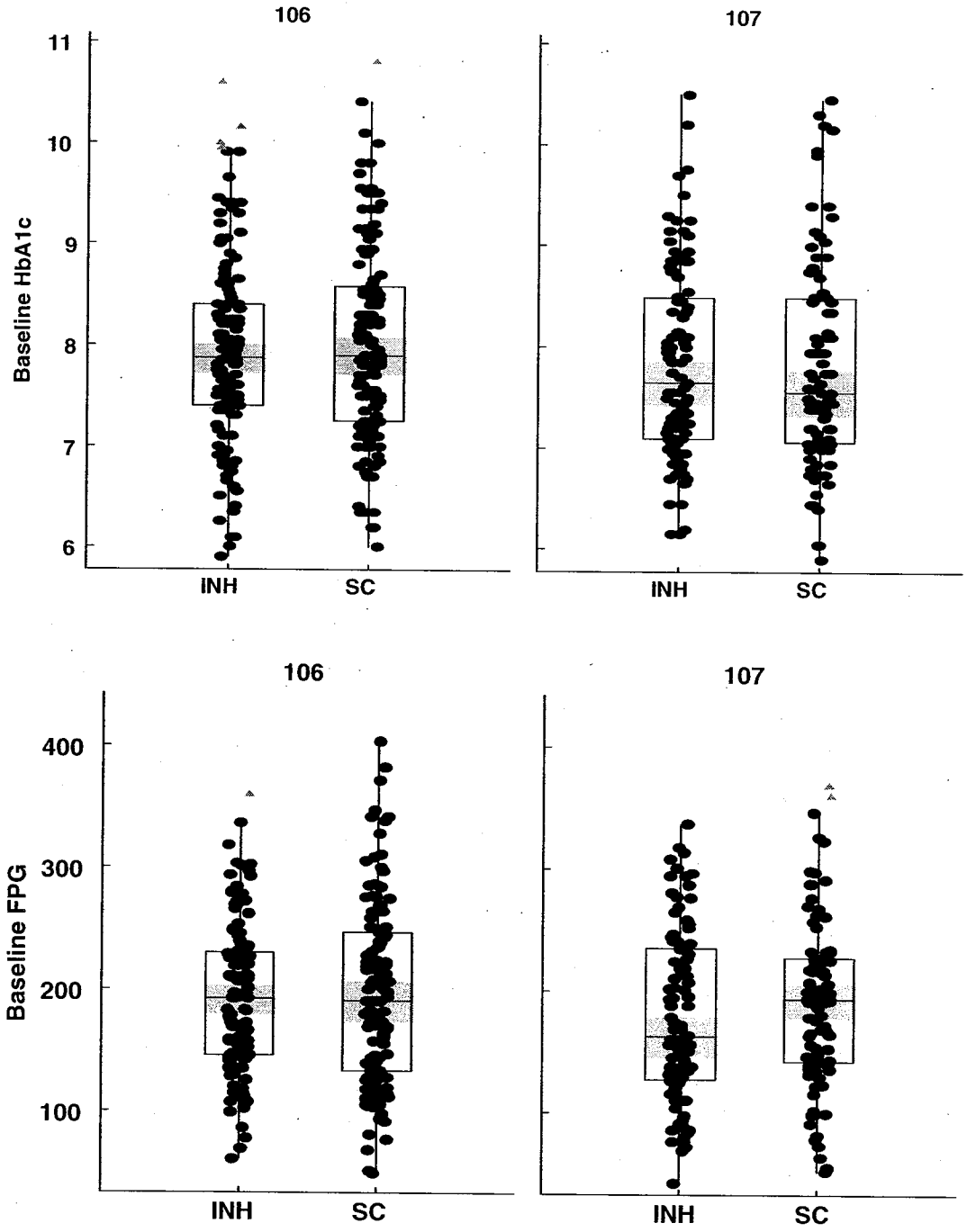
Study 106



Study 107



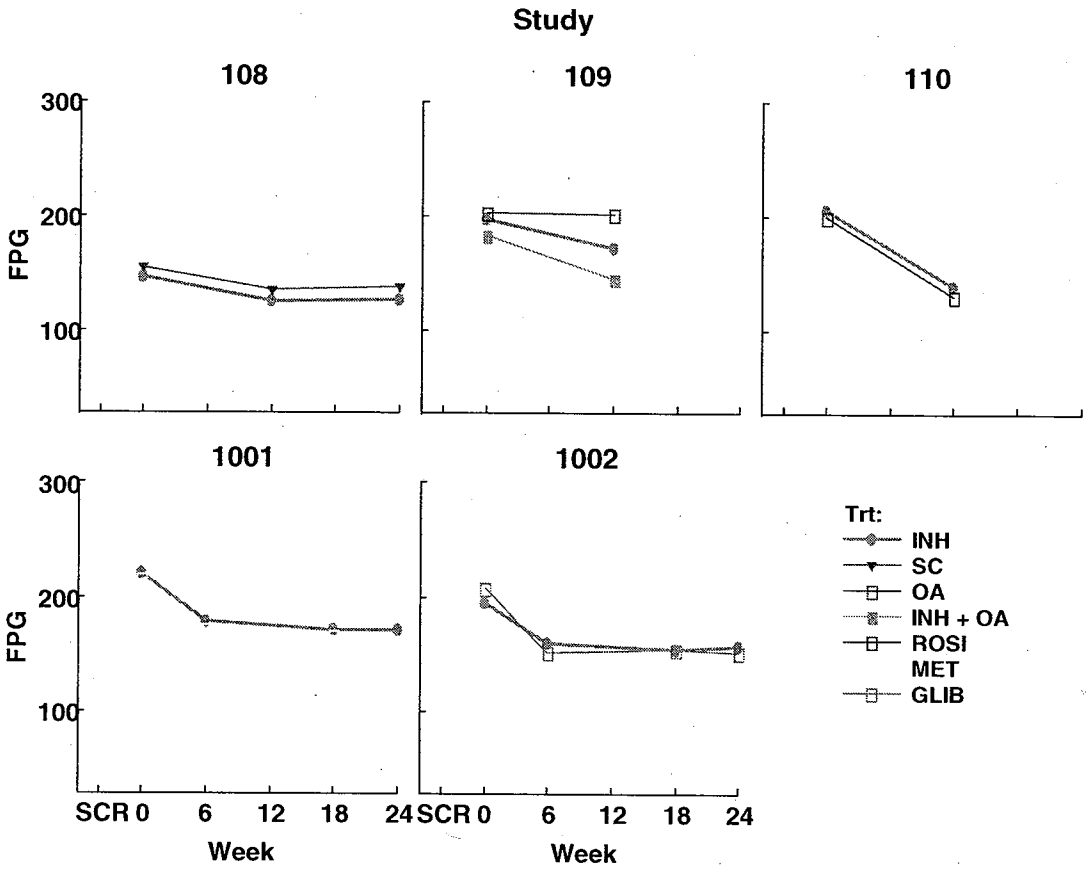
6.4 Baseline FPG and HbA1c for Type 1 Studies 106 and 107



6.5 Oral anti-diabetic therapies used in Phase 3 studies of Type 2 diabetes

Study	Screening	Run-in	On-study
109	Stable regimen of 2 OA's 1. Sulf. or repaglinide glipizide≥10mg daily or glimepiride≥4mg daily or glyburide≥10mg daily or repaglinide≥2mg TID 2. glitazone or metformin metformin≥1.7mg daily or troglitazone≥400mg daily rosiglitazone 4mg daily pioglitazone≥30mg daily	Maintain screening dose Pts on troglitazone were switched to another glitazone when it was removed from the market	Maintain screening dose for patients remaining on 2 OA's
110	NA (diet and exercise only)	NA (diet and exercise only)	For pts rand. to rosiglitazone: fixed dose of 4 mg BID (maximum marketed dose)
1001	Sulfonylurea alone glibenclamide (stand.)≥10mg daily or glibenclamide (micro.)≥7mg daily or glicazide≥160mg daily or glimepiride≥3mg daily	Maintain screening dose	Maintain screening dose of sulf. for all pts For pts rand. to metformin: starting dose of 500 mg and titrated, based on FPG, to max of 2.5 g daily over a minimum of 6 weeks or maximum of 18 weeks
1002	Metformin≥1.5g daily	Maintain screening dose	Maintain screening dose of met. for all pts For pts rand. to glibenclamide: starting dose of 2.5 mg and titrated, based on FPG, to max of 5 mg twice daily over a minimum of 6 weeks or maximum of 24 weeks

6.6 Type 2 FPG overtime all studies



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6.7 Definition of hypoglycemia

The following is excerpted directly from the protocol of Study 107 (the same definition was used in other studies as well); the underlining and bolding was added by the reviewer.

Subjects are instructed to check blood glucose in the event they experience symptoms of hypoglycemia. Subjects will record all hypoglycemic episodes on their weekly glucose monitoring worksheets.

Hypoglycemia is defined as one of the following:

- Characteristic symptoms of hypoglycemia with no blood glucose check. Clinical picture must include prompt resolution with food intake, subcutaneous glucagon, or intravenous glucose.

- Characteristic symptoms of hypoglycemia with blood glucose check showing glucose 59 mg/dl or less. Symptoms associated with a blood glucose of 60 mg/dl or greater cannot be reported as hypoglycemia.

- Any glucose measurement 49 mg/dl or less, with or without symptoms.

Every hypoglycemic event must be characterized with respect to its severity.
In order to characterize the event as severe, all 3 of the following criteria must be met:
1. The subject was unable to treat himself or herself.
2. The subject exhibited at least one of the following neurological symptoms:
    a) memory loss,
    b) confusion,
    c) uncontrollable behavior,
    d) irrational behavior,
    e) unusual difficulty in awakening,
    f) suspected seizure,
    g) seizure,
    h) loss of consciousness.
3. Either:
    a) If blood glucose was measured and was 49 mg/dl or less or,
    b) If the blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

Events that do not meet all 3 criteria for severe hypoglycemia are characterized as mild-moderate.

The "FDA" definition of hypoglycemia is blood glucose level of less than or equal to 36 mg/dL AND/OR requiring assistance, which was applied retrospectively. According to the program code provided by the applicant, an hypoglycemic event was counted as an FDA event if the patient had an hypoglycemic event as defined in the protocol (see above) and the glucose value recorded on the CRF-Hypoglycemic Episode Report was 36 or less and/or the answer to "Was the subject unable to self treat?" on the CRF was yes.

6.8 Hypoglycemic events for all Phase 3 Studies

The table below shows the number of events observed for all 3 definitions of hypoglycemia for the Phase 3 studies reviewed in this document. In each box, the top number is the sample size, the middle number is the number of patients with at least one event and the bottom number is the total number of events.

	Total		**"FDA"**		**Severe**	
TYPE 1						
	INH	Control	INH	Control	INH	Control
Study 106	136	132	136	132	136	132
At least 1 event	134 (**99%**)	130 (**98%**)	118 (**87%**)	116 (**88%**)	24 (**18%**)	19 (**14%**)
All events	6303	6454	1357	1315	43	35
Study 107	103	103	103	103	103	103
At least 1 event	102 (**99%**)	101 (**98%**)	91 (**88%**)	94 (**91%**)	18 (**17%**)	13 (**13%**)
All events	5306	5915	971	1327	43	19
TYPE 2						
Study 108	146	149	146	149	146	149
At least 1 event	111 (**76%**)	106 (**71%**)	34 (**23%**)	28 (**19%**)	3	1
All events	1109	1301	80	104	4	1
Study 109	102	INH+OA 100	102	INH+OA 100	102	INH+OA 100
At least 1 event	68 (**67%**)	78 (**78%**)	17 (**17%**)	21 (**21%**)	1	0
All events	365	477	23	48	1	0
Study 110	75	67	75	67	75	67
At least 1 event	36 (**48%**)	5 (**7.5%**)	9 (**12%**)	0	0	0
All events	153	9	15	0	0	0
Study 1001	214	196	214	196	214	196
At least 1 event	112 (**52%**)	53 (**27%**)	15 (**7%**)	7 (**4%**)	1	0
All events	374	180	20	9	1	0
Study 1002	234	222	234	222	234	222
At least 1 event	75 (**32%**)	69 (**31%**)	13 (**6%**)	12 (**5%**)	0	0
All events	214	203	27	23	0	0

6.9 SAS code for modeling hypoglycemic events

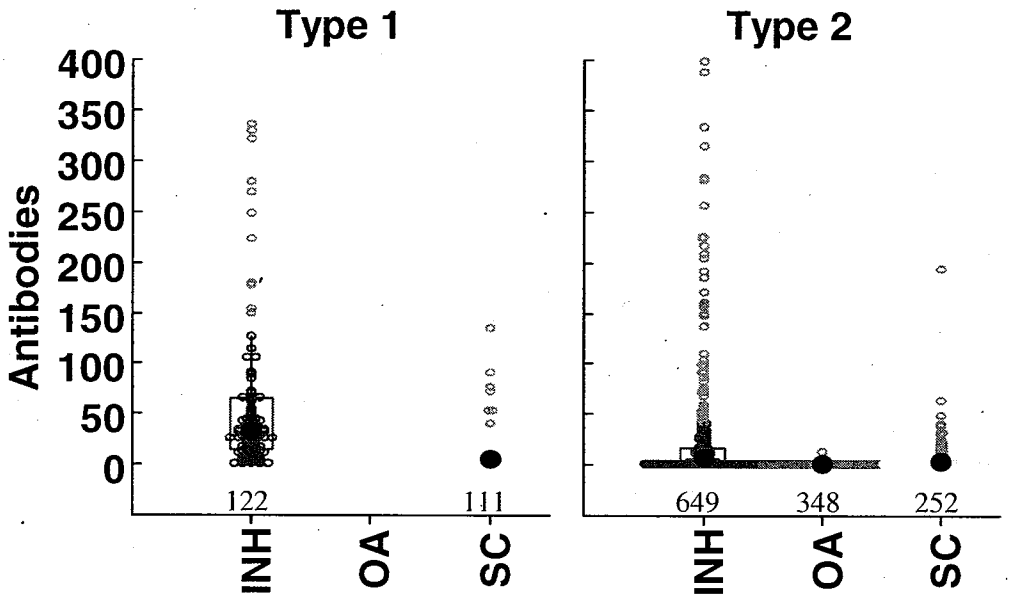
Applicant's code

```
proc phreg;
 model (startday,stopday)*status(0) = trt / alpha=0.05 rl;
```

Reviewer's code

```
proc phreg  covsandwich(aggregate);
 model (startday,stopday)*status(0) = trt / alpha=0.05 rl;
  id patid;
```

6.10 Boxplot of antibodies at Week 24 by diabetes type and treatment



A few outliers have been excluded from these boxplots in order to more clearly show the boxplots.

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Joy Mele
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Todd Sahlroot
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S. Edward Nevius
10/19/2005 05:03:22 PM
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Concur with review.

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: September 29, 2005

Between: Division of Metabolic and Endocrine Review Team for Exubera
NDA 21-868

And: Joy D. Mele, M.S.
Division of Biometrics 2

Subject: Comments on labeling

I have the following comments on the Clinical Studies section of the proposed labeling for Exubera:

Page 5, second paragraph under Clinical Studies

I recommend deleting this paragraph. Shouldn't hypoglycemia be reported with adverse events?

I think FDA-defined events should not be reported in the labeling. These events were counted post-hoc; the protocol was not designed to collect these events. Analyses of the FDA-defined events showed that these events were broadly defined and can not be characterized as severe events. About 20% of the FDA events were not accompanied by symptoms; about half the events were rated as mild. Severe hypoglycemia for Type 1 patients should be reported either as an incidence (at least 1 event) and/or as medians not as events/patient-month.

Tables 2, 3, 4, 5 and 6 (comments applicable to all tables)
I recommend simplifying the tables by excluding age, gender and weight from all the tables; this information could be contained in the text.

Sample sizes should be included in all tables.

Percentages of patients with <8% at endpoint should be sufficient; the odds ratios do not provide any useful additional information.

A footnote stating that a negative treatment difference favors Exubera should be included.

I recommend removing hypoglycemia from the efficacy tables and putting information about hypoglycemia elsewhere in the label. Hypoglycemic data should not be presented as events/patient-months.

The patient representative on the advisory committee recommended that dosing for Exubera be given in units. Is this reasonable? Can this be done?

Should post-prandial glucoses be included in the tables?

Pages 7-8, first section under Type 2 diabetes
I recommend excluding the paragraphs on the bottom of page 7 and Table 3. The study comparing Exubera to rosiglitazone should not be described in the labeling. The trial is too short to allow for a fair comparison of the two products.

Patient reported outcomes
I did not review the patient reported outcomes since these are not usually reported in labeling. If the clinical staff agrees to keep this data in the label, I would recommend that all p-values be reported as $P<0.05$ since these endpoints were secondary or tertiary endpoints. I am concerned that we do not have adequate information regarding patient requested discontinuations that may play a part in interpretation of these QOL measures.

The results of the two add-on trials (Studies 1001 and 1002) were not included in the labeling. These trials were large, well-designed trials showing that add-on Exubera had a comparable effects to add-on metformin or glibenclamide. Is this valuable information for physicians?

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joy Mele
9/28/2005 10:13:41 AM
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Labeling comments refer to originally submitted labeling and labeling revisions sent by Pfizer via email on 9/26/05.

Todd Sahlroot
9/28/2005 10:33:56 AM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-868/N-000
Name of drug:	Exubera (Insulin [RDNA Origin] INH powder
Indication:	For use in controlling the hyperglycemia associated with type 1 and type 2 diabetes mellitus (DM) in adults
Applicant:	Pfizer Inc.
Dates:	Received 12/27/04
Review priority:	S
Biometrics division:	Division of Biometrics II
Statistical reviewer:	Joan Buenconsejo, Ph.D. (HFD – 715)
Concurring reviewers:	Jon T. Sahlroot, Ph.D.
	S. Edward Nevius, Ph.D.
Medical division:	Division of Metabolic and Endocrine Drug Products (HFD-510)
Clinical team:	Karen Mahoney, M.D.
	David Orloff, M.D.
	Sally Seymour, M.D. (HFD-570)
	Eugene Sullivan, M.D. (HFD-570)
Project manager:	Oluchi Elekwachi, Pharm D.

Keywords: NDA review, clinical studies, safety, Mixed Model Repeated Measures

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Twelve completed and 2 ongoing Controlled Phase 2/3 studies were included in the submission. The main focus of this review was to assess the quality of the data, to assess the computation techniques used by the applicant and to assist the medical officer Dr. Sally Seymour with her clinical review of the pulmonary safety of the inhaled insulin (Exubera) in adult (age 18 years and over) subjects with Type 1 or Type 2 diabetes mellitus (DM).

I conclude that the data quality and analytical techniques used by the applicant in analyzing the pulmonary safety data are acceptable.

In Pooled Type 1, I find that respiratory adverse events were higher in the inhaled insulin group compared to the comparator group, particularly on increased cough. Only 2% of the 698 subjects in the inhaled insulin group discontinued due to respiratory events. There is evidence that inhaled insulin consistently showed a greater decline in FEV_1 and DLco from baseline over time particularly at early timepoints compared to the comparator group. Treatment differences were of a magnitude of about 40 mL for FEV1 at the end of the study and about 0.5 mL/min/mmHg for DLco at the end of the study. Although there are declines in FRC, FVC, and TLC scores in each of the treatment groups (i.e. inhaled insulin and comparator), the treatments were comparable over time. There is no evidence of any consistent correlation between the change from baseline in pulmonary function tests and antibody titers. In terms of PFT measures and insulin dose, correlations were generally small, usually no greater in absolute value than 0.15.

In Pooled Type 2, I find that respiratory adverse events were higher in the inhaled insulin group compared to the comparator group, particularly on increased cough. Only 2% of the 1277 subjects in the inhaled insulin group and 0.1% of the 1132 subjects in the comparator discontinued due to respiratory events. There is evidence that inhaled insulin consistently showed a greater numerical decline in FEV_1 and DLco from baseline over time compared to the comparator group. However, the majority of these differences were not statistically significant as indicated by the confidence intervals for these changes. Treatment differences were of a magnitude of about 40 mL for FEV1 at the end of the study (same as Type 1 data) and about 0.4 mL/min/mmHg for DLco at week 84/91. A similar conclusion can be drawn for FRC, FVC, and TLC scores. Although treatment group differences slightly favored the comparator group, the differences were comparable in the sense that the confidence intervals include the zero difference. There is no evidence of consistent correlation between the change from baseline in pulmonary function tests and antibody titers. In terms of PFT measures and insulin dose, correlations were generally small, usually no greater in absolute value than 0.15.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

1.2.1 BACKGROUND

The primary objective of this statistical review is to assess the quality of the data, to assess the computation techniques used by the applicant and to assist the medical officer Dr. Sally Seymour with her clinical review of the pulmonary safety of the inhaled insulin (Exubera) in adult (age 18 years and over) subjects with Type 1 or Type 2 diabetes mellitus (DM). This includes detailed evaluations and treatment comparisons of the five pulmonary function tests (PFT), namely, the forced expiratory volume in 1 second (FEV1), carbon monoxide diffusion capacity (DLco), forced vital capacity (FVC), total lung capacity (TLC), and the functional residual capacity (FRC). In this review, I also evaluated the respiratory adverse events, the results from chest x-rays and thoracic high resolution computed tomography scan (HRCT). The relationships between PFT and antibody titers, as well as on dosing exposure were also assessed.

In my review, I focused mainly on the 12 completed and 2 ongoing Controlled Phase 2/3 studies included in the submission (Table 1). Most of the safety data and serious adverse event data presented in this review are based on cut-off dates of June 25, 2004 and September 1, 2004, respectively. I also included in my review the new safety update for the ongoing Study 1022 that was submitted on April 26, 2005 (actual data was submitted on July 5, 2005). Individual, pooled type 1, and pooled type 2 data from these Controlled Phase 2/3 studies with interim (Study 1029 and 1022) and final study reports have been re-analyzed and will be discussed in this review.

To simplify the discussion of pulmonary safety, subjects are grouped based on the treatment actually received. Subjects treated with INH with or without subcutaneous basal insulin, or oral antidiabetic agents (OAs) are considered to be INH- treated subjects. Subjects treated with subcutaneous short- acting (SC) insulin or with OAs alone are considered to be Comparator-treated subjects. No subjects were randomized to receive SC regular insulin with INH or OAs. All subjects with type 1 DM received basal insulin in addition to INH or SC insulin.

In the pooled studies, PFT measurements were summarized by treatment and analysis timepoints by descriptive statistics and graphical presentations. Treatment effects on the selected pulmonary function tests were analyzed and summarized with the unadjusted and adjusted models using all treated subjects. In this case, treated subjects are defined as subjects who received at least one dose of study treatment and have a baseline PFT measurement. An unadjusted model was fitted to the observed change from baseline PFT measurements by visits (time). Because of the longitudinal nature of the data, a repeated measure with treatment, time and, protocol as fixed effects, and a random effect associated with each subject was fitted to the observed change from baseline PFT measurements. Two additional repeated analyses conducted by the applicant were also included in the summary that includes covariates in the model. One of the adjusted models by the applicant was the repeated measures model with the categorical variables (treatment, month, center, gender) and the continuous variables (baseline, age, height) fitted to the change from baseline PFT measurements, and the other adjusted model was the repeated measures model with only treatment and time fitted to the change from baseline PFT measurements.

Missing PFT measurements were not imputed in the final model. However, to assess the robustness of the observed PFT measurements, imputation using last observation carried forward (LOCF) was also carried out.

Incidence of respiratory adverse events, and the results from chest x-rays and the thoracic high resolution computed tomography scan (HRCT) were summarized by treatment by descriptive statistics. The relationships between the change from baseline of PFT measurements and the antibody titer, as well as the dosing exposure were also summarized by treatment and analysis timepoints by graphical presentations.

1.2.2 SPONSOR'S RESULTS AND CONCLUSION

The following summarizes some of the applicant's results and conclusions:

> Pre- clinical studies of inhaled insulin (INH) pulmonary safety, with up to 6 months of INH exposure, were unremarkable. In clinical studies, involving controlled INH treatment for up to 24 months and uncontrolled INH treatment for up to approximately 84 months, cough, dyspnea, epistaxis, and increased sputum occurred in a greater proportion of INH- treated than comparator- treated subjects. Respiratory serious adverse events occurred at similar incidence among subjects receiving INH or comparator therapies. Discontinuations due to respiratory adverse events were more common among INH- than comparator- treated subjects.
>
> Pre- and post- exposure chest x- rays and high resolution computed tomography (HRCT) scans have not demonstrated lung pathology associated with INH treatment.
>
> Pulmonary function test result declines associated with INH treatment were small, nonprogressive beyond 2 weeks, and reversible following cessation of treatment. Small differences in change from baseline lung function (forced expiratory volume in 1 second [FEV1] and carbon monoxide diffusion capacity [DLco]) favoring comparator therapy have been observed in most of the 3- and 6-month controlled Phase 2/ 3 studies in the INH development program. Importantly, the treatment group differences were not driven by outlier values among INH- treated subjects. In long- term controlled studies these small treatment group differences did not progress beyond 3 months, with ongoing exposure up to 2 years. In Study 1027, in which FEV1 and DLco were measured frequently, the treatment group differences were fully manifest by 2 weeks of treatment and did not progress thereafter. Cessation of INH therapy following controlled exposure for as long as 2 years has shown rapid resolution of the treatment group differences in FEV1 and DLco. That these treatment group differences in lung function arise early and are small, non- progressive, and reversible supports the overall respiratory safety of INH therapy.
>
> Subjects with mild to moderate asthma or COPD did not experience any unexpected findings related to the safety and efficacy of INH in Phase 2/ 3 studies. Specifically, there was no evidence that these special populations experience altered INH absorption or clinical deteriorations in the status of their diabetes or underlying respiratory disease.
>
> Overall, the safety and efficacy of INH among subjects with and without notable pulmonary function test (PFT) declines were comparable. INH therapy was well tolerated by subjects in the clinical development program.

1.3 STATISTICAL ISSUE S AND FINDINGS

The following were the statistical issues identified after reviewing this NDA submission:

1. Analysis Population
2. Handling of Missing Data
3. Selection of Appropriate Covariance Structure

These issues did not affect the overall conclusion of the pulmonary safety of the inhaled insulin, but I find that it is worth noting in this review. Post-hoc analyses had been conducted to address and clarify some of these issues. A more detailed description of these issues can be found in Section 5.1.

2 INTRODUCTION

2.1 OVERVIEW

This is a review of the pulmonary safety data of the inhaled human insulin therapeutic regimen (Exubera) in adult (age 18 years and over) subjects with Type 1 or Type 2 diabetes mellitus (DM). The study drug is indicated for use in controlling the hyperglycemia associated with Type 1 and Type 2 diabetes mellitus (DM) in adults. Exubera is proposed to be administered before each meal as part of an individualized DM control regimen that may include other insulin formulation or oral hypoglycemic agents.

Currently, the applicant, Pfizer Inc, is seeking FDA approval of EXUBERA (insulin [rDNA origin] powder for oral inhalation) 1 mg and 3 mg unit dose blisters in accordance with the proposed package insert. EXUBERA (also referred to as INH) is a novel treatment system for diabetes mellitus (DM) which combines a dry powder formulation of a recombinant human insulin with a customized inhaler and was designed to permit the easy and reproducible delivery of insulin for the control of hyperglycemia in patients with DM. It is delivered with a novel, reusable pulmonary inhaler that is purely mechanical, and requires no batteries, electronics or external power source

The primary objective of this statistical review is to assess the quality of the data, to assess the computation techniques used by the applicant and to assist the medical officer Dr. Sally Seymour with her clinical review of the pulmonary safety of the inhaled insulin (Exubera) in adult (age 18 years and over) subjects with Type 1 or Type 2 diabetes mellitus (DM).

In my review, I focused mainly on the 12 completed and 2 ongoing Controlled Phase 2/3 studies included in the submission (Table 1). Most of the safety data and serious adverse event data presented in this review are based on cut-off dates of June 25, 2004 and September 1, 2004, respectively. I also included in my review the new safety update for the ongoing Study 1022 that was submitted on April 26, 2005 (actual data was submitted on July 5, 2005). Individual, pooled type 1, and pooled type 2 data from these Controlled Phase 2/3 studies with interim (Study 1029 and 1022) and final study reports have been re-analyzed and will be discussed in this review.

Table 1: Controlled PFT Phase 2/3 Studies

Diabetes Type	Contributing Study	PFT	INH	Comparator	Total
Type 1 DM	Controlled Studies*	Total	698	705	1403
	102, 106, 107, 1022**, 1026, 1027	FEV1	686	692	1378
		FVC	686	692	1378
		DLco	684	691	1375
		FRC	686	689	1375
		TLC	686	690	1376
Type 2 DM	Controlled Studies*	Total	1277	1132	2409
	103, 104, 108, 109, 110, 1001**, 1002**, 1029***	FEV1	1267	1119	2386
		FVC	1266	1118	2384
		DLco	1234	1094	2328
		FRC	1247	1100	2347
		TLC	1264	1115	2379

*All Phase 2/3 Controlled Studies
**Studies 1022, 1001, and 1002 include 2 years of exposure data.
*** Study 1029 is truncated at 1 year of exposure, consistent with the 1-year interim analyses

2.2 DATA SOURCES

This statistical review is based on data submitted for Pulmonary Safety.

The electronic submission of this NDA can be found on the internal network drive at
\\Cdsesub1\n21868\N_000\2004-12-27\

The clinical study report for all Pulmonary Safety Studies, as well as its amendments and updates are located at
\\Cdsesub1\n21868\N_000\2004-12-27\clinstat
\\Cdsesub1\n21868\N_000\2005-06-22
\\Cdsesub1\n21868\N_000\2005-07-05\clinstat

The electronic datasets for all the studies and its amendments and updates are under
\\Cdsesub1\n21868\N_000\2004-12-27\crt\datasets
\\Cdsesub1\n21868\N_000\2005-07-05\crt\datasets

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

A detailed clinical review of the efficacy of Exubera can be found in Dr. Karen M. Mahoney's review. Meanwhile, a detailed statistical review of the efficacy of Exubera can be found in Ms. Joy Mele's review.

3.2 EVALUATION OF SAFETY

The overall clinical review of the safety of Exubera can be found in Dr. Karen M. Mahoney's review. Meanwhile, a detailed review of the pulmonary safety of Exubera can be found in Dr. Sally Seymour's review.

The safety review in this section consists of two parts. The first part includes a brief description of the safety assessments such as the pulmonary function tests, adverse events reports, and some laboratory exams such as chest X-rays and thoracic high resolution computed tomography, as well as a brief summary of the statistical analysis plan of the applicant. The second part of this safety review section includes a collective summary of the pooled pulmonary safety data by type of diabetes.

3.2.1 SAFETY EVALUATIONS

1. Safety Assessments

According to the applicant, extensive safety analyses have been conducted to screen for safety signals in the INH clinical development program. The following are some of the safety monitoring programs the applicant has conducted:

a. Pulmonary Function Test

Comprehensive pulmonary function testing (spirometry, lung volumes, diffusion capacity and oxygen saturation) was performed (see Table 2 and Table 3 for individual studies). In early Controlled Phase 2/ 3

studies (Studies 102, 103, 104, 106, 107, 108, 109, 110, 1009, 1001 and 1002), PFTs were measured in local laboratories according to standards of the American Thoracic Society or local country standards. Subjects were to repeat the pulmonary function test 3- times at each evaluation, and the maximum test result from the 3 was to be recorded on the subject's CRF. However, no further attempt was made to standardize the equipment or methodologies. In Studies 1022, 1026, 1027, and 1029, standardized pulmonary function testing equipment and centralized data analysis were used.

b. Adverse Events

All observed or volunteered adverse events were recorded by the investigator on the CRF regardless of treatment group or suspected causal relationship to study drug. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre- existing illnesses were recorded. Objective test findings (e. g., ECG changes, abnormal laboratory test results) that resulted in a change in study drug dosage or resulted in discontinuation, and clinically significant changes in physical examination findings, as judged by the investigator, were also recorded as adverse events.

Exacerbation of pre- existing illness, including the disease under study, was defined as a manifestation (sign or symptom) of the illness that indicated a significant increase in the severity of the illness as compared to the severity noted at the start of the study. It may include worsening or increase in severity of signs or symptoms of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/ complication. Exacerbation of a pre- existing illness was to be considered when a subject required new or additional concomitant drug or non- drug therapy for the treatment of that illness during the study. Lack of or insufficient clinical response, benefit, efficacy, or therapeutic effect was not to be recorded as an adverse event. The investigator was required to make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

For all adverse events, the investigator pursued and obtained information adequate to determine both the outcome of the adverse event and to assess whether it met the criteria for classification as a serious adverse event. The investigator was to obtain sufficient information to determine the causality of the adverse event and record the causality assessment on the CRF. If the adverse event or its sequelae persisted, follow- up was performed until resolution or stabilization at a level acceptable to the investigator and sponsor.

c. Other

Chest x-rays were performed at baseline and end of study for most Controlled Phase 2/ 3 studies (Studies 106, 107, 108, 109, 110, 1001, 1002, and 1027). Additional chest x-rays were performed at 1 year in controlled 2- year Studies 1022, and 1029. In extension studies, chest x-rays were performed at approximately yearly intervals. Baseline and end- of- study High Resolution Computed Tomography (HRCT) of the thorax were performed in subjects randomized to participate in the HRCT sub- study in Studies 106, 107, and 108. In Study 1029, thoracic HRCT is to be performed in a sub-set of subjects at baseline, 1 year, and 2 years.

2. Analysis Plan

To simplify the discussion of pulmonary safety, subjects are grouped based on the treatment actually received. Subjects treated with INH with or without subcutaneous basal insulin, or oral antidiabetic agents (OAs) are considered to be INH- treated subjects. Subjects treated with subcutaneous short- acting (SC) insulin or with OAs alone are considered to be Comparator-treated subjects. No subjects were randomized to receive SC regular insulin with INH or OAs. All subjects with type 1 DM received basal insulin in addition to INH or SC insulin.

For the Controlled PFT Phase 2/ 3 Studies, the objective was to estimate treatment group differences in change from baseline PFT parameters over time. Analyses were performed separately for the Type 1 and Type 2 pooled protocol sets. The pooled Type 1 data includes information and data from Studies 102, 106, 107, 1022 (two-year study report), 1026, and 1027, while the pooled Type 2 data includes information and data from Studies 103, 104, 108, 109, 110, 1001, 1002, and 1029. The accuracy of the data from individual studies was confirmed by re-analyzing each of the individual data sets. In this section, an overview of the pooled data will be described. Some analyses were added as per the request by Dr. Seymour, some data were re-analyzed because of the addition of new data, and some analyses were done to assist Dr. Seymour in understanding the pulmonary safety of the inhaled insulin.

The analysis population evaluable for adverse events includes all subjects who received study drug for at least one day. All studies in the INH clinical program were open- label, making assignment of causality to adverse events subject to bias. Therefore, all-causality adverse events were emphasized by the applicant, as well as in my review. Respiratory adverse event data are presented for adults (subjects >= 18 years old) only. In terms of the PFT measurements, all subjects who received at least one dose of study treatment and have a baseline PFT measurement were evaluable for the analyses of PFT decline. Additionally, according to the applicant, for a subject to be included in the analysis for DLco, the subject must have a baseline and a post-baseline DLco measurement. This approach by the applicant (i.e. restricting subjects who only have post-baseline for DLco score) may not be ideal unless imputation (such as last observation carried forward) is carried out. Therefore, all subjects who received at least one dose of study treatment and have a baseline PFT measurement were included in the analyses of PFT decline. For insulin antibodies, population used includes all available data from all subjects regardless of whether they have baseline and/ or post- baseline data.

In the pooled data, the applicant specified in their study report (NOT protocol) that repeated measures analysis of variance was used to simultaneously estimate the mean change from baseline for each treatment group and its corresponding treatment difference at each assessment time point. Treatment comparison based on group means (inhaled insulin minus comparator insulin) was also done using the PROC MIXED procedure for mixed model repeated measure (MMRM) analysis in SAS. A random coefficients model was fitted to the observed PFT data where a random intercept and a random slope were associated with each subject. The variance-covariance structure chosen by the applicant was the Spatial Power form, which assumes higher correlation between neighboring time points than farther time points. From these estimates, treatment group differences (Inhaled Insulin – Comparator) and associated 95% confidence intervals in change from baseline PFTs were estimated at each assessment time point. Two statistical models were used for the MMRM analysis:

(1) Unadjusted Model • Treatment group, categorical variable • Visit, categorical variable • Subject, random effect
(2) Covariate Adjusted Model • Treatment group, categorical variable • Visit, categorical variable • Protocol, categorical variable • Baseline PFT, continuous variable • Age at baseline (years), continuous variable • Baseline height (meters), continuous variable • Gender (1= Male, 0= Female), categorical variable • Subject, random effect

According to the applicant, this analysis was to provide information on the profile of group mean change in FEV1 and DLco during early treatment of inhaled insulin. A detailed discussion of this MMRM model is described in the Statistical Issues and Findings Section

Although the variance-covariance structure (i.e. Spatial Power) chosen by the applicant appears to be reasonable, I also conducted additional analyses using unstructured correlation matrix and compound symmetry as the within-subject variance-covariance structure to determine whether the applicant had selected an appropriate covariance structure.

I also carried out additional analyses that looked into the effects of data imputation based on last observation carried forward in each of the individual studies, and using the imputed data in the pooled analysis. This approach was tricky since the treatment duration across studies was different thereby the imputed data were also at different time points. Furthermore, as noted previously, the analysis population in this type of approach should be restricted to subjects who had at least one post-baseline PFT measurements.
I compared the results from the imputed data with the results using the observed cases only, as well as with the mixed model.

As an added exploratory analysis, I also carried out responder analysis to assess the response (i.e. reduction of PFT scores) profile of the subjects in the Inhaled insulin group and the comparator group. The responder analysis in this scenario is based on percent reduction in mean PFT values from baseline. In other words, these are proportion of subjects who had a decline in PFT score from baseline. The percent decrease was classified in 1-percent increments (e.g. > 0% decrease, =1%, =2%, ... =10% reduction in PFT scores from Baseline), and in 5-percent increments (e.g. =15%, =20%,..., =60%) giving cumulative distribution functions of PFT reduction from Baseline by treatment groups. In this analysis, patients who withdrew from the study were not included in the analysis since it is difficult to predict what their PFT measures would be after discontinuation.

Incidence of respiratory adverse event, and the results from chest x-rays and the thoracic high resolution computed tomography scan (HRCT) were summarized by treatment by descriptive statistics. The relationships between the change from baseline of PFT measurements and the antibody titer, as well as the dosing exposure were also summarized by treatment and analysis timepoints.

Table 2: Analysis Population of Type 1 Data

PFT	Study	Treatment Duration (in weeks)	Number of Subjects INH	Number of Subjects Comparator	Overall Week	Overall Inhaled	Overall Comparator
DLco	102	12	35	37	12	447	452
	106	24	135	134	24	549	551
	107	24	102	105	36	290	290
	1022	12, 24, 36, 48, 60, 72, 84, 96	290	290	48	290	290
	1026	12, 24	23	22	60	290	290
	1027	12	99	103	72	290	290
					84	290	290
					96	290	290
FEV1	102	12	35	37	12	686	692
	106	12 and 24	136	135	24	552	552
	107	12 and 24	103	105	36	290	290
	1022	12, 24, 36, 48, 60, 72, 84, 96	290	290	48	290	290
	1026	12, 24,	23	22	60	290	290
	1027	12	99	103	72	290	290
					84	290	290
					96	290	290
FRC	102	12	35	35	12	447	450
	106	24	136	135	24	552	551
	107	24	103	104	36	290	290
	1022	12, 24, 36, 48, 60, 72, 84, 96	290	290	48	290	290
	1026	12, 24	23	22	60	290	290
	1027	12	99	103	72	290	290
					84	290	290
					96	290	290
FVC	102	12	35	37	12	686	692
	106	12 and 24	136	135	24	552	552
	107	12 and 24	103	105	36	290	290
	1022	12, 24, 36, 48, 60, 72, 84, 96	290	290	48	290	290
	1026	12, 24,	23	22	60	290	290
	1027	12	99	103	72	290	290
					84	290	290
					96	290	290
TLC	102	12	35	35	12	447	450
	106	24	136	135	24	552	552
	107	24	103	105	36	290	290
	1022	12, 24, 36, 48, 60, 72, 84, 96	290	290	48	290	290
	1026	12, 24	23	22	60	290	290
	1027	12	99	103	72	290	290
					84	290	290
					96	290	290