Advisory Committee Briefing Document

EXUBERA®

(insulin [rDNA origin] powder for oral inhalation)

1 mg & 3 mg

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Endocrinologic and Metabolic Drugs Advisory Committee

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABE	Average bioequivalence
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ANCOVA	Analysis of covariance
APSD	Aerodynamic particle size distribution
ASP	Insulin aspart
AUC	Area under the curve
BE	Bioequivalence
BDI	Baseline dyspnea index
BID	Twice a day
BL	Baseline
BMI	Body mass index
CI	Confidence interval
Cmax	Maximum observed concentration
COPD	Chronic obstructive pulmonary disease
COSTART	Coding Symbols Thesaurus of Adverse Reaction Terms
CPMP	Committee for Proprietary Medicinal Products
CSR	Clinical study report
CVw	Intrasubject (within-subject) coefficient of variation
DCCT	Diabetes Control and Complications Trial
D/E	Diet and exercise
DLco	Carbon monoxide diffusing capacity of the lung
DLva	Carbon monoxide diffusing capacity of the lung adjusted for alveolar volume
DM	Diabetes mellitus
ED	Emitted dose
ES	Esoterix
EU	European Union
F	Relative bioavailability
FAS	Full analysis set
FEF 25-75%	Forced expiratory flow
FEV1	Forced expiratory volume in one second
FPD	Fine particle dose
FVC	Forced vital capacity
GCP	Good clinical practice
GDM	Gestational diabetes mellitus
GIR	Glucose infusion rate
GLA	Insulin glargine
GLI	Glibenclamide (glyburide)
GLZ	Glitazone
HbA1c	Glycated hemoglobin A
HCP	Health care provider
HE	Hypoglycemic event
HRCT	High resolution computerized tomography
ICH	International Conference on Harmonization
ICR	Insufficient clinical response
INH	Inhaled insulin
INH mono	Inhaled insulin monotherapy
ITT	Intent-to-treat
LIS	Insulin lispro
LOCF	Last observation carried forward
LST	Large simple trial
MANCOVA	Multivariate analysis of covariance
MedDRA	Medical Dictionary for Regulatory Activities
MET	Metformin

MMAD	Mass median aerodynamic diameter
NA	Not applicable
NHANES	National Health and Nutrition Examination Surveys
NOD	Non-obese diabetic
NPH	Neutral protamine hagedorn
OA	Oral agent(s)
OR	Odds ratio
PFT	Pulmonary function test
PGDM	Pregestational DM
PI	Package insert
PIL	Patient information leaflet
PRO	Patient-reported outcomes
PSD	Particle size distribution
QOL	Quality of life
REG	Regular
REP	Repaglinide
Rhu-insulin	Recombinant human insulin
RIA	Radioimmunoassay
RLB	Radioligand binding
ROS	Rosiglitazone
RR	Risk ratio
RV	Residual volume
SAE	Serious adverse event
SAT	Treatment satisfaction
SC	Subcutaneous
SD	Standard deviation
SU	Sulfonylurea
TDI	Transitional dyspnea index
THIN	The Health Improvement Network
TID	Three times a day
TLC	Total lung capacity
Tmax	Time of first occurrence of Cmax
Treatment-related	Treatment-related per investigator
U	Units
UKPDS	United Kingdom Prospective Diabetes Study
UL	Ultralente® SC insulin
ULD	Underlying lung disease
USPI	Unites States package insert

EXUBERA® FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

1. EXECUTIVE SUMMARY

New Drug Application (NDA) 21-868 was submitted by Pfizer to request approval for EXUBERA®(also referred to as INH), an inhaled rapid-acting human insulin, for the treatment of adult patients with diabetes mellitus (DM) for the control of hyperglycemia.

The Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Division of Metabolic and Endocrine Drug Products has asked that an Advisory Committee meeting be held on 8 September 2005 as part of the review process for the INH NDA. This briefing document has been prepared to assist members of the Advisory Committee in assessing the benefit-risk profile of INH.

Development Objective

INH has been developed by Pfizer in partnership with sanofi-aventis and in collaboration with Nektar Therapeutics to provide a non-invasive, easy to administer, titratable, and reliable alternative to subcutaneously (SC) injected regular or rapid-acting insulin for the treatment of DM.

Diabetes is a growing epidemic in the United States. There are currently 18 million patients with DM, and the population with type 2 DM is expected to increase approximately 20% by 2010. Within the last decade, intensive insulin regimens have been shown to provide a significant reduction in the serious and costly complications that are due to the chronic hyperglycemia of poorly controlled DM. Despite the introduction of new therapies for DM, glycemic control is worsening. Only 42% of patients achieve the recommended American Diabetes Association target of HbA_{1c} <7%. Many patients fail to appropriately initiate and intensify insulin treatment due to the poor acceptability of injection therapy.

It has been estimated that a typical patient with DM on the recommended dosage regimen of four insulin injections per day must inject approximately 15,000 times in one decade. SC insulin treatment is complicated by the need to store insulin solutions correctly, the need to use syringes appropriately, impact on the environment, physiological and anatomical factors on insulin absorption, and inherent potential liabilities regarding needle-stick injuries to other parties.

INH can be administered immediately before meals eliminating the need for mealtime injections. It has the potential to reduce the risk of diabetic complications by facilitating appropriate initiation or intensification of insulin therapy by patients reluctant to use SC regular or rapid-acting insulin. Its use should lead to an improved quality of life for the growing population of patients with DM.

Product Description

INH is insulin powder for oral inhalation used with a specially designed pulmonary inhaler. The insulin is human insulin of rDNA origin that is a rapid-acting, blood glucose-lowering agent. It is produced by recombinant technology using a non-pathogenic laboratory strain of *Escherichia coli* (K 12).

INH is provided in pre-dispensed unit dose blisters containing a nominal insulin dose of 1 mg or 3 mg in a homogenous powder formulation containing sodium citrate, mannitol, glycine, and sodium hydroxide. A patient dispenses the drug by placing a blister in the inhaler, pumping the handle of the inhaler, pressing a button (causing the blister to be pierced and the insulin powder to be dispersed in the holding chamber), and inhaling the aerosolized powder. Under standardized *in vitro* conditions, INH delivers a specific emitted mass of powder from the inhaler, a fraction of which is emitted as fine particles capable of reaching the deep lung.

Development Program

Insulin's mechanism of action and benefit/risk profile in the treatment of DM is well established. The INH development program has focused on confirming that the effectiveness of insulin delivered by the pulmonary route is the same as for subcutaneously delivered insulin and determining if there are any unique consequences of pulmonary delivery.

Non-Clinical Program

A non-clinical program was conducted, and the results support the comprehensive safety assessment for long-term clinical administration of INH.

Pharmacology studies show that the aventis rhu-insulin is biologically equivalent to other human insulins and that, as in humans, insulin inhalation powder administered by the pulmonary route to rats, monkeys or dogs is absorbed into the bloodstream in a dose-dependent manner and produces the expected pharmacodynamic response of lowering glucose. The studies also provide evidence that chronic administration of insulin inhalation powder does not result in accumulation in the lung.

One- and 6-month inhalation studies were conducted in the rat and monkey to specifically assess the potential for respiratory tract toxicity, since the systemic effects of rhu-insulin have been well characterized in animal studies using subcutaneous administration. Insulin powder for inhalation was well tolerated in rats and monkeys treated daily for up to 6 months. In monkeys given insulin powder for inhalation for 1 to 6 months at mean doses of approximately 0.2 and 0.6 mg/kg/day, there was no indication of any insulin/excipient-induced toxicological effects. Rats given insulin powder for inhalation daily or up to 6-months at doses up to approximately 6 mg/kg/day showed no toxicological effects. In both species, high doses were limited by hypoglycemia.

There was little or no detectable insulin antibody generation, and no insulin or excipient-related effects were observed on respiratory and pulmonary function parameters in animals. No exposure-related histopathological changes were seen in the respiratory tract or bronchial lymph nodes of rats and monkeys. In addition, there was no effect of the excipient or insulin exposure on cell proliferation indices in alveolar or bronchiolar lung regions of rats or monkeys in the 6-month study.

Clinical Program

The clinical development program for INH described in the NDA is comprehensive including 32 single-dose clinical pharmacology studies and 23 Phase 2/3 studies. All single-dose clinical pharmacology studies and 17 Phase 2/3 studies were complete at the time of submission. Studies have been conducted in the target population: patients with type 1 or type 2 DM. Long-term efficacy and safety have been evaluated. The ongoing Phase 3 studies provide additional information about the long-term safety of INH.

The Phase 2/3 clinical development program has been conducted in three parts:

- **Phase 2** studies,
- **Phase 3 Group I** studies designed to collect primary evidence of efficacy, and
- **Phase 3 Group II** studies designed specifically to collect long-term safety data.

The **Phase 2** clinical program included 3 controlled clinical trials and indicated favorable efficacy and safety/toleration. Following the end-of-Phase 2 meeting, the **Phase 3 Group I** studies were initiated and

included 7 controlled clinical trials (including one paired study 1001/1002) designed to collect primary evidence of efficacy (i.e. having HbA_{1c} as the primary endpoint). Efficacy results from these trials confirmed and established the efficacy of INH in the treatment of patients with Type 1 and Type 2 DM. Safety results included two findings not identified earlier: (1) an INH-associated decrease in FEV_1 and DLco shown by Pulmonary Function Tests; and (2) an INH-associated increase in insulin antibodies. To further investigate these findings, the **Phase 3 Group II** studies were initiated and included 5 controlled clinical trials focused on safety (i.e. having pulmonary function as the primary endpoint) and 1 controlled trial focused on glycemic pharmacodynamics. At this time, the pediatric development program was paused until the safety database for adult patients was more complete.

One additional **Phase 3b** trial in the treatment of patients with Type 2 DM was initiated prior to NDA submission.

As of 13 December 2004, the integrated safety databases (single-dose clinical pharmacology studies were summarized separately from Phase 2/3 studies) comprised data from 4,961 unique individuals, 3,605 of whom received INH, either alone or in combination with SC insulin or OA. Of these INH-treated patients, 331 were <18 years of age and 3,274 were adults (≥ 18 years of age), 392 of whom were ≥65 years of age. In Phase 2/3 Studies, 2,789 patients received INH, of whom, 291 were <18 years of age and 2,498 were adults (≥ 18 years of age) with 348 patients ≥65 years of age. The majority of adult patients (1698/2498 [68%]) were treated with INH for more than one year, with 821 treated for more than 2 years, 153 treated for more than 3 years, and 15 patients treated for more than 7 years.

Clinical Pharmacology Program

The clinical pharmacology program focused on the assessment of the biopharmaceutics, pharmacokinetics, and pharmacodynamics of INH. Studies were conducted in healthy patients and in patients with type 1 or type 2 DM, as well as in relevant subgroups such as children, the obese, the elderly, smokers, and patients with respiratory tract disorders. Because the metabolism of insulin is well known, no investigations on the distribution and elimination of INH or in subpopulations with renal or hepatic impairment were conducted.

The biopharmaceutic investigations across different populations of patients demonstrated that the relative bioavailability (F) of INH is approximately 10% relative to SC regular insulin in nonsmoking patients with DM. Administration of INH produced dose-separated and dose-linear exposure over the studied dose range of 1 to 6 mg achieved with combinations of nominal 1 mg and 3 mg blisters. Within-patient variability of INH pharmacokinetic parameters was generally comparable to that of SC regular insulin in patients with DM.

Results of the pharmacokinetic and pharmacodynamic investigations showed that in healthy patients, INH is absorbed as rapidly as the SC rapid-acting insulin analog lispro and more rapidly than SC regular human insulin. Accordingly, the onset of action of INH is as rapid as SC insulin lispro and more rapid than SC regular insulin. The duration of action of INH is longer than SC insulin lispro and comparable to SC regular insulin. Similar results were observed in patients with DM where INH was compared with SC regular insulin. The relative bioavailability of INH relative to SC insulin tended to be greater in obese patients than in patients with normal weight, due to lower SC insulin exposure in these obese patients. The studies suggest that in contrast to SC regular insulin, where insulin exposure apparently varies with patient's body mass index (BMI), the absorption of INH is more consistent across the diabetic populations independent of BMI. In general, the rate and extent of INH absorption do not vary significantly across different populations (age, gender, BMI, types of DM) except in smokers.

The clinical pharmacology program supports the preprandial use of INH in the treatment of adults with type 1 or type 2 DM and demonstrates that INH is an easy to use, titratable, and reliable alternative to SC insulin.

Efficacy

INH has been studied in patients with type 1 and type 2 DM across a variety of treatment regimens. In clinical trials of patients with type 1 DM or insulin-using patients with type 2 DM, a regimen of INH three times a day plus SC basal insulin resulted in similar reductions in HbA_{1c} from baseline compared to a regimen of SC short-acting insulin plus SC basal insulin. The percentages of patients achieving HbA_{1c} <8% (the American Diabetes Association treatment Action Level at the time of study conduct) or <7% were comparable to or better than those achieved with the SC insulin regimen.

The efficacy of INH was further confirmed in clinical trials of patients with type 2 DM who had not previously used insulin. A regimen of INH three times a day either alone or in combination with OAs, resulted in a greater improvement from baseline in HbA_{1c} compared to that observed for patients on a regimen of OAs alone. A higher percentage of INH-treated patients (either as monotherapy or in combination with OAs) achieved HbA_{1c} <8% or <7% compared to OA treatment.

Glycemic control (assessed by HbA_{1c}) was maintained for 2 years (24 months) in controlled studies of patients with type 1 and type 2 DM (insulin-using at study entry), for 2 years in controlled studies of patients with type 2 DM (non-insulin-using at study entry), and for prolonged periods of time in uncontrolled extension studies. It is notable that this maintenance of glycemic control occurred despite less frequent contact with the clinic during the extension studies compared to the parent studies.

A significant finding of the clinical development program is that INH is preferred to SC insulin and oral antidiabetic regimens. Patients with type 1 or type 2 DM treated with INH reported significantly higher treatment satisfaction compared to those on a SC insulin regimen on a variety of scales including: Burden, Efficacy, Flexibility, General Satisfaction, Pain, Side Effects, Social Function, and Overall Quality of Life. Patients with type 2 DM treated with INH also reported significantly higher treatment satisfaction on a number of scales (Advocacy, Efficacy, General Satisfaction, Preference, and Overall Satisfaction) compared to those who received OA alone.

The results show that INH is a fully efficacious and preferable alternative to SC insulin.

Safety

INH is safe for use in the target population, namely, adults with DM. The adverse effects of INH use identified during the clinical development program included some expected with the use of insulin, such as hypoglycemia, and others related to the novel pulmonary route of delivery, such as augmented antibody formation and respiratory adverse effects.

Hypoglycemia was the most commonly reported adverse event during the course of the clinical development program. The overall rate of hypoglycemia was lower in patients with type 1 or type 2 DM who received an INH treatment regimen compared to a SC insulin treatment regimen despite similar glycemic control. The overall rate of hypoglycemia was greater in patients with type 2 DM who received INH compared to OA alone, as would be expected when comparing insulin to OA therapy. In both the SC insulin and INH treatment groups, the occurrence of hypoglycemia noticeably declined with time in study.

The pulmonary safety of INH has been extensively characterized.

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 patients, and discontinuations for respiratory adverse events were more common in INH-treated patients. However, respiratory serious adverse events occurred at similar incidence among patients receiving INH or comparator therapies.

Pre- and post-exposure chest x-rays and high resolution computed tomography (HRCT) scans have not demonstrated radiographic evidence of lung pathology associated with INH treatment.

INH treatment is associated with decreases in pulmonary function test results that were small, non-progressive beyond 2 weeks, and reversible following cessation of treatment. Small INH-associated decreases in change from baseline lung function (forced expiratory volume in 1 second [FEV_1] and carbon monoxide diffusion capacity [DLco]) were observed in most of the 3- and 6-month controlled Phase 2/3 studies in the INH development program. Importantly, these decreases were not driven by outlier values among INH-treated patients. In Study 1027, in which FEV_1 and DLco were measured frequently, the INH-associated decreases compared to SC insulin were fully manifest by 2 weeks of treatment and did not progress thereafter. In long-term controlled studies these small INH-associated decreases did not progress with ongoing exposure up to 2 years. Cessation of INH therapy following exposure for as long as 3 years has shown rapid resolution of the INH-associated decreases in FEV_1 and DLco. That these INH-associated decreases in lung function arise early and are small, non-progressive, and reversible supports the overall respiratory safety of INH therapy.

Patients 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 compared to patients without these disorders.

INH treatment is associated with increases in insulin antibody levels greater than those observed among patients treated with SC short-acting insulin (either human insulin or insulin analog) or OAs. Among INH-treated patients, these antibody levels were higher for patients with type 1 than type 2 DM. Among patients with type 2 DM, insulin antibody levels were higher among patients who were insulin using rather than non-insulin-using at baseline. Among patients with type 1 DM, pediatric patients (< 18 years old) and female patients developed higher insulin antibody levels than did older patients or males.

Mean insulin antibody levels in INH-treated patients increased during the first 6 months of therapy and reached a plateau after approximately 6-12 months of therapy. Discontinuation of INH therapy resulted in a decrease in insulin antibody levels. Insulin antibodies associated with INH exposure were qualitatively similar to those induced by SC insulin exposure.

Extensive comparisons of insulin antibody levels with potential clinical sequelae of insulin antibody action were performed using the INH clinical development database. No associations between insulin antibody levels and insulin dose requirements, indices of glycemic control, or adverse clinical outcomes, including decreased pulmonary function test results, have been identified. No consistent safety signals were identified among patients with the highest insulin antibody levels.

Overall, the comprehensive safety results support INH as a safe alternative to SC insulin.

Benefit-Risk

The accepted standard of care for treatment of type 1 DM is intensive insulin therapy. In type 2 DM, no single treatment is suitable for all patients, and secondary failures associated with loss of efficacy are common. Chronic poor control of both type 1 and type 2 DM leads to significant diabetes complications. This has led to a change in the paradigm for treating type 2 DM, which includes the early introduction of insulin to achieve better glycemic control with the aim of preventing long-term complications. However,

all currently available insulin therapies must be delivered using a needle – the same route of administration used since the discovery of insulin in the 1920s.

The injection route for insulin delivery has proven to be a barrier to the attainment of good glycemic control for many patients with DM. Limitations of insulin injection therapy include poor patient acceptability and inconvenience. There is an urgent and pressing need for therapies that can assist glycemic control for patients with DM.

INH, because it delivers insulin by an alternative, non-invasive route of administration, represents the next major therapeutic advance in the progressive history of DM treatment. INH has been evaluated in a comprehensive clinical development program. A total of 3,605 patients (3,274 adults) have received INH. The majority of adult patients (1698/2498 [68%]) were treated with INH for more than one year, with 821 treated for more than 2 years, 153 treated for more than 3 years, and 15 patients treated for more than 7 years.

Results from the clinical development program show that an INH treatment regimen provides a rapid onset of glucose-lowering action and assists glycemic control, as assessed by HbA_{1c}, in patients with type 1 or type 2 DM. INH is well tolerated and safe: the overall incidence of adverse events is generally similar to other insulin diabetes therapies. The most common INH-specific adverse events were seen in the respiratory system. Most respiratory adverse events were mild or moderate in severity and decreased in prevalence with time on study. Patients reported that most cough occurred within seconds to minutes of INH inhalation, indicating that most cough among INH-treated patients was due to a mild irritant effect associated with dry powder inhalation as opposed to an underlying functional or structural etiology. Short-term studies have been associated with decreases in parameters of lung function, FEV_1 and DLco, for patients on INH versus patients not on INH. These INH-associated decreases in lung function have been small in magnitude, occur within weeks, stabilize over time and reverse upon cessation of therapy.

Results also indicate that INH is more acceptable in terms of patient satisfaction and convenience, and was associated with quality of life improvements in physical and psychologic domains.

The benefits of INH are its greater patient acceptance and preference, supporting its potential favorable impact on glycemic control and prevention of long-term diabetic complications. With appropriate labeling of the product, the sponsor's commitment to identifying and implementing an extensive risk management strategy, and taking into consideration the limitations of existing therapies, it is the sponsor's view that the benefits of INH treatment outweigh the risks.

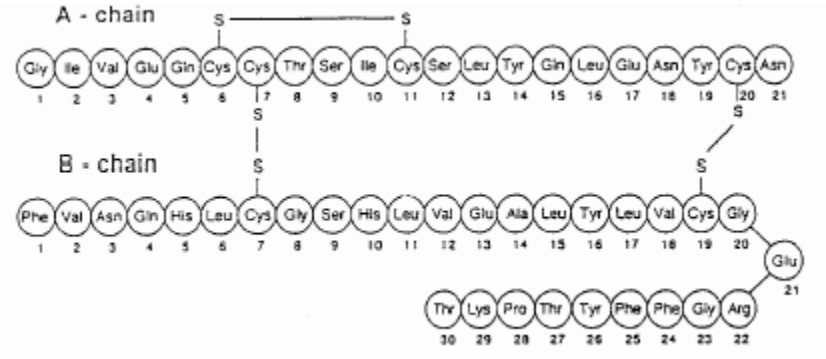
2. PRODUCT DEVELOPMENT RATIONALE

2.1. Pharmacologic Class

EXUBERA® (INH) is a novel treatment system for DM developed by Pfizer in partnership with sanofi-aventis and in collaboration with Nektar Therapeutics. INH, a dry powder formulation of a recombinant human insulin (rhu-insulin) combined with a customized inhalation system, was designed to permit the easy and reproducible delivery of insulin for the control of hyperglycemia. The product is administered immediately prior to meals (within 10 minutes) as part of an individualized DM control regimen that may include other insulin formulations or OAs.

Insulin, a polypeptide hormone produced by the pancreas in response to elevations in blood glucose, is an absolute requirement for the treatment of type 1 DM and is used in the treatment of type 2 DM, as necessary.[1] The structural formula of human insulin is shown in Figure 1. The rhu-insulin used for INH is identical to endogenous human insulin.

Figure 1. Structural Formula of Human Insulin



Insulin's mode of action and metabolism are well understood and will not be described here.

Numerous insulin preparations are available, and most are produced by recombinant DNA technology. They have an identical amino acid sequence to human insulin or are analogs of human insulin and can be differentiated by their time-action profiles. All currently available insulin preparations must be delivered by needle – the same method of administration used since the discovery of insulin in the 1920s.

2.2. Problem Statement

2.2.1. DM Background Information

DM is a group of metabolic diseases characterized primarily by elevated blood glucose levels and secondarily by the development of long-term microvascular and macrovascular complications such as neuropathy, retinopathy, foot ulceration and amputation, heart disease, and renal failure. The root cause of DM is an inherited and/or acquired inability to produce or respond to insulin. The two predominant forms of DM are[2]:

Type 1 DM (ß-cell destruction, usually leading to absolute insulin deficiency)

Type 2 DM (results from a progressive insulin secretory defect on the background of insulin resistance)

DM is a widespread and growing problem. In 1995, approximately 135 million adults worldwide were estimated to have DM, and current trends suggest that number will increase to 300 million by 2025.[3] Type 2 DM is the most commonly occurring form of DM and accounts for 85-95% of DM cases.[4] DM is a leading cause of death, non-traumatic amputations, end-stage renal disease, and blindness, and people with DM experience greater disability and poorer quality of life than the general population.[5] The estimated annual direct cost of DM in 1998 varied from US $0.54 billion in Denmark to US $60 billion in the United States.[6] More recently, DM costs in the US for 2002 were assessed at $132 billion in medical expenditures and lost productivity.[7] On a per-family basis, costs are estimated to range from 10-25% of family income around the world.[8] Hence, DM places a tremendous burden on both the individual and society. Much of this burden can be directly attributed to the development of the long-term complications identified above.[9, 10, 11]

2.2.2. Importance of Glycemic Control in DM

Over the past several decades, it has become clear that chronic hyperglycemia is an important causative factor in the development of many diabetic complications. The Diabetes Control and Complications Trial (DCCT)[12] and the Stockholm Diabetes Intervention Study[13] showed that improvement of glycemic control by an intensive insulin treatment regimen using multiple daily insulin injections delayed the onset and slowed the progression of microvascular complications in individuals with type 1 DM. The DCCT further showed that the benefits of improved glycemic control occurred over the range of glycated hemoglobin (HbA_{1c}) values suggesting that, at any HbA_{1c} level, improvement is beneficial.[14] Similar benefits of tight control have been demonstrated in the type 2 population in the UK Prospective Diabetes Study (UKPDS)[15], which compared intensive insulin or sulfonylurea treatment to diet, and in the Kumamoto Study[16], which evaluated intensive insulin treatment. Furthermore, the cost effectiveness of intensive treatment has been demonstrated in both type 1 and type 2 DM.[17,18,19]

A reduction in cardiovascular events along with improved glycemic control was also noted in the DCCT and UKPDS, but the results were not statistically significant. A subsequent epidemiological analysis of the UKPDS cohort showed a statistically significant effect of HbA_{1c} lowering with an approximate 14% reduction in myocardial infarction for every 1% reduction in HbA_{1c}.[20] Some potential disadvantages of intensive treatment were also identified: increased weight gain and hypoglycemia.

These studies also highlight the importance of insulin as part of a treatment regimen for patients with type 2 DM in order to improve glycemic control. Additional support for the role of insulin in the treatment of type 2 DM comes from a better understanding of the disease's natural history. It is now clear that insulin deficiency is as much a part of the development of type 2 DM as is insulin resistance and that type 2 DM is characterized by a progressive deterioration of glycemic control due to β-cell dysfunction.[21,22]

The UKPDS has shown that within 3 years following diagnosis, 50% of patients with type 2 DM will need more than one pharmacological agent to sustain glycemic control, and that by 9 years post-diagnosis 75% of patients will require multiple therapies with a majority of patients requiring insulin.[23,24] There is also evidence to suggest that early provision of insulin therapy can help correct underlying pathogenetic abnormalities in type 2 DM and improve glycemic control.[25] This has resulted in recommendations by some experts for intensive treatment with insulin to be initiated early in the course of type 2 DM or when diet and exercise fail.[26,27]

Despite these important findings and their incorporation into current guidance on target HbA_{1c} levels[28], many patients do not achieve good glycemic control. In the United States, according to surveys, an estimated 18% of patients with DM have an HbA_{1c} level greater than 9.5%, and less than half (42%) of patients achieve the current recommended American Diabetes Association target (HbA_{1c} <7%).[29,30]

Furthermore, the situation is worsening. A recent review has described the changes in demographics, drug treatment and glycemic control among patients with type 2 DM diagnosed between the 1988-1994 and the 1999-2000 National Health and Nutrition Examination Surveys (NHANES).[31] During this period, the number of prevalent cases increased by 2 million, and the percentage of patients with HbA_{1c} <7% declined from 44.5% to 35.8%.

Expert panels including the American Association of Clinical Endocrinologists have further suggested that the target goal should be lowered to more closely approximate a normal HbA_{1c} of 6.0% (target of 6.5% specified for type 2 DM).[32] Even fewer patients reach this target with current therapies.

2.2.3. Barriers to Achievement of Good Glycemic Control

In many patients, the limitations of current insulin therapies may prevent achievement of optimal glycemic control.

Like most therapeutic proteins, insulin is delivered by injections, which are associated with poor patient acceptance, inconvenience, and anxiety. Zambanini et al., in a survey of 115 patients with type 1 or type 2 DM, found that 25% of patients experienced anxiety due to injections and 14% of patients avoided injections due to anxiety.[33] Patients with anxiety due to injection fears may also perform fewer home glucose measurements resulting in poorer self-management and poorer glycemic control.[34] The result may be reduced compliance or adherence to insulin injection regimens, especially regimens that depend on multiple daily injections of insulin, or a reluctance to initiate such regimens.[35] In a systematic review undertaken to assess the extent of poor adherence and persistence with diabetes medication and to link adherence rates with glycemic control, Cramer concluded that many patients are poorly adherent with prescribed medication, which may result in poor glycemic control.[36] Indeed, more than 50% of US patients with type 1 DM use a suboptimal program of only 1 to 2 insulin injections per day.[37] Furthermore, patients with type 2 DM may defer initiating treatment with insulin until OA therapy has ceased to be effective despite maximum doses over a prolonged period of time, during which patients have had continued poor glycemic control.[38]

Another characteristic of injectable insulin that may impact achievement of glycemic control is its considerable intrasubject variability of metabolic effect (absorption and activity), due to factors such as deterioration of formulation potency, leakage, injection site characteristics, presence of lipoatrophy/lipohypertrophy, and skin temperature. Intrasubject variability has been estimated as ranging from 15-25% for SC regular insulin and from 25-35% for long-acting insulin.[39]

In addition, many currently used insulin therapies do not appropriately match the physiological insulin response seen in people without DM.[40] One commonly used regimen, the split-mixed, employs a combination of short-acting regular insulin and an intermediate insulin given twice daily. Because regular insulin must be administered 30-45 minutes before meals, this regimen requires careful timing of injections and meals. As a result of an overlap in time of effect for regular and neutral protamine hagedorn (NPH) insulin, patients may be predisposed to hypoglycemia in the mid-morning.[41] The adoption of an intensive regimen using newer premixed insulins and insulin analogs that more closely mimic the normal mealtime burst of insulin and which allow greater flexibility regarding timing of meals are a recent advance.[41,42] Nevertheless, such regimens necessitate multiple daily injections.

2.2.4. Role of Inhaled Insulin in DM Treatment

Because long-term control of blood glucose remains a challenge due to the limitations of injectable insulin therapy, there is a need for more acceptable modes of insulin delivery. As shown in this briefing document, INH is comparable to SC regular insulin and superior to OA in enabling patients with DM to achieve and maintain glycemic control. Because of its efficacy and delivery method, it is highly

acceptable to patients and is preferred to alternative treatments. In addition, because it is rapid-acting with a faster onset of action than SC regular insulin, it can replace pre-meal rapid-acting insulin injections. Thus, INH offers dosing just before meals and optimal postprandial glucose control without the disadvantages of injections. For this reason, INH can overcome barriers to optimal glycemic control both in those who have an absolute requirement for insulin, and in those who are candidates for adding it to their treatment regimen but have been reluctant to start injection therapy.

2.3. Scientific Rationale and Product Development

Since the introduction of subcutaneous insulin injection therapy, alternative, noninvasive routes of insulin delivery have been under active investigation. These alternatives, which include nasal, rectal, ocular, vaginal, transdermal, oral, buccal, and pulmonary routes, have been detailed in a number of recent reviews.[43,44,45,46,47,48,49] While some of these routes remain under investigation, others have lost viability, and the pulmonary route has emerged as the most promising alternative to SC injections. The emergence of the pulmonary route as a frontrunner is due largely to characteristics of the alveoli. Key features include an exceptionally large absorptive area (approximately 100 m^2), adequate permeability to macromolecules, extensive vascularization, minimal mucociliary clearance mechanisms, and lower chemical and enzymatic degradation (compared to the gastrointestinal system).[50] These features allow fast absorption of insulin into the bloodstream, resulting in rapid onset of action after inhalation, which is important in keeping peak glucose levels at more physiological values.

Although the feasibility of pulmonary delivery of insulin was demonstrated as early as 1925, exploitation of this method had to await (1) the understanding that particle size and density are important determinants of efficient insulin delivery and (2) technological advances in controlling particle size that allowed reliable and sufficient insulin delivery to the alveoli.

The drug substance is HMR4006, a rhu-insulin produced from the host-vector system *Escherichia coli* K12 I35/pINT90d by sanofi-aventis. The potency and impurity profile is comparable to other human insulins and meets United States and European pharmacopeial requirements.

The drug product, insulin powder for inhalation, consists of rhu-insulin spray dried from an aqueous solution containing insulin, mannitol, glycine, sodium citrate, and sodium hydroxide. The spray-dried powder is filled into single-dose blisters containing 1 mg or 3 mg insulin. These doses were chosen based on both technical and clinical practice considerations. The blisters are used in conjunction with a proprietary inhaler that is reusable, mechanical, contains no batteries or electronics, and requires no external power source. Aerosolization is independent of patient inspiratory effort.

During the development program, changes to the formulation and inhaler have been undertaken to optimize the product performance. These included changes in the formulation from 20% to 60% insulin, while maintaining the same excipients, and a change of the insulin drug substance manufacturer from Eli Lilly to sanofi-aventis. The drug substance supplied by Lilly was used primarily in the 20% formulation as the 1 mg packaged strength with the 3 mg packaged strength comprised of the 60% formulation. Additionally, there was a change from the P2 to P3 inhaler versions. Each change occurring during development has been carefully studied and documented. The form, fit, and function of the insulin pulmonary inhaler (P3) have remained unchanged throughout the clinical development program and have been shown to be highly reliable in the clinic.

Early Phase 1, and parent Phase 2 studies (102, 103, 104) used the 20% formulation. All clinical studies conducted after February 1999, including biopharmaceutic, clinical pharmacology, Phase 2 extension studies (102E, 103E, 104E, 1036), and all Phase 3 studies (106, 107, 108, 109, 110, 1001, 1002, 1009,

1017, 1022, 1026, 1027, 1028, 1029, and 1030), used the 60% formulation. Throughout the submission, this formulation is referred to as the Phase 3 formulation.

Because the aerodynamic particle size distribution (APSD) of the emitted aerosol cloud determines where the dose deposits in the respiratory tract thereby influencing absorption, APSD measurements were performed during development for product characterization purposes. Several parameters were measured including Mass Median Aerodynamic Diameter (MMAD), Fine Particle Dose (FPD), and Emitted Dose (ED), and these were used to assess the relationship between *in vitro* aerosol performance and *in vivo* systemic insulin exposure.

Early in the development program, ED, which measures the dose delivered from the inhaler to the patient, was used to monitor the impact of major formulation changes. It later became clear that FPD, which defines the mass of particles within the respirable range, more accurately reflects the effective dose reaching the lungs compared to ED. The INH program has focused on a cutoff value of FPD <3.3 μm, rather than 5 μm typically used for locally- acting inhaled medications, based on published data[49] indicating the importance of smaller particle sizes on delivery to the distal lung for systemic absorption.

2.4. Nonclinical Development Program

Pharmacology studies demonstrating the systemic bioavailability of insulin inhalation powder and its subsequent glucose lowering effect were conducted in rats, dogs, and monkeys. Toxicology studies evaluated the potential toxicity of insulin inhalation powder and excipients to the respiratory tract. One- and 6-month toxicology studies in rats and monkeys used the 20% formulation. An additional 1-month rat study was conducted using the 60% formulation to confirm toxicological equivalence of the two insulin formulations. These studies were supported by additional studies using injected Lilly and sanofi-aventis rhu-insulins. In addition, lung cell proliferation indices and insulin antibody titers were measured.

There were no toxicological findings relevant to human systemic or pulmonary risk with the insulin inhalation powder at doses up to approximately 40X and 4X for rat and monkey compared to the clinical starting dose of 0.15 mg/kg/day. It is recognized that because doses for patients with DM are individually titrated based on patient need, a range of doses both above and below this value will be used in clinical practice. The apparently low safety margins of this product, compared to those for small molecule drugs, are dictated by the dose-limiting effect of hypoglycemia.

2.5. Clinical Development Program

The clinical development program for INH is comprehensive: studies have been conducted in patients with type 1 and type 2 DM, long-term efficacy and safety have been evaluated, and both the elderly and children have been included, although an indication in children is not sought at this time due to limited long-term, controlled safety data in this population. The program comprises 32 single-dose clinical pharmacology studies and 23 Phase 2/3 studies (including a multi-dose, 6-month, exploratory clinical pharmacology study [Study 1026]). All clinical pharmacology studies and 17 Phase 2/3 studies are complete. The ongoing Phase 3 studies provide additional information about the long-term safety of INH.

Note: clinical studies referenced in this document are identified by numbers of two different types: A217XXXX or 217-XXX. For simplicity, the prefix (A217 or 217-) is not used.

2.5.1. Clinical Pharmacology Program

Since insulin's mode of action and metabolism are well known, and efficacy is assured once it is delivered to the circulation, the INH clinical pharmacology program was designed to support an

understanding of insulin's pharmacokinetics and pharmacodynamics when delivered via the pulmonary route, as well as to support product characterization and development.

Fifteen clinical pharmacology studies conducted in late development used the same insulin formulation and inhaler as those used in the Phase 3 trials. These studies characterize the pharmacokinetics and pharmacodynamics of INH in healthy patients, patients with type 1 and type 2 DM, and in populations of special interest such as smokers, patients with chronic obstructive pulmonary disease (COPD), the elderly, and the obese. The studies are listed by type in the following table:

Table 1. Clinical Pharmacology Studies using the Phase 3 Formulation

Study Type/Category	Study Number
Pharmacokinetics and Relative Bioavailability	
Healthy Patients	016, 017, 023, 1005, 1006, 1012, 1014 1015, 1016, 1020
Patients with Type 1 DM	021, 018
Patients with Type 2 DM	1003, 1004, 1007
Special Populations	
Children and Adolescents with Type 1 DM	018
Elderly, Obese Patients with Type 2 DM	1004
Gestational DM	1007
Nondiabetic Patients with COPD	1005
Smokers	
Nondiabetic	016, 1020
Type 2 DM	1003
Japanese Patients	023, 1016
Pharmacodynamics	
Healthy Patients	017, 1016
Patients with DM	1003, 1004, 1007, 021, 1026 (Phase 3)

Not listed in the table above are 17 studies that used early powder formulations and inhaler versions. Their results guided the development of optimal insulin formulations, inhaler, and dosing instructions.

2.5.2. Phase 2/3 Clinical Development Program

The INH Phase 2/3 program was designed to demonstrate the efficacy and safety of INH in insulin-requiring patients with type 1 or type 2 DM and patients with type 2 DM whose disease is poorly controlled by OA(s) or by diet and exercise. Seventeen Phase 2/3 studies (including the multi-dose clinical pharmacology Study 1026) with INH have been completed, and six studies (Studies 1017, 1022, 1028, 1029, 1030, and 1036) were ongoing as of the safety database cut-off date. For accounting purposes, Studies 102E, 103E, and 104E (the original extensions of Studies 102, 103, and 104) are considered completed although they have been combined into Study 1036, which is ongoing.

The Phase 2/3 clinical development program has been conducted in three parts:

- **Phase 2** studies,
- **Phase 3 Group I** studies designed to collect primary evidence of efficacy, and
- **Phase 3 Group II** studies designed specifically to collect long-term safety data.

The **Phase 2** clinical program was initiated in 1996 and included 3 exploratory controlled clinical trials:

- Study 102 – a 12-week (3-month) controlled trial comparing INH to SC insulin in the treatment of patients with Type I DM;

- Study 103 – a 12-week (3-month) controlled trial comparing INH to SC insulin in the treatment of patients with insulin-requiring Type 2 DM;
- Study 104 – a 12-week (3-month) controlled trial comparing INH to oral agents in the treatment of patients with Type 2 DM failing oral agents.

Based on the results of the Phase 2 clinical program, an End-of-Phase 2 meeting was held with FDA on 03 June 1998. Following a review of the Clinical Pharmacology and Phase 2 results, agreement was reached with FDA on the design parameters for a Phase 3 program that included 5 controlled 24-week (6-month) clinical trials with HbA_{1c} as the primary endpoint (2 studies vs. SC insulin in patients with type 1 DM [one of which would use an intensive control regimen], 1 study vs. SC insulin in patients with insulin-requiring type 2 DM, and 2 studies in patients with Type 2 DM [one in patients failing oral agents and one in patients failing diet and exercise]). The program was also to include an uncontrolled extension trial of at least one-year duration. The main Phase 3 program was agreed to permit enrollment of patients aged 12-65 years for type 1 DM and aged 35-80 years for type 2 DM. In addition, agreement was reached on the conduct of a single 12-week (3-month) controlled trial vs. SC insulin in the treatment of pediatric patients aged 6-11 years. It was concluded that results from this trial would be included in the INH product label. Following this meeting the Phase 3 Group I studies were initiated in 1999 and included 7 controlled clinical trials focused on efficacy (i.e. having HbA_{1c} as the primary endpoint):

Phase 3 – Group I Studies (Designed to Collect Primary Evidence of Efficacy)

- Study 106 – a 24-week (6-month) controlled trial comparing INH to SC insulin in the treatment of patients with type 1 DM;
- Study 107 – a 24-week (6-month) controlled trial comparing INH to SC insulin in the treatment of patients with type 1 DM using an intensive insulin regimen;
- Study 108 – a 24-week (6-month) controlled trial comparing INH to SC insulin in the treatment of insulin-requiring type 2 DM;
- Study 109 – a 12-week (3-month) controlled trial comparing INH to oral agent in the treatment of patients with type 2 DM failing oral agents;
- Study 110 – a 12-week (3-month) controlled trial comparing INH to oral agent in the treatment of patients with type 2 DM failing diet and exercise;
- Study 1001/1002 – two paired 24-week (6-month) controlled trials comparing INH to oral agent in the treatment of patients with type 2 DM failing sulfonylurea (Study 1001) or failing metformin (Study 1002). Subsequent protocol amendments have extended the duration of these trials to, at first, 52-weeks (1-year) and then 104-weeks (2-years). These protocol amendments were put in-place after learning of the INH-associated pulmonary function test changes and, logistically, were not in-place at all study sites when participating patients completed the 6-month trial period. While a subset of patients were able, therefore, to participate in the 52-week and 104-week protocol amendments, all randomized patients participated in the initially planned for 24-week (6-month) trial period.
- Study 1009 – a 12-week (3-month) controlled trial comparing INH to SC insulin in the treatment of pediatric patients (aged 6-11 years) with type 1 DM.

Efficacy results from these Phase 3 Group I trials confirmed and established the efficacy of INH in the treatment of patients with type 1 and type 2 DM. Safety results included two findings not identified in the Phase 2 studies: (1) an INH-associated decrease in FEV_1 and DLco shown by sequential pulmonary function tests and (2) an INH-associated increase in insulin antibodies.

Based on the results of the Phase 3 Group I and additional Clinical Pharmacology trials, a meeting was held with FDA on August 18th, 2000. Following a review of the trial results, FDA stated that, in the

absence of a concurrent standard-care control group, it would be very difficult to interpret the significance of the safety findings. FDA stated that at least one-year well-controlled safety data were required for an NDA submission. FDA invited the submission of protocols for review. Subsequently, protocol outlines were provided and a meeting focused on INH pulmonary safety was held with FDA on April 16th, 2001. At this meeting, guidance was provided that a proposed additional well-controlled long-term database should include patients with chronic obstructive pulmonary disease (COPD) [100 patients], patients with asthma (100 patients), patients with type 1 DM and no underlying lung disease (100 patients) – all studied for 1 year in a controlled fashion. In addition, data from the protocol extension of Studies 1001/1002 would provide additional information on the long-term pulmonary safety of INH.

Following this meeting, the Phase 3 Group II studies were designed, protocols were shared with FDA, and the trials were initiated in 2002. The Phase 3 Group II studies included 5 controlled clinical trials focused on safety (i.e. having pulmonary function as the primary endpoint) and 1 controlled trial focused on glycemic pharmacodynamics:

Phase 3 Group II Studies (Designed Specifically to Collect Long-term Safety Data)

- Study 1022 – a 104-week (2-year) controlled trial comparing INH to SC insulin in the treatment of patients with type 1 DM and without underlying lung disease. A subsequent protocol amendment has extended the duration of these trials to 5-years – with the addition of a 3-year treatment period following the initial 2-year treatment period and a 6-month withdrawal period;
- Study 1029 – a 104-week (2-year) controlled trial comparing INH to SC insulin in the treatment of insulin requiring patients with type 2 DM. A subsequent protocol amendment has extended the duration of these trials to 5-years – with the addition of a 3-year treatment period following the initial 2-year treatment period and a 6-month withdrawal period;
- Study 1028 – a 52-week (1-year) controlled trial comparing INH to SC insulin in the treatment of patients with asthma and type 1 or insulin-requiring type 2 DM;
- Study 1030 – a 52-week (1-year) controlled trial comparing INH to SC insulin in the treatment of patients with COPD and type 1 or insulin-requiring type 2 DM;
- Study 1027 – a 24-week (6-month) controlled trial comparing INH to SC insulin with frequent measurement of Pulmonary Function during a 12-week (3-month) treatment period and a subsequent 12-week (3-month) withdrawal period in patients with type 1 DM;
- Study 1026 – a 24-week (6-month) controlled trial comparing INH to SC insulin with measurement of glycemic pharmacodynamics in patients with type 1 DM.

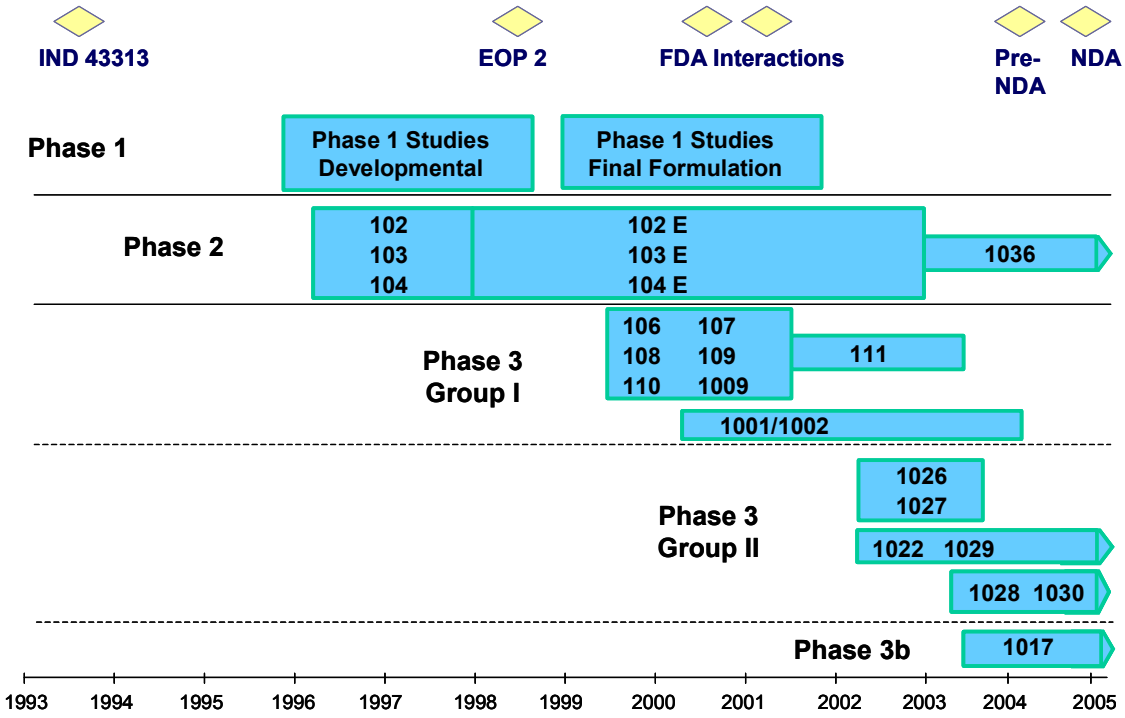
The program was also to include uncontrolled extension trials (Studies 111 and 1036) of up to 36 months and of >7 years duration, respectively. Study 111 was additionally amended to include a controlled, 24-week (6-month) randomized withdrawal period comparing INH to SC insulin.

At this time, the pediatric development program was paused until the safety database from adult patients was more complete.

One additional **Phase 3b** 52-week (1-year) controlled trial focusing on efficacy and comparing triple oral therapy to INH combined with one or 2 oral agent(s) in the treatment of patients with Type 2 DM failing sulfonylurea and metformin was initiated prior to NDA submission.

An overview of the clinical development program is shown in Figure 2 and key features of the Phase 2/3 studies are in Table 2.

Figure 2. Clinical Development Program



EOP = end of Phase 2

Table 2. Phase 2/3 Clinical Studies

Study No. (Duration) [N]*	Type Age (years)	Treatment Groups	Primary Objective
Phase 2 Studies			
102 (12 weeks) [72]	Type 1 DM 18-55	TID INH + bedtime UL Pre-study SC regimen	Exploratory efficacy - Similarity of change from BL HbA1c %
103 (12 weeks) [56]	Type 2 DM insulin-using 35-65	TID INH + bedtime UL Pre-study SC regimen	Exploratory efficacy - Similarity of change from BL HbA1c %
104 (12 weeks) [69]	Type 2 DM failing OA 35-65	TID INH + pre-study OA Pre-study OA (SU and/or MET)	Exploratory efficacy - Ability of INH regimen to lower HbA1c by >1%
Phase 3 Group I Studies (Designed to Collect Primary Evidence of Efficacy)			
106 (24 weeks) [334]	Type 1 DM 12-65	TID INH + bedtime UL SC regimen (BID REG + BID NPH)	Efficacy - Non-inferiority of INH to SC regimen in change from BL HbA1c %
107 (24 weeks) [327]	Type 1 DM 12-65	TID INH + BID NPH SC regimen (TID REG + BID NPH)	Efficacy - Non-inferiority of INH to SC regimen in change from BL HbA1c %
108 (24 weeks) [298]	Type 2 DM-insulin-using 35-80	TID INH +bedtime UL SC regimen (BID REG + BID NPH)	Efficacy - Non-inferiority of INH to SC regimen in change from BL HbA1c %

Study No. (Duration) [N]*	Type Age (years)	Treatment Groups	Primary Objective
109 (12 weeks) [306]	Type 2 DM failing OA 35-80	TID INH (monotherapy) TID INH + pre-study OA Pre-study OA (SU or REP and MET or GLZ)	Efficacy - Superiority of INH regimens to OA in change from BL HbA1c %
110 (12 weeks) [143]	Type 2 DM failing D/E 35-80	TID INH BID ROS	Efficacy - Superiority of INH to OA in patients (%) achieving HbA1c <8%
1001† (24/104 weeks) [423]	Type 2 DM-failing SU 35-80	TID INH + SU MET + SU	Efficacy - Superiority/non-inferiority of INH regimen to OA in change from BL HbA1c %/ Safety
1002† (24/104) weeks) [470]	Type 2 DM-failing MET 35-80	TID INH + MET GLI + MET	Efficacy - Superiority/non-inferiority of INH regimens to OA in change from BL HbA1c %/Safety
1009 (12 weeks) [120]	Type 1 DM 6-11	TID INH + OD or BID NPH or UL SC insulin BID + OD or BID NPH or UL	Efficacy - Similarity of INH to SC regimen in change from BL HbA1c %
Phase 3 Group II Studies (Designed Specifically to Collect Long-term Safety Data)			
1022‡ (2 + 3 years) [580]	Type 1 DM 18-65	TID INH + bedtime or BID NPH or UL or bedtime insulin GLA SC regimen (BID or TID REG or LIS or ASP + QD or BID NPH or UL or QD GLA)	Safety
1029‡ (2 + 3 years) [625]	Type 2 DM insulin-using 35-75	TID INH + bedtime or BID NPH or UL or bedtime insulin GLA SC regimen (BID or TID REG or LIS or ASP + QD or BID NPH or UL or QD GLA)	Safety
1028‡ (1 year) [95]	Type 1 and 2 DM with asthma 18-65 (type 1) 18-75 (type 2)	INH regimen SC insulin regimen	Safety
1030‡ (1 year) [57]	Type 1 and 2 DM with COPD 30-65 (type 1) 30-75 (type 2)	INH regimen SC insulin regimen	Safety
1026 (24 weeks) [45]	Type 1 DM 18-50	TID INH + BID NPH SC regimen (TID REG + BID NPH)	Pharmacodynamic -change from baseline postprandial glucose
1027 (24 weeks) [226]	Type 1 DM 25-65	TID INH + NPH or UL or GLA SC regimen (BID or TID SC REG or LIS + QD or BID NPH or UL or QD GLA)	Safety (lung function)

Study No. (Duration) [N]*	Type Age (years)	Treatment Groups	Primary Objective
111 (to 36 months) [1290]	Type 1 and 2 DM Phase 3 completers** Long-term safety	TID INH + long-acting insulin or other antidiabetic agent, as appropriate	Safety
1036‡ > 7 years [173]	Type 1 and 2 DM Phase 2 completers** Long-term safety	TID INH + other antidiabetic agent, as appropriate	Safety
Phase 3b			
1017‡ (1 year) [74]	Type 2 DM- failing SU+MET 18 – 80	ROS + MET + SU INH + MET + SU, INH + MET	Efficacy - change from BL HbA1c %

* N = number of patients treated (INH-treated patients only in Studies 1036 and 111) or randomized (Study 1017)
** Study 1036 combines parent plus extension data from parent Studies 102, 103, and 104 and corresponding extension studies 102E, 103E, and 104E for patients who completed Studies 102, 103, or 104. Study 111 includes parent plus extension study data for patients who completed Studies 106, 107, 108, 109, 110, and 1009. Study 111 was additionally amended to include a controlled, 24-week (6-month) randomized withdrawal period comparing INH to SC insulin.
†The 6-month interim analyses of Studies 1001 and 1002 had dual objectives: noninferiority in low stratum patients (HbA1c ≥8% to ≤9.5% at entry) and superiority in high stratum patients (HbA1c >9.5 to ≤12% at entry).
‡Ongoing studies: 1022 and 1029 have planned interim analyses at 1 year and 2 years. Study 1028 had planned interim analyses on patients who completed up to and including 26 weeks of treatment as of 10 September 2004 and who completed up to and including 52 weeks of treatment as of 31 January 2005. In the first interim analysis, all treated patients including those with treatment beyond 26 weeks were included in the analysis of standard safety measures. Study 1030 had planned interim analyses on patients who completed up to and including 26 weeks of treatment as of 16 September 2004 and who completed up to and including 52 weeks of treatment as of 10 February 2005. In the first interim analysis, all treated patients including those with treatment beyond 26 weeks were included in the analysis of standard safety measures.
ASP =insulin aspart; BID=twice a day; BL= baseline; COPD=chronic obstructive pulmonary disease; D/E=diet and exercise; GLA=glargine; GLI = glibenclamide; GLZ=glitazone; INH=inhaled insulin; LIS=lispro; MET=metformin; NPH=neutral protamine hagedorn SC insulin; OA=oral agent; REG=regular insulin; REP = repaglinide; ROS=rosiglitazone; SC=subcutaneous insulin; SU=sulfonylurea; TID=three times a day; UL=Ultralente® SC insulin

Because a pediatric indication is not sought at this time, the results of Study 1009 and results for adolescent patients (age <18 years) from Studies 106 and 107 are not discussed unless otherwise noted.

2.5.3. Clinical Development Safety Database

Routine safety data and serious adverse event (SAE) data are presented based on a cut-off date of 13 December 2004. Safety data for all Phase 2/3 studies, with the exception of Studies 1017, 1028, and 1030, are reported on an integrated basis. Study 1017 is a Phase 3b study at an early stage of active treatment and with blinded data. Studies 1028 and 1030 include patients who are not representative of the general population of patients with DM. Interim results for Studies 1028 and 1030 are included as Appendix 1**.** Data for all Phase 1 studies are reported on an integrated basis (separately from data for Phase 2/3 studies) with the exception of Study HA001, a pilot, proof-of-concept study conducted by Nektar.

The integrated safety databases comprise data from 4,961 unique individuals, 3,605 of whom received INH. Of these 3,274 were adults (≥ 18 years of age) and 392 were ≥65 years of age (Table 3).

Table 3. Number of INH-treated Patients by Age Groups in INH Clinical Development Program

	All Patients	Patients ≥18 years	Patients ≥65 years	Patients <18 years
Total	3605	3274	392	331
Phase 2/3 Studies	2789	2498	348	291
Type 1 DM	1209	918	3	291
Type 2 DM	1580	1580	345	0
Phase 1 Studies	821	776	44	45
Healthy/Non-DM	696	676	21	20
DM	125	100	23	25

5 Patients <18 years received INH as participants in both Phase 1 and Phase 2/3 studies.
Cutoff date: 13 December 2004

In Phase 2/3 studies, the majority of adult patients with type 1 (66.5%) and type 2 DM (68.9%) have been treated with INH for more than one year. Median exposure durations were 20.9 and 20.7 months for patients with type 1 and type 2 DM, respectively. Exposure of adult patients to INH in the Phase 2/3 clinical development program is shown by various treatment durations in Table 4.

Table 4. Duration of Exposure to Inhaled Insulin by Diabetes Type: Adult Patients in All Phase 2/3 Studies

	Number (%) of Patients		
Exposure (Months)	**Type 1 N=918**	**Type 2 N=1580**	**Total N=2498**
>0	918 (100.0)	1580 (100.0)	2498
>3 months	774 (84.3)	1463 (92.6)	2237
>6	684 (74.5)	1295 (82.0)	1979
>12	610 (66.5)	1088 (68.9)	1698
>24	304 (33.1)	517 (32.7)	821
>36	48 (5.2)	105 (6.7)	153
>84	9 (1.0)	6 (0.4)	15
Median exposure (months)	20.90	20.65	
Overall exposure (patient-months)	17893.6	31928.9	

Cutoff date: 13 December 2004

2.6. Regulatory Agency Advice

On 1 September 1993, Inhale Therapeutic Systems submitted IND 43,313 to the Division of Endocrine and Metabolic Drug Products for the indication of treatment of DM. Sponsorship of the IND was transferred to Pfizer on 17 May 1995.

An End-of-Phase 2 meeting was held on 3 June 1998 to review the completed Phase 2 program results and discuss the proposed Phase 3 program. Other meetings were held on 18 August 2000, 16 April 2001, 29 November 2001, 5 April 2002, and 15 November 2002 to discuss various aspects of the evolving safety evaluation plan. In December 2000, the Division deferred the provision of a Written Pediatric Request until the safety and efficacy review of adult patient data was complete. At the pre-NDA meeting held on 9 June 2004, the Division indicated that there were sufficient efficacy and general safety data to allow review of the NDA.

A similar and parallel dialogue was held with regulatory agencies in Europe; and has resulted in submission of an MAA in Europe in February 2004.

3. OVERVIEW OF BIOPHARMACEUTICS

Studies that provide important information relevant to bioavailability, bioequivalence (BE), dose proportionality, and dosage form equivalence are discussed in this section. All studies discussed below used the Phase 3 formulation, unless otherwise noted.

3.1. Bioavailability

In fasted healthy patients, the mean bioavailability of INH estimated relative to SC regular insulin (F) ranged from 4% to 9% (Table 5).

Table 5. Mean Relative Bioavailability of Inhaled Insulin in Healthy Patients

Study	N	Dose INH	SC	F[a] % (CV%)	95% CI
017[b]	15	2x3 mg	18 U	9[h] (40%)[c]	
023[d]	12	1x1 mg	6 U	6.1[e](NA)	(3.8, 9.7)
	12	2x1 mg	6 U	8.9[e](NA)	(5.6, 14)
016[f]	30	2x1 mg	6 U	4.9 (NA)	(3.2, 7.5)
1006	26	3x1 mg	9 U	5.8[g] (NA)	NA
	26	1x3 mg	9 U	4.2[g] (NA)	NA
1014	76	1x3 mg CLN	9 U	6.7 (49)[c]	NA
	76	1x3 mg COM	9 U	6.6 (44)[c]	NA
1015	76	1x1 mg CLN	3 U	6.4 (54%)[c]	NA
	76	1x1 mg COM	3 U	5.8 (58%)[c]	NA
1016	16	1x1 mg		5.7[h] (65%)[c]	NA
	16	1x3 mg		5.9[h] (54%)[c]	NA
	16	2x3 mg	12 U	6.9[h] (55%)[c]	NA
1020	10	1x1 mg	3 U	8[f] (NA)	NA

Means are geometric; CLN = clinical scale; COM = commercial scale
a F: Relative bioavailability, assessed from ratio of Inhaled versus SC and calculated from dose standardized AUC0-360 values.: F=[(AUCINH/(DoseINH*27.5)]/(AUCSC/DoseSC)*100%
b Euglycemic clamp study
c CV of arithmetic mean; results calculated from C-peptide corrected AUC values
d Results for male Caucasian patients, calculated from C-peptide corrected insulin concentrations
e calculated from AUC0-480
f Results for nonsmokers
g Adjusted geometric mean
h calculated from AUC0-600

In various types of patients with DM (including children and adolescents with type 1 DM (Study 018), adults with type 1 DM (Study 021), adults with type 2 DM (Study 1003), elderly/obese patients with type 2 DM (Study 1004), and patients with gestational or pregestational type 2 DM (Study 1007), the mean bioavailability of INH relative to SC regular insulin was approximately 10% (range 8-11%)[Table 6].

Table 6. Mean Relative Bioavailability of Inhaled Insulin in Patients with Diabetes Mellitus

Study	N	Dose INH	SC	F[a] (%)	95% CI (%)
Type 2 DM, fasting					
1003[b]	14	6 mg	18 U	11[b]	
1004[c]	20	4 mg	12 U	11	7, 15
1007[d]	12	3 mg	9 U	10	
Type 1 DM, postprandial					
021[e]	4	3 mg	9 U	10.7	
	13	4 mg	12 U	9.2	
	3	6 mg	18 U	8.2	
018[e] (6-11yr)	10	1, 2, 3 mg	3, 6, 9 U	8.4	
018[e] (12-17yr)	12	2, 3, 4 mg	6, 9, 12 U	8.8	

Means are geometric
a F: Relative bioavailability, assessed from ratio of Inhaled versus SC and calculated from dose standardized AUC0-360 values; F = (AUCINH/(DoseINH·27.5))/(AUCSC/DoseSC) 100%
b Euglycemic clamp study; data for nonsmokers; F calculated from AUC0-480; adjusted geometric mean
c In elderly, obese patients under fasting condition
d In patients with gestational or pregestational type 2 DM
e Inhaled insulin was administered 5 to 10 minutes before meal

INH bioavailability relative to SC insulin tends to be higher in patients with type 2 DM compared to patients with type 1 DM. Patients with type 2 DM are heavier and typically have greater amounts of subcutaneous body fat around injection sites than patients with type 1 DM and, consequently, tend to have decreased exposure to SC insulin.

In general, age, gender, and BMI do not have apparent effects on the bioavailability of INH. Absorption of INH is significantly increased in patients who smoke (see Section 4.1.4).

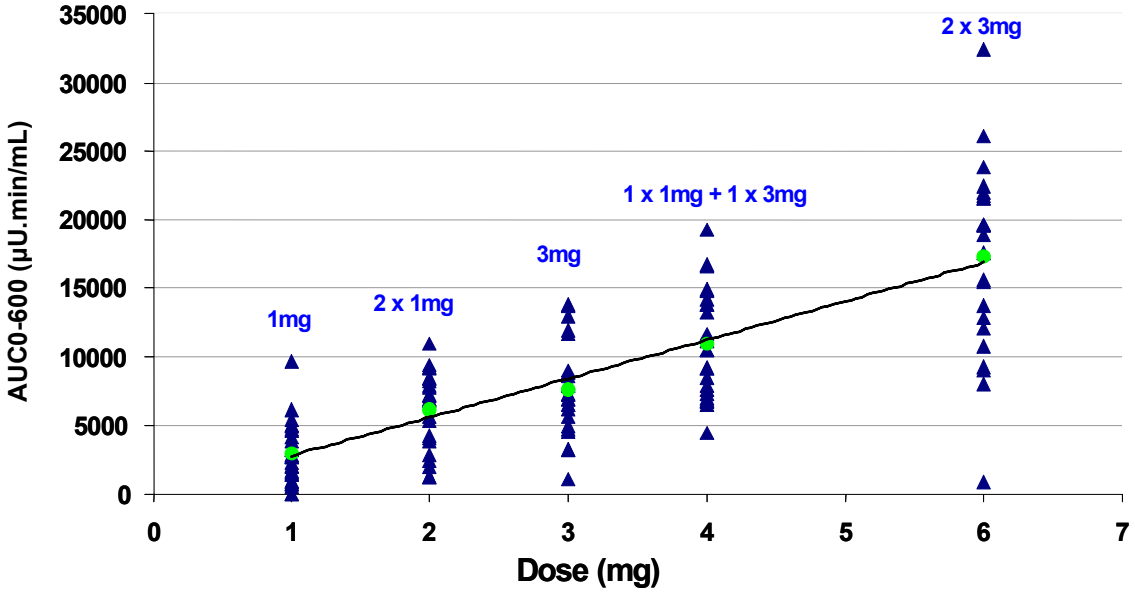
3.2. Dose Proportionality

The systemic exposure of inhaled insulin increases linearly as the dose increases from 1 to 6 mg. The exposure to insulin is considered dose proportional over the studied inhaled dose range of 1 mg to 6 mg.

The dose proportionality of the Phase 3 formulation was assessed in healthy patients over the range of 1 to 6 mg in Study 1012. This dose range was chosen as representative of that expected to be used as a starting dose by patients with DM. Five dose levels (1, 2, 3, 4, and 6 mg) of INH, achieved using 1 mg and 3 mg blisters alone or in combination, were compared.

Following administration of INH, both C_{max} and AUC_{0-600} increased in a linear manner with increasing INH dose as shown in Figure 3.

Figure 3. Individual and Arithmetic Mean AUC0-600 Values Following Two Single-Dose Administrations of 1, 2, 3, 4, or 6 mg Inhaled Insulin to Healthy Patients (Study 1012)



The assessment of dose proportionality was based on the bioequivalence criteria for dose normalized AUC_{0-600}. Although formal bioequivalence criteria for dose proportionality were not met (90% CI needed to fall within the 80, 125% range), the results did not show any systematic deviations either higher or lower across the dose comparisons (the majority of the ratios estimated in the statistical model for AUC_{0-600} and C_{max} were between ~90% and 112%). As such, the exposure to insulin was considered dose-proportional and importantly increased linearly over the inhaled dose range of 1 mg to 6 mg.

The results of this study are generally consistent with reports in the literature for SC insulin. Absorption of SC human insulin or insulin analogs over different dose ranges has been studied using descriptive analyses.[51,52,53] An approximate linear relationship between dose and AUC or Cmax was reported at 0.025 to 0.075 U/kg for the rapid insulin analog, aspart.[51] Published data of SC human insulin and insulin lispro show nonlinearity at SC doses >0.2 U/kg.[53] Because of numerous variables associated with SC insulin use (e.g., site of injection, exercise, injection technique, and degradation with loss of efficacy over time), apparent equivalent clinical dosing cannot be assumed even with currently marketed SC insulin products.[54]

3.3. Dose Strength Equivalence

Study 1006, conducted in healthy patients, assessed the dose strength equivalence of three successive inhalations of 1 mg blisters vs. one inhalation of a 3 mg blister. T_{max} was comparable between the two treatments; however, the other parameters (C_{max}, F, and AUC_{0-360}) were not shown to be dose equivalent.

Three inhalations of 1 mg resulted in an AUC_{0-360} (and F) that was approximately 40% higher than one inhalation of 3 mg. C_{max} was about 30% higher (Table 7).

Table 7. Statistical Analysis of Insulin Pharmacokinetic Parameter Group Means for the 3x1 mg and 1x3 mg Treatments (Study 1006)

Parameter	3x1 mg	1x3 mg	Ratio/Difference	90% CI
AUC0-360* (µU.min/mL)	2600	1860	140%	(117%, 167%)
Cmax* (µU/mL)	31.0	24.5	127%	(108%, 148%)
F (%)†	5.80	4.15	140%	(117%, 167%)
Tmax (min)	44	42	2	(-4, 9)

Adjusted geometric means for AUC, Cmax, and F, adjusted arithmetic mean for Tmax
* Baseline adjusted values
†AUCinhaled/AUCsc; calculated from dose-standardized AUCs

In blisters of lower fill mass, the inhaler, as designed, is more efficient in breaking up or de-agglomerating the powder. The result is a finer aerodynamic particle size compared to blisters of greater fill mass. Accordingly, the systemic insulin delivered from three 1 mg blisters is not equivalent to the systemic insulin delivered from one 3 mg blister. Therefore, three 1 mg blisters should not be substituted for one 3 mg blister. This statement, along with directions if no 3 mg blisters are available[1], is proposed in the dosage and administration section of the USPI.

3.4. Bioequivalence of Clinical and Commercial Scale Products

Bioequivalence of the clinical and commercial scale 3 mg blisters was demonstrated by average bioequivalence (ABE) criteria. For the 1 mg blisters, overall assessment of available analyses shows that the two blister scales are bioequivalent.

Studies 1014 and 1015 assessed the bioequivalence of the clinical and commercial scale 3 mg and 1 mg products, respectively, using the ABE decision criterion in accordance with US FDA and EU guidances[55,56]. Bioequivalence was demonstrated in Study 1014 (Table 8).

Table 8. Summary of Average BE Analysis for the Blisters from Clinical and Commercial Scale Production for C-peptide-Corrected Insulin Pharmacokinetics

Parameter	N	COM	CLN		
1014 (3 mg blister)	40	Adjusted Geometric Means		Ratio (%)	90% CI
AUC0-360 (µU. min/ mL)		4620	4750.	97.2	91.7, 103
Cmax (µU/ mL)		25.5	25.9	98.7	93.1, 105
		Adjusted Arithmetic Means		Difference	
Tmax (min)		45	51	-6	-14, 2
1015 (1 mg blister)	40	Adjusted Geometric Means		Ratio (%)	
AUC0-360 (µU. min/ mL)		1610	1780	90.7	78.8, 104
Cmax (µU/ mL)		10.6	11.4	93.3	84.9, 103
		Adjusted Arithmetic Means		Difference	
Tmax (min)		65	63	3	-10, 15

CLN = clinical; COM = commercial

In Study 1015, the 1 mg BE assessment, ABE results for the primary analysis set narrowly missed the accepted criteria for bioequivalence. However, ABE was achieved in three other analysis sets, including an analysis data set from 67 of the 75 patients who had at least one non-hemolyzed pharmacokinetic profile for both the clinical and commercial blister. The results of this analysis are shown in Table 9 and indicate that the clinical and commercial 1 mg blisters are bioequivalent. The ratios for the AUC and

[1] "Do not substitute three 1 mg blisters for one 3 mg blister. If 3 mg blisters are unavailable, use only two 1 mg blisters as replacement."

Cmax are 94.7% and 99.6%, respectively and the 90% confidence intervals for both fall well within the 80-125% bioequivalence intervals.

Table 9. Summary of Average BE Analysis for the Blisters from Clinical and Commercial Scale Production for C-peptide-Corrected Insulin Pharmacokinetics (N=67 analysis)

Parameter	Adjusted Geometric Mean		Ratio % (COM/CLN)	90% CI
	COM	CLN		Ratio
AUC_{0-360} (μU.min/mL)	1670	1770	94.7	85.2, 105.3
Cmax (μU/mL)	11.2	11.2	99.6	92.3, 107.4
	Adjusted Arithmetic Mean		Difference (COM - CLN)	Difference)
Tmax (min)	61	58	3	-6, 12

CLN = clinical scale, CI = confidence interval, COM = commercial scale

3.5. Clinical Studies to Assess/Characterize the Early Product

Some INH Phase 1 studies were pilot studies conducted to characterize the INH system and assist in its development. Most of the formulations and inhalers used in these studies were developmental prototypes, and some were prepared specifically to examine particular properties under investigation. These studies resulted in the use of the final 60% formulation, the P3 inhaler version, and standard inhalation procedure that were used in the Phase 3 clinical studies.

The studies showed that particle size influences INH bioavailability: powders of small particle size have higher bioavailability than larger particle size powders. They also showed that fill mass influences delivery efficiency: a lower fill mass produces a higher FPD <3.3 μm resulting in increased INH absorption, and that FPD <3.3 μm is a better predictor than ED of *in vivo* performance (absorption) of INH. Finally, the standard inhalation maneuver was demonstrated to be robust and to produce consistently desired insulin delivery.

3.6. Biopharmaceutics Summary

These studies demonstrated that:

- The bioavailability of INH is approximately 10% relative to SC regular insulin in patients with DM.
- Administration of INH produced dose-separated and dose-linear exposure over the studied dose range of 1 to 6 mg.
- Consecutive administration of three 1 mg blisters results in a greater insulin exposure than one 3 mg blister; therefore, three 1 mg blisters should not be substituted for one 3 mg blister.
- FPD is a better predictor of insulin exposure than ED.

4. OVERVIEW OF CLINICAL PHARMACOLOGY

Studies that provide important information relevant to an understanding of the pharmacokinetics and pharmacodynamics of INH are discussed in this section.

Certain types of studies ordinarily conducted as part of a clinical pharmacology program were considered not applicable to the INH development program because the mode of action and behavior of insulin, once delivered to the blood, are well understood. These include plasma protein binding studies, because it is well known that human insulin circulates in blood as the free monomer with a volume of distribution that approximates the volume of extracellular fluid. Also not performed were specific metabolism studies, because the degradation of insulin by peripheral tissues is well established. In addition, drug interaction studies were not conducted, because many orally administered substances are known to affect the glucose-lowering ability of insulin. There were also no studies using any other human biomaterials or population pharmacokinetic studies. The presence of endogenous insulin and/or exogenously administered concomitant intermediate- or long-acting insulin inherent in the Phase 3 population with DM provided logistical constraints on the ability to characterize the pharmacokinetics using population pharmacokinetic modeling. Rather, the pharmacokinetics of INH were characterized using traditional noncompartmental analyses in healthy patients, patients with type 1 and type 2 DM, as well as in special populations.

4.1. Pharmacokinetics of Inhaled Insulin

4.1.1. Healthy Patients and Patients with DM

In healthy patients, INH was absorbed as rapidly as SC insulin lispro and more rapidly than SC regular insulin. In patients with DM, INH was absorbed more rapidly than SC regular insulin.

Healthy Patients

The pharmacokinetics of INH were evaluated in fasted healthy patients in Studies 017, 023, 016, 1005, 1006, 1012, 1014, 1015, and 1020. All studies included SC regular insulin as a comparator with the exception of Study 1012. Study 017 also included SC insulin lispro as a comparator. In healthy patients, the mean time to peak insulin concentration ranged from 41 to 89 minutes compared with 63 to 148 minutes for SC regular insulin and 52 minutes for SC insulin lispro (Table 10). Mean C_{max} and exposure (AUC) for INH were comparable to SC regular insulin.

Table 10. Mean Pharmacokinetic Parameters in Healthy Patients

Study (No. Patients)	Cmax[a] (μU/mL) [Ratio % (90% CI)]	Tmax[a] (min) [Difference (90% CI)]	AUC0-360[a] (μU.min/mL) [Ratio % (90% CI)]	F[b] (%)
017[c] (18)				
INH – 2 x 3 mg	66.9 [110 (86,139)]	55 [-93 (-132, -54)]	12300 [84 (72, 99)]	9
SC – 18 U	61.0	148	14600	
SC lispro – 18 U	150 [45 (35, 57)][d]	52 [4 (-36, 43)] [d]	22500 [55 (47, 64)] [d]	6 [d]
023[e] (13)				
INH 1 x 1	12.8 [-]	44 [-]	1470[f] [-]	6.1
INH 2 x 1	33.2 [-]	41 [-]	4300 [f] [-]	8.9
SC – 6 U	29.9	73	5260 [f]	
016[g] (30)				
INH – 2 x 1 mg	15.8 [-]	53 [-]	1430 [-]	4.9
SC – 6 U	21.5	63	3200	
1005[h] (8)				
INH – 1 x 3 mg	25.4 [-]	43 [-]	1990 [-]	18
SC – 9 U	16.9	110	1520	
1006 (27)				
INH – 3 x 1 mg	31.0 [-]	44 [-]	2600 [-]	5.8
INH – 1 x 3 mg	24.5 [-]	42 [-]	1860 [-]	4.2
SC – 9 U	29.9	79	4890	
1012[c] (25)				
INH – 1 x 1 mg	15.6 [-]	63 [-]	1900 [-]	-
INH – 2 x 1 mg	25.6 [-]	88 [-]	4620 [-]	-
INH – 1 x 3 mg	34.4 [-]	76 [-]	5990 [-]	-
INH – 4 mg	47.3 [-]	76 [-]	8980 [-]	-
INH - 2 x 3 mg	74 [-]	89 [-]	13400 [-]	-
1014 (40)				
INH – 3 mg COM	25.5 [-]	45 [-]	4620 [-]	6.6
INH – 3 mg CLN	25.9 [-]	51 [-]	4750 [-]	6.7
SC – 9 U	38.1	96	7810	
1015 (40)				
INH – 1 mg COM	10.6 [-]	65 [-]	1610 [-]	5.8
INH – 1 mg CLN	11.4 [-]	63 [-]	1780 [-]	6.4
SC – 3 U	16.4	97	3040	
1020[g] (10)				
INH – 1 mg	9.68 [83 (64, 108)]	53 [-58 (-135, -15)]	1650 [71 (52, 97)]	8
SC – 3 U	11.6	90	2320	

Means are geometric for Cmax, AUC, and F, arithmetic for Tmax
INH = inhaled insulin; SC = SC regular insulin except in study 017, where both SC regular insulin and SC insulin lispro were used; COM = commercial scale; CLN = clinical scale
- indicates SC regular insulin treatment or comparison with SC treatment not performed in the study
a Baseline adjusted values; results shaded in grey are C-peptide corrected values.
b Ratio of INH versus SC, calculated from dose standardized AUC0-360
c Euglycemic clamp study
d Means for SC insulin lispro or INH versus insulin lispro comparison values
e Results for male Caucasian patients
f AUC0-480
g Results for nonsmokers
h Results for healthy evaluable patients (patients who did not receive carbohydrate)

Patients with DM

The pharmacokinetics of INH were evaluated in patients with type 1 or type 2 DM (in the fasting or postprandial state depending upon the study) in Studies 1003, 1004, 1007, 101, 021, and 018. All studies

included SC regular insulin as a comparator. In patients with DM, as with healthy patients, INH was more rapidly absorbed than SC regular insulin, and INH T_{max} (38 to 78 minutes) was significantly less than SC regular insulin T_{max} (75 to 258 minutes)(Table 11).

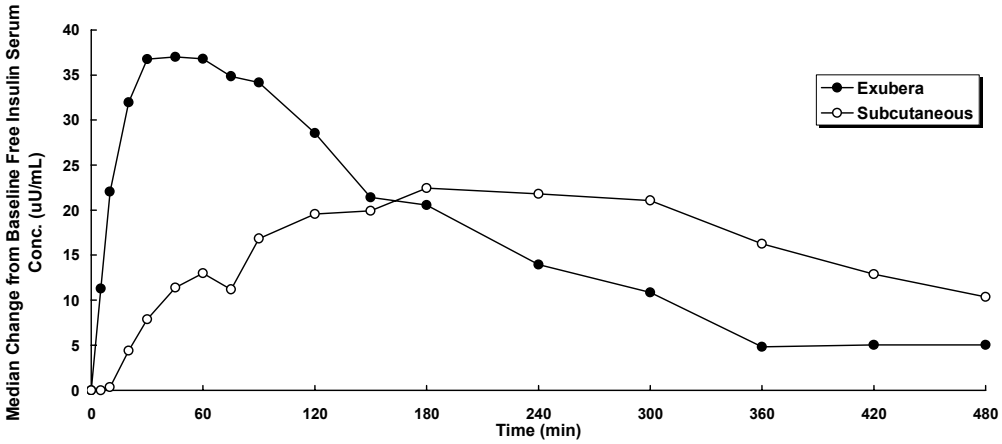
Table 11. Mean Pharmacokinetic Parameters in Patients with DM

Study (No. Patients)	Cmax[a] (µU/mL) [Ratio % (90% CI)]	Tmax[a] (min) [Difference (90% CI)]	AUC[a] (µU.min/mL) [Ratio % (90% CI)]	F[b] (%)
Type 2 DM Fasting				
1003[c] (14)				
INH – 6 mg	49.2 [-]	60 [-]	6770 [-][d]	11 [d]
SC – 18 U	26.5	258	6420 [-][d]	
1004[c] (20)				
INH 4 mg	48.6 [170 (131, 221)]	38 [-62 (-82, -42)]	4700 [97 (68, 139)]	11
SC 12 U	28.6	100	4820	
1007[f] (13)				
INH – 3 mg	39.0 [183 (116, 290)] [k]	46 [-37 (-75, 1)] [k]	2440 [93 (55, 155)] [k]	10
SC – 9 U	21.3	83	2630	
Type 2 DM Postprandial				
101[g] (16)				
INH – 3 – 6 x 1 mg [h]	87.6 [94 (76, 116)]	54 [-21 (-31, -11)]	11500 [84 (65, 108)] [i]	-
SC – 0.2/kg	93.3	75	13800 [i]	
Type 1 DM Postprandial				
021[g] (22)				
INH – 3,4, 6 mg	35.2 [107 (84, 136)	61 [-75 (-93, -57)]	6140[j] [84 (65, 103)]	8.2-10.7
SC – 9, 12, 18 U	32.9	136	7340 [j]	
018[g] 6-11 yrs (13)				
INH – 1, 2, 3 mg	27.1 [118 (79, 178)]	68 [-66 (-104, -28)]	3760 [82 (42, 158)]	8.4
SC – 3, 6, 9 U	22.9	134	4590	
018[g] 12-17 yrs (14)				
INH – 2, 3, 4 mg	32.8 [103 (59, 178)]	78 [-29 (-56, -2)]	5730 [83 (63, 110)	8.8
SC – 6, 9, 12 U	31.9	107	6880	

INH = inhaled insulin; SC = SC regular insulin
Unless specified otherwise, adjusted geometric mean for AUC0-360, Cmax, and F; adjusted arithmetic mean for Tmax
a Baseline adjusted values; AUC from 0 to 360 minutes unless indicated otherwise
b Ratio of Inhaled versus SC, calculated from dose standardized AUC values
c Euglycemic clamp study
d AUC0-480
e In elderly, obese patients
f In patients with gestational or pregestational type 2 diabetes mellitus
g Insulin was administered 10 minutes before meal; dose based on body weight
h 1 mg/18 kg of body weight, rounded to the nearest whole number, using an earlier formulation (I-004)
i AUC0-240
j AUC0-120 = 2880 (INH), 2360 (SC)
k 95% CI

At doses up to 6 mg INH and 18 U SC regular insulin, the postprandial C_{max} was comparable for INH-treated and SC regular insulin-treated patients with DM, while fasting C_{max} was higher after INH than after SC regular insulin in patients with type 2 DM. Systemic exposure following INH administration was greater compared to SC regular insulin for up to 2 hours postdose. After 6 hours, total exposure to INH and SC regular insulin were similar. The serum insulin concentration-time profiles of INH and SC regular insulin are shown for patients with type 2 DM in Figure 4.

Figure 4. Median Change from Baseline Serum Concentration of Free Insulin in Nonsmoking Patients with Type 2 Diabetes Mellitus Following Administrations of 2x3 mg Inhaled Insulin and 18 U Subcutaneous Insulin (Study 1003)



A non-parametric analysis of T_{max} in Studies 018, 017, 021, 1003, 1004, and 1007 was conducted to comply with the recent European guidance on bioavailability and bioequivalence.[56] The results were consistent with those already discussed and showed that the median time to reach the maximum insulin concentration was substantially shorter for INH compared to SC regular insulin (Table 12).

Table 12. Nonparametric Analysis of Tmax

Study	Median Tmax (min) Test (T) Inhaled Insulin	Median Tmax (min) Reference (R) SC regular insulin	Difference* (T-R)	90 or 95%CI**
021	52.5	120	-78.8	(-97.5, -55) †
018				
6-11 yrs	90	150	-60	(-127.5, -15)‡
12-17 yrs	90	90	-30	(-60, 0) ‡
1003 Nonsmokers	45	240	--	--
1004	30	90	-53.8	(-76.3, -41.3) †
1007	45	60	-30	(-82.5, 0) ‡
017	50	120	-69.4	(-140, -40) †
	50	50 (lispro)	3.8	(-10, 21) †

*Hodges Lehmann estimate
**Moses confidence interval; 90 or 95% CI were reported consistent with those provided in the individual study reports.
†90% CI
‡95% CI
--Comparative analysis not performed

4.1.2. Special Populations

Single-dose INH pharmacokinetics were evaluated in the following special populations: patients with gestational DM (GDM) or pregestational DM (PGDM), patients with chronic obstructive pulmonary disease (COPD), patients with mild asthma, and patients with an experimental rhinovirus infection. In general, the rate and extent of INH absorption did not vary significantly across these different populations

except in ex-smokers with COPD, in whom increased and faster absorption was demonstrated vs. healthy patients.

Patients with GDM or PGDM

The pharmacokinetics of INH in pregnant patients with GDM or PGDM were assessed in Study 1007. In patients with GDM or PGDM, INH was absorbed more rapidly than SC regular insulin. The time to peak insulin concentration was 46 minutes for INH compared to 83 minutes for SC regular insulin (Table 11). The pharmacokinetic results suggest that 3 mg INH is absorbed more rapidly, yet provides comparable insulin exposure to 9 U SC regular insulin. These results are consistent with observations in INH studies in non-pregnant subjects with type 2 DM.

Patients with COPD

The safety, tolerability, and bioavailability of INH in ex-smokers with COPD compared to healthy patients were evaluated in Study 1005. The effect of bronchodilator use on the bioavailability of INH in patients with COPD was also examined. INH was absorbed faster and to a greater extent in non-smoking patients with COPD (T_{max}: 24-30 minutes; AUC_{0-360}: 3250-3760 μU.min/mL) compared to healthy patients (T_{max}: 43 minutes; AUC_{0-360}: 1990 μU.min/mL).

Table 13. Mean Pharmacokinetic Parameters for COPD and Healthy Patients

		AUC_{0-360}* (μU.min/mL)		Cmax* (μU/mL)		Tmax (min)		
	N	INH	SC	INH	SC	INH	SC	F (%)
Chronic Bronchitis								
Pre-albuterol	12	3250		41.9		28		23
Post-albuterol	12	3470	1520	46.5	14.9	30	61	25
Emphysema								
Pre-albuterol	12	3550		43.5		24		10
Post-albuterol	12	3760	3870	48.1	24.1	30	79	11
Healthy	8	1990†	1520†	25.4†	16.9†	43†	110†	18.0† 7.6‡

INH = inhaled insulin; SC = SC regular insulin
* Baseline adjusted values; geometric mean for AUC, F and Cmax; arithmetic mean for Tmax
† Results for evaluable patients (patients who did not receive carbohydrate)
‡ Excluding an outlier value, which was 3 standard deviations higher than the mean value due to the low AUC value following SC administration

The reason for this difference is unknown. INH pharmacokinetics appeared to be similar between patients with emphysema and those with chronic bronchitis. Relative bioavailability of INH was higher in patients with bronchitis (23-25%) than those with emphysema (10-11%) due to an unexpectedly low systemic exposure of SC regular insulin in patients with bronchitis.

Administration of albuterol 30 minutes before or 30 minutes after INH administration did not appear to affect the absorption of INH in patients with emphysema or bronchitis. However, in a subset of patients with emphysema who were albuterol responders, absorption of INH appeared to be enhanced when albuterol was administered 30 minutes before INH compared to when it was administered 30 minutes after INH.

Patients with Mild, Controlled Asthma

Study 009 evaluated the pharmacokinetics of 1 mg and 3 mg INH of an early formulation in patients with mild asthma but no DM and compared them with healthy controls. Subjects with mild asthma tended to

absorb less inhaled insulin than healthy subjects although the differences in pharmacokinetic parameters are not statistically significant between the two populations (Table 14).

Table 14. Pharmacokinetic Parameters in Mild Asthmatic Patients and Healthy Patients

Parameter	Asthmatic (N=24)	Normal (N=12)	Ratio (%) or Difference	95% CI
$AUC_{0\text{-}360}$ Inhaled 1 mg (µU·min/mL)	146	175	83%	(35%, 200%)
$AUC_{0\text{-}360}$ Inhaled 3 mg (µU·min/mL)	701	1220	58%	(26%, 129%)
$AUC_{0\text{-}360}$ SC (µU·min/mL)	3720	3530	105%	(81%, 136%)
F* (1 mg/SC)	0.01	0.02	82%	(33%, 206%)
F* (3 mg/SC)	0.02	0.04	54%	(23%, 126%)
Cmax Inhaled 1 mg (µU/mL)	3.21	3.76	85%	(48%, 151%)
Cmax Inhaled 3 mg (µU/mL)	10.8	13.6	80%	(47%, 133%)
Cmax SC (µU/mL)	23.2	19.9	117%	(82%, 166%)
Tmax Inhaled 1 mg (min)	31	31	-1	(-18, 16)
Tmax Inhaled 3 mg (min)	36	47	-11	(-35, 13)
Tmax SC (min)	83	76	7	(-35, 49)

* AUC values were dose-normalized prior to calculation of F (Inhaled AUC/SC AUC)

Patients with Experimental Rhinovirus Infection

The effect of a rhinoviral challenge on the bioavailability and toleration of INH was examined in healthy volunteers in Study 010. There was no evidence that the bioavailability of INH is altered by the presence of a rhinoviral infection (Table 15); however, the degree of variability observed in this study precludes a definitive conclusion. Throughout the clinical development program, few patients with adverse events indicative of an upper respiratory infection or allergy stopped using INH.

Table 15. Summary of Statistical Analysis of Pharmacokinetic Parameters for Evaluation of Rhinoviral Challenge Effect (Study 010)

		Adjusted Geometric Means*						
Parameter	Day	Cold (N=13)	VNC (N=7)	Saline (N=4)	Cold vs VNC Adjusted Ratio * (90% CI)	p-value	Cold vs Saline Adjusted Ratio * (90% CI)	p-value
AUC (µU.min/ml)	3	703	1209	455	0.58 (0.33, 1.04)	0.1218	1.55 (0.76, 3.14)	0.301
	4	692	584	782	1.19 (0.57, 2.48)	0.6940	0.89 (0.36, 2.19)	0.819
Cmax (µU/ml)	3	11.88	13.58	6.48	0.88 (0.48, 1.61)	0.7083	1.83 (0.85, 3.97)	0.190
	4	11.27	7.71	8.18	1.46 (0.80, 2.66)	0.2856	1.38 (0.64, 2.94)	0.474
		Arithmetic Means			Estimated Difference (90% CI)	p-value	Estimated Difference (90% CI)	p-value
Tmax (min)	3	35.8	40.7	33.8	-4.9 (-19.8, 9.9)	0.5718	2.0 (-16.0, 20.1)	0.849
	4	47.3	50.0	22.5	-2.7 (-15.9, 10.5)	0.7287	24.8 (8.7, 40.9)	0.0148

* For AUC and Cmax the Day 1 log (AUC) or log (Cmax) was used as a covariate in the statistical model.
Day 1: Before inoculation; Days 3 and 4: Post-inoculation
VNC = Virus No Cold: patients who did not contract a cold after viral inoculation; Cold: patients who developed a cold

4.1.3. Effect of Intrinsic Factors

Age

There is no apparent effect of age on the pharmacokinetics of INH. The pharmacokinetics of INH in children and adolescents (aged 6-17 years) with type 1 DM and in elderly, obese patients with type 2 DM were examined in Studies 018 and 1004, respectively. The results are shown in Table 16. The rate of insulin absorption in children and adolescents with type 1 DM and in elderly patients with type 2 DM was significantly faster for INH than for SC regular insulin. AUC values of INH were similar and not statistically different from those of SC regular insulin. These results were consistent with those for healthy patients and patients with DM discussed above in Section 4.1.1. The bioavailability of INH relative to SC regular insulin in children and adolescents with type 1 DM was approximately 8-9%, which is similar to the relative bioavailability in Study 021 conducted in adults aged 23-43 years with type 1 DM. The relatively higher F value (11%) in Study 1004 (elderly, obese, type 2 DM) was similar to F values observed for the non-smokers in Study 1003 (type 2 DM) and is due to decreased SC absorption seen in obese, type 2 DM patients.

Table 16. Effects of Age on the Pharmacokinetics of Inhaled Insulin

Study	Age (y) (mean)	N	Dose INH (mg)	SC (U)	AUC_{0-360}[a] (µU.min/mL) INH	AUC_{0-360}[a] (µU.min/mL) SC	Cmax[a] (µU/mL) INH	Cmax[a] (µU/mL) SC	Tmax (min) INH	Tmax (min) SC	F (%)
018[b]	6-11 (8.8)	10	1, 2, or 3	3, 6, or 9	3760[c]	4590[c]	27.1[c]	22.9[c]	68	134	8.4[d]
	12-17 (14.2)	12	2, 3, or 4	6, 9, or 12	5730[c]	6880[c]	32.8[c]	31.9[c]	78	107	8.8[d]
021	23-43 (32.4)	22	3, 4, or 6	9, 12, or 18	6140	7340	35.2	32.9	61	136	8.2-10.7[d]
1003[e]	43-68 (55.6)	14	6	18	6770[f]	6420[f]	49.2	26.5	60	258	11[f]
1004[g]	63-80 (71.6)	20	4	12	4700	4820	48.6	28.6	38	100	11[d]

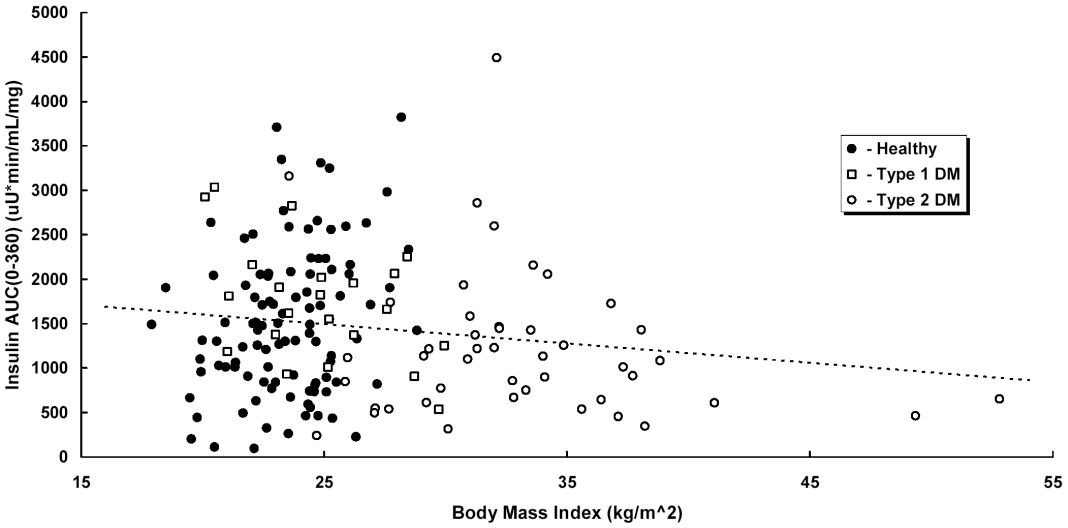
INH = inhaled insulin; SC = SC regular insulin
Adjusted geometric means for AUC, Cmax; and F; Adjusted arithmetic means for Tmax.
a Baseline adjusted values
b Insulin administered pre-meal
c No baseline adjustment
d Geometric mean
e euglycemic clamp study; data for nonsmokers
f AUC0-480; adjusted geometric mean
g In fasting, obese, type 2 patients

Body Mass Index (BMI)

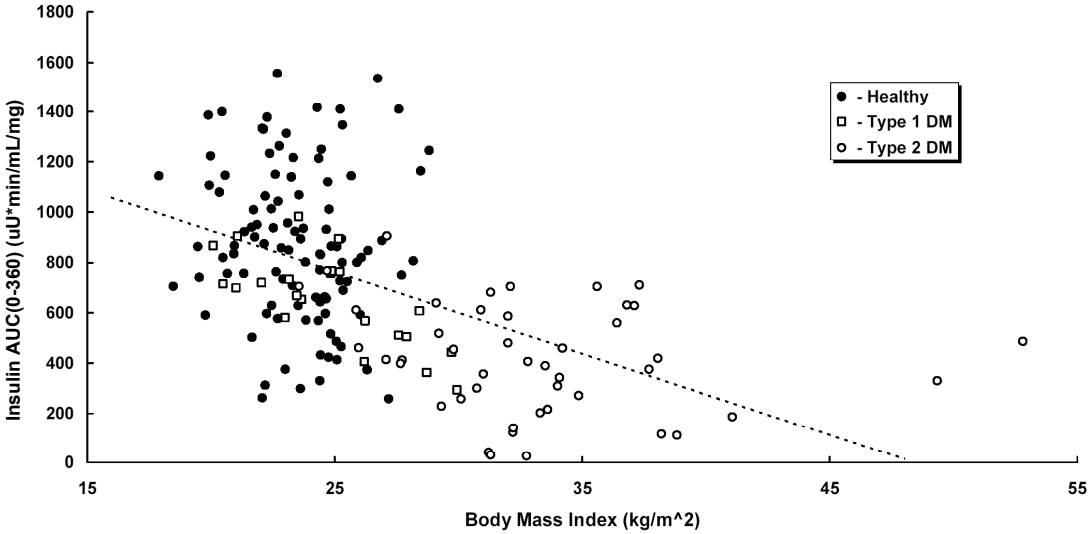
There is no apparent effect of BMI on the pharmacokinetics of INH. The relationship between insulin exposure and BMI was explored with data from studies in healthy patients (1014, 1015, and 1006), in patients with type 2 DM (1003, 1004, and 1007) and in patients with type 1 DM (021). These studies include both inhaled (using Phase 3 formulation) and SC regular insulin treatments, and they provide experience over a wide range of BMI. The dose-normalized AUC_{0-360} was plotted against the BMI. INH exposure is apparently independent of BMI, while SC regular insulin exposure was reduced with increasing BMI (Figure 5).

Figure 5. Relationship between Dose Normalized Insulin AUC0-360 and Body Mass Index in Healthy Patients and Patients with Type 1 or Type 2 Diabetes Mellitus

Following Administration of Inhaled Insulin



Following SC Administration of Regular Insulin



AUC values are normalized by mg dose for inhaled insulin; by unit dose for SC regular insulin.

Consistent with findings from the studies discussed above, these data also suggest that in contrast to SC regular insulin where exposure tends to vary with patient's BMI, exposure of INH is more consistent across the population of patients with DM and independent of BMI.

Gender

There is no apparent effect of gender on the pharmacokinetics of INH. While no study was specifically designed to evaluate gender effect on INH pharmacokinetics, a descriptive analysis of pharmacokinetic parameters separated by gender was performed with pooled data from Studies 1014, 1015, 1004, and 021 to examine for a gender effect. These studies were selected as representative studies that included both male and female healthy patients (1014, 1015) and patients with type 1 (021) and type 2 (1004) DM. There were no apparent differences in insulin AUC, C_{max} and T_{max} between male and female patients for INH (Figure 6, Figure 7, and Figure 8).

Figure 6. Insulin Exposure by Gender in Healthy Patients and Patients with Type 1 or Type 2 Diabetes Mellitus

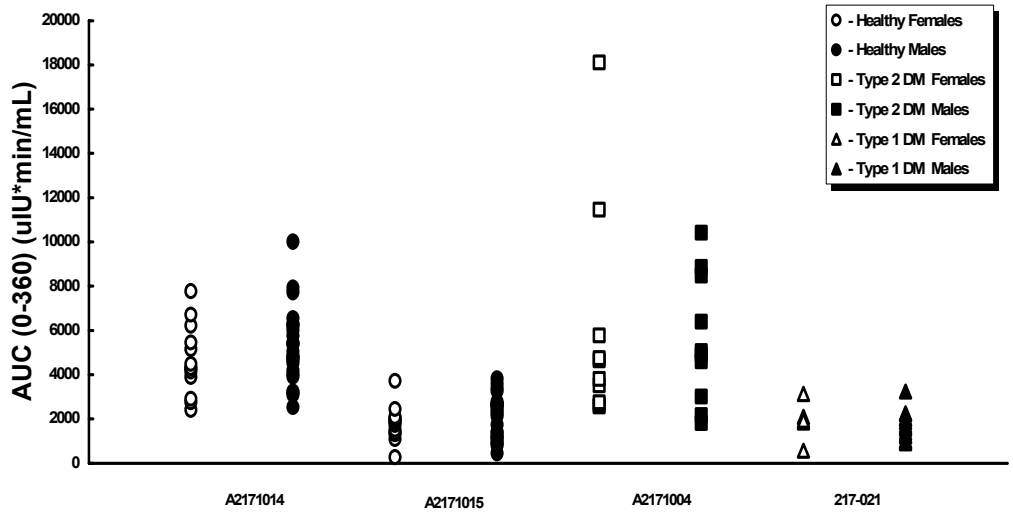


Figure 7. Maximal Concentrations of Insulin by Gender in Healthy Patients and Patients with Type 1 or Type 2 Diabetes Mellitus

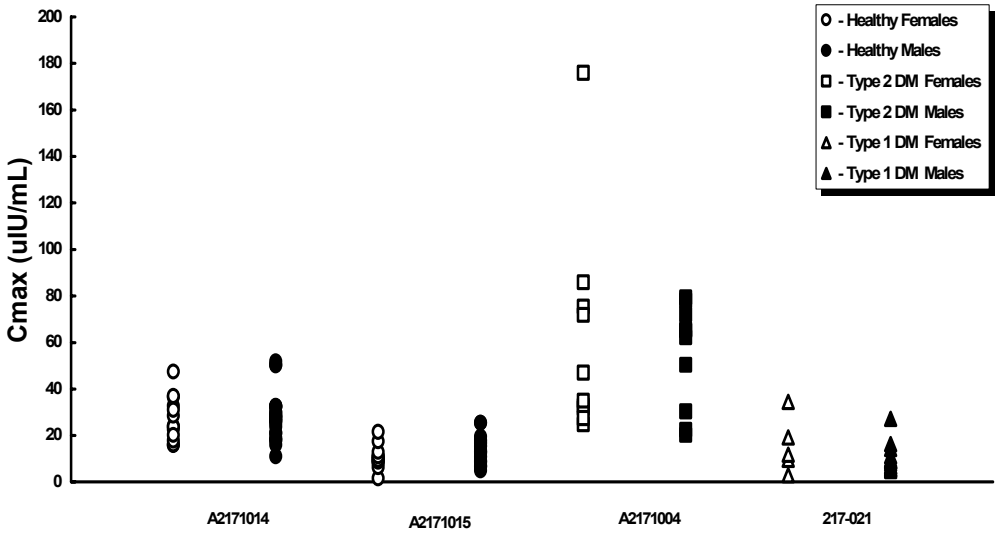
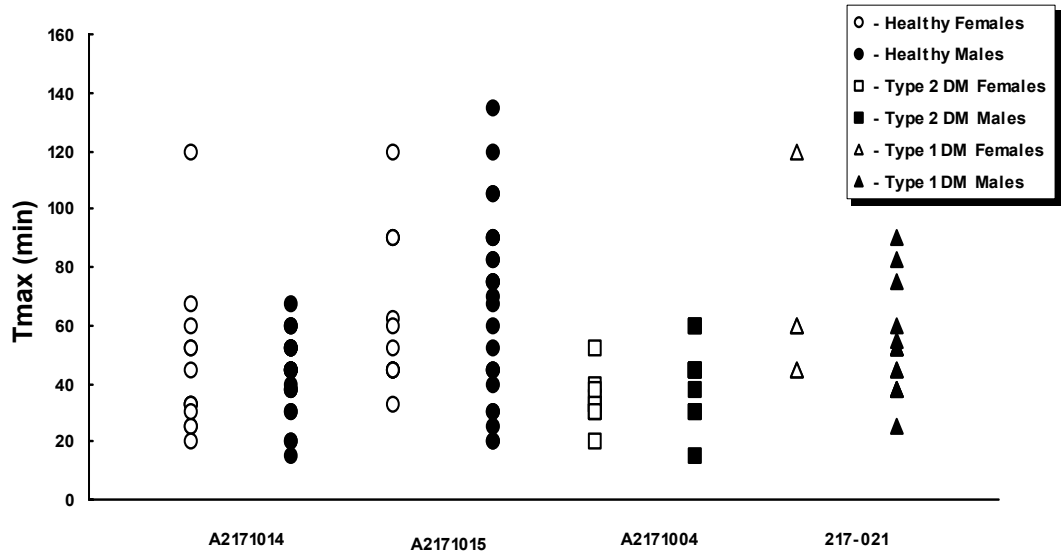


Figure 8. Time to Reach Maximal Insulin Concentrations by Gender in Healthy Volunteers and Patients with Type 1 or Type 2 Diabetes Mellitus



Each point represents the mean value following two administrations of inhaled insulin for each patient.
Data for 217-021 were normalized by dose.

Race/Ethnicity

There were too few patients of different racial or ethnic backgrounds to draw general conclusions about the effect of race or ethnicity on the pharmacokinetics of INH. The pharmacokinetics of INH in Japanese

patients was evaluated in Studies 1016 and 023. The results suggest that the pharmacokinetics of INH is similar for Japanese and Caucasian patients (Table 17 and Table 18).

Table 17. Inhaled Insulin Pharmacokinetics in the Japanese Population (Study 1016)

	INH			
Parameters*	**1 x 1 mg (n=16)**	**1 x 3 mg (n=16)**	**2 x 3 mg (n=16)**	**SC regular insulin**
Cmax (μU/mL)	15.3 ± 5.9 (14.0)	35.1 ± 12.7 (32.1)	67.0 ± 26.8 (61.5)	70.6 ± 17.4 (68.6)
Tmax (min)	86.9 ± 83.6 [75]	54.4 ± 30.0 [55]	69.4 ± 51.0 [50]	94.1 ± 34.0 [90]
AUC0-600 (μU·min/mL)	2570 ± 1660 (1970)	7240 ± 3690] (6050)	16000 ± 8290 (14200)	15200 ± 2740 (14900)
F (%)	7.4 ± 4.8 [6.5]	7.2 ± 3.9 [7.5]	7.8 ± 4.3 [7.1]	---

Arithmetic Mean ± SD (Geometric Mean) [Median]
* Baseline adjusted values

Table 18. Inhaled Insulin Pharmacokinetics in the Japanese and Caucasian Populations (Study 023)

	INH 1x1mg			INH 2x1 mg			SC		
Parameter*	**J**	**C**	**Ratio/Diff (95% CI)**	**J**	**C**	**Ratio/Diff (95% CI)**	**J**	**C**	**Ratio/Diff (95% CI)**
AUC_{0-480} (μU·min/mL)	1440	1470	98% (61, 157)	2960	4300	69% (43, 110)	4820	5260	92% (57, 146)
Cmax (μU/mL)	14.7	12.8	115% (74, 178)	22.1	33.2	67% (43, 103)	37.8	29.9	126% (82, 195)
Tmax (min)	33	44	-11 (-32, 9)	37	41	-4 (-24, 16)	65	73	-8 (-28, 13)
F (%)	6.5	6.1	107% (60, 191)	6.7	8.9	75% (42, 134)	-	-	

J = Japanese; C = Caucasian; Diff = Difference
Results estimated from C-peptide corrected insulin concentrations
Geometric mean for AUC, F, and Cmax; arithmetic mean for Tmax
* Baseline adjusted values

Other Intrinsic Factors

The effect of renal or hepatic impairment on the pharmacokinetics of INH has not been studied. Careful glucose monitoring and dose adjustment of INH may be necessary in patients with renal/hepatic impairment. This information is noted in the Clinical Pharmacology and Precautions sections of the proposed USPI.

4.1.4. Effect of Extrinsic Factors

Smoking

Smoking increases the rate of absorption and bioavailability of INH. INH should not be used in smokers, and this is noted in the Contraindications section of the proposed USPI.

Because smoking is known to increase the permeability of the human lung to aerosols, the effect of smoking on the pharmacokinetics and pharmacodynamics of INH was evaluated in smokers who did not have DM in Studies 016, 1020, and 005 and in smokers with type 2 DM in Study 1003, while the effect of cessation of smoking was assessed in Studies 016 and 1020. Study 1020 also assessed the effects of resumption of smoking on INH absorption after short-term smoking cessation.

Smokers achieved greater maximal insulin concentrations (C_{max} 3-5 times higher) faster (T_{max} 20-30 minutes earlier) than nonsmokers. Smokers had greater insulin exposure (AUC 2-3 times higher) following INH than nonsmokers (Table 19).

Table 19. Inhaled Insulin Pharmacokinetics in Smokers and Nonsmokers

Study	N	Dose (mg)	AUC* (µU.min/mL)		Cmax*.(µU/mL)		Tmax (min)		F** (%)	
			S	NS	S	NS	S	NS	S	NS
1003[a]	S:14 NS:14	6	13200	6770	147	49.2	32	60	13	11
016[b]	S:35 NS:30	2	4850	1430	72.3	15.8	31	53	19	4.9
1020[b]	S:20 NS:10	1	2580	1650	26.8	9.68	20	53	12	8

S = Smoker, NS = Nonsmoker
Geometric mean for AUC, Cmax and F, arithmetic mean for Tmax; median Tmax presented for study A2171020.
*Baseline adjusted values; AUC0-360 for 016, and1020; AUC0-480 for 1003.
**Relative to SC regular insulin:18U in 1003, 6 U in 217-016, and 3 U in 1020
[a] In patients with type 2 DM
[b]In healthy non-diabetic patients

The relative bioavailability of INH was 12-19% in smokers compared with 4.9-11% in nonsmokers.

In Study 016, cessation of smoking for 3 weeks reduced INH absorption by approximately 50%.

Table 20. Effects of Smoking Cessation in Inhaled Insulin Pharmacokinetic Parameters (Study 016)

	AUC0-360* (µU.min/mL)	Cmax* (µU/mL)	Tmax (min)	F (%)
INH1	4850	72.3	31	19
INH2	2860	35.7	41	11
INH3	3410	44.6	39	13
INH1-NS	1430	15.8	53	4.9

INH1: Administration of inhaled insulin prior to smoking cessation
INH2: Administration of inhaled insulin after 3 weeks of smoking cessation
INH3: Administration of inhaled insulin after 13 weeks of smoking cessation
INH1-NS: Administration of inhaled insulin to nonsmokers
Geometric mean for AUC, Cmax and F; arithmetic mean for Tmax
* Baseline adjusted values

No further reduction in absorption was observed after 13 weeks of smoking cessation. In Study 1020, absorption of INH was increased in smokers compared to non-smokers 12 hours after stopping smoking. Reduced absorption was apparent within 3 days of stopping smoking, and abstaining from smoking for 7 days resulted in nearly normal absorption. Resumption of smoking for 2 to 3 days after 1 week of smoking cessation restored the INH absorption to levels observed during smoking (Table 21).

Table 21. Effects of Smoking Cessation and Resumption in Inhaled Insulin Pharmacokinetic Parameters (Study 1020)

	AUC0-360* (μU.min/mL)	Cmax* (μU/mL)	Tmax (min)	F (%)
INH1	2580	26.8	22	12
INH2	3160	33.3	23	15
INH3	2320	18.5	38	11
INH4	1890	15.9	42	9
INH5 (smoking resumption)	3160	29.2	30	15
INH1-NS	1650	9.68	55	8

INH1: Administration of inhaled insulin prior to smoking cessation
INH2: Administration of inhaled insulin after 12 hours of smoking cessation
INH3: Administration of inhaled insulin on Day 3 of smoking cessation period
INH4: Administration of inhaled insulin on Day 7 of smoking cessation period
INH5: Administration of inhaled insulin after resumption of smoking for 2 to 3 days
INH1-NS: Administration of inhaled insulin to nonsmokers
Geometric mean for AUC, Cmax and F; arithmetic mean for Tmax
* Baseline adjusted values

Other Extrinsic Factors

Many substances affect glucose metabolism, and their use may require dose adjustments of human insulin; therefore, no specific studies of interactions with these types of concomitant medications were performed. Specific examples of concomitant medications that may affect glucose levels are noted in the proposed USPI.

4.1.5. Reproducibility/Variability

The total and inter-subject variability of INH pharmacokinetic parameters were comparable to or higher than observed with SC regular insulin. The intrasubject variability of INH pharmacokinetics was generally comparable to or lower than SC regular insulin in patients with type 1 or type 2 DM.

As insulin dosages are titrated individually for each patient, the intrasubject reproducibility/variability of INH is clinically important. Two studies were performed in patients with DM that included intrasubject variability (CVw) of INH in comparison with SC regular insulin as a major objective. The results are shown in Table 22.

Table 22. Intrasubject Variability for Insulin Pharmacokinetics in Patients with Diabetes Mellitus

	CVw (%) AUC0-120			CVw (%) AUC0-360			CVw (%) Cmax			SDw Tmax		
Study	INH CVw	SC CVw	Ratio (90% CI)	INH CVw	SC CVw	Ratio (90% CI)	INH CVw	SC CVw	Ratio (90% CI)	INH SDw	SC SDw	Ratio (90% CI)
1004*	22.9	46.8	49 (33, 73)	30.6	43.1	71 (48, 106)	26.9	36.2	74 (50, 111)	15	75	20 (14, 30)
021§	36.4	41.2	88 (59, 131)	31.8	26.2	122 (82, 181)	50.2	24.6	204 (137, 304)	31	42	74 (49, 109)

CVw: intrasubject coefficient of variation; SDw: intrasubject standard deviation
CVw (original scale) for log transformed AUC and Cmax has been approximated by standard deviation (log scale) * 100
*In fasting, elderly, obese patients with type 2 DM
§ Pre-meal administration of insulin in patients with type 1 DM

In Study 021 conducted in patients with type 1 DM, no difference in the CVws for AUC_{0-120}, AUC0-360, or T_{max} between INH and SC regular insulin were observed, and the CVw for C_{max} was approximately 2-fold greater for INH compared with SC regular insulin. In contrast to the greater CVw for pharmacokinetic C_{max}, however, the CVw of pharmacodynamic C_{maxglc} (maximum glucose concentration) for INH was comparable to that of SC regular insulin, suggesting that the greater CVw in pharmacokinetic C_{max} does not have a significant effect on the pharmacodynamic response, and as a result, patients using INH are not at significant risk of experiencing hypoglycemic events. In fact, INH was associated with a lower risk of hypoglycemia compared to SC insulin in the Phase 2/3 studies (See Section 5.3). It should also be noted that the CVw of pharmacokinetic Cmax for the rapid-acting insulin analog, insulin aspart, is 3-fold greater (in terms of standard deviation) than that of SC regular insulin. The CVw estimates for insulin aspart are presented in the NDA for insulin aspart.[52] The applicant knows of no safety or efficacy issues related to the greater CVw of insulin aspart Cmax.

Study 1004, conducted in elderly, obese patients with type 2 DM, demonstrated that the intrasubject variability of INH is comparable to or better than SC regular insulin in patients with type 2 DM. Because of the similarity in INH pharmacokinetics between elderly and younger adult obese patients with type 2 DM, these results are likely generalizable to younger patients.

It should also be noted that in INH studies, patients did not have prior experience inhaling insulin. Variability may have been exaggerated due to patients' lack of experience in using INH, especially when compared to SC insulin, which was administered by medical staff or patients familiar with injection techniques. An analysis of the possible effect of patients' inexperience with INH on intrasubjectvariability suggested that with increasing use of the product, variability declines (Table 23).

Table 23. Assessment of Effect of Use Experience on Variability of Inhaled Insulin AUC and Cmax

	CV (%)						
	AUC_{0-60}	AUC_{0-120}	AUC_{0-180}	AUC_{0-360}	AUC_{0-480}	AUC_{0-600}	Cmax
Study 1003*							
All 3 periods		64.5		73.9	74.3		50.6
Last 2 periods		43.3		51.8	52.1		44.7
Study 1012†							
All 6 periods						55.5	43.2
Last 5 periods						37.6	30.9
Last 4 periods						41.6	33.7
Last 3 periods						30.7	29.0
Last 2 periods						29.9	26.2
Study 1014‡							
All 4 periods				22.2			22.2
Last 3 periods				22.0			20.0
Last 2 periods				18.0			20.5
Study 1016†							
All 3 periods	28.0	27.2	32.4	36.2	36.6	36.9	28.8
Last 2 periods	19.8	27.5	29.8	36.1	34.5	33.7	31.0

Intrasubject CV = (intrasubject standard deviation of log-transformed parameters) * 100.

*Nonsmoker group only. The analysis used the nonsmoking inhaled insulin group as the evaluable subjects, and used the re-numbered 'period' in the statistical model. This differed from the variability analysis performed in the study report, where both smoking and nonsmoking inhaled insulin groups are chosen for the analysis, and the 'period' wasn't included in the mixed model.

†Dose normalized parameter values were used in the analysis due to multiple doses used in different inhaled groups. Data from all dose levels were combined in the analysis. Intrasubject variability was not estimated in the 1016 study report.

‡Data from treatments with the clinical and commercial formulation were combined in the analysis.

Intrasubject variability of the 1 mg and 3 mg clinical and commercial formulations was evaluated in healthy patients in Studies 1006, 1014, and 1015. There were no statistically significant differences in the intrasubject variability for C_{max} and AUC when the 3x1 mg and 1x3 mg clinical blisters were compared. The intrasubject variability for AUC and C_{max} was generally comparable between the clinical and commercial scale blisters for both the 1 mg and 3 mg strengths.

4.2. Pharmacodynamics of Inhaled Insulin

4.2.1. Healthy Patients and Patients with DM

In healthy patients, INH displayed the rapid onset of action of SC insulin lispro and the duration of action of SC regular human insulin. Similarly, in patients with type 2 DM, INH exhibited a more rapid onset of action than SC regular human insulin. The glucose lowering activity over the first 120 minutes after administration was significantly greater for INH than SC regular insulin. In patients with type 1 DM, the rise in postprandial blood glucose 1 hour after INH administration was lower than after SC regular insulin. In patients with type 2 DM, the post-prandial glucose lowering-activity was comparable for INH- and SC regular insulin-treated patients.

Healthy Patients

Glucose levels were measured in all studies conducted in healthy patients under fasting conditions. In general, glucose responses to INH reflected the insulin levels in these studies.

The pharmacodynamics of INH in healthy patients was specifically studied using the euglycemic clamp technique in fasting patients in Studies 017 (healthy patients) and 1016 (healthy Japanese patients). In these studies, the glucose level was held nearly constant to a pre-defined level by varying the glucose infusion rate (GIR), and the insulin action profile was evaluated from the glucose infusion rate. Study 1016 is discussed in Section 4.2.3.

Study 017 compared the pharmacodynamic responses to three doses of different insulin preparations: INH (2x3 mg), SC insulin lispro (18 U), and SC regular insulin (18 U). INH showed a statistically significant earlier onset of glucose-lowering activity reflected in $T_{50\text{-early}}$ than SC regular insulin (Table 24).

Table 24. Statistical Analysis of GIR Pharmacodynamics following Inhaled Insulin Compared with Following SC insulin lispro or Regular Insulin

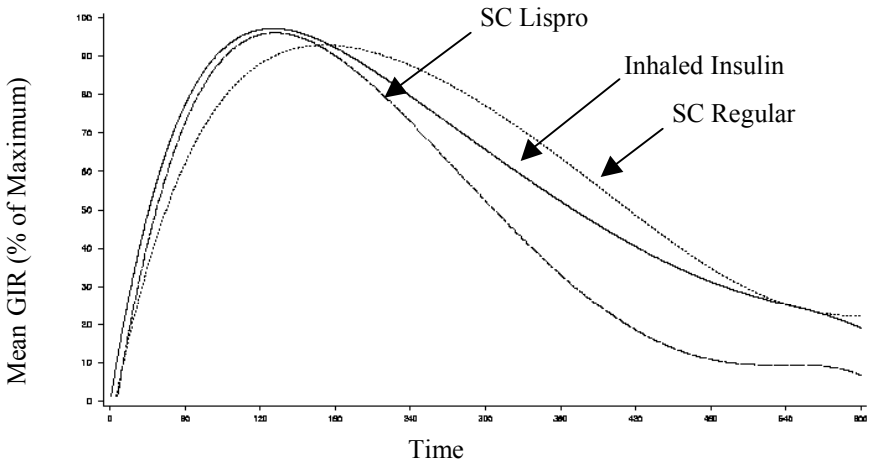
Parameter	INH (A)	Lispro (B)	SC (C)	Ratio/Difference*	90% CI
GIR $AUC_{0\text{-}60}$ (g/kg)	0.23	0.24	0.17	134% (A/C)	(107%,168%)
				140% (B/C)	(112%, 176%)
				96% (A/B)	(76%, 120%)
GIR $AUC_{0\text{-}180}$ (g/kg)	1.21	1.45	1.17	103% (A/C)	(90%, 119%)
				124% (B/C)	(108%, 142%)
				84% (A/B)	(73%, 96%)
GIR $AUC_{0\text{-}360}$ (g/kg)	2.36	2.74	2.60	91% (A/C)	(80%, 103%)
				105% (B/C)	(93%, 119%)
				86% (A/B)	(76%, 98%)
GIR $AUC_{0\text{-}600}$ (g/kg)	3.03	3.16	3.44	88% (A/C)	(77%, 101%)
				92% (B/C)	(80%, 105%)
				96% (A/B)	(84%, 110%)
GIRmax (mg/kg/min)	8.71	11.2	9.77	89% (A/C)	(79%, 101%)
				115% (B/C)	(101%, 130%)
				78% (A/B)	(69%, 88%)
GIR Tmax (min)	143	137	193	-49 (A-C)	(-77, -21)
				-56 (B-C)	(-84, -28)
				7 (A-B)	(-22, 35)
T50-early (min)	32	41	48	-17 (A-C)	(-24, -10)
				-7 (B-C)	(-14, 0)
				-10 (A-B)	(-17, -3)
T50-late (min)	387	313	415	-29 (A-C)	(-71, 13)
				-103 (B-C)	(-145, -61)
				74 (A-B)	(32, 116)

Adjusted geometric means for AUCs and GIRmax and adjusted arithmetic means for Tmax, T50-early and T50-late; AUC and GIRmax are baseline adjusted values
INH = inhaled insulin; SC = SC regular insulin
* Ratio of AUC or Cmax, difference of Tmax, T50-early or T50-late

GIR T_{max} of INH was comparable to that of SC insulin lispro and significantly shorter than that of SC regular human insulin. The duration of action reflected in the difference between GIR $T_{50\text{-late}}$ and GIR $T_{50\text{-early}}$ of INH was longer than that of SC insulin lispro (this difference reached statistical significance) and comparable to that of SC regular human insulin.

The mean change from baseline GIR (expressed as a percentage of GIR_{max}) for each treatment over time is shown graphically in Figure 9.

Figure 9. Mean GIR Normalized to GIR_{max} for Each Patient and Treatment versus Time (Study 017)



Individual mean values over time were fitted to the polynomial function to smooth the profile for this graphical presentation.

Patients with DM

The glucose response to INH in patients with DM was assessed in fasting patients with type 2 DM in Studies 1004 and 1003, and in fasting patients with gestational DM (GDM) and postgestational DM (PGDM) in Study 1007. The postprandial pharmacodynamics of INH was assessed in patients with type 1 DM in Study 021 and in patients with type 2 DM in Study 101. The pharmacodynamic results and statistical analyses are presented in (Table 25 and Table 26).

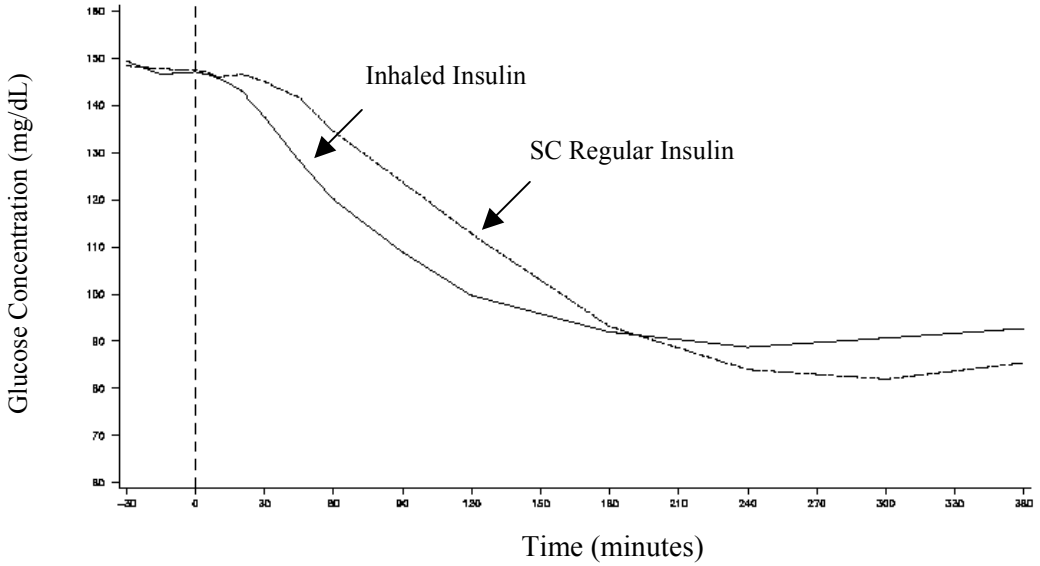
Table 25. Adjusted Mean Glucose Parameters in Patients with Diabetes Mellitus

Study	Parameter	Comparison	Adjusted Mean*	Ratio/Difference†	90% CI
Fasting Type 2					
1004	AUC0-120glc	Inhaled vs SC	2570 vs 1400	184%	129%, 264%
	AUC0-360glc	Inhaled vs SC	14800 vs 14300	104%	82%, 131%
	Cmaxglc	Inhaled vs SC	58.8 vs 66.9	88%	70%, 111%
	Tmaxglc	Inhaled vs SC	248 vs 278	-31	-69, 7
1007	AUC0-360glc	Inhaled vs SC	6080 vs 5580	109%	80%, 148%
	Cmaxglc	Inhaled vs SC	28.8 vs 28.1	103%	81%, 130%
	Tmaxglc	Inhaled vs SC	210 vs 275	-65	-142, 12
Postprandial					
Type 1					
021	AUC0-120glc	Inhaled vs SC	19700 vs 21000	94%	88%, 100%
	C60	Inhaled vs SC	174 vs 189	92%	86%, 99%
	C120	Inhaled vs SC	178 vs 185	96%	87%, 106%
	C240	Inhaled vs SC	102 vs 84	122%	99%, 149%
	Cmaxglc	Inhaled vs SC	206 vs 216	95%	88%, 102%
Type 2					
101	AUC0-180glc	Inhaled vs SC	44500 vs 45600	98%	90%, 106%
	Cmaxglc	Inhaled vs SC	281 vs 288	98%	91%, 105%
	C120	Inhaled vs SC	261 vs 267	98%	88%, 109%
	Excursion	Inhaled vs SC	124 vs 160	77%	68%, 88%

Parameter Units: AUCglc (mg.min/dL); Cmaxglc (mg/dL); Tmaxglc (min); C60, C120, C240 (mg/dL); Excursion (mg/dL)
*Adjusted geometric mean for AUC and Cmax, adjusted arithmetic mean for Tmax and excursion
†Ratio of AUC or Cmax, difference of Tmax or excursion

In Study 1004, the glucose-lowering activity over the first 120 minutes, $AUC_{0\text{-}120glc}$, was significantly greater for INH than for SC regular insulin. The difference in AUC_{glc} lessened over time. The time to peak glucose-lowering activity, T_{maxglc}, occurred approximately 31 minutes earlier for INH than for SC regular insulin, although the difference in T_{maxglc} between the two insulin treatments did not reach statistical significance. The glucose concentration profile is shown in Figure 10.

Figure 10. Mean Glucose Concentrations After 4 mg Inhaled Insulin or 12 U Subcutaneous Regular Insulin to Fasting Patients with Type 2 DM



INH pharmacodynamics in fasting patients with type 2 DM was also evaluated using the euglycemic clamp technique in Study 1003, a study in smokers and nonsmokers. Consistent with results in healthy patients, in nonsmokers INH had a faster onset of action than SC regular insulin and a comparable duration of action (Table 26).

Table 26. Mean* Glucose Infusion Rate Parameters for Patients with Type 2 DM (Study 1003-Nonsmokers)

	GIR AUC_{0-120} (g/kg)	GIR AUC_{0-240} (g/kg)	$GIRAUC_{0-480}$ (g/kg)	GIRmax (mg/kg/min)	GIRTmax (min)	T50-early (min)	T50-late (min)
Inhaled Insulin	0.10	0.25	0.44	2.05	161	57	346
SC regular	0.028	0.19	0.67	2.82	322	139	428

* Adjusted geometric means for AUC and GIRmax; Least square means for Tmax, T50-early and T50-late; AUC and GIRmax are baseline adjusted values

Postprandial pharmacodynamic responses to INH were addressed in patients with type 1 DM in Study 021. Results from this study showed that INH produced a lower postprandial glucose concentration at 1 hour postdose, and the postprandial glucose-lowering activity was generally comparable to that obtained with SC regular insulin over the first 4 hours after treatment. As an apparent 16% lower insulin AUC0-360 was observed for INH compared with equivalent doses of SC regular insulin, it would be expected that when insulin doses resulting in comparable systemic exposure for INH and SC insulin were administered, INH would likely demonstrate better postprandial glycemic control due to its more rapid absorption compared to SC regular insulin. Post-prandial glucose-lowering activity was comparable for INH and SC insulin-treated patients with type 2 DM.

4.2.2. Special Populations

INH produced a more rapid glucose response than SC regular insulin in patients with GDM or PGDM type 2 DM in Study 1007 (Table 25). The results were consistent with the changes in the pharmacokinetics profile (Section 4.1.2), and the response profile was similar to that produced in non-pregnant patients with type 2 DM (Section 4.2.1).

4.2.3. Effect of Intrinsic Factors

Pharmacodynamic results comparing INH to SC insulin for Japanese patients in Study 1016 were consistent with the pharmacokinetic results for that study (Section 4.1.3) and were generally similar to results observed in non-Japanese patients: INH resulted in an earlier onset of action than and a similar offset of action to SC regular insulin (Table 27).

Table 27. GIR Parameters Following Administration of 1 mg, 3 mg, or 6 mg of Inhaled Insulin and 12 U SC Regular Insulin to Healthy Japanese Male Patients (N=16) (Study 1016)

	GIR AUC0-60 (mg/kg)	GIR AUC0-600 (mg/kg)	GIRmax (mg/kg/min)	GIR Tmax (min)	T50-early (min)	T50-late (min)
INH 1x1 mg	32.9	753	2.73	200	80	389
INH 1x3 mg	105	1520	4.72	154	47	376
INH 2x3 mg	128	2370	6.45	174	41	446
SC 12 U	82.9	2460	7.94	174	61	360

INH = inhaled insulin; SC = SC regular insulin
Geometric mean for GIR AUC and GIRmax, arithmetic mean for GIR Tmax, T50-early and T50-late

4.2.4. Effect of Extrinsic Factors

As was the case for pharmacokinetics, smoking significantly altered the pharmacodynamics of INH in both healthy patients and patients with type 2 DM.

The pharmacodynamic effect of INH in smokers with type 2 DM was evaluated in Study 1003 using the glucose clamp procedure. The time action profile showed changes consistent with the PK profile: smokers experienced a more rapid onset of action (shorter glucose infusion rate [GIR] T_{max}, and $T_{50\text{-early}}$), greater maximum effect (GIR_{max}), and a greater total effect (GIR AUC) (mainly from a much greater effect during the first 2-3 hours after dosing), compared with nonsmokers.

4.2.5. Reproducibility/Variability

The intrasubject variability of INH pharmacodynamics was assessed in patients with type 2 DM in Studies 1004 (elderly, obese) and 1003 (a study in smokers and nonsmokers), and in patients with type 1 DM in Study 021. The intrasubject variability of INH in glucose-lowering activity was generally comparable to SC regular insulin in patients with type 1 or type 2 DM, regardless of smoking status.

4.3. Insulin Deposition/Disposition

Because rhu insulin is identical to endogenous insulin, the systemic distribution and elimination is expected to be the same, although this has not been studied. Insulin deposition, however, was examined in an exploratory scintigraphic study (Study 008) using ^{99m}Tc-labeled insulin powder of various particle sizes (1 µm, 2 µm, 4 µm), an early prototype inhaler and powder formulation. The study showed that of the labeled material delivered to the body from the inhaler, approximately 70% reached the lung with the remaining 30% being deposited in the oropharynx (Table 28).

Table 28. Distribution of Radiolabel (Study 008)

	A	B	C
Amount delivered to body*(%)	50.5*	66.6*	41.6*
	Percent of total-body dose (%)		
Oropharynx	34.3	28.7	32.0
Total lung	65.4	70.7	66.6

A: treatment with labeled insulin blister of about 4 µm MMAD particle size powder
B: treatment with labeled insulin blister of about 2 µm MMAD particle size powder
C: treatment with labeled insulin blister of about 1 µm MMAD particle size powder
*As percentage of total count

Due to limitations imposed by atypical delivery efficiency of the powders that were specially prepared for the study, the results of this exploratory study cannot be directly applied to the clinical formulation and device. Nevertheless, the results provide evidence of the deposition of INH in the lung consistent with literature data for aerosols of similar particle size ranges. Furthermore, there is no evidence from human or animal studies of accumulation of insulin inhalation powder in the lung.

4.4. Special Studies - Relationship of Insulin Pharmacodynamics and Antibody Levels

Treatment with INH for 24 weeks resulted in elevated insulin antibodies in patients with DM, but there was no evidence of impaired postprandial glucose control or prolongation of insulin action.

In the INH Phase 2/3 development program, administration of INH has been associated with increased mean insulin antibody levels to values greater than those experienced by patients treated with SC insulin or OAs. Because insulin antibodies could theoretically have an impact on glucose control, Study 1026, an exploratory 24-week, prospective, randomized, open-label, parallel-group comparative trial, was conducted in 45 patients with type 1 DM to understand the effects, if any, of elevated insulin antibody levels on postprandial glucose responses to insulin.

As was observed in the Phase 2/3 clinical trials, 24 weeks of treatment with INH produced a greater increase in insulin antibody levels than did SC regular insulin treatment. The change-from-baseline postprandial glucose and the GIR pharmacodynamics of the INH regimen were not different, however, from those in patients who used a SC insulin regimen. The results provided no evidence that the increased antibody levels in INH-treated patients affected postprandial glucose tolerance or prolonged the duration of action of inhaled insulin (Table 29, Table 30, and Table 31).

Table 29. Summary of Insulin Antibody Levels (Study 1026)

	Mean (Median) Insulin Antibodies (µU/mL)					
	Observed				Change from Baseline	
	N	INH	N	SC	INH	SC
Baseline	23	3.50 (1.05)	22	2.62 (1.05)		
Week 12	23	51.8 (24.0)	21	2.43 (1.05)	48.3 (20.3)	0.05 (0.00)
Week 24	23	101 (54.0)	18	4.30 (1.05)	97.9 (51.2)	1.87 (0.00)

Baseline is the week-3 assessment
INH = inhaled insulin; SC = SC regular insulin

Table 30. Summary of Postprandial Glucose Results: Analysis of Change from Week 0 Baseline in Postprandial Glucose Parameters (Study 1026)

Parameter		Change from Week 0 (week x/week 0) Inhaled	Subcutaneous	Ratio / Difference Ratio (INH/SC)	90% CI
$Cmax_{glc}$ * (mg/dL)	Week 12	0.99	1.05	94%	(89%,100%)
	Week 24	0.98	0.99	99%	(95%, 103%)
AUC0-60glc * (mg.min/dL)	Week 12	0.98	1.06	93%	(88%, 99%)
	Week 24	0.96	0.98	98%	(92%, 105%)
AUC0-120glc * (mg.min/dL)	Week 12	0.97	1.10	88%	(81%, 97%)
	Week 24	0.95	0.97	98%	(88%, 108%)
		(week x – week 0)		Difference (INH – SC)	
$Tmax_{glc}$ (min)**	Week 12	–40	–6	–34	(–65, –2)
	Week 24	–29	–30	1	(–39, 42)

INH = inhaled insulin; SC = SC regular insulin
*Adjusted geometric mean changes vs baseline. The changes from week 0 values are ratios of week 12 or 24 to the baseline value.
** Adjusted arithmetic mean changes

Table 31. GIR Pharmacodynamics: Analysis of Change from Week 0 Baseline in GIR Parameters (Study 1026)

Parameter		Change from Week 0 (week x/week 0)* Inhaled	Subcutaneous	Ratio / Difference Ratio (INH/SC)	90% CI
GIR AUC0-60 (mg/kg)	Week 12	1.19	0.91	130%	(87%, 194%)
	Week 24	0.84	0.94	89%	(50%, 158%)
GIR AUC0-120 (mg/kg)	Week 12	0.94	0.96	99%	(74%, 131%)
	Week 24	0.76	1.02	75%	(51%, 111%)
GIRmax (mg/kg/min)	Week 12	0.92	1.01	91%	(77%, 108%)
	Week 24	0.83	1.00	82%	(68%, 99.8%)
		(week x – week 0)†		Difference (INH – SC)	
GIR Tmax (min)	Week 12	–27	19	–46	(–119, 28)
	Week 24	–15	–37	22	(–34, 79)
GIR T50-early (min)	Week 12	0	16	–16	(–80, 47)
	Week 24	–6	–24	18	(–7, 43)
GIR T50-late (min)	Week 12	–35	19	–54	(–139, 31)
	Week 24	–8	–54	46	(–37, 129)
Duration of Insulin Action (T50-late minus T50early)	Week 12	–9	17	–27	(–109, 56)
	Week 24	–3	–32	29	(–49, 108)

INH = inhaled insulin; SC = SC regular insulin
*Adjusted geometric mean changes; changes from week 0 values are ratios of week 12 or 24 to the baseline value.
†Adjusted arithmetic mean changes; changes from week 0 values are differences of week 12 or 24 from the baseline value.

Insulin antibodies are also discussed in Section 6.6.

4.5. Clinical Pharmacology Summary

The data from the clinical pharmacology development program support the following conclusions:

- INH is absorbed more rapidly than SC regular insulin and as rapidly as SC insulin lispro.
- Age, gender, and BMI do not have apparent effects on the pharmacokinetics of INH.
- INH is apparently absorbed more rapidly in patients with COPD (without DM) compared to healthy patients.
- INH is absorbed more rapidly and to a greater extent in smokers (with or without DM) compared to nonsmokers.
- INH combines the rapid onset of action seen with SC rapid-acting insulin analogs such as SC insulin lispro and the duration of action of the short-acting SC regular human insulin.
- The intrasubject variability of INH pharmacokinetic and associated pharmacodynamic parameters is comparable to that of SC regular insulin in patients with DM.

5. OVERVIEW OF EFFICACY

This section provides an overview of the efficacy data. As mentioned in the Clinical Program Overview, the Phase 2/3 clinical development program has been conducted in three parts: Phase 2 studies, Phase 3 Group I Studies designed to collect primary evidence of efficacy, and Phase 3 Group II designed specifically to collect long-term safety data. The discussion here is based on results of individual studies grouped together by type of DM: type 1, type 2 insulin-using at study entry, and type 2 non-insulin-using at study entry. Data were pooled within each grouping to enable a discussion of the efficacy of INH in special populations.

5.1. Description of the Clinical Program

The efficacy of INH has been assessed in 20 (17 completed, 3 ongoing) studies. As mentioned in the Clinical Program Overview, the Phase 2/3 clinical development program has been conducted in three parts: Phase 2 studies, Phase 3 Group I studies designed to collect primary evidence of efficacy, and Phase 3 Group II studies designed specificall to collect long-term safety data. These Phase 2/3 studies were designed to evaluate the role of INH as part of a treatment regimen across the spectrum of patients who would be expected to use the product: insulin-using patients with type 1 (102, 106, 107, 1009, 1022, 1026, 1027) or type 2 (103, 108, 1029) DM, patients with type 2 DM poorly controlled by diet and exercise (110), and patients with type 2 DM poorly controlled with one or more OAs (104, 109, 1001, 1002).

This efficacy summary focuses on results for adult patients from 3- and 6-month completed, controlled Phase 3 Group I Studies (106, 107, 108, 109, 110); and analyses performed at 6 months in Phase 3 Group I Studies 1001 and 1002, all of which had efficacy as a primary endpoint. Supportive information is provided by the controlled Phase 2 Studies (102, 103, and 104), the controlled Phase 3 Group II Studies designed specifically to collect long-term safety data (1022, 1026, 1027, and 1029), and the uncontrolled long-term extensions of Phase 2/3 studies (102E, 103E, 104E, 1036, 111). The efficacy of INH beyond 6 months is addressed in the 2-year interim analyses of ongoing controlled Phase 3 Group II Studies 1022 and 1029, with data from completed amendments of 2-year Studies 1001 and 1002, and with data from the Phase 2/3 extension studies in which some patients have received INH for more than 7 years. It should be noted that Studies 1022 and 1029 were originally designed as 2-year controlled trials that have now been extended to 5-year controlled trials for the primary purpose of obtaining longer-term (i.e. 5 year) PFT data. The 2-year timepoint, which was the full duration of the study as originally designed, has now become an "interim" timepoint. Analyses of these interim timepoints have been completed; they provide important efficacy assessment and are included in this document.

The study groupings are summarized in Table 32

Table 32. Controlled Phase 2/3 INH Clinical Program – Study Categories

	Phase 2	Phase 3 Group I (Primary Efficacy)	Phase 3 Group II (Long-term Safety**)
Type 1 DM	102	106, 107, 1009*	1022, 1026, 1027
Type 2 DM insulin-using	103	108	1029
Type 2 DM oral agent-using	104	109, 1001/1002	1001/1002
Type 2 DM diet and exercise alone		110	

* Pediatric study

**1026 was a 6-month glucose-pharmacodynamics study and 1027 was a 3+3 month study specifically designed to look at PFT/antibody onset and offset. The 6-month original protocol of Studies 1001/1002 was designed to collect primary evidence of efficacy, while the 12-month and 24-month amended protocols were designed specifically to collect long-term safety data.

5.1.1. Patient Population

Patients with previously diagnosed type 1 DM or type 2 DM were eligible for participation in the clinical development program. Those who had previously received insulin treatment must have been on a stable insulin regimen involving at least two injections daily of insulin or an insulin analog for at least two months prior to screening. Those with type 2 DM, and not taking insulin at study entry, must have been on a stable regimen of diet and exercise or OA therapy for at least two months prior to screening. A demonstrated fasting plasma C-peptide level of ≤ 0.2 pmol/ml or ≥ 0.2 pmol/ml was required for patients with type 1 DM or type 2 DM, respectively.

The exclusion criteria applied in the INH Phase 2/3 program were chosen to guarantee the appropriate evaluation of efficacy and safety, and to assure participant safety, while still allowing generalization to a broad target population. Patients with "brittle" diabetes or a predisposition to severe hypoglycemia were excluded, as were patients with clinically significant major organ disorders. Well-controlled, stable disorders, such as essential hypertension and complications directly related to diabetes (e.g., peripheral neuropathy, mild nephropathy, or retinopathy) were not grounds for exclusion. Because INH is administered by inhalation, additional exclusion criteria relating to the respiratory system were applied. These included poorly controlled asthma, significant chronic obstructive pulmonary disease (COPD), other significant respiratory disease, significantly abnormal chest X-ray or pulmonary function test results, or smoking within 6 months of randomization.

5.1.2. Study Design

Studies, other than Phase 2/3 extensions, employed a randomized, multi-center (Study 1026: single center), active-controlled, open-label, parallel-group design. Qualified patients entered a 4-week baseline lead-in period during which they received instruction regarding diet (as recommended by the American Diabetes Association) and performed home glucose monitoring. Patients were instructed to perform 30 minutes of moderate exercise at least three days per week. During the lead-in period, patients received their usual or a similar treatment regimen as specified in the protocol. Patients were also taught how to administer INH using the insulin inhalation device.

During the treatment period, patients returned to the clinic at specified times and were contacted at other times by telephone. Patients had to perform home blood glucose monitoring at least 4 times daily, just prior to meals and at bedtime. In Study 107, home glucose monitoring was performed 5 times daily with an additional measurement made 2 hours following a meal. Home glucose monitoring results were assessed regularly and dosing regimens were adjusted as appropriate.

Sustacal® meal studies were performed in Studies 102, 103, 104, 106, 107, 108, 109, and 110. Interpretation of the test meal post-prandial glucose results was patient to several limitations: (1) Baseline glucose concentrations prior to insulin dosing and meal challenge were not controlled and standardized, (2) Insulin doses administered prior to meal challenge were variable and not necessarily optimized for calorie loads, and (3) Some variability was possible with regard to proper execution of these tests. Study 1026 was conducted to address these limitations and included standardized meal challenges as well as euglycemic clamp studies.

Studies 1001 and 1002 were amended to increase in duration from 24 to 52 and then to 104 weeks. Patients in studies 1001 and 1002 were allowed to alter their treatment regimens after 6 months by addition of another OA or SC insulin, if appropriate.

Patients who completed the Phase 2 Studies 102, 103, or 104 were eligible to enroll in open-label, extensions of those studies after amendment of the original protocols. At the completion of the parent study, eligible patients could choose INH or the control regimen for the first one-year extension and

thereafter, if applicable. Most patients who continued in the extension studies voluntarily selected INH as their treatment. Thus, in these Phase 2 extensions, a naïve patient cohort, which included patients who did not participate in the parent study, was recruited to serve as a matched control. HbA_{1c} and fasting plasma glucose were determined at specified times in order to assess long-term glycemic control. No new matched control patients were recruited after one year because of difficulty in enrollment. Due to the difficulty of retaining patients in the control groups (most wanted to switch to the INH treatment regimen), the control arm was completely dropped at the two-year time point. The Phase 2 extension studies were combined into a single study, Study 1036, in 2003.

Patients who completed studies 106, 107, 108, 109, 110, or 1009 were eligible to enter Study 111, an open-label, uncontrolled, nonrandomized, long-term safety study of up to three years. All patients in Study 111, including those coming from the control arm of a previous study, received INH; thus, there were no control patients in Study 111. Study 111 was amended in 2002 to allow the evaluation of trends in pulmonary function after discontinuation of inhaled insulin. Patients were randomized to receive INH for an additional 6 months of treatment or to immediately discontinue INH. The pulmonary function of both groups was monitored for six months after discontinuation of inhaled insulin.

Because all studies were open label due to the unique delivery system for INH, a number of steps were taken to ensure against the introduction of bias into analyses. These included treating different treatment groups equally (treatment to goal: trying to get best glycemic control while minimizing hypoglycemia), handling all patients in a uniform way, requiring all patients (even those receiving OAs) to monitor blood glucose, and usage of variable block sizes in the randomization.

5.1.3. Study Drug Administration

INH was supplied as 1 mg and 3 mg doses. Early Phase 2/3 protocols recommended using 1 or 2 inhalations of either 1 or 3 mg of insulin three times daily immediately prior to meals and following glucose monitoring. Based on a review of data from the entire Phase 2/3 program, over 60% of patients used more than 2 inhalations for at least one dosing session.

Initial INH doses in Studies 102, 103, 104, 106, 107, 108, 109, 110, 1009, 1001, and 1002 were based on body weight ranges as shown in Table 33.

Table 33. INH Initial Dosing Guidelines

	Initial Dose (Number of Inhalations)		
Body Weight (kg)	**1 mg Strength**	**3 mg Strength**	**Approximate SC insulin Dose Equivalent (U)**
20-44	1	-	3
45-59	2	-	6
60-79	-	1	9
80-99	1	1	12
>100	-	2	18

Upon completion of these studies, the inhaled insulin dosing data were reviewed to evaluate the appropriateness of the dosing guidelines used, and to understand the relationship between actual dose taken and body weight. It was observed that, on average, patients with type 1 DM received INH treatment at a dose of 0.15 mg/kg body weight per day during the first week of treatment, and patients with type 2 DM received an average dose of 0.13 mg/kg body weight per day (Table 34).

Table 34. Total Average Daily Inhaled Insulin Dose per Kilogram of Body Weight During the First Week of Treatment - Controlled Phase 2/3 Studies 102, 103, 104, 106, 107, 108, 109, 110, 1009

			Average Total Daily Inhaled Insulin Dose (mg/kg)				
Type	**Study**	**N**	**Mean**	**Median**	**SD**	**Min**	**Max**
Type 1							
	1009	61	0.191	0.156	0.112	0.068	0.647
	102	34	0.147	0.143	0.048	0.061	0.268
	106	170	0.153	0.145	0.061	0.042	0.473
	107	162	0.130	0.118	0.066	0.021	0.380
	Total	427	0.149	0.140	0.074	0.021	0.647
Type 2 Non-Insulin-Using at Study Entry							
	104	33	0.117	0.125	0.045	0.024	0.256
	109	207	0.125	0.121	0.056	0.012	0.347
	110	75	0.111	0.110	0.047	0.026	0.261
	Total	315	0.121	0.120	0.053	0.012	0.347
Type 2 Insulin-Using at Study Entry							
	103	28	0.147	0.146	0.045	0.061	0.246
	108	149	0.133	0.134	0.054	0.027	0.304
	Total	177	0.136	0.138	0.052	0.027	0.304
All Type 2	Total	492	0.126	0.125	0.053	0.012	0.347
All Type 1 and 2	Total	919	0.137	0.131	0.065	0.012	0.647

With this experience, a starting dose of 0.15mg/kg body weight per day, divided among 3 pre-meal doses, was suggested for use in subsequent studies. This dose was felt to be a reasonable starting point for most people from which to evaluate individual requirements since most patients titrated their dose upwards thereafter.

Subsequent recommended INH dosing was based on the patient's empiric response and was intended to achieve specific pre-meal and bedtime target glucose values, depending upon the study (Table 35).

Table 35. Blood Glucose Target Values

	Blood Glucose, mg/dL	
Study	**Pre-meal Target**	**Pre-Bedtime Target**
102, 103, 104	100-160	100-160
106, 108, 1009, 109, 110, 111, 1001*, 1002*	80-140	100-160
107	80-120	100-140
1022, 1026**, 1027, 1029	80-120	100-140

*A pre-bedtime target was not specified in Studies 1001 and 1002
**1026 also had a 2-hour postprandial target of <180 mg/dL (9.9 mmol/L)

As with any insulin, the dosage of INH was to be individualized and determined in accordance with the needs of the patient. Dose adjustment could be required based on the meal size and nutrient composition, time of day (e.g., higher insulin requirements in the morning), pre-meal blood glucose concentration and recent or anticipated exercise.

Treatment regimens are shown by study in Table 2. Many of the comparators and regimens used, as well as the standards of efficacy applied, were in common use at the time when these trials were originally designed and conducted. Thus, insulin analogs were not allowed in the earlier phase 2/3 studies (with the exception of Study 1009), but were allowed in Studies 1022, 1027, and 1029. In addition, Studies 107

and 1026, and subsets of Studies 1022 and 1029 can be considered comparisons of intensive treatment regimens since the comparator arms in these studies included TID short-acting insulin. Patients with type 1 DM or type 2 DM (insulin-using) received an intermediate- or long-acting SC insulin in addition to their short-acting insulin (INH or SC insulin).

Similar principles of dose adjustment to those described for INH were employed for SC insulin treatment. No dosage adjustments of any OA were permitted during the studies, except in Studies 1001 and 1002, which had protocol-specified dosage adjustments to OAs. Following the removal of troglitazone from the market, patients who received troglitazone were required to switch immediately to rosiglitazone.

5.2. Efficacy Data Analysis

The objective of Studies 106, and 107, conducted in patients with type 1 DM, and Study 108, conducted in insulin-using patients with type 2 DM, was to demonstrate that INH is non-inferior to SC insulin. The objective of Studies 102 and 1009 (type 1 DM) and Study 103 (type 2 DM) was to show similarity of INH to SC insulin.

Studies 104, 109, and 110, conducted in patients with type 2 DM not using insulin at study entry, were designed to demonstrate the superiority of INH to oral agent comparator treatments with regard to the primary endpoint.

Studies 1001 and 1002, also conducted in patients with type 2 DM not using insulin at study entry, compared INH to an OA (metformin in Study 1001, glibenclamide [glyburide] in Study 1002) as adjunctive therapy after 24 weeks of treatment. Patients were stratified on the basis of baseline HbA_{1c} (low stratum: $8\% \leq HbA_{1c} \leq 9.5\%$; high stratum: $9.5\% < HbA_{1c} \leq 12\%$). The objective of both studies was to demonstrate the superiority of INH in high stratum patients and the non-inferiority of INH in low stratum patients compared to the alternative treatment.

The Phase 2/3 extension studies (1036, 111) and some Phase 3 studies (1001 [2-year], 1002 [2-year], 1026, 1022, 1027, and 1029) were performed to evaluate safety primarily (Study 1026 was designed to evaluate pharmacokinetic and pharmacodynamic parameters). They included a number of efficacy parameters in common with the other Phase 2/3 Studies as secondary endpoints.

5.2.1. Endpoints

The change in HbA_{1c} from baseline to end of study was the primary efficacy endpoint except in Study 110, in which the primary endpoint was the percent of patients achieving adequate glycemic control (defined as $HbA_{1c} < 8\%$) at end of study. The use of change from baseline in HbA_{1c} as the primary endpoint is in accordance with available guidance.

The main secondary endpoints were:

- Percent of patients attaining end-of-study $HbA_{1c} < 8.0\ \%$ or $< 7.0\ \%$ (except Study 110)
- Mean end-of-study change from baseline in HbA_{1c} (Study 110, only)
- Change in fasting plasma glucose and meal glucose response (2-hour post-prandial glucose concentration and glucose increment)
- Body weight
- Hypoglycemic events (incidence)
- Mean daily insulin doses
- Patient-reported outcomes

Some studies included minor, additional secondary endpoints such as total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and serum insulin.

Definition of Hypoglycemia

Three definitions of hypoglycemia were applied:

1. Protocol-specified mild-moderate: (1) Characteristic symptoms of hypoglycemia without glucose measurement and prompt resolution with food intake, SC glucagons, or intravenous glucose, or (2) characteristic symptoms of hypoglycemia with measured blood glucose of ≤ 59 mg/dL, or (3) a glucose measurement of ≤ 49 mg/dL with or without symptoms.
2. Protocol-specified severe:
   Phase 2 Studies: patient required the assistance of another person; patient experienced coma and/or seizure. The Phase 3 definition of severe was applied retrospectively to the Phase 2 studies for consistency.
   Phase 3 Studies: (1) patient was unable to treat him/herself; and (2) patient exhibited at least one neurological symptom (memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness); and (3) patient had a measured blood glucose of ≤ 49 mg/dL or, if blood glucose was not measured, symptoms resolved with oral carbohydrates, SC glucagon, or intravenous glucose. All three conditions had to be met for an event to be considered severe.
3. Agency-specified definition: patient had a blood glucose level of ≤ 36 mg/dL or required assistance.

Results based on the third definition were applied retrospectively to all studies at the request of the agency.

5.2.2. Summary of Statistical Methods

Analysis Sets

The Intent-to-Treat (ITT) Set (also termed Full Analysis Set [FAS]) was defined as all randomized patients with a baseline and at least one windowed post-baseline measurement. This set was analyzed according to the randomized treatment group and was the protocol-specified primary analysis population in superiority trials.

The Evaluable Set (also termed Per Protocol Set) was a subset of the ITT set and included patients without major protocol violations, who had participated for at least half of the planned duration of the study, received the protocol-required treatment as assigned by the randomization scheme, and had at least one evaluable post-baseline HbA_{1c} measurement. This was the protocol-specified primary analysis set for non-inferiority trials in accordance with ICH E-9, Section 5.2.3.

Missing data were handled using a last observation carried forward (LOCF) approach. In the event of missing final visit data, the last windowed post-baseline measurement was carried forward for the ITT analysis and the last evaluable post-baseline measurement was carried forward for the Evaluable analysis.

At the request of the agency, all results discussed here are for the Full Analysis Set, regardless of study objective.

Primary Efficacy Endpoint

Non-Inferiority Studies (102, 103, 106, 107, 108, 1001 6-month [low stratum]) and 1002 6-month [low stratum])

An analysis of covariance (ANCOVA) model with baseline HbA_{1c} as a continuous covariate, and indicator variables for center and treatment group (inhaled vs. comparator) was fitted to the end-of-study change from baseline HbA_{1c} values and the two-sided 95% confidence interval (CI) of the difference between treatments (INH – comparator) was constructed. The model for Study 1001/1002 had terms for baseline, country, and stratum by treatment. Non-inferiority of INH was demonstrated if the upper limit of the 95% CI did not exceed the pre-specified non-inferiority margin (1.0 % for Phase 2 Studies 102, 103; 0.5 % for Phase 3 Group I Studies 106, 107, 108, 1001, 1002). The FDA specified the use of 0.4% as the non-inferiority margin, and this is noted in the appropriate tables and figures.

Superiority Studies (104, 109, 110, 1001 6-month [high stratum] and 1002 6-month [high stratum])

The same ANCOVA model described for non-inferiority studies was used for the Phase 2 Study 104, and the Phase 3 Group I Study 109, and the p-value associated with the difference between treatments was calculated.

For the Phase 3 Group I Study 110, a logistic regression model with baseline HbA_{1c} as a continuous covariate, and indicator variables for center and treatment group (INH vs. OA) was fitted to the end-of-study natural log of the odds of achieving versus not achieving end-of-study $HbA_{1c} < 8.0\%$. Based on this model, the covariate adjusted odds ratio (OR) was derived by taking the exponent of the coefficient of the treatment group term. Also, the two-sided 95% CI and the p-value associated with the OR were calculated. An OR > 1 indicates that a higher percentage of INH patients attained end-of-study $HbA_{1c} < 8.0\%$, while an OR < 1 indicates a higher percentage of OA patients attained end-of-study $HbA_{1c} < 8.0\%$.

Superiority of INH to OA was demonstrated if the p-value for the difference between treatments was ≤ 0.05 in Studies 104 and 109, and ≤ 0.025 in the high stratum of Studies 1001 and 1002. In Study 110, superiority of INH to OA was demonstrated if the p-value associated with the OR was ≤ 0.05.

Table 36 outlines the statistical criteria on non-inferiority and superiority for the Phase 3 Group I studies that were designed to collect primary evidence of efficacy.

Table 36. Primary Efficacy Endpoint (HbA1c Change from Baseline to End of Study) Analysis - Statistical Criteria

	Pre-specified Non-inferiority Margin		Pre-specified Superiority P-value	
	0.5%	**1.0%**	**≤ 0.05**	**≤ 0.025**
Non-inferiority Studies				
Phase 2: 102, 103		√		
Group I Phase 3: 106, 107, 108	√			
Group I Phase 3: 1001/1002 6-month (low stratum)	√			
Superiority Studies				
Phase 2: 104			√	
Group I Phase 3: 109			√	
Group I Phase 3: 1001/1002 6-month (high stratum)				√
Group I Phase 3: 110			√	

Secondary Efficacy Endpoints

Secondary continuous endpoints such as fasting plasma glucose, 2-hour post-prandial glucose, glucose increment, and body weight were analyzed with an ANCOVA model analogous to the one used for the analysis of the primary endpoint (end-of-study change from baseline in HbA_{1c}). The two-sided 95% CI of the difference between treatments (INH – comparator) was constructed based on these differences.

The percent of patients attaining target end-of-study HbA_{1c} levels was analyzed with a logistic regression model including center and treatment groups as covariates. Based on this model, the covariate adjusted OR and its two-sided 95% CI were calculated.

Survival analysis based on a counting process approach for analyzing recurrent events was performed for the estimation of the risk ratio (RR), defined as the hypoglycemic risk for treatment with INH relative to comparator. A value of RR > 1 indicates a higher risk of hypoglycemia in the INH group, while a value of RR < 1 indicates a lower risk of hypoglycemia in the INH group. The two-sided 95% CI of the RR was also calculated.

The average daily insulin dose was summarized with descriptive statistics by treatment group and analysis time points.

Quality of life (QOL) and treatment satisfaction (SAT) were assessed in Studies 106, 107, 108, 109, 110, 1001, and 1002. The overall null hypothesis was that the effect of INH on quality of life/ patient satisfaction was not different from that offered by the comparator on any QOLSAT scales. This hypothesis was tested against the alternative hypothesis of a difference in either direction. Multivariate analysis of covariance (MANCOVA) was used to test the overall null hypothesis by analyzing the vector of QOLSAT changes from baseline to end of study, using a LOCF approach. Correlations between changes from baseline in HbA_{1c} and changes from baseline in QOL summary factor scores were evaluated using linear and non-linear regression techniques. Comparative patient preference was assessed in Studies 106, 107, 108, and 109: a paired within-person analysis was conducted to evaluate differences on the absolute treatment satisfaction scores referring to injection, and the same questions referring to the inhaler.

Analyses of Patient Subpopulations

To evaluate the effects of INH in patient subpopulations (age, race, gender, and BMI), data from individual studies were pooled and are presented using summary statistics for HbA_{1c} and hypoglycemia. The analysis of the effect of INH across different age groups includes data from patients <18 years of age (Studies 106, 107, 1009). The subpopulations of race, gender, and BMI, are limited to patients ≥ 18 years of age.

The efficacy of INH was also investigated in a subpopulation of 155 adult patients (74 of whom received INH) identified as having mild underlying lung disease (asthma and/or chronic obstructive pulmonary disease). The results are discussed in Section 6.5.

Persistence of Efficacy

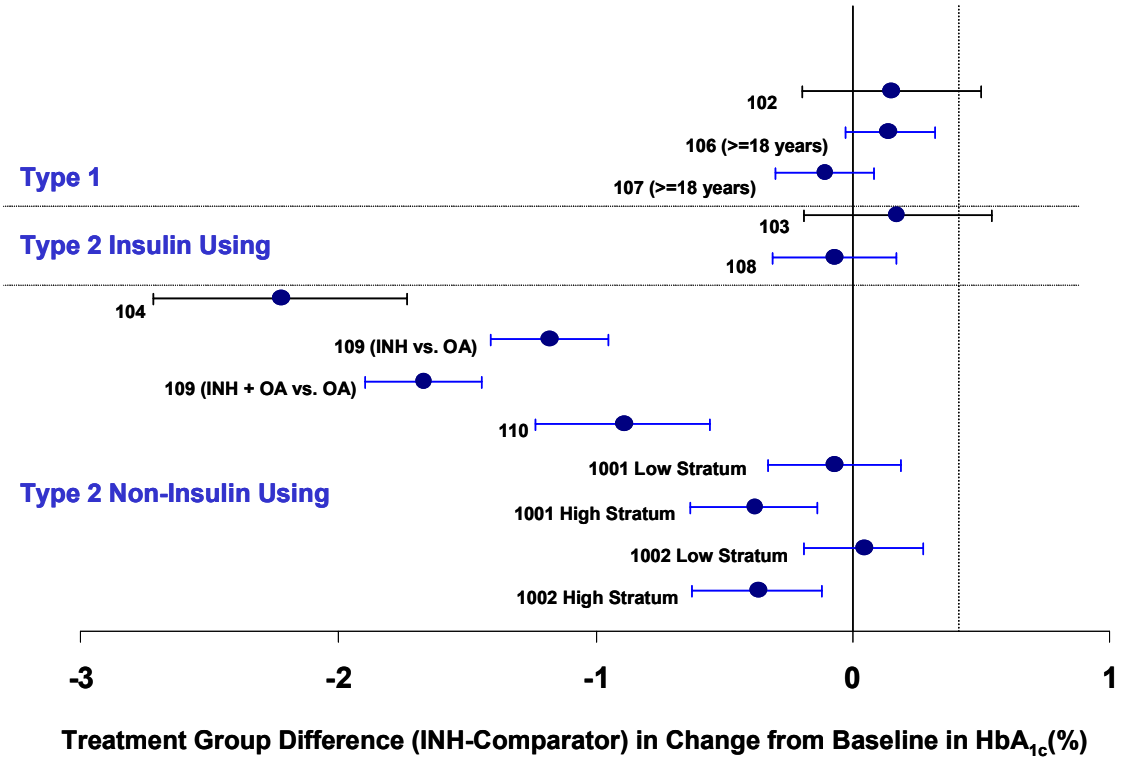
Long-term (≥12 months) use of INH was evaluated in the 1- and 2-year interim analyses of controlled Studies 1022 (type 1 DM) and Study 1029 (type 2 DM, insulin-using), in the 2-year controlled Studies 1001 and 1002 (type 2 DM, non-insulin-using), and in the Phase 2/3 extension studies. In the case of the Phase 2/3 extension studies, data from the previous (parent) studies and the respective extension studies were combined to represent each patient's entire INH exposure experience.

5.3. Efficacy of Inhaled Insulin in the Treatment of Patients with DM

5.3.1. Overview

INH was as effective as SC regular insulin in promoting glycemic control, as assessed by end-of-study change from baseline HbA_{1c}, in patients with type 1 DM, and in patients with type 2 DM who used SC insulin. In patients with type 2 DM who were failing treatment with diet and exercise or OA therapy, INH was superior to OA therapy. The analysis of the difference between treatment groups for adult patients in mean end-of-study change from baseline HbA_{1c}, is summarized for the Phase 2/3 Studies with efficacy as the primary endpoint in Figure 11. In this figure, the CI lines for the Phase 2 studies 102, 103, and 104 are shown using the color black, and the CI lines for the Phase 3 Group I Studies are shown using the color blue.

Figure 11. Treatment Group Differences and 95% Confidence Intervals in Change from Baseline HbA_{1c} (%), Adult Patients – Full Analysis Set



Treatment group difference: <0 favors INH, >0 favors comparator
Protocol-specified non-inferiority margin: 0.5% for Studies 106, 107, 108, 1001 Low Stratum, and 1002 Low Stratum, 1.0% for Studies 102 and 103. FDA-specified non-inferiority margin of 0.4% is indicated by the dotted line..

5.3.2. Study Populations

Within the study groupings (type 1 DM, type 2 DM insulin-using at study entry, type 2 DM non-insulin-using), study populations for all controlled studies were generally balanced across studies and between treatment groups with respect to age, gender, race, and BMI. Patients were predominantly white in all studies, although fully 20% of the type 2 DM population was non-white. Study populations were also balanced across studies and between treatment groups with respect to screening HbA_{1c}, C–peptide, years since diagnosis, and dose of insulin (both short-acting and long-acting, where applicable).

The similarities of the baseline characteristics for patients within each of the three patient groupings (type 1 DM, type 2 DM insulin-using, type 2 DM non-insulin-using) support the validity of comparing results across studies and pooling data across studies (within each grouping) for efficacy evaluations in different subpopulations of patients.

Discontinuation rates ranged between 0% and 18% of patients in any treatment group across the controlled studies (Table 37).

Table 37. Patient Evaluation Groups – Adult Patients with Type 1 or Type 2 DM

N (%)	Randomized	Treated	Completed*	Discontinued	Analyzed for efficacy (FAS)†
Patients with Type 1 DM					
Phase 2 Study					
Study 102					
INH	35	35	35 (100.0)	0	35 (100.0)
SC insulin	37	37	35 (94.6)	2 (5.4)	36 (97.3)
Phase 3 Group I Studies (Designed to Collect Primary Evidence of Efficacy)					
Study 106					
INH	137	137	120 (87.6)	17 (12.4)	136 (99.3)
SC insulin	136	135	123 (91.1)	12 (8.9)	132 (97.8)
Study 107					
INH	103	103	97 (94.2)	6 (5.8)	103 (100.0)
SC insulin	105	105	96 (91.4)	9 (8.6)	103 (98.1)
Phase 3 Group II Studies (Designed Specifically to Collect Long-term Safety Data)					
Study 1022 (1 year)					
INH	291	290	237 (81.7)	53 (18.3)	288 (99.3)
SC insulin	291	290	252 (86.9)	38 (13.1)	286 (98.6)
Study 1022 (2 year)					
INH	291	290	217 (74.8)	68 (23.4)	288 (99.3)
SC insulin	291	290	224 (77.2)	58 (20.0)	286 (98.6)
Study 1026					
INH	24	23	22 (95.7)	1 (4.3)	23 (100.0)
SC insulin	23	22	18 (81.8)	4 (18.2)	20 (90.9)
Study 1027					
INH	110	110	94 (85.5)	16 (14.5)	106 (96.4)
SC insulin	116	116	102 (87.9)	14 (12.1)	108 (93.1)
Insulin-using Patients with Type 2 DM					
Phase 2 Study					
Study 103					
INH	28	28	25 (89.3)	3 (10.7)	28 (100.0)
SC insulin	28	28	26 (92.9)	2 (7.1)	27 (96.4)
Phase 3 Group I Studies (Designed to Collect Primary Evidence of Efficacy)					
Study 108					
INH	149	149	132 (88.6)	17 (11.4)	146 (98.0)
SC insulin	150	149	140 (94.0)	9 (6.0)	149 (100.0)
Phase 3 Group II Studies (Designed Specifically to Collect Long-term Safety Data)					
Study 1029 (1 year)					
INH	316	314	257 (81.8)	57 (18.2)	313 (99.7)
SC insulin	314	311	258 ((83.0)	53 (17.0)	304 (97.7)
Study 1029 (2 year)					
INH	316	316	225 (71.2)	86 (27.2)	303 (95.9)
SC insulin	314	311	237 (76.2)	72 (23.2)	301 (96.8)
Non-insulin-using Patients with Type 2 DM					
Phase 2 Study					
Study 104					
INH + OA	33	33	33 (100.0)	0	32 (97.0)
OA	36	36	36 (100.0)	0	36 (100.0)
Phase 3 Group I Studies (Designed to Collect Primary Evidence of Efficacy)					
Study 109					
INH	105	104	97 (93.3)	7 (6.7)	102 (98.1)
INH + OA	102	103‡	99 (96.1)	4 (3.9)	100 (97.1)
OA	102	99	93 (93.9)	6 (6.1)	96 (97.0)
Study 110					
INH	76	75	71 (94.7)	4 (5.3)	75 (100.0)
Ros	69	68	63 (92.6)	5 (7.4)	67 (98.5)
Study 1001-6 month					
INH + SU	225	222	206 (92.8)	15 (6.8)	214 (96.4)
MET + SU	202	201	175 (87.1)	23 (11.4)	196 (97.5)
Study 1002-6 month					
INH +MET	243	239	219 (91.6)	20 (8.4)	234 (97.9)
GLI + MET	233	231	205 (88.7)	26 (11.3)	222 (96.1)

*Studies 1022 and 1029 are ongoing: results are shown for interim analysis of patients who completed 12 months of treatment and 24 months.
†Full Analysis Set Study 1026 = all randomized patients with a baseline and a post-baseline, postprandial glucose Cmax value from meal challenge study.
‡One patient received INH + OA but was randomized to another treatment

Most discontinuations in each treatment group were for non-treatment-related reasons, including administrative reasons. Of these, patient default was the primary cause of non-treatment related discontinuations and included discontinuations for withdrawn consent, protocol violations, or losses to follow-up. Treatment-related discontinuations resulted primarily from adverse events, lab abnormalities, or insufficient efficacy. In each study, the proportion of patients discontinuing for each reason was generally similar among the treatment groups. Importantly, no patients discontinued due to device failures and only two patients (both with type 1 DM and who both received INH) discontinued because of hypoglycemia across the controlled Phase 2/3 Studies as of 25 June 2004.

5.3.3. Efficacy in Patients with Type 1 DM

HbA1c

The change in HbA_{1c} from baseline to end of study was the primary endpoint in Studies 102, 106, and 107 and a secondary endpoint in Studies 1022, 1026, and 1027. Results of all controlled studies in patients with type 1 DM are shown in Table 38.

Based on the upper limit of 95% confidence intervals (CI) of the adjusted treatment group difference in mean change from baseline in these studies and the pre-specified non-inferiority margins (1.0% in the Phase 2 Study 102, 0.5% in the Phase 3 Group I Studies 106 and 107), INH was non-inferior to SC insulin in promoting and maintaining glycemic control in patients with type 1 DM. In addition, both Phase 3 Group I Studies 106 and 107 also met the requirement for non-inferiority of INH to SC insulin based on the specified margin of 0.4%.

Further support for the non-inferiority of INH to SC insulin comes from the Phase 3 Group II Studies 1022, 1026 and 1027, in which the end-of-study change from baseline HbA_{1c} was a secondary endpoint. Results for INH-treated and SC insulin-treated patients in both Studies 1026 and 1027 were consistent with the results of Studies 102, 106, and 107. Glycemic control was maintained over 24 months for INH- and SC insulin-treated patients in ongoing Study 1022.

Table 38. Analysis of Change from Baseline in Glycated Hemoglobin (HbA_{1c}, %) – Adult Patients with Type 1 Diabetes (Full Analysis Set (ITT))

Study	N*	Unadjusted Mean [SD] Baseline	End of Study	Change	Adjusted Difference (95% CI)†
Phase 2 Study					
102					
INH	35	8.5 [1.1]	7.9 [1.0]	-0.6 [1.0]	0.15 (-0.20, 0.50)
SC insulin	36	8.5 [1.1]	7.7 [0.9]	-0.8 [0.9]	
Phase 3 Group I Studies (Designed to Collect Primary Evidence of Efficacy)					
106					
INH	136	7.9 [0.9]	7.7 [1.0]	-0.2 [0.8]	0.14 (-0.03, 0.32)
SC insulin	132	8.0 [1.0]	7.6 [0.9]	-0.4 [0.8]	
107					
INH	103	7.8 [0.9]	7.5 [0.9]	-0.3 [0.8]	-0.11 (-0.30, 0.08)
SC insulin	103	7.8 [1.0]	7.6 [1.0]	-0.2 [0.8]	
Phase 3 Group II Studies (Designed Specifically to Collect Long-term Safety Data)					
1022 (1 year)‡					
INH	288	7.4 [1.1]	7.4 [1.1]	0.0 [0.0]	0.27 (0.16, 0.38)
SC insulin	286	7.5 [1.1]	7.2 [1.1]	-0.3 [0.9]	
1022 (2 year)‡					
INH	288	7.4 [1.1]	7.5 [1.1]	0.1 [0.1]	0.25 (0.13, 0.37)
SC insulin	286	7.5 [1.1]	7.3 [1.2]	-0.2 [1.0]	
1026					
INH	23	6.8 [0.7]	6.7 [0.9]	-0.1 [0.4]	Not performed
SC insulin	21	7.1 [0.6]	7.1 [1.0]	-0.1 [0.8]	
1027					
INH	95	7.6 [1.2]	7.1 [1.0]	-0.5 [0.9]	0.07 (-0.07, 0.21)
SC insulin	101	7.6 [1.0]	7.0 [0.8]	-0.5 [0.8]	

*N for Week 24 Study 1026 and Week 12 Study 1027; all other studies LOCF
†Adjusted mean difference between groups (INH – SC) in change from baseline and 95% CI (90% in Study 1022 and 1027) were based on the primary model with terms for baseline, treatment, and center.
‡Study 1022 1-year Month 12 LOCF, 2-year Month 24 LOCF
Protocol-specified non-inferiority margin: 0.5% for Studies 106 and 107, 1.0% for Study 102. FDA specified non-inferiority margin: 0.4%.

Secondary Endpoints

Based on results from the Phase 3 Group I Studies 106 and 107, the two treatment groups had a similar percentage of patients achieving glycemic control (HbA_{1c} <8% or <7%) and had similar body weight changes. INH produced a greater reduction in fasting plasma glucose versus SC insulin. Although inconsistent results were obtained for post-prandial glucose and the post-prandial glucose increment in Studies 106 and 107, there was no difference in post-prandial glucose control between INH and SC insulin treatment based on the results of the Phase 3 Group II Study 1026, a study specifically designed to assess insulin pharmacokinetics/pharmacodynamics following administration of INH and SC insulin.

Overall, INH-treated patients with type 1 DM had a lesser risk of experiencing a hypoglycemic event compared to SC insulin-treated patients (Table 39).

Table 39. Analysis of Hypoglycemic Events According to Definition of Blood Glucose ≤36 mg/dL and/or Requiring Assistance – Adult Patients with Type 1 DM (Full Analysis Set (ITT))

Study	N	N (%) with Event	Total Events	Total Patient-Months	Event Rate*	Risk Ratio (95% CI)†
All Patients						
INH	691	547 (79.2)	5134	4931.1	1.041	0.95 (0.91, 0.98)
SC insulin	686	533 (77.7)	5515	5102.3	1.081	
102						
INH	35	11 (31.4)	29	99.5	0.292	0.56 (0.36, 0.88)
SC Insulin	36	11 (30.6)	55	105.2	0.523	
106						
INH	136	118 (86.8)	1357	714.0	1.901	1.03 (0.96, 1.11)
SC Insulin	132	116 (87.9)	1315	718.0	1.831	
107						
INH	103	91 (88.3)	971	570.0	1.704	0.72 (0.67, 0.79)
SC insulin	103	94 (91.3)	1327	562.1	2.361	
1022 (1 year)						
INH	288	234 (81.3)	2241	3129.8	0.716	1.02 (0.96, 1.08)
SC insulin	286	232 (81.1)	2290	3308.1	0.692	
1022 (2 year)						
INH	288	244 (84.7)	3186	5899.4	0.5	0.94 (0.91, 0.98)
SC insulin	286	243 (85.0)	3575	6290.5	0.6	
1026						
INH	23	20 (87.0)	246	126.6	1.943	0.96 (0.80, 1.15)
SC insulin	21	18 (85.7)	222	111.0	2.000	
1027						
INH	106	73 (68.9)	290	291.2	0.996	0.96 (0.81, 1.12)
SC insulin	108	62 (57.4)	306	297.9	1.027	

* Number of events/patient-month.
† Risk ratio and 95% CI were based on a counting process approach for recurrent time-to-event data.

HE rates by onset time of day showed a generally similar rate throughout the day for both treatment groups with the possible exception of a greater mid-day increase in the SC insulin group (Figure 12), and HE rates declined noticeably over time in both treatment groups at all times of day (Figure 12 and Figure 13). HE rates by onset time of day are presented per 100 subject-months in Figure 12.

Figure 12. Hypoglycemic Event Rates in Adult Patients with Type 1 DM– Presented by Time of Day

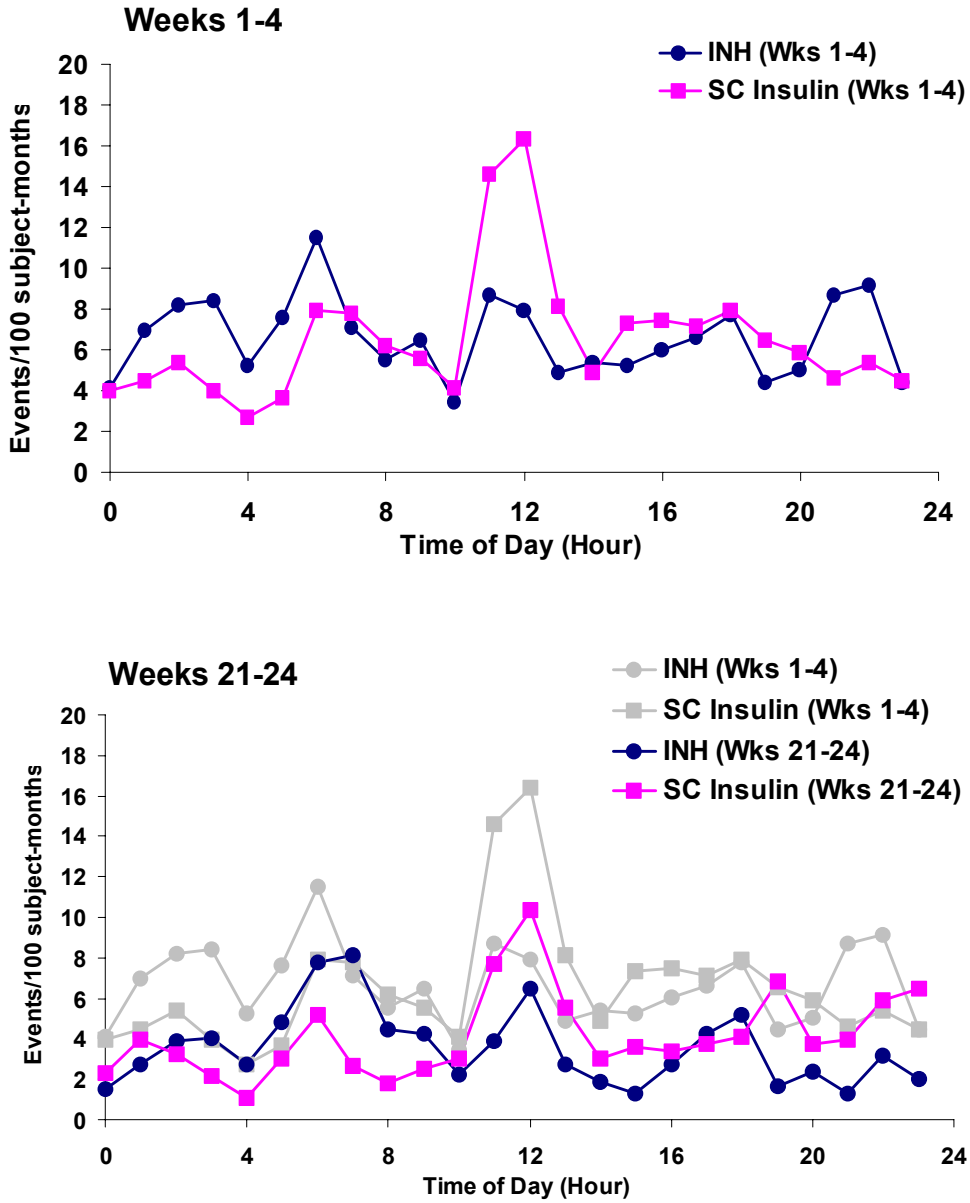
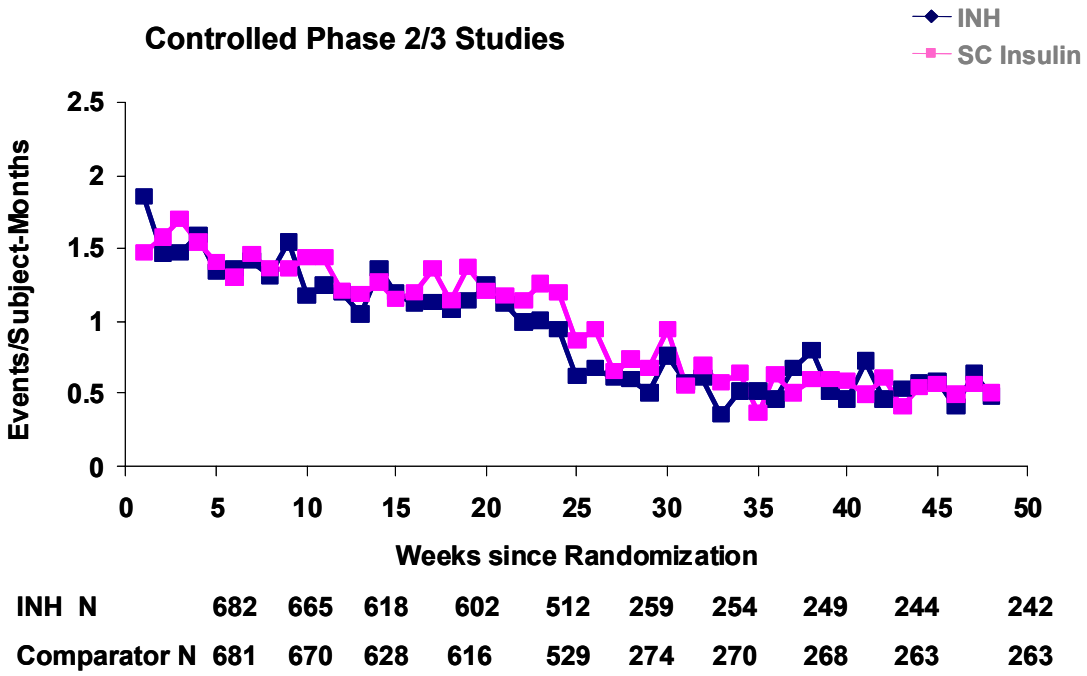
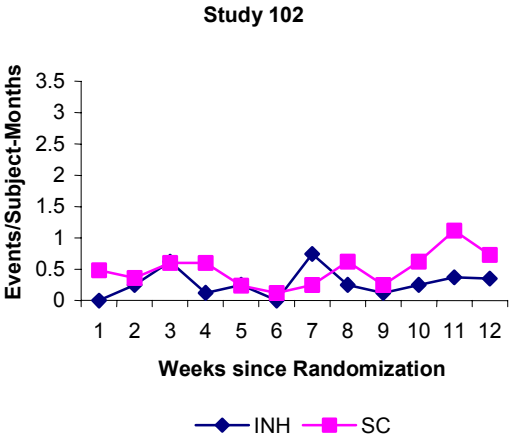
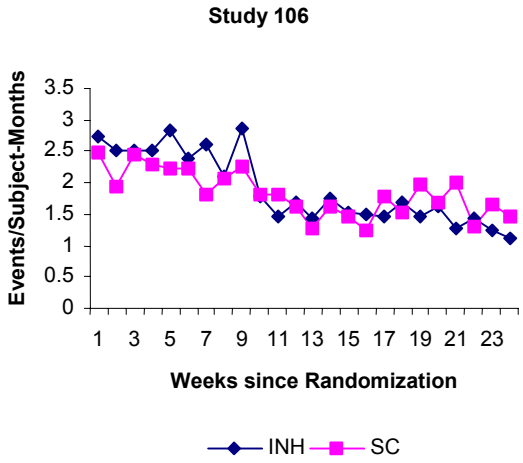
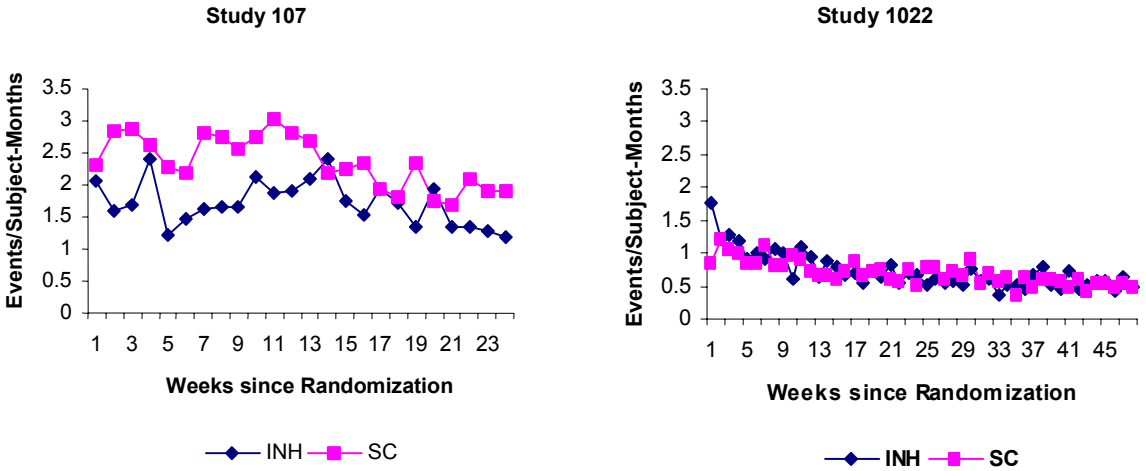


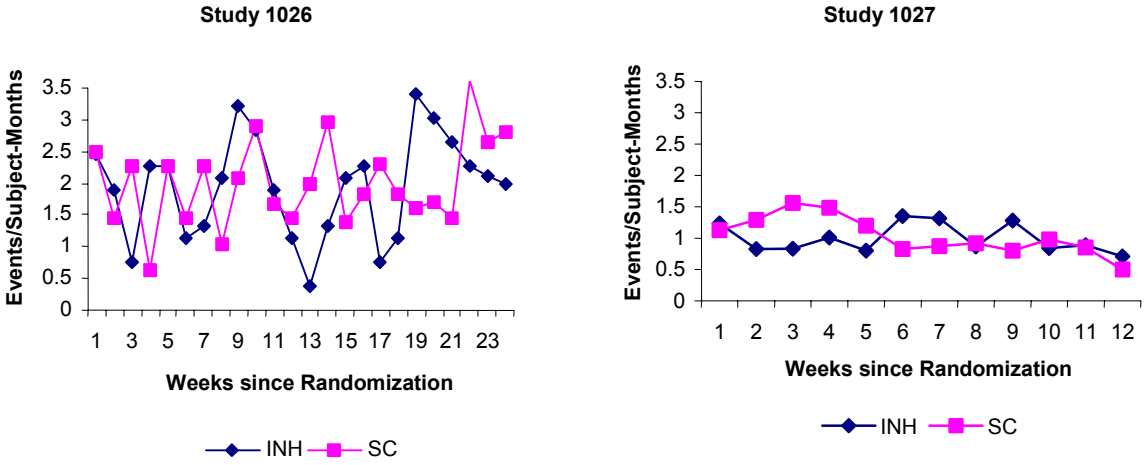
Figure 13. Hypoglycemic Event Rates in Adult Patients with Type 1 DM– Time since Randomization











Results for Study 1022 through 2 years of treatment are in Section 5.4

Patient Reported Outcomes

Patients preferred INH to SC insulin. This preference was reflected in more favorable Patient-Reported Outcomes in patients treated with INH, both in terms of treatment satisfaction and quality of life. Generally, these results were correlated with the level of glycemic control.

5.3.4. Efficacy in Patients with Type 2 DM

HbA1c

The change in HbA_{1c} from baseline to end of study was the primary endpoint in Studies 103, 104, 108, 109, 1001 (6-month), and 1002 (6-month), and a secondary endpoint in Study 110. Results are shown in Table 40.

INH was non-inferior to treatment with SC insulin in patients with type 2 DM who were insulin-using at study entry (Phase 2 Study 103 and Phase 3 Group I Study 108), based on the 95% confidence intervals for the adjusted treatment differences and the pre-defined non-inferiority margins (1.0% in the Phase 2 Study 103, 0.5% in the Phase 3 Group I Study 108). In addition, the Phase 3 Group I Study 108 met the requirement for non-inferiority of INH to SC insulin based on the specified margin of 0.4%. In the Phase 3 Group II Study 1029, in which the change in HbA_{1c} from baseline to end of study was a secondary endpoint, INH and SC insulin-treated patients had similar reductions in HbA_{1c} over 24 months of treatment.

In the Phase 2 Study 104 and the Phase 3 Group I Studies 109, 110, and the high strata of Phase 3 Group I Studies 1001 and 1002 conducted in patients who were non-insulin-using at study entry, the use of INH was associated with a greater reduction in mean HbA_{1c} than in patients on an OA regimen. Superiority was demonstrated in Phase 2 Study 104 and Phase 3 Group I Study 109, and the high strata of Phase 3 Group I Studies 1001 and 1002 based on the p-values. No p-value is shown for the analysis of the Phase 3 Group I Study 110, as change from baseline in mean HbA_{1c} was not the primary endpoint in this study. For patients in the low strata of Studies 1001 and 1002, the reduction in mean HbA_{1c} was similar for INH-treated patients and OA only-treated patients. The upper bound of the 95% CI did not exceed 0.5%; therefore, in both studies the objective of demonstrating non-inferiority in the low stratum was met.

In the Phase 3 Group I Study 110, the primary endpoint was the percentage of patients achieving acceptable glycemic control (HbA_{1c} <8%) at end of study. Significantly more INH-treated patients (82.7%) than rosiglitazone-treated patients (58.2%) achieved HbA_{1c} <8% in this study. Based on the odds ratios (INH/rosiglitazone) and the associated 95% CIs, this difference was significant (p=0.0003). Thus, the study objective was met for the primary endpoint.

Table 40. Analysis of Change from Baseline in Glycated Hemoglobin (HbA_{1c}, %) - Patients with Type 2 DM (Full Analysis Set (ITT))

		Unadjusted Mean [SD]			
Study	**N**	**Baseline**	**End of Study**	**Change**	**Adjusted Difference (95% CI)***
Insulin-using at Study Entry					
Phase 2 Study					
103					
INH	28	8.6 [1.4]	8.0 [1.3]	-0.7 [0.7]	0.17 (-0.19, 0.54)
SC insulin	27	8.1 [1.2]	7.3 [1.1]	-0.7 [0.7]	
Phase 3 Group I Studies (Designed to Collect Primary Evidence of Efficacy)					
108					
INH	146	8.1 [1.1]	7.4 [1.5]	-0.7 [1.2]	-0.07 (-0.31, 0.17)
SC insulin	149	8.2 [1.1]	7.6 [1.1]	-0.6 [1.1]	
Phase 3 Group II Studies (Designed Specifically to Collect Long-term Safety Data)					
1029 (1 year)†					
INH	313	7.7 [1.1]	7.2 [1.2]	-0.5 [1.0]	0.07 (-0.05, 0.18)
SC insulin	304	7.8 [1.1]	7.2 [1.1]	-0.6 [1.0]	
1029I (2 year)†					
INH	314	7.7 [1.1]	7.3 [1.3]	-0.3 [1.0]	0.09 (-0.04, 0.23)
SC insulin	303	7.8 [1.1]	7.3 [1.2]	-0.5 [1.1]	
Non-insulin-using at Study Entry					
Phase 2 Study					
104					
INH+OA	32	9.8 [1.3]	7.5 [1.1]	-2.3 [1.2]	-2.22 (-2.72, -1.73)
OA	36	9.9 [1.3]	9.8 [1.4]	-0.1 [1.2]	P-value <0.001
Phase 3 Group I Studies (Designed to Collect Primary Evidence of Efficacy)					
109					
INH	102	9.3 [0.9]	7.9 [1.0]	-1.5 [1.0]	-1.18 (-1.41, - 0.95)[a] P-value <0.001
INH+OAs	100	9.2 [1.0]	7.3 [0.6]	-1.9 [0.9]	-1.67 (-1.90, -1.44)[b]
OAs	96	9.3 [1.0]	9.1 [1.1]	-0.3 [0.9]	P-value <0.001
110					
INH	75	9.5 [1.1]	7.2 [1.0]	-2.3 [1.2]	-0.89 (-1.23, -0.55)
ROS	67	9.4 [0.9]	8.0 [1.3]	-1.4 [1.2]	
1001 - 6 month (L)					
INH+SU	101	8.8 [0.5]	7.4 [0.8]	-1.4 [0.8]	-0.07 (-0.33, 0.19)
MET+SU	93	8.8 [0.5]	7.4 [0.8]	-1.4 [0.9]	P-value 0.610
1001 - 6 month (H)					
INH +SU	113	10.5 [0.7]	7.9 [1.0]	-2.7 [1.1]	-0.38 (-0.63, -0.14)
MET+SU	103	10.6 [0.9]	8.3 [1.2]	-2.4 [1.2]	P-value 0.002
1002 - 6 month (L)					
INH +MET	125	8.6 [0.5]	7.2 [0.8]	-1.4 [0.8]	0.04 (-0.19, 0.27)
GLI+MET	119	8.7 [0.5]	7.1 [0.9]	-1.6 [0.9]	P-value 0.733
1002 - 6 month (H)					
INH MET	109	10.4 [0.7]	7.5 [1.1]	-2.9 [1.2]	-0.37 (-0.62, -0.12)
GLI+ MET	103	10.6 [0.7]	8.0 [1.2]	-2.6 [1.2]	P-value 0.004

*Adjusted mean difference between groups (INH – comparator) in change from baseline and 95% CI (90% in Study 1029) were based on the primary model with terms for baseline, treatment, and center. For Studies 1001/1002, the primary model included terms for baseline, country, and stratum by treatment.
The 6-month interim analyses of Studies 1001 and 1002 had dual objectives: noninferiority in low stratum (L) and superiority in high stratum (H).
†Study 1029 1-year Month12 LOCF, 2-year Month 24 LOCF
a Comparison of INH monotherapy to OA; b Comparison of INH+OA to OA
L=low stratum (HbA1c ≥8% to ≤9.5% at entry); H=high stratum (HbA1c >9.5% to ≤12% at entry)
Protocol-specified non-inferiority margin: 0.5% for Study 108, 1.0% for Study 103. FDA specified non-inferiority margin: 0.4%.

Secondary Endpoints

The results for patients with type 2 DM who were using insulin at study entry generally were similar to those seen for patients with type 1 DM. Similar percentages of INH- and SC insulin-treated patients achieved HbA_{1c} <8% at end-of-study. However, HbA_{1c} <7% was achieved by a significantly greater percentage of patients in the INH group. Patients who received INH also demonstrated a greater decline in fasting plasma glucose and similar declines in 2-hour postprandial glucose levels and post-prandial glucose increment compared to patients who received SC insulin. Patients receiving INH treatment remained weight neutral while patients using SC insulin gained weight.

INH-treated patients with type 2 DM had a lesser or similar risk of experiencing a hypoglycemic event compared to SC insulin-treated patients (Table 41). The use of INH was associated with a generally higher incidence of hypoglycemic events, compared to OA treatment, as would be expected with the use of any insulin.

Table 41. Analysis of Hypoglycemic Events According to Definition of Blood Glucose ≤36 mg/dL and/or Requiring Assistance – Patients with Type 2 DM (Full Analysis Set (ITT))

Study Insulin-Using at Study Entry	N	N (%) with Event	Total Events	Total Patient-Months	Event Rate*	Risk Ratio† (95% CI)
All Patients						
INH	487	132 (27.1)	353	4139.0	0.085	
SC Insulin	480	123 (25.6)	576	4265.1	0.135	0.62 (0.55, 0.71)
103						
INH	28	3 (10.7)	5	76.1	0.066	
SC Insulin	27	2 (7.4)	3	76.9	0.039	1.61 (0.38, 6.72)
108						
INH	146	34 (23.3)	80	793	0.101	
SC Insulin	149	28 (18.8)	104	824	0.126	0.80 (0.60, 1.07)
1029 (1 year)						
INH	313	95 (30.4)	268	3269.9	0.082	
SC insulin	304	93 (30.6)	469	3364.2	0.139	0.58 (0.50, 0.67)
1029 (2 year)						
INH	314	107 (34.1)	413	6288.9	0.066	
SC insulin	303	115 (38.0)	692	6466.6	0.107	0.61 (0.55, 0.68)

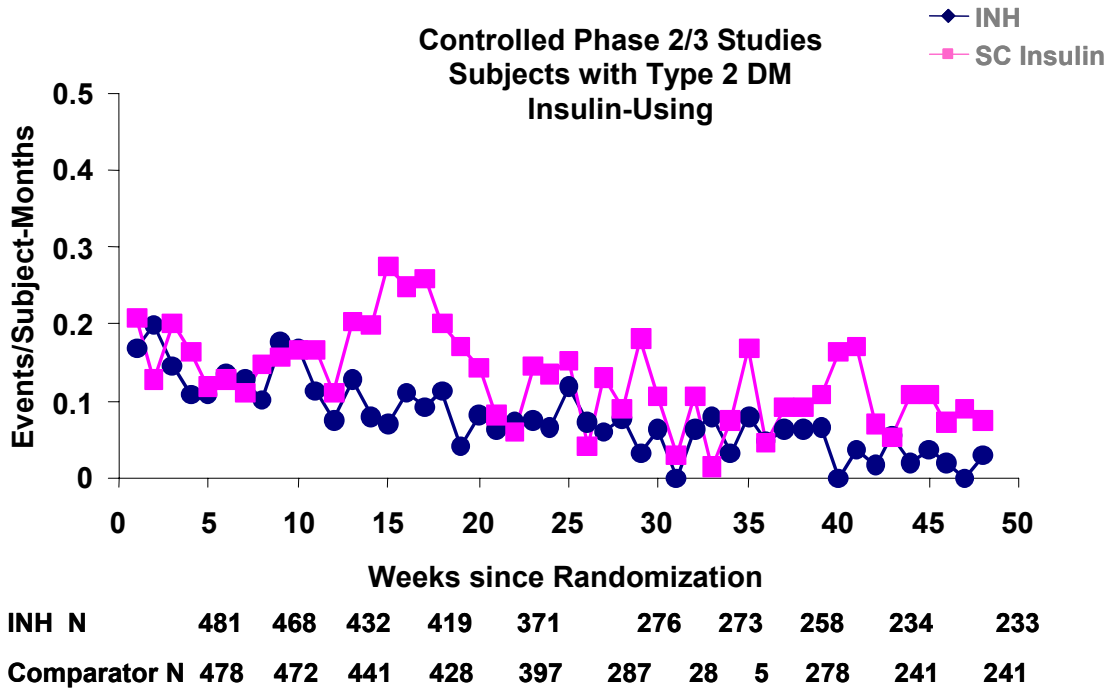
Table 41. Analysis of Hypoglycemic Events According to Definition of Blood Glucose ≤36 mg/dL and/or Requiring Assistance – Patients with Type 2 DM (Full Analysis Set (ITT)) (Cont'd)

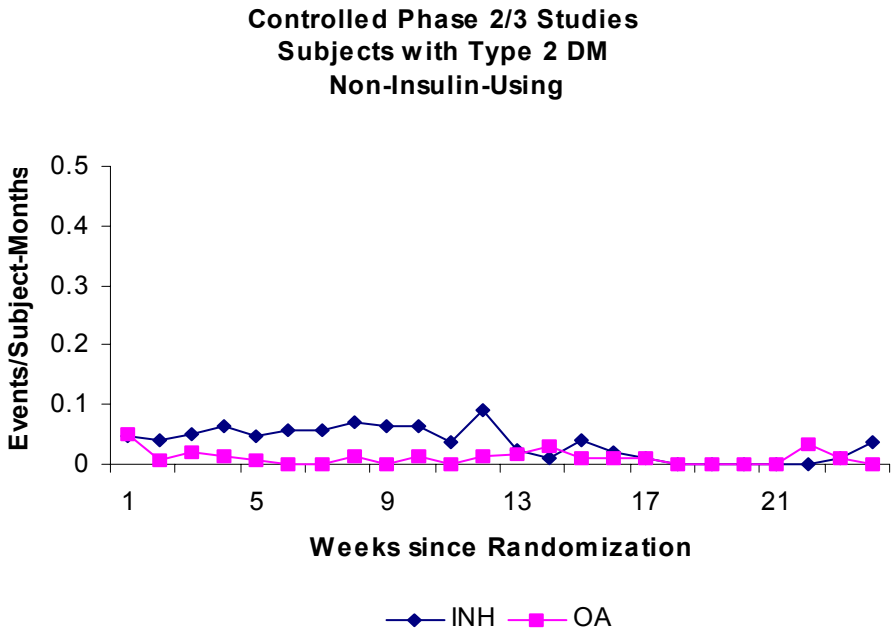
Non-Insulin-Using at Study Entry						
All patients						
INH	757	77 (10.2)	135	3320.1	0.041	
Comparator	617	19 (3.1)	32	2803.8	0.011	3.48 (2.37, 5.12)
104						
INH	32	2 (6.3)	2	88.5	0.023	
OA	36	0 (0)	0	99.4	0	Not estimable
109						
INH	102	17(16.7)	23	283.3	0.081	
INH + OA	100	21 (21.0)	48	284.3	0.169	
OA	96	0 (0)	0	266.3	0.000	Not estimable
110						
INH	75	9 (12.0)	15	214.6	0.07	
ROS	67	0 (0)	0	186.9	0	Not estimable
1001 – 6 month (L)						
INH+SU	101	4 (4.0)	6	555.5	0.011	
MET +SU	93	1 (1.1)	3	505.6	0.006	1.83 (0.46, 7.32)
1001 – 6 month (H)						
INH+SU	113	11 (9.7)	14	630.7	0.022	
MET+SU	103	6 (5.8)	6	554.5	0.011	2.09 (0.80, 5.44)
1002 – 6 month (L)						
INH+MET	125	7 (5.6)	16	683.7	0.023	
GLI+MET	119	9 (7.6)	15	634.0	0.024	1.01 (0.50, 2.05)
1002 – 6 month (H)						
INH+MET	109	6 (5.5)	11	579.7	0.019	
GLI+MET	103	3 (2.9)	8	557.3	0.014	1.33 (0.53, 3.30)

*Number of events/patient-month.
†Risk ratio and 95% CI were based on a counting process approach for recurrent time-to-event data.

Hypoglycemic event rates declined with duration of therapy, likely due to increasing familiarity with the apparatus and the dosing regimen and were much lower than those observed in patients with type 1 DM (Figure 14).

Figure 14. Hypoglycemic Events in Patients with Type 2 DM – Time Since Randomization





Patient Reported Outcomes

Patients preferred INH to SC insulin. This preference was reflected in more favorable Patient-Reported Outcomes in patients treated with INH, both in terms of treatment satisfaction and quality of life. Generally, these results were correlated with the level of glycemic control.

In patients with type 2 DM who were not well-controlled with OA or with diet and exercise, the improved glycemic control for patients who were treated with INH was further supported by a number of the secondary efficacy parameters. The percentage of patients achieving glycemic control (HbA_{1c} <8% or <7%) was higher among those who received INH versus OA in most studies although the difference between treatment groups did not always attain statistical significance. Fasting plasma glucose and the 2-hour post-prandial plasma glucose levels declined for patients who received INH versus OA in Study 109, while the decrease in fasting plasma glucose was similar across treatment groups for Studies 110, 1001, and 1002. Within any study, patients receiving INH tended to gain more weight than patients receiving OA therapy, but these increases were significantly different only in Studies 109 and 1001 and may also reflect better glycemic control.

Hypoglycemic event rates were lower for patients with type 2 DM compared to those with type 1 DM. The use of INH was associated with a generally higher incidence of hypoglycemic events, mainly during the first half of the study period, compared to OA therapy across groups, as would be expected with the use of any insulin. No diurnal pattern of hypoglycemic events was apparent.

Despite the ease of taking oral medications, INH still scored relatively well on scales of treatment satisfaction and quality of life. Patients preferred INH to OA therapy (Study 109). Although there was generally little difference between the two treatment groups on changes in quality of life scores, the efficacy and general satisfaction subscales proved more favorable for INH in Studies 109 and 110 and neutral for Studies 1001 and 1002.

5.4. Long-Term Efficacy of Inhaled Insulin

Treatment with INH provided glycemic control, as indicated by HbA_{1c}, over a prolonged period of time. Maintenance of glycemic control was accompanied by a decrease in hypoglycemic event rates and stabilization of dosing. In addition, patients preferred INH to SC insulin both in terms of overall satisfaction and convenience/ease of use.

The efficacy of INH was evaluated over two years in the ongoing, controlled Phase 3 Group II Studies 1022 and 1029, over 2 years in amended Studies 1001 and 1002, and in the uncontrolled Phase 2/3 extension studies. Most patients who completed a parent study entered the corresponding extension study. Because Studies 1001 and 1002 were amended twice to a final length of 104 weeks and had a larger number of discontinuations than anticipated, comparisons were made between patients who entered the extensions and those who did not, between patients who discontinued prematurely and those who continued, and between those who completed 104 weeks of treatment and those who did not. No differences were seen with respect to baseline demographic characteristics and key baseline variables such as HbA_{1c}, pulmonary function test (PFT) results, and antibodies.

The discontinuation rates for the long-term studies, particularly the uncontrolled extensions, were higher than in the 3- and 6-month controlled studies, consistent with the burden of participating in studies of longer duration. Nevertheless, the uncontrolled extensions enabled adequate assessment of long-term efficacy as HbA_{1c} levels were maintained in both a “Completers” cohort and an “All Patients” cohort, indicating that selective discontinuation did not affect the efficacy results. As in the shorter, controlled studies, most patients discontinued for non-treatment-related reasons, the most common reason being “default” (Table 42).

Table 42. Reasons for Discontinuation from Parent plus Extension Studies – All Patients with Type 1 or Type 2 DM

	Related to Study Drug				Not Related to Study Drug			
N (%)	Adverse Event	Lab Result	ICR	Other	Adverse Event	Lab Result	Other[a]	Default[b]
Study 1036 (Includes Studies 102, 102E, 103, 103E, 104, 104E)								
INH	6 (3.5)	0	1 (0.6)	0	10 (5.8)	0	25 (14.5)	55 (31.8)
Study 111 (Includes Studies 106, 107, 108, 109, 110, and 1009)								
INH	41 (3.2)	1 (0.1)	40 (3.1)	0	24 (1.9)	0	100 (7.8)	262 (20.3)
Study 1001/1002-2 year								
INH	12 (2.5)	0	1 (0.2)	0	13 (2.8)	1 (0.2)	19 (4.0)	24 (5.4)
OA	8 (1.8)	0	7 (1.6)	0	10 (2.3)	0	24 (5.1)	30 (6.8)

[a]Other includes protocol violation
[b]Default includes lost to follow-up, and patient no longer willing to participate, or withdrawn consent.
ICR=insufficient clinical response

HbA_{1c}

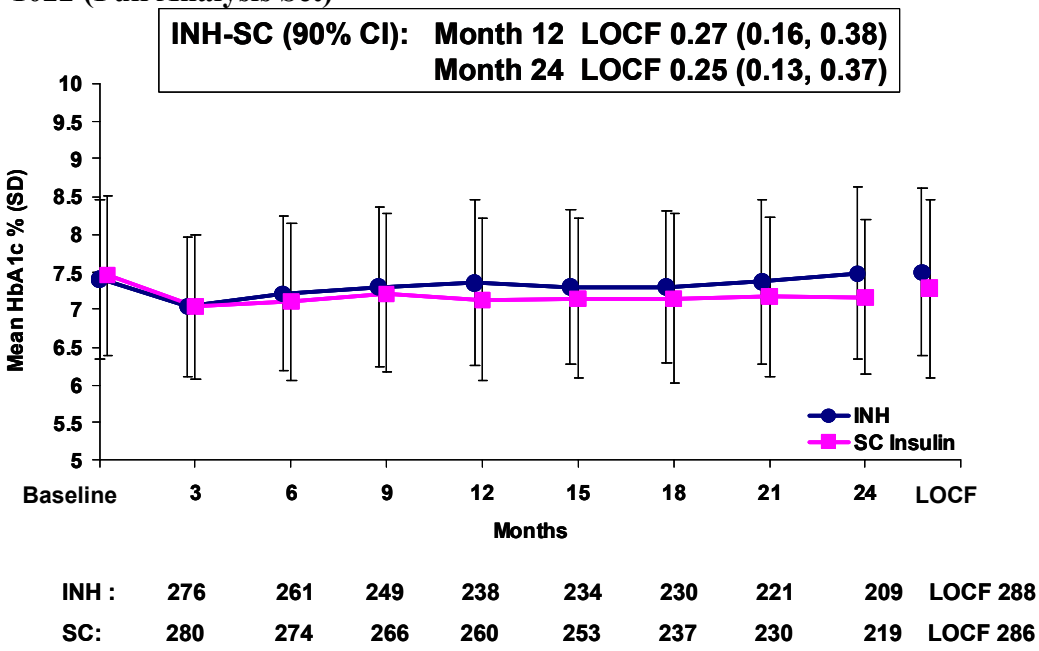
Results from the INH clinical development program support the long-term efficacy of INH in the treatment of patients with type 1 DM and patients with type 2 DM.

In patients with type 1 DM, glycemic control was maintained over 24 months (2 years) in the Phase 3 Group II Study 1022 (a controlled comparison of a TID INH regimen versus a BID or TID SC insulin regimen that allowed short-acting insulin analogs). Furthermore, this study demonstrated the similarity of INH to SC insulin both at 12 months and at 24 months (Table 43 and Figure 15) based on the adjusted mean treatment group difference and 90% CI (shown in the in-text box of Figure 15). In the Phase 3 Extension Study 111, patients with type 1 DM who completed 2 years of treatment were able to reduce HbA_{1c} from 7.7% to 7.5%. In the Phase 2 Extension Study 102E, HbA_{1c} was maintained at 8.1 for three years and was 8.5% at the four-year time point for patients who completed four years of treatment. These results are shown in Table 43.

Table 43. Glycated Hemoglobin (HbA_{1c}, %) by Duration of INH Treatment – Adult Patients with Type 1 DM, Phase 2/3 Long-Term or Extension Study

	Mean HbA_{1c}, % [SD]						
Study	Screening	Baseline	12 mos	18 mos	24 mos	36 mos	48 mos
1022 (Full Analysis Set)							
INH (N=288)	-	7.4 [1.1]	7.4 [1.1]	7.3 [1.0]	7.5 [1.1]	-	-
SC (N=286)	-	7.5 [1.1]	7.1 [1.1]	7.2 [1.1]	7.2 [1.0]	-	-
Phase 2 Extension (48-month completers)							
INH (N=31)	8.8 [1.2]	8.0 [1.0]	8.1 [1.1]	8.1 [1.1]	8.1 [1.0]	8.1 [1.1]	8.5 [1.1]
111 (24-month completers)							
INH (N = 237)	-	7.7 [0.9]	7.6 [1.1]	7.6 [1.0]	7.5 [1.0.]	-	-

Figure 15. Efficacy Sustained – Patients with Type 1 DM HbA1c Secondary Endpoint – Study 1022 (Full Analysis Set)



A similar maintenance of glycemic control was seen for all patients with type 1 DM in Study 111, including 6 patients who remained on INH for a total of 3 years. For the "All Patients" cohort in Study 102E, HbA_{1c} was 8.1% at baseline, 8.3% at three years, and was 8.2% at 7 years for 18 patients who reached that timepoint.

In patients with insulin-using type 2 DM, glycemic control was maintained over 24 months of INH treatment in Study 1029 (a controlled comparison of a TID INH regimen versus a BID or TID SC insulin regimen that allowed short-acting insulin analogs). At both 12 and 24 months, the glycemic control achieved with INH was similar to that provided by SC insulin (Table 44 and

Figure 16) based on the adjusted mean treatment group difference and associated 90% CI (shown in

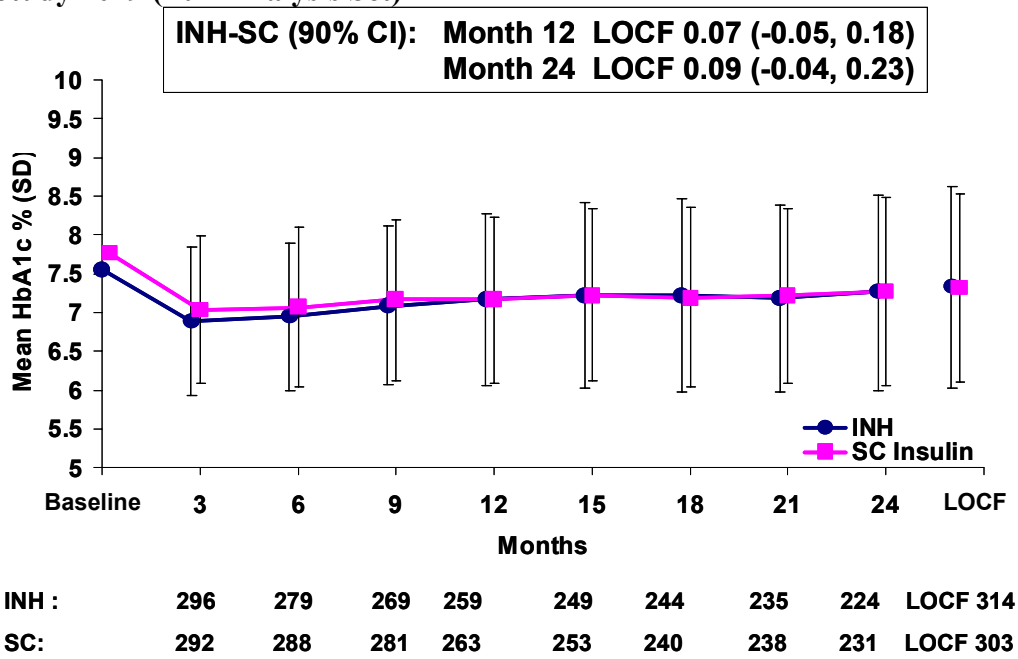
Figure 16). Improvement in glycemic control was maintained for 2 years in Study 1001/1002, and throughout the Phase 2 extension studies, and Study 111 (Table 44).

Table 44. Glycated Hemoglobin (HbA_{1c}, %) by Duration of INH Treatment - Patients with Type 2 DM, Phase 2/3 Long-Term or Extension Study

	Mean HbA_{1c}, % [SD]						
Study	**Screening**	**Baseline**	**12 mos**	**18 mos**	**24 mos***	**36 mos**	**48 mos**
1029 (Full Analysis Set)							
INH (N=313)	-	7.7 [1.1]	7.2 [1.1]	7.2 [1.2]	7.3 [1.3]	-	-
SC (N=304)	-	7.8 [1.1]	7.2 [1.1]	7.2 [1.2]	7.3 [1.2]	-	-
1001/1002 (All Patients)**							
INH (N=457)	-	9.6 [1.1]	-	-	7.8 [1.2]	-	-
OA (N=423)	-	9.7 [1.1]	-	-	8.0 [1.2]	-	-
1001/1002 (2-yr completers)							
INH (N=158)	-	9.6 [1.0]	-	-	7.7 [1.4]	-	-
OA (N=146)	-	9.6 [1.2]	-	-	8.1 [1.3]	-	-
Phase 2 Extension Studies (48-mos completers)							
INH (N=57)	9.3 [1.4]	9.1 [1.6]	7.9 [1.2]	7.8 [1.0]	7.9 [1.3]	8.0 [1.4]	8.1 [1.3]
111 (24-mos completers)							
INH (N = 384)	-	8.7 [1.2]	7.3 [1.1]	7.2 [1.0]	7.2 [0.9]	-	-

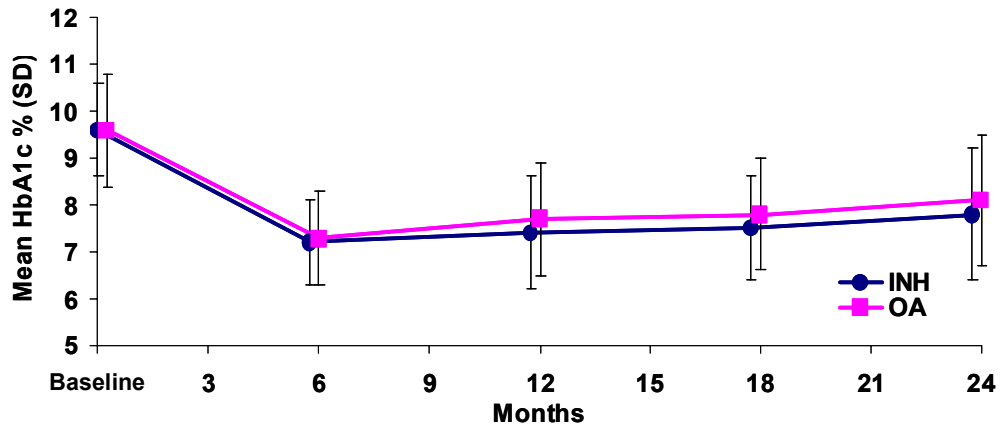
* Study 1001/1002 Month 24 LOCF
**number of patients at baseline shown

Figure 16. Efficacy Sustained – Patients with Type 2 DM - HbA1c Secondary Endpoint – Study 1029 (Full Analysis Set)



The results for Study 1001/1002 are also shown graphically in Figure 17. The in-text box shows the point estimates and 90% confidence intervals for the adjusted treatment difference in change from baseline in HbA_{1c}.

Figure 17. Efficacy Sustained – Patients with Type 2 DM Oral Agents- HbA1c Secondary Endpoint – Study 1001/1002 (24-month Completers)

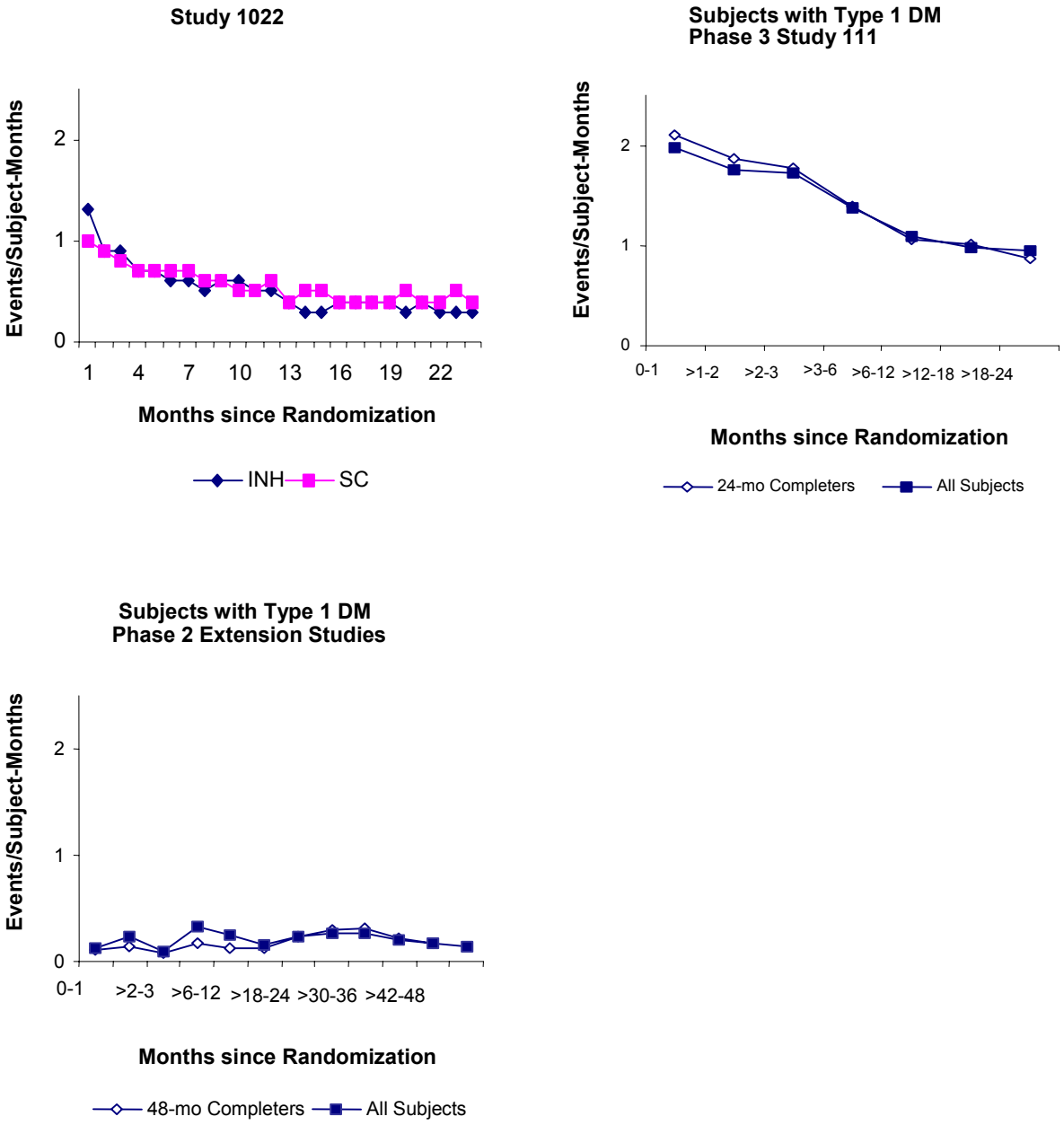


INH :	158	156	156	157	155
SC:	146	143	142	141	141

Hypoglycemic Events

In patients with type 1 DM, event rates declined in both treatment groups in controlled Study 1022 over the course of 24 months (Figure 18).

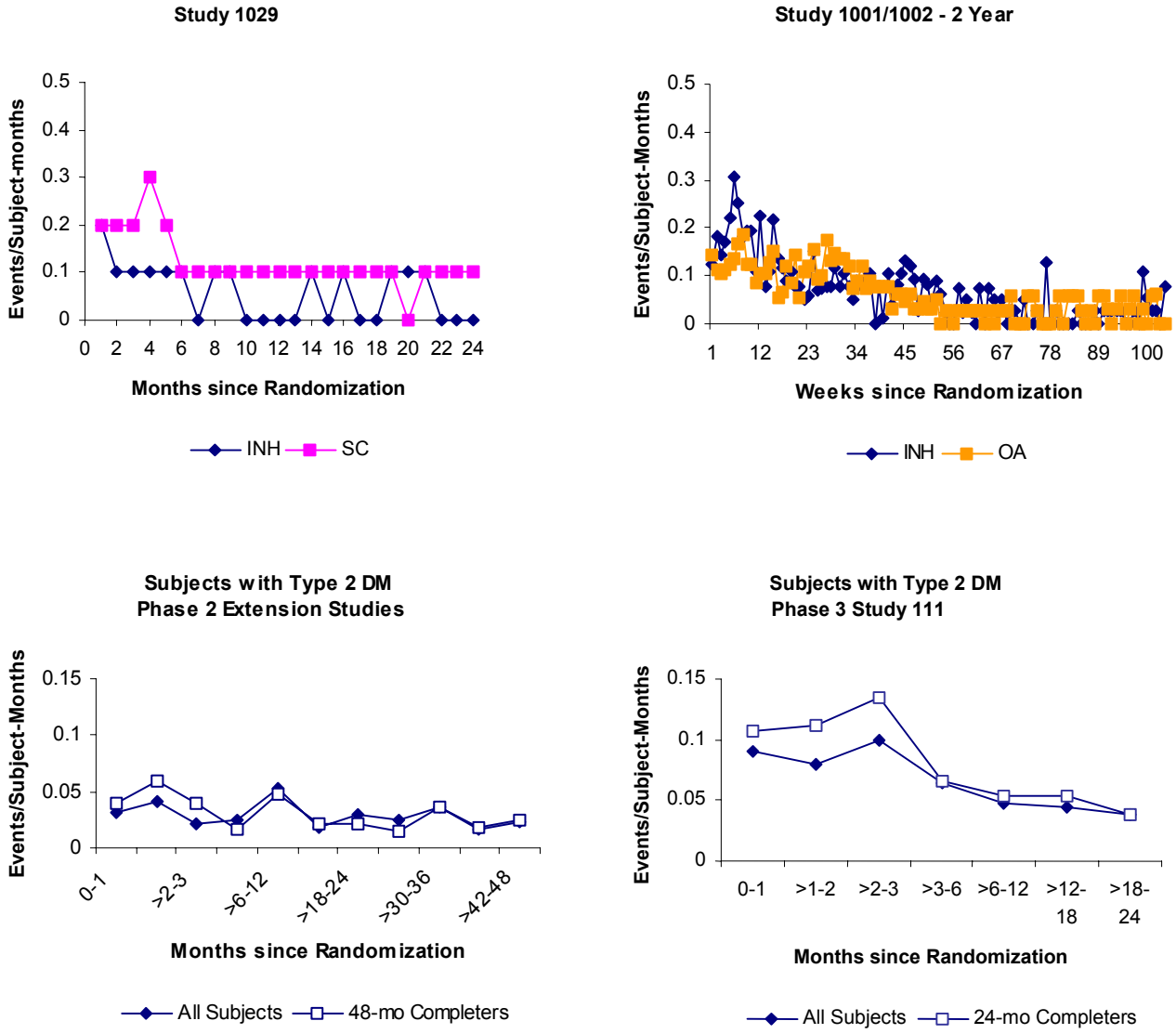
Figure 18. Hypoglycemic Event Rates in Patients with Type 1 DM – Time since Randomization



A similar decline was seen for INH-treated patients (both 24-month completers and the all patients cohort) with type 1 DM in the uncontrolled Phase 3 extension Study 111. No trend was observed for INH-treated patients in the Phase 2 Study 102 and its uncontrolled extension probably due to the much

lower HE rates in the Phase 2 study and extension compared to the Phase 3 studies. Declines in hypoglycemic event rates were also seen over time for INH-treated patients with type 2 DM (Figure 19).

Figure 19. Hypoglycemic Event Rate in Patients with Type 2 DM – Time since Randomization



Patient-Reported Outcomes (PRO)

PRO data were collected in the 102E and 103E Phase 2 extension studies. From baseline (parent studies) to year one (extension study), significantly greater improvements were observed in the INH group compared with the SC insulin group in terms of overall satisfaction (37.9% vs. 3.1%) and convenience/ease of use (43.2% vs. –0.9%).

In Studies 102E and 103E, significantly more patients either preferred to remain with, or switched to, INH therapy. Of the 60 patients who received INH during the parent studies, 51 (85.0%) chose to continue treatment, 8 (13.3%) switched to SC insulin, and 1 (1.7%) did not continue. Of the 61 patients who received SC insulin, 13 (21.3%) chose to continue the same insulin treatment, 46 (75.4%) switched to INH, and 2 (3.3%) did not continue.

In other classes of drugs, where we have knowledge of how they have performed in the real world, improvements in health-related quality of life have translated into meaningful benefit.[57,58]

5.5. Efficacy in Special Populations

Analyses to assess the efficacy (change from baseline in HbA_{1c} and hypoglycemic event rates) of INH in different subpopulations based on age, race, gender, and BMI were performed using pooled data from controlled Phase 2/3 studies. Data were summarized for patients with type 1 DM, type 2 DM using insulin, and type 2 DM not using insulin at study entry.

In general, there was no evidence of the impact of any of these characteristics on either HbA_{1c} or hypoglycemic event rates. Because of the age limits applied to ensure the ability of studies to answer the fundamental questions for which they were designed, there were few patients with type 1 DM ≥ 65 years of age; therefore, it is difficult to draw conclusions about efficacy in this subpopulation. Also, while it is difficult to draw definitive conclusions about the effect of race because of the limited number of non-white patients, the Phase 2/3 results were generally consistent across racial groups. Overall, the Phase 2/3 results were consistent with those seen in the Phase 1 development program in which no apparent affect of age, gender, or BMI on the pharmacokinetics of INH was demonstrated.

5.6. Dose Response/Dosing Regimen

Classic dose-response studies were not performed because the dose-response relationship of insulin is understood.

The average total daily dose of both short-acting and any intermediate- or long-acting basal insulin was monitored during studies to provide general information about dosing trends and were expressed on a weight basis for selected time points at which body weight was measured. The total average daily dose of INH generally increased by several milligrams during the course of the 3-6 month Phase 2/3 studies. This increase was likely accounted for by changes in body weight and/or titration against the efficacy endpoint, since the dose corrected for body weight increased minimally.

These results are consistent with those reported by the UKPDS for patients with type 2 DM in whom small increases in insulin dose were noted over time.[15]

5.7. Clinical Relevance of Observed Effects

Many people are not able to achieve and maintain optimal glycemic control due to the limitations of SC injectable therapy. Thus, there is a need for a therapy that provides the effectiveness of insulin without the limitations associated with injection therapy.

INH provides effective treatment for patients with type 1 or type 2 DM. In clinical trials of patients with type 1 DM or insulin-using patients with type 2 DM, a regimen of INH three times a day plus an SC basal insulin resulted in similar changes in HbA_{1c} from baseline compared to a regimen of SC short-acting insulin plus SC basal insulin. The percentages of patients achieving HbA_{1c} <7% were comparable to or better than those achieved with the SC insulin regimen. Fasting plasma glucose was significantly lower

following INH treatment compared to an SC insulin regimen. The overall rate of hypoglycemia was lower for INH-treated patients than for those who received an SC insulin regimen.

The efficacy of INH was further confirmed in clinical trials of patients with type 2 DM who had not previously used insulin. A regimen of INH three times a day either alone or in combination with OAs, resulted in a greater improvement from baseline in HbA_{1c} compared to that observed for patients on a regimen of OAs alone. A higher percentage of INH-treated patients (either as monotherapy or in combination with OAs) achieved $HbA_{1c} < 7\%$ compared to OA treatment. Not unexpectedly, a higher hypoglycemic event rate and greater tendency to increased weight were observed for INH-treated patients compared to OA-treated patients. In Study 1001, weight gain was more pronounced when INH was added to sulfonylurea than when metformin was added to sulfonylurea. In Study 1002, comparable weight gain was seen for patients who received INH or glibenclamide despite greater improvements in glycemic control for INH-treated patients. INH may thus be a preferable alternative to the addition of a sulfonylurea when patients are poorly controlled on metformin.

Glycemic control (assessed by HbA_{1c}) was maintained for 2 years (24 months) in controlled studies of patients with type 1 and type 2 DM (insulin-using), for 2 years in controlled studies of patients with type 2 DM (non-insulin-using), and for prolonged periods of time in uncontrolled extension studies. This finding contrasts the results of the UKPDS[15], in which it was observed that glycemic control deteriorated with time. It is notable that this maintenance of glycemic control occurred despite less frequent contact with the clinic during the extension studies compared to the parent studies. In addition, dose generally did not increase appreciably, and hypoglycemic event rates declined with long-term treatment.

A significant finding of the clinical development program is that INH is preferred to SC insulin and oral antidiabetic regimens. Treatment with INH resulted in statistically and clinically significant improvements in health-related quality of life measures and treatment satisfaction compared to other regimens. The clear preference for INH to other treatment regimens, coupled with the efficacy that only insulin can provide, means that INH can provide a bridge to more intensive insulin regimens. It will also help patients who need the efficacy of insulin to achieve glycemic control yet are reluctant to start injecting insulin.

The results discussed above were obtained using the clinical product. The commercial product has performance equivalent to the clinical product in terms of aerosol properties. These include the key aerosol metrics of emitted dose uniformity and fine particle dose, where the mean is comparable and the range is encompassed within the breadth of the performance of the clinical product. Patient experience with the commercial product is, therefore, expected to be the same as with the clinical product.

5.8. Efficacy Summary

The results of the clinical development program show that INH allows patients with type 1 or type 2 DM to achieve and maintain effective glycemic control as assessed by HbA_{1c} levels:

- INH was as effective as SC regular insulin in patients with type 1 DM and in patients with type 2 DM who use SC insulin.
- INH was superior to OA therapy in patients with type 2 DM who were failing treatment with diet and exercise or OA therapy.
- The efficacy of INH was maintained for prolonged periods of time.
- INH was preferred to SC insulin and oral antidiabetic regimens.

6. OVERVIEW OF SAFETY

6.1. Background

As INH is the first inhaled insulin to be considered for marketing approval, the comprehensive safety evaluation has paid special attention to the novel mode of delivery. Pre-clinical toxicology and clinical pharmacology studies have identified no safety issues related to INH except for smoking, which is consequently contraindicated in the proposed USPI.

Clinical safety evaluation of INH included assessment of adverse events (AEs), serious adverse events (SAEs), premature discontinuation, laboratory test abnormalities, vital signs, electrocardiogram (ECG) parameters, and chest x-ray and high resolution computed tomography (HRCT) results. In addition, pulmonary safety was evaluated by examining respiratory AEs and SAEs, discontinuations due to respiratory AEs, and pulmonary function test results. The extent, characterization, and clinical sequelae of insulin antibody formation were evaluated by measuring serum antibody levels and by assessing the relationship of antibody levels with adverse events and efficacy measures. It should be noted that hypoglycemic events in the safety discussion (and any safety narratives) are events defined according to protocol-specified criteria, unless otherwise noted.

This section contains a review of the safety data from 31 clinical pharmacology studies and 20 Phase 2/3 studies which assessed efficacy and safety of INH in patients with type 1 DM and type 2 DM. All studies, with the exception of Phase 2/3 studies 1022, 1029, and 1036, had completed as of 25 June 2004, the general safety cutoff date for the NDA. A 4-Month Safety Update was submitted using a cutoff date of 13 December 2004. Where possible, the safety data discussed in this section derive from the most comprehensive source; i.e., the 4-Month Safety Update. Clinical safety evaluation of INH for the 4-Month Safety Update included assessment of AEs, SAEs, premature discontinuation, and laboratory test abnormalities.

Studies were grouped and their data pooled according to similarity of study design. Data for adult patients with type 1 DM and type 2 DM are presented separately within each pool. Studies included in each of the following groups are listed in Table 45.

- The Controlled Phase 2/3 Studies set allows comparison of safety parameters between INH- and comparator-treated patients.
- The All Phase 2/3 Studies set, comprised of controlled and uncontrolled studies, integrates safety data from the largest possible number of INH-treated patients to facilitate the detection of uncommon adverse events. General safety data are summarized only for patients who received INH because there is little additional comparator data to that provided by the Controlled Phase 2/3 set. Each patient's entire INH exposure is represented in this data set; i.e., exposure in parent plus extension study. SAEs were reported for all patients, including those receiving comparator treatments.
- The Clinical Pharmacology Studies set is comprised of studies (generally single dose) performed to describe the pharmacokinetic and pharmacodynamic properties of INH.

Table 45. Description of Study Groupings

Studies	Studies Included
Controlled Phase 2/3	
Type 1 DM	102, 106*, 107*, 1009*, 1022, 1026, 1027
Type 2 DM	103, 104, 108, 109, 110, 1001, 1002, 1029
All Phase 2/3	
Type 1 DM	102, 102E†, 106, 107, 111‡, 1009, 1022, 1026, 1027, 1036†‡
Type 2 DM	103, 103E†, 104, 104E†, 108, 109, 110, 111‡, 1001, 1002, 1029, 1036†‡
Clinical Pharmacology	001, 002, 003, 004, 005, 006, 007, 008, 009, 010, 011, 012, 014, 015, 016, 017, 018, 019, 021, 023, 101, 1003, 1004, 1005, 1006, 1007, 1012, 1014, 1015, 1016, 1020

*Studies 106 and 107 included adolescents as well as adults; Study 1009 was conducted exclusively in patients aged 6-11 years.
†Studies 102E, 103E, and 104E are uncontrolled extensions of Studies 102, 103, and 104, respectively, and were combined into Study 1036 in 2003.
‡Studies 111 and 1036 include patients with type 1 and type 2 DM.

Additional study groupings used to evaluate pulmonary safety and insulin antibodies are described in Section 6.5.2.1and Section 6.6.2.1, respectively.

For the purposes of evaluating general safety, data from the Controlled Phase 2/3 and All Phase 2/3 sets were provided using a database cutoff date of 13 December 2004. The Clinical Pharmacology set was not updated as of 13 December 2004. All clinical pharmacology studies had completed by this date except for two newly initiated clinical studies, Studies 1056 and 1057. Few patients in Study 1056, and none in Study 1057, had received study drug as of 13 December 2004.

Because a pediatric indication is not sought at this time, the focus of the discussion in the present document will be on data from adult patients.

Four other studies (Phase 1 Study HA001; Phase 3 Studies 1017, 1028, 1030) are not included in the study groupings listed above because they do not contribute to the integrated databases for the reasons noted in Section 2.5.3. Results for Studies 1028 and 1030 are reported separately in Appendix 1.

All patients who received at least one dose of study drug were eligible to be included in the safety assessment. Patients who received different treatments at different times contributed data for each applicable treatment group.

In the integrated safety database 3,605 (3,274 were ≥ 18 years) received INH as monotherapy or in combination with SC basal insulin or OAs by the cutoff date of 13 December 2004. A total of 1,981 received a comparator SC insulin regimen (short-acting plus basal), of whom 1,787 were ≥ 18 years, and 648 (all were ≥ 18 years) received OA(s) without INH for at least part of a clinical study. The number of adult patients treated in the INH clinical program is shown by study groupings in Table 46.

Table 46. Number of Adult Patients (≥ 18 Years of Age) Treated in the Inhaled Insulin Clinical Development Program

Study Type	INH	SC	OA	Total
Clinical Pharmacology Studies				
Studies in non-diabetic patients	676	473	0	679
Studies in patients with DM	100	97	0	100
Subtotal	**776**	**570**	**0**	**779**
Controlled Phase 2/3 Studies				
Type 1 Patients	698	705	0	1403
Type 2 Patients	1279	488	644	2411
Subtotal	1977	1193	644	3814
All Phase 2/3 Studies				
Type 1 Patients	918	721	0	1413
Type 2 Patients	1580	496	648	2421
Subtotal	**2498**	**1217**	**648**	**3834**
All Studies	**3274**	**1787**	**648**	**4613**

INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, and Total=number of distinct patients.
Cutoff date: 13 December 2004

The duration of exposure to study drug is summarized for the Phase 2/3 Studies in Table 47. Numbers of patients with specified durations of INH exposure are shown in Table 4.

Table 47. Duration of Exposure to Study Medication by Diabetes Type and Treatment Group: Adult Patients

	Number (%) of Patients				
	Type 1		Type 2		
Exposure	INH	SC	INH	SC	OA
Controlled Phase 2/3 Studies	N=698	N=705	N=1,279	N=488	N=644
Median (months)	5.59	5.65	5.88	14.75	5.60
Overall (patient-months)	7208.0	7566.0	13385.1	6060.1	6452.9
All Phase 2/3 Studies	N=918	NA	N=1580	NA	NA
Median (months)	20.9	-	20.65	-	-
Overall (patient-months)	17893.6	-	31928.9	-	-

INH=inhaled insulin, N=number of patients, NA=not applicable, OA=oral antidiabetic agents, and SC=subcutaneous short-acting insulin
Cutoff date: 13 December 2004

In the controlled Phase 2/3 studies, primary diagnosis, duration since first diagnosis, and demographic and clinical characteristics for both type 1 DM and type 2 DM patients were similar across treatment groups (Table 48 and Table 49). Genders were represented approximately equally among patients with type 1 DM. The proportion of females (approximately 37%) was lower among patients with type 2 DM in the INH and SC insulin groups. Most patients in each treatment group were white. Mean age (range) was 38 years (18-65) for adult patients with type 1 DM and approximately 57 years (23-80) for patients with type 2 DM. Mean BMI (range) was 25.3 kg/m^2 (18-36) for adult patients with type 1 DM exposed to INH and 30.2 kg/m^2 (18-51) for patients with type 2 DM.

Table 48. Primary Diagnosis and Mean Duration Since First Diagnosis: Adult Patients in Phase 2/3 Studies

	Number of Patients (Mean Duration Since First Diagnosis [years])					
	INH		SC		OA	
Diagnosis	Male	Female	Male	Female	Male	Female
Controlled Phase 2/3 Studies (N=3814)						
Type 1 DM	390 (18.9)	308 (18.0)	385 (18.3)	320 (18.2)	0	0
Type 2 DM	796 (10.9)	483 (10.0)	307 (13.8)	181 (12.7)	361 (8.1)	283 (7.6)
All Phase 2/3 Studies (N=2498)						
Type 1 DM	513 (18.9)	405 (17.9)	NA	NA	NA	NA
Type 2 DM	991 (10.8)	589 (9.8)	NA	NA	NA	NA

INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, and NA=not applicable; comparator patients are not included in the All Phase 2/3 Studies.
Cutoff date: 13 December 2004

Table 49. Patient Demographic Characteristics: Adult Patients in Controlled Phase 2/3 Studies

	Number (%) of Patients				
	Type 1		Type 2		
	INH	SC	INH	SC	OA
N	698	705	1279	488	644
Gender [number (%) of patients]:					
Male	390 (55.9)	385 (54.6)	796 (62.2)	307 (62.9)	361 (56.1)
Female	308 (44.1)	320 (45.4)	483 (37.8)	181 (37.1)	283 (43.9)
Age (yr):					
Mean	38.0	38.0	57.2	55.6	56.6
Range	18-65	18-65	28-80	23-78	29-80
Race [number (%) of patients]:					
White	616 (88.3)	642 (91.1)	1,044 (81.6)	348 (71.3)	569 (88.4)
Hispanic	43 (6.2)	35 (5.0)	94 (7.4)	63 (12.9)	28 (4.3)
Black	24 (3.4)	11 (1.6)	86 (6.7)	46 (9.4)	23 (3.6)
Asian	7 (1.0)	6 (0.9)	21 (1.6)	11 (2.3)	12 (1.9)
Other	8 (1.1)	11 (1.6)	34 (2.7)	20 (4.1)	12 (1.9)
BMI* (kg/m^2):					
Mean	25.3	25.3	30.2	30.1	30.4
Range	18-36	17-35	18-51	20-40	18-57

*Body Mass Index
INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, and N= number of patients.
Cutoff date: 13 December 2004

Demographic characteristics for adult patients exposed to INH in All Phase 2/3 Studies are shown in Table 50.

Table 50. Patient Demographic Characteristics: Adult Patients in All Phase 2/3 Studies

	Number (%) of Patients	
	Type 1 DM	Type 2 DM
N	918	1580
Gender [number (%) of patients]:		
Male	513 (55.9)	991 (62.7)
Female	405 (44.1)	589 (37.3)
Age (yr):		
Mean	38.1	56.6
Range	18-65	23-80
Race [number (%) of patients]:		
White	825 (89.9)	1266 (80.1)
Hispanic	48 (5.2)	127 (8.0)
Black	27 (2.9)	113 (7.2)
Asian	7 (0.8)	29 (1.8)
Other	11 (1.2)	45 (2.8)
BMI* (kg/m^2):		
Mean	25.4	30.3
Range	17-36	18-51

*Body Mass Index
Cutoff date: 13 December 2004

6.2. Overall Safety Profile – Common and Non-serious Adverse Events

All patients who received at least one dose of study drug after randomization were included in the AE evaluation. AEs occurring during and/or within one day after the period of protocol-specified treatment were included in the overall assessment. Treatment-related AE's (determined by the investigator) were included regardless of time of occurrence relative to treatment. All AEs were coded to the COSTART dictionary. Because studies were open label, assignment of causality may have been patient to bias. For this reason, the focus of this discussion is on all-causality AEs.

6.2.1. Common and Non-serious Adverse Events in Phase 2/3 Controlled Studies

Patients with Type 1 DM

The overall incidences of all-causality and treatment-related adverse events and severe adverse events in the Controlled Phase 2/3 Studies were comparable between the INH and SC treatment groups (Table 51).

Table 51. Summary of Adverse Events: Adult Patients in Controlled Phase 2/3 Type 1 Studies

	Number (%) of Patients			
	All Causality		Treatment-Related	
	INH	SC	INH	SC
	N=698	N=705	N=698	N=705
Patients with AEs	694 (99.4)	696 (98.7)	688 (98.6)	683 (96.9)
Patients with severe AEs	175 (25.1)	183 (26.0)	135 (19.3)	146 (20.7)

INH=inhaled insulin, SC=subcutaneous short-acting insulin
Cutoff date: 13 December 2004

Common adverse events among type 1 patients of Controlled Phase 2/3 studies are listed by preferred COSTART term in Table 52 in order of decreasing frequency of all-causality events in the INH group.

Table 52. Common Adverse Events (≥ 5% incidence in any group) by Preferred Term: Adult Patients in Controlled Phase 2/3 Type 1 Studies

		Number (%) of Patients			
		All Causality		Treatment-Related	
Body system*	Preferred term	INH N=698	SC N=705	INH N=698	SC N=705
MN	Hypoglycemia**	676 (96.8)	678 (96.2)	676 (96.8)	678 (96.2)
R	Respiratory tract infection	297 (42.6)	292 (41.4)	14 (2.0)	12 (1.7)
R	Cough increased	204 (29.2)	62 (8.8)	146 (20.9)	5 (0.7)
R	Pharyngitis	126 (18.1)	112 (15.9)	41 (5.9)	10 (1.4)
N	Tremor	125 (17.9)	129 (18.3)	115 (16.5)	114 (16.2)
BW	Flu syndrome	114 (16.3)	115 (16.3)	2 (0.3)	5 (0.7)
BW	Headache	109 (15.6)	113 (16.0)	35 (5.0)	37 (5.2)
R	Rhinitis	100 (14.3)	72 (10.2)	14 (2.0)	2 (0.3)
BW	Accidental injury	85 (12.2)	83 (11.8)	13 (1.9)	5 (0.7)
BW	Asthenia	82 (11.7)	92 (13.0)	62 (8.9)	71 (10.1)
R	Sinusitis	70 (10.0)	51 (7.2)	3 (0.4)	2 (0.3)
SA	Sweating	62 (8.9)	76 (10.8)	56 (8.0)	68 (9.6)
D	Nausea	61 (8.7)	48 (6.8)	19 (2.7)	12 (1.7)
N	Dizziness	59 (8.5)	51 (7.2)	50 (7.2)	41 (5.8)
N	Anxiety	53 (7.6)	39 (5.5)	18 (2.6)	16 (2.3)
D	Diarrhea	52 (7.4)	36 (5.1)	5 (0.7)	2 (0.3)
R	Respiratory disorder	51 (7.3)	29 (4.1)	15 (2.1)	1 (0.1)
MS	Arthralgia	46 (6.6)	40 (5.7)	9 (1.3)	7 (1.0)
BW	Back pain	40 (5.7)	40 (5.7)	6 (0.9)	5 (0.7)
D	Gastroenteritis	39 (5.6)	37 (5.2)	0	1 (0.1)
BW	Pain	37 (5.3)	40 (5.7)	3 (0.4)	4 (0.6)
D	Increased appetite	27 (3.9)	42 (6.0)	25 (3.6)	35 (5.0)
N	Confusion	26 (3.7)	39 (5.5)	25 (3.6)	37 (5.2)
U	Vaginitis	12 (3.9)	16 (5.0)	1 (0.3)	2 (0.6)

*BW=Body as a Whole, D=Digestive, MN=Metabolic and Nutritional, MS=musculoskeletal, N=Nervous, R=Respiratory, SA=Skin and Appendages, and U=Urogenital.
INH=inhaled insulin, SC=subcutaneous short-acting insulin, and N=number of patients
**Protocol-specified definition of hypoglycemia
Cutoff date 13 December 2004.

The most frequently reported all-causality event among INH-treated patients in the Controlled Phase 2/3 Studies was hypoglycemia, consistent with the physiologic effect of insulin, followed by respiratory tract infection, cough, pharyngitis, and tremor. The incidence of hypoglycemia, defined as a blood glucose level of ≤ 36 mg/dL and/or requiring assistance, was lower among INH- than SC insulin-treated patients (Table 39). The incidence of all-causality cough was greater in the INH than SC group. Some adverse events (e.g., asthenia, tremor, dizziness, sweating, headache) may have been manifestations of hypoglycemia.

The most frequently reported treatment-related events among INH-treated patients were hypoglycemia, cough, and tremor. Treatment-related cough, pharyngitis, rhinitis, and respiratory disorder were more common in the INH group than in the SC group.

Of all-causality adverse events occurring at ≥ 1% but less than 5% incidence in any treatment group and, therefore, not included in Table 52, chest pain, dry mouth, taste perversion, hyperglycemia, arthrosis, dyspnea, epistaxis, and sputum increased occurred at greater incidence in the INH than SC group, and syncope, depression, pruritus, and skin ulcer occurred at greater incidence in the SC than INH group. Investigator terms for events coding to the preferred term "chest pain" were imprecise and included terms not indicative of cardiac events. The incidences of specific cardiac-related adverse events were similar between the two treatment groups (Section 6.7).

The most common severe adverse event in Controlled Phase 2/3 studies was hypoglycemia, which occurred at comparable frequencies in the two treatment groups both on an all-causality and a treatment-related basis (Table 53). The remaining severe adverse events occurred in ≤ 1.1% of patients in each group, without a clear imbalance in incidence between treatment groups.

Table 53. Severe Adverse Events Occurring in ≥ 5 Patients in Either Group by Preferred Term: Adult Patients in Controlled Phase 2/3 Type 1 Studies

		Number (%) of Patients			
		All Causality		Treatment-Related	
Body system*	Preferred term	INH N=698	SC N=705	INH N=698	SC N=705
MN	Hypoglycemia**	126 (18.1)	140 (19.9)	125 (17.9)	140 (19.9)
BW	Accidental injury	7 (1.0)	2 (0.3)	0	0
BW	Headache	5 (0.7)	7 (1.0)	1 (0.1)	2 (0.3)
CV	Migraine	5 (0.7)	3 (0.4)	2 (0.3)	1 (0.1)
BW	Flu syndrome	2 (0.3)	8 (1.1)	0	1 (0.1)
CV	Syncope	2 (0.3)	5 (0.7)	0	2 (0.3)

*BW=Body as a Whole; CV=Cardiovascular; D=Digestive; MN=Metabolic and Nutritional; MS=Musculoskeletal, N=Nervous.
**Protocol-specified definition of hypoglycemia
INH=inhaled insulin, SC=subcutaneous short-acting insulin, and N=number of patients.
Cutoff date: 13 December 2004

A similar pattern of adverse event incidence occurred among adults in the Controlled Phase 2/3 and All Phase 2/3 Studies.

AEs that occurred with higher incidence in INH than SC group in the Controlled Phase 2/3 Studies (cough, respiratory disorder, chest pain, dry mouth, hyperglycemia, dyspnea, epistaxis, and sputum increased) were assessed by age, gender, race, by interval of treatment with INH, and according to INH dose at event onset time.

There was no effect of demographic characteristics on the incidence of AEs except that the incidence of increased sputum increased with increasing age in the INH group, but not the SC group. Increased sputum also occurred with greater incidence for male patients than female patients in the INH group, but not the SC group. The majority of evaluated adverse events decreased, and none increased, in prevalence with increasing interval of treatment among INH-treated patients. Furthermore, the overall incidence of all-causality and treatment-related adverse events did not vary with INH dose at the event onset. The incidence of increased sputum appeared to be greater among patients receiving higher INH doses.

Patients with Type 2 DM

Among patients with type 2 DM, the overall incidence of all-causality adverse events was comparable between the INH and SC groups and lower in the OA group. The overall incidence of all-causality severe

adverse events was comparable among treatment groups. The overall incidence of treatment-related adverse events and severe adverse events was lowest in the OA group, intermediate in the INH group and greatest in the SC group. The majority of adverse events were mild or moderate in severity, rather than severe (Table 54).

Table 54. Summary of Adverse Events: Controlled Phase 2/3 Type 2 Studies

	Number (%) of Patients					
	All Causality			Treatment-Related		
	INH	SC	OA	INH	SC	OA
	N=1279	N=488	N=644	N=1279	N=488	N=644
Patients with AEs	1200 (93.8)	474 (97.1)	525 (81.5)	959 (75.0)	413 (84.6)	273 (42.4)
Patients with severe AEs	185 (14.5)	75 (15.4)	87 (13.5)	47 (3.7)	27 (5.5)	8 (1.2)

INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, N=number of patients, and AEs=adverse events.
Cutoff date: 13 December 2004

The most common adverse events among patients with type 2 DM in Controlled Phase 2/3 studies are listed by preferred COSTART term in Table 55. Consistent with the physiologic effects of insulin, hypoglycemia was the most common all-causality adverse event for INH- and SC-treated type 2 patients. Hypoglycemia occurred at slightly lower incidence in the INH than SC group, at 61.9% and 74.6%, respectively, and was least common in the OA group, at 28.7%. Respiratory tract infection was the second most common event in all treatment groups and occurred at lower incidence in the INH than SC group. Of the remaining listed adverse events, all-causality cough and headache occurred at greater incidence among patients receiving INH than SC insulin. However, the incidence of headache was comparable between the INH and OA groups. Among patients in the OA group, hypoglycemia was the most common all-causality adverse event, followed by respiratory tract infection, diarrhea, and headache.

On a treatment-related basis, hypoglycemia and tremor were the most common adverse events among type 2 patients of both insulin-treated groups. Treatment-related hypoglycemia occurred at slightly lower incidence in the INH than SC group, and tremor occurred at comparable incidences between these two groups. Among other common treatment-related adverse events, cough and pharyngitis were more common in the INH than SC group, and accidental injury, back pain, and retinal disorder were more common in the SC than INH group. The most common treatment-related events in the OA group were hypoglycemia, diarrhea, and tremor (Table 55).

Table 55. All-Causality Common Adverse Events (≥ 5% incidence in any group) by Preferred Term: Controlled Phase 2/3 Type 2 Studies

		Number (%) of Patients					
		All-Causality			Treatment-Related		
Body system*	Preferred term	INH N=1279	SC N=488	OA N=644	INH N=1279	SC N=488	OA N=644
MN	Hypoglycemia**	792 (61.9)	364 (74.6)	185 (28.7)	790 (61.8)	364 (74.6)	178 (27.6)
R	Respiratory tract infection	365 (28.5)	172 (35.2)	127 (19.7)	14 (1.1)	7 (1.4)	4 (0.6)
R	Cough increased	275 (21.5)	41 (8.4)	24 (3.7)	156 (12.2)	11 (2.3)	1 (0.2)
N	Tremor	221 (17.3)	96 (19.7)	58 (9.0)	192 (15.0)	84 (17.2)	29 (4.5)
BW	Flu syndrome	170 (13.3)	64 (13.1)	59 (9.2)	1 (0.1)	1 (0.2)	0
BW	Headache	168 (13.1)	36 (7.4)	67 (10.4)	51 (4.0)	13 (2.7)	6 (0.9)
BW	Asthenia	161 (12.6)	70 (14.3)	59 (9.2)	124 (9.7)	47 (9.6)	17 (2.6)
SA	Sweating	148 (11.6)	64 (13.1)	42 (6.5)	125 (9.8)	56 (11.5)	24 (3.7)
N	Dizziness	142 (11.1)	66 (13.5)	38 (5.9)	107 (8.4)	45 (9.2)	18 (2.8)
R	Pharyngitis	119 (9.3)	44 (9.0)	38 (5.9)	27 (2.1)	3 (0.6)	0
CV	Hypertension	112 (8.8)	43 (8.8)	49 (7.6)	19 (1.5)	20 (4.1)	3 (0.5)
R	Rhinitis	107 (8.4)	48 (9.8)	19 (3.0)	23 (1.8)	5 (1.0)	1 (0.2)
BW	Back pain	103 (8.1)	57 (11.7)	40 (6.2)	12 (0.9)	14 (2.9)	0
BW	Accidental injury	102 (8.0)	62 (12.7)	41 (6.4)	9 (0.7)	10 (2.0)	0
BW	Pain	93 (7.3)	44 (9.0)	35 (5.4)	21 (1.6)	11 (2.3)	0
D	Diarrhea	93 (7.3)	31 (6.4)	68 (10.6)	5 (0.4)	2 (0.4)	34 (5.3)
MS	Arthralgia	85 (6.6)	45 (9.2)	39 (6.1)	9 (0.7)	12 (2.5)	2 (0.3)
D	Nausea	79 (6.2)	28 (5.7)	33 (5.1)	25 (2.0)	12 (2.5)	9 (1.4)
MN	Peripheral edema	74 (5.8)	32 (6.6)	27 (4.2)	22 (1.7)	13 (2.7)	10 (1.6)
R	Respiratory disorder	70 (5.5)	45 (9.2)	11 (1.7)	16 (1.3)	5 (1.0)	0
R	Sinusitis	67 (5.2)	46 (9.4)	15 (2.3)	4 (0.3)	4 (0.8)	0
D	Dyspepsia	64 (5.0)	31 (6.4)	31 (4.8)	11 (0.9)	3 (0.6)	8 (1.2)
N	Anxiety	54 (4.2)	34 (7.0)	15 (2.3)	22 (1.7)	16 (3.3)	0
U	Urinary tract infection	54 (4.2)	28 (5.7)	24 (3.7)	2 (0.2)	0	1 (0.2)
SS	Retinal disorder	51 (4.0)	11 (2.3)	34 (5.3)	5 (0.4)	9 (1.8)	1 (0.2)
BW	Abdominal pain	50 (3.9)	19 (3.9)	40 (6.2)	7 (0.5)	5 (1.0)	14 (2.2)
N	Hypesthesia	29 (2.3)	26 (5.3)	10 (1.6)	15 (1.2)	15 (3.1)	2 (0.3)

*BW = Body as a Whole; CV=Cardiovascular, D = Digestive; MS = Musculoskeletal; MN = Metabolic and Nutritional; N = Nervous; R= Respiratory; SA = Skin and Appendages; SS=special senses; and U=urogenital.
INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, and N=number of patients.
**Protocol-specified definition of hypoglycemia
Cutoff date: 13 December 2004

Of all-causality adverse events occurring at ≥ 1% but less than 5% incidence in any treatment group and, therefore, not included in Table 55, dry mouth, dyspnea, and sputum increased occurred at greater incidence in the INH than both comparator groups. In addition, atrial fibrillation, cholelithiasis, goiter, arthritis, agitation, confusion, dermatitis, and nail disorder occurred at greater incidence in the SC than the INH or OA group.

The most common severe adverse event among insulin-treated type 2 patients in Controlled Phase 2/3 studies was hypoglycemia, and the incidence of severe hypoglycemia was greater among SC insulin- than INH-treated patients, at 5.1% and 1.9%, respectively. The remaining events occurred at incidences of ≤ 0.9% without a clear imbalance between treatment groups (Table 56).

Table 56. Severe Adverse Events Occurring in ≥ 5 Patients in Any Group by Preferred Term: Controlled Phase 2/3 Type 2 Studies

		Number (%) of Patients					
		All Causality			Treatment-Related		
Body system*	Preferred term	INH N=1279	SC N=488	OA N=644	INH N=1279	SC N=488	OA N=644
MN	Hypoglycemia**	24 (1.9)	25 (5.1)	1 (0.2)	24 (1.9)	25 (5.1)	1 (0.2)
BW	Headache	10 (0.8)	1 (0.2)	6 (0.9)	1 (0.1)	0	0
CV	Myocardial infarct	8 (0.6)	2 (0.4)	6 (0.9)	0	0	0
BW	Pain	8 (0.6)	1 (0.2)	5 (0.8)	2 (0.2)	0	0
BW	Abdominal pain	7 (0.5)	1 (0.2)	3 (0.5)	1 (0.1)	0	0
R	Cough increased	7 (0.5)	1 (0.2)	0	6 (0.5)	0	0
BW	Back pain	6 (0.5)	4 (0.8)	3 (0.5)	0	0	0
BW	Chest pain	6 (0.5)	1 (0.2)	2 (0.3)	0	0	0
BW	Cellulitis	5 (0.4)	2 (0.4)	0	0	0	0
D	Diarrhea	5 (0.4)	1 (0.2)	6 (0.9)	1 (0.1)	0	2 (0.3)
SS	Retinal disorder	5 (0.4)	0	1 (0.2)	0	0	0
MS	Tenosynovitis	5 (0.4)	0	0	0	0	0
R	Bronchitis	5 (0.4)	0	0	0	0	0
CV	Angina pectoris	3 (0.2)	1 (0.2)	6 (0.9)	0	0	0
MS	Arthralgia	2 (0.2)	2 (0.4)	6 (0.9)	0	0	0

*BW=Body as a Whole; CV=Cardiovascular; D=Digestive; MS=Musculoskeletal; MN=Metabolic and Nutritional; N=Nervous, R=Respiratory; SS=Special Senses; and U=Urogenital.
INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, and N=number of patients.
**Protocol-specified definition of hypoglycemia
Cutoff date: 13 December 2004

A generally similar pattern was seen for the Controlled Phase 2/3 and All Phase 2/3 Studies.

AEs that occurred with higher incidence in INH than comparator group in the Controlled Phase 2/3 protocol set (cough, dry mouth, dyspnea, and sputum increased) were assessed by age, gender, race, by interval of treatment with INH, and according to INH dose at event onset time.

There was no effect of demographic characteristics on the incidence of AEs with the exception of BMI: the incidences of all-causality headache, dyspnea, chest pain, and increased sputum were increased in INH-treated patients with a BMI ≥ 30 kg/m^2 compared to patients with a BMI < 30 kg/m^2.

The overall prevalence of all-causality and treatment-related adverse events decreased with increasing interval of treatment for adult type 2 patients regardless of treatment.

The overall incidence of all-causality and treatment-related adverse events did not vary systematically by dose of INH at the time of the event onset with the exception of dyspnea, but this may have been confounded by the effect of BMI noted above. Dyspnea was not associated with higher INH dose in patients with type 1 DM, among whom there were few obese patients. This disparity between the association of INH dose and dyspnea occurrence by type of DM, combined with the association of BMI with dyspnea occurrence, strongly supports obesity, rather than INH dose, as the factor affecting dyspnea occurrence

6.2.2. Common and Non-serious Adverse Events in Clinical Pharmacology Studies

Safety and toleration results from the clinical pharmacology studies were consistent with results for studies of longer duration. The incidence of AEs was higher among INH-treated patients (40.1%) than SC insulin-treated patients (29.5%) in the Phase 1 studies, but rates for both treatment groups were lower

than in the Phase 2/3 studies. The most common all-causality adverse events for INH-treated patients were hypoglycemia, headache, dizziness, and cough increased. Hypoglycemia occurred with similar incidence in both treatment groups. The other 3 AEs occurred with greater incidence (all were <10%) in the INH group. Six severe adverse events occurred in the INH group: headache (N=4), myocardial infarct, and dizziness. None was considered related to treatment.

6.3. Overall Safety Profile – Discontinuations, Serious Adverse Events, and Deaths

6.3.1. Discontinuations

Patients with Type 1 DM

The discontinuation rates among adult type 1 patients in the Controlled Phase 2/3 Studies were comparable between the INH and SC insulin treatment groups, and the majority of discontinuations in both treatment groups were not related to study drug (Table 57). Discontinuation rates related to study drug, and to adverse events related to study drug were greater for the INH group than the SC insulin group.

Table 57. Summary of Discontinuations Among Adult Type 1 Patients: Controlled Phase 2/3 Studies

	Number (%) of Patients	
	INH N=698	SC N=705
Total discontinuations	**108 (15.5)**	**93 (13.2)**
Related to study drug	**30 (4.3)**	**5 (0.7)**
Adverse event	15 (2.1)	2 (0.3)
Insufficient clinical response	12 (1.7)	3 (0.4)
Laboratory abnormality	3 (0.4)	0
Not related to study drug	**75 (10.7)**	**88 (12.5)**
Adverse event	9 (1.3)	5 (0.7)
Patient died	**3 (0.4)**	**0**

INH=inhaled insulin, SC=subcutaneous short-acting insulin.
Cutoff date: 13 December 2004

The discontinuation rates of INH-treated adult patients for All Phase 2/3 type 1 studies, both related to study drug and not related to study drug, were greater than those for Controlled Phase 2/3 Type 1 studies (Table 58). This difference between protocol sets is expected given the greater duration of treatment represented by the All Phase 2/3 Studies relative to the Controlled Phase 2/3 Studies.

Table 58. Summary of Discontinuations Among Adult Type 1 Patients Treated with Inhaled Insulin: All Phase 2/3 Studies

	Number (%) of Patients N=918
Total discontinuations	**304 (33.1)**
Related to study drug	**61 (6.6)**
Adverse event	24 (2.6)
Insufficient clinical response	34 (3.7)
Laboratory abnormality	3 (0.3)
Not related to study drug	**237 (25.8)**
Adverse event	13 (1.4)
Patient died	**6 (0.7)**

Cutoff date: 13 December 2004

The most common all-causality adverse events leading to discontinuation among adult INH-treated patients were cough (N=10, one of which was severe), and dyspnea (N=3, none severe). Of the remaining adverse events resulting in discontinuation among INH-treated patients, two hypoglycemic events and one asthma were severe (Table 59).

Table 59. All-Causality Adverse Events Resulting in Discontinuation in ≥ 2 Adult Type 1 Patients in Either Group: Controlled Phase 2/3 Studies

		Number (%) of Patients	
Body system*	**Preferred term**	**INH N=698**	**SC N=705**
R	Cough increased	10 (1.4)	0
R	Dyspnea	3 (0.4)	0
MN	Hypoglycemia**	2 (0.3)	1 (0.1)
R	Asthma	2 (0.3)	0
R	Pharyngitis	2 (0.3)	0
R	Respiratory disorder	2 (0.3)	0
U	Breast carcinoma	1 (0.1)	2 (0.3)

*MN=Metabolic and Nutritional; R=Respiratory, and U=Urogenital.
INH=inhaled insulin, SC=subcutaneous short-acting insulin, and N=number of patients.
**Protocol-specified definition of hypoglycemia
Cutoff date: 13 December 2004

Adverse events that resulted in patients temporarily interrupting treatment with study drug occurred infrequently but with a greater overall incidence in the INH (4.7%) than in the SC insulin group (1.3%) The most common causes were respiratory tract infection, cough, pharyngitis, and bronchitis.

Although respiratory tract infection was more commonly associated with temporarily interrupting treatment in the INH group than in the SC insulin group, the majority of INH-treated patients who experienced all-causality adverse events potentially indicative of respiratory infection or allergy did not discontinue the study or temporarily interrupt treatment. A total of 438 (62.8%) INH-treated patients experienced one or more of the following events: asthma, bronchitis, laryngitis, pharyngitis, pneumonia, respiratory tract infection, rhinitis, and sinusitis. However, only 5 patients discontinued and only 16 patients temporarily interrupted treatment due to one or more of these events (Table 60).

Table 60. Temporary and Permanent Discontinuation due to Selected Respiratory Adverse Events Indicative of Potential Infection or Allergy: Controlled Phase 2/3 Studies - Type 1 Patients (Age >= 18 Years)

	INH N=698 SME=7207	**SC N=705 SME=7565**
	Number of Patients (%)	
Patients with selected respiratory adverse events	438 (62.8)	416 (59.0)
Patients discontinued due to selected events	5 (1.1)	0
Patients temporarily discontinued due to selected events	16 (3.7)	0
Patients permanently or temporarily discontinued due to selected events	19 (4.3)	0
	Number of Events (%)	
Number of selected respiratory adverse events	1087	977
Selected events resulting in discontinuation	7 (0.6)	0
Selected events resulting in temporary discontinuation	21 (1.9)	0
Selected events resulting in any discontinuation	28 (2.6)	0

Includes data up to 1 day after last dose of study treatment.
INH=inhaled insulin, N=number of patients, SC=subcutaneous short-acting insulin, and SME=patient-months of exposure
Cutoff date: 13 December 2004

Results for the All Phase 2/3 Studies were consistent with the Controlled Phase 2/3 Studies. The most common AEs resulting in discontinuation were cough, respiratory disorder, dyspnea, hypoglycemia, and pharyngitis. In addition, asthma was a cause of discontinuation for 3 patients. Cough and respiratory tract infection were the most common adverse events associated with temporarily interrupting treatment.

Patients with Type 2 DM

Overall discontinuation rates among type 2 patients in the Controlled Phase 2/3 Studies were comparable among treatment groups, and the majority of discontinuations in all treatment groups were not related to study drug. The rates of discontinuation related to study drug, and to adverse events related to study drug were greatest and comparable among INH- and OA-treated patients, and least among SC-treated patients (Table 61).

Table 61. Summary of Discontinuations: Controlled Phase 2/3 Type 2 Patients

	Number (%) of Patients		
	INH N=1279	SC N=488	OA N=644
Total discontinuations	**177 (13.8)**	**74 (15.2)**	**93 (14.4)**
Related to study drug	**39 (3.0)**	**4 (0.8)**	**20 (3.1)**
Adverse event	27 (2.1)	0	10 (1.6)
Insufficient clinical response	12 (0.9)	4 (0.8)	10 (1.6)
Not related to study drug	**134 (10.5)**	**69 (14.1)**	**70 (10.9)**
Adverse event	23 (1.8)	6 (1.2)	11 (1.7)
Patient died	**4 (0.3)**	**1 (0.2)**	**3 (0.5)**

INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, and N=number of patients.
Cutoff date: 13 December 2004

The overall rates of all discontinuations, discontinuations related to study drug, and discontinuations due to adverse events related to study drug were greater among INH-treated patients in the All Phase 2/3 Studies than the Controlled Phase 2/3 Studies (Table 62). This difference is expected given the greater duration of treatment represented by the All Phase 2/3 Studies relative to the Controlled Phase 2/3 Studies.

Table 62. Summary of Discontinuations Among Type 2 Patients Treated with Inhaled Insulin: All Phase 2/3 Studies

	Number (%) of Patients
	N=1580
Total discontinuations	**469 (29.7)**
Related to study drug	**82 (5.2)**
Adverse event	63 (4.0)
Insufficient clinical response	19 (1.2)
Not related to study drug	**374 (23.7)**
Adverse event	50 (3.2)
Patient died	**13 (0.8)**

Cutoff date: 13 December 2004

Adverse events in the respiratory body system were the most common adverse events leading to discontinuation among INH-treated patients; 30 patients (2.3%) discontinued for this reason. Common

adverse events that resulted in discontinuation in the INH group included cough, asthma, dyspnea, headache, bronchitis, and respiratory tract infection. Diarrhea and myocardial infarction were the most common causes of discontinuation among OA-treated patients (Table 63).

Table 63. All-Causality Adverse Events Resulting in Discontinuation in ≥ 2 Type 2 Patients in Any Treatment Group: Controlled Phase 2/3 Studies

		Number (%) of Patients		
		INH	SC	OA
Body system*	Preferred term	N=1279	N=488	N=644
R	Cough increased	14 (1.1)	0	0
R	Asthma	7 (0.5)	0	0
R	Dyspnea	5 (0.4)	0	1 (0.2)
BW	Headache	3 (0.2)	0	1 (0.2)
R	Bronchitis	3 (0.2)	0	0
R	Respiratory tract infection	3 (0.2)	0	0
R	Respiratory disorder	3 (0.2)	0	0
BW	Chest pain	2 (0.2)	0	1 (0.2)
D	Nausea	2 (0.2)	0	1 (0.2)
CV	Myocardial infarct	1 (0.1)	0	3 (0.5)
BW	Abdominal pain	1 (0.1)	0	2 (0.3)
D	Diarrhea	0	0	4 (0.6)
U	Kidney function abnormal	0	0	2 (0.3)

*BW = Body as a Whole, CV=Cardiovascular, D = Digestive, OA=oral agent, R= Respiratory, and U=Urogenital.
INH=inhaled insulin, SC=subcutaneous short-acting insulin, and N=number of patients.
Cutoff date: 13 December 2004

Temporary treatment interruption due to adverse events among patients with type 2 DM occurred at comparable overall incidence in the INH (6.6%) and OA group (6.8%). A smaller proportion of patients in the SC group (1.6%) stopped temporarily. Adverse events in the respiratory, body as a whole, and the metabolic and nutritional body systems were the most common causes in the INH group, and events in the digestive body system were the most common causes in the OA treatment group. Hypoglycemia was the most common cause for both INH- and SC insulin-treated patients. Among INH-treated patients, respiratory tract infection, cough, and bronchitis were the next most common events associated with temporary interruption of treatment (Table 64).

Table 64. All-Causality Adverse Events Resulting in Temporary Treatment Interruption in ≥ 2 Type 2 Patients in Any Treatment Group: Controlled Phase 2/3 Studies

		Number (%) of Patients		
Body system*	**Preferred term**	**INH N=1280**	**SC N=492**	**OA N=644**
MN	Hypoglycemia**	15 (1.2)	3 (0.6)	3 (0.5)
R	Respiratory tract infection	9 (0.7)	1 (0.2)	0
R	Cough increased	8 (0.6)	0	0
R	Bronchitis	6 (0.5)	0	0
R	Dyspnea	5 (0.4)	0	0
CV	Myocardial infarct	5 (0.4)	0	1 (0.2)
R	Asthma	4 (0.3)	0	0
BW	Flu syndrome	3 (0.2)	0	1 (0.2)
R	Pharyngitis	3 (0.2)	0	0
BW	Cellulitis	3 (0.2)	0	0
CV	Coronary artery disorder	3 (0.2)	0	0
BW	Chest pain	3 (0.2)	0	0
D	Vomiting	2 (0.2)	1 (0.2)	1 (0.2)
M	Bone fracture accidental	2 (0.2)	0	1 (0.2)
CV	Angina pectoris	2 (0.2)	0	0
D	Gastroenteritis	2 (0.2)	0	0
D	Nausea	1 (0.1)	1 (0.2)	2 (0.3)
SA	Sweating	1 (0.1)	0	3 (0.5)
N	Tremor	1 (0.1)	0	3 (0.5)
D	Diarrhea	1 (0.1)	0	12 (1.9)
N	Tremor	1 (0.1)	0	2 (0.3)
BW	Abdominal pain	0	0	3 (0.5)
BW	Malaise	0	0	2 (0.3)
D	Dyspepsia	0	0	2 (0.3)
D	Flatulence	0	0	2 (0.3)
D	Increased appetite	0	0	2 (0.3)
N	Dizziness	0	0	2 (0.3)

*BW = Body as a Whole, CV=Cardiovascular, D = Digestive, M=Musculoskeletal, MN = Metabolic and Nutritional, N=Nervous, R= Respiratory, and SA=Skin and Appendages.
INH=inhaled insulin, OA = oral agent, SC=subcutaneous short-acting insulin, and N=number of patients.
**Protocol-specified definition of hypoglycemia
Cutoff date: 13 December 2004

Although respiratory tract infection was one of the more common adverse events resulting in temporarily stopping treatment, the majority of INH-treated patients with type 2 DM experiencing all-causality adverse events indicative of potential respiratory infection or allergy did not discontinue or temporarily stop study drug. A total of 577 (45.1%) INH-treated patients experienced one or more of the following events: asthma, bronchitis, laryngitis, pharyngitis, pneumonia, respiratory tract infection, rhinitis, and sinusitis (Table 65). Only 12 (2.1%) patients discontinued, and only 18 patients (3.1%) temporarily stopped receiving study drug due to one or more of these events.

Table 65. Temporary and Permanent Discontinuation due to Selected Respiratory Adverse Events Indicative of Potential Infection or Allergy: Controlled Phase 2/3 Studies - Type 2 Patients

	INH N=1279 SME=13384	SC N=488 SME=6060	OA N=644 SME=6452
	Number of Patients (%)		
Patients with selected events	577 (45.1)	258 (52.9)	194 (30.1)
Patients discontinued due to selected events	12 (2.1)	0	0
Patients temporarily discontinued due to selected events	18 (3.1)	0	0
Patients permanently or temporarily discontinued due to selected events	27 (4.7)	0	0
	Number of Events (%)		
Number of selected events	1152	529	328
Selected events resulting in discontinuation	15 (1.3)	0	0
Selected events resulting in temporary discontinuation	20 (1.7)	0	0
Selected events resulting in permanent or temporary discontinuation	35 (3.0)	0	0

Includes data up to 1 day after last dose of study treatment.
INH=inhaled insulin, N=number of patients, OA=oral agents, SC=subcutaneous short-acting insulin, and SME=patient-months of exposure
Cutoff date: 13 December 2004

Results for the All Phase 2/3 Studies were consistent with the Controlled Phase 2/3 Studies. The most common AEs resulting in discontinuation were cough, respiratory disorder, dyspnea, asthma, and coronary artery disorder.

Hypoglycemia, respiratory tract infection, and cough were the most common adverse events associated with temporarily stopping treatment.

Discontinuations in Clinical Pharmacology Studies

Thirty-two (3.9%) INH-treated patients and 7 (1.1%) SC insulin-treated patients discontinued. Thirty patients discontinued for reasons considered unrelated to treatment. Two INH-treated patients discontinued due to treatment-related adverse events (emesis and pruritus).

6.3.2. Serious Adverse Events

Patients with Type 1 DM

The total numbers of all-causality and treatment-related SAE cases among adult patients in the Controlled Studies and All Phase 2/3 Studies are presented in Table 66. When adjusted for exposure (cases per 1,000 patient-months of exposure), the incidences of both all-causality and treatment-related SAE cases were lower among INH- than SC insulin-treated type 1 patients in the Controlled Phase 2/3 Studies. In the All Phase 2/3 set, the number of all-causality and treatment-related serious adverse event cases were greater in the INH than the SC treatment group, as expected due to the greater INH than SC exposure in this set.

Table 66. Summary of Serious Adverse Event Cases: Adult Type 1 Patients in Controlled and All Phase 2/3 Studies

Data Set/ Treatment	N	SME	All-causality SAE Cases	Treatment-related SAE Cases	All-causality SAE Cases per 1,000 SME	Treatment-related SAE Cases per 1,000 SME
Controlled Phase 2/3 Studies						
INH	698	7,207	57	27	7.9	3.7
SC	705	7,565	78	32	10.3	4.2
All Phase 2/3 Studies						
INH	918	NA	135	51	NA	NA
SC	NA	NA	79	32	NA	NA

A case is a single event or a series of related events not separated in time, and occurring in a single patient.
N=number of patients, and SME=patient-months of exposure. INH=inhaled insulin, SC=subcutaneous short-acting insulin, and NA=not applicable (data not available)
Cutoff date: 13 December 2004

In the Controlled Phase 2/3 Studies, adult type 1 patients experienced all-causality SAEs most frequently in the Metabolism and Nutrition Disorders and the Nervous System Disorders system organ classes. The incidence of SAEs in the Nervous System Disorders and Psychiatric Disorders system organ classes was greater among SC- than INH-treated patients (Table 67).

Table 67. All-Causality Serious Adverse Events by System Organ Class: Adult Type 1 Patients in Controlled Phase 2/3 Studies

	Number (%) of Patients	
	INH N=698	SC N=705
System Organ Class	SME=7207	SME=7565
Metabolism and nutrition disorders	29 (4.2)	40 (5.7)
Nervous system disorders	11 (1.6)	24 (3.4)
Infections and infestations	5 (0.7)	9 (1.3)
Cardiac disorders	5 (0.7)	7 (1.0)
Injury, poisoning, and procedural complications	5 (0.7)	5 (0.7)
General disorders and administration site conditions	4 (0.6)	1 (0.1)
Renal and urinary disorders	3 (0.4)	2 (0.3)
Gastrointestinal disorders	2 (0.3)	5 (0.7)
Neoplasms benign, malignant and unspecified	2 (0.3)	3 (0.4)
Musculoskeletal and connective tissue disorders	2 (0.3)	2 (0.3)
Pregnancy, puerperium and perinatal conditions	2 (0.3)	2 (0.3)
Eye disorders	2 (0.3)	1 (0.1)
Hepatobiliary disorders	2 (0.3)	0
Psychiatric disorders	0	9 (1.3)
Skin and subcutaneous tissue disorders	0	2 (0.3)
Reproductive system and breast disorders	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (0.1)

N=number of patients, and SME=patient-months of exposure.
INH=inhaled insulin, and SC=subcutaneous short-acting insulin.
Cutoff date: 13 December 2004

The most common all-causality SAEs occurring among adult type 1 patients in both treatment groups were hypoglycemia and loss of consciousness. These events were slightly less common among INH- than SC insulin-treated patients, as were convulsion and depression (Table 68).

Table 68. All-Causality Serious Adverse Events With ≥ 3 Occurrences in Either Treatment Group: Adult Type 1 Patients in Controlled Phase 2/3 Studies

	Number of Events (Events per 1,000 Patient-Months)	
	INH	SC
	N=698	N=705
Preferred Term	SME=7207	SME=7565
Hypoglycemia	25 (3.5)	36 (4.8)
Loss of consciousness	8 (1.1)	12 (1.6)
Myocardial infarction	3 (0.4)	3 (0.4)
Diabetic ketoacidosis	3 (0.4)	1 (0.1)
Convulsion	2 (0.3)	8 (1.1)
Depression	0	5 (0.7)

INH=inhaled insulin, N=number of patients, SC=subcutaneous short-acting insulin, and SME=patient-months of exposure.
Cutoff date 13 December 2004

In the All Phase 2/3 Studies, consistent with the Controlled Phase 2/3 Studies, INH-treated adult type 1 patients experienced all-causality SAEs most frequently in the Metabolism and Nutrition Disorders, followed by the Nervous System Disorders, Cardiac Disorders, and Infections and Infestations system organ classes. Among SC insulin-treated patients, SAEs of the psychiatric disorders system organ class were also common.

The most common all-causality SAE occurring among adult type 1 patients in the All Phase 2/3 Studies was hypoglycemia, consistent with the findings in the Controlled Phase 2/3 Studies.

Hypoglycemia was the most common treatment-related SAE among adult patients with type 1 DM in both treatment groups in each of the Phase 2/3 studies groupings, and most of the remaining treatment-related SAEs were events attributable to hypoglycemia. The sole exception was a patient in Study 1022, who died due to an unknown cause. The occurrence rate of treatment-related hypoglycemia as an SAE was lower among INH- than SC insulin-treated patients for the Controlled Phase 2/3 Studies (Table 69).

Table 69. Treatment-Related Serious Adverse Events among Adult Type 1 Patients in Controlled and All Phase 2/3 Studies

	Number of Events (Events per 1,000 Patient-Months)			
	Controlled Phase 2/3 Studies		All Phase 2/3 Studies	
	INH	SC	INH	SC
	N=698	N=705	N=918	SME=NA
Preferred Term	SME=7207	SME=7565	SME=NA	SME=NA
Hypoglycemia	25 (3.5)	32 (4.2)	48	32
Grand mal convulsion	1 (0.1)	0	1	0
Hypoglycemic coma	1 (0.1)	0	1	0
Death	1 (0.1)	0	1	0
Loss of consciousness	0	1 (0.1)	0	1
Convulsions	0	0	1	0
Delirium	0	0	1	0

INH=inhaled insulin, NA=not applicable (data not available), SC=subcutaneous short-acting insulin, and SME=patient-months of exposure
The SAEs of grand mal convulsion, hypoglycemic coma, and death due to unknown cause occurred in three separate individuals.
Cutoff date: 13 December 2004

Patients with Type 2 DM

For patients with type 2 DM, the rates of all-causality SAEs (cases/1000 patient-months) were comparable among treatment groups (INH: 11.0, SC: 12.2, OA: 12.1), and the rates of treatment-related SAE cases were greater for SC insulin- than for INH- or OA-treated patients (Table 70).

Table 70. Summary of Serious Adverse Event Cases*: Type 2 Patients in Controlled and All Phase 2/3 Studies

Data Set/ Treatment	N	SME	All-causality SAE Cases	Treatment-related SAE Cases	All-causality SAE Cases per 1000 SME	Treatment-related SAE Cases per 1000 SME
Controlled Phase 2/3 Studies						
INH	1279	13384	147	12	11.0	0.9
SC	488	6060	74	14	12.2	2.3
OA	644	6452	78	2	12.1	0.3
All Phase 2/3 Studies						
INH	NA	NA	396	20	NA	NA
SC	NA	NA	77	14	NA	NA
OA	NA	NA	79	2	NA	NA

*A case is a single event or a series of related events not separated in time, and occurring in a single patient.
INH=inhaled insulin, N=number of patients, NA=not applicable (data not available), OA=oral antidiabetic agents, SC=subcutaneous short-acting insulin, and SME=patient-months of exposure.
Cutoff date: 13 December 2004

Among type 2 patients in the Controlled Phase 2/3 Studies, all-causality SAEs in the Cardiac Disorders system organ class occurred in the greatest proportion of patients in all treatment groups. The incidence of Cardiac Disorders was comparable among treatment groups. Consistent with the findings among patients with type 1 DM, SAEs of the Metabolism and Nutritional Disorders and Psychiatric Disorders system organ class occurred among more type 2 patients in the SC group than the INH group (Table 71).

Table 71. All-Causality Serious Adverse Events by System Organ Class: Type 2 Patients in Controlled Phase 2/3 Studies

System Organ Class	Number (%) of Patients INH N=1279 SME=13384	SC N=488 SME=6060	OA N=644 SME=6452
Cardiac disorders	30 (2.3)	15 (3.1)	14 (2.2)
Infections and infestations	21 (1.6)	10 (2.0)	5 (0.8)
Nervous system disorders	18 (1.4)	12 (2.5)	12 (1.9)
Neoplasms benign, malignant and unspecified	15 (1.2)	5 (1.0)	4 (0.6)
Gastrointestinal disorders	11 (0.9)	8 (1.6)	11 (1.7)
Musculoskeletal and connective tissue disorders	9 (0.7)	6 (1.2)	9 (1.4)
General disorders and administration site conditions	9 (0.7)	5 (1.0)	6 (0.9)
Injury, poisoning, and procedural complications	9 (0.7)	5 (1.0)	3 (0.5)
Respiratory, thoracic and mediastinal disorders	9 (0.7)	5 (1.0)	2 (0.3)
Metabolism and nutritional disorders	7 (0.5)	14 (2.9)	4 (0.6)
Vascular disorders	7 (0.5)	2 (0.4)	3 (0.5)
Renal and urinary disorders	5 (0.4)	1 (0.2)	3 (0.5)
Skin and subcutaneous tissue disorders	3 (0.2)	2 (0.4)	0
Hepatobiliary disorders	3 (0.2)	1 (0.2)	4 (0.6)
Investigations	3 (0.2)	0	1 (0.2)
Psychiatric disorders	2 (0.2)	8 (1.6)	1 (0.2)
Endocrine disorders	2 (0.2)	0	0
Immune system disorders	2 (0.2)	0	0
Surgical and medical procedures	1 (0.1)	1 (0.2)	2 (0.3)
Blood and lymphatic system disorders	1 (0.1)	1 (0.2)	0
Eye disorders	1 (0.1)	0	2 (0.3)
Reproductive system and breast disorders	1 (0.1)	0	2 (0.3)

INH=inhaled insulin, N=number of patients, OA=oral antidiabetic agents, SC=subcutaneous short-acting insulin,, and SME=patient-months of exposure.
Cutoff date: 13 December 2004

INH did not appear to be associated with an increased likelihood of experiencing a respiratory SAE. SAEs related to the respiratory system are discussed in Section 6.5.

The most common specific all-causality SAEs among INH-treated type 2 patients in the Controlled Phase 2/3 Studies were myocardial infarction, chest pain, angina, hypoglycemia, and coronary artery disease. In each insulin-treated group, myocardial infarction, chest pain, and angina occurred at incidences less than those in the OA group, and the incidence of coronary artery disease was comparable between the INH and SC treatment groups. With the exception of hypoglycemia and loss of consciousness, both of which occurred most frequently in the SC group, there were no clear imbalances in the rates of occurrence of specific SAEs among treatment groups (Table 72).

Table 72. All-Causality Serious Adverse Events With ≥ 3 Occurrences in Any Treatment Group: Type 2 Patients in Controlled Phase 2/3 Studies

	Number of Events (Events per 1,000 Patient-Months)		
	INH	**SC**	**OA**
	N=1279	**N=488**	**N=644**
Preferred Term	**SME=13384**	**SME=6060**	**SME=6452**
Myocardial infarction*	11 (0.8)	5 (0.8)	7 (1.1)
Chest pain	7 (0.5)	1 (0.2)	4 (0.6)
Angina†	6 (0.4)	2 (0.3)	5 (0.8)
Hypoglycemia	5 (0.4)	13 (2.1)	2 (0.3)
Coronary artery disease	5 (0.4)	3 (0.5)	0
Cellulitis	4 (0.3)	3 (0.5)	0
Loss of consciousness	3 (0.2)	6 (1.0)	1 (0.2)
Prostate cancer	3 (0.2)	1 (0.2)	0
Inguinal hernia	3 (0.2)	1 (0.2)	0
Transient ischemic attack	3 (0.2)	1 (0.2)	0
Cardiac failure congestive	3 (0.2)	0	1 (0.2)
Appendicitis	3 (0.2)	0	0
Asthma	3 (0.2)	0	0
Renal colic	3 (0.2)	0	0
Pneumonia	2 (0.1)	3 (0.5)	0
Depression	1 (0.1)	3 (0.5)	0
Bipolar disorder	1 (0.1)	3 (0.5)	0
Atrial fibrillation	0	3 (0.5)	0

*Includes terms "acute myocardial infarction" and "myocardial infarction"
†Includes terms "angina pectoris" and "angina unstable"
INH=inhaled insulin, N=number of patients, OA=oral antidiabetic agents, SC=subcutaneous short-acting insulin, and SME=patient-months of exposure.
Cutoff date: 13 December 2004

In the All Phase 2/3 Studies, consistent with the Controlled Phase 2/3 Studies, INH-treated patients with type 2 DM experienced SAEs most frequently in the Cardiac Disorders system organ class, followed by the Infections and Infestations, Nervous System Disorders, and Neoplasms system organ classes.

Hypoglycemia was the most common treatment-related SAE among type 2 patients in the Controlled Phase 2/3 Studies, and occurred at a greater rate in the SC group than in any other treatment group. The remaining events occurred at comparable rates across treatment groups (Table 73).

Table 73. Treatment-Related Serious Adverse Events among Type 2 Patients in Controlled Phase 2/3 Studies

	Number of Events (Events per 1,000 Patient-Months)		
	INH N=1279	SC N=488	OA N=644
Preferred Term	SME=13384	SME=6060	SME=6452
Hypoglycemia	5 (0.4)	13 (2.1)	2 (0.3)
Asthma	3 (0.2)	0	0
Blood glucose decreased	1 (0.1)	0	0
Vocal cord polyp	1 (0.1)	0	0
Drug hypersensitivity	1 (0.1)	0	0
Metastatic bronchial carcinoma	1 (0.1)	0	0
Cough	1 (0.1)	0	0
Bronchospasm	1 (0.1)	0	0
Loss of consciousness	0	1 (0.2)	0
Pancreatitis	0	1 (0.2)	0

INH=inhaled insulin, N=number of patients, OA=oral antidiabetic agents, SC=subcutaneous short-acting insulin, and SME=Patient-months of exposure
Cutoff date: 13 December 2004

Four SAEs occurred in three patients who received INH during the Phase 1 clinical development program. None were considered related to treatment. Two events were attributed to coronary artery disease, and two events in one patient were considered related to pregnancy.

The SAE data do not suggest an increased risk of adverse clinical outcome associated with INH use.

6.3.3. Deaths

As of 13 December 2004, 32 patients have died while in the INH clinical development program.

Twenty-eight patients (all adults) died while receiving study drug or within 30 days of the last administration of study drug. This total includes 9 (0.5%) patients who received INH and 7 (approximately 0.3%) patients who received comparator in Controlled Phase 2/3 studies and Studies 1028 and 1030. Additionally, 12 (0.8%) patients who received INH in an extension study died. The larger number of deaths in INH-treated patients in the extension studies is not unexpected given the large number of patients treated with INH (1,449) rather than comparator (45), as well as the longer duration of treatment for INH-treated patients.

The majority of these deaths were due to cardiovascular events, primarily myocardial ischemia. Analysis of cardiovascular AEs and SAEs revealed a comparable risk of ischemic heart disease, arrhythmias and heart failure in INH- and comparator-treated patients. There is no indication that deaths due to myocardial infarction were accompanied by hypoglycemia.

The remaining four deaths occurred after 30 days following the last administration of study drug. A 2 day old infant, conceived while its mother was receiving INH in Study 1022, died as the result of poorly controlled maternal DM approximately 6 months after the mother discontinued INH treatment. Three patients with type 2 DM who received OAs in Controlled Phase 2/3 studies also died.

There were no deaths reported in the clinical pharmacology studies.

None of the deaths that occurred in the INH development program as of 13 December 2004 were attributed to treatment by study investigators. One patient with type 1 DM who received INH in Study 1022 died of an unknown cause. In the absence of autopsy results and a definitive cause of death, the sponsor could not rule out the possibility that the death might have been related to the treatment regimen. The event has therefore been categorized as a treatment-related SAE.

6.4. Overall Safety Profile - Other Safety Parameters

A wide variety of laboratory abnormalities occurred among study patients. As would be expected in a population with DM, the most commonly reported laboratory abnormality was glycosuria. There were no clear differences among treatment groups in median laboratory test values or in the incidence of abnormal test results for patients with either type 1 or type 2 DM.

Median changes in laboratory test results between baseline and last observation for patients in Controlled Phase 2/3 studies were comparable between treatment groups for adult patients with type 1. For patients with type 2 DM, median changes were similar among treatment groups with one exception: Serum triglyceride concentrations decreased from baseline to last observation among INH-treated type 2 patients relative to comparator-treated patients. Serum triglycerides changed from baseline to last observation by –12, 4, and 7 mg/dL for the INH, SC, and OA groups, respectively. However, patients were permitted to use medications to control serum lipid concentrations during studies, rendering a comparison of lipid concentrations of questionable value.

Treatment with INH had no apparent clinically significant effect on vital signs, physical examination findings, or ECG test results in patients with type 1 or type 2 DM.

6.5. Pulmonary Safety

6.5.1. Pre-Clinical Pulmonary Safety Observations

Pre-clinical studies of INH pulmonary safety were unremarkable. The INH pre-clinical toxicology program included studies in both rats and monkeys in which insulin was administered for 6 months by the pulmonary route at doses up to approximately 40 and 4 times the clinical starting dose of 0.15 mg/kg/day, respectively. Assessment of several respiratory and pulmonary function parameters revealed no exposure-related effects. After histopathological examination, no exposure-related pathological responses were observed in representative compartments of the respiratory tract (nasal turbinates, larynx, trachea, and lung including airways and parenchyma) or lung-associated lymph nodes in either species. In addition, pulmonary tissues (bronchioles and alveoli) from these studies were stained with markers for cell proliferation, and no biologically-significant difference in cellular proliferation indices attributable to inhaled insulin were seen in either species.

6.5.2. Clinical Pulmonary Safety Observations

6.5.2.1. Background

This document presents integrated and study-specific safety data from completed and ongoing Phase 2/3 studies. Routine safety data and serious adverse event data presented in this document are based on the cutoff date of 13 December 2004 unless otherwise noted. Evaluations of HRCTs and PFTs are based on the cutoff date of 25 June 2004 except for HRCT data from Study 1029, discussed separately from pooled data, which are based on a cutoff date of 08 July 2005.

The database evaluated for INH pulmonary safety comprises 2,498 INH-treated patients with durations of treatment of up to 7 years. Of these patients, 1,887 were evaluable for pulmonary function tests in controlled studies, and 112 and 48 were evaluable for HRCT results in controlled and uncontrolled

studies, respectively. A total of 150 patients were evaluable with mild to moderate underlying lung disease (asthma or chronic obstructive pulmonary disease) (Table 74 and Table 75).

Table 74. Number of Inhaled Insulin-Treated Patients Evaluated and Duration of Treatment by Study Population

	Number of Patients in Controlled Studies (All Patients)	
Duration of INH Treatment (months)	**Controlled Phase 2/3 Studies Evaluable for AEs, DCs, and SAEs**	**Patients with ULD* Evaluable for AEs, DCs, SAEs, and PFTs**
>0	1975 (2496)	150
>3	1451 (2238)	102
>6	899 (1977)	64
>12	589 (1581)	24
>24	56 (748)	2
>36	(153)	0
>48	(85)	0
>60	(74)	0
>72	(51)	0

*The number of patients with ULD is the combination of those from the Controlled PFT Phase 2/3 protocol set (described below) and Studies 1028 and 1030 (6-month interim analyses).
AE=adverse event, DC=study discontinuation, INH=inhaled insulin, PFT=pulmonary function test, SAE=serious adverse event, and ULD=underlying lung disease at baseline.
Cutoff date: 25 June 2004

Table 75. Number of Inhaled Insulin-Treated Patients Evaluated in HRCT and PFT Analyses and Duration of Treatment

	Number of Patients in Controlled Studies (Number in Uncontrolled Studies)	
Duration of INH Treatment (months)	**HRCT***	**PFTs†**
Baseline	112	1887 (1149)
3	0 (2)	1422 (1146)
6	53 (7)	1355 (1128)
12	59 (27)	774 (1028)
24	0 (11)	143 (731)
36	0 (1)	(111)
48	0	(88)
60	0	(75)
72	0	(61)
84	0	(27)

*The listed durations of treatment for patients in uncontrolled studies are those completed by the patients. HRCT measurements were not planned for these patients, and the times of measurement fall between listed time points
†These numbers are based on FEV1 and DLco evaluations. Data presented from uncontrolled studies in this document include data from the controlled parent studies. Therefore, the total numbers of patients evaluated for PFTs is less than the sum of those evaluated in controlled and uncontrolled studies.
AE=adverse event, DC=study discontinuation, HRCT=high resolution computed tomography, INH=inhaled insulin, PFT=pulmonary function test, SAE=serious adverse event, and ULD=underlying lung disease at baseline.
Cutoff date: 25 June 2004

Fifty-nine INH-treated patients were evaluated for HRCTs after one year and are included in the table above. As of 08 July 2005, HRCT data on additional patients in Study 1029 are available: a total of 95 INH- and 97 SC insulin-treated have been evaluated after one year and 71 INH- and 73 SC insulin-treated have been evaluated after two years.

For the purposes of evaluating the pulmonary safety of INH, protocols were grouped and their data pooled according to study completion status and the population under study. In addition to the Controlled Phase 2/3 Studies and All Phase 2/3 Studies described in Section 6.1, the following groupings were identified.

Controlled PFT Phase 2/3 Studies

The Controlled PFT Phase 2/3 Studies set was used for the detailed analysis of PFTs, cough, and a description of patients with mild to moderate underlying lung disease. This set comprised Controlled Phase 2/3 studies with interim or final clinical study reports (CSRs) as of 25 June 2004 and is identical to the Controlled Phase 2/3 set, except that data from ongoing Studies 1022 and 1029 are truncated at 1 year of exposure, consistent with the 1-year interim analyses and includes 1,333 and 2,260 patients with type 1 and type 2 DM, evaluable for FEV_1 (Table 91) and 1,299 and 2,184 evaluable for DLco (Table 100). All data from completed studies are included.

Patients Evaluated by Thoracic High Resolution Computed Tomography

Patients evaluated by high resolution computed tomography (HRCT) based on the cutoff date of 25 June 2004 included:

A sub-population of 116 patients (53 of whom received INH) participated in a randomized HRCT sub-study of controlled Studies 106, 107, and 108 in which thoracic HRCT scans were performed at baseline and at end of study (week 24). Because the number of patients in this sub-study was small, the summary of data was performed without separating patients by DM type.

An additional 118 patients with type 2 DM (59 of whom received INH) who were participating in an ongoing 5-year HRCT sub-study of controlled Study 1029, and who had HRCT data at baseline and one year.

Fifty-one patients with type 1 or type 2 DM (48 of whom received INH) who participated in the uncontrolled extension Studies 111 and 104E were evaluated by HRCT as part of unscheduled clinical assessments performed at the discretion of the investigator. These "for-cause" HRCT evaluations, therefore, were performed on patients with known or suspected illness.

Patients evaluated by high resolution computed tomography (HRCT) based on the cutoff date of 08 July 2005 included:

A total of 196 patients with type 2 DM (98 of whom received INH) who were participating in the ongoing 5-year HRCT sub-study of controlled Study 1029, and who had HRCT data at baseline and after either one or two years of treatment. Of these, 144 patients (71 of whom received INH) had HRCT at baseline and after two years of treatment. A total of 118 of the 196 patients were included in the data based on the cutoff date of 25 June 2004.

Patients with Mild to Moderate Underlying Lung Disease

Data for patients with underlying lung disease (categorized as mild to moderate asthma or chronic obstructive pulmonary disease (COPD)) were gathered from two sources. The first source was an analysis of the Controlled PFT Phase 2/3 database for patients who met the following criteria:

- Asthma – A present history of asthma at study entry

- COPD – The ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) < 70% at baseline, and a history of smoking

The second source were patients enrolled in Studies 1028 and 1030 which were designed to examine the safety and efficacy of inhaled insulin in these populations. The specific inclusion criteria are detailed in Appendix 1.

Patients meeting the criteria for both asthma and COPD were considered to have COPD for the purpose of this discussion. Patients with asthma, with COPD, and with neither disorder were analyzed separately for efficacy and safety. Data for these comparisons are presented with DM types combined.

Three populations of patients with mild to moderate underlying lung disease are discussed:

- A sub-population of 155 adult patients (74 of whom received INH) identified from the Controlled PFT Phase 2/3 Studies as meeting criteria compatible with mild to moderate ULD,
- A cohort of 152 adult patients (76 of whom received INH) identified at entry to Studies 1028 and 1030 (6-month analyses), and
- A combination of the above two populations, that is, 307 adult patients (150 of whom received INH) with mild to moderate ULD. This population is referred to as the integrated ULD cohort.

Controlled Studies Discussed Individually

PFT data from the following studies, in addition to being included in the Controlled PFT Phase 2/3 Studies, are discussed individually.

Studies 1022 and 1029 are ongoing, randomized, SC insulin controlled studies in patients with type 1 DM and type 2 DM, respectively. In both studies, PFT results are being monitored throughout the course of treatment. The studies were originally designed to have a 2-year dosing period followed by a 6-month withdrawal observation period. Recently, both studies were extended to include an additional 3 years of dosing (following the 6-month withdrawal observation period). Data from the planned 2-year interim analyses of Studies 1022 and 1029 are available and are discussed individually.

Study 1027 is a completed, randomized, comparator-controlled study in patients with type 1 DM in which PFT results were monitored intensively throughout a 3-month course of treatment (baseline, and weeks 1, 2, 3, 4, 6, 8, 12) with INH or SC insulin, and during a 3-month follow-up period after cessation of active treatment (weeks 2, 4, 8, and 12 after treatment cessation). This study was designed to examine the time course, magnitude, and reversibility of the effect of INH on pulmonary function in patients with type 1 DM. Study 1027 is notable for its primary objective of characterizing PFT results during INH treatment, for the frequency of PFT measurements during the study, and for its inclusion of planned PFT measurement during a withdrawal period.

Studies 1001 and 1002 are completed, randomized, comparator-controlled studies in patients with type 2 DM and include controlled data collected over 2 years of study drug exposure. PFTs were performed at baseline and weeks 24, 36, 52, 65, 78, 91, and 104 of active treatment. Importantly, PFTs also were performed at 6 and 12 weeks after discontinuation of active treatment.

A total of 31.3% of patients (285 of 912) did not enter the extensions of Studies 1001 and 1002 beyond the original 6-month core study. However, the cohort continuing in the amended studies beyond 6 months was representative, with respect to pulmonary function, of the patients in the core 6-month study. Of the 285 patients who did not enter into the extensions, approximately half (80 INH-treated and

69 OA-treated patients) did so due to lack of ethics committee and/or regulatory approval by the time these patients completed month 6 of treatment. In addition, 27 INH-treated and 32 OA-treated patients chose not to continue in the extension phase of the studies, and 26 INH-treated and 46 OA-treated patients were not suitable for the extension phase because they had withdrawn from the study prior to month 6. The mean differences (95% confidence intervals) in change from baseline FEV_1 and DLco between the groups who entered the extension phase of the studies and those who did not were -0.002 L (-0.039, 0.036) and -0.315 mL/min/mmHg (-0.914, 0.284), respectively. These results indicate that the two populations were similar with respect to pulmonary function.

Studies 1028 and 1030 are ongoing, randomized, comparator-controlled studies involving patients with mild to moderate asthma and COPD, respectively. PFTs are to be performed at baseline and weeks 1, 2, 3, 4, 6, 12, 18, 26, 39, and 52 of active treatment, and at 2 and 6 weeks after completion of active treatment. At present, few patients have completed active treatment, and efficacy and safety data are presented based on interim analyses of these studies. Studies 1028 and 1030 are not pooled with other controlled studies for general safety assessment, but are presented in the discussion of INH efficacy and safety among patients with mild to moderate ULD in Section 6.5.2.9.

Extension Studies Discussed Individually

In addition to the Controlled PFT Phase 2/3 Studies and other controlled studies, 4 extension studies, Studies 102E/1036, 103E/1036, 104E/1036, and 111, contribute to the PFT assessment individually. Studies 102E, 103E, and 104E are extensions of the Phase 2 Studies 102, 103, and 104, respectively and include only adults (age ≥ 18 years). In 2003, Studies 102E, 103E, and 104E were collapsed into a single protocol, Study 1036, which is ongoing. Patients were evaluated for PFTs through up to 84 months of continuous INH therapy in the Phase 2 extension studies and their parent controlled studies as of the time of the data cut off (25 June 2004). Similarly, Study 111 is a completed extension of Phase 3 Studies 106, 107, 108, 109, 110, and 1009. Patients were evaluated for PFTs through up to 36 months of continuous INH therapy in Study 111 and its parent controlled studies. With the exception of a small cohort of patients who received comparator in the Phase 2 extension studies (N=45; N=23 at 24 months), all patients in Phase 2 or Phase 3 extension studies received INH as the short-acting insulin component of their diabetic therapy.

PFTs were measured every 3 to 6 months in the phase 2 extension studies and Study 111. PFT data during INH exposure in the controlled parent studies are included in the analysis of these extension studies. Altogether, approximately 730 adult patients were evaluable for PFTs following at least 24 months of continuous INH treatment in the Phase 2 and Phase 3 extension studies.

Study 111 was amended in January 2002 to allow patients receiving INH to be randomized to either continue or discontinue INH therapy over a 6-month period. This amendment was designed to evaluate the effects of planned INH discontinuation on pulmonary function. Approximately 400 patients were randomized into each arm of this phase of the study. PFTs were performed at months 1, 3, and 6 post randomization.

6.5.2.2. Respiratory Exclusion Criteria

Respiratory exclusion criteria in Phase 2 studies included any active respiratory disease or significantly abnormal screening chest x-ray or PFT results. As a result of the favorable respiratory safety profiles of adult patients with DM who received INH in Phase 2, these exclusion criteria were relaxed in the Phase 3 program to allow participation of patients with mild to moderate underlying lung disease or mildly to moderately reduced lung function (DLco or FEV_1 as low as 70% of predicted). Studies 1028 and 1030, specifically designed to study the safety of INH in patients with underlying lung disease, and presented

separately in this document, allowed participation of patients with DLco and/or FEV_1 as low as 50% of predicted.

6.5.2.3. Methodology for Pulmonary Safety Monitoring

Extensive safety analyses have been conducted to screen for pulmonary safety signals in the INH clinical development program. Pulmonary safety monitoring included regular reporting of adverse events, serious adverse events, study discontinuations, and PFT results. 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. 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. A list of PFTs performed is provided in Section 6.5.2.8.

Chest x-rays were performed at baseline and end of study for most Controlled Phase 2/3 studies. 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 HRCT of the thorax, as described previously, were performed in patients randomized to participate in the HRCT sub-study in Studies 106, 107, and 108. In Study 1029, thoracic HRCT is performed in a sub-set of patients at baseline, 1 year, and 2 years.

Full clinical evaluations were performed on patients experiencing one or more of the following: confirmed ≥15% decline in FEV_1, DLco, total lung capacity (TLC), or FVC; significant change in chest x-ray or HRCT findings; or new onset and persistent signs or symptoms of respiratory disease. Narratives were written to describe the precipitating events and clinical findings for patients with declines of ≥15% from baseline and into the abnormal range in FEV_1, DLco, total lung capacity (TLC), or FVC at last visit on study drug, for patients who exhibited a clinically significant worsening of radiographic findings at the last visit on study drug, for patients with a pulmonary serious adverse event, amd for patients with a pulmonary adverse event leading to discontinuation.

Cough and dyspnea were characterized using a cough questionnaire and the Baseline and Transitional Dyspnea Indices (BDI and TDI), respectively, in Studies 1022, 1027, and 1029. The cough questionnaire was administered only to patients who experienced cough, unexplained by a concomitant condition, as an adverse event and assessed 6 domains of cough on a quantitative scale, including: cough frequency at night, cough frequency during the day, cough severity during the day, cough timing relative to short-acting insulin dosing, cough severity relating to short-acting insulin dosing, and cough productivity. After measuring dyspnea at baseline, using the BDI, the TDI instrument was administered to all patients at multiple times and described changes from baseline in 3 domains of dyspnea on a quantitative scale, including: functional impairment, magnitude of task, and magnitude of effort.

6.5.2.4. Respiratory Adverse Events

When patients with type 1 and type 2 DM in the Controlled Phase 2/3 Studies were evaluated together, all-causality cough, dyspnea, epistaxis, and increased sputum occurred at greater incidence among INH-treated than SC insulin-treated adult patients of either DM type. Respiratory disorder and pharyngitis occurred at greater incidence among INH- than comparator-treated patients with type 1 DM only (incidence of respiratory disorder was greater for SC-treated patients with type 2 DM compared to INH), and voice alteration occurred at greater incidence among INH- than comparator-treated patients with type 2 DM only (Table 76). Cough and dyspnea are discussed in detail below.

Table 76. All-Causality Respiratory Adverse Events: Adults in Controlled Phase 2/3 Studies (Presented in Alphabetical Order)

	Number (%) of Patients				
	Type 1 DM		Type 2 DM		
Preferred Term	INH N=698	SC N=705	INH N=1279	SC N=488	OA N=644
All Respiratory Adverse Events	520 (74.5)	440 (62.4)	741 (57.9)	287 (58.8)	219 (34.0)
Apnea	0	0	1 (0.1)	0	0
Asthma	9 (1.3)	9 (1.3)	26 (2.0)	11 (2.3)	3 (0.5)
Atelectasis	0	0	0	1 (0.2)	0
Bronchiectasis	0	0	0	1 (0.2)	0
Bronchiolitis	1 (0.1)	0	0	0	0
Bronchitis	22 (3.2)	29 (4.1)	62 (4.8)	17 (3.5)	26 (4.0)
Carcinoma of lung	0	0	1 (0.1)	0	1 (0.2)
Cough increased	204 (29.2)	62 (8.8)	275 (21.5)	41 (8.4)	24 (3.7)
Dyspnea	31 (4.4)	6 (0.9)	44 (3.4)	9 (1.8)	9 (1.4)
Edema pharynx	0	2 (0.3)	1 (0.1)	0	0
Emphysema	0	0	1 (0.1)	1 (0.2)	0
Epistaxis	9 (1.3)	3 (0.4)	15 (1.2)	2 (0.4)	5 (0.8)
Hemoptysis	0	0	1 (0.1)	0	0
Hyperventilation	1 (0.1)	1 (0.1)	0	0	0
Hypoventilation	1 (0.1)	0	0	0	0
Laryngitis	8 (1.1)	3 (0.4)	7 (0.5)	2 (0.4)	2 (0.3)
Lung disorder	1 (0.1)	0	4 (0.3)	1 (0.2)	0
Lung edema	0	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)
Lung fibrosis	0	0	0	1 (0.2)	0
Nasal polyp	1 (0.1)	1 (0.1)	0	0	0
Pharyngitis	126 (18.1)	112 (15.9)	119 (9.3)	44 (9.0)	38 (5.9)
Pleural disorder	1 (0.1)	0	0	1 (0.2)	0
Pneumonia	6 (0.9)	8 (1.1)	11 (0.9)	7 (1.4)	4 (0.6)
Pneumothorax	0	0	0	1 (0.2)	0
Respiratory disorder	51 (7.3)	29 (4.1)	70 (5.5)	45 (9.2)	11 (1.7)
Respiratory distress syndrome	0	1 (0.1)	0	1 (0.2)	0
Respiratory tract infection	297 (42.6)	292 (41.4)	365 (28.5)	172 (35.2)	127 (19.7)
Rhinitis	100 (14.3)	72 (10.2)	107 (8.4)	48 (9.8)	19 (3.0)
Sinusitis	70 (10.0)	51 (7.2)	67 (5.2)	46 (9.4)	15 (2.3)
Sputum increased	27 (3.9)	8 (1.1)	34 (2.7)	4 (0.8)	3 (0.5)
Voice alteration	1 (0.1)	1 (0.1)	16 (1.3)	0	2 (0.3)
Yawn	1 (0.1)	1 (0.1)	0	0	0

DM=diabetes mellitus, N=Number of patients, INH=inhaled insulin, SC=subcutaneous short-acting insulin, and OA=oral agents.
Cutoff date: 13 December 2004

Cough

Cough, referred to as the COSTART preferred term "Cough increased" in the adverse event tables, is the respiratory adverse event with the largest differential in incidence among treatment groups in the Controlled Phase 2/3 Studies (Table 52). Cough among INH-treated patients usually was mild, decreased with duration of INH treatment, and occurred in association with the act of INH inhalation for most affected patients (as assessed by the use of a cough questionnaire).

The majority of adult type 1 or type 2 patients who experienced cough in Controlled Phase 2/3 studies had maximum cough severities considered mild by the investigator, and the distributions of cough severities were comparable among treatment groups (Table 77).

Table 77. Maximum Severity of Cough in Controlled Phase 2/3 Studies: Adult Patients with Type 1 or Type 2 Diabetes Combined

	Number (%)* of Patients		
	INH	**SC**	**OA**
Patients with cough	**479**	**103**	**24**
Mild	406 (84.7)	87 (84.5)	20 (83.3)
Moderate	65 (13.6)	15 (14.6)	4 (16.7)
Severe	8 (1.7)	1 (1.0)	0

*Percentages were calculated using the number of patients with cough as the denominator.
INH=inhaled insulin, SC=subcutaneous short-acting insulin, and OA=oral antidiabetic agents.
Cutoff date: 13 December 2004

Cough incidence (defined as onset of an event during the time interval) and prevalence (defined as the presence of the event during the time interval) were greatest during the first month of INH exposure, decreased over the subsequent 3 months, and remained low thereafter among adults in Controlled PFT Phase 2/3 studies. The incidence of cough during the first 1-month interval was 15.9% and 9.2%, and the prevalence of cough was 16.5% and 9.8% for INH-treated patients with type 1 and type 2 DM, respectively. During the final 1-month interval of treatment in Controlled PFT Phase 2/3 studies (> 5-6 months of INH exposure), cough incidence had decreased to 3.4% and 2.3%, and cough prevalence was 8.5% and 7.1% among patients with type 1 and type 2 DM, respectively. Among comparator-treated patients, cough incidence and prevalence did not exceed 3.7% for patients with type 1 DM or 1.6% for those with type 2 DM (Table 78).

Table 78. Incidence and Prevalence of Reported Cough and Discontinuations due to Cough During the First 6 Months of Exposure Controlled PFT Phase 2/3 Studies - Type 1 and Type 2 Patients (Age >= 18 Years)

Treatment Group	Interval of Treatment+	N	Incidence (% of Patients)*	Prevalence (% of Patients)**	D/C due to Event (% of Patients)
Type 1 DM					
Inhaled Insulin	0 - 1 Month	698	111 (15.9)	115 (16.5)	2 (0.3)
	> 1 - 2 Months	684	39 (5.7)	92 (13.5)	3 (0.4)
	> 2 - 3 Months	665	29 (4.4)	76 (11.4)	1 (0.2)
	> 3 - 4 Months	539	9 (1.7)	44 (8.2)	0 (0.0)
	> 4 - 5 Months	511	11 (2.2)	36 (7.0)	0 (0.0)
	> 5 - 6 Months	504	17 (3.4)	43 (8.5)	1 (0.2)
	Overall (1st 6 months)	698	179 (25.6)	183 (26.2)	7 (1.0)
Comparator	0 - 1 Month	705	17 (2.4)	19 (2.7)	0 (0.0)
	> 1 - 2 Months	682	17 (2.5)	25 (3.7)	0 (0.0)
	> 2 - 3 Months	672	12 (1.8)	22 (3.3)	0 (0.0)
	> 3 - 4 Months	540	1 (0.2)	9 (1.7)	0 (0.0)
	> 4 - 5 Months	519	1 (0.2)	8 (1.5)	0 (0.0)
	> 5 - 6 Months	511	4 (0.8)	6 (1.2)	0 (0.0)
	Overall (1st 6 months)	705	49 (7.0)	50 (7.1)	0 (0.0)
Type 2 DM					
Inhaled Insulin	0 - 1 Month	1277	118 (9.2)	125 (9.8)	4 (0.3)
	> 1 - 2 Months	1244	43 (3.5)	113 (9.1)	3 (0.2)
	> 2 - 3 Months	1221	35 (2.9)	103 (8.4)	2 (0.2)
	> 3 - 4 Months	914	14 (1.5)	68 (7.4)	0 (0.0)
	> 4 - 5 Months	865	9 (1.0)	54 (6.2)	0 (0.0)
	> 5 - 6 Months	855	20 (2.3)	61 (7.1)	2 (0.2)
	Overall (1st 6 months)	1277	215 (16.8)	221 (17.3)	11 (0.9)
Comparator	0 - 1 Month	1132	10 (0.9)	16 (1.4)	0 (0.0)
	> 1 - 2 Months	1098	9 (0.8)	15 (1.4)	0 (0.0)
	> 2 - 3 Months	1086	10 (0.9)	17 (1.6)	0 (0.0)
	> 3 - 4 Months	878	6 (0.7)	12 (1.4)	0 (0.0)
	> 4 - 5 Months	839	4 (0.5)	9 (1.1)	0 (0.0)
	> 5 - 6 Months	821	6 (0.7)	11 (1.3)	0 (0.0)
	Overall (1st 6 months)	1132	42 (3.7)	47 (4.2)	0 (0.0)

Includes events with onset or present during the study (+ 1 day lag) regardless of whether the patient was taking study drug at the time of the event.
+Based on elapsed duration of treatment.
* Based on new onset of event in each time interval.
** Based on presence of event in each time interval.
Type 1 DM Includes Protocols: 102(3-Month), 106(6-Month), 107(6-Month), 1022(12-Month), 1026(6-Month), 1027(3-Month)
Type 2 DM Includes Protocols: 1001(24-Month), 1002(24-Month), 103(3-Month), 104(3-Month), 108(6-Month), 109(3-Month), 110(3-Month), 1029(12-Month)
Cutoff date: 25 June 2004

The mean and median duration of cough events among patients who experienced cough was greater among those receiving INH than comparator. Median cough duration was 2.3 and 1.9 weeks among INH- and SC insulin-treated adult patients with type 1 DM, respectively, and 3.0 and 2.3 weeks among INH- and comparator-treated patients with type 2 DM, respectively (Table 79).

Table 79. Duration of Reported Cough Based on Reported Start/Stop Date of Event During the First 6 Months of Exposure Controlled PFT Phase 2/3 Studies - Type 1 and Type 2 Patients (Age >=18 Years)

				Duration (Weeks)*		
Treatment Group	Number of Patients Reporting Event	Median Exposure Duration (weeks)+	Total Number of Events	Mean	SD	Median
Type 1 DM						
Inhaled Insulin	179	25.14	232	5.36	8.09	2.29
Comparator	49	26.14	54	3.37	4.13	1.93
Type 2 DM						
Inhaled Insulin	215	25.86	259	7.70	11.85	3.00
Comparator	42	26.14	45	5.08	9.15	2.29

Includes events with onset during the study (+ 1 day lag) regardless of whether the patient was taking study drug at the time of the event.
+ Based on the number of weeks the patient was in the study during the first 6 Months (includes off-drug days).
*Duration = number of weeks from the reported onset of each event to the reported end of each event (summary statistics are based on the number of reported events)
Type 1 Includes Protocols: 102(3-Month), 106(6-Month), 107(6-Month), 1022(12-Month), 1026(6-Month), 1027(3-Month)
Type 2 Includes Protocols: 1001(24-Month), 1002(24-Month), 103(3-Month), 104(3-Month), 108(6-Month), 109(3-Month), 110(3-Month), 1029(12-Month)
Cutoff date: 25 June 2004

The majority of reported cough events appeared to occur in association with the act of INH inhalation. In Studies 1022, 1027, and 1029, cough was characterized in detail using a cough questionnaire. Among the INH-treated patients who experienced cough in these studies and who completed the cough questionnaire, the majority indicated that their cough occurred within seconds to minutes after INH inhalation (Table 80). In addition, most patients who experienced cough and completed the cough questionnaire indicated that the cough was rare or occasional during the day, absent or rare at night, mild in severity, and non-productive.

Table 80. Timing of Cough in Relation to Inhaled Insulin Dosing: Inhaled Insulin-Treated Patients in Studies 1022, 1027, and 1029

		Range* of Numbers (%) of Patients Across Observation Periods		
Study	N	Unaware of Coughing	Seconds to Minutes After Dosing	Hours After or No Relationship with Dosing
1022	24-47	2 (5.6)-9 (33.3)	12 (44.4)-35 (74.5)	5 (10.6)-9 (37.5)
1027†	8-16	0 (0)-4 (30.8)	5 (62.5)-9 (90.0)	1 (6.3)-3 (30.0)
1029	20-41	2 (6.5)-8 (26.7)	9 (45.0)-23 (71.9)	6 (16.7)-7 (35.0)

*Patients in each study were evaluated for cough at multiple time points. The presented ranges represent the minimum and maximum numbers reported at any time point after baseline for each study.
†For Study 1027, data from only the comparative phase of the study are presented.
N=number of patients who reported cough in a given week and completed the cough questionnaire.
Cutoff date: 25 June 2004

Study discontinuation due to cough was not common in Controlled Phase 2/3 studies as of 25 June 2004. Twenty of 1,975 (1.0%) INH-treated and no comparator-treated adult patients discontinued Controlled Phase 2/3 studies due to cough (Table 84). Of the 18 discontinuations due to cough occurring during the first 6 months of INH exposure in Controlled PFT Phase 2/3 studies, 12 took place during the first 2 months (Table 78).

PFT results for patients who experienced cough as an adverse event are presented in Section 6.5.2.8.1. The changes from baseline in FEV_1 were similar between INH-treated patients reporting cough and those not reporting cough.

In summary, cough was a common adverse event among INH-treated patients in Controlled Phase 2/3 studies. The majority of cough events were mild, of short duration, non-productive, rare or occasional during the day, and absent or rare at night. In addition, cough was temporally associated with the act of INH inhalation and was not associated with declines in FEV_1. These results indicate that most cough among INH-treated patients was due to a mild irritant effect associated with dry powder inhalation as opposed to an underlying functional or structural etiology. Cough occurred and resolved soon after INH therapy was begun and resulted in discontinuation among approximately 1% of patients in Controlled Phase 2/3 studies, indicating that cough was generally well tolerated.

Dyspnea

Dyspnea was an uncommon respiratory adverse event that occurred at greater incidence among INH- than comparator-treated patients in the Controlled Phase 2/3 Studies, occurring in 4.4 and 0.9% of type 1 patients receiving INH and SC insulin, respectively, and 3.4, 1.8, and 1.4% of type 2 patients receiving INH, SC insulin, and OAs, respectively (Table 81). Dyspnea among INH-treated patients usually was mild, and changes in self-reported dyspnea scores using the Transitional Dyspnea Index (TDI) were negligible and clinically insignificant among INH-treated patients who completed the TDI. Dyspnea rarely resulted in study discontinuation.

The majority of adult type 1 or type 2 patients who experienced dyspnea in Controlled Phase 2/3 studies had maximum dyspnea severities considered mild by the investigator. The distributions of patients with mild and moderate dyspnea were comparable among treatment groups (Table 81). Two INH-treated patients, and no comparator-treated patients experienced severe dyspnea. Of the two cases of severe dyspnea, one occurred in an INH-treated patient with type 2 DM in Study 109 and was considered by the investigator to be a serious adverse event related to obesity and stress. The second occurred in an INH-treated patient with type 2 DM in Study 1002 and was considered by the investigator to be related to anxiety. Both events resulted in study discontinuation. In the Controlled Phase 2/3 patients, there were five SAEs of dyspnea, four on comparator treatment and one on INH (6.5.2.5).

Table 81. Maximum Severity of Dyspnea in Controlled Phase 2/3 Studies: Patients with Type 1 or Type 2 Diabetes Combined

	Number (%)* of Patients		
	INH	SC	OA
Patients with dyspnea	**75**	**15**	**9**
Mild	46 (61.3)	9 (60.0)	8 (88.9)
Moderate	27 (36.0)	6 (40.0)	1 (11.1)
Severe	2 (2.7)	0	0

*Percentages were calculated using the number of patients with dyspnea as the denominator.
INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, and N=number of patients evaluable for adverse events.
Cutoff date: 13 December 2004

TDI results from Studies 1022, 1027, and 1029 revealed small and clinically insignificant mean decreases from baseline for INH-treated patients and similar scores between treatment groups. Mean changes for each measured domain ranged from –0.04 to +0.04 for INH-treated patients, and –0.04 to +0.04 for SC insulin-treated patients, on the following scale:

-3 = major deterioration
-2 = moderate deterioration
-1 = minor deterioration
0 = no change
+1 = minor improvement
+2 = moderate improvement, and
+3 = major improvement.

Median changes from baseline were 0 for all dyspnea domains for each treatment group. It should be noted that a TDI change of 1 is considered the minimally important difference.[59, 60]

Study discontinuation due to dyspnea was uncommon, occurring in 8 of 1,975 (0.4%), 0 of 1,193 (0%), and 1 of 644 (0.2%) patients in the INH, SC, and OA groups, respectively (Table 84).

In summary, dyspnea was a relatively uncommon adverse event with a higher incidence among INH- than comparator-treated patients in Controlled Phase 2/3 studies. The majority of dyspnea cases were mild, and dyspnea rarely resulted in discontinuation. In Studies 1022, 1027, and 1029, changes in self-reported dyspnea scores were negligible and clinically insignificant for both INH- and SC insulin-treated patients.

6.5.2.5. Respiratory Serious Adverse Events

Respiratory Serious Adverse Event Incidence

One respiratory SAE (pneumonitis) was reported among adult patients with type 1 DM as of the cut-off date of 13 December 2004. The event occurred in a patient treated with SC insulin.

One respiratory SAE (pleural effusion) occurred among patients with type 1 DM in the All Phase 2/3 Studies). The event occurred in a pediatric patient receiving INH in Study 111. The effusion was unilateral, exudative and asymptomatic. Specialists had not identified a cause for the effusion, despite a thorough assessment. The investigator could not exclude the possibility that the effusion was treatment-related. As this patient was followed, an independent consultant who is an acknowledged expert in pleural disorders reviewed the case. The consultant concluded that the pleural effusion was unlikely to have been related to INH treatment, but was unable to completely exclude the possibility. In July 2004, approximately 3 years after INH treatment had been discontinued, the principal investigator, who continues to treat this now 17-year-old patient with DM, reported that the patient has exhibited normal somatic growth and is in general doing well from a metabolic standpoint. He continues to be active in sports without respiratory limitations. The patient's most recent HRCT scan in September 2003, revealed a small residual right-sided pleural effusion.

Respiratory SAEs among patients with type 2 DM are summarized in Table 82 and Table 83 for the Controlled Phase 2/3 Studies and the All Phase 2/3 Studies, respectively.

Among patients with type 2 DM, the number of respiratory SAEs per 10,000 patient-months was low in both treatment groups and similar between groups in the Controlled Phase 2/3 Studies. There were more events of asthma among INH-treated patients, and of dyspnea among comparator-treated patients.

Table 82. All-Causality Respiratory* Serious Adverse Events Among Patients with Type 2 Diabetes by Treatment and Preferred Term: Controlled Phase 2/3 Studies

	INH (13384 SME†)		Comparator (12512 SME)	
Preferred Term	Number of Events	Events per 10,000 SME	Number of Events	Events per 10,000 SME
Asthma	3‡	2.24	0	0
Bronchospasm	1‡	0.75	0	0
Cough	1‡	0.75	0	0
Dyspnea	1	0.75	4	3.20
Epistaxis	1	0.75	0	0
Pneumothorax	1	0.75	1	0.80
Respiratory Distress	0	0	1	0.80
Respiratory Failure	1	0.75	1	0.80
Vocal cord polyp	1‡	0.75	0	0

*Events in the Respiratory, Thoracic and Mediastinal Disorders category according to MedDRA.
†SME=patient-months of exposure.
‡ Treatment-related per investigator
INH=inhaled insulin with or without subcutaneous basal insulin or oral agents.
Cutoff date: 13 December 2004

Almost all patients in uncontrolled extension studies received INH, leading to greater exposure and, predictably, more SAEs in the INH than comparator group (Table 83).

Table 83. All-Causality Respiratory* Serious Adverse Events Among Patients with Type 2 Diabetes by Treatment and Preferred Term: All Phase 2/3 Studies

	INH	Comparator
Preferred Term	Number of Events	Number of Events
Asthma	3†	0
Atelectasis	1	0
Bronchospasm	1‡	0
Cough	1‡	0
Dyspnea	5	4
Epistaxis	1	0
Lung disorder	1‡	0
Pleural effusion	1	0
Pneumothorax	1	1
Pulmonary embolism	1	0
Pulmonary edema	2‡	0
Respiratory distress	1‡	1
Respiratory failure	1	1
Vocal cord polyp	1‡	0

*Events in the Respiratory, Thoracic and Mediastinal Disorders category according to MedDRA.
†All three events were considered treatment-related by the investigator.
‡One event was considered treatment-related by the investigator.
INH=inhaled insulin.
Cutoff date: 13 December 2004

Lung Neoplasms

Lung neoplasms are listed under the "Neoplasms Benign, Malignant and Unspecified" MedDRA system organ class and are, therefore, not included in Table 82 or Table 83. New-onset malignant lung neoplasms were not more common among INH- than comparator-treated patients in the All Phase 2/3 Studies, and

the number of malignant neoplasms among INH-treated patients was not greater than that expected based on an epidemiologic analysis of the data as of the cutoff date of 13 December 2004.

Among the neoplasms reported as SAEs in the All Phase 2/3 Studies, 5 cases (1 benign, and 4 malignant) involved the lung. All cases were among former smokers with type 2 DM. Of these 5 patients, 2 (1 INH- and 1 OA-treated) had malignant neoplasms that were not evident prior to treatment. The treatment groups and event terms for all 5 cases were:

- INH (4 cases)

  Benign lung neoplasm, a hamartoma, detected in a 75-year-old patient after 510 days of treatment in Study 111.

  Lung adenocarcinoma, identified as a squamous carcinoma by the investigator, detected in a 62-year-old patient after 98 days of treatment in Study 1002. The lesion had been noted as a pulmonary nodule on chest x-ray at screening.

  Lung squamous cell carcinoma detected in a 72-year-old patient after 481 days of treatment in Study 111. This neoplasm also was considered to have been pre-existing based on re-examination of chest x-rays conducted at screening. In this case, neither the investigator nor the sponsor could rule out completely the possibility that INH had contributed to the tumor's growth, and the event was considered to be treatment-related.

  Metastatic bronchial carcinoma detected in a 67-year-old patient after 663 days of treatment in Study 1002. The patient had a history of occupational asbestos exposure. The tumor was identified as a primary bronchial carcinoma with cutaneous metastases. In the investigator's opinion the tumor was possibly related to INH exposure, and the event was considered to be treatment-related.

- SC (0 cases)

- OA (1 case)

  Lung neoplasm malignant detected in a 57-year-old patient after 63 days of treatment in Study 1002. The tumor was bronchial carcinoma.

The expected number of malignant lung cancer cases in INH-treated patients in the clinical development program was calculated by applying the age-and sex-specific lung cancer incidence rates by smoking status among patients with DM in the Northern California Kaiser Permanente Database study to the INH clinical program patient population. The observed number of malignant lung cancer cases in patients exposed to INH (3) was lower than the expected number of lung cancer cases (6.99; 95% confidence interval 5.23-8.98) based on the reference data.

There is no evidence from the preceding data to suggest that INH use is associated with lung cancer risk.

Other Notable Respiratory Events

Other notable respiratory events reported as of the cutoff date of 13 December 2004 are discussed in this section.

Eight events of pleural effusion were reported in the Phase 2/3 clinical development program as of 13 December 2004. Seven events occurred in adult patients with type 2 DM, and one occurred in a pediatric patient with type 1 DM. All events occurred in INH-treated patients: seven occurred in uncontrolled extension studies, and one occurred in the controlled COPD trial 1030. The higher number of pleural effusion events among INH-treated subjects relative to comparator is not unexpected given the larger number of patients treated with INH (INH: 1449; Comparator: 45) in the extension studies. No events of pleural effusion have been reported in the controlled 2-year studies (Studies 1001/1002, 1022, 1029).

In six of seven adult patients, the pleural effusions developed in the setting of medical conditions that are well known to cause pleural effusions (acquired immunodeficiency syndrome, pulmonary edema, post-operative, pneumonia). In the remaining adult patient, small pleural effusions were noted on routine chest x-ray that spontaneously resolved while continuing INH therapy. The etiology of the pleural effusion in the pediatric patient is unknown, despite a complete diagnostic evaluation. Brief clinical descriptions of each event are provided below:

- A 13-year-old male pediatric patient with type 1 DM treated with INH in extension Study 111 reported a Serious Adverse Event of pleural effusion on treatment day 351, as detailed in Section 6.5.2.5. INH treatment was discontinued. The principal investigator could not exclude a causal relationship to INH treatment. The patient continues to be active in sports without respiratory limitations. The patient's most recent HRCT scan in September 2003 revealed a small residual right-sided pleural effusion.
- A 60-year-old male patient with type 2 DM treated with INH in extension Study 103E reported a Serious Adverse Event of bilateral pleural effusions attributed to acquired immunodeficiency syndrome on treatment day 411. INH treatment was discontinued. The patient was treated with bilateral chest tubes and the pleural effusions resolved. The principal investigator attributed the pleural effusions to acquired immunodeficiency syndrome.
- A 65-year-old male patient with type 2 DM treated with INH in extension Study 111 reported an Adverse Event of pleural effusion in the setting of pulmonary edema on treatment day 524. INH treatment was discontinued. The patient had a history of angina and irregular heartbeat, and had undergone coronary artery bypass surgery and percutaneous transluminal coronary angioplasty in the past. Two months prior to onset of the pleural effusion, stress echocardiogram displayed evidence of exercise-induced cardiac ischemia. Follow-up chest imaging confirmed resolution of the pleural effusion with persistence of cardiomegaly. The principal investigator attributed the pulmonary edema and pleural effusion to study drug.
- A 58-year-old male patient with type 2 DM treated with INH in extension Studies 103E and 1036 reported an Adverse Event of pleural effusion (minute bilateral pleural effusions as noted on chest x-ray) on treatment day 433. INH treatment was continued without interruption. No treatment was provided for the pleural effusions, which resolved on repeat chest x-ray on day 461. The principal investigator attributed the pleural effusions to pulmonary fluid collections. The patient continued on to complete 2596 days of INH treatment. The patient had a history of ischemic heart disease.
- A 58-year-old male patient with type 2 DM treated with INH in extension Study 111 reported an Adverse Event of pleural effusion post-open heart surgery on treatment day 589. INH treatment was temporarily discontinued due to the surgery. On treatment day 569, the patient was diagnosed with mitral valve regurgitation, coronary artery disease and severe aortic stenosis requiring subsequent cardiac surgery. Peri-operative complications included atrial fibrillation and pleural effusion. The pleural effusion resolved with treatment of the cardiac problems. The principal investigator attributed the pleural effusions to cardiomegaly. The patient continued on to complete 849 days of INH treatment.
- A 64-year-old male patient with type 2 DM treated with INH in extension Study 111 developed an Adverse Event of pleural effusion on treatment day 472 in the post-operative setting of a left radical

nephrectomy. The patient underwent nephrectomy on day 471 secondary to chronic pyelonephritis. On day 472 a pneumothorax and pleural effusion developed that was attributed to the surgical procedure and treated with chest tube drainage. The pleural effusion resolved with treatment. The patient temporarily stopped INH dosing during days 471-477 and went on to complete 655 days of INH treatment. The principal investigator attributed the pleural effusion to the surgical procedure.

- A 67-year-old male patient with type 2 DM treated with INH in extension Study 111 reported an Adverse Event of moderate pleural effusion on treatment day 562 post-coronary artery bypass surgery (day 560). Other post-operative complications included cardiomegaly and moderate atelectasis. INH treatment was discontinued. The pleural effusion resolved with treatment. The principal investigator attributed the pleural effusion to the coronary artery bypass surgery.
- A 72-year-old male patient with type 2 DM treated with INH in controlled Study 1030 developed an Adverse Event of pleural effusion on treatment day 35 in the setting of pneumonia. The patient developed pneumonia on treatment day 35 attributed to immobility secondary to fracture of right tibia and fibula. INH treatment was discontinued. Pneumonia and pleural effusion resolved with medical treatment. The principal investigator attributed the pleural effusion to pneumonia.

Pulmonary fibrosis was reported in a patient with type 2 DM who received INH in Study 111. The event initially was considered a treatment-related serious adverse event by the investigator, and an investigator letter describing the event was distributed. Previously unrecognized fibrotic changes were subsequently identified on the patient's baseline chest x-ray, and the event was re-categorized by the investigator as an adverse event not related to treatment. Another investigator letter was distributed clarifying the event. This patient also experienced dyspnea and a decline in DLco.

Two other known adverse event cases of pulmonary fibrosis occurred in the INH clinical program. A patient with type 2 DM, experienced lung fibrosis identified by chest x-ray noted 28 days after ending approximately 1 year of treatment with OAs in Study 1002. The investigator considered the event to be not related to study drug. In addition, lung fibrosis was noted in a patient with type 2 DM treated with INH in Study 111, after 504 days on study. The event was mild, did not lead to discontinuation, and the investigator considered the event to be not related to study drug.

Two adverse events of sarcoidosis were reported among INH-treated patients in extension studies. Mild sarcoidosis was noted in a patient with type 1 DM treated with INH in Study 111, after 237 days of treatment. Chest x-rays with observable changes from screening and indicative of lymphadenopathy and sarcoidosis were reported on study days 455 and 538, but no changes from screening were noted on the chest x-ray taken on study day 901. The investigator did not assign causality to the event, prompting treatment-related causality to be assigned for the event in accordance with established procedures. Mild sarcoidosis also was noted in a patient with type 2 DM treated with INH in Study 111, after receiving INH for approximately 24 months. The investigator considered the event to be an SAE of unknown causality, and the event resulted in discontinuation. Sarcoidosis was not reported for any patient during controlled studies.

6.5.2.6. Study Discontinuations due to Respiratory Adverse Events

Study discontinuations due to respiratory adverse events were more frequent among INH-treated patients than SC insulin- or OA-treated patients (Table 84). Cough was the respiratory adverse event most commonly associated with discontinuation.

Table 84. All-Causality Respiratory Adverse Events Resulting in Discontinuation Among Adult Type 1 and Type 2 Patients: Controlled Phase 2/3 Studies

	Number (%) of Patients				
	Type 1		Type 2		
Protocol Set/ Event Term	INH N=698	SC N=705	INH N=1277	SC N=488	OA N=644
All respiratory events	14 (2.0)	0	30 (2.3)	0	2 (0.3)
Asthma	2 (0.3)	0	7 (0.5)	0	0
Bronchitis	0	0	3 (0.2)	0	0
Carcinoma of lung	0	0	1 (0.1)	0	1 (0.2)
Cough increased	10 (1.4)	0	14 (1.1)	0	0
Dyspnea	3 (0.4)	0	5 (0.4)	0	1 (0.2)
Laryngitis	1 (0.1)	0	0	0	0
Pharyngitis	2 (0.3)	0	1 (0.1)	0	0
Respiratory disorder	2 (0.3)	0	3 (0.2)	0	0
Respiratory tract infection	1 (0.1)	0	3 (0.2)	0	0
Sinusitis	1 (0.1)	0	0	0	0
Sputum increased	1 (0.1)	0	1 (0.1)	0	0

N=number of patients, INH=inhaled insulin, SC=subcutaneous short-acting insulin, and OA=oral antidiabetic agents.
Cutoff date: 13 December 2004

6.5.2.7. Chest X-ray and High Resolution Computed Tomography

The incidence of change in chest x-ray results between baseline and last observation in Controlled Phase 2/3 studies was greater in the INH than comparator treatment groups. The results of HRCT, a more sensitive and specific diagnostic method, were balanced between treatment groups.

Chest X-ray

A summary of significant changes in chest x-ray findings between baseline and last observation in Controlled Phase 2/3 Studies is presented in Table 85. Significant changes in chest x-ray between baseline and last observation included pulmonary as well as non-pulmonary changes. The incidences of significant changes were low in all treatment groups and for both DM types, and were greater among INH- than comparator-treated patients.

Table 85. Incidence of Significant Changes in Chest X-ray Between Baseline and Last Observation: Controlled Phase 2/3 Studies

	Number (%) of Patients [N]		
	INH	SC	OA
Type 1 patients	12 (2.2) [543]	6 (1.1) [544]	NA
Type 2 patients	42 (4.4) [962]	9 (2.5) [365]	11 (2.6) [420]

N=number of patients evaluable, INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, and NA=not applicable.
Cutoff date: 25 June 2004

As of 25 June 2004, a total of 54 (3.6%) INH-treated patients exhibited significant changes in their chest x-ray findings from baseline in the controlled Phase 2/3 studies (Table 85). Of these 54 patients, 2 were considered less abnormal and 52 were considered more abnormal. Abnormalities localized to the lung parenchyma occurred in 31 patients, to the lung vasculature in 6, to the rib and vertebral structures (fractures) in 6, and to the mediastinal structures in 11. Since 25 June 2004, of the 31 patients with changes in the lung parenchyma, 25 received follow-up imaging subsequent to the initial observation of

change. Resolution of the parenchymal abnormalities occurred in 22 of these patients, with the remaining 3 patients exhibiting one case each of stage 4 lung adenocarcinoma (1), thymoma (1), and left lung base atelectasis or fibrosis (1). All 6 patients with chest x-ray changes localized to the pulmonary vasculature demonstrated evidence of mild pulmonary edema. All 6 patients demonstrated resolution of the pulmonary edema on follow-up imaging. The most common abnormality localized to the mediastinal structures was cardiomegaly or left ventricular hypertrophy, occurring in 9 patients. The remaining 2 patients demonstrated a widened upper mediastinum (1) and a new pacer lead placement (1).

In the controlled Study 1022, the incidence of a more abnormal chest x-ray at month 24 was balanced between treatment groups (n=7 for INH and n=5 for comparator) (Table 86).

Table 86: Incidence of Significant Changes in Chest X-ray between Baseline and 24 Months in Type 1 Patients: Study 1022

Treatment Group	Number Examined	More Abnormal N (%)	Less Abnormal N (%)
INH	246	7 (2.8)	0
Comparator	254	5 (2.0)	1 (0.4)

In the INH group, the changes from baseline included a right superior segment radio-opaque structure (questionable calcified pulmonary nodule) (1), a question of a left lower lobe density that was not observed on a follow-up chest CT (1), a density in the right lower lobe that was diagnosed as mycobacterium avium complex on further diagnostic evaluation (1), a left mid-lung field density that was diagnosed as a nipple shadow on further imaging (1), a patient with new left rib fractures (1), and 2 patients with increased bronchovacular markings (2). These latter 2 patients showed resolution of the prominent bronchovascular markings on follow-up chest x-rays while on INH therapy.

In controlled Study 1029, there were 3 more patients in the INH group (n=9) who exhibited a more abnormal chest x-ray at 24 months versus comparator (n=6) (Table 87).

Table 87: Incidence of Significant Changes in Chest X-ray between Baseline and 24 Months in Type 2 Patients: Study 1029

Treatment Group	Number Examined	More Abnormal N (%)	Less Abnormal N (%)
INH	266	9 (3.4)	1 (0.4)
Comparator	263	6 (2.3)	3 (1.1)

In the INH group, the changes from baseline included bibasilar atelectasis after coronary artery bypass surgery (1), interstitial pulmonary changes (1), suspected reticular interstitial disease predominating at the lung base (1), atelectatic changes right middle retrocardiac region (1), early cardiomegaly (1), bilateral mild pulmonary fibrosis (1), single lead pacer present (1), disc disease in lower thoracic spine (1), and bibasilar interstitial infiltration (1). This latter patient was part of the HRCT sub-study in Study 1029, and showed no significant changes in HRCT over the 2-year treatment period.

All patients with new, clinically significant chest x-ray abnormalities were evaluated at their local sites.

HRCT

INH use, compared with SC insulin use, was not associated with an increased incidence of more abnormal HRCT findings at last observation than at baseline in the 6-month HRCT sub-study conducted as part of Studies 106, 107, and 108. The incidence of worsening HRCT results was balanced between the comparator and INH treatment groups (Table 88).

Table 88. Incidence of Significant Changes in Thoracic High Resolution Computed Tomography Results Between Baseline and Last Observation: Patients Evaluated by HRCT in Studies 106, 107, and 108

		Number (%) of Patients	
		INH	SC
WNL at Baseline	WNL at End of Study	N=53	N=63
Yes	Yes	43 (81.1)	49 (77.8)
	No	3 (5.7)	4 (6.3)
No	Yes	0	2 (3.2)
	No	7 (13.2)	8 (12.7)
	No significant change	5 (9.4)	6 (9.5)
	More abnormal	1 (1.9)	2 (3.2)
	Less abnormal	1 (1.9)	0

INH=inhaled insulin, SC=subcutaneous short-acting insulin, and WNL = within normal limits.

FEV_1 and DLco were analyzed for patients evaluated by HRCT in Studies 106, 107, and 108 to ensure that the group was representative of the remainder of the study populations. Patients evaluated by HRCT experienced changes in FEV_1 and DLco equivalent to those of the larger Controlled PFT Phase 2/3 Studies, indicating that the population evaluated by HRCT is a representative sub-sample of the Controlled PFT Phase 2/3 Studies.

HRCT was performed at yearly intervals in a subset of patients in Study 1029. INH use, compared with SC insulin use, was not associated with an increased incidence of more abnormal HRCT findings after 12 months or 24 months. In this sub-study, the incidence of worsening HRCT results was greater for the comparator than INH treatment group after 12 months; after 24 months, the incidence of worsening HRCT results was comparable between treatment groups (Table 89).

Table 89. Incidence of Significant Changes in Thoracic High Resolution Computed Tomography Results Between Baseline and Last Observation: Patients Evaluated by HRCT in Study 1029 at 1 Year and 2 Years of Exposure

		Number (%) of Patients					
		Month 12		Month 24		Month 24 (LOCF)	
Within normal limits:		INH	SC	INH	SC	INH	SC
at Baseline	at Specified Time Point	N=95	N=97	N=71	N=73	N=98	N=98
Yes	Yes	64 (67.4)	63 (64.9)	41 (57.7)	49 (67.1)	62 (63.3)	62 (63.3)
	No	4 (4.2)	13 (13.4)	9 (12.7)	9 (12.3)	9 (9.2)	15 (15.3)
No	Yes	6 (6.3)	5 (5.2)	4 (5.6)	6 (8.2)	8 (8.2)	7 (7.1)
	No	21 (22.1)	16 (16.5)	17 (23.9)	9 (12.3)	19 (19.4)	14 (14.3)
	No significant change	20 (21.1)	11 (11.3)	17 (23.9)	7 (9.6)	19 (19.4)	10 (10.2)
	More abnormal	0	2 (2.1)	0	1 (1.4)	0	2 (2.0)
	Less abnormal	1 (1.1)	3 (3.1)	0	1 (1.4)	0	2 (2.0)

INH=inhaled insulin, SC=subcutaneous short-acting insulinN=number of patients who have a baseline and the corresponding post-baseline HRCT measurement.

The results of patients to date who have completed all three scans (baseline, one year and two year HRCT scan) at the time of this analysis are summarized in Table 90. These results show a balanced incidence

between the number of INH-treated patients and the number of SC-treated patients with a normal scan at baseline and an abnormal scan at 24 months. Additionally, for patients with an abnormal baseline HRCT who had either a normal or abnormal HRCT at 12 months, there was no additional worsening of the HRCT scan at 24 months. A listing of HRCT scan findings with significant changes from baseline demonstrated that the types of HRCT abnormalities identified were similar between treatment groups.

Table 90. Incidence of Significant Changes in Thoracic High Resolution Computed Tomography Results Between Baseline and Each Observation: Patients Evaluated by HRCT in Study 1029 at 1 Year and 2 Years of Exposure

Within normal limits:			Number (%) of Patients	
			INH	SC
at Baseline	at Month 12	at Month 24	N=69	N=72
Yes	Yes	Yes	38 (55.1)	45 (62.5)
		No	6 (8.7)	5 (6.9)
	No	Yes	1 (1.4)	3 (4.2)
		No	3 (4.3)	4 (5.6)
No	Yes	Yes	2 (2.9)	4 (5.6)
		No	0	0
		No significant change	0	0
		More abnormal	0	0
		Less abnormal	0	0
	No	Yes	2 (2.9)	2 (2.8)
		No	17 (24.6)	9 (12.5)
		No significant change	17 (24.6)	7 (9.7)
		More abnormal	0	1 (1.4)
		Less abnormal	0	1 (1.4)

INH=inhaled insulin, SC=subcutaneous short-acting insulin, N=number of patients who have all three HRCT measurements (baseline, Month 12 and Month 24)

Of the 48 patients who received HRCT scans as part of a medical evaluation after INH treatment during uncontrolled extension studies, 39 had received continuous exposure to INH of ≥ 1 year and 12 had received INH continuously for ≥ 2 years. Most patients had normal scans despite evaluation in response to a medical condition.

6.5.2.8. Pulmonary Function Testing

Pulmonary function has been monitored in all Phase 2/3 INH clinical trials to date. In early Controlled Phase 2/3 Studies (Studies 102, 103, 104, 106, 107, 108, 109, 110, 1001, 1002, and 1009), using non-standardized methodologies available in local PFT laboratories, declines in mean FEV_1 and DLco occurred among both INH- and comparator-treated patients over 12 or 24 weeks (3 or 6 months) of exposure, with small but consistent treatment group differences favoring comparator. These INH-associated decreases were of a magnitude of 30-50 mL for FEV_1 and 0.5-1.0 mL/min/mmHg for DLco and were the result of a small shift in the entire distribution curve for FEV_1 and DLco rather than of a small number of patients with extreme changes.

Long-term (up to 2-year) controlled data indicate that lung function decreased from baseline in all treatment groups and that the INH-associated decreases in FEV_1 and DLco were not progressive. That is, after the initial post-baseline measurement, occurring at 3 or 6 months of exposure, the INH-associated decreases in FEV_1 and DLco remained constant and did not increase. These observations have been

corroborated and expanded upon by Group II Phase 3 studies (Studies 1026 and 1027, and 2-year interim analyses of Studies 1022 and 1029), in which standardized pulmonary testing equipment, testing procedures, and centralized data analysis were used to measure PFTs. Long-term uncontrolled studies did not reveal unexpected declines in FEV_1 or DLco after up to 7 years of INH exposure. When PFTs were measured earlier and more frequently, in type 1 Study 1027, the INH-associated decreases in FEV_1 and DLco were noted at 2 weeks of exposure, with no further progression thereafter and with resolution of the treatment group differences within 2 weeks of planned INH discontinuation. Similarly, the INH-associated decreases in FEV_1 and DLco resolved within 6 weeks after INH discontinuation following up to 2 years of exposure in controlled type 2 Studies 1001 and 1002.

There are, therefore, small decreases in FEV_1 and DLco associated with INH treatment. These decreases, however, have been demonstrated to occur early in treatment, are of a magnitude (~1% of baseline FEV_1) that is not clinically significant, non-progressive, and reversible upon discontinuation of INH treatment.

For this presentation, analyses were performed on only adult patients (≥ 18 years old), with patients with type 1 or type 2 DM evaluated separately.

The specific PFTs evaluated are as follows:

- Spirometry
  - Forced expiratory volume in 1 second (FEV_1)
  - Forced vital capacity (FVC)
  - FEV_1/FVC ratio
  - Forced expiratory flow (FEF 25-75%)
- Other PFTs
  - Single-breath carbon monoxide diffusion capacity (DLco)
  - Single-breath carbon monoxide diffusion capacity adjusted for alveolar volume (DLva)
  - Residual volume (RV)
  - Total lung capacity (TLC)
  - RV/TLC ratio

An adjusted statistical model was used to evaluate all PFT parameters in the Controlled PFT Phase 2/3 Studies and in the individual studies contributing to the discussion.

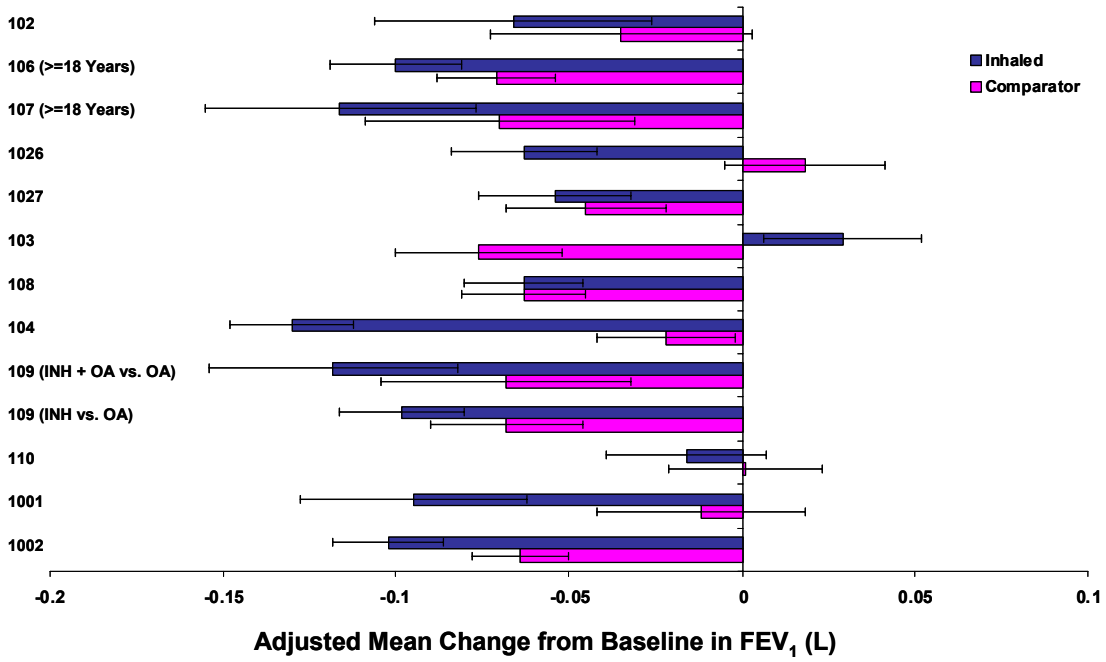
FEV_1 and DLco are emphasized in the following discussion because FEV_1 is a robust measure of airway function, and DLco is a sensitive measure of pulmonary gas exchange. The remaining PFT parameters are considered secondary endpoints in this discussion and will be summarized together.

6.5.2.8.1. FEV_1

Controlled PFT Phase 2/3 Studies (as of 25 June 2004)

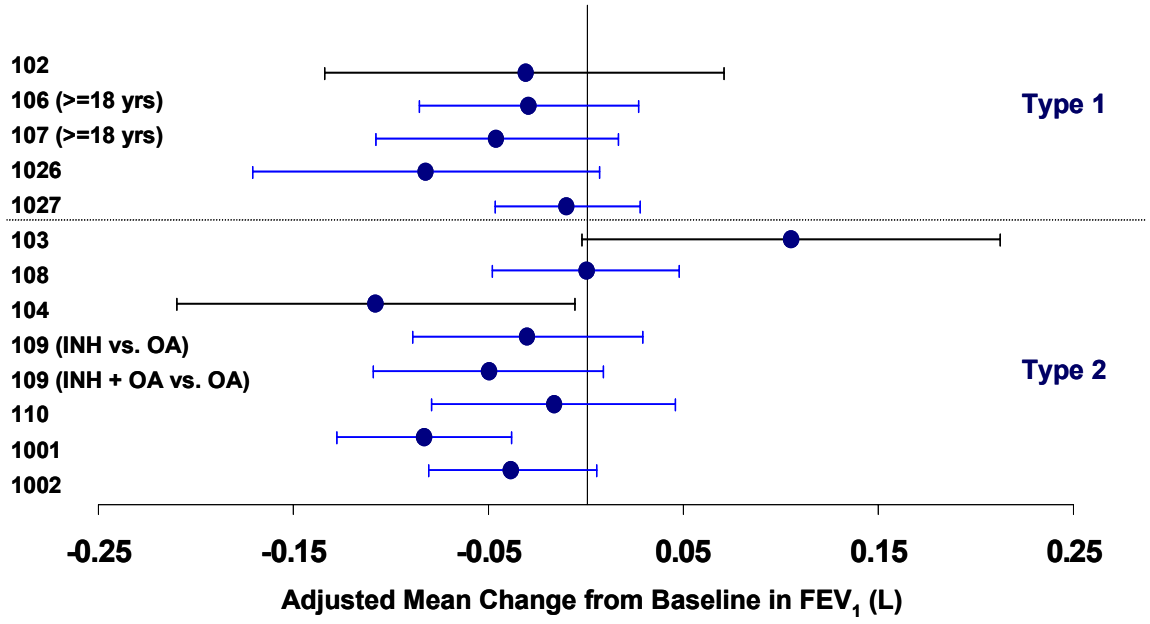
FEV_1 among adults declined over time in most controlled studies in both the INH and comparator treatment groups. In addition, there were small but consistent treatment group differences in mean change from baseline in FEV_1 favoring comparator therapy in most of the 3- and 6-month Controlled PFT Phase 2/3 studies (Figure 20 and Figure 21).

Figure 20. Adjusted Mean Change from Baseline in FEV_1 (L): 3- and 6-Month Controlled PFT Phase 2/3 Studies (Full Analysis Set)



For Study 1027, data from the comparative phase are presented

Figure 21. Adjusted Mean Treatment Group Differences and 95% Confidence Intervals for FEV_1 Change from Baseline (L): 3- and 6-Month Controlled PFT Phase 2/3 Studies (Full Analysis Set)



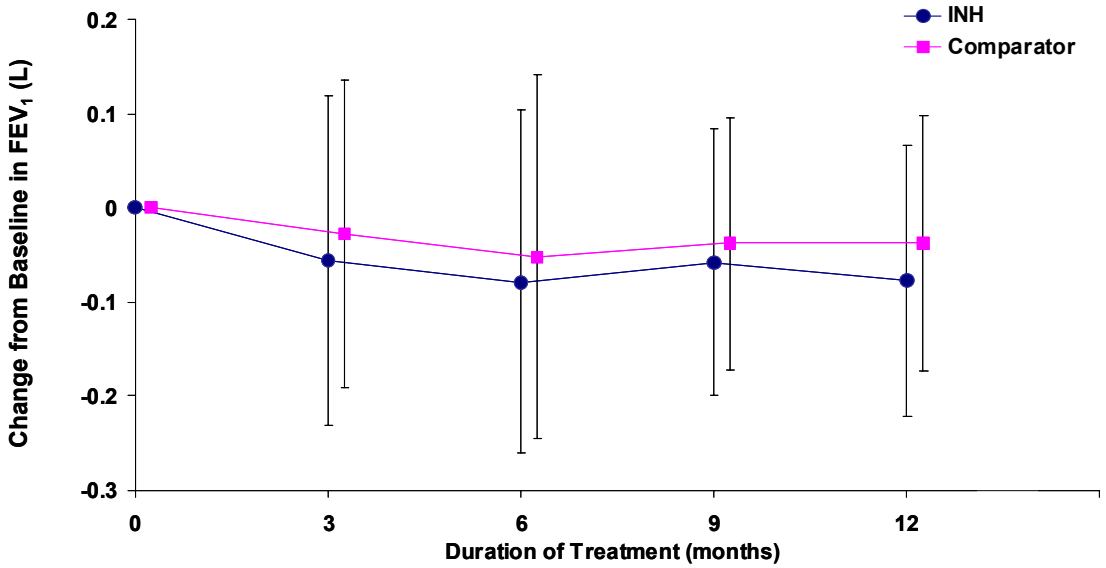
In the pooled Controlled PFT Phase 2/3 Studies, similar treatment group differences in mean change from baseline in FEV_1 favoring comparator therapy are apparent among adult patients with type 1 or type 2 DM after 3 months of therapy. Importantly, however, the treatment group differences stabilized after their first post-baseline measurement and remained comparable at subsequent time points, indicating that the effect of INH on FEV_1 is not progressive (Table 91; Figure 22, Figure 23).

Table 91. Mean Baseline, Mean Change from Baseline, and Adjusted Treatment Group Difference in Change from Baseline FEV_1 in Controlled PFT Phase 2/3 Studies (Full Analysis Set)

Patient Group Time in Study	Mean Baseline and Change from Baseline (L) INH (N)	 Comparator (N)	Adjusted Difference* (95% CI)
Type 1 ≥18 years old			
Mean baseline	3.491 (671)	3.454 (662)	
3 months	-0.056 (659)	-0.028 (634)	-0.028 (-0.046, -0.010)
6 months	-0.079 (507)	-0.052 (512)	-0.026 (-0.046, -0.007)
9 months	-0.058 (251)	-0.038 (263)	-0.020 (-0.047, 0.006)
12 months	-0.077 (238)	-0.038 (258)	-0.041 (-0.069, -0.013)
Type 2			
Mean baseline	2.922 (1,216)	2.929 (1,044)	
3 months	-0.064 (763)	-0.028 (648)	-0.043 (-0.063, -0.023)
6 months	-0.074 (848)	-0.049 (795)	-0.024 (-0.042, -0.005)
9 months	-0.092 (577)	-0.075 (532)	-0.009 (-0.031, 0.013)
12 months	-0.105 (536)	-0.071 (496)	-0.028 (-0.051, -0.004)
24 months	-0.170 (143)	-0.128 (125)	-0.040 (-0.088, 0.008)

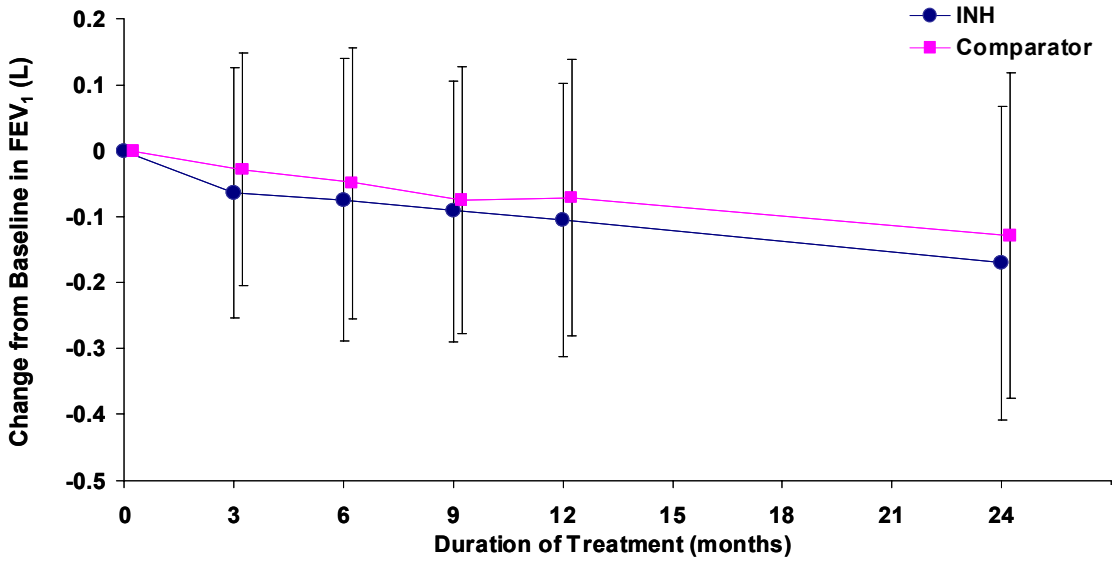
*A negative mean value indicates a lesser increase or a greater decrease in the INH than comparator group.
INH=inhaled insulin, N=number of patients, and CI=confidence interval.

Figure 22. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time: Type 1 Patients in Controlled PFT Phase 2/3 Studies (Full Analysis Set)



Number of subjects at baseline, 3, 6, 9 and 12 months, INH is 671, 659, 507, 251, 238. Comparator is 662, 634, 512, 263, and 258

Figure 23. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time: Type 2 Patients in Controlled PFT Phase 2/3 Studies (Full Analysis Set)



Number of subjects at baseline, 3, 6, 9, 12 and 24 months, INH is 1,216, 763, 848, 577, 536, 143. Comparator is 1,044, 648, 795, 532, 496, and 125.

The distributions in percent change from baseline in FEV_1 at the 3-month timepoint for patients with type 1 and type 2 DM are depicted in Figure 24 and Figure 25. These figures demonstrate that the observed mean changes from baseline in FEV_1 are driven by small, stable shifts in the distribution curves of FEV_1 among the broad population of patients treated with INH rather than by a small number of patients with extreme values.

Figure 24. Percent Change from Baseline in FEV_1 at 3 Months - Controlled PFT Phase 2/3 Studies – Adult Patients with Type 1 DM (Full Analysis Set)

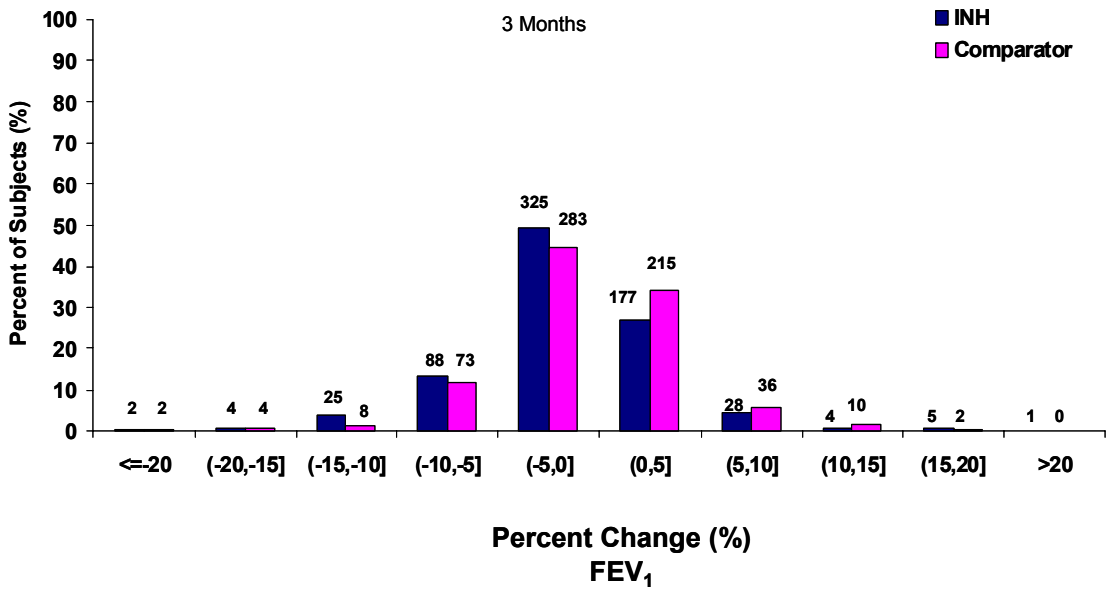
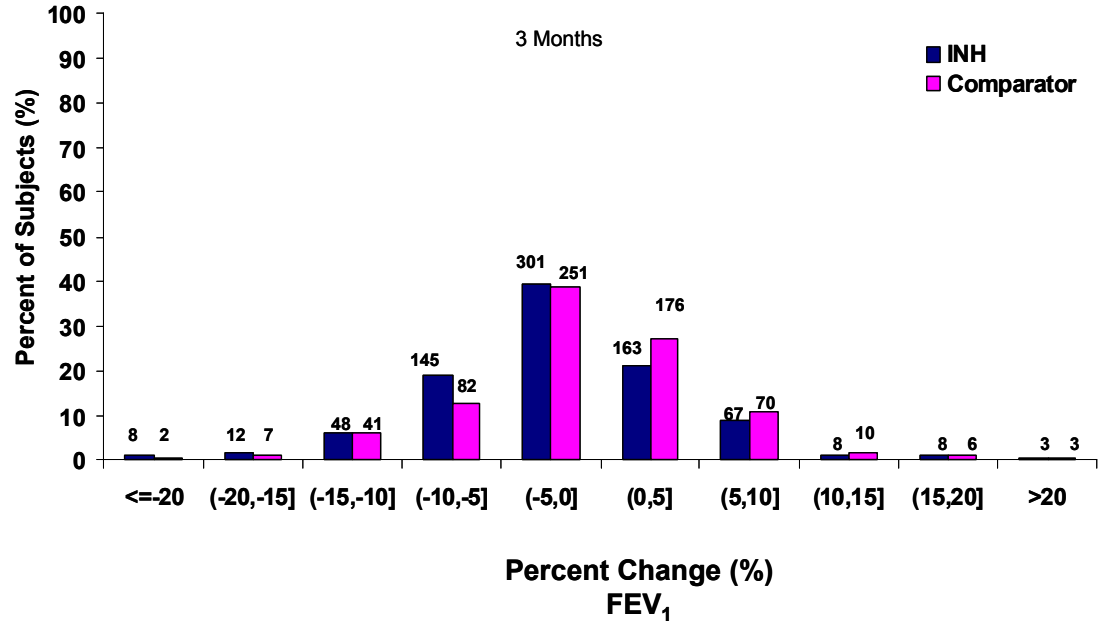


Figure 25. Percent Change from Baseline in FEV_1 at 3 Months - Controlled PFT Phase 2/3 Studies –Patients with Type 2 DM (Full Analysis Set)



Controlled Study 1022

Similar to the larger Controlled PFT Phase 2/3 protocol set, which includes data from the 1-year interim analysis of Study 1022, both INH- and SC insulin-treated patients with type 1 DM experienced small declines in FEV_1 over the course of the 24-month (2-year) treatment period of Study 1022, with a greater initial decline in the INH treatment group. The INH-associated decrease in FEV_1 was small, fully manifest at the first assessment timepoint (month 3), and did not progress during the 2 years of continued treatment (Table 92, Figure 26).

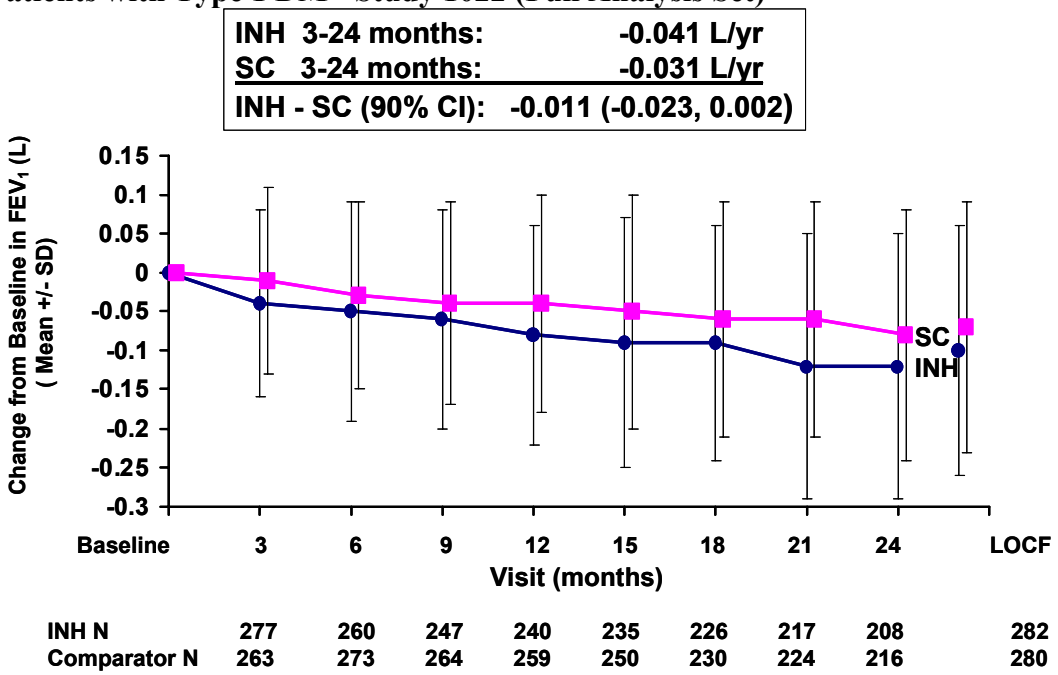
Estimates of the annual rate of change (slope) in FEV_1 between months 3 and 24 of treatment have been performed to further investigate the treatment effects on longer-term INH therapy (Figure 26 in-text box). In this analysis, the annual rate of change (slope) for each treatment group was estimated using a random effects model for longitudinal data.[61] Based on these estimates, the treatment group difference in annual rate of change was estimated along with the 90% confidence interval for this difference. The annualized change in FEV_1 was similar between INH- and SC insulin-treated patients starting from the first postbaseline visit, providing additional evidence that the INH effect on FEV_1 is nonprogressive.

Table 92. Mean Baseline, Change from Baseline, and Adjusted Treatment Group Difference in Change from Baseline in FEV_1 (L) by Time in Study 1022 (Full Analysis Set)

	Mean Baseline and Change from Baseline (L)		
Time in Study	INH (N)	SC (N)	Adjusted Difference* (90% CI)
Baseline	3.50 (282)	3.47 (280)	
Week 12	-0.04 (277)	-0.01 (263)	-0.021 (-0.041, -0.002)
Month 6	-0.05 (260)	-0.03 (273)	-0.017 (-0.036, 0.003)
Month 9	-0.06 (247)	-0.04 (264)	-0.014 (-0.034, 0.006)
Month 12	-0.08 (240)	-0.04 (259)	-0.038 (-0.058, -0.018)
Month 15	-0.09 (235)	-0.05 (250)	-0.041 (-0.062, -0.021)
Month 18	-0.09 (226)	-0.06 (230)	-0.027 (-0.048, -0.006)
Month 21	-0.12 (217)	-0.06 (224)	-0.046 (-0.067, -0.024)
Month 24	-0.12 (208)	-0.08 (216)	-0.034 (-0.056, -0.013)
Month 24 (LOCF)	-0.10 (282)	-0.07 (280)	-0.023 (-0.044, -0.002)

*A negative value indicates a lesser increase or a greater decrease in the INH than comparator group.
N=number of patients, INH=Inhaled insulin, SC=subcutaneous short-acting insulin, CI=confidence interval; 90% confidence intervals are presented, as specified by the protocol.

Figure 26. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in Patients with Type 1 DM - Study 1022 (Full Analysis Set)



Controlled Study 1029

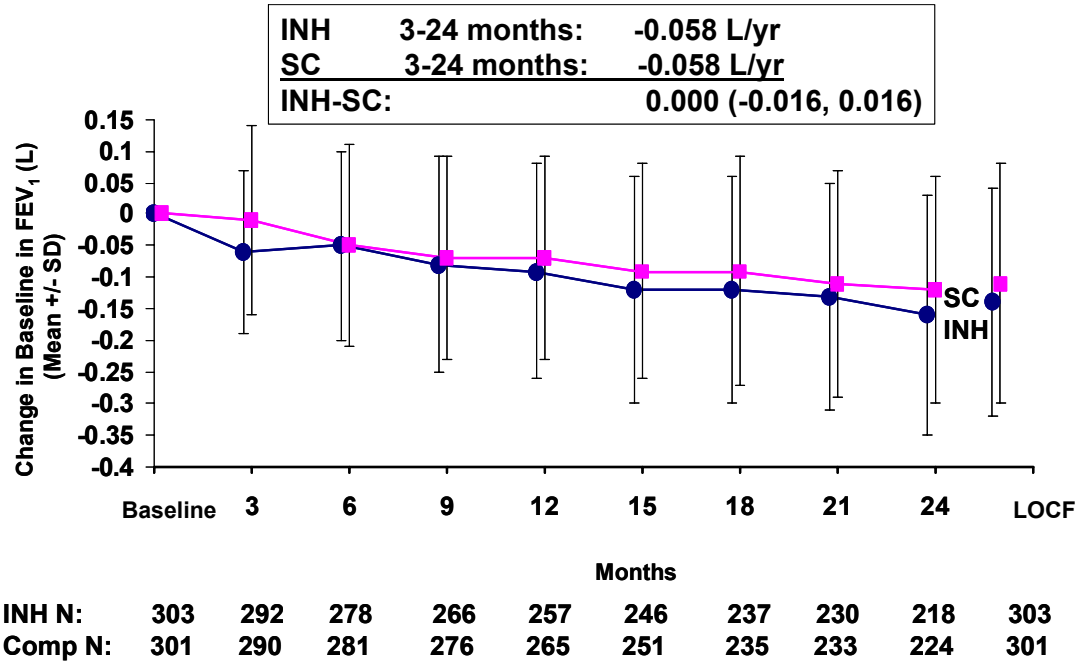
Results from Study 1029 show that both INH- and SC insulin-treated patients with type 2 DM (insulin-using) experienced small declines in FEV_1 over the course of the 24-month (2-year) treatment period, with a greater initial decline in the INH treatment group. The INH-associated decrease in FEV_1 was small, fully manifest at the first assessment timepoint (month 3), and did not progress during the 2 years of continued treatment (Table 93 and Figure 27). Estimates of the annual rate of change (slope) in FEV_1 between months 3 and 24 of treatment provide additional evidence that the INH effect on FEV_1 is non-progressive (Figure 27 in-text box).

Table 93. Mean Baseline, Change from Baseline, and Adjusted Treatment Group Difference in Change from Baseline in FEV_1 by Time in Study 1029 (Full Analysis Set)

	Mean Baseline and Change from Baseline (L)		
Time in Study	INH (N)	SC (N)	Adjusted Difference* (90% CI)
Baseline	2.91 (303)	2.93 (301)	-0.043 (-0.065, -0.020)
Week 12	-0.06 (292)	-0.01 (290)	-0.006 (-0.028, 0.017)
Month 6	-0.05 (278)	-0.05 (281)	-0.011 (-0.034, 0.012)
Month 9	-0.08 (266)	-0.07 (276)	-0.019 (-0.042, 0.005)
Month 12	-0.09 (257)	-0.07 (265)	-0.025 (-0.048, -0.001)
Month 15	-0.12 (246)	-0.09 (251)	-0.027 (-0.051, -0.002)
Month 18	-0.12 (237)	-0.09 (235)	-0.020 (-0.045, 0.004)
Month 21	-0.13 (230)	-0.11 (233)	-0.035 (-0.060, -0.009)
Month 24	-0.16 (218)	-0.12 (224)	-0.023 (-0.047, 0.002)
Month 24 (LOCF)	-0.14 (303)	-0.11 (301)	-0.043 (-0.065, -0.020)

*A negative value indicates a lesser increase or a greater decrease in the INH than comparator group.
N=number of patients, INH=Inhaled insulin, SC=subcutaneous short-acting insulin, CI=confidence interval; 90% confidence intervals are presented, as specified by the protocol.

Figure 27. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in Patients with Type 2 DM (Insulin-using) - Study 1029 (Full Analysis Set)



Controlled Study 1027

Study 1027 provides additional detail of the kinetics of the onset, magnitude, and reversibility of the INH-associated PFT effect in adult patients with type 1 DM. Similar to the larger Controlled PFT Phase 2/3 protocol set, in Study 1027 both INH- and SC insulin-treated patients with type 1 DM experienced small declines in FEV_1 favoring comparator therapy over the course of the 12-week comparative portion of the study. Also consistent with the preceding data, this treatment group difference occurred early in

the study and did not progress thereafter. The treatment group difference in mean change from baseline FEV_1 was fully manifest within 2 weeks of treatment initiation and did not change significantly during the remainder of the 12-week comparative phase, supporting the observation, in the Controlled PFT Phase 2/3 Studies, that the effect of INH on FEV_1 is not progressive (Table 94 and Figure 28).

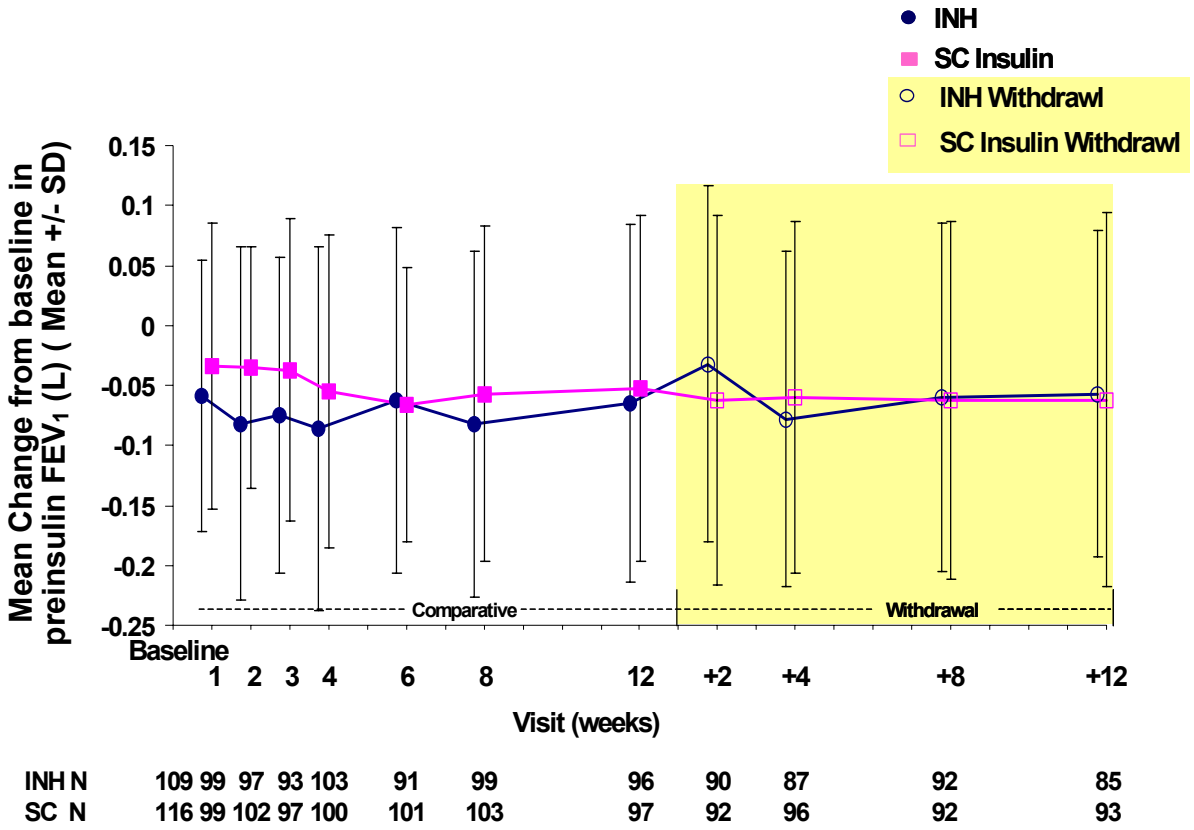
The treatment group difference in FEV_1 resolved within 2 weeks after INH cessation in Study 1027. In this study, PFT measurements were made during a 12-week follow-up period, after INH therapy had ceased. By the time of the first FEV_1 measurement during the wash-out period (2 weeks after INH discontinuation) the treatment group difference in FEV1 had resolved, indicating that the effect of INH on FEV_1 is rapidly reversible upon cessation of INH treatment (Table 94 and Figure 28).

Table 94. Mean Baseline, Change from Baseline, and Adjusted Treatment Group Difference in Change from Baseline in FEV_1 (L) by Time in Patients with Type 1 DM - Study 1027 (Full Analysis Set)

	Mean Baseline and Change from Baseline (L)		
Time in Study	**INH (N)**	**SC (N)**	**Adjusted Difference* (90% CI)**
Mean baseline	**3.333 (109)**	**3.303 (116)**	
Comparative phase			
1 week	-0.059 (99)	-0.034 (99)	-0.022 (-0.053, 0.009)
2 weeks	-0.082 (97)	-0.035 (102)	-0.044 (-0.075, -0.013)
3 weeks	-0.075 (93)	-0.037 (97)	-0.032 (-0.063, -0.001)
4 weeks	-0.086 (103)	-0.055 (100)	-0.026 (-0.057, 0.005)
6 weeks	-0.062 (91)	-0.066 (101)	0.004 (-0.028, 0.035)
8 weeks	-0.082 (99)	-0.057 (103)	-0.021 (-0.052, 0.010)
12 weeks	-0.065 (96)	-0.053 (97)	-0.010 (-0.041, 0.022)
Follow-up phase†			
2 weeks	-0.032 (90)	-0.063 (92)	0.041 (0.007, 0.076)
4 weeks	-0.078 (87)	-0.060 (96)	-0.012 (-0.046, 0.022)
8 weeks	-0.060 (92)	-0.062 (92)	0.006 (-0.029, 0.040)
12 weeks	-0.057 (85)	-0.062 (93)	0.014 (-0.021, 0.049)

*A negative value indicates a lesser increase or a greater decrease in the INH than comparator group.
†All patients received subcutaneous insulin as the only short-acting insulin during the follow-up phase.
N=number of patients, INH=Inhaled insulin, SC=subcutaneous short-acting insulin, CI=confidence interval; 90% confidence intervals are presented, as specified by the protocol.

Figure 28. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in Patients with Type 1 DM: Onset and Withdrawal - Study 1027 (Full Analysis Set)



Controlled Studies 1001 and 1002

Also consistent with the larger Controlled PFT Phase 2/3 Studies, in Studies 1001 and 1002 combined, the cohort of patients with type 2 DM completing 104 weeks of INH or comparator therapy experienced declines in FEV_1 at the first post-baseline measurement at 6 months favoring comparator therapy. Again, this treatment group difference did not increase after the first FEV_1 measurement at 6 months, further supporting the evidence that the effect of INH on FEV_1 is not progressive (Table 95 and Figure 29). Similar trends in FEV_1 over time and after INH discontinuation were seen when all patients, rather than the 104-week cohort, were evaluated.

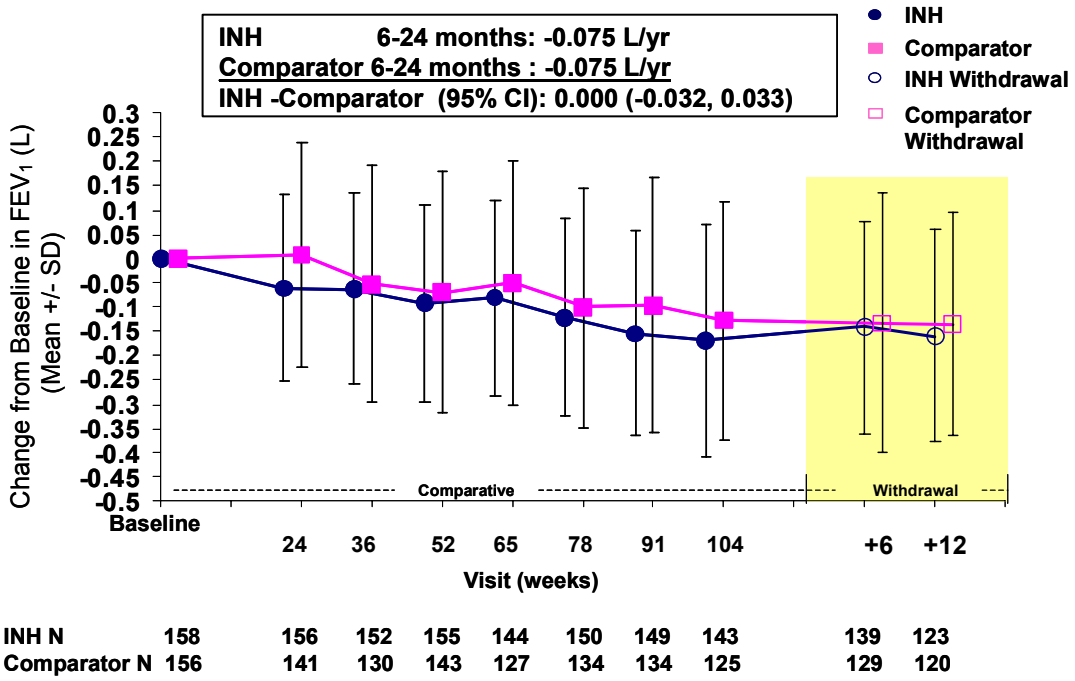
Treatment group differences in FEV_1 resolved after INH cessation in Studies 1001 and 1002. In these studies, PFT measurements were made during a 12-week follow-up period, after INH therapy had ceased. By the time of the first FEV_1 measurement during the wash-out period (6 weeks after INH discontinuation) the mean treatment group difference in FEV_1 had diminished, indicating that the effect of INH on FEV_1 is reversible, even after long-term exposure (Table 95 and Figure 29). Estimates of the annual rate of change (slope) in FEV_1 between months 6 and 24 of treatment provide additional evidence that the INH effect on FEV_1 is non-progressive (Figure 29 in-text box).

Table 95. Mean Baseline, Change from Baseline, and Adjusted Treatment Group Difference in Change from Baseline in FEV_1 (L) by Time in Studies 1001 and 1002: 104-Week Cohort

	Mean Baseline and Change from Baseline (L)		
Time in Study	**INH (N)**	**Oral Agents (N)**	**Adjusted Difference* (95% CI)**
Mean baseline	**2.852 (158)**	**2.826 (145)**	
Comparative phase			
24 weeks	-0.060 (156)	0.008 (141)	-0.063 (-0.111, -0.014)
36 weeks	-0.063 (152)	-0.052 (130)	-0.007 (-0.057, 0.043)
52 weeks	-0.093 (155)	-0.070 (143)	-0.019 (-0.067, 0.030)
65 weeks	-0.082 (144)	-0.050 (127)	-0.029 (-0.079, 0.020)
78 weeks	-0.121 (150)	-0.101 (134)	-0.017 (-0.066, 0.032)
91 weeks	-0.155 (149)	-0.096 (134)	-0.054 (-0.106, -0.002)
104 weeks	-0.170 (143)	-0.128 (125)	-0.039 (-0.093, 0.015)
Follow-up phase†			
6 weeks	-0.142 (139)	-0.133 (129)	-0.004 (-0.058, 0.051)
12 weeks	-0.158 (123)	-0.136 (120)	-0.014 (-0.066, 0.039)

*A negative value indicates a lesser increase or a greater decrease in the INH than comparator group.
†Patients did not receive INH during the follow-up phase.
N=number of patients, INH=Inhaled insulin, CI=confidence interval.

Figure 29. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in Studies 1001/1002 (104-Week Cohort)



Extension Studies 102E/1036, 103E/1036, and 104E/1036

FEV_1 values are available for adult type 1 and type 2 patients receiving up to 84 months (7 years) of continuous INH therapy in ongoing Phase 2 extension studies 102E/1036, 103E/1036, and 104E/1036. In addition, FEV_1 was measured in a small cohort of patients (N=23) receiving comparator therapy for 24 months, in these studies. In the Phase 2 extension studies, FEV_1 among INH-treated patients declined most rapidly between baseline and the first post-baseline measurement at 3 months, and then declined more slowly and consistently thereafter (Figure 30 and Figure 31). After the initial decline at 3 months, the INH and comparator treatment groups changed at similar rates (Figure 30). This is consistent with the longitudinal data presented above, from the Controlled PFT Phase 2/3 Studies and Studies 1001, 1002 and 1027, which show a small, but non-progressive treatment group difference in change from baseline in FEV_1 associated with INH use.

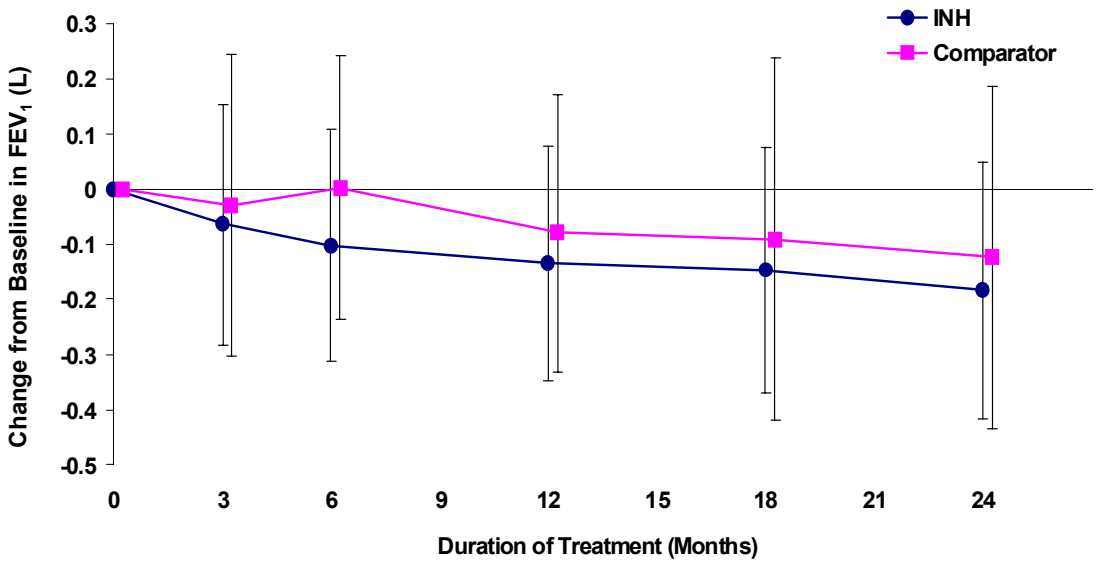
The adjusted mean (95% confidence interval) difference in annualized rate of FEV_1 change between INH and comparator patients treated for at least 24 months was –0.009 (-0.059, 0.041) L/year. Because the decrease in FEV_1 was greatest at the first post baseline measurement at 3 months, the calculated annualized rates of change in FEV_1 are the product of initial, relatively rapid, but small, decreases in FEV_1 followed by prolonged slower decreases. The prolonged decreases in FEV_1 were similar between treatment groups (Table 96, Figure 30, Figure 31).

Table 96. Mean Baseline, Mean Change from Baseline, and Annualized Rate of Change in FEV_1 (L) by Time in Studies 102E/1036, 103E/1036, and 104E/1036

Time in Study (N)	Mean Baseline (L)	Mean Change from Baseline (L)	Adjusted Annualized Rate of Change (L/year)
24-month cohort			
INH (116)	3.285	-0.184	-0.080
Comparator (23)	3.226	-0.124	-0.071
48-month cohort (88)	3.303	-0.307	-0.054
84 months (27)	3.241	-0.409	-0.059
			Adjusted Mean Difference between Slopes (L/min/mmHg/year) [95% CI]
INH vs. Comparator			
24-month cohort			-0.009 (-0.059, 0.041)

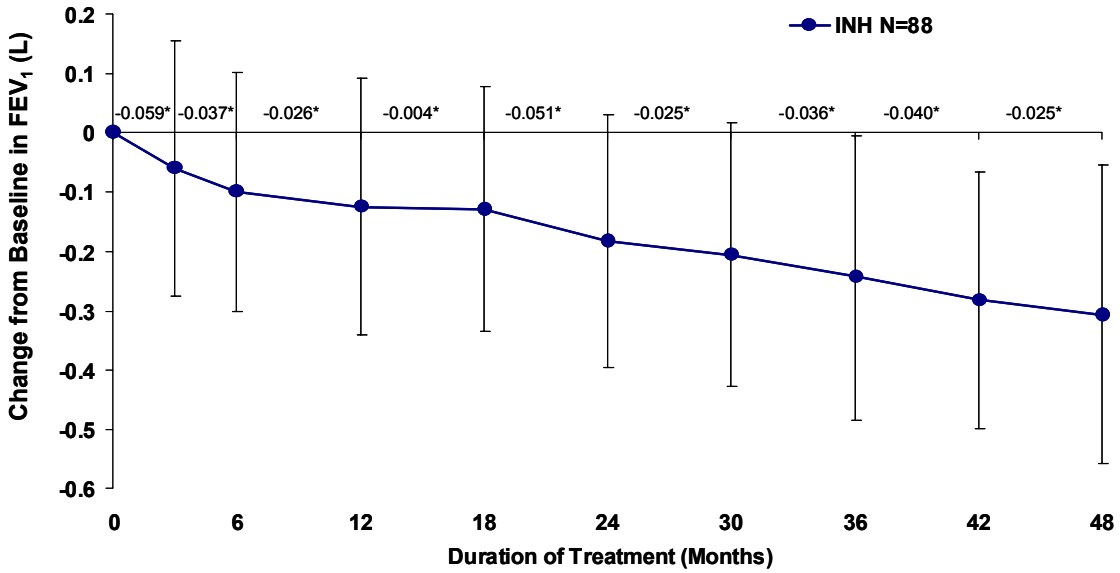
INH=inhaled insulin, N=number of patients

Figure 30. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in Studies 102E/1036, 103E/1036, and 104E/1036 (24-Month Cohort)



Number of subjects at baseline, 3, 6, 12, 18 and 24 months, INH is 116, 115, 115, 116, 116, and 116. Comparator is 23, 23, 23, 23, 23 and 23.

Figure 31. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in Studies 102E/1036, 103E/1036, and 104E/1036: 48-Month Cohort



* Adjusted difference in change from baseline between consecutive time points

Extension Study 111

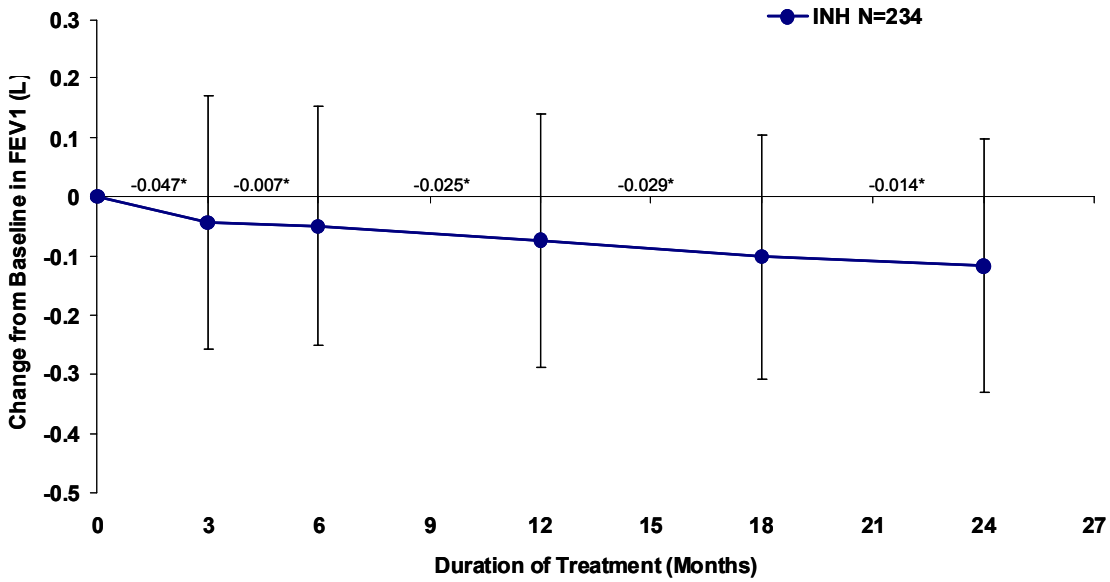
In Study 111, data were analyzed separately based on DM type. Among adult patients with type 1 or type 2 DM, FEV_1 decreased between baseline and month 24 at annualized rates approximating those observed in Studies 102E, 103E, and 104E, in which data from patients with type 1 or type 2 DM were analyzed together (Table 97, Figure 32 and Figure 33). Consistent with data discussed previously, in Study 111 the decrease in FEV_1 among adult patients with type 1 or type 2 DM was greater during the first 3 months of treatment than during any 3-month period thereafter (Figure 32, Figure 33). Therefore, the calculated annualized rates of change in FEV_1 displayed below are the product of an initial, relatively rapid, but small, decrease in FEV_1 followed by a prolonged slower decrease similar in magnitude to that observed for comparator-treated patients in extension Studies 102E/1036, 103E/1036, and 104E/1036. The prolonged decreases in FEV_1 are expected sequelae of aging and DM. Similar trends in FEV_1 over time were seen when all patients, rather than the 24-month cohort, were evaluated.

Table 97. Mean Baseline, Mean Change from Baseline, and Annualized Rate of Change in FEV_1 (L) at 24 Months in Study 111: 24-Month Cohort

Patient Group (N)	Mean Baseline (L)	Mean Change from Baseline (L)	Adjusted Annualized Rate of Change (L/year) [95% CI]
Type 1 ≥ 18 years old (234)	3.501	-0.117	-0.047 [-0.061, -0.034]
Type 2 (381)	2.998	-0.172	-0.074 [-0.084, -0.063]

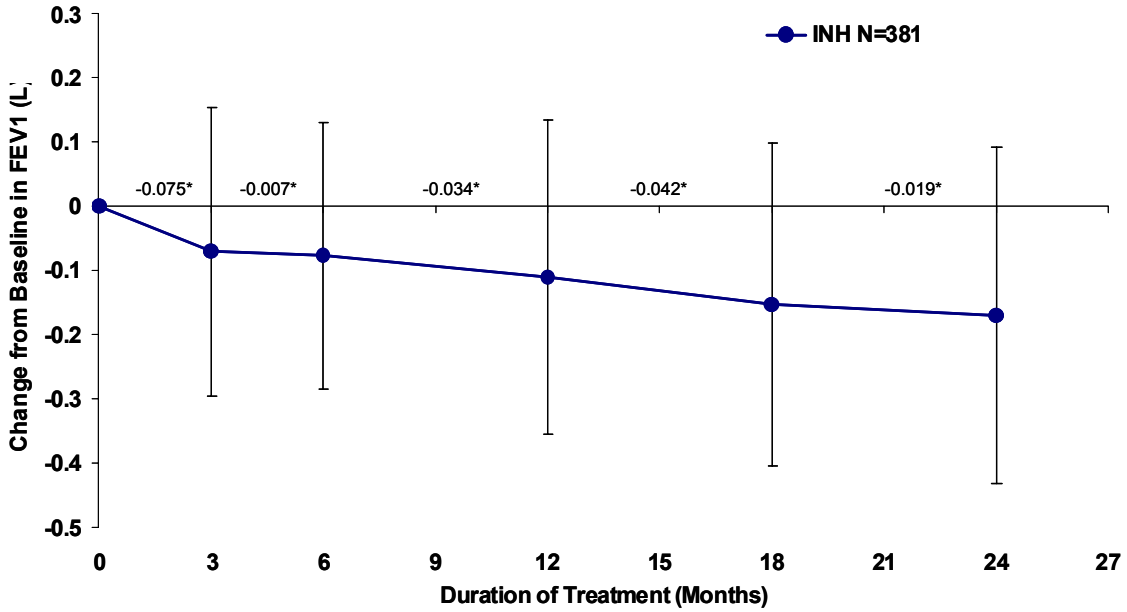
CI=confidence interval.

Figure 32. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in Study 111 and Controlled Parent Studies Among Adult Type 1 Patients: 24-Month Cohort



* Adjusted difference in change from baseline between consecutive time points

Figure 33. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in Study 111 and Controlled Parent Studies Among Adult Type 2 Patients: 24-Month Cohort



* Adjusted difference in change from baseline between consecutive time points

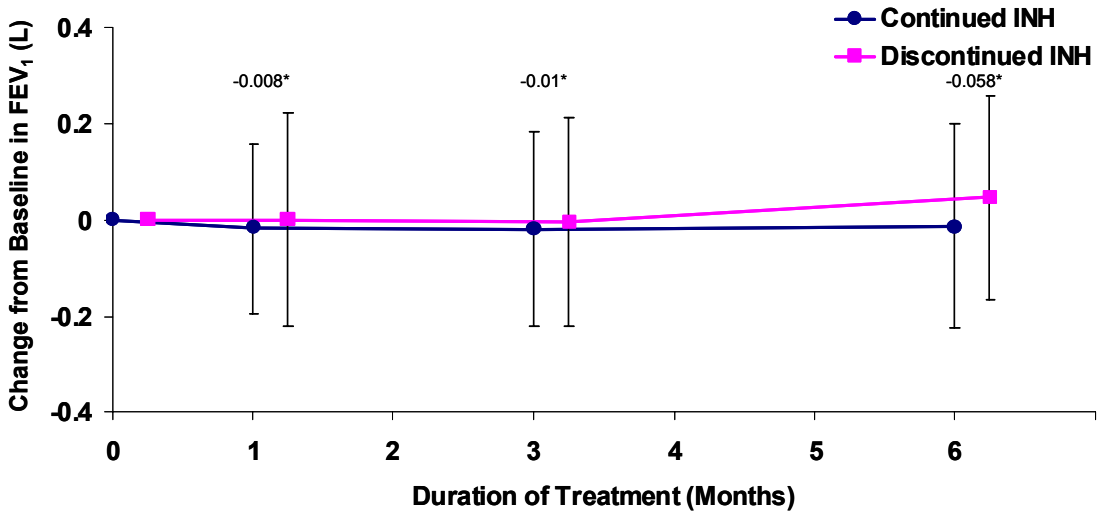
Planned discontinuation of INH treatment for 6 months in Study 111 resulted in changes in FEV_1 favoring the group discontinuing INH therapy (Table 98, Figure 34, and Figure 35) further supporting the observation that the effect of INH on FEV_1 is reversible even after long-term exposure. This effect was fully manifest within 6 months of discontinuation among patients with type 1 DM and within 1 month of discontinuation among patients with type 2 DM. The adjusted mean treatment differences (discontinued INH – continued INH) 6 months after discontinuing INH treatment were similar in magnitude and opposite in direction to that observed within the first 3-6 months of treatment initiation in Controlled PFT Phase 2/3 studies (Table 91 and Table 98). Moreover, discontinuation of INH treatment was associated with a slight shift of the overall distribution of FEV_1 percent change toward higher positive values, a reversal of the distribution pattern associated with the initiation of therapy (Figure 36).

Table 98. Mean Baseline, Mean Change from Baseline, and Adjusted Treatment Group Difference in Change from Baseline in FEV_1 (L) Among Adults in the Discontinuation Phase of Study 111 (Primary Analysis Set*)

	Change from Baseline**(L)		
Patient Group Time in Study	**Continued INH (N)**	**Discontinued INH (N)**	**Adjusted Difference† (90% CI)**
Type 1 DM			
Mean Baseline	3.489 (115)	3.429 (122)	
1 month	-0.018 (104)	0.001 (118)	-0.008 (-0.053, 0.037)
3 months	-0.019 (113)	-0.005 (119)	-0.010 (-0.054, 0.035)
6 months	-0.013 (109)	0.046 (116)	-0.058 (-0.103, -0.013)
Type 2 DM			
Mean Baseline	2.761 (198)	2.822 (203)	
1 month	-0.018 (191)	0.029 (201)	-0.052 (-0.084, -0.021)
3 months	-0.028 (195)	0.027 (199)	-0.060 (-0.091, -0.029)
6 months	-0.002 (192)	0.030 (197)	-0.037 (-0.068, -0.005)

*Primary Analysis Set consist of patients who had at least 1 baseline FEV1 measurement, two post-baseline FEV1 measurements, and received study drug for at least 50% of the duration of the comparative phase.
**Baseline for the discontinuation phase of Study 111 was the last value prior to or within 7 days after initiating randomized treatment.
†A negative value indicates a greater increase or lesser decrease in the group that discontinued than continued INH treatment.
N=number of patients, INH=inhaled insulin, CI=confidence interval, and DM=diabetes mellitus.

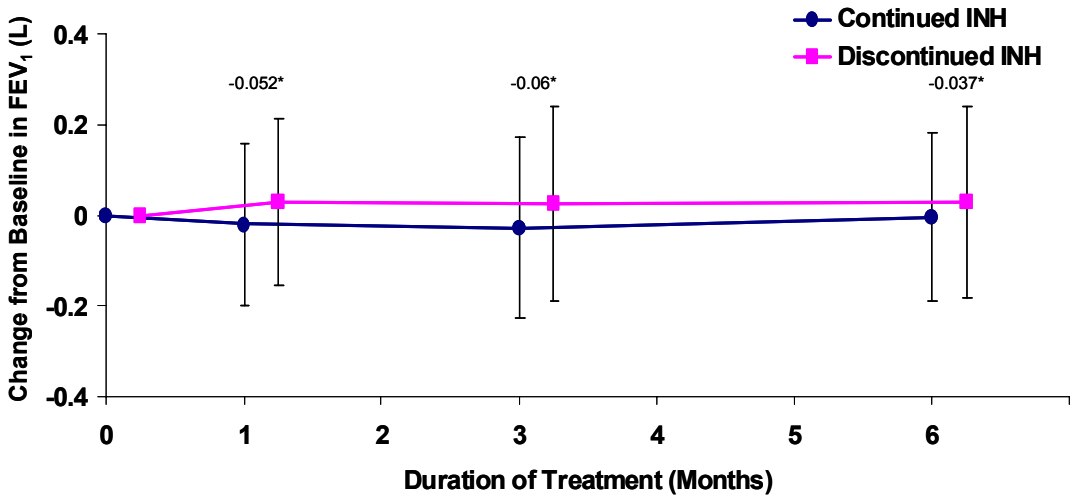
Figure 34. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in the Discontinuation Phase of Study 111: Adult Type 1 Patients (Primary Analysis Set)



Number of subjects at baseline, 1, 3, and 6 months, Continued is 115, 104, 113, and 109. Discontinued is 122, 118, 119, and 116.

* Adjusted difference between treatment groups (Continue-Discontinue Inhaled Insulin) in change from baseline at each time point

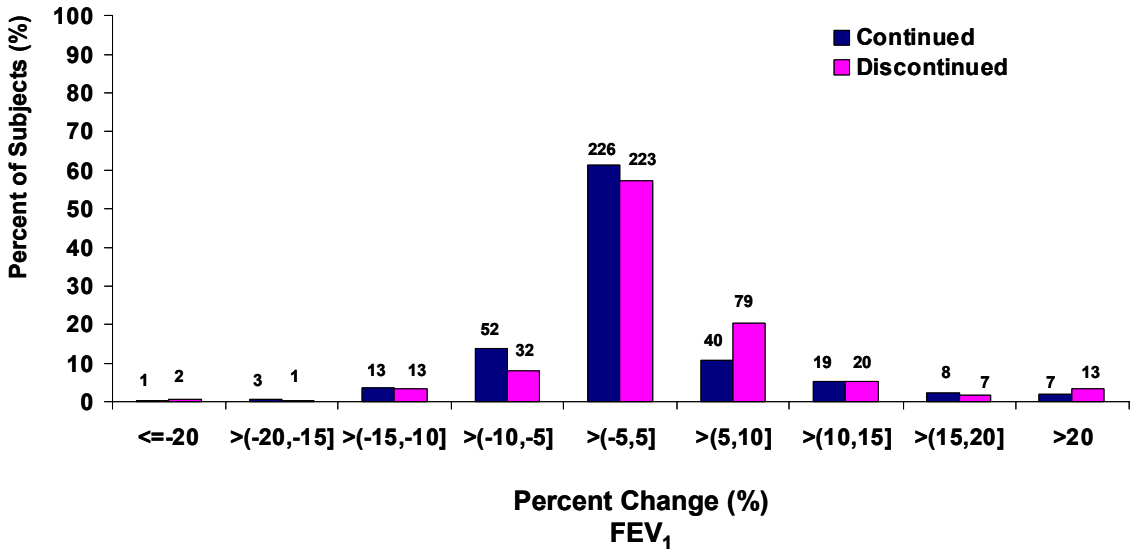
Figure 35. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in the Discontinuation Phase of Study 111: Adult Type 2 Patients (Primary Analysis Set)



Number of subjects at baseline, 1, 3, and 6 months, Continued is 198, 191, 195, and 192. Discontinued is 203, 201, 199, and 197.

* Adjusted difference between treatment groups (Continue-Discontinue Inhaled Insulin) in change from baseline at each time point

Figure 36. Percent Change from Baseline to Month 6 (LOCF) in FEV_1 in the Discontinuation Phase of Study 111: Patients with Type 1 or Type 2 DM (Primary Analysis Set)



FEV_1 Among Patients Who Experienced Cough

Patients who reported cough as an adverse event in Controlled PFT Phase 2/3 studies did not experience greater declines in FEV_1 than those who did not report cough (Table 99). These results indicate that the cough experienced by these patients was not a manifestation of excessive declines in FEV_1.

Table 99. Mean Baseline and Change From Baseline in FEV_1 (L) Among Patients Who Did and Did Not Report Cough as an Adverse Event in Controlled PFT Phase 2/3 Studies (Full Analysis Set)

	Mean Baseline and Change from Baseline (L)			
	Patients Experiencing Cough		Patients Not Experiencing Cough	
Time in Study	INH (N)	Comparator (N)	INH (N)	Comparator (N)
Mean Baseline	3.043 (429)	3.193 (107)	3.148 (1,458)	3.129 (1,599)
3 months	-0.052 (352)	-0.032 (88)	-0.063 (1,070)	-0.028 (1,194)
6 months	-0.065 (322)	-0.052 (90)	-0.079 (1,033)	-0.050 (1,217)
9 months	-0.086 (220)	-0.086 (66)	-0.080 (608)	-0.060 (729)
12 months	-0.098 (197)	-0.124 (65)	-0.096 (577)	-0.054 (689)
24 months	-0.131 (28)	-0.135 (6)	-0.179 (115)	-0.128 (119)

N=number of patients, and INH=inhaled insulin.

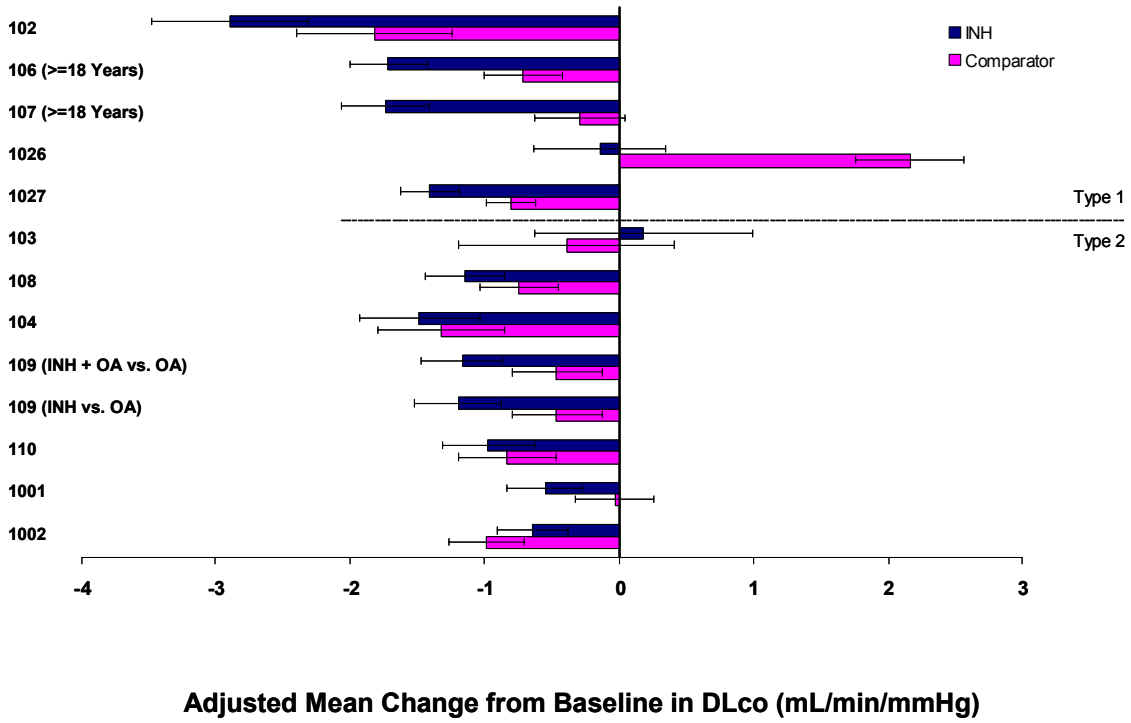
In summary, FEV_1 declined during treatment among both INH- and comparator-treated patients, with small but consistent treatment group differences favoring comparator. These INH-associated decreases in FEV_1 occurred soon after treatment was initiated, were small and non-progressive, and were reversible upon discontinuation of INH treatment.

6.5.2.8.2. DLco

Controlled PFT Phase 2/3 Studies

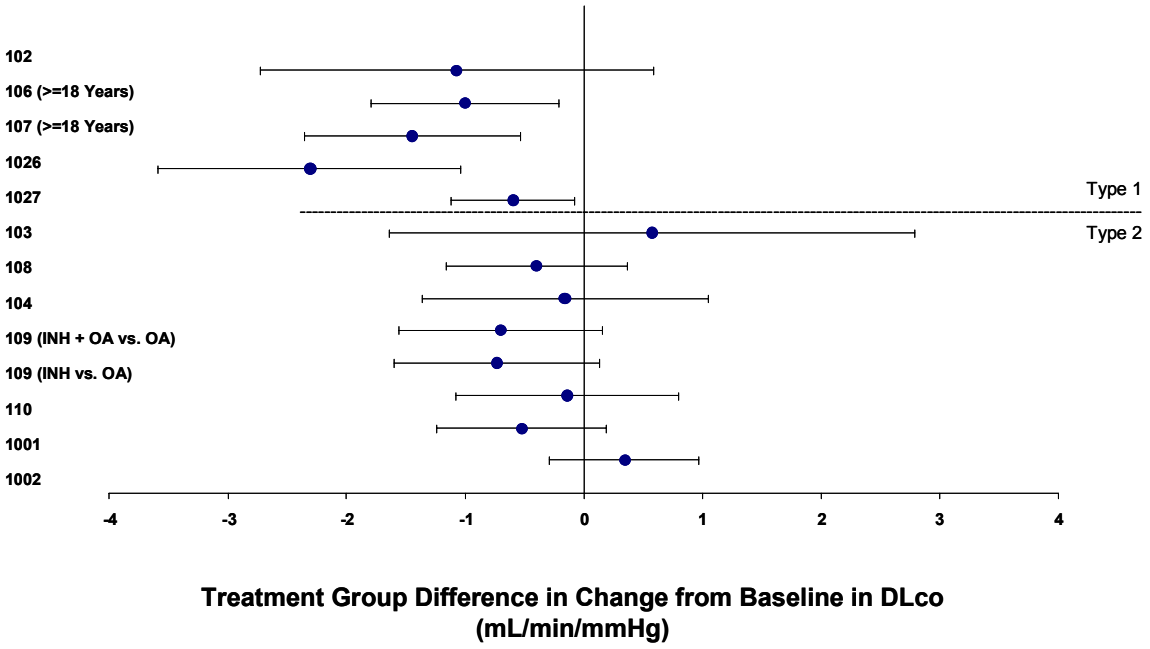
DLco among adults declined over time in most controlled studies in both the INH and comparator treatment groups. In addition, there were small but consistent treatment group differences in mean change from baseline in DLco favoring comparator therapy in most of the 3- and 6-month Controlled PFT Phase 2/3 studies (Figure 37 and Figure 38).

Figure 37. Adjusted Mean Change in Baseline in DLco (mL/min/mmHg): 3- and 6-Month Controlled PFT Phase 2/3 Studies (Full Analysis Set)



For Study 1027, data from the comparative phase are presented.

Figure 38. Adjusted Mean Treatment Group Differences and 95% Confidence Intervals for DLco Change from Baseline (mL/min/mmHg): 3- and 6-Month Controlled PFT Phase 2/3 Studies (Full Analysis Set)



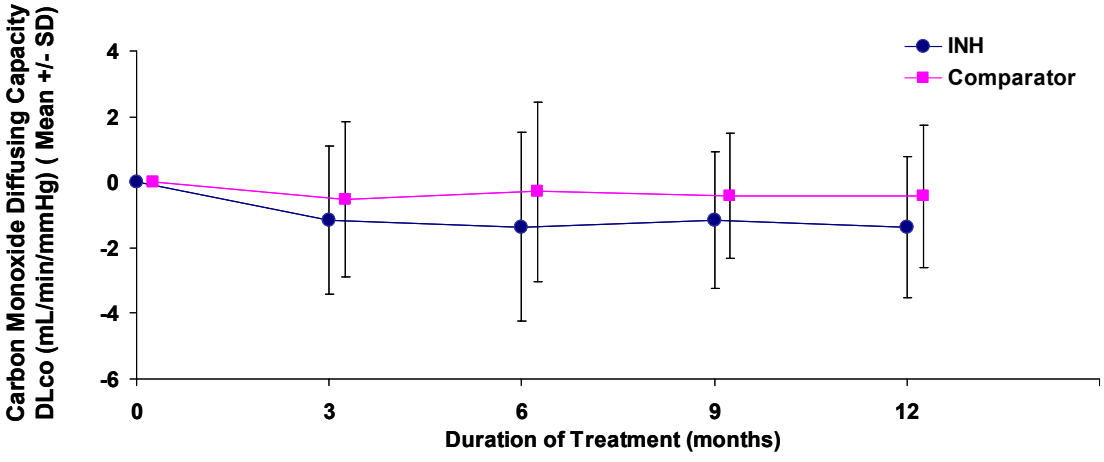
In the pooled Controlled PFT Phase 2/3 Studies, similar treatment group differences in mean change from baseline in DLco favoring comparator therapy are apparent among adult patients with type 1 or type 2 DM after 3 months of therapy. Importantly, however, the treatment group differences stabilized after their first post-baseline measurement and remained comparable at subsequent time points, indicating that the effect of INH on DLco is not progressive (Table 100, Figure 39, Figure 40).

Table 100. Mean Baseline, Mean Change from Baseline, and Adjusted Treatment Group Difference in Change from Baseline DLco (mL/min/mmHg) in Controlled PFT Phase 2/3 Studies (Full Analysis Set)

	Mean Baseline and Change from Baseline (mL/min/mmHg)		
Patient Group Time in Study	**INH (N)**	**Comparator (N)**	**Adjusted Difference* (95% CI)**
Type 1 ≥ 18 years old			
Mean baseline	27.982 (651)	27.546 (648)	
3 months	-1.159 (428)	-0.529 (416)	-0.677 (-0.979, -0.375)
6 months	-1.360 (503)	-0.285 (507)	-0.966 (-1.249, -0.682)
9 months	-1.154 (250)	-0.408 (266)	-0.752 (-1.114, -0.390)
12 months	-1.374 (237)	-0.425 (256)	-0.882 (-1.281, -0.484)
Type 2			
Mean baseline	25.063 (1,174)	24.892 (1,010)	
3 months	-0.666 (618)	-0.388 (501)	-0.222 (-0.517, 0.072)
6 months	-0.540 (808)	-0.395 (769)	-0.174 (-0.436, 0.088)
9 months	-0.660 (265)	-0.731 (271)	0.102 (-0.240, 0.444)
12 months	-0.742 (518)	-0.591 (487)	-0.110 (-0.429, 0.208)
24 months	-1.529 (129)	-1.583 (116)	0.323 (-0.352, 0.997)

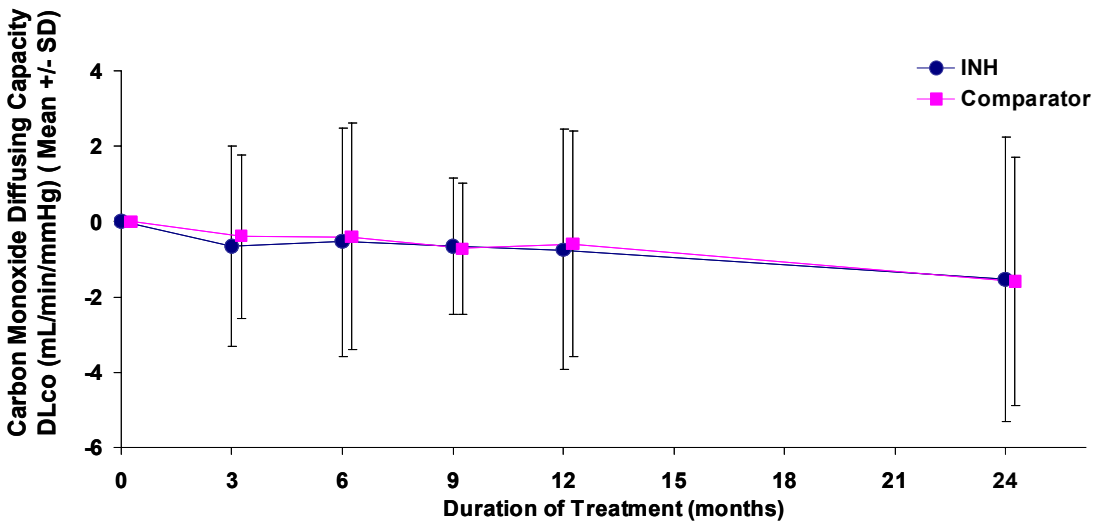
*A negative mean value indicates a lesser increase or a greater decrease in the INH than comparator group.
INH=inhaled insulin, N=number of patients, and CI=confidence interval.

Figure 39. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time: Type 1 Patients in Controlled PFT Phase 2/3 Studies (Full Analysis Set)



Number of subjects at baseline, 3, 6, 9 and 12 months, INH is 651, 428, 503, 250, 237. Comparator is 648, 416, 507, 266, and 256

Figure 40. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time: Type 2 Patients in Controlled PFT Phase 2/3 Studies (Full Analysis Set)



Number of subjects at baseline, 3, 6, 9, 12 and 24 months, INH is 1,174, 618, 808, 265, 518, 129. Comparator is 1,010, 501, 769, 271, 487 and 116.

The distributions in percent change from baseline in DLco at the 3-month timepoint for each of the pooled patient cohorts are depicted in Figure 41 and Figure 42. These figures demonstrate that the observed mean changes from baseline in DLco are driven by slight shifts in the distribution curves of DLco among the broad population of patients treated with INH rather than by a small number of patients with extreme values.

Figure 41. Percent Change from Baseline in DLco at 3 Months - Controlled PFT Phase 2/3 Studies – Adult Patients with Type 1 DM (Full Analysis Set)

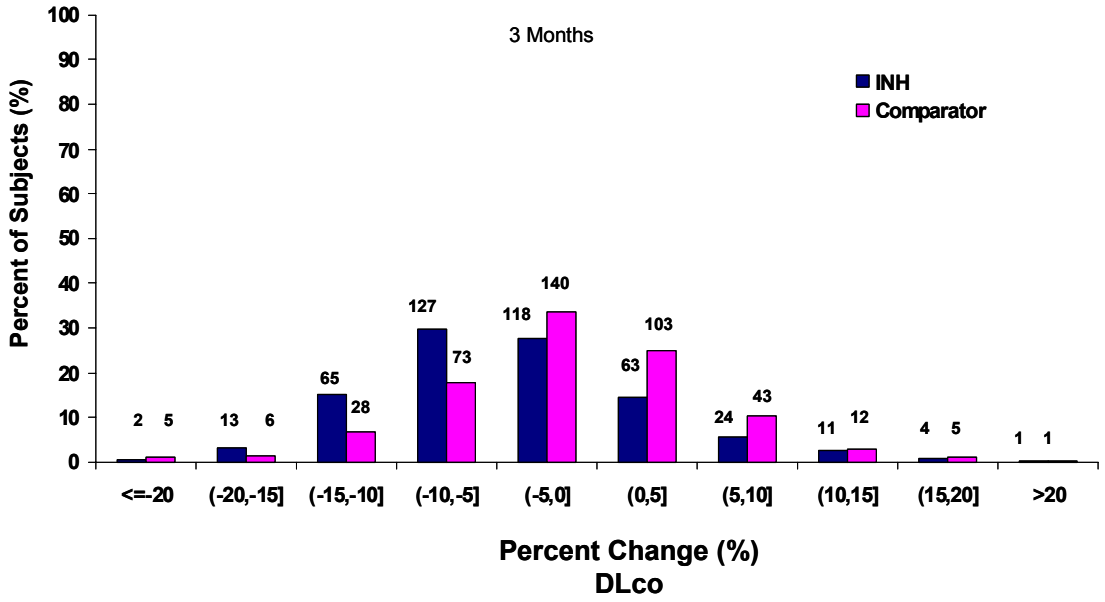
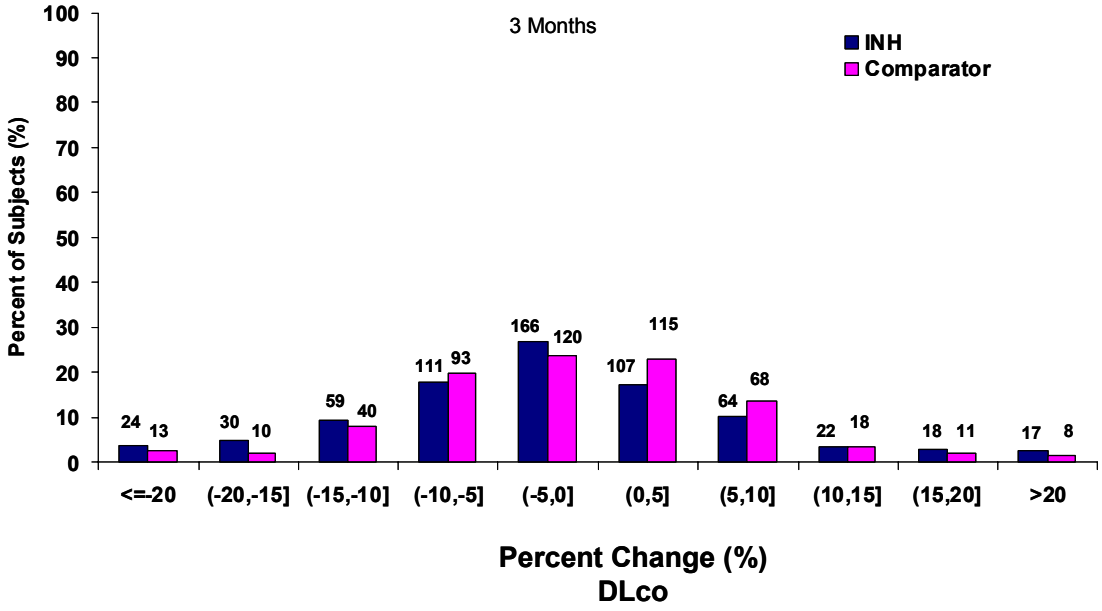
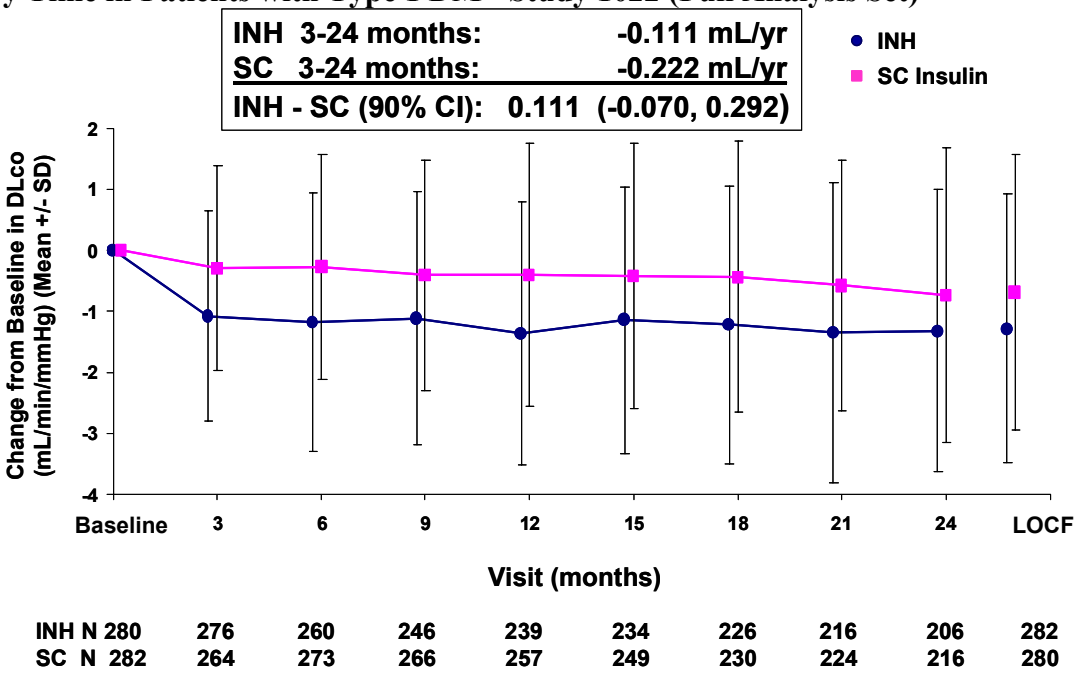


Figure 42. Percent Change from Baseline in DLco at 3 Months - Controlled PFT Phase 2/3 Studies –Patients with Type 2 DM (Full Analysis Set)



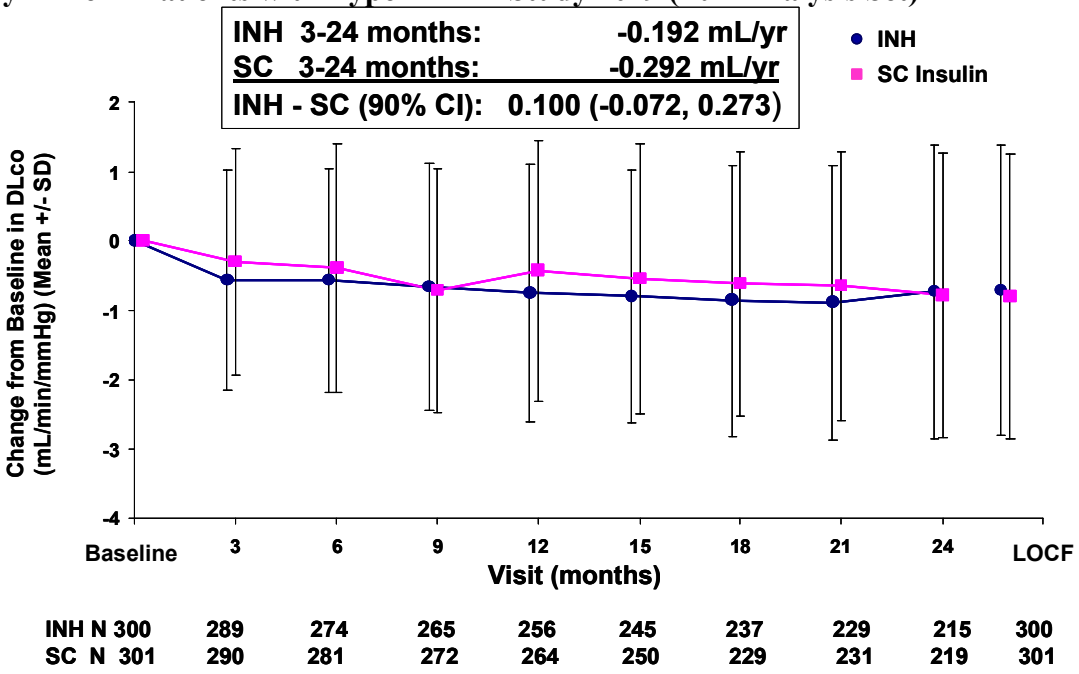
Similar trends in DLco over time were seen in Studies 1022 (Figure 43) and 1029 (Figure 44) when their data were examined individually rather than pooled in the Controlled PFT Phase 2/3 Studies.

Figure 43. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time in Patients with Type 1 DM - Study 1022 (Full Analysis Set)



INH N	280	276	260	246	239	234	226	216	206	282
SC N	282	264	273	266	257	249	230	224	216	280

Figure 44. Mean Change from Baseline and Standard Deviation in Dlco (mL/min/mmHg) by Time in Patients with Type 2 DM - Study 1029 (Full Analysis Set)



INH N	300	289	274	265	256	245	237	229	215	300
SC N	301	290	281	272	264	250	229	231	219	301

Controlled Study 1027

Study 1027 provides additional detail of the kinetics of the onset, magnitude, and reversibility of the INH-realted PFT effect in adult patients with type 1 DM. Similar to the larger Controlled PFT Phase 2/3 Studies, in Study 1027 both INH- and SC insulin-treated patients with type 1 DM experienced declines in DLco favoring comparator therapy over the course of the 12-week comparative portion of the study. Also consistent with the preceding data, this treatment group difference occurred early in the study and did not progress thereafter.

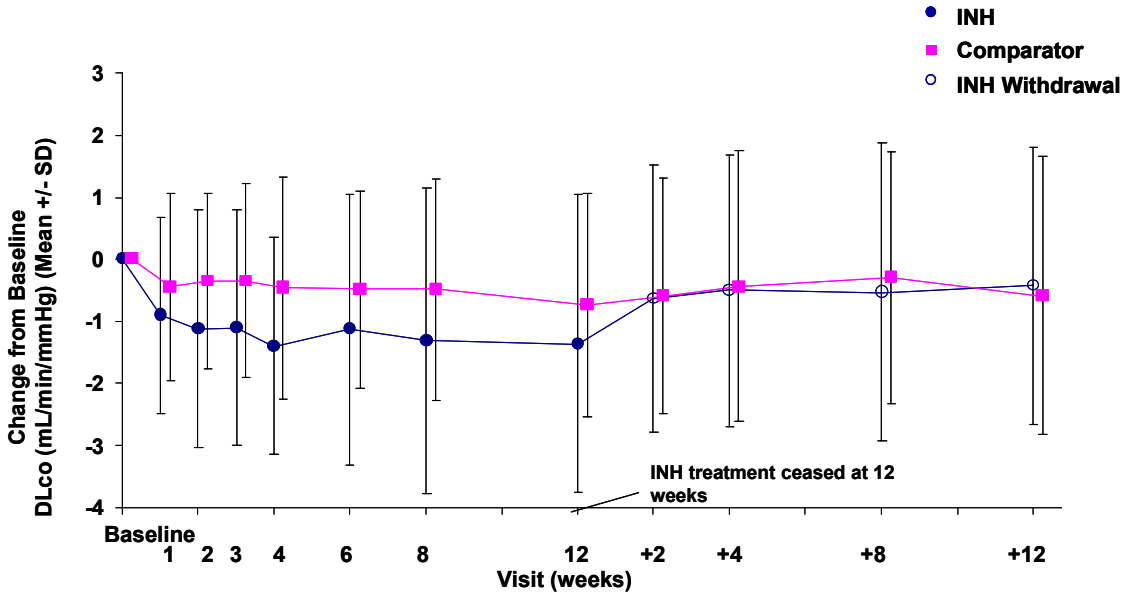
The treatment group difference in mean change from baseline DLco was fully manifest within 2 weeks of treatment initiation and did not change significantly during the remainder of the 12-week comparative phase, supporting the observation, in the Controlled PFT Phase 2/3 Studies, that the effect of INH on DLco is not progressive. The treatment group difference in DLco resolved within 2 weeks after INH cessation in Study 1027. In this study PFT measurements were made during a 12-week follow-up period, after INH therapy had been stopped. By the time of the first DLco measurement during the wash-out period (2 weeks after INH discontinuation), the treatment group difference in DLco had resolved, indicating that the effect of INH on DLco is rapidly reversible upon cessation of INH treatment (Table 101 and Figure 45).

Table 101. Mean Baseline, Change from Baseline, and Adjusted Treatment Group Difference in Change from Baseline in DLco (mL/min/mmHg) by Time in Study 1027 (Full Analysis Set)

	Mean Baseline and Change from Baseline (mL/min/mmHg)		
Time in Study	**INH (N)**	**SC (N)**	**Adjusted Difference* (90% CI)**
Mean baseline	**26.909 (109)**	**27.049 (116)**	
Comparative phase			
1 week	-0.905 (96)	-0.444 (98)	-0.385 (-0.809, 0.039)
2 weeks	-1.122 (97)	-0.349 (102)	-0.740 (-1.159, -0.321)
3 weeks	-1.108 (93)	-0.345 (97)	-0.683 (-1.107, -0.259)
4 weeks	-1.400 (103)	-0.461 (100)	-0.898 (-1.317, -0.479)
6 weeks	-1.134 (92)	-0.487 (101)	-0.652 (-1.083, -0.221)
8 weeks	-1.317 (99)	-0.490 (102)	-0.768 (-1.193, -0.344)
12 weeks	-1.359 (95)	-0.740 (97)	-0.597 (-1.033, -0.162)
Follow-up phase†			
2 weeks	-0.626 (90)	-0.592 (92)	-0.043 (-0.559, 0.473)
4 weeks	-0.506 (87)	-0.440 (96)	-0.052 (-0.566, 0.463)
8 weeks	-0.529 (91)	-0.301 (92)	-0.149 (-0.665, 0.367)
12 weeks	-0.426 (85)	-0.585 (93)	0.204 (-0.321, 0.729)

*A negative value indicates a lesser increase or a greater decrease in the INH than comparator group.
†All patients received subcutaneous insulin as the only short-acting insulin during the follow-up phase.
N=number of patients, INH=Inhaled insulin, SC=subcutaneous short-acting insulin, CI=confidence interval; 90% confidence intervals are presented, as specified by the protocol.

Figure 45. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time in Study 1027 (Full Analysis Set)



Number of subjects at baseline, 1, 2, 3, 4, 6, 8, 12 weeks and withdrawal weeks 2, 4, 8 and 12. INH is 109, 96, 97, 93, 103, 92, 99, 95, 90, 87, 91, 85. Comparator is 116, 98, 102, 97, 100, 101, 102, 97, 92, 96, 92, 93.

Controlled Studies 1001 and 1002

Also consistent with the larger Controlled PFT Phase 2/3 protocol set, in Studies 1001 and 1002 combined, the cohort of patients with type 2 DM completing 104 weeks of INH or comparator therapy experienced declines in DLco at the first post-baseline measurement at 6 months favoring comparator therapy. The treatment group difference in change from baseline DLco appeared to diminish with ongoing exposure, with the difference slightly favoring the INH group after 104 weeks of exposure, further supporting the evidence that the effect of INH on DLco is not progressive (Table 102; Figure 46). Similar trends in DLco over time and after INH discontinuation were seen when all patients, rather than the 104-week cohort, were evaluated.

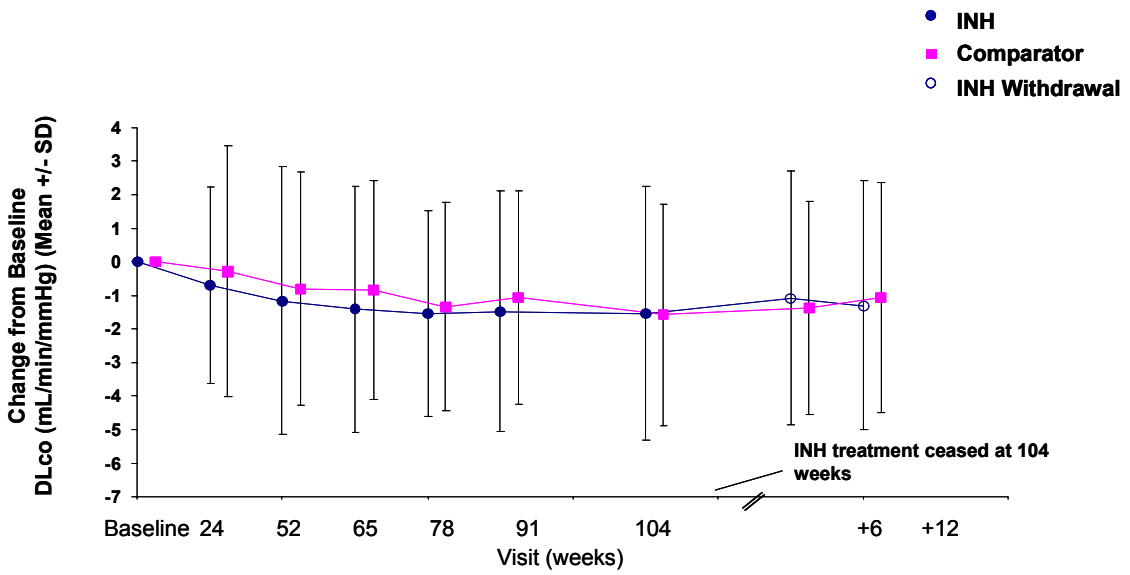
Treatment group differences in DLco resolved after INH cessation in Studies 1001 and 1002. In these studies, PFT measurements were made during a 12-week follow-up period, after INH therapy had ceased. By the time of the first DLco measurement during the wash-out period (6 weeks after INH discontinuation), the treatment group difference in DLco had diminished, indicating that the effect of INH on DLco is reversible, even after long-term exposure (Table 102; Figure 46).

Table 102. Mean Baseline, Change from Baseline, and Adjusted Treatment Group Difference in Change from Baseline DLco (mL/min/mmHg) by Time in Studies 1001 and 1002: 104-Week Cohort

	Mean Baseline and Change from Baseline (mL/min/mmHg)		
Time in Study	**INH (N)**	**Oral Agents (N)**	**Adjusted Difference* (95% CI)**
Mean baseline	25.613 (150)	25.528 (143)	
Comparative phase			
24 weeks	-0.688 (142)	-0.281 (139)	-0.275 (-1.002, 0.452)
52 weeks	-1.172 (141)	-0.808 (138)	-0.260 (-1.030, 0.510)
65 weeks	-1.407 (128)	-0.843 (121)	-0.419 (-1.181, 0.343)
78 weeks	-1.548 (129)	-1.338 (119)	-0.082 (-0.769, 0.605)
91 weeks	-1.478 (135)	-1.063 (126)	-0.267 (-0.989, 0.455)
104 weeks	-1.529 (129)	-1.583 (116)	0.112 (-0.655, 0.880)
Follow-up phase†			
6 weeks	-1.096 (123)	-1.368 (119)	0.279 (-0.473, 1.030)
12 weeks	-1.304 (104)	-1.072 (111)	-0.084 (-0.888, 0.721)

*A negative value indicates a lesser increase or a greater decrease in the INH than comparator group.
†All patients received subcutaneous insulin as the only short-acting insulin during the follow-up phase.
N=number of patients, INH=Inhaled insulin, CI=confidence interval.

Figure 46. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time in Studies 1001 and 1002: 104-Week Cohort



Number of subjects at baseline, 24, 52, 65, 78, 91, 104 weeks and withdrawal weeks 6 and 12. INH is 150, 142, 141, 128, 129, 135, 129, 123, and 104. Comparator is 143, 139, 138, 121, 119, 126, 116, 119, and 111.

Extension Studies 102E/1036, 103E/1036, and 104E/1036

DLco values are available for adult type 1 and type 2 patients receiving up to 84 months of continuous INH therapy in ongoing Phase 2 extension studies 102E/1036, 103E/1036, and 104E/1036. In addition, DLco was measured in a small cohort of patients (N=21) receiving comparator therapy for 24 months in these studies. In the Phase 2 extension studies, DLco among INH-treated patients declined slightly and rapidly between baseline and the first post-baseline measurement at 6 months, and then declined more slowly and consistently thereafter (Figure 47 and Figure 48). After the initial decline at 6 months, the INH and comparator treatment groups changed at similar rates in the 24-month cohort (Table 103 and Figure 47). This is consistent with the data presented from the Controlled PFT Phase 2/3 protocol set and Studies 1001, 1002, and 1027, which show a small but non-progressive treatment group difference in change from baseline in DLco associated with INH use.

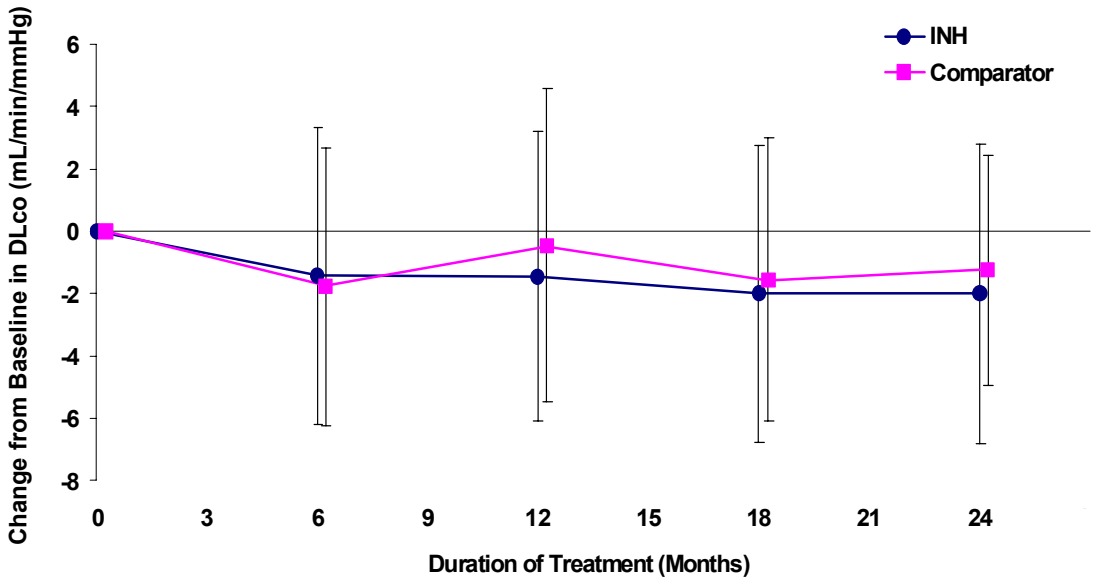
The adjusted mean (95% confidence interval) difference in annualized rate of DLco change between INH and comparator patients treated for at least 24 months was –0.252 (–1.162, 0.657) mL/min/mmHg/year. Because the decrease in DLco was greater during the first 6 months of treatment than nearly any interval thereafter, the calculated annualized rates of change in DLco are the products of initial, relatively rapid, but small, decreases in DLco followed by prolonged slower decreases. The prolonged decreases in DLco were similar between treatment groups and are expected sequelae of aging and DM (Table 103; Figure 47 and Figure 48).

Table 103. Mean Baseline, Mean Change from Baseline, and Annualized Rate of Change in DLco (mL/min/mmHg) by Time in Studies 102E/1036, 103E/1036, and 104E/1036

Time in Study (N)	Mean Baseline (mL/min/mmHg)	Mean Change from Baseline (mL/min/mmHg)	Adjusted Annualized Rate of Change (mL/min/mmHg/year)
24-month cohort			
INH (113)	26.438	-2.012	-0.925
Comparator (21)	26.992	-1.240	-0.673
48-month cohort (82)	25.991	-1.827	-0.304
84 months (26)	25.768	-1.014	-0.407
			Adjusted Mean Difference between Slopes (mL/min/mmHg/year) [95% CI]
INH vs. Comparator 24-month cohort			-0.252 (-1.162, 0.657)

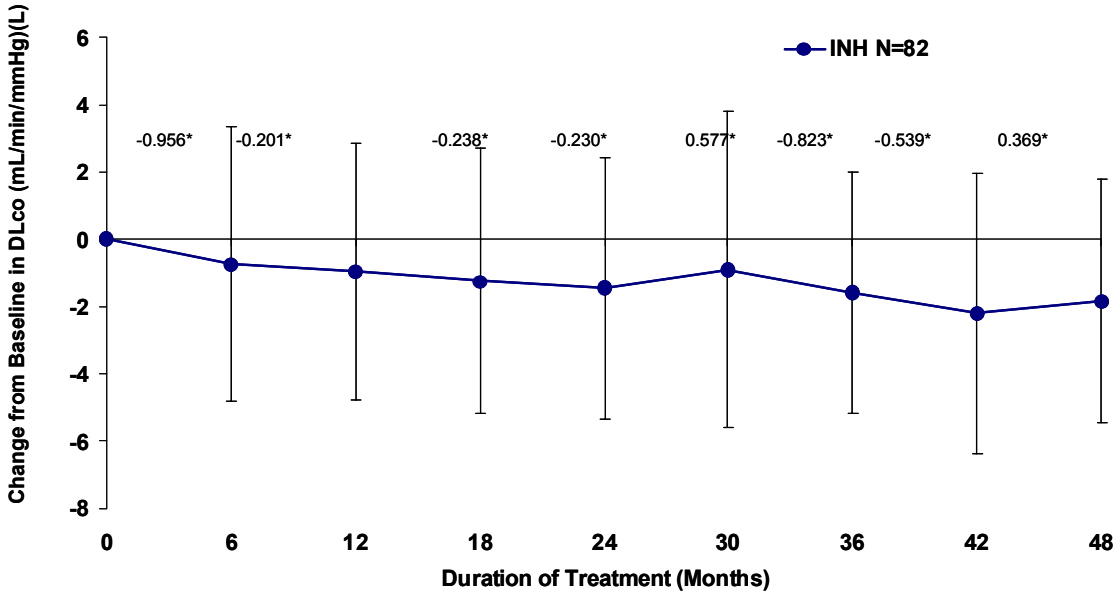
N=number of patients, and INH=inhaled insulin.

Figure 47. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time in Studies 102E, 103E, and 104E: 24-Month Cohort



Number of subjects at baseline, 6, 12, 18 and 24 months, INH is 113, 110, 108, 107, and 113. Comparator is 21, 21, 20, 18, and 21.

Figure 48. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time in Studies 102E, 103E, and 104E: 48-Month Cohort



* Adjusted difference in change from baseline between consecutive time points

Extension Study 111

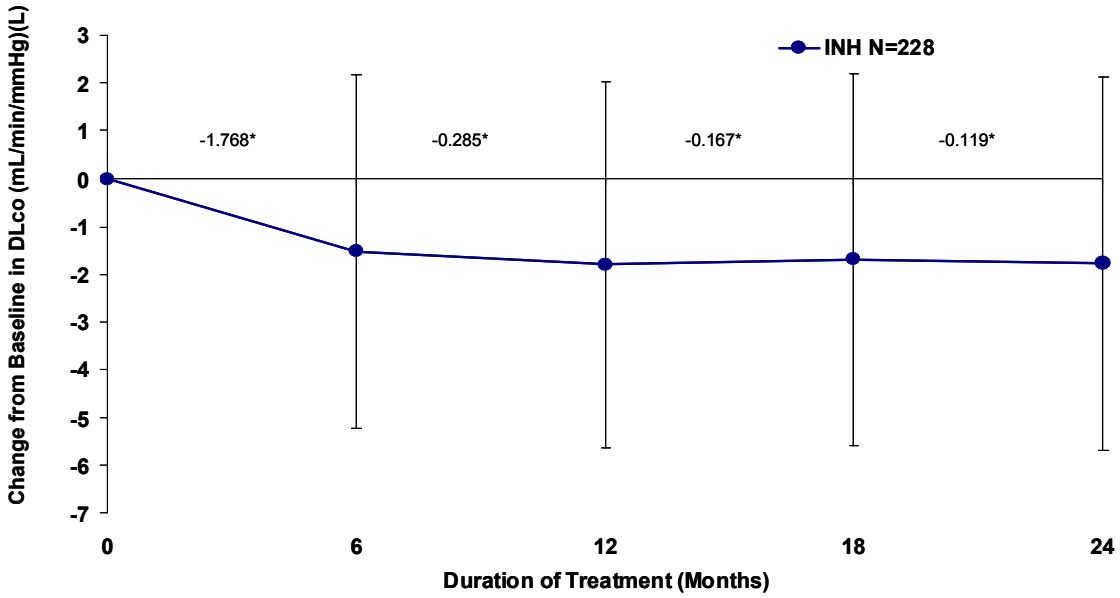
In Study 111, data were analyzed separately based on DM type. Among adult patients with type 1 DM, DLco decreased between baseline and month 24 at annualized rates similar to those observed in Studies 102E/1036, 103E/1036, and 104E/1036, in which data from patients with type 1 or type 2 DM were analyzed together (Table 104; Figure 49 and Figure 50). Consistent with the data presented previously, in Study 111 the decrease in DLco among adult patients with type 1 or type 2 DM was greater during the first 6 months of treatment than during any 6-month period thereafter (Figure 49 and Figure 50). Therefore, the calculated annualized rates of change in DLco displayed below are the product of an initial, relatively rapid, but small, decrease in DLco, followed by a prolonged slower decrease similar in magnitude to that observed for comparator-treated patients in extension Studies 102E/1036, 103E/1036, and 104E/1036. The prolonged decreases in DLco are expected sequelae of aging and DM. Similar trends in DLco over time were seen when all patients, rather than the 24-month cohort, were evaluated.

Table 104. Mean Baseline, Change from Baseline, and Annualized Rate of Change in DLco (mL/min/mmHg) at 24 Months in Study 111: 24-Month Cohort

Patient Group (N)	Mean Baseline (mL/min/mmHg)	Mean Change from Baseline (mL/min/mmHg)	Adjusted Annualized Rate of Change (95% CI) [mL/min/mmHg/yr]
Type 1 ≥ 18 years old (228)	27.940	-1.782	-0.584 [-0.785, -0.383]
Type 2 (370)	25.008	-1.724	-0.634 [-0.816, -0.452]

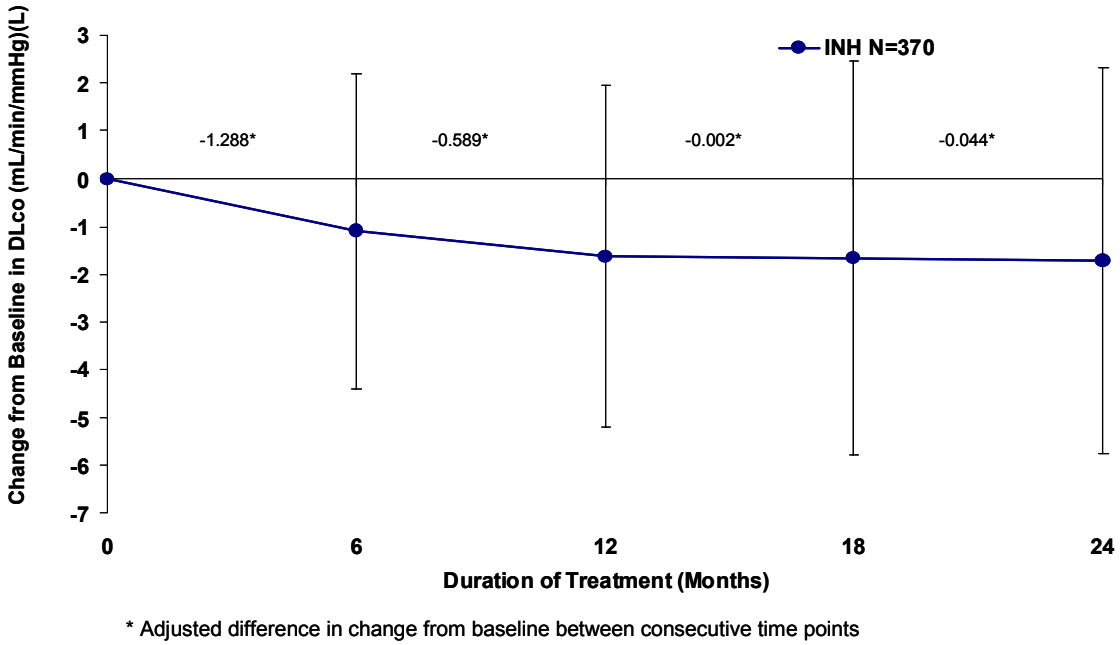
N=number of patients, and CI=confidence interval.

Figure 49. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time in Study 111 and Controlled Parent Studies: Adult Type 1 Patients - 24-Month Cohort



* Adjusted difference in change from baseline between consecutive time points

Figure 50. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time in Study 111 and Controlled Parent Studies: Adult Type 2 Patients - 24-Month Cohort



* Adjusted difference in change from baseline between consecutive time points

Planned discontinuation of INH treatment for 6 months in Study 111 resulted in a sustained increase in DLco by 1 month post-discontinuation among patients with type 1 DM, and an increase at 1 and 3 months post-discontinuation among patients with type 2 DM (Table 105; Figure 51, and Figure 52). Discontinuation of INH treatment was associated with a slight shift of the overall distribution of DLco change toward higher positive values, a reversal of the treatment-related distribution pattern associated with the initiation of therapy (Figure 53).

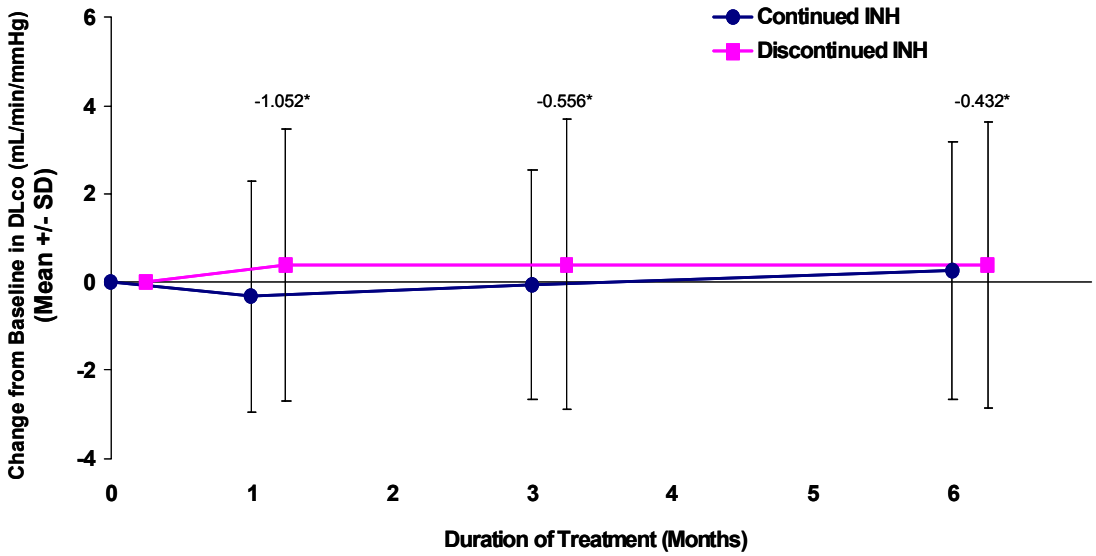
The treatment effect of INH on DLco that occurs in the first 3-6 months of INH treatment, therefore, is reversible, resolving within 1 month of discontinuation of long-term therapy.

Table 105. Mean Baseline, Mean Change from Baseline, and Adjusted Treatment Group Difference in Change from Baseline in DLco (mL/min/mmHg) Among Adults in the Discontinuation Phase of Study 111 (Primary Analysis Set*)

	Mean Baseline and Mean Change from Baseline**(mL/min/mmHg)		
Patient Group Time in Study	Continued INH (N)	Discontinued INH (N)	Adjusted Difference† (90% CI)
Type 1 DM			
Mean baseline	26.494 (115)	26.821 (120)	
1 month	-0.347 (103)	0.389 (114)	-1.052 (-1.664, -0.439)
3 months	-0.079 (113)	0.386 (117)	-0.556 (-1.155, 0.043)
6 months	0.254 (107)	0.383 (113)	-0.432 (-1.044, 0.181)
Type 2 DM			
Mean baseline	22.855 (192)	23.497 (200)	
1 month	-0.267 (185)	0.279 (197)	-0.684 (-1.143, -0.225)
3 months	-0.214 (189)	0.613 (195)	-0.939 (-1.397, -0.481)
6 months	0.208 (184)	-0.048 (190)	0.104 (-0.360, 0.569)

*Primary Analysis Set consist of patients who had at least 1 baseline PFT measurement, two post-baseline FEV1 measurements, and received study drug for at least 50% of the duration of the comparative phase.
**Baseline for the discontinuation phase of Study 111 was the last value prior to or within 7 days after initiating randomized treatment.
†A negative value indicates a greater increase or lesser decrease in the group that discontinued than continued INH treatment.
INH=inhaled insulin, and CI=confidence interval.

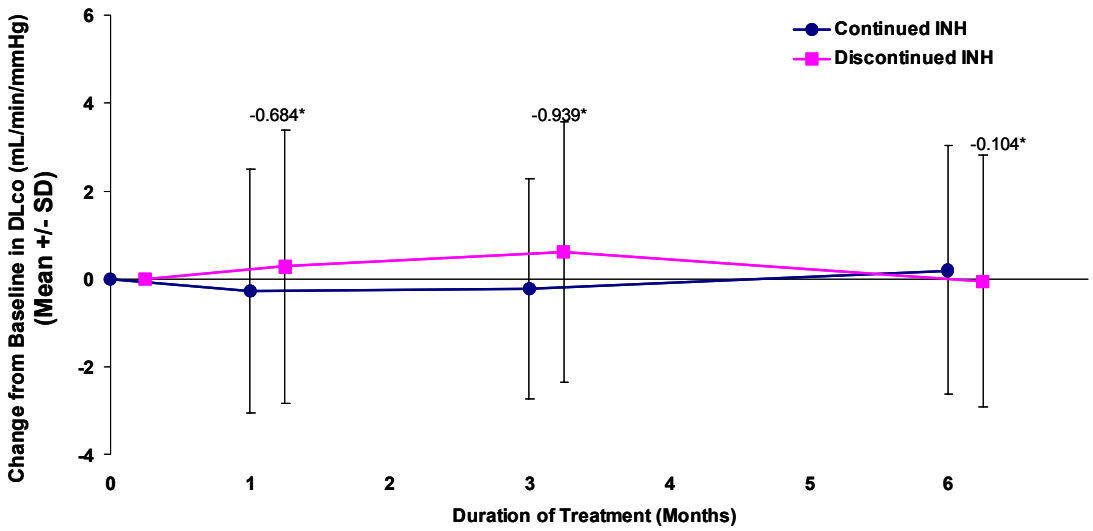
Figure 51. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time in the Discontinuation Phase of Study 111: Adult Type 1 Patients (Primary Analysis Set)



Number of subjects at baseline, 1, 3, and 6 months, Continued INH is 115, 103, 113, and 107. Discontinued INH is 120, 114, 117, and 113.

* Adjusted difference between treatment groups (Continue-Discontinue Inhaled Insulin) in change from baseline at each time point

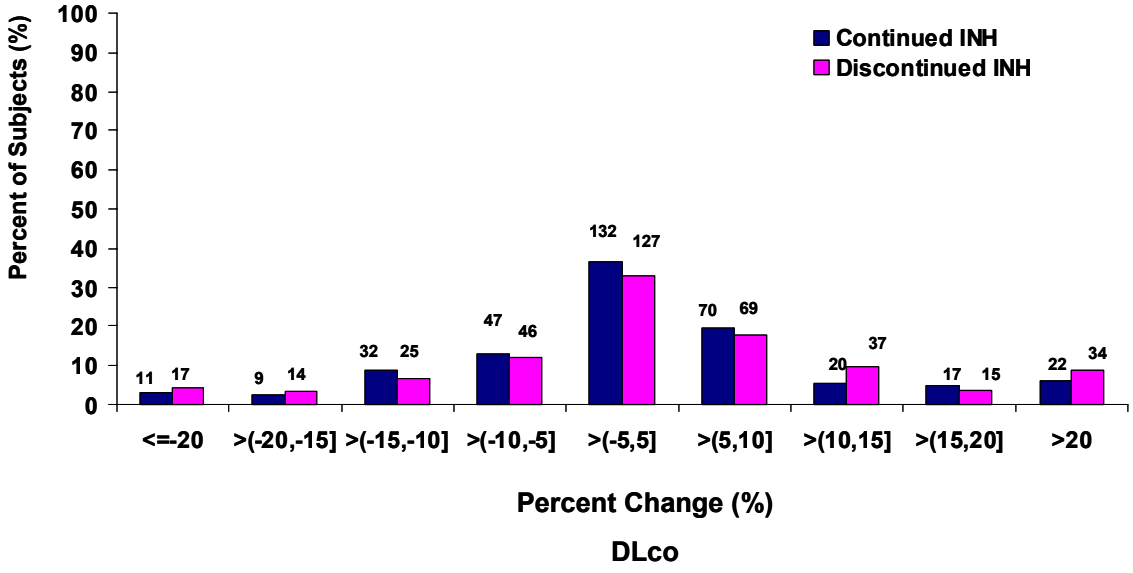
Figure 52. Mean Change from Baseline and Standard Deviation in DLco (mL/min/mmHg) by Time in the Discontinuation Phase of Study 111: Adult Type 2 Patients (Primary Analysis Set)



Number of subjects at baseline, 1, 3, and 6 months, Continued INH is 192, 185, 189, and 184. Discontinued INH is 200, 197, 195, and 190.

* Adjusted difference between treatment groups (Continue-Discontinue Inhaled Insulin) in change from baseline at each time point

Figure 53. Percent Change from Baseline to Month 6 (LOCF) in DLco in the Discontinuation Phase of Study 111: Patients with Type 1 or Type 2 DM (Primary Analysis Set)



In summary, DLco declined during treatment among both INH- and comparator-treated patients, with small but consistent treatment group differences favoring comparator. These INH-associated decreases in DLco occurred soon after treatment was initiated, were small and non-progressive, and were reversible upon discontinuation of INH treatment.

6.5.2.9. Efficacy and Safety of INH Use in Adult Patients with Mild to Moderate Underlying Lung Disease

Patients with mild to moderate underlying lung disease (ULD), defined as mild to moderate asthma or COPD, did not experience compromised efficacy or safety while receiving INH.

The evaluation of the integrated ULD cohort demonstrated that INH-treated patients with mild to moderate ULD:

- maintained glycemic control comparable to that of comparator-treated patients,
- required doses of INH on a mg/kg basis comparable to those of INH-treated patients without ULD, suggesting that the presence of mild to moderate asthma or COPD does not significantly alter INH absorption,

- experienced hypoglycemia (defined as blood glucose concentrations ≤ 36 mg/dL and/or requiring assistance) at event rates comparable to those of comparator-treated patients,
- experienced severe or serious respiratory adverse events at incidences comparable to those of comparator-treated patients,
- had respiratory medication requirements similar to those of comparator-treated patients,
- developed insulin antibodies at levels comparable to those of INH-treated patients without ULD, and
- experienced INH-associated decreases in FEV_1 and DLco that were small and nonprogressive, similar to those observed in patients without ULD.

6.5.2.10. Patients With Notable Declines in Pulmonary Function Test Results

Characteristics of the Study Populations

The group of patients with the greatest declines in pulmonary function test results was evaluated separately in order to explore potential predictors of notable PFT declines and potential safety signals among patients with such declines. A 'notable' PFT decline was defined as a decline from baseline to last observation of ≥ 15% in FEV_1, TLC, or FVC, and/or ≥ 20% in DLco in Controlled PFT Phase 2/3 studies (as of 25 June 2004).

Notable PFT declines were more common among INH-treated than comparator-treated patients. This is not unexpected given the demonstrated shift in the distribution curves in change from baseline FEV_1 and DLco toward lower values in the INH than comparator groups (Section 6.5.2.8). In addition, notable PFT declines were more common among patients with type 2 than type 1 DM in both treatment groups. The majority of patients in all treatment groups in Controlled PFT Phase 2/3 studies did not have notable declines in PFT results (Table 106).

Table 106. Adult Patients With or Without Notable* PFT Declines: Controlled PFT Phase 2/3 Studies

	Number (%) of Patients [N]			
	With Notable PFT Decline		Without Notable PFT Decline	
	INH	Comp	INH	Comp
Type 1	51 (7.3) [698]	34 (4.8) [705]	612 (87.7) [698]	627 (88.9) [705]
Type 2	167 (13.1) [1277]	120 (10.6) [1132]	1007 (78.9) [1277]	885 (78.2) [1132]
All Patients	218 (11.0) [1975]	154 (8.4) [1837]	1619 (82.0) [1975]	1512 (82.3) [1837]

*Notable declines are defined as declines from baseline to last observation of ≥ 15% in FEV1, TLC, or FVC, and/or ≥ 20% in DLco.
PFT=pulmonary function test, N=number of patients evaluable, INH=inhaled insulin, and Comp=comparator.
In addition to the patients categorized above, 138 and 171 INH- or comparator-treated patients, respectively, were missing PFT values at last observation and were, therefore, categorized 'indeterminate' with respect to PFT declines.

The incidences of notable declines in the 4 evaluated PFT parameters are presented in (Table 107).

Table 107. Adult Patients with Notable* Declines in FEV_1, DLco, TLC, or FVC: Controlled PFT Phase 2/3 Studies

	Number (%) of Patients [N]							
	FEV_1		DLco		TLC		FVC	
	INH	Comp	INH	Comp	INH	Comp	INH	Comp
Type 1	9 (1.3) [698]	7 (1.0) [705]	26 (3.7) [698]	19 (2.7) [705]	18 (2.6) [698]	12 (1.7) [705]	8 (1.1) [698]	6 (0.9) [705]
Type 2	64 (5.0) [1277]	38 (3.4) [1132]	71 (5.6) [1277]	42 (3.7) [1132]	48 (3.8) [1277]	46 (4.1) [1132]	45 (3.5) [1277]	33 (2.9) [1132]
All Patients	73 (3.7) [1975]	45 (2.4) [1837]	97 (4.9) [1975]	61 (3.3) [1837]	66 (3.3) [1975]	58 (3.2) [1837]	53 (2.7) [1975]	39 (2.1) [1837]

*Notable declines are defined as declines from baseline to last observation of ≥ 15% in FEV1, TLC, or FVC, and/or ≥ 20% in DLco.
N=number of patients, FEV1=forced expiratory volume in 1 second, DLco=carbon monoxide diffusion capacity, TLC=total lung capacity, and FVC=forced vital capacity.

The distributions of diabetes types within each PFT decline category were comparable between treatment groups. However, there were differences between PFT decline categories, with type 2 patients over-represented among patients with notable PFT declines in both the INH and comparator treatment groups (Table 108).

Table 108. Adult Patients With and Without Notable* PFT Declines by Type of Diabetes: Controlled PFT Phase 2/3 Studies

PFT Decline Status/ Diabetes Type	Number (%) of Patients		
	INH	Comparator	All Patients
With notable decline	N=218	N=154	N=372
Type 1	51 (23.4)	34 (22.1)	85 (22.8)
Type 2	167 (76.6)	120 (77.9)	287 (77.2)
Without notable decline	N=1619	N=1512	N=3131
Type 1	612 (37.8)	627 (41.5)	1239 (39.6)
Type 2	1007 (62.2)	885 (58.5)	1892 (60.4)

*Notable declines are defined as declines from baseline to last observation of ≥ 15% in FEV_1, TLC, or FVC, and/or ≥ 20% in DLco.
PFT=pulmonary function test, INH=inhaled insulin, and N=number of patients evaluable.

Patients with notable PFT declines were slightly older than were those without notable declines, consistent with the greater proportion of type 2 patients in the group with notable PFT declines. The remaining demographic characteristics were comparable between patients who did or did not experience notable PFT declines and between treatment groups (Table 109).

Table 109. Demographic Characteristics of Adult Patients With and Without Notable* PFT Declines: Controlled PFT Phase 2/3 Studies

	With Notable Decline		Without Notable Decline	
	INH N=218	COMP N=154	INH N=1619	COMP N=1512
Mean age (yr)	54.2	52.1	49.6	48.4
Gender (%male/%female)	(59/41)	(49/51)	(60/40)	(58/42)
Mean body weight (kg)	85.5	83.8	83.0	82.2
Mean BMI (kg/m^2)	29.4	29.7	28.3	28.2

*Notable declines are defined as declines from baseline to last observation of ≥ 15% in FEV1, TLC, or FVC, and/or ≥ 20% in DLco.
PFT=pulmonary function test, INH=inhaled insulin, COMP=comparator, N=number of patients evaluable, and BMI=body mass index.

The mean durations of exposure to study drug were comparable between the INH and comparator groups for each PFT decline category, at 9.7 and 10.1 months for patients with a notable PFT decline, and 8.5 and 9.0 months for patients without a notable PFT decline.

The distribution of baseline percent predicted FEV_1 and DLco values differed between patients with or without notable PFT declines in both treatment groups. Baseline FEV_1 or DLco values of > 120% of predicted were more common among patients with than without notable PFT declines. A similar differential in incidence was not apparent when values ≤ 80% of predicted were compared.

Study design appears to have contributed to apparent incidence of notable PFT declines. In the early Phase 2/3 studies (Studies 102, 103, 104, 106, 107, 108, 109, 110, 1001, and 1002), baseline values for PFT parameters were based on a single measurement, and patients were permitted to be re-tested if they failed to meet PFT-associated inclusion criteria during the first testing session. The screening PFT values were considered the baseline values for the study.

In contrast, in the more recent Phase 3 studies (Studies 1022, 1026, 1027, and 1029) PFTs for screening were performed separately from those which established baseline values, and patients were not allowed to re-attempt to qualify for a study if they failed to meet PFT-associated inclusion criteria. In addition, baseline PFT values were calculated as the mean of 2-3 separate tests, and testing methodology was standardized across sites.

In the early Phase 2/3 studies, 14.9% (41/275) and 10.5% (29/277) of INH- and comparator-treated type 1 patients, respectively, experienced notable PFT declines compared with 2.4% (10/423) and 1.2% (5/428) of type 1 patients in the more recent Phase 3 studies. Similarly, 15.7% (151/963) and 13.4% (110/821) of INH- and comparator-treated type 2 patients, respectively, experienced notable PFT declines in the early Phase 2/3 studies compared with 5.1% (16/314) and 3.2% (10/311) of INH- and comparator-treated patients, respectively, in the more recent Phase 3 studies. Only a small portion of patients with notable PFT declines remains when more rigorous criteria and testing methods were used to establish baseline.

In summary, patients with notable PFT declines in Controlled Phase 2/3 PFT studies were more likely than those without notable declines to have type 2 DM and were noticeably more likely to have high baseline FEV_1 or DLco values (> 120% of predicted) and to have participated in studies with designs allowing baseline to be defined by single PFT values or that permitted patients to be retested if they failed to meet PFT-associated incusion criteria during the first testing session.

Efficacy of INH Among Patients With Notable Declines in Pulmonary Function Test Results

There is no indication that the efficacy of INH is different between patients with and without notable PFT declines and mean daily doses of INH per kg body weight required to maintain glycemic control were comparable between PFT decline categories. There is no indication from these results to suggest that patients experiencing notable PFT declines required or were exposed to higher INH doses on a mg/kg basis compared with patients without notable PFT declines.

Safety of INH in Patients With Notable Declines in Pulmonary Function Test Results

Patients with notable PFT declines experienced respiratory adverse events at similar incidence compared to those without notable PFT declines (Table 110).

Table 110. Summary of All-Causality and Treatment-Related Adverse Events and Respiratory Adverse Events Among Adult Patients With and Without Notable* PFT Declines: Controlled PFT Phase 2/3 Studies

	Number (%) of Patients			
	With Notable Decline		Without Notable Decline	
	INH N=218	COMP N=154	INH N=1619	COMP N=1512
All Events				
All causality				
Patients with AEs	202 (92.7)	142 (92.2)	1568 (96.8)	1420 (93.9)
Patients with severe AEs	28 (12.8)	19 (12.3)	262 (16.2)	251 (16.6)
Treatment-related				
Patients with AEs	175 (80.3)	99 (64.3)	1382 (85.4)	1181 (78.1)
Patients with severe AEs	14 (6.4)	8 (5.2)	150 (9.3)	150 (9.9)
Respiratory Events†				
All causality				
Patients with AEs	130 (59.6)	86 (55.8)	1028 (63.5)	770 (50.9)
Patients with severe AEs	5 (2.3)	2 (1.3)	20 (1.2)	8 (0.5)
Treatment-related				
Patients with AEs	53 (24.3)	4 (2.6)	357 (22.1)	92 (6.1)
Patients with severe AEs	3 (1.4)	0	7 (0.4)	0

*Notable declines are defined as declines from baseline to last observation of ≥ 15% in FEV_1, TLC, or FVC, and/or ≥ 20% in DLco.
†Respiratory events are adverse events in the Respiratory system organ class according to COSTART.
PFT=pulmonary function test, INH=inhaled insulin, COMP=comparator treatment, N=number of subjects evaluable, and AE=adverse event
Cutoff date: 25 June 2004

The number of respiratory SAEs was low for patients with and without notable PFT declines, and there were no clear differences in respiratory SAE occurrence between PFT decline categories (Table 111).

Table 111. All-Causality Respiratory* Serious Adverse Events Among Patients With and Without Notable† PFT Declines: Adult Patients in Controlled PFT Phase 2/3 Studies

	Number of Patients (Number per 10,000 SME‡)			
	With Notable Decline		Without Notable Decline	
Preferred Term	INH N‡=218 SME=2111	Comparator N=154 SME=1554	INH N=1619 SME=13783	Comparator N=1512 SME=13605
Asthma	1 (4.7)§	0	2 (1.5)§	0
Bronchospasm	0	0	1 (0.7)§	0
Cough	0	0	1 (0.7)§	0
Dyspnea	0	1 (6.4)	1 (0.7)	2 (1.5)
Epistaxis	1 (4.7)	0	0	0
Hypoxia	0	0	0	1 (0.7)
Pneumothorax	0	0	1 (0.7)	1 (0.7)
Respiratory Distress	0	0	0	1 (0.7)
Respiratory Failure	0	0	1 (0.7)	0
Vocal cord polyp	1 (4.7)§	0	0	0

*Events in the Respiratory, Thoracic and Mediastinal Disorders category according to MedDRA.
† Notable declines are defined as declines from baseline to last observation of ≥ 15% in FEV_1, TLC, or FVC, and/or ≥ 20% in DLco.
‡SME=subject-months of exposure. N=number of subjects.
§One of the reported events was treatment-related per investigator
INH=inhaled insulin with or without subcutaneous basal insulin or oral agents.
Cutoff date: 25 June 2004

There were not clear differences in discontinuation rates between PFT decline categories. Overall rates of study discontinuation were similar between treatment groups and between PFT decline categories. The rates of study discontinuation related to study drug and due to treatment-related adverse events were greater among INH- than comparator-treated patients for both PFT decline categories but did not differ between PFT decline categories for INH-treated patients.

6.6. Insulin Antibodies

6.6.1. Pre-Clinical Antibody Observations

Pre-clinical studies with recombinant human insulin administered by inhalation did not reveal pathologic or immunologic issues of concern.

The inhaled insulin pre-clinical toxicology program did not reveal any histological evidence of exposure-related inflammatory or immune-mediated hypersensitivity reactions in the respiratory tract. A weak antibody response to insulin inhalation powder was observed in the rat but not the monkey. The antibody results from the inhalation studies in rats are consistent with the results of a 4-week study in rats involving subcutaneous injection of recombinant human insulin.

The lack of detectable antibodies in monkeys exposed to insulin by inhalation is consistent with results of an intramuscular immunogenicity study conducted with human insulin in monkeys by Zwickl et al.[62] The immunogenicity of insulin lispro (human insulin analog), native human sequence insulin, and purified porcine insulin were compared in Rhesus monkeys over a 6-week period. In this study, the animals received an initial intramuscular immunization of insulin in Complete Freund's adjuvant at a dose of 10 µg/monkey. This was followed by 5 weekly boosts of insulin in Incomplete Freund's adjuvant. Using an enzyme-linked immunosorbent assay (ELISA) to measure insulin-specific IgG antibody in serum, it was determined that none of the insulin preparations stimulated antibody formation. Thus, these data indicate that human insulin is non-immunogenic in monkeys, even when a strong adjuvant is used.[62]

6.6.2. Clinical Antibody Observations

6.6.2.1. Definition of Study Populations

For the purposes of evaluating the magnitude and potential sequelae of insulin antibody formation, protocols were grouped and their data pooled according to similarity of study design, the population under study, and the assay used to quantify insulin antibodies.

Controlled Phase 2/3 Studies

For an assessment of adverse events correlating with antibodies, the Controlled Phase 2/3 Studies based on the cutoff date of 25 June 2004 (the original NDA cut-off date) is referenced (Table 112), unless otherwise noted. The population eligible for safety assessment is composed of all adult patients who were randomized and received at least one dose of study drug.

Table 112. Patient Groupings Within the Controlled Phase 2/3 Protocol Set Used for Adverse Event Evaluation

		N	
Patient Grouping	**Contributing Studies**	**INH**	**COMP**
Type 1 DM			
Type 1 patients ≥ 18 years old	102, 106, 107, 1022, 1026, 1027	698	705
Type 2 DM			
Type 2 patients	103, 104, 108, 109, 110, 1001, 1002, 1029	1277	1132
All patients, type 1 and type 2		1975	1837

N=number of subjects evaluable for adverse events, INH=inhaled insulin, COMP=comparator, DM=diabetes mellitus, Type 1 subjects=subjects with type 1 diabetes, and Type 2 subjects=subjects with type 2 diabetes.

Controlled IAB Phase 2/3 Studies

The Controlled Insulin Antibody (IAB) Phase 2/3 Studies (the primary studies for assessing safety in relation to insulin antibodies) is a subset of the Controlled Phase 2/3 Studies used for general safety evaluation in the Summary of Clinical Safety. Insulin antibodies were not measured in Studies 102 and 103. These studies, therefore, are excluded from the Controlled IAB Phase 2/3 Studies. Antibody data for Studies 1022 and 1029 were truncated at 1 year of exposure, consistent with the 1-year interim analyses. The composition of the Controlled IAB Phase 2/3 Studies is presented in Table 113.

For assessing antibody formation and its potential sequelae in a precise manner, the Controlled IAB Phase 2/3 Studies was sub-divided based on type of DM, previous insulin exposure (for type 2 patients), and method of insulin antibody measurement, as described in Section 6.6.2.2. In this document, adults (patients ≥ 18 years old) will be emphasized, consistent with the population for which approval is being sought. However, in the description of antibody levels by patient age, pediatric patients (patients < 18 years old) will be included. The groupings of patients used, and the contributing studies, are presented in Table 113.

Patients with type 1 DM evaluated using the Esoterix assay are from studies with 3-, 6-, and 12-month comparative treatment phases (Studies 1027, 1026, and 1022, respectively). In order to present data from all 3 studies and to present data according to consistent exposure durations, 3- and 6- month data are provided as pooled data in in-text tables. In addition, full longitudinal 24-month data are provided for Study 1022 individually. Because of the differing durations of treatment among these 3 studies, only Study 1022 is used for evaluating antibody concentrations across demographic categories.

Similarly, patients with type 2 DM evaluated using the Esoterix assay are from studies with 1- and 2-years of completed comparative treatment (Studies 1029 and pooled Studies 1001 and 1002, respectively). When data from these studies are presented together, only 1-year data will be provided as in-text tables. In addition, 1- and 2-year longitudinal data will be presented for Study 1029 and pooled Studies 1001 and 1002, respectively.

Table 113. Patient Groupings Within the Controlled IAB Phase 2/3 Protocol Set

		N	
Patient Grouping	**Contributing Studies**	**INH**	**COMP**
Mayo Assay*			
Type 1 DM			
Type 1 patients ≥ 18 years old	106, 107	215	203
Type 1 patients < 18 years old	106, 107, 1009	138	138
Type 2 DM			
Type 2 patients insulin-using at study entry	108	134	133
Type 2 patients non-insulin-using at study entry	104, 109, 110	290	181
Esoterix Assay*			
Type 1 DM			
Type 1 patients ≥ 18 years old	1022, 1026, 1027	415†	420†
Type 2 DM			
Type 2 patients insulin-using at study entry	1029	276 (203)‡	281 (212)‡
Type 2 patients non-insulin-using at study entry	1001, 1002	430 (148)§	385 (141)§

*The Mayo and Esoterix assays for insulin antibodies are described in Section 6.6.2.2.
†Number of subjects at baseline.
‡Number of subjects treated for 6 months (1 year)
§Number of subjects treated for 6 months (2 years)
N=number of subjects, INH=inhaled insulin, COMP=comparator, DM=diabetes mellitus.

Other Controlled Studies

In addition to the pooled Controlled IAB Phase 2/3 protocol set, individual controlled Studies 1026, 1027, 1001, 1002, 1022, and 1029 contribute to the antibody assessment.

Extension Studies

The Phase 2 and Phase 3 extension studies in the INH clinical development program provide uncontrolled, longitudinal data on the effects of prolonged INH exposure on insulin antibody formation. Altogether, more than 700 adult patients were evaluable for antibody formation after at least 24 months of INH exposure in the Phase 2 and Phase 3 extension studies combined.

6.6.2.2. Insulin Antibody Measurement Methodology

Increases in insulin antibody levels associated with INH treatment were first observed in Phase 3 Studies 106, 107, 108, 109, 110, and 1009, all performed in North America. A semi-quantitative radioligand binding (RLB) assay (the Mayo Assay) performed at Mayo Medical Laboratories (Rochester, MN) was used to measure insulin antibodies at baseline and at study completion in each of these early studies. The Mayo assay also was used for routine measurement of antibodies in Studies 102E/1036, 103E/1036, 104E/1036, and 111. Results from the Mayo assay are expressed as "% binding". The lower limit of quantitation for this assay is 3% binding.

Because the Mayo assay is limited with respect to quantifying the highest levels of insulin antibodies, a quantitative RLB assay for insulin antibodies was developed and validated extensively in collaboration with Esoterix, Inc. (Calabasas Hills, CA).[63] This tube-based Esoterix (ES) assay determines

antibody-binding capacity in units of μU of insulin bound per mL of serum. More recently, a filter plate version of the ES assay was developed and validated in order to increase sample throughput and to decrease sample volume requirements. This assay modification was validated and compared to the previous tube version. The linear region of each ES assay version has been determined, and those samples with insulin concentrations above the linear region are diluted and re-tested. In addition, the lower limit of quantitation and the assay precision have been determined, and positive and negative controls are included in each analytical run for quality control. Because of its defined performance characteristics, the ES assay was chosen for the measurement of insulin antibodies in Phase 3 studies. The tube-based version was used for Studies 1001 and1002, and the filter-plate version was used for Studies 1026, 1027, 1022, and 1029. In order to identify samples with the highest insulin antibody levels from studies in which the Mayo assay was used, all available samples with >60% binding were re-tested using the ES assay. A clinical summary of patients with the highest identified insulin antibody levels (patients identified by retesting Mayo samples as well as those with >2,000 μU/mL on at least one occasion from studies using the Esoterix assay) is discussed in Section 6.6.3.8.

6.6.2.3. Insulin Antibody Data in Patients with Type 1 DM

INH-treated patients with type 1 DM experienced greater end-of-study and change-from-baseline insulin antibody levels than did SC insulin-treated patients. Predisposing factors to developing higher antibody levels associated with INH treatment appear to have been young age (< 18 years old) and female gender for patients with type 1 DM.

With long-term exposure to INH, mean and median insulin antibody levels reached a plateau at approximately 6-12 months of exposure. When INH therapy was discontinued, there were declines in mean and median insulin antibody levels evident within 4 weeks among patients with type 1 DM.

Controlled IAB Phase 2/3 Studies

Patients with type 1 DM who switched from SC short-acting insulin to INH at the beginning of a Controlled IAB Phase 2/3 study experienced an increase in mean and median insulin antibody levels by 3 and 6 months of treatment when evaluated using either the Mayo or Esoterix assay. Control patients who were maintained on their prior regimen consisting exclusively of SC insulin did not experience a similar increase (Table 114). No data are available comparing insulin antibody development upon initiating INH versus SC insulin in patients with new-onset type 1 DM.

Table 114. Mean and Median Insulin Antibody Levels at Baseline and 3 or 6 Months of Treatment by Method of Evaluation: Adult Type 1 Patients in Controlled IAB Phase 2/3 Studies

Mayo Assay (Studies 106 and 107)				
	Serum Antibody Level (% Binding)* (N) [SD]			
	Mean		**Median**	
Time Point	**INH**	**SC**	**INH**	**SC**
Baseline	5.7 (215) [9.8]	6.1 (203) [10.3]	1.5	1.5
End of study (6 months)	27.7 (215) [20.7]	7.1 (203) [11.8]	25.0	1.5
Change from baseline	22.0 (215) [17.9]	1.0 (203) [5.3]	20.5	0.0

Esoterix Assay (Studies 1022, 1026, and 1027)				
	Serum Antibody Level (µU/mL)† (N) [SD]			
	Mean		**Median**	
	INH	**SC**	**INH**	**SC**
Baseline	28.3 (415) [187.7]	20.9 (420) [80.5]	3.6	3.5
3 months	121.7 (393) [300.1]	21.3 (397) [71.6]	31.0	3.6
Change from baseline	102.1 (386) [285.4]	-0.19 (389) [28.7]	25.0	0.0
6 months	179.9 (283) [239.1]	24.5 (290) [91.9]	83.0	4.4
Change from baseline	160.6 (278) [224.3]	1.18 (286) [20.78]	72.5	0.0

*Values less than the limit of quantitation (3.0 % binding) were imputed as 1.5% binding.
†Values less than the limit of quantitation (2.1µU/mL) were imputed as 1.05 µU/mL.
N=number of subjects evaluated for antibody levels at each time point, SD=standard deviation, INH=inhaled insulin, and SC=subcutaneous short-acting insulin.
Additional summary statistics (25th and 75th percentiles, minimum and maximum values) are presented in the source tables.

Pediatric patients with type 1 DM appeared to have had greater antibody levels at baseline and after treatment with INH than did adult patients with type 1 DM. There were no apparent differences in antibody levels between adult patients 18-44 or 45-64 years of age.

Adult females with type 1 DM appear to have had a greater increase in insulin antibody levels in response to INH than did adult males with type 1 DM. Adult females treated with INH had numerically higher change from baseline mean and median antibody levels at end of study in Studies 106 and 107 and at 12 months in Study 1022 than did adult males treated with INH, despite having similar antibody levels at baseline.

White and Hispanic patients appear to have experienced greater increases in insulin antibody levels than did black patients. This relationship was suggested at the end of 6-month Studies 106 and 107 and at 12 months in Study 1022. The numbers of patients in non-white race categories, however, preclude a thorough assessment of antibody levels by race.

Short-Term Controlled Studies 1026 and 1027

Studies 1026 and 1027 provide short-term longitudinal data on insulin antibody formation among patients with type 1 DM. These data show that changes in serum antibody levels begin to occur early in the course of INH treatment and that discontinuation of INH treatment results in decreases in serum antibody levels. The validated Esoterix assay was used for insulin antibody measurement in these studies.

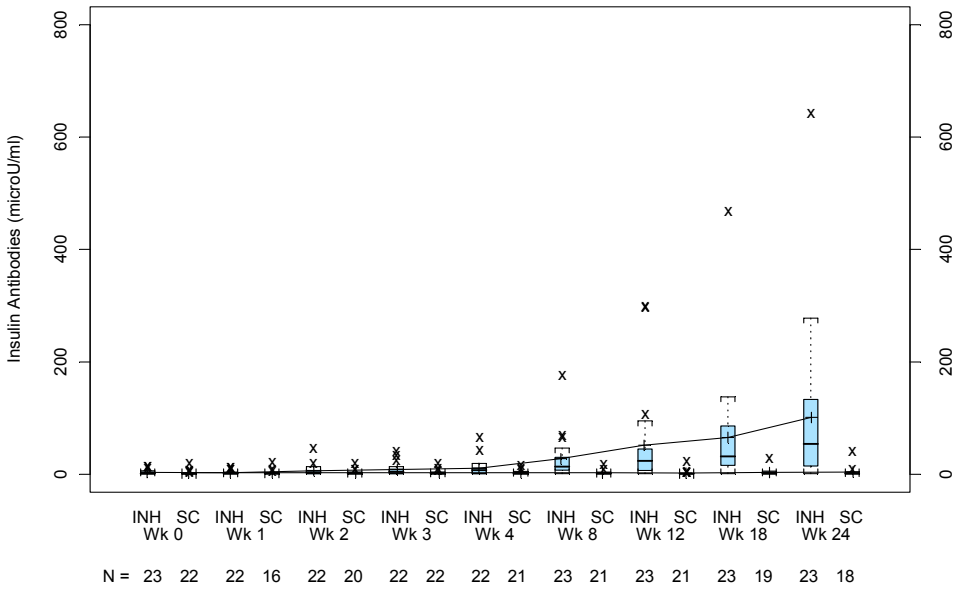
Patients exposed to INH in Study 1026 experienced an increase in serum insulin antibody levels apparent by week 2 of treatment, and insulin antibody levels continued to increase through 24 weeks of exposure. A similar increase did not occur among patients treated with SC insulin (Table 115; Figure 54).

Table 115. Mean and Median Change from Baseline in Insulin Antibody Levels by Time: Study 1026

	Baseline and Change from Baseline Serum Antibody Level (µU/mL)* (N) [SD]			
	Mean		Median	
Time Point	INH	SC	INH	SC
Baseline values	3.5 (23) [3.9]	2.6 (22) [4.1]	1.1	1.1
Change from baseline				
Week 1	-0.1 (22) [1.5]	0.5 (16) [0.8]	0.0	0.0
Week 2	2.8 (22) [8.7]	0.3 (20) [0.7]	0.0	0.0
Week 3	5.0 (22) [9.3]	0.5 (22) [0.9]	0.5	0.0
Week 4	7.2 (22) [13.6]	0.4 (21) [1.3]	2.5	0.0
Week 8	24.2 (23) [37.3]	0.3 (21) [1.3]	13.0	0.0
Week 12	48.3 (23) [82.6]	0.1 (21) [1.3]	20.3	0.0
Week 18	62.0 (23) [97.4]	1.0 (19) [2.2]	31.0	0.0
Week 24	97.9 (23) [140.4]	1.9 (18) [5.2]	51.2	0.0

*Values less than the limit of quantitation (2.1 µU/mL) were imputed as 1.05 µU/mL.
N=number of subjects evaluated for antibody levels at baseline the noted time point, SD=standard deviation, INH=inhaled insulin, and SC=subcutaneous short-acting insulin.

Figure 54. Insulin Antibody Levels in Study 1026 by Time



The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.
INH=inhaled insulin, SC=subcutaneous short-acting insulin, and Wk=week of study.

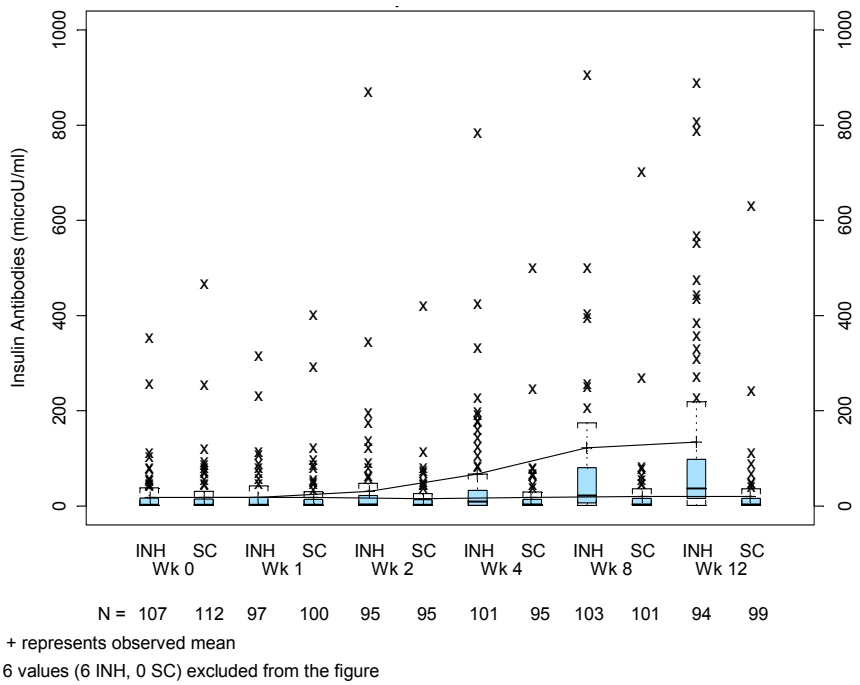
Study 1027 provides longitudinal data on insulin antibody formation during 12 weeks of treatment with INH and for 12 weeks following INH discontinuation in patients with type 1 DM. Patients exposed to INH in Study 1027 experienced an increase in serum insulin antibody levels apparent by week 2, and insulin antibody levels continued to increase through 12 weeks of exposure. A similar increase did not occur among patients treated with SC insulin (Table 116; Figure 55). Discontinuation of INH treatment resulted in declines in mean and median antibody levels clearly apparent by 4 weeks of follow-up. By 12 weeks after INH discontinuation, mean serum insulin antibody levels had decreased by approximately 62%, and median serum insulin antibody levels had decreased by approximately 34% (Table 116 and Table 120).

Table 116. Mean and Median Change from Baseline in Insulin Antibody Levels by Time: Study 1027

	Baseline and Change from Baseline Serum Antibody Level (µU/mL)* (N) [SD]			
	Mean		Median	
Time Point	INH	SC	INH	SC
Baseline values	17.1 (97) [40.6]	17.4 (99) [54.4]	2.4	2.7
Change from baseline				
Comparative phase				
Week 1	-0.5 (90) [5.8]	-0.1 (89) [8.9]	0.0	0.0
Week 2	5.3 (87) [22.7]	-1.1 (85) [6.0]	0.0	0.0
Week 4	28.7 (94) [79.6]	0.2 (89) [5.3]	5.6	0.0
Week 8	93.2 (97) [356.0]	3.2 (96) [25.3]	15.0	0.0
Week 12	112.9 (91) [218.1]	2.9 (95) [19.4]	28.0	0.0
Follow-up phase†				
Week 2	83.1 (87) [163.7]	2.3 (88) [21.1]	27.0	0.0
Week 4	61.8 (84) [122.6]	3.8 (92) [25.5]	19.5	0.0
Week 8	42.2 (85) [74.7]	4.1 (92) [25.3]	19.0	0.0
Week 12	33.3 (85) [61.7]	5.2 (93) [33.9]	13.0	0.0

*Values less than the limit of quantitation (2.1 µU/mL) were imputed as 1.05 µU/mL.
†All subjects received subcutaneous insulin as the only short-acting insulin during the follow-up phase.
N=number of subjects evaluated for antibody levels at baseline and the noted time point, SD=standard deviation, INH=inhaled insulin, and SC=subcutaneous short-acting insulin.

Figure 55. Insulin Antibody Levels in the Comparative Phase of Study 1027 by Time



The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.
INH=inhaled insulin, SC=subcutaneous short-acting insulin, and Wk=week of study.

Long-Term Controlled Study 1022

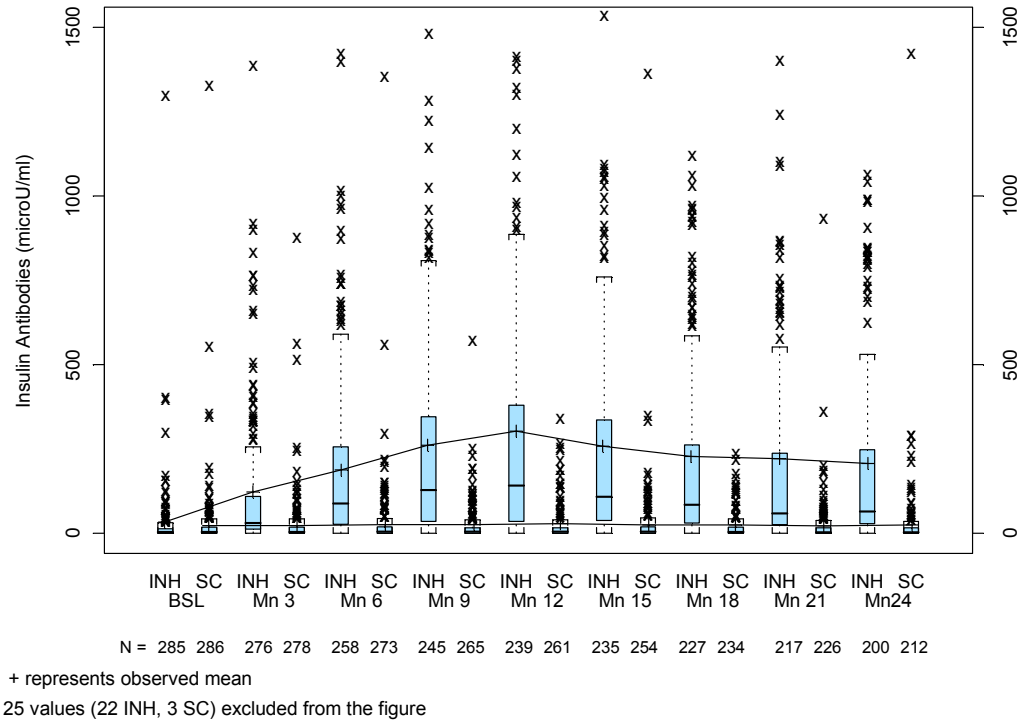
Based on the scheduled 2-year interim analysis, INH-, but not SC insulin-treated patients with type 1 DM in Study 1022 experienced increases in mean and median serum insulin antibody levels. Among INH-treated patients the majority of the increase occurred during the initial 6 months of treatment, and insulin antibody levels stabilized by 9-12 months of exposure (Table 117).

Table 117. Mean and Median Change from Baseline in Insulin Antibody Levels by Time: Study 1022

	Baseline and Change from Baseline Serum Antibody Level (µU/mL)* (N) [SD]			
	Mean		Median	
Time Point	INH	SC	INH	SC
Baseline values	33.6 (285) [224.6]	23.5 (286) [91.7]	4.5	4.2
Change from baseline				
Week 3	26.3 (263) [172.5]	-1.7 (261) [34.0]	1.4	0.0
Week 6	107.9 (266) [709.6]	0.4 (260) [37.7]	8.3	0.0
Week 12	102.8 (271) [315.2]	-1.3 (274) [32.1]	24.0	0.0
Week 18	118.7 (263) [205.2]	-0.8 (271) [26.4]	42.2	0.0
Month 6	167.9 (253) [230.7]	1.1 (269) [21.4]	76.3	0.0
Month 9	243.2 (241) [365.1]	0.9 (262) [27.5]	123.0	0.0
Month 12	286.9 (234) [459.8]	3.2 (258) [61.5]	129.1	0.0
Month 15	242.1 (230) [453.8]	-1.2 (251) [31.5]	101.5	0.0
Month 18	210.6 (222) [338.8]	-2.2 (231) [41.4]	80.5	0.0
Month 21	205.1 (213) [367.5]	-5.1 (224) [41.7]	52.2	0.0
Month 24	189.6 (196) [307.2]	-1.2 (210) [29.5]	52.6	0.0

*Values less than the limit of quantitation (2.1 µU/mL) were imputed as 1.05 µU/mL.
N=number of patients evaluated for antibody levels baseline and the noted time point, SD=standard deviation, INH=inhaled insulin, and SC=subcutaneous short-acting insulin.

Figure 56. Insulin Antibody Levels in Study 1022 by Time



Values > 1532 are excluded from the figure.
The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.
BSL=baseline, INH=inhaled insulin, Mn=month of study, and SC=subcutaneous short-acting insulin.

Long-Term Extension Studies 111 and 102E/1036

Consistent with the results of Study 1022, serum insulin antibody levels in patients with type 1 DM in extension studies increased during exposure to INH, with the majority of the increase appearing to occur during the initial 6 months of treatment. Insulin antibody levels reached a plateau after approximately 6-12 months of exposure, and began to decrease after 18 months of continuous exposure.

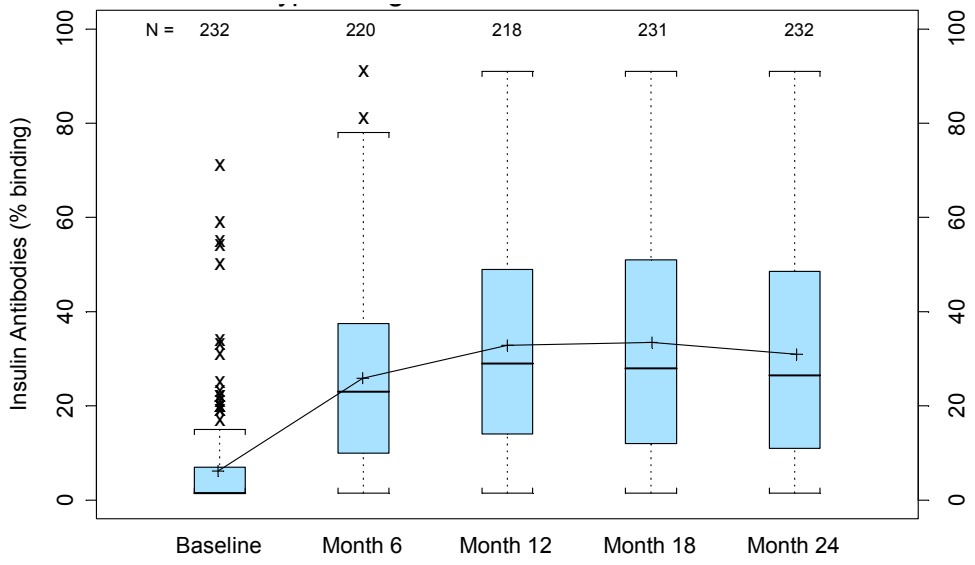
In Study 111, antibody data for type 1 patients with at least 24 months of INH exposure indicate that the greatest increase in mean and median insulin antibody levels occurred during the first 6 months of inhaled insulin exposure, that a plateau was reached by approximately 6-12 months of exposure, and that insulin antibody levels declined between 18 and 24 months of exposure (Table 118; Figure 57).

Table 118. Mean and Median Change from Baseline in Insulin Antibody Levels by Time: Adult Type 1 Patients with At Least 24 Months of Exposure to Inhaled Insulin in Study 111

	Baseline and Change from Baseline Serum Antibody Level (% Binding)*	
Time Point (N)	**Mean [SD]**	**Median**
Baseline values (232)	6.2 [9.8]	1.5
Change from baseline		
6 months (220)	19.6 [16.1]	17.5
12 months (218)	26.8 [20.1]	24.0
18 months (231)	27.3 [20.9]	23.5
24 months (232)	24.8 [20.6]	20.0

*Values below the limit of quantitation (3.0% binding) were imputed as 1.5% binding.
N=number of subjects evaluated for antibody levels baseline and the noted time point, and SD=standard deviation.

Figure 57. Insulin Antibody Levels Among Adult Type 1 Patients with At Least 24 Months of Exposure to Inhaled Insulin in Study 111 by Time



The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.

In Study 102E/1036, mean and median insulin antibody levels decreased with continued INH treatment beyond 36 months (Table 119). Antibody data from earlier time points for this study were not collected, consistent with the protocol for Study 102. These data are consistent with the observation in Study 111 that serum insulin antibody levels do not continue to rise beyond approximately 12 months with long-term INH exposure and suggest that exposure beyond 36 months results in at least partial resolution of the antibody response to INH.

Table 119. Observed Insulin Antibodies by Time: Studies 102E/1036

	Serum Antibody Level (% Binding)*	
Time Point (N)	**Mean [SD]**	**Median**
36 months (31)	30.6 [24.0]	26.0
48 months (28)	26.0 [18.9]	19.0
54 months (27)	24.4 [19.9]	16.0
60 months (26)	23.8 [21.2]	14.0
66 months (23)	23.0 [19.5]	16.0
72 months (21)	25.4 [24.7]	13.0

*Values below the limit of quantitation (3.0% binding) were imputed as 1.5% binding.
N=Number of subjects evaluable for antibody levels at each time point, and SD=standard deviation.

Effects of INH Discontinuation

Discontinuation of INH therapy in patients with type 1 DM results in a decline in serum insulin antibody levels. This has been demonstrated in 2 studies with planned discontinuation phases in patients with type 1 DM; Studies 1027 and 111. The designs of these 2 studies differ, and their data are presented differently. In Study 1027, by design, all patients receiving INH discontinued INH treatment after 12 weeks and switched to a subcutaneous insulin regimen, and their antibody data are presented in contrast to those of the comparator group, all of whom continued to receive SC insulin. This study, therefore, compares antibody levels in patients discontinuing INH treatment with those in patients never exposed to INH. In Study 111, however, all patients received INH until the discontinuation phase of the study, at which point, by design, approximately one half of the patients discontinued and the remainder continued INH use. Study 111, therefore, compares antibody levels in patients discontinuing INH treatment with those in patients continuing INH treatment.

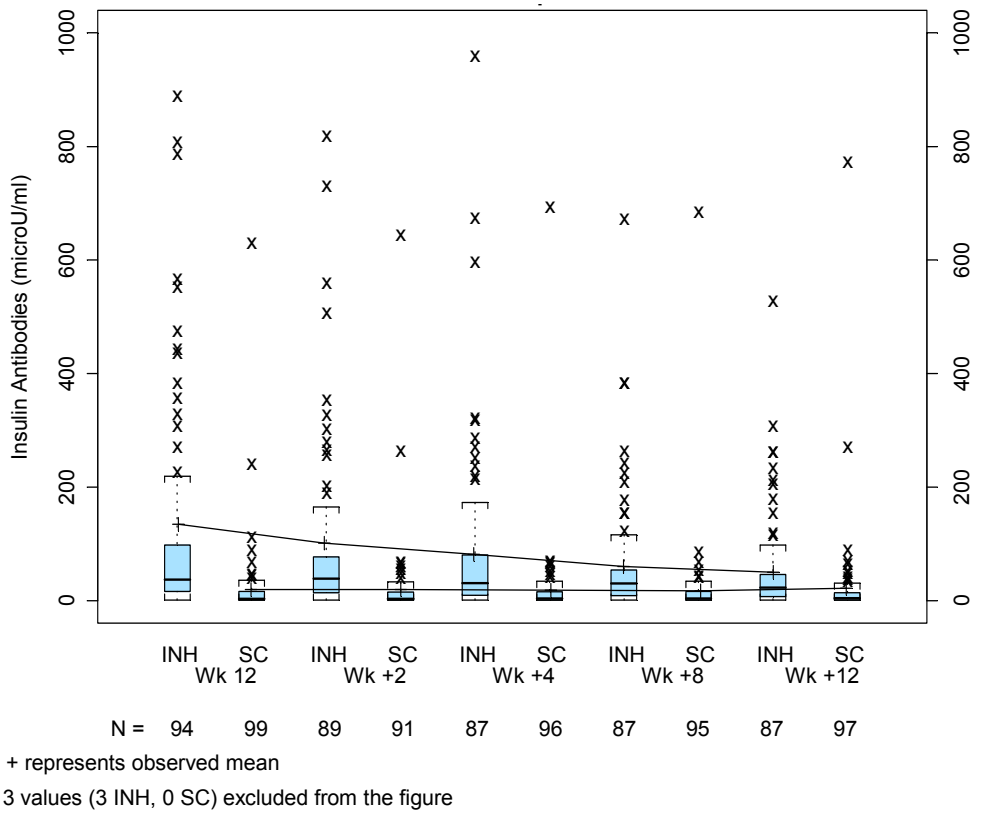
As presented previously, in Study 1027 mean and median serum insulin antibody levels clearly decreased within 4 weeks of INH discontinuation after a 12-week period of INH treatment. By 12 weeks after discontinuation, mean and median insulin antibody levels had decreased by approximately 62% and 34%. At the end of the 12-week follow-up period, serum insulin antibody levels remained greater among patients previously exposed to INH than among those never exposed. However, there was no indication that the decline in serum insulin antibody levels had ceased by the end of the follow-up period (Table 120; Figure 58).

Table 120. Observed Insulin Antibody Levels in the Follow-Up Phase of Study 1027

	Serum Antibody Level (µU/mL)* (N) [SD]			
	Mean		Median	
Time Point	INH	SC	INH	SC
Baseline values				
	17.1 (97) [40.6]	17.4 (99) [54.4]	2.4	2.7
Final values during active treatment				
Week 12	132.5 (93) [243.7]	19.5 (99) [68.4]	35.0	3.3
Values after discontinuation				
Week +2†	101.2 (89) [189.4]	19.9 (91) [72.7]	39.0	3.5
Week +4†	80.0 (86) [150.0]	18.4 (96) [71.3]	29.0	3.8
Week +8†	60.3 (87) [100.6]	17.5 (95) [70.6]	30.0	3.8
Week +12†	50.3 (87) [82.8]	21.6 (97) [82.8]	23.0	4.4

*Values less than the limit of quantitation (2.1 µU/mL) were imputed as 1.05 µU/mL.
†Weeks +2, +4, +8 and +12 are weeks 2, 4, 8, and 12 following discontinuation of INH treatment.
N=number of subjects evaluable for antibodies at each time point, SD=standard deviation, INH=inhaled insulin, and SC=subcutaneous short-acting insulin.

Figure 58. Insulin Antibody Levels in the Follow-Up Phase of Study 1027



The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.
Week 12 is the time of final treatment with INH or SC insulin during the comparative phase of the study, and weeks +2, +4, +8 and +12 are weeks 2, 4, 8, and 12 following planned discontinuation.
INH=inhaled insulin treatment during the comparative phase, SC=subcutaneous short-acting insulin treatment during the comparative phase, and Wk=week.

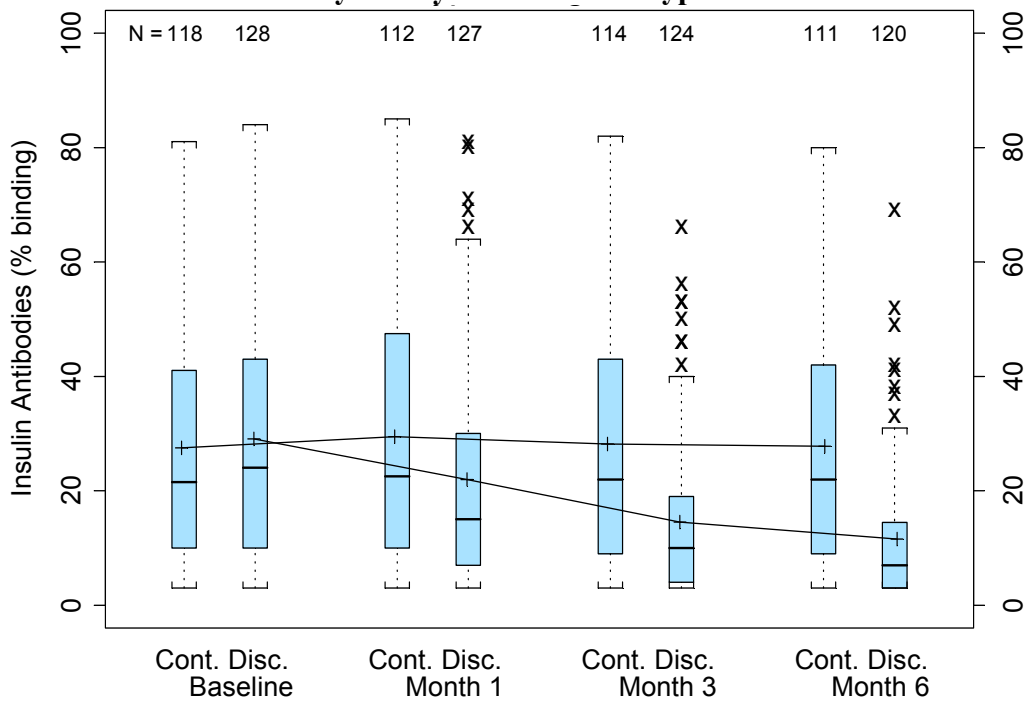
Similarly, in Study 111, serum insulin antibody levels decreased after planned discontinuation of long-term INH treatment. Prior to entry into the comparative discontinuation phase of Study 111, patients were randomized either to continue INH therapy or to discontinue INH therapy and use SC insulin and/or OAs for a 6-month period of observation. Mean and median insulin antibody levels declined over this 6-month period among patients with type 1 DM who discontinued INH therapy, but not among those who continued to receive INH. Among patients with type 1 DM, mean and median antibody levels fell by more than 50% in the initial 3 months and by more than 60% after 6 months (Table 121 and Figure 59).

Table 121. Change from Baseline* in Insulin Antibody Levels during the Comparative Discontinuation Phase of Study 111 by Time: Adult Type 1 Patients

	Baseline and Change from Baseline Antibody Level (% Binding)† (N) [SD]			
	Mean		Median	
Time Point	Continued	Discontinued	Continued	Discontinued
Baseline values	27.5 (118) [21.2]	29.1 (128) [22.4]	21.5	24.0
Change from baseline				
Month 1	2.0 (112) [5.0]	-6.7 (127) [8.0]	1.0	-5.0
Month 3	0.3 (114) [6.2]	-14.8 (124) [12.7]	0.0	-11.5
Month 6	-0.2 (111) [6.5]	-18.2 (120) [15.3]	0.0	-15.0

*Baseline is defined as the last measurement prior to randomization to the comparative phase of the study.
†Values below the limit of quantitation (3.0% binding) were imputed as 1.5% binding.
N=number of subjects, and SD=standard deviation.

Figure 59. Insulin Antibody Levels Among Adult Type 1 Patients in the Comparative Discontinuation Phase of Study 111 by Time: Adult Type 1 Patients



The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.
Cont. and Disc.=continued and discontinued inhaled insulin treatment, respectively

6.6.2.4. Insulin Antibody Data in Patients with Type 2 DM

INH-treated patients with type 2 DM experienced greater end-of-study and change-from-baseline insulin antibody levels than did comparator-treated patients, whether the comparator was SC insulin or one or more OAs. Increases in insulin antibodies were greater among INH-treated patients with type 2 DM who were using SC insulin at study entry than among those who were not.

With long-term exposure of patients with type 2 DM to INH, mean and median insulin antibody levels reached a plateau at approximately 12 months of exposure. When INH therapy was discontinued, there were declines in mean and median insulin antibody levels evident at 6 weeks among patients with type 2 DM.

Controlled IAB Phase 2/3 Studies

Patients with type 2 DM who were using SC insulin at study entry and who switched short-acting insulin to INH at the beginning of a Controlled IAB Phase 2/3 study experienced increases in mean and median insulin antibody levels by end of study. Control patients who maintained a regimen consisting exclusively of SC insulin did not experience similar increases (Table 122). No data are available comparing insulin antibody formation following initiation of INH versus SC insulin in patients with type 2 DM not previously exposed to insulin.

Patients with type 2 DM who were not using insulin at study entry also experienced an increase in mean and median insulin antibody levels at end of study after treatment with INH. Control patients, who were not treated with insulin of any kind, did not experience an increase in either mean or median insulin antibody levels (Table 122).

The increase in insulin antibody levels observed among INH-treated patients with type 2 DM was smaller than that experienced by patients with type 1 DM (Table 114 and Table 122). Similarly, the increase in insulin antibody levels among type 2 patients without previous exposure to SC insulin was smaller than that experienced by those who were insulin-using at study entry (Table 122).

Table 122. Mean and Median Insulin Antibody Levels at Baseline and End of Study or 1 Year of Treatment by Method of Evaluation: Type 2 Patients in Controlled IAB Phase 2/3 Studies

Mayo Assay (Studies 104, 108, 109, and 110)		Serum Antibody Level (% Binding)* (N) [SD]			
		Mean		Median	
Cohort	Time Point	INH	Comparator	INH	Comparator
Type 2 patients insulin-using at study entry	Baseline	2.7 (134) [4.3]	4.1 (133) [9.3]	1.5	1.5
	End of study (6 months)	12.8 [18.2]	4.0 [8.0]	5.0	1.5
	Change from baseline	10.2 [16.1]	-0.1 [3.3]	3.5	0.0
Type 2 patients non-insulin-using at study entry	Baseline	1.8 (290) [4.6]	1.5 (181) [0.3]	1.5	1.5
	End of study (3 months)	6.0 [8.0]	1.5 [0.0]	1.5	1.5
	Change from baseline	4.3 [9.2]	-0.0 [0.3]	0.0	0.0

Esoterix Assay (Studies 1001, 1002, and 1029)		Serum Antibody Level (µU/mL) (N) [SD]			
		Mean		Median	
Cohort	Time Point	INH	Comparator	INH	Comparator
Type 2 patients insulin-using at study entry†	Baseline	12.2 (307) [36.9]	14.9 (307) [86.5]	1.1	1.1
	1 year	78.2 (203) [187.0]	14.6 (212) [102.9]	17.0	1.1
	Change from baseline	68.5 (202) [178.7]	3.5 (208) [59.7]	13.5	0.0
Type 2 patients non-insulin-using at study entry‡	Baseline	1.1 (452) [2.2]	1.0 (415) [0.2]	1.0	1.0
	1-year	16.7 (321) [48.4]	1.0 (280) [0.1]	5.4	1.0
	Change from baseline	15.6 (316) [48.9]	-0.0 (276) [0.21]	4.4	0.0

*Values less than the limit of quantitation (3.0% binding) were imputed as 1.5% binding.
†Values less than the limit of quantitation (2.1 µU/mL) were imputed as 1.05 µU/mL.
‡Values less than the limit of quantitation (2.0 µU/mL) were imputed as 1.0 µU/mL.
N=number of subjects evaluated for antibody levels at each time point, SD=standard deviation, and INH=inhaled insulin.

There was no consistent effect of age on insulin antibody levels across insulin antibody assay methods for type 2 patients who were either insulin-using or non-insulin-using at study entry. Among type 2 patients who were insulin-using at study entry and evaluated using the Mayo assay, change from baseline in insulin antibody levels appears to be greater among patients ≥ 65 years of age than among those < 65 years of age. A similar pattern is not apparent among those who were non-insulin-using at study entry. The pattern appears to be reversed for patients evaluated by the Esoterix assay. That is, among type 2 patients evaluated by the Esoterix assay, change from baseline in insulin antibody levels appears to be greater among patients ≥ 65 years of age than among those < 65 years of age for patients who were non-insulin-using at study entry but not for those who were insulin-using.

No relationships between insulin antibodies and gender were apparent among patients with type 2 DM.

No consistent relationships between insulin antibodies and race were apparent among patients with type 2 DM.

Long-Term Controlled Studies 1001, 1002, and 1029

Long-term exposure of patients with type 2 DM to INH resulted in increases in serum insulin antibody levels. The greatest increases appear to have occurred during the initial 6 months of treatment, and insulin antibody levels reached a plateau and, in Studies 1001 and 1002 began to decline, after 6 months of treatment.

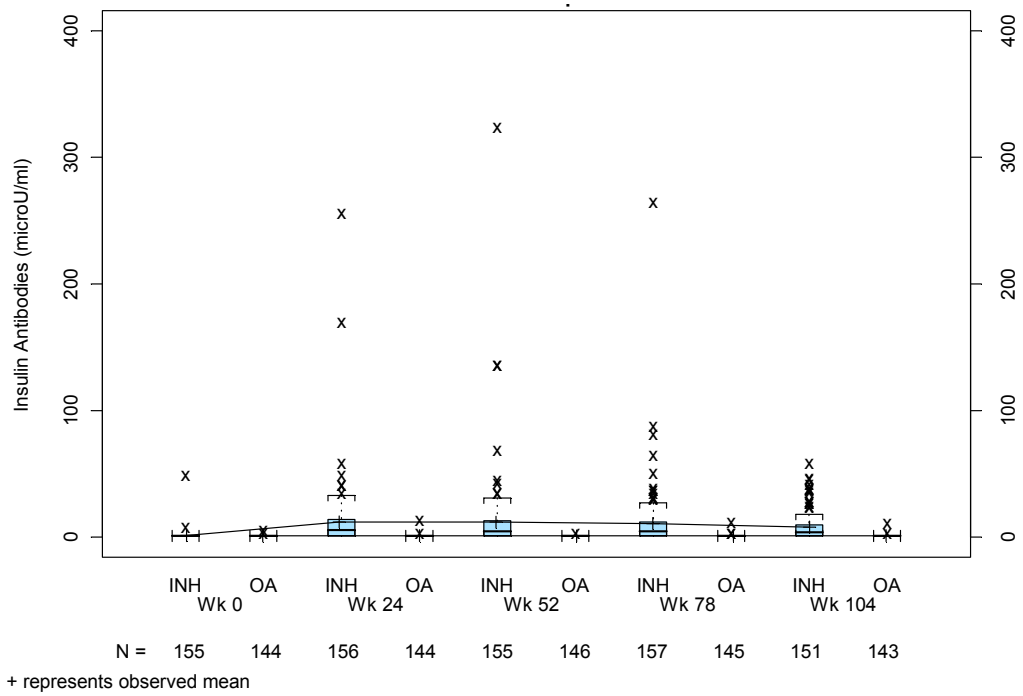
Patients with type 2 DM in Studies 1001 and 1002 were not using insulin at study entry and were failing sulphonylurea and metformin therapy, respectively. The patients were randomized to receive either another OA or INH as adjunctive therapy. Patients completing 2 years of treatment in Studies 1001 and 1002 experienced increased mean and median serum insulin antibody levels while using INH but not comparator therapy. The observed increase occurred in the first 6 months of therapy, and mean and median antibody levels decreased thereafter (Table 123; Figure 60). Planned discontinuation of INH after 2 years of exposure resulted in further decreases in mean and median antibody levels. By 12 weeks after INH discontinuation, mean and median serum insulin antibody levels had decreased by approximately 57% and 75%, respectively (Table 127).

Table 123. Mean Baseline, and Mean and Median Change from Baseline in Insulin Antibody Levels in Studies 1001 and 1002: 2-Year Cohort

	Serum Antibody Level (µU/mL)* (N) [SD]			
	Mean		Median	
Time Point	INH	OA	INH	OA
Baseline Values	1.3 (155) [3.8]	1.0 (144) [0.3]	1.0	1.0
Change from baseline				
Month 6	10.7 (153) [26.0]	0.1 (142) [1.0]	4.6	0.0
Month 12	10.6 (152) [31.2]	-0.0 (144) [0.2]	3.6	0.0
Month 18	9.5 (154) [24.8]	0.1 (143) [0.5]	3.5	0.0
Month 24	6.5 (148) [11.4]	0.0 (141) [0.5]	2.9	0.0

*Values less than the limit of quantitation (2.0 µU/mL) were imputed as 1.0 µU/mL.
N=number of subjects completing 2 years of treatment and evaluated at each time point, SD=standard deviation, INH=inhaled insulin, and OA=oral antidiabetic agents.

Figure 60. Insulin Antibody Levels in Studies 1001 and 1002 by Time: 2-Year Cohort



The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.
INH=inhaled insulin, OA=oral agents, and Wk=week of study.

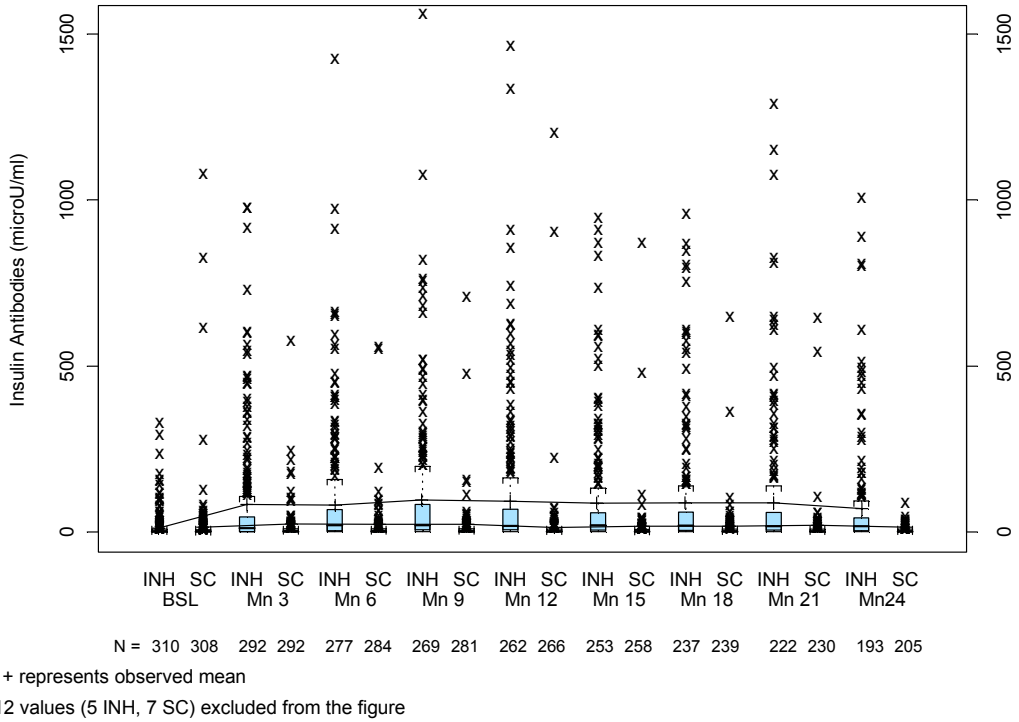
Long-term exposure of patients with type 2 DM to INH in Study 1029, in which patients were insulin-using at study entry, resulted in increases in serum insulin antibody levels. The median levels reached their maximum at 6-9 months of treatment. Mean insulin antibody levels remained relatively constant after 12 weeks of exposure. The greatest mean value occurred at 9 months of exposure (Table 124).

Table 124. Mean Baseline, and Mean and Median Change from Baseline in Insulin Antibody Levels in Study 1029

	Serum Antibody Level (µU/mL)* (N) [SD]			
	Mean		Median	
	INH	SC	INH	SC
Baseline values	12.09(310) [36.75]	14.87(308) [86.4]	1.05	1.05
Change from baseline				
Week 3	15.74 (264) [77.08]	-1.08 (262) [27.13]	0	0
Week 6	59.78 (281) [430.4]	3.02 (279) [69.45]	0	0
Week 12	69.26 (287) [214.32]	9.34 (289) [176.46]	7.45	0
Week 18	65.44 (266) [149.4]	8.21 (281) [159.27]	11.63	0
Month 6	66.63 (273) [151.9]	7.00 (281) [147.36]	16.95	0
Month 9	81.95 (265) [200.86]	6.87 (278) [148.34]	16.95	0
Month 12	79.54 (259) [181.93]	-2.69 (263) [76.95]	14.95	0
Month 15	74.64 (249) [184.21]	0.31 (255) [82.89]	15.95	0
Month 18	74.70 (234) [188.16]	0.24 (237) [82.32]	12.43	0
Month 21	74.61 (219) [183.5]	2.11 (228) [95.8]	13.60	0
Month 24	58.99 (191) [153.72]	-1.09 (203) [79.27]	10.60	0

*Values less than the limit of quantitation (2.1 µU/mL) were imputed as 1.05 µU/mL.
N=number of subjects completing 2 years of treatment and evaluated at each time point, SD=standard deviation, INH=inhaled insulin, and OA=oral antidiabetic agents.

Figure 61. Insulin Antibody Levels in Study 1029 by Time



Values > 1560 are excluded from the figure.
The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.
INH=inhaled insulin, SC=subcutaneous short-acting insulin, Wk=week of study, and Mn=month of study.

Long-Term Extension Studies 111, 103E/1036, and 104E/1036

Consistent with the results of Studies 1001, 1002, and 1029, serum insulin antibody levels in patients with type 2 DM in extension studies increased during exposure to INH. The greatest increases occurred during the initial 6 months of treatment, and insulin antibody levels reached a plateau by approximately 6-12 months of exposure.

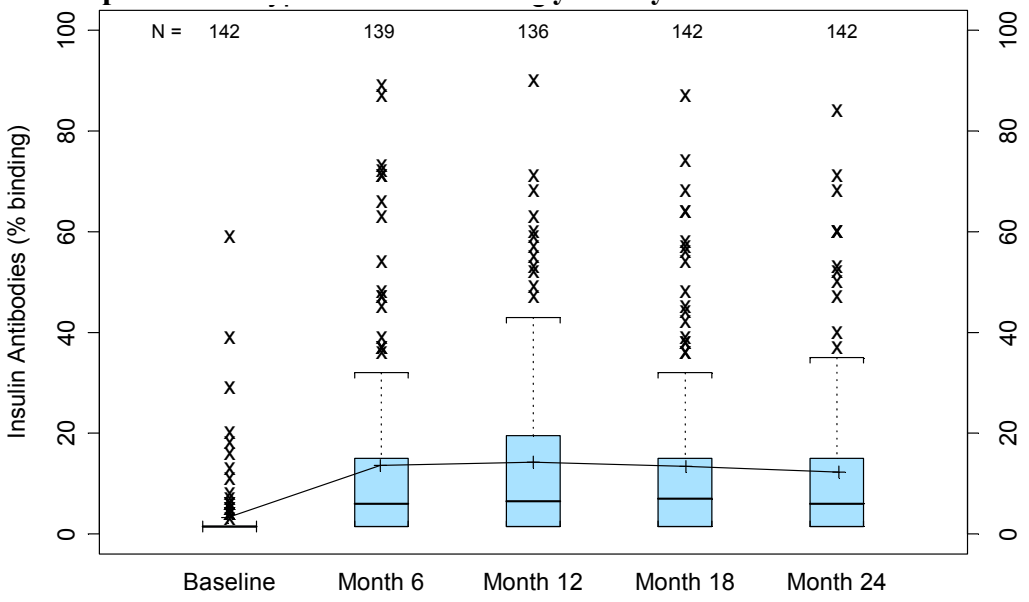
Among type 2 patients treated for at least 24 months in Study 111, the maximal increase in mean and median insulin antibody levels generally occurred during the first 6 months of inhaled insulin exposure. A plateau was reached within 12 months of exposure for patients with type 2 DM, whether or not they were insulin-using at study entry (Table 125; Figure 62, and Figure 63).

Table 125. Mean and Median Change from Baseline in Insulin Antibody Levels by Time: Type 2 Patients with At Least 24 Months of Exposure to Inhaled Insulin in Study 111

		Change from Baseline Serum Antibody Level (% Binding)*	
Cohort	**Time Point (N)**	**Mean [SD]**	**Median**
Type 2 patients insulin-using at study entry	Baseline values (142)	3.2 [6.7]	1.5
	Change from baseline		
	6 months (139)	10.4 [16.5]	3.5
	12 months (136)	10.9 [16.3]	4.0
	18 months (142)	10.2 [15.4]	4.5
	24 months (142)	9.0 [14.9]	3.5
Type 2 patients non-insulin-using at study entry	Baseline values (229)	1.8 [5.2]	1.5
	Change from baseline		
	6 months (208)	5.5 [10.9]	1.5
	12 months (212)	7.2 [13.0]	3.5
	18 months (211)	5.7 [11.9]	2.5
	24 months (229)	5.7 [12.0]	2.5

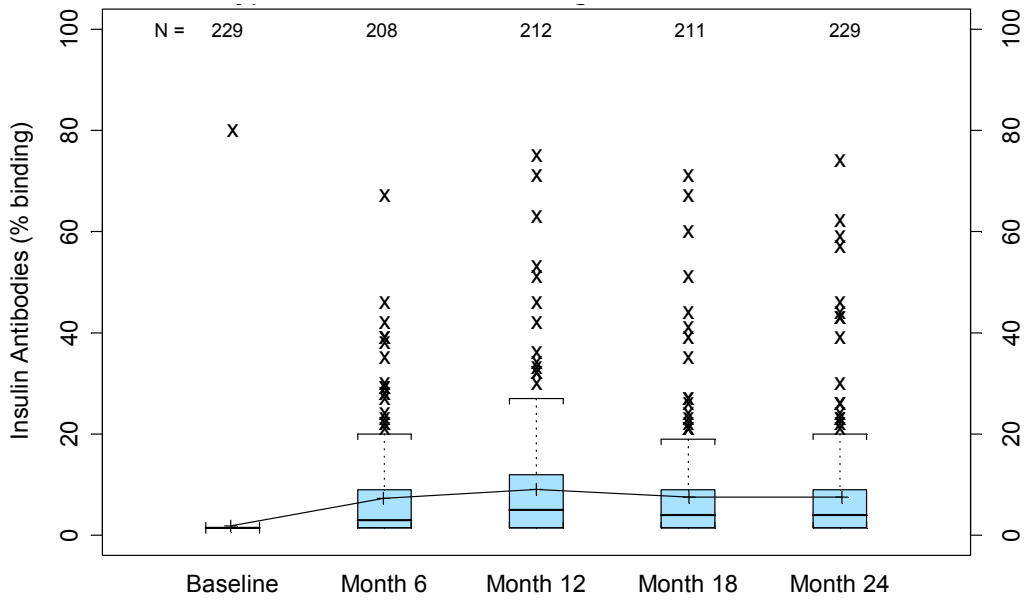
*Values below the limit of quantitation (3.0% binding) were imputed as 1.5% binding.
N=number of subjects evaluated for antibody levels at each time point, and SD=standard deviation.

Figure 62. Insulin Antibody Levels Among Insulin-Using Type 2 Patients with At Least 24 Months of Exposure to Inhaled Insulin in Study 111 by Time



The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.

Figure 63. Insulin Antibody Levels Among Non-Insulin-Using Type 2 Patients with at least 24 Months of Exposure to Inhaled Insulin in Study 111 by Time



The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.

A similar longitudinal pattern in insulin antibody levels occurred in Study 104E/1036. Among patients exposed to INH for up to 66 months in Study 104E, mean insulin antibody levels were greatest at 12 months of exposure and did not increase further with time. In Study 103E/1036 median insulin antibody levels did not increase after 36 months of exposure (Table 126). Antibody data from earlier time points for this study were not collected. These data support the observation that insulin antibody levels do not continue to rise beyond approximately 12 months of treatment with long-term INH exposure.

Table 126. Observed Insulin Antibodies by Time: Studies 103E/1036 and 104E/1036

		Serum Antibody Level (% Binding)*	
Study	**Time Point (N)**	**Mean [SD]**	**Median**
103E/1036†	36 months (22)	8.6 [14.9]	2.8
	48 months (21)	8.3 [14.6]	1.5
	54 months (20)	6.2 [10.9]	1.5
	60 months (17)	9.7 [20.5]	1.5
	66 months (16)	8.8 [19.2]	1.5
	72 months (13)	12.6 [23.5]	1.5
104E/1036	Baseline (57)	1.5 [0.0]	1.5
	6 months (58)	4.6 [5.4]	1.5
	12 months (48)	5.9 [8.5]	2.3
	24 months (41)	4.5 [7.1]	1.5
	36 months (37)	3.9 [6.9]	1.5
	48 months (32)	3.5 [7.4]	1.5
	54 months (30)	3.5 [7.7]	1.5
	60 months (24)	3.8 [8.3]	1.5
	66 months (8)	2.9 [1.7]	2.3

*Values below the limit of quantitation (3.0% binding) were imputed as 1.5% binding.
†Antibody levels were not measured at baseline, 6 months, 12 months, or 24 months in Study103E/1036.
Subjects in Study 103E/1036 were insulin-using at study entry; those in Study 104E/1036 were not.
N=Number of subjects evaluable for antibody levels at each time point, and SD=standard deviation.

Effects of INH Discontinuation

Discontinuation of INH therapy in patients with type 2 DM results in a decline in serum insulin antibody levels. This effect has been demonstrated in 3 studies with planned discontinuation phases in patients with type 2 DM; Studies 1001, 1002, and 111.

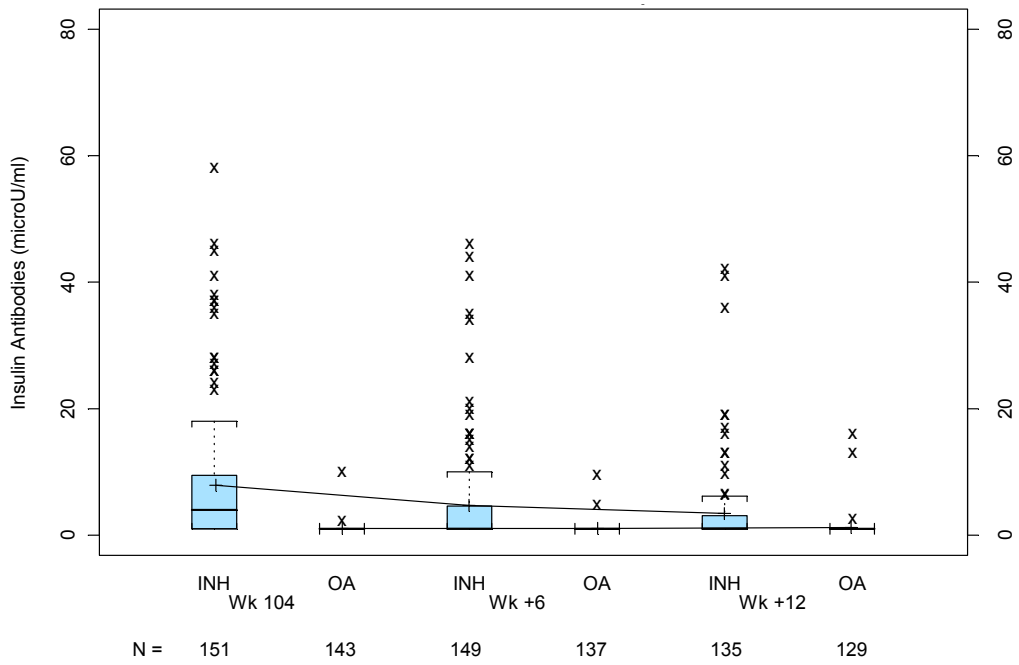
As discussed previously in this section, in Studies 1001 and 1002 mean and median serum insulin antibody levels among INH-treated patients completing 2 years of treatment decreased by approximately 57% and 75%, respectively during a 12-week follow-up period following INH discontinuation. At the end of the 12-week follow-up period, mean serum insulin antibody levels had noticeably decreased, and median serum insulin antibody levels had returned to baseline values (Table 127; Figure 64).

Table 127. Observed Insulin Antibody Levels in the Discontinuation Phase of Studies 1001 and 1002: 2-Year Cohort

	Serum Antibody Level (µU/mL)* (N) [SD]			
	Mean		Median	
Time Point	**INH**	**OA**	**INH**	**OA**
Baseline values				
	1.3 (155) [3.8]	1.0 (144) [0.3]	1.0	1.0
Final values during active treatment				
Week 104	7.9 (151) [10.6]	1.1 (143) [0.8]	4.0	1.0
Values after discontinuation				
Week +6†	4.7 (149) [8.1]	1.1 (137) [0.8]	1.0	1.0
Week +12†	3.4 (135) [6.5]	1.2 (129) [1.7]	1.0	1.0

*Values less than the limit of quantitation (2.0 µU/mL) were imputed as 1.0 µU/mL.
†Weeks +6 and +12 are weeks 6 and 12 following discontinuation of INH treatment.
N=number of subjects evaluable for antibodies at each time point, SD=standard deviation, INH=inhaled insulin, and OA=oral antidiabetic agents.

Figure 64. Insulin Antibody Levels in the Follow-Up Phase of Studies 1001 and 1002: 2-Year Cohort



The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.
Week 104 is the time of final treatment with INH or OAs during the comparative phase of the study, and weeks +6 and +12 are weeks 6 and 12 after comparative treatment.
INH=inhaled insulin treatment during the comparative phase, OA=oral agent treatment during the comparative phase, and Wk=week.

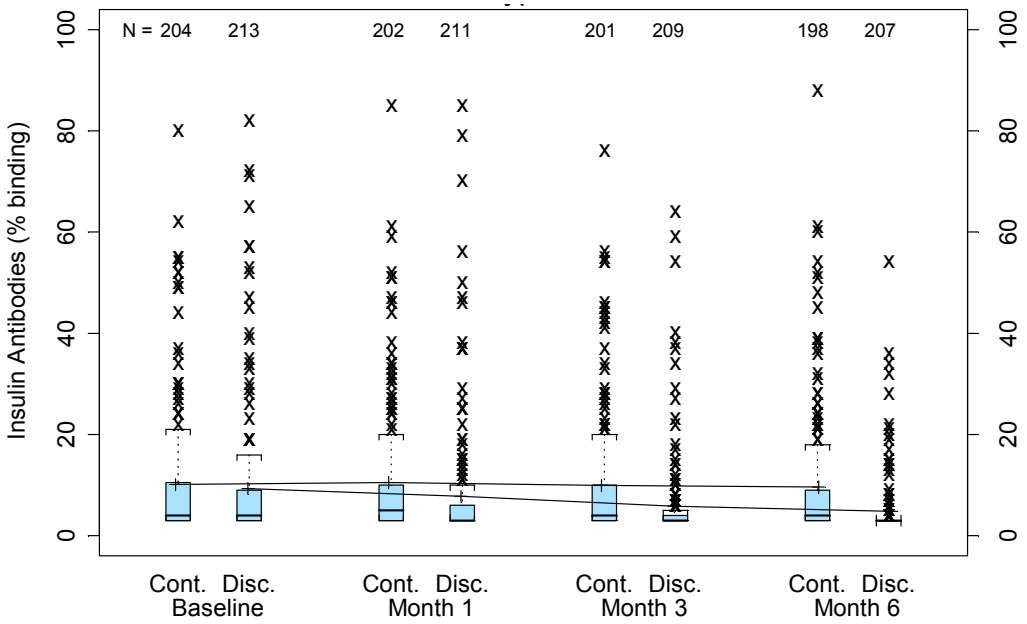
In Study 111, prior to entry into the comparative discontinuation phase, patients were randomized either to continue INH therapy or to discontinue INH therapy and use SC insulin and/or OAs for a 6-month period of observation. For patients with type 2 DM, median insulin antibody levels remained approximately constant over the 6-month period of observation in both treatment groups. However, for the group that discontinued INH therapy, there was a decrease in mean antibody level. In addition, 75th percentile antibody levels decreased from 9.0 to 3.0% binding at baseline and month 6, respectively, for the group that discontinued INH, but exhibited a smaller change (11.0 to 9.0% binding) over the same treatment interval for the group that continued INH therapy (Table 128; Figure 65).

Table 128. Change from Baseline* in Insulin Antibody Levels During the Comparative Discontinuation Phase of Study 111 by Time: Adult Type 2 Patients

	Baseline and Change from Baseline Antibody Level (% Binding)† (N) [SD]			
	Mean		Median	
Time Point	Continued	Discontinued	Continued	Discontinued
Baseline values	10.1 (204) [13.1]	9.3 (213) [13.4]	4.0	4.0
Change from baseline				
Month 1	0.3 (202) [4.6]	-1.6 (211) [5.2]	0.0	0.0
Month 3	-0.3 (201) [5.2]	-3.4 (209) [7.0]	0.0	0.0
Month 6	-0.3 (198) [6.4]	-4.6 (207) [9.0]	0.0	-1.0

*Baseline is defined as the last measurement prior to randomization for the comparative phase of the study.
†Values less than the limit of quantitation (3.0% binding) were imputed as 1.5% binding.
N=number of subjects evaluated at baseline and the noted time point, and SD=standard deviation.

Figure 65. Insulin Antibody Levels Among Adult Type 2 Patients in the Comparative Discontinuation Phase of Study 111 by Time



The box plots represent the median (center horizontal line), mean (indicated by '+'), and the 25th and 75th percentiles (bottom and top edges of box). Whiskers extend from the box to the farthest point within 1.5 times the interquartile range (75th minus 25th percentile). Values beyond that are indicated by 'x'.
Cont. and Disc.=continued and discontinued inhaled insulin treatment, respectively

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6.6.2.5. Qualitative Characterization of Inhaled Insulin-Associated Antibodies

Insulin antibodies that develop during INH treatment are qualitatively similar to those developing during SC insulin treatment.

A preliminary study has been completed in which anti-insulin immunoglobulin classes were characterized in 88 serum samples from a randomly-selected group of patients with type 1 DM treated with INH or SC insulin and with a wide range of insulin antibody levels. In this study, serum anti-insulin IgG levels correlated directly with total insulin antibody levels, and anti-insulin IgA, IgE, and IgM levels were below

the limit of quantitation for both INH- and SC insulin-treated patients. These results indicate that INH and SC insulin induce a qualitatively similar antibody response, each inducing IgG without evidence for induction of antibodies of other classes.

Routine insulin antibody radioligand binding assays use low concentrations of radio-labeled monoiodinated insulin and detect antibodies of relatively high binding affinities. High affinity insulin binding activity is thought to be more clinically significant than low affinity binding, at least with respect to effects on post-prandial glucose tolerance.[64] Insulin binding activity in the serum of patients treated with injectable insulin(s) has been shown to consist predominantly of polyclonal anti-insulin IgG, a heterogeneous population of antibodies with a range of binding affinities. Two published reports in which complete insulin binding capacity profiles were measured in asymptomatic patients with type 1 DM treated with injectable insulin(s) suggest that low affinity antibodies with high binding capacity are common in patients who also have high affinity insulin antibodies detectable by routine insulin antibody assays. [65, 66] There was no evidence from these reports that the low affinity, high capacity antibodies were of clinical significance. However, low affinity insulin antibodies have been hypothesized to play a role in rare cases of either spontaneous autoimmune hypoglycemia (Hirata's syndrome) or paraprotein-associated hypoglycemia. With regard to insulin antibodies related to insulin therapy, one case report described labile DM in a patient with type 1 DM using injectable isophane and regular (soluble) insulins and with a very large low affinity binding capacity (240,000 µU/ml) as well as substantial high affinity binding (150 µU/ml).[67]

In consideration of these findings, all serum samples obtained from each treatment group in Study 1026 at study completion or at the time of early termination from the study were analyzed using a validated assay to determine insulin binding capacity profiles. Binding capacity was assessed at four concentrations of insulin ranging from $1.4x10^{-10}$ M (=21.1 µU/ml) to $1.0x10^{-7}$ M (=15,100 µU/ml). The lowest concentration of insulin allows for detection of higher affinity antibodies and is identical to that used in the routine Esoterix insulin antibody assay. Higher concentrations of insulin allow for detection of lower affinity antibodies.

The resulting insulin binding capacity profile data from Study 1026, consistent with published studies of insulin binding profiles in patients treated with injectable insulin(s), show that the majority of total insulin binding capacity in INH-treated patients is of low affinity and high binding capacity.[65, 66] Also consistent with published data from patients treated with injectable insulin(s), all samples with significant levels of INH-associated low affinity antibody binding also contained easily measurable quantities of higher affinity antibodies detected by the routine insulin antibody radioligand binding assay conditions.

6.6.3. Clinical Impact Analysis

To examine the potential clinical impact of the INH-associated rise in insulin antibodies, extensive exploratory data analyses have been performed using scatter plots, general and specialized adverse event tables, and binary distribution plots.

6.6.3.1. Methods of Analysis

Four methods were used:

1. *Scatter Plots* created between insulin antibody levels and clinical parameters that could plausibly be impacted by insulin antibodies were used to screen for potential signals which might warrant further, more definitive investigation.
2. *Binary Distribution Plots* were created to compare the distribution of insulin antibodies in patients with and without selected clinical findings.

3. *Time Plots* of hypoglycemic event rates, FEV_1 decreases, and antibody levels.
4. *Adverse Events* of an allergic nature were specifically extracted from adverse event tables for Controlled Phase 2/3 studies and reviewed below.

6.6.3.2. Insulin Antibodies and Insulin Action

Interference with insulin action could manifest as elevation in glycated hemoglobin (HbA_{1c}), impaired post-prandial glucose tolerance, or increased insulin dose requirements. Overall trends (detailed below) across the program suggest that INH and SC insulin are comparable with respect to HbA_{1c} and post-prandial glucose control. Furthermore, in controlled studies, there is no consistent relationship between insulin antibody levels and insulin doses.

- HbA_{1c}
  There is no indication from the INH clinical database that insulin antibodies are associated with changes in HbA_{1c} based on scatter plots in which end-of-study and change-from-baseline insulin antibody levels are plotted against end-of-study and change-from-baseline for all patient groups from Controlled IAB Phase 2/3 studies. No consistent associations between variables are apparent.

- Post-Prandial Glucose
  There is no indication from the INH clinical database that insulin antibodies are associated with post-prandial glucose control. Plasma post-prandial glucose concentrations were measured as part of standardized liquid meal challenge tests. Post-prandial plasma glucose concentrations and insulin antibody levels were measured in Phase 2/3 Studies 104, 106, 107, 108, 109, and 110. . No consistent associations between variables are apparent based upon scatter plots in which end-of-study insulin antibody levels are plotted against end-of-study post-prandial glucose concentrations and increments.

  Because of the limitations associated with post-prandial glucose data from these studies, an additional exploratory study (Study 1026) was performed. The primary objective of this study was to estimate the week-24 change from baseline plasma post-prandial glucose C_{max} and area under the curve ($AUC_{0\text{-}120}$), using standardized solid meal challenge tests with baseline glucose stabilization, in patients with type 1 DM treated with INH or SC insulin. This study showed no evidence for significant changes from baseline with regard to post-prandial glucose control associated with either an INH or SC insulin regimen or associated with insulin antibody levels. These results do not suggest a relationship between insulin antibodies and rigorously measured post-prandial glucose responses (See also Section 4.4).

- Insulin Dose
  There is no indication from the INH clinical database to suggest that insulin antibodies are associated with required doses of either long- or short-acting insulin based on scatter plots in which insulin antibody levels are plotted against long- and short-acting insulin doses in Controlled IAB Phase 2/3 studies. No consistent associations between variables are apparent.

- Fasting Plasma Glucose
  There is no evidence from the INH clinical database to suggest that insulin antibodies are associated with fasting plasma glucose concentrations based on scatter plots in which end-of-study insulin antibody levels are plotted against end-of-study fasting plasma glucose concentrations. No consistent associations between variables are apparent.

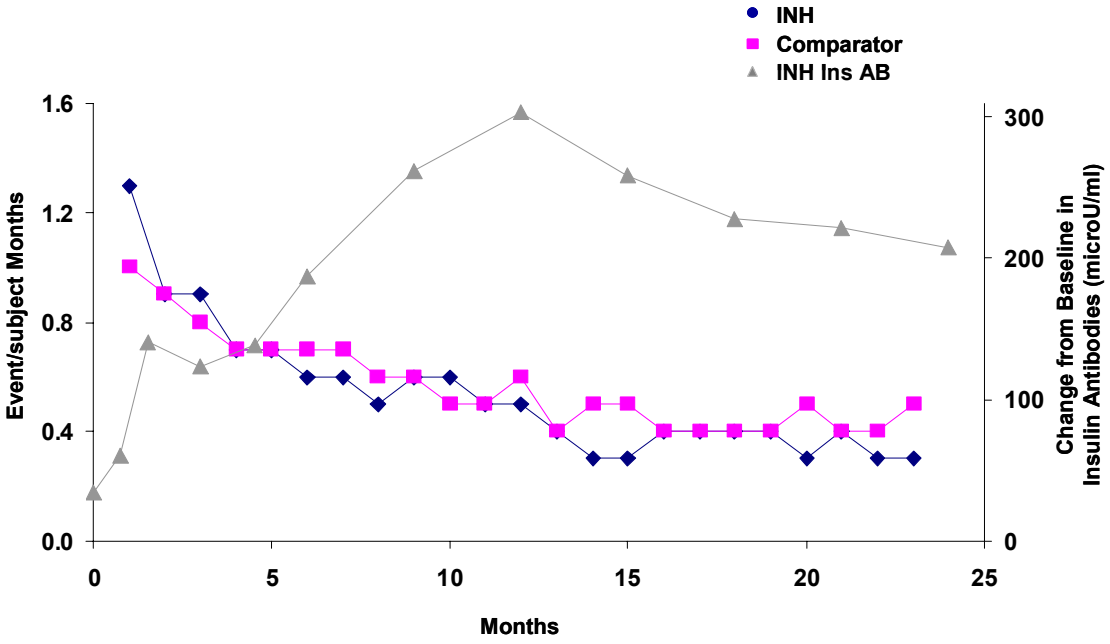
6.6.3.3. Insulin Antibodies and Hypoglycemia

There is no evidence from the INH clinical database to suggest that insulin antibodies are associated with the likelihood of experiencing a hypoglycemic event.

No consistent associations between variables are apparent based on scatter plots in which end-of-study insulin antibodies are plotted against the monthly incidence of hypoglycemic events or in which end-of-study insulin antibodies of a range of affinities from Study 1026 are plotted against the monthly incidence of hypoglycemic events.

Perhaps most importantly, there is no temporal association between the occurrence of hypoglycemia and the development of insulin antibodies. Data from Study 1022, the controlled study with the largest number of type 1 patients and the longest duration in the INH clinical development program is provided as an example (Figure 66).

Figure 66. Mean Insulin Antibody Levels and Hypoglycemic Event Rate by Time in Study 1022



Hypoglycemia is defined as a measured blood glucose concentration of ≤ 36 mg/dL or requiring assistance.

A syndrome of early morning hypoglycemia has been described in patients receiving insulin by implanted intraperitoneal pumps.[68] Intraperitoneal delivery of insulin is associated with insulin antibody formation, and it has been surmised that the antibodies may cause the clinical syndrome in these patients by prolonging or delaying the duration of insulin action. In contrast, no consistent relationships between hypoglycemia onset time and antibody strata are discernible in the INH clinical development program.

In addition, prospective euglycemic clamp procedures were performed during exploratory Study 1026. Duration of insulin action, in this study, was indicated by the time interval between 50% of maximal glucose infusion rates occurring late and early during the glucose infusion period ($t_{50(late)}$-$t_{50(early)}$) measured during 12-hour euglycemic clamp studies. Scatter plots from this study in which change from

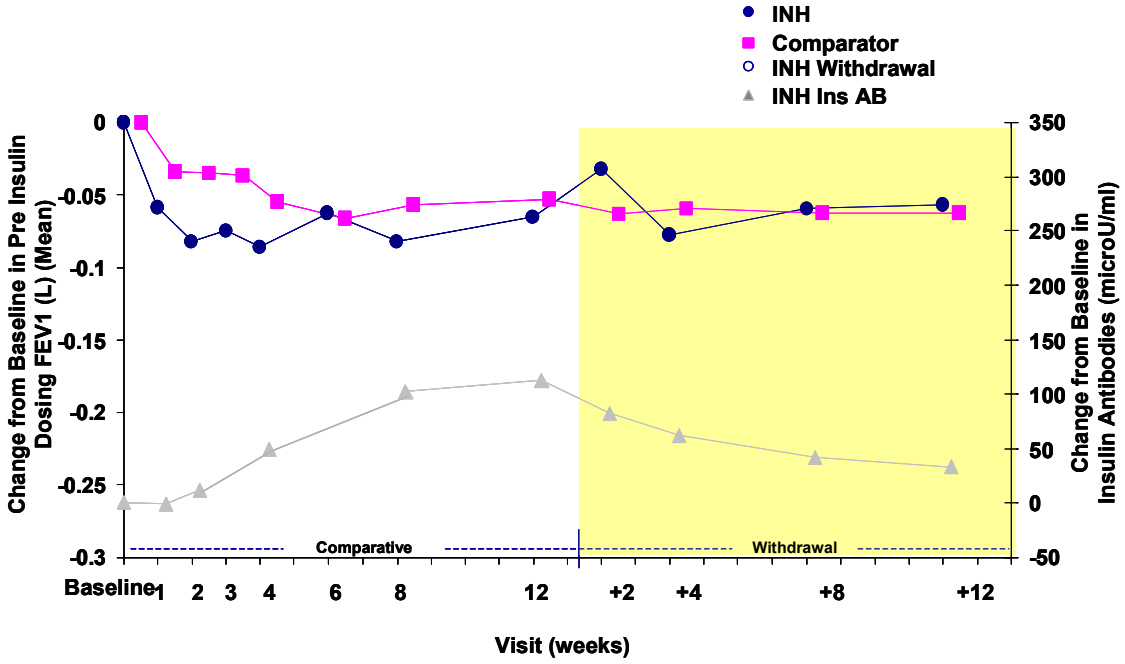
baseline and end of study insulin antibody levels are plotted against change from baseline $t_{50(late)}$-$t_{50(early)}$ do not suggest a relationship between insulin antibodies and alterations in duration of insulin action. Additional scatter plots also demonstrate a lack of association between the duration of insulin action and fasting plasma glucose concentration.

6.6.3.4. Insulin Antibodies and Pulmonary Function

Available clinical data do not indicate that insulin antibody levels are associated with changes in pulmonary function. No consistent associations are apparent between insulin antibody levels plotted against pulmonary function parameters forced expiratory volume in one second (FEV_1) and single-breath carbon monoxide diffusion capacity (DLco) for Controlled IAB Phase 2/3 studies. Similarly no unusual distribution of antibodies has been noted in patients with and without ≥ 15% decreases from baseline in FEV_1 or ≥ 20% decreases from baseline in DLco for Controlled IAB Phase 2/3 studies, or for patients with and without reported cough or dyspnea.

As for hypoglycemia, it is important to note that there is no temporal association between changes in pulmonary function and the development of insulin antibodies. Data from Study 1027 is provided as an example (Figure 67).

Figure 67. FEV_1 and Mean Insulin Antibody Levels in Study 1027 by Time



6.6.3.5. Inhaled Insulin and Allergic Adverse Events

The incidences of specific all-causality events of an allergic nature were comparable among treatment groups in the Controlled Phase 2/3 Studies as of 13 December 2004. All-causality adverse events of an allergic nature for the Controlled Phase 2/3 Studies are presented in Table 129 and Table 130. Pruritus and urticaria were more common among SC insulin- than INH-treated patients with type 1 DM but occurred at more comparable incidences among treatment groups for type 2 patients. Similarly, contact dermatitis was more common among INH- than SC insulin-treated patients with type 1 DM but occurred

at comparable incidences among treatment groups for type 2 patients. Asthma was more common among INH- or SC insulin-treated than OA-treated patients with type 2 DM but occurred at comparable incidences between treatment groups for type 1 patients. Allergic rhinitis was more common among INH- than SC insulin-treated patients with type 1 DM, but was less common in INH-treated patients than SC insulin-treated patients with type 2 DM. These data do not suggest the presence of a treatment-associated difference in the incidence of adverse events of an allergic nature.

Table 129. Summary of All-Causality Adverse Events of an Allergic Nature Among Adults by Body System and Preferred Term: Adult Type 1 Patients in Controlled Phase 2/3 Studies

	Number (%) of Patients	
	INH N=698	**SC N=705**
Body as a Whole		
Allergic Reaction	34 (4.9)	28 (4.0)
Anaphylactoid Reaction	0	0
Appl./Inj./Incision/Insertion Site Pain	3 (0.4)	2 (0.3)
Appl./Inj./Incision/Insertion Site Reaction	1 (0.1)	0
Appl./Inj./Incision/Insertion/Device Complication	2 (0.3)	1 (0.1)
Face Edema	2 (0.3)	2 (0.3)
Granuloma	1 (0.1)	1 (0.1)
Metabolic and Nutritional		
Lipodystrophy	3 (0.4)	1 (0.1)
Respiratory		
Asthma	9 (1.3)	9 (1.3)
Rhinitis	100 (14.3)	72 (10.2)
Skin and Appendages		
Angioedema	1 (0.1)	0
Contact Dermatitis	4 (0.6)	1 (0.1)
Dermatitis	4 (0.6)	3 (0.4)
Eczema	2 (0.3)	2 (0.3)
Maculopapular Rash	1 (0.1)	2 (0.3)
Petechial Rash	0	0
Pruritus	2 (0.3)	10 (1.4)
Rash	19 (2.7)	17 (2.4)
Urticaria	1 (0.1)	4 (0.6)
Vesiculobullous Rash	5 (0.7)	5 (0.7)
Special Senses		
Conjunctivitis	16 (2.3)	11 (1.6)

INH=inhaled insulin, N=Number of subjects, and SC=subcutaneous short-acting insulin.
Cutoff date: 13 December 2004

Table 130. Summary of All-Causality Adverse Events of an Allergic Nature Among Adults by Body System and Preferred Term: Type 2 Patients in Controlled Phase 2/3 Studies

	Number (%) of Patients		
	INH N=1279	SC N=488	OA N=644
Body as a Whole			
Allergic Reaction	32 (2.5)	14 (2.9)	12 (1.9)
Anaphylactoid Reaction	0	1 (0.2)	1 (0.2)
Appl./Inj./Incision/Insertion Site Pain	2 (0.2)	2 (0.4)	1 (0.2)
Appl./Inj./Incision/Insertion Site Reaction	0	0	0
Appl./Inj./Incision/Insertion/Device Complication	3 (0.2)	1 (0.2)	1 (0.2)
Face Edema	9 (0.7)	4 (0.8)	1 (0.2)
Granuloma	1 (0.1)	0	0
Metabolic and Nutritional			
Lipodystrophy	4 (0.3)	2 (0.4)	1 (0.2)
Respiratory			
Asthma	26 (2.0)	11 (2.3)	3 (0.5)
Rhinitis	107 (8.4)	48 (9.8)	19 (3.0)
Skin and Appendages			
Angioedema	0	0	0
Contact Dermatitis	6 (0.5)	2 (0.4)	2 (0.3)
Dermatitis	3 (0.2)	8 (1.6)	1 (0.2)
Eczema	6 (0.5)	3 (0.6)	1 (0.2)
Maculopapular Rash	2 (0.2)	2 (0.4)	1 (0.2)
Petechial Rash	1 (0.1)	0	0
Pruritus	25 (2.0)	4 (0.8)	12 (1.9)
Rash	53 (4.1)	21 (4.3)	13 (2.0)
Urticaria	5 (0.4)	5 (1.0)	2 (0.3)
Vesiculobullous Rash	9 (0.7)	3 (0.6)	1 (0.2)
Special Senses			
Conjunctivitis	18 (1.4)	9 (1.8)	8 (1.2)

INH=inhaled insulin, N=Number of subjects, OA=oral agents, and SC=subcutaneous short-acting insulin
Cutoff date: 13 December 2004

One INH-treated patient who was insulin-using at entry to Study 1029 experienced an apparent hypersensitivity reaction characterized by bronchospasm and questionable allergic reaction to INH as treatment-related serious adverse events. This patient had a peak serum antibody level of 632 µU/mL approximately 2 months after initiating treatment, which was approximately 1 month after the serious adverse event. In comparison, the mean antibody level among INH-treated patients in Study 1029 was 75.58 µU/mL with a range of 1.05 – 7,296.00 µU/mL at 6 weeks of exposure. This patient's symptoms resolved promptly after discontinuation of INH and symptomatic treatment, despite the persistence of circulating insulin antibodies. There was no accompanying skin rash or angioedema reported.

6.6.3.6. Insulin Antibodies and Other Adverse Events

The following is a list of clinical parameters that have been analyzed using binary distribution plots to screen for evidence of both precedented and unprecedented syndromes potentially associated with insulin antibodies. Data from Studies 104, 106, 107, 108, 109, 110, and 1009 were used for the figures, and the Mayo assay was used to measure insulin antibodies. These analyses have not revealed unusual distributions of insulin antibody levels in patients with the specified clinical findings.

- Any Serious Adverse Event

- Discontinuation due to adverse events or laboratory abnormalities
- Adverse event group name "potential arthralgia" includes dictionary terms arthralgia, arthritis, arthrosis, joint disorder
- Adverse event group name "potential coronary artery disease" includes dictionary terms myocardial infarct, myocardial ischemia, chest pain, coronary artery disorder, coronary occlusion, angina pectoris
- Adverse event group name "potential non-coronary macrovascular disease" includes dictionary terms arterial thrombosis, arteriosclerosis, carotid thrombosis, cerebral ischemia, cerebrovascular accident, embolus, vascular disorder, mesenteric arterial occlusion
- Adverse event group name "potential neuropathy" includes dictionary terms neuropathy, paresthesia, hypesthesia, neuritis, neuralgia
- Adverse event group name "potential myopathy" includes dictionary terms myopathy, myositis, leg cramps, myalgia
- Adverse event group name "potential retinal disorder" includes dictionary terms retinal disorder, retinal hemorrhage, retinal detachment, vascular anomaly, eye hemorrhage
- Adverse event group name "potential nephropathy" includes dictionary terms nephrosis, albuminuria, creatinine increased
- Adverse event group name "potential pharyngitis" includes dictionary terms pharyngitis and laryngitis
- Adverse event group name "autoimmune disease" includes dictionary terms thyroiditis, hyperthyroidism, immune system disorder, alopecia, erythema nodosa, myasthenia, multiple sclerosis, Guillain-Barre syndrome, myoclonus, sclerosing cholangitis, rheumatoid arthritis, discoid lupus erythematosis, contact dermatitis, scleroderma, polymyositis, psoriasis, polyarteritis nodosa, granulomatosis, vasculitis, granulocytosis, arteritis
- Adverse event dictionary term "vesiculobullous rash"
- Adverse event dictionary term "rash"
- Abnormal serum creatinine
- End-of-study ALT (alanine aminotransferase) at or above 2 times the normal range
- New onset hypertension

6.6.3.7. Insulin Antibodies and Serum Insulin Levels

Chronic (12-24 week) INH or SC insulin administration does not appear to impact serum free insulin concentrations measured prior to insulin dosing.

Data from early Phase 3 studies appeared to suggest a relationship between insulin antibody and serum free insulin levels. An evaluation of the insulin assay used in these studies indicated that insulin antibodies interfered with the assay results. When the Linco insulin assay (Linco Research, Inc,; St. Charles, MO), which was not affected by insulin antibodies, was used in Study 1026, there was no indication that fasting plasma free insulin levels changed after 3-6 months of chronic dosing.

6.6.3.8. Patients with Highest Observed Antibody Levels

Consistent safety signals were not identified among patients with the highest observed antibody levels.

The following is a summary of clinical findings in the 37 patients with the highest antibody levels. Twenty-three patients were identified by retesting of samples with Mayo assay results >60% binding as described in Section 6.6.2.2.

Eleven (30%) of the 37 patients with the highest insulin antibody levels were pediatric patients, and 33 (89%) had type 1 DM. These observations are not surprising given the higher insulin antibody levels

generally observed among pediatric patients relative to adults and among patients with type 1 relative to type 2 DM.

No particular adverse event occurred consistently in these patients. In the majority of cases, the various adverse events that were reported resolved despite persistence of insulin antibodies.

Overall, 14 of these 37 patients ended their study drug treatments with, or had at the 1-year data cut point for ongoing studies, HbA_{1c} levels which were > 0.5 percentage points higher than their levels at screening, and 10 patients had HbA_{1c} declines of > 0.5 percentage points relative to their levels at screening. Of the 12 cases with worsening glycemic control, only 1 was associated with progressive increases in HbA_{1c}. This patient was discontinued from the Study 111 after approximately 2 years and 3 months of INH treatment. The investigator reported the reason for this discontinuation as a protocol violation; "elevated HbA_{1c}".

Insulin dosing patterns over time were variable in these patients. No cases of severe insulin resistance were identified.

Twelve of the 37 patients (32%) were withdrawn from the studies prematurely (Table 131). Three of the 37 patients (8%) discontinued due to known or possible respiratory issues: shortness of breath attributed to anxiety, reactive airway disease attributed to bronchial spasm, and non-productive cough attributed to study treatment. One patient discontinued due to laboratory abnormality, "elevated insulin antibodies". There were no clear clinical sequelae attributed to the insulin antibodies in this case. Overall, there was no consistent reason for the reported study discontinuations.

Table 131. Status of Patients with the Highest Observed Insulin Antibody Levels in All Phase 2/3 Studies

Status	Number of patients
All Evaluated subjects	37
Completed Study 111	16
D/C for insufficient clinical response	3
D/C for withdrawn consent	3
D/C for adverse events	3
D/C for laboratory abnormality	1
D/C for protocol violation	1
D/C for "Other"	1
Ongoing as of 1-year exposure date	9

D/C=discontinued.

No consistent radiographic abnormalities were identified in these patients.

Insulin antibodies did not appear to be related to changes in total hypoglycemic event rates over time, and, although some fasting plasma glucose values were low and/or low-normal in some of these patients, the variability among the values precludes concluding a causal relationship between insulin antibodies and fasting plasma glucose.

In conclusion, consistent safety signals were not detected among the 37 patients with the highest insulin antibody levels. The small sample size, however, and the lack of an appropriate comparator group limit the utility of this analysis.

6.6.4. Inhaled Insulin Drug Substance and Immunogenicity

There is no evidence that an inherent immunogenicity of the insulin drug substance used in INH clinical trials explains the antibody response observed in INH-treated patients. In sanofi-aventis Study 3002, 476 insulin-naïve patients with type 2 DM were randomized to receive either sanofi-aventis human insulin or Huminsulin® (Eli Lilly human insulin) subcutaneously for 1 year. Both patient groups had comparable insulin antibody development.

Data from Study 1026 also suggests no unusual immunogenicity associated with sanofi-aventis insulin administered subcutaneously. In this study, patients with type 1 DM who had not been treated with sanofi-aventis insulin for at least 6 months prior to screening were randomized to receive either an INH or a SC insulin regimen, using sanofi-aventis insulin, for a period of 6 months. There was little change in mean and median antibody levels in the SC insulin group but a clear increase in mean and median insulin antibody levels among patients receiving INH.

The above data suggest that there is no unusual immunogenicity associated with the insulin drug substance used in INH clinical trials. Alterations in immunogenicity occurring after processing of the drug substance into the inhaled insulin drug could not be assessed with these data.

6.7. Cardiac Safety

Data from the INH clinical database do not indicate that INH treatment, in comparison with SC insulin or OA treatment, is associated with compromised cardiac safety. There is no evidence that INH affects systolic or diastolic blood pressure, heart rate, or ECG results. In addition, review of adverse events and serious adverse events indicates that INH treatment is not associated with an increased occurrence of myocardial ischemia, cardiac arrhythmia, or cardiac failure.

The overall incidences of cardiovascular adverse events and SAEs were comparable among treatment groups for both type 1 and type 2 patients in the Controlled Phase 2/3 Studies (Table 132).

Table 132. All-Causality Cardiac Adverse Events and Serious Adverse Events: Adult Patients in Controlled Phase 2/3 Studies

	Number (%) of Patients				
	Type 1 Patients		Type 2 Patients		
	INH	SC	INH	SC	OA
	N=698 SME=7207	N=705 SME=7565	N=1279 SME=13384	N=488 SME=6060	N=644 SME=6452
Adverse events*	86 (12.3)	78 (11.1)	242 (18.9)	93 (19.1)	106 (16.5)
Serious adverse events†	5 (0.7)	7 (1.0)	30 (2.3)	15 (3.1)	14 (2.2)

*Subjects with adverse events of the Cardiovascular System according to COSTART
†Subjects with serious adverse events of the Cardiac Disorders system organ class according to MedDRA
INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral agents, N=number of subjects, and SME=subject-months of exposure.
Cutoff date: 13 December 2004

The incidences of cardiovascular adverse events and cardiac SAEs consistent with myocardial ischemia were comparable among treatment groups. The adverse event, but not the SAE, "chest pain" in type 1 patients was more common in the INH than SC group. However, the incidence of chest pain was comparable among treatment groups in type 2 patients (Table 133 and Table 134). In addition, investigator terms for events coding to the preferred term "chest pain" as an adverse event were imprecise and included terms not indicative of cardiac events. Overall, specific adverse event and SAE incidences indicate that INH is not associated with increased risk of myocardial ischemia.

Table 133. All-Causality Adverse Events Consistent with Myocardial Ischemia: Adult Patients in Controlled Phase 2/3 Studies

	Number (%) of Patients				
	Type 1 Patients		Type 2 Patients		
	INH	SC	INH	SC	OA
Preferred term	N=698	N=705	N=1279	N=488	N=644
Cardiovascular events					
Angina pectoris	2 (0.3)	3 (0.4)	12 (0.9)	2 (0.4)	16 (2.5)
Coronary artery disorder	0	3 (0.4)	6 (0.5)	1 (0.2)	0
Coronary occlusion	0	0	2 (0.2)	1 (0.2)	0
Myocardial infarct	2 (0.3)	1 (0.1)	11 (0.9)	3 (0.6)	6 (0.9)
Myocardial ischemia	1 (0.1)	0	3 (0.2)	1 (0.2)	1 (0.2)
Other adverse events					
Chest pain	27 (3.9)	12 (1.7)	61 (4.8)	20 (4.1)	21 (3.3)
Chest pain substernal	0	0	2 (0.2)	2 (0.4)	0

INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral agents, and N=number of subjects.
Cutoff date: 13 December 2004

Table 134. All-Causality Serious Adverse Events Consistent with Myocardial Ischemia: Adult Patients in Controlled Phase 2/3 Studies

	Number of Events (Events per 1,000 Patient-Months)				
	Type 1 Patients		Type 2 Patients		
	INH	SC	INH	SC	OA
	N=698	N=705	N=1279	N=488	N=644
Preferred Term	SME=7207	SME=7565	SME=13384	SME=6060	SME=6452
Cardiac Disorders					
Acute myocardial infarction	0	0	4 (0.3)	0	2 (0.3)
Angina pectoris	1 (0.1)	0	2 (0.1)	1 (0.2)	4 (0.6)
Angina unstable	0	1 (0.1)	4 (0.3)	1 (0.2)	1 (0.2)
Coronary artery disease	0	2 (0.3)	5 (0.4)	3 (0.5)	0
Coronary artery occlusion	0	0	1 (0.1)	2 (0.3)	0
Coronary artery stenosis	0	0	1 (0.1)	0	0
Myocardial infarction	3 (0.4)	3 (0.4)	7 (0.5)	5 (0.8)	5 (0.8)
Myocardial ischemia	0	0	1 (0.1)	1 (0.2)	0
Other disorders					
Chest pain	2 (0.3)	1 (0.1)	7 (0.5)	1 (0.2)	4 (0.6)

INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral agents, N=number of subjects, and SME=subject-months of exposure.
Cutoff date: 13 December 2004

Similarly, specific adverse event and SAE incidences do not suggest that INH treatment is associated with an increased risk of cardiac arrhythmia or cardiac failure.

6.8. Safety in Special Populations

Elderly Patients

Overall, the data support the safety and toleration of INH, compared with SC insulin or OAs, in the treatment of elderly patients with type 2 DM. There were only 3 patients ≥ 65 years old with type 1 DM in the NDA database. Additionally, the data do not indicate that special dosing considerations are required for elderly patients with type 2 DM since intrasubject variability in pharmacokinetic profile and

glucose lowering ability among INH-treated elderly, obese patients was comparable to or lower than that for SC-treated patients (Section 4.1.5).

Adolescents and Children

The safety results for pediatric patients were consistent with those of adult patients with type 1 DM. An indication in pediatric patients is not sought at this time.

Obese Patients

Overall, the data support the safety and toleration of INH, compared with SC insulin or OAs, in the treatment of obese patients with type 2 diabetes. In the Controlled Phase 2/3 Studies, the number of type 1 patients with BMI $\geq$ 30 kg/m^2 was too small, however, to allow specific, definitive comparisons to be made of adverse event incidence between obese and non-obese patients. Additionally, the data do not indicate that special dosing considerations are required for obese patients since, as noted above, intra-subject variability in pharmacokinetic profile and glucose lowering ability among INH-treated elderly, obese patients was comparable to or lower than that for SC-treated patients (Section 4.1.5).

Patients with Mild to Moderate Asthma and/or COPD

The safety and toleration of INH in patients with mild to moderate asthma or COPD was evaluated in Clinical Pharmacology Studies 009 and 1005, respectively, in a subpopulation of patients with mild to moderate asthma or COPD in Controlled Phase 2/3 studies, and in Studies 1028 and 1030. The results of the Phase 2/3 Studies are discussed in detail in Section 6.5 and synopses of Studies 1028 and 1030 are appended. Patients with mild to moderate asthma or COPD did not experience any unexpected findings related to the safety and efficacy of INH compared to patients without these disorders. The data indicate that INH is as well tolerated by patients with mild to moderate asthma or COPD as by patients with neither disorder. As with other insulins, INH dose will require titration to effect in all patients. The data do not suggest that special dosing considerations will be required for patients with mild to moderate asthma or COPD.

Intercurrent Respiratory Illness

Patients with intercurrent respiratory illness (e.g., bronchitis, upper respiratory tract infections, rhinitis) rarely discontinued or temporarily interrupted treatment with INH (Section 6.3.1). There was no evidence of increased risk of hypoglycemia or worsening glycemic control in INH-treated patients with intercurrent respiratory illness compared to SC insulin-treated patients (Table 135 and Table 136).

Table 135. Fasting Plasma Glucose Concentration Among Patients with Intercurrent Respiratory Illness

	Mean (Change from Baseline) Fasting Plasma Glucose (mg/dL) [N]			
	Not During Intercurrent Respiratory Illness		During Intercurrent Respiratory Illness	
Patient Group*	INH	Comparator	INH	Comparator
Type 1	161.5 (-19.4) [170]	171.6 (-1.4) [159]	170.6 (-10.1) [177]	175.8 (2.9) [164]
Type 2 insulin-using at study entry	138.1 (-13.0) [111]	151.5 (-6.3) [95]	136.5 (-13.5) [115]	144.4 (-12.3) [99]
Type 2 non-insulin-using at study entry	186.3 (-28.5) [98]	191.0 (-23.3) [65]	183.6 (-31.3) [102]	192.5 (-21.5) [70]

*Patient group refers to DM type and, for patients with type 2 DM, previous insulin exposure.
INH=inhaled insulin.
Cutoff date: 25 June 2004

Table 136. Hypoglycemic Event Rates* Among Patients with Intercurrent Respiratory Illness

	Crude Hypoglycemic Event Rate (Events per Subject-Month) [N]			
	Not During Intercurrent Respiratory Illness		During Intercurrent Respiratory Illness	
Patient Group†	INH	Comparator	INH	Comparator
Type 1	0.969 [414]	0.950 [383]	1.049 [416]	1.294 [384]
Type 2 insulin-using at study entry	0.077 [260]	0.151 [232]	0.074 [261]	0.213 [234]
Type 2 non-insulin-using at study entry	0.112 [296]	0.101 [189]	0.142 [296]	0.047 [191]

*Hypoglycemia is defined as blood glucose ≤ 36 mg/dL and/or a patient's requiring assistance.
†Patient group refers to DM type and, for patients with type 2 DM, previous insulin exposure.
INH=inhaled insulin.
Cutoff date: 25 June 2004

As with SC insulin, close monitoring of blood glucose concentrations and dose adjustment may be required in INH-treated patients during intercurrent respiratory illness.

Renal/Hepatic Impairment

The effect of renal or hepatic impairment on the pharmacokinetics of INH has not been studied. As with other insulins, the dose requirements for INH may be reduced in patients with renal or hepatic impairment, and this is noted in the proposed USPI.

Smoking

Because smoking enhances the rate of absorption and bioavailability of INH, INH should not be used in smokers as indicated in the proposed USPI.

Interactions with Medications

It is well established that many substances affect glucose metabolism and their use may require dose adjustments of human insulin; therefore, no specific studies of interactions with these types of concomitant medications, examples of which are listed in the proposed USPI, were performed.

Pregnancy

Animal reproduction studies have not been conducted with INH, and the safety of INH in pregnant or lactating women has not been evaluated in long-term studies. INH should be designated as "Pregnancy: Category C" and should be given to a pregnant women only if clearly needed, as noted in the proposed USPI.

Pregnancy was an exclusion criterion in Phase 2/3 Studies and in all Phase 1 studies except Study 1007, which evaluated the pharmacokinetics and pharmacodynamics of INH in women with GDM or PGDM. The absorption of INH in patients with GDM or PGDM was consistent with that in non-pregnant patients with type 2 DM and no safety concerns emerged during this study.

Twelve women, ten of them treated with INH, became pregnant while participating in the Phase 2/3 studies. All patients were discontinued, as required by the protocol. The patients and their outcomes are listed in Table 137. These data do not suggest a safety risk attributable to INH, especially when

compared to the known incidence of perinatal complications associated with pregnancy in patients with diabetes.

Table 137. Pregnancy Occurrence and Outcome: All Phase 2/3 Studies

Study/ (Age in years) [DM type]	Days on INH prior to DC	Estimated Gestation at Last INH Dose	Last IAB level	Last HbA1c	Pregnancy Outcome
INH-Treated Patients					
111/(29) [1]	243	1-2 months	14% binding	8.4%	No complications during C-section delivery.
111/ (37) [2]	209	4 weeks	21% binding	7.9%	Spontaneous abortion, with an abnormal fetal karyotype. Reported causality: Not attributed to study drug.
111/(22) [1]	916	unknown	23% binding	9.2%	Spontaneous abortion. Reported causality: Possibly related to high HbA1c. 11% binding (1-month post spontaneous abortion)
102E/(31) [1]	207	6 weeks	Not measured	8.9%	Healthy male birth by C-section at 36 weeks. No problems were reported.
1022/(27) [1]	42	2 months	24 µU/mL	7.8%	Male birth.
106/(28) [1]	53	unknown	< 3% binding	5.5%	Unknown, patient moved out of state.
1022/(21) [1]	110	11 weeks	20 µU/mL	9.2%	Premature labor at 31 weeks gestation. C-section delivery at 32 weeks. The neonate had cardiomegaly and was macrosomic for gestational age and died 2 days after delivery.
1022/(25) [1]	176	unknown	89 µU/mL	9.0%	Spontaneous abortion shortly after becoming pregnant.
1022/(42) [1]	304	5 weeks	185 µU/mL	7.2%	Spontaneous abortion at 10 weeks.
1027/(31) [1]	86	3 months	31 µU/mL	5.6%	Healthy baby born. During first hour post birth, the infant experienced a decline in blood glucose levels. No intervention was required. Blood glucose returned to normal level 1 hour after birth.
Comparator-Treated Patients					
1022/(29) [1]	NA	NA	4.7 µU/mL	6.9%	Baby born at 37 weeks at a weight of 3,880g with APGAR scores of 6 and 9. The baby had a hypoglycemic event and was considered large for 37 weeks.
1022/(20) [1]	NA	NA	< 2 µU/mL	6.2%	No complications/limitations during pregnancy.

DM=diabetes mellitus, DC=discontinuation, IAB=insulin antibody, HbA1c=glycated haemoglobin, C-section=cesarian section, APGAR=appearance/pulse/grimace/activity/respiration, NA=not available
Data cutoff: 25 June 2004. The sponsor has learned of two additional pregnancies that occurred in the clinical development program as of 13 December 2004. The patients were discontinued and follow-up continues.

Withdrawal and Rebound

As is the case with SC insulin, withdrawal from INH treatment or transfer to another insulin requires close metabolic monitoring under medical supervision.

The effect of withdrawal of INH and its replacement by SC insulin or OAs was evaluated in Studies 111, 1001, 1002, and 1027. Discontinuation of INH resulted in a transient increased incidence of hypoglycemia as the replacement treatment regimen was established in Study 111 (Table 138).

Table 138. Analysis of Hypoglycemic Event Rates (Study 111)

	Primary Analysis Set				
Treatment (post-baseline interval)	**N (%) with event**	**Total Events**	**Total Patient-months**	**Event Rate***	**Risk Ratio (95% CI)**
Patients with Type 1 DM					
INH (0-4 weeks)	134 (78.4)	624	157.3	4.0	0.89 (0.86, 0.92)**
INH (> 8-12 weeks)	126 (73.7)	660	157.3	4.2	
INH (> 20-24 weeks)	123 (73.7)	637	152.8	4.2	
INH (overall)	158 (92.4)	4290	1034.0	4.1	
DCINH (0-4 weeks)	147 (78.6)	959	172.0	5.6	
DCINH (> 8-12 weeks)	141(75.4)	807	172.0	4.7	
DCINH (> 20-24 weeks)	130 (71.0)	749	168.0	4.5	
DCINH (overall)	176 (94.1)	5342	1148.0	4.7	
Patients with Type 2 DM					
INH (0-4 weeks)	38 (19.2)	81	182.1	0.4	0.62 (0.57, 0.69)**
INH (> 8-12 weeks)	37 (18.7)	83	182.1	0.5	
INH (> 20-24 weeks)	22(11.3)	44	178.0	0.2	
INH (overall)	75 (37.9)	443	1191.1	0.4	
DCINH (0-4 weeks)	49 (24.1)	167	186.7	0.9	
DCINH (> 8-12 weeks)	46 (22.7)	110	186.7	0.6	
DCINH (> 20-24 weeks)	35 (17.5)	88	181.9	0.5	
DCINH (overall)	98 (48.3)	727	1226.8	0.6	

*Number of events/subject-months
**Ratio of event rates of continue INH vs. discontinue INH; Risk ratio and 95% CI were based on a counting process approach for recurrent time-to-event data.
DCINH=discontinuation of INH treatment

FEV_1 and DLco increased after INH withdrawal relative to INH continuation, and insulin antibody levels decreased.

6.9. Safety Summary

These studies demonstrated that:

- The overall incidence of all causality adverse events was similar for INH- and SC insulin-treated patients with type 1 DM. Among patients with type 2 DM, the overall incidence of all-causality adverse events was comparable between the INH and SC groups and lower in the OA group.
- Hypoglycemia was the most common adverse event for INH- and SC insulin-treated patients, consistent with the physiologic effects of insulin, and it occurred in nearly all patients with type 1 DM and the majority of patients with type 2 DM. The event rates for hypoglycemia, defined as blood glucose concentration ≤ 36 mg/dL and/or requiring assistance, were lower among INH- than among SC-treated adults, and hypoglycemic event rates decreased with time in study.
- The all-causality respiratory adverse events cough and dyspnea occurred at greater incidence in INH- than in comparator-treated patients with type 1 or type 2 DM. Most respiratory adverse events were mild or moderate in severity and decreased in prevalence with time in study. Patients reported that most cough occurred within seconds to minutes of INH inhalation, indicating that most cough among

INH-treated patients was due to a mild irritant effect associated with dry powder inhalation as opposed to an underlying functional or structural etiology.

- INH treatment was not associated with any clear changes in laboratory test results, or ECG findings, or with consistent chest x-ray or HRCT findings
- Patients who were treated with INH in controlled studies rarely discontinued studies prematurely. When patients did so, the reasons for discontinuation usually were unrelated to study drug. Although occurring infrequently, discontinuations due to cough and dyspnea were more common in INH- vs. SC insulin-treated patients with type 1 DM. Discontinuations due to cough, asthma, and dyspnea were more common in INH- vs. comparator-treated patients with type 2 DM.
- The incidence of all-causality SAEs was lower for INH- than for SC insulin-treated patients with type 1 DM in Controlled Phase 2/3 protocol studies. For patients with type 2 DM, the incidences of all-causality SAE cases were comparable among treatment groups. The majority of all-causality SAEs was due to hypoglycemia in patients with type 1 DM and myocardial infarction, chest pain, and angina in patients with type 2 DM.
- INH treatment was not associated with an increased incidence of pulmonary SAEs or abnormalities in chest x-ray and HRCT results. Pulmonary function test result declines associated with INH treatment were small, non-progressive beyond 2 weeks, and reversible upon discontinuation of INH treatment. Patients with mild to moderate ULD did not experience adverse clinical outcomes while receiving INH compared to patients without ULD. The efficacy, safety, and toleration profiles of patients with the greatest declines in PFT results were comparable to the efficacy, safety, and toleration profiles of patients with lesser declines in PFT results.
- INH treatment was associated with increased insulin antibody levels relative to comparator therapies. The response was more pronounced in patients with type 1 DM compared to type 2 DM. Insulin antibody levels reached a plateau after approximately 6-12 months of treatment, and discontinuation of INH treatment resulted in a decline in insulin antibody levels. There is no apparent association between INH-associated insulin antibodies and adverse clinical outcomes or changes in glycemic control.
- INH treatment was not associated with an increased risk of cardiac injury or dysfunction
- INH is safe for use in the elderly and the obese.

Overall, the data from the INH clinical program support the conclusion that INH treatment in adult patients with type 1 or type 2 DM is well tolerated and safe.

7. BENEFITS, RISKS, AND RISK MANAGEMENT PROGRAM

Prior to the discovery of insulin, the life expectancy of a juvenile patient with DM was less than one year following diagnosis.[69] The discovery of insulin in the 1920s is, therefore, one of the great turning points in medical history. In the 80 years since insulin was introduced, significant technological advances have been made in DM therapy. Insulin therapy has evolved from partially purified animal products to highly purified rhu-insulins and insulin analogs. Despite these advances, all currently available insulins must be delivered using a needle – the same route of administration used since the discovery of insulin in the 1920s. INH, because it delivers insulin by an alternative, noninvasive route of administration, represents a major therapeutic advance in the progressive history of DM treatment.

DM is a growing global health problem: from 135 million adults in 1995 to a projected 300 million people worldwide by the year 2025. More people are developing DM at a younger age due to poor diets and the adoption of sedentary lifestyles. Despite the technological advances in insulin therapy and an understanding of the importance of good glycemic control in managing DM and preventing complications of the disease, more than half of patients in Western Europe and the United States fail to achieve the recommended target of HbA_{1c} <7%. Indeed, nearly 20% of patients are above 9.5%. These patients are at a significantly increased risk for cardiovascular disease, end-stage renal disease, and a host of microvascular complications that adversely affect the quality of life for patients with DM and are extremely costly on a societal level. Consequently, there is an urgent and pressing need for therapies that can assist in improving glycemic control for patients with DM.

The injection route for insulin delivery has proven to be a barrier to the attainment of good glycemic control for many patients with DM. Limitations of insulin injection therapy include poor patient acceptability, due to the delivery mode. It has been estimated that a typical patient with DM on the recommended dosage regimen of four insulin injections per day has to endure more than 15,000 injections in one decade.[48] For this reason, many patients do not adopt or cannot maintain the more complicated and aggressive intensive insulin treatment regimens that would allow them to achieve good glycemic control. Others (those with type 2 DM) may defer starting treatment with insulin until OA therapy has ceased to be effective despite maximum doses over a prolonged period of time, during which patients have had continued poor glycemic control. In short, many patients are suboptimally treated and do not achieve good glycemic control because of the limitations of injection therapy.

To counter these limitations, non-invasive delivery methods of insulin have been under active investigation for many years. Because of its mode of delivery via the pulmonary system, INH has emerged as the most promising non-invasive alternative to insulin injection therapy. With a faster onset of action than SC regular insulin and a comparable onset of action to insulin lispro, INH can replace pre-meal rapid-acting insulin injections, thus providing easy coordination with meals and effective postprandial glucose control without the disadvantages of injections.

INH has been evaluated in a comprehensive clinical development program. A total of 3,605 patients (3,274 adults) have received INH. Most patients have been treated for at least one year, with some patients receiving INH for more than 84 months. Results from the clinical development program provided in Pfizer's pending New Drug Application show that an INH treatment regimen provides a rapid onset of glucose-lowering action, effective glycemic control, as assessed by HbA_{1c}, in patients with type 1 or type 2 DM, and that an INH regimen is preferred by patients to either a SC insulin or OA treatment regimen.

In clinical trials conducted in patients with type 1 or type 2 DM, INH in combination with intermediate- or long-acting insulin provided reductions in HbA_{1c} levels comparable to a regimen including SC short-acting insulin. The percentage of patients who achieved the target of HbA_{1c} <7% was comparable between treatment groups for patients with type 1 DM and was higher for patients with type 2 DM who received INH compared to a SC insulin regimen. In patients with type 2 DM previously failing treatment with OA or diet and exercise, INH either alone or in combination with OA provided greater reductions in HbA_{1c} compared to OA treatment. A higher percentage of patients taking INH either alone or in combination with OA achieved the target of HbA_{1c} <7% compared to OA treatment. Furthermore, glycemic control was maintained by patients with type 1 or type 2 DM for prolonged periods of time. Thus, INH provides effective glycemic control for patients with type 1 or type 2 DM; and for patients with type 2 DM who are failing on conventional therapy, the addition of INH results in improved control.

INH treatment was preferred by patients to either SC insulin or oral antidiabetic agent regimens. In addition, patients with type 1 or type 2 DM treated with INH had statistically and clinically significant improvements in patient-reported health-related quality of life and treatment satisfaction when compared with SC insulin.

Results of the clinical development program have indicated that INH is safe for use in the target population, namely, adults with DM. The adverse effects of INH use identified during the clinical development program included some expected with the use of insulin, such as hypoglycemia, and others related to the novel pulmonary route of delivery, including antibody formation and small PFT declines.

As with all insulin, hypoglycemic reactions may be associated with the administration of INH. Hypoglycemia was the most commonly reported adverse event during the course of the clinical development program, but event rates were lower in INH-treated patients with type 1 or type 2 DM compared to SC insulin despite similar glycemic control. Hypoglycemic event rates in patients with type 2 DM (non-insulin-using at study entry) were higher for INH-treated patients compared to OA(s) alone, as expected with the improved glycemic control provided by INH. However, in patients with type 1 DM or type 2 DM, most events were mild or moderate in severity, and only two patients, both with type 1 DM, discontinued as a result of hypoglycemia. INH should not be used by smokers or those who have stopped smoking for 6 months or less prior to starting INH treatment, and 3 x 1 mg blisters are not interchangeable with a 1 x 3 mg blister.

Although INH-treated patients experienced greater end-of-study and change from baseline insulin antibody levels than comparator-treated patients, there is no evidence of an association between INH-associated antibodies and adverse clinical outcomes or changes in glycemic control. As with other insulins, rare, but potentially serious, generalized allergy to insulin may occur.

Because of its novel mode of delivery, the effect of INH on the respiratory system has been extensively evaluated. Increased cough was observed in patients who received INH compared to other treatment regimens. Most coughs were mild, occurred and resolved soon after treatment with INH had begun, and rarely resulted in discontinuation of treatment. Increased cough has been associated with the use of other dry powder inhaler medications. Most patients who experienced intercurrent respiratory illness were able to continue using INH without an increased risk of hypoglycemia or worsened glycemic control compared to SC insulin. Pulmonary function test result declines associated with INH treatment were small, non-progressive beyond 2 weeks, and reversible upon discontinuation of INH treatment. Patients with mild to moderate asthma or COPD may use INH, but patients with severe disease should not use it due to the limited clinical experience in this population. Bronchospasm has been rarely reported in patients using INH.

The risks that have been identified and thoroughly investigated during the INH clinical development program are addressed in the proposed USPI. Recognizing that INH utilizes a novel route of insulin administration, the sponsor is committed to a comprehensive risk management program to further refine our understanding of the product profile, to optimize patient safety, and to realize the long-term therapeutic benefits of this novel treatment. Important identified or potential risks and subpopulations having limited data are addressed in the draft Risk Management Plan (RMP)(Table 139). For each risk and subpopulation, the planned or ongoing risk minimization and assessment activities are shown. Table 140 contains a summary of completed, ongoing and proposed risk management studies (with estimated study start and end dates).

Table 139. Activities to Minimize Risk and Ongoing/Proposed Studies

	Activities to Minimize Risk			Ongoing/Proposed Studies and Activities to Assess Risk								
	Package Insert/ Patient Inform. Leaflet	Health Care Education/ Customer Care	Blister Package Differentiation	Large Simple Trial (5 yr)	Long Term PFT Safety Study (5 yr)	Epi Lung Cancer Study (12 yr)	Asthma/ COPD Studies	Drug Interaction Studies/ Passive Smoking	Pediatric Studies	Mechanistic Studies – Clinical and Pre-Clinical Studies (see note)	Enhanced Pharmaco-vigilance Program	Data Capture Aid
Important Identified and Potential Risks												
Smoking-induced alterations in Pharmacokinetics	√	√						√			√	√
Changes in Pulmonary Function	√	√		√	√		√	√	√	√	√	√
Increased Insulin Antibody Levels	√	√			√				√	√	√	√
Asthma and COPD	√	√					√				√	√
Rare Pulmonary Events	√	√		√		√					√	√
1 and 3 mg dose inequivalence	√	√	√								√	√
Limited Information												
Congestive Heart Failure	√	√									√	√
Very Elderly Patients (>75 years old)	√	√		√	√						√	√
Pregnancy	√	√									√	√
Pediatrics	√	√							√		√	√

Note: Mechanistic studies include studies investigating the mechanism of the INH-associated PFT changes and studies characterizing the INH-associated antibody response

Table 140. Risk Management Study Timelines – Completed, Ongoing and Proposed Studies

	Completed	Ongoing	New	Start	End
Bronchodilator - Steroid Study (Study 1056)	√				
Passive Smoking Study (Study 1057)	√				
Long-Term PFT Studies (Studies 1022/1029*)		√			2012
Asthma (Study 1028)		√			2008
COPD (Study 1030)		√			2011
Large Simple Trial (Real World - Study 1069)			√	2006	2014
Epidemiologic Study of Lung Cancer (Study 1071)			√	2006	2019
Pediatric Studies			√	2006	2009
PFT Mechanisms - Clinical					
BAL (Studies 1052/1053)		√			2006
Proposed Clinical Trials			√	2006	2008
Expanded PFT Analysis			√	2005	2006
PFT Mechanisms – Pre-Clinical					
Proposed Mouse Model Study			√	2006	2008
Insulin Antibodies					
IgG Subclass Study			√	2005	2006
NOD** Mouse Beta Cell Preservation Study			√	2006	2007

*5-year extensions of Studies 1022 and 1029
**Non-obese diabetic
Start and End dates are estimates.

The activities to minimize risk include:

- Within the proposed Package Insert (PI) and the Patient Information Leaflet (PIL), specific contraindications, warnings and recommendations are included to alert physicians, pharmacists, and patients to the proper prescription and use of INH.
- Education of health care providers (HCPs) and provision of patient education materials to assist HCPs to teach patients the proper use of INH.
- A Customer Care Program with a call center with toll free access will be available in each market where INH is launched. This program will respond to device-related inquiries, provide rapid device replacement, and direct safety or product complaint issues to the appropriate sources.
- Package differentiation of 1 mg and 3 mg blisters.

The program will include an enhanced pharmacovigilance program focused on the detection of adverse events that are novel or unexpected in terms of their clinical nature, severity, and/or frequency. Using the resources of established adverse event reporting, a cross-functional team (Risk Management Committee) will be charged with anticipating, detecting, analyzing, and responding to safety issues.

In addition to the established reporting systems, a structured questionnaire (Data Capture Aid) will be utilized to elicit detailed follow-up whenever a specific event (targeted events listed below) is reported. The objective of the Data Capture Aid, which is a risk management initiative, is to enhance the quality and depth of data collection for targeted events. This tool consists of a structured data collection instrument providing standardized prompts to ensure consistency and completeness in the medical assessment of each adverse event report. Adverse events targeted for enhanced information gathering for INH include the following: (1) pulmonary events: bronchospasm and airway obstruction, bronchiolitis and bronchiolitis obliterans, pulmonary fibrosis, pleural effusions, sarcoidosis, hypersensitivity pneumonitis, respiratory tract neoplasm; (2) events potentially related to insulin antibodies: immunologic insulin resistance, unusually prolonged hypoglycemia or persistent nocturnal hypoglycemia despite down titration of insulin; (3) hypoglycemia potentially related to dose substitution of 3x1 mg for 1x3 mg blisters; and (4) novel or unexpected events in terms of severity or frequency.

The Risk Management Plan provides for continued risk identification, assessment, and management in patients who use INH once marketed. To aid in the management of INH use, a *Customer Care Program* will be established where INH is launched. The *Customer Care Program* will be available to patients and health care personnel and will have the following functions:

- Training health care personnel to assist patients in proper use of INH;
- Providing rapid device replacement; if warranted;
- Responding to questions or complaints; and
- Facilitating safety and adverse event reporting.

The *Customer Care Program* will be accessible at any time of day through a Call Center with a toll-free telephone number, which will be included on many of the INH printed materials. Personnel answering calls will be trained to assist with general inquiries and to efficiently direct requests for medical information, reports of potential adverse events, or product complaints to the appropriate sponsor resources. The 24-hour Call Center will ensure prompt resolution of device-related issues. Malfunctioning devices will be replaced free of charge within the same day or by the next day either directly by the Call Center or through agreements with local suppliers in the distribution chain in each country. Each country in which INH is marketed will have contingency plans for supplying devices in extreme emergencies.

Healthcare professionals will be the primary source of patient training and medical advice for INH. At INH launch, considerable effort will be focused to introduce and educate health care providers (HCPs) on how to appropriately use the INH system. Efforts will be focused on educating HCPs and providing them with a variety of clear INH patient-education materials so that HCPs may integrate INH training into their existing insulin training programs.

Patient training materials will be available in multiple formats including print and video and will be developed following the usage guidelines as approved in the PI and PIL. Materials will educate patients on appropriate use and maintenance of the inhaler and blisters and will also advise patients on important precautions (e.g., lack of interchangeability of 1 mg and 3 mg blisters; appropriate use and maintenance of the inhaler; warning not to smoke tobacco). Reminder tools (e.g., refrigerator magnets) will also be provided for the biweekly replacement of the Insulin Release Unit. Where allowed by local law, direct contacts with patients to remind them of to replace the Insulin Release Unit will be explored. The Customer Care program will abide by all local regulatory guidelines with respect to regulatory requirements and patient privacy regulations.

The recently completed studies include:

- Bronchodilator – Steroid Study (Study 1056). In study 1056, INH was found to be well tolerated by non-diabetic, non-smoking patients with mild or moderate asthma [(38 moderate asthmatics (unmedicated screening FEV_1 ≥50% to <80% of predicted) and 41 mild asthmatics (unmedicated screening FEV_1 ≥80% to 100% of predicted)]. The results of Study 1056 show that on average, INH AUC0-360 and Cmax were lower in asthmatics than normals and increased by approximately 25% to 50% when administered 30 minutes after a single dose of salbutamol. Administration of fluticasone 30 minutes prior to INH did not have a significant effect on the pharmacokinetics of INH. Administration of INH 10 minutes prior to salbutamol did not have a significant effect on the bronchodilatory effect of salbutamol.

- Passive Smoking Study (Study 1057). The effect of passive cigarette smoke exposure on the pharmacokinetics of INH has been studied in a recently completed study (Study 1057). The results of

this study in healthy non-smoking volunteers indicate that passive exposure to cigarette smoke at levels consistent with what may be encountered in a variety of social settings results in a decrease in the bioavailability of insulin. Mean plasma insulin AUC_{0-360} was decreased on average by 17% and mean Cmax by 29%. This effect is opposite to and more modest than the effect of chronic cigarette smoking, and therefore does not present a safety risk to patients who are using INH and who are passively exposed to cigarette smoke. The decrease in INH bioavailability is consistent with an increase in 99mTc-DTPA lung clearance half-life that has been observed in response to acute passive cigarette smoke exposure as published by Yates et al.[70] The results of the present study and the work published by Yates et al. suggest that passive or side-stream cigarette smoke exposure decreases lung permeability.

The ongoing and proposed studies include:

- Long-term PFT Studies (5-year Extensions of Studies 1022/1029). Protocols 1022 and 1029 are proposed to be amended to obtain 5-year continuous (rather than 3-year continuous) and 7-year cumulative controlled PFT and respiratory safety data. In addition, the subset of patients in Study 1029 who have been evaluated with HRCT will continue to have HRCT evaluations at approximately yearly intervals and at end of study. All patients who have successfully completed 2 years of comparative treatment and six months of washout in these studies will be eligible to enter a 5-year extension during which time standardized PFTs will continue to be obtained every three months. Based on present projections, it is estimated that a total of approximately 272 type 1 and type 2 patients (n~135 on INH) from a combination of Studies 1022 and 1029 will complete seven years of comparative treatment in these amended studies. These studies will utilize the highly standardized PFT methodology already in place and, assuming an annual attrition rate of 20%, have the power to detect an additional treatment group difference in FEV_1 of 36 ml beyond that observed at the initial 3-month time point. This additional treatment-group difference translates into an approximate additional 5 ml/yr treatment group difference in FEV_1 decline between months 3 and 90 of the studies. A six-month withdrawal phase at the end of the extension studies will investigate reversibility of the excess decline in pulmonary function, if present.

- Asthma (Study 1028). This is the ongoing study to examine pulmonary safety of INH in adult patients with type 1 or 2 DM and a diagnosis or history of mild intermittent or mild to moderate persistent asthma for at least six months. A summary of the interim report is appended.

- COPD (Study 1030). This is the ongoing study to examine the pulmonary safety of INH for the treatment of type 1 and 2 DM in adults with COPD. A summary of the interim report is appended.

- Large Simple Trial (Study 1069: Real World Study). This is a proposed large post marketing, real world surveillance study will be conducted in 5000 patients with diabetes mellitus. This Large Simple Trial (LST) will be open label with 1:1 random assignment to INH or usual care with follow-up per usual medical care. This long-term real-world observational study will assess the patients with larger declines in lung function in routine clinical practice. The primary objective of the study is to estimate the relative risk of persistent decline in FEV_1, which is defined as exceeding 20% from baseline between INH-treated and comparator-treated diabetic patients. Spirometry measurements (FEV_1) will be obtained at baseline and at a frequency consistent with the approved PI. This study will target enrolment of a minimum of 10% very elderly (≥75 years of age) patients. The PI will be used to determine appropriate patient selection by the physician. The duration of the study is estimated to be 5 years and will have 80% power to detect a minimum relative risk of 1.8. Study updates will be provided on a yearly basis. The design of this study will be finalized in agreement with regulatory agencies.

- Epidemiologic Study of Lung Cancer. This is a proposed 12-year prospective population-based cohort study to compare lung cancer mortality between INH-treated and non-INH-treated patients. The Health Improvement Network (THIN) database in the UK, a primary care electronic medical record database, will be used to conduct the study. The THIN database includes nearly 2 million patients and is representative of the UK population with regard to age, sex, and geographic distribution. Currently, about 57,000 diabetic patients are registered in THIN. Detailed information on demographics, primary care diagnoses, prescription treatment, and outcomes are routinely recorded in the database. High quality smoking exposure data will be collected through a standard questionnaire specifically developed for this study. Based on preliminary power calculations, this study will have approximately 80% power to detect a relative risk of 1.5 for potential increased lung cancer risk associated with INH over a 12-year period. The estimate is based on the assumption that lung cancer mortality in diabetic patients is 1.5/1000 person-years, 100% participation rate of diabetic patients in THIN, 50% of 57,000 diabetic patients enrolled within 1 year, 10% lost to follow-up. The study will be initiated after INH is marketed in the U.K. Study progress and updated power estimates will be reviewed at pre-stated intervals.

- Pediatric Studies. A pediatric study program will be finalized in agreement with regulatory agencies.

- PFT Mechanism – Clinical Studies. The specific mechanism underlying the small INH-associated decreases in PFT (FEV_1 and DLco) is presently unknown. In recognition of the importance of understanding the mechanism responsible for these effects a thorough assessment of potential underling mechanisms is planned. A conceptual framework of mechanisms that could potentially underlie the observed PFT effect has been developed in concert with a group of external pulmonary consultants. This framework includes four potential mechanisms, all of which would decrease FEV_1 as a consequence of a reduction in airway caliber:

    (1) Airway smooth muscle contraction has been excluded based on results of completed and ongoing Phase 3 Group II clinical Studies 1027 and 1028. Namely, it has been demonstrated that the administration of INH does not cause an acute reduction FEV_1 within an hour of administration (Study 1027), and the administration of inhaled bronchodilators does not ameliorate the observed treatment group difference in change from baseline FEV_1 in a group of asthmatic diabetic patients treated with INH (Study 1028).

    (2) While airway inflammation cannot be completely excluded as a mechanism at present, the lack of inflammatory changes in the respiratory tract seen in the pivotal rat and monkey inhalation toxicology studies, the rapidity of the onset and offset of the treatment effect on PFTs demonstrated in Study 1027, the long-term stability of treatment group differences in lung function observed in the controlled clinical studies, and the absence of treatment-related findings by HRCT provide significant data against this hypothesis. Nonetheless, bronchoalveolar lavage Studies 1052 and 1053 have been initiated to directly assess for primary evidence of inflammation changes in the airway lining fluid of INH-treated type 1 and type 2 diabetics, respectively.

        - Study 1052. This is an ongoing bronchoalveolar lavage clinical study in patients with type 1 DM. It is a non-randomized, comparator-controlled sequential design study consisting of two treatment periods of 12 weeks each in patients with type 1 DM. The target enrollment is 20 patients, and the primary endpoint is changes in bronchoalveolar lavage (BAL) fluid, total cell count, and differential. The secondary endpoints include

changes in albumin and fibrinogen concentrations in BAL fluid, changes in Airways Visual Inspection Scale, and HRCT findings.

- Study 1053. This is an ongoing bronchoalveolar lavage study in patients with type 2 DM. It employs the same protocol as Study 1052 except that the study is being conducted in patients with type 2 DM.

(3) Osmotically-Mediated Fluid Shifts in the Airway Wall. To study this hypothesis it is proposed to conduct a new clinical trial.

- Proposed Clinical Mechanism Study. A 4-week, double blind crossover study in normal controls will examine the hypothesis that INH effect on PFTs is mediated as a consequence of osmotically-mediated fluid shifts in the airway wall. The primary endpoint will be treatment group differences in change from baseline FEV_1 and DLco.

(4) Physiologic Mechanisms. The kinetics of the onset and offset of the INH treatment effect on FEV_1 has been delineated in clinical Study 1027. Specifically, treatment group differences in change from baseline FEV_1 have been demonstrated to occur within 2 weeks of treatment initiation and to resolve within 2 weeks of discontinuation of therapy. The following pre-clinical and clinical proposals will address physiological mechanisms that could be mediating these effects.

- Expanded PFT Analysis. To investigate this hypothesis, spirometric and volumetric data derived from the controlled Phase 2/3 database will be analyzed (FVC, FEV_1, FEF_{25-75}, FEV_1/FVC ratio, TLC, RV, and RV/TLC). This analysis will be performed on all patients, patients who did not exhibit large declines in FEV_1 (<20% decline from baseline), and those patients who did experience large declines in FEV_1 (>20% from baseline). The results of this analysis will assist assessing whether mechanisms mediating both the small, INH-induced FEV_1 declines and larger FEV_1 declines observed in a small minority of diabetics patients are similar or represent distinct phenomena.

- PFT Mechanism – Pre-Clinical Studies. A pre-clinical study in a mouse model will provide a detailed assessment of pulmonary physiology in conjunction with an assessment of the integrity of the surfactant system in INH exposed animals.

- Insulin Antibody Studies. Two studies are proposed to study INH-associated insulin antibodies.

  - IgG Subclass Study. The objective of this study is to characterize insulin antibody IgG subclass profiles in patients with insulin antibodies. Anti-insulin IgG subclass profiles will be determined in samples from INH and SC insulin treated patients.

  - Non-obese diabetic (NOD) Mouse Beta-cell Preservation Study. The objective of this study is to evaluate the cellular immune response to intrapulmonary insulin administration in an animal model of type 1 DM. There is no evidence from the literature or from clinical trial data that INH poses an immunologic safety risk. However, based on multiple research reports, a study is proposed to test the hypothesis that the intrapulmonary administration of insulin can ameliorate the autoimmune process (as measured by onset of diabetes and histopathologic evaluation of lymphocytic islet inflammation) in the NOD mouse model. Such experiments will begin with evaluating techniques for intrapulmonary insulin

administration. Using a suitable method, intrapulmonary insulin will then be administered to pre-diabetic and/or NOD mice. Diabetes onset and pancreatic histopathology will be assessed compared to subcutaneous insulin administration and placebo controls.

The overall goal of the INH Risk Management Plan is to best ensure the safe and effective use of INH in the treatment of appropriate patients.

In conclusion, INH, an innovative non-invasive alternative to SC insulin, has been investigated in a comprehensive clinical development program. It has been shown to be safe and effective in providing glycemic control for adult patients with type 1 or type 2 DM when used as directed. With appropriate labeling and risk management, it is the sponsor's view that the benefits of INH clearly outweigh the risks. Approval of NDA 21-868 will assist the achievement of effective glycemic control and a reduction in diabetic complications by helping patients to adopt and/or maintain sufficiently intensive insulin treatment regimens.

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Appendix 1 Interim Results Studies A2171028 and A2171030

PROTOCOL A2171028: EFFICACY AND SAFETY OF INHALED HUMAN INSULIN (INH) COMPARED WITH SUBCUTANEOUS HUMAN INSULIN IN THE THERAPY OF ADULT SUBJECTS WITH TYPE 1 OR TYPE 2 DIABETES MELLITUS AND CHRONIC ASTHMA: A ONE-YEAR, MULTICENTER, RANDOMIZED, OUTPATIENT, OPEN-LABEL, PARALLEL-GROUP COMPARATIVE TRIAL

Interim Report: This interim report contains efficacy data from subjects who were treated up to and including 52 weeks; for standard safety, all treated subjects are included and all available data are analyzed through Week 52. Randomization and enrollment in this study are not yet complete: 72 INH subjects have been treated, and 11 have completed; 67 SC subjects have been treated, and 22 have completed.

Study Objectives: This study examines the safety (in particular, pulmonary safety), toleration, and efficacy of inhaled insulin for the treatment of type 1 and type 2 diabetes in adults with asthma. The primary objective of this interim report is to assess post-bronchodilator FEV_1 (forced expiratory volume in one second) and DLco (carbon monoxide diffusion capacity). Secondary objectives are to evaluate the effects of inhaled insulin versus SC insulin on asthma control, the frequency and severity of asthma exacerbations, and glycemic control.

Study Design: This is an open-label, 15-month, parallel-group, outpatient study comparing inhaled with SC human insulin treatment. Following a 3-week baseline run-in period during which all subjects receive SC insulin, subjects are being randomized to one year of treatment with either inhaled or SC insulin as their short-acting insulin; both groups use intermediate- or long-acting SC insulin. At the end of the treatment period, all subjects have a 6-week post-study run-out during which they use only SC insulin. Subjects are followed weekly for the first four weeks of the study to assess safety and adjust insulin dosing. Thereafter, follow-up occurs at increasing intervals up to 3 months for the last half of the study. All subjects perform daily self-monitoring of blood glucose (SMBG) and twice daily measure and record their peak flow/FEV_1, asthma symptoms, and bronchodilator use using an electronic peak flow meter/symptom diary. Pulmonary function (spirometry and single breath DLco), methacholine reactivity (selected sites), asthma control, and diabetes control are being assessed during regularly scheduled clinic visits throughout the year. Methacholine reactivity is optional for subjects and is not included in this report; it may be included in the final report if sufficient numbers of subjects participate.

Evaluation Groups:	**INH**	**SC**
Assigned to Treatment 139	n (%)	n (%)
Treated	72	67
Completed*	11 (15.3)	22 (32.8)
Discontinued	15 (20.8)	4 (6.0)
Ongoing at data cut-off	46 (63.9)	41 (61.2)
Analyzed for HbA1c:		
Full Analysis Set (HbA1c)	66 (91.7)	64 (95.5)
Analyzed for FEV1:		
Full analysis set (FEV1)	70 (97.2)	65 (97.0)
Analyzed for safety:		
Adverse events	72 (100)	67 (100)
Laboratory tests	70 (97.2)	66 (98.5)

*Subjects who have completed at least the comparative phase of the study, but not necessarily the follow-up phase

Diagnoses and Criteria for Inclusion of Subjects: A history of mild-to-moderate persistent or mild intermittent asthma (according to American Thoracic Society definitions) for at least six months prior to screening is required; subjects may be males or nonpregnant, nonlactating females, and may be ages 18-65, inclusive, for type 1 diabetes, or ages 18-75, inclusive, for type 2 diabetes. All are required to have been on a stable SC insulin administration schedule (at least BID for the 2 months prior to screening), and to have screening and pre-randomization glycosylated hemoglobin (HbA1c) between 5.5% and 11%, inclusive.

Efficacy Results: Treatment effects on mean HbA1c (%) are summarized in the following table.

Summary of Mean HbA1c (%) (Full Analysis Set, HbA1c)

Treatment Group	BL (SD)	Week 6 (SD)	Week 12 (SD)	Week 26 (SD)	Week 52 (SD)
INH	7.56 (1.05) N=66	7.13 (0.89) N=62	7.27 (0.96) N=51	7.40 (1.09) N=37	7.11 (1.05) N=10
SC	7.32 (1.09) N=64	6.94 (0.95) N=63	7.05 (0.98) N=47	7.48 (1.48) N=43	6.91 (1.06) N=22

Hypoglycemic events were also recorded. The hypoglycemic event rate decreased over time in the INH but not in the SC group. The overall crude event rate was 0.33 per subject-month in the INH group and 0.29 in the SC group. A hypoglycemic event was defined as any event during which the subject required assistance or during which the subject's blood glucose was ≤36 mg/dL. In this interim report, only this definition of hypoglycemic event is used. The final report will use this and two other definitions cited in the protocol.

Safety Results: During the randomized study period, 72 subjects received 399 subject-months of exposure to inhaled insulin, and 67 subjects received 474 subject-months of exposure to SC insulin.

The occurrence of adverse events and laboratory test result abnormalities according to the study database is summarized below.

Number of Subjects Evaluated (With Event) [Disc'd Due to Event]

	Inhaled Insulin	SC
All-causality adverse events[a]	72 (70) [5]	67 (62) [0]
T/R adverse events (per investigator)[b]	72 (64) [4]	67 (53) [0]
All-causality serious adverse events[c]	72 (4) [0]	67 (2) [0]
Laboratory test abnormalities (normal baseline)	68 (21) [0]	65 (20) [0]
Laboratory test abnormalities (abnormal baseline)	57 (19) [0]	46 (13) [0]

T/R=treatment-related; Disc'd=discontinued.
[a]All-causality adverse events reported during study drug treatment or within a 1-day lag period.
[b]Treatment-related adverse events, regardless of treatment-emergence or timing relative to study drug.
[c]From Tables 6.1.1; discontinuations due to serious adverse events are from Table 4.2.1.

Overall, the majority of adverse events were of mild or moderate severity. The most frequently reported all-causality adverse events were protocol-defined hypoglycemia, asthma, and respiratory tract infection. Subjects with protocol-defined, severe hypoglycemia (9 [12.5%] INH; 7 [10.4%] SC) accounted for the majority of all-causality and treatment-related incidence of severe adverse events. Five INH subjects and no SC subjects discontinued the study due to adverse events. Four of the INH subjects discontinued the study due to treatment-related adverse events.

Pulmonary Function Test Results

An important objective was to assess the impact of inhaled insulin on the lung function of diabetic asthmatics chronically dosed with either INH or SC insulin. This objective was met by measuring observed and change from baseline post-bronchodilator lung function (FEV_1 and DLco) and bronchodilator responsiveness in subjects who completed PFTs before and 30 minutes after the administration of an inhaled bronchodilator (albuterol). The INH group had a larger initial decline in FEV_1 and DLco measured 30 minutes after bronchodilator use. This treatment group difference was apparent by Week 1 and appears to be fully manifest after 4 to 6 weeks of treatment as summarized in the following table. At Week 52, there appears to be an increased divergence between the two treatment groups with a greater decline observed in the INH group; however, the results after Week 26 are based on very small numbers of subjects and appear to be influenced by fluctuations in lung function for a few subjects. The declines after Week 26 have not been observed in other studies.

Post-Bronchodilator FEV_1 (L) and DLco (mL/min/mm Hg): Mean Baseline and Change from Baseline

	FEV_1 (L)				DLco (mL/min/mm Hg)			
		INH Insulin		SC Insulin		INH Insulin		SC Insulin
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	70	2.502 (0.779)	65	2.704 (0.800)	70	23.121 (6.336)	65	23.649 (6.574)
Δ Week 1	64	-0.077 (0.172)	59	-0.031 (0.120)	63	-0.536 (1.358)	59	-0.330 (1.236)
Δ Week 2	63	-0.042 (0.144)	54	-0.033 (0.134)	63	-0.705 (1.416)	53	-0.477 (1.211)
Δ Week 3	62	-0.091 (0.187)	57	-0.038 (0.131)	61	-0.646 (1.405)	57	-0.512 (1.166)
Δ Week 4	55	-0.093 (0.148)	61	-0.024 (0.155)	55	-1.053 (1.405)	60	-0.522 (1.310)
Δ Week 6	61	-0.103 (0.263)	62	-0.035 (0.131)	61	-1.218 (1.687)	62	-0.503 (1.384)
Δ Week 12	46	-0.104 (0.174)	49	-0.092 (0.152)	46	-1.066 (1.619)	47	-0.621 (1.289)
Δ Week 18	42	-0.088 (0.221)	48	-0.066 (0.160)	42	-1.195 (1.750)	47	-0.696 (1.347)
Δ Week 26	33	-0.094 (0.235)	42	-0.049 (0.177)	33	-0.920 (2.098)	42	-0.658 (1.595)
Δ Week 39	17	-0.110 (0.204)	29	-0.038 (0.199)	17	-1.176 (2.057)	29	-0.641 (1.510)
Δ Week 52	10	-0.278 (0.572)	17	-0.122 (0.236)	10	-1.755 (2.832)	17	-0.545 (1.646)

Conclusions:

This study examined the efficacy and pulmonary safety of INH in subjects with mild-to-moderate persistent or intermittent asthma. Glycemic control was maintained in both groups. Relative to baseline, declines in pre-and post-bronchodilator pulmonary function test results occurred in both treatment groups; through the first 26 weeks of the study, the declines in DLco and FEV_1 were larger in the INH group, and of a magnitude similar to that observed in previous studies. The declines were larger at weeks 39 and 52 than previously observed, but the numbers of subjects at these time points is very small. The magnitudes of the pre-bronchodilator declines were generally not altered after bronchodilator treatment. The responsiveness of FEV_1 to bronchodilator therapy was little changed during 52 weeks of INH treatment. Adverse events were generally balanced between treatment groups, but the crude event rates of both types of protocol-defined asthma exacerbations (severe and non-severe) were higher overall in the INH group. This study will continue to explore the safety profile for INH use in this special population of diabetic subjects with asthma.

PROTOCOL A2171030: EFFICACY AND SAFETY OF INHALED HUMAN INSULIN (INH) COMPARED WITH SUBCUTANEOUS HUMAN INSULIN IN THE THERAPY OF ADULT SUBJECTS WITH TYPE 1 OR TYPE 2 DIABETES MELLITUS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A ONE-YEAR, MULTICENTER, RANDOMIZED, OUTPATIENT, OPEN-LABEL, PARALLEL-GROUP COMPARATIVE TRIAL

Interim Report: This interim report contains efficacy data from subjects who were treated up to and including 52 weeks. For standard safety, all treated subjects are included and all available data are analyzed through Week 52. Randomization and enrollment in this study are not yet complete: 35 INH subjects have been treated with 15 having completed; 32 SC subjects have been treated and 15 have completed.

Study Objectives: This study examines the safety (in particular, pulmonary safety), toleration, and efficacy of inhaled insulin for the treatment of type 1 and type 2 diabetes in adults with chronic obstructive pulmonary disease (COPD). The primary objective is to assess post-bronchodilator FEV_1 (forced expiratory volume in one second) and DLco (carbon monoxide diffusion capacity). Secondary objectives are to evaluate the effect of inhaled insulin versus SC insulin on COPD control, the frequency and severity of COPD exacerbations, and glycemic control.

Study Design: This is an open-label, 15-month, parallel-group, outpatient study comparing inhaled with SC human insulin treatment. Following a 3-week baseline run-in period during which all subjects receive SC insulin, subjects are being randomized to one year of treatment with either inhaled or SC insulin as their short-acting insulin; both groups use intermediate- or long-acting SC insulin. At the end of the treatment period, all subjects have a 6-week post-study run-out during which they use only SC insulin. Subjects are followed weekly for the first four weeks of the study to assess safety and adjust insulin dosing. Thereafter, follow-up occurs at increasing intervals up to 3 months for the last half of the study. All subjects perform daily self-monitoring of blood glucose (SMBG) and record their bronchodilator use. Pulmonary function (spirometry and single breath DLco), methacholine reactivity (selected sites), and diabetes control are being assessed during regularly scheduled clinic visits throughout the year. Methacholine reactivity is optional for subjects and is not included in this report; it may be included in the final report if sufficient numbers of subjects participate.

Evaluation Groups:	INH	SC
Assigned to Treatment 67	n (%)	n (%)
Treated	35	32
Completed*	15 (42.9)	15 (46.9)
Discontinued	5 (14.3)	6 (18.8)
Ongoing at data cut-off	15 (42.9)	11 (34.4)
Analyzed for HbA1c:		
Full Analysis Set (HbA1c)	34 (97.1)	32 (100)
Analyzed for FEV1:		
Full analysis set (FEV1)	35 (100)	32 (100)
Analyzed for safety:		
Adverse events	35 (100)	32 (100)
Laboratory tests	34 (97.1)	32 (100)

*Subjects who have completed at least the comparative phase of the study, but not necessarily the follow-up phase

Diagnoses and Criteria for Inclusion of Subjects: Subjects were to have COPD; all subjects were required to have a ≥10 pack-year history of smoking and FEV1 <80%, and one or both of the following: a) fixed airflow obstruction or b) productive cough with no alternative explanation. Subjects not meeting the smoking criterion but otherwise meeting criteria a) and b) were considered for inclusion on an individual basis. Subjects may be males or nonpregnant, nonlactating females, and may be ages 30-65, inclusive, for type 1 diabetes, or ages 30-75, inclusive, for type 2 diabetes. All are required to have been on a stable SC insulin administration schedule (at least BID for the 2 months prior to screening), and to have screening and pre-randomization glycosylated hemoglobin (HbA1c) between 5.5% and 11%, inclusive.

Efficacy Results: Treatment effects on mean HbA1c (%) are summarized in the following table.

Summary of Mean HbA1c (%) (Full Analysis Set, HbA1c)

Treatment Group	BL (SD)	Week 6 (SD)	Week 12 (SD)	Week 26 (SD)	Week 52 (SD)
INH	7.39 (1.05) N=34	7.10 (0.90) N=33	7.00 (0.89) N=30	7.02 (0.90) N=27	7.15 (1.01) N=15
SC	7.32 (1.01) N=32	6.85 (0.72) N=28	6.83 (0.81) N=29	6.95 (1.00) N=22	6.87 (1.18) N=15

Efficacy was maintained in both treatment groups over the 52-week measurement period. For hypoglycemic events, the overall crude event rate was lower (relative to baseline) in both groups at the end of treatment; in addition, the majority of hypoglycemic events in the INH group occurred during the first month of treatment. A hypoglycemic event was defined as any event during which the subject required assistance or during which the subject's blood glucose was ≤36 mg/dL. In this interim report, only this definition of hypoglycemic events is used. The final report will use this and two other definitions cited in the protocol. The overall crude hypoglycemic event rate was 0.08 per subject-month in the INH group and 0.06 in the SC group.

Safety Results: During the randomized study period, 35 subjects received 292 subject-months of exposure to inhaled insulin, and 32 subjects received 267 subject-months of exposure to SC insulin.

Number of Subjects Evaluated (With Event) [Disc'd Due to Event]

	Inhaled Insulin	SC
All-causality adverse events[a]	35 (35) [1]	32 (31) [1]
T/R adverse events (per investigator)[b]	35 (32) [1]	32 (28) [0]
All-causality serious adverse events[c]	35 (5) [1]	31 (10) [1]
Laboratory test abnormalities (normal baseline)	34 (6) [0]	32 (8) [0]
Laboratory test abnormalities (abnormal baseline)	33 (7) [0]	29 (5) [0]

T/R=treatment-related; Disc'd=discontinued .
[a]All-causality adverse events reported during study drug treatment or within a 1-day lag period.
[b]Treatment-related adverse events, regardless of treatment-emergence or timing relative to study drug.
[c]From Table 6.1.1; discontinuations due to serious adverse events from Table 4.2.1.

Overall, the majority of adverse events were of mild or moderate severity. The most frequently reported all-causality adverse events were protocol-defined hypoglycemia and respiratory tract infection. Subjects with protocol-defined, severe hypoglycemia (5 [14.3%] INH; 7 [21.9%] SC) accounted for the majority of all-causality and treatment-related incidence of severe adverse events.

Pulmonary Function Test Results

An important objective was to assess the impact of inhaled insulin on the lung function of diabetic subjects with COPD and chronically dosed with either INH or SC insulin. This objective was achieved by measuring observed and change from baseline post-bronchodilator lung function (FEV_1 and DLco) and bronchodilator responsiveness in subjects who completed PFTs before and 30 minutes after the administration of an inhaled bronchodilator (ipratropium). The INH treatment group had a larger initial decline in post-bronchodilator FEV_1 than the SC treatment group. This noticeable treatment group difference was realized by Week 1, but did not appear to change over time. The INH treatment group had a larger initial decline in post-bronchodilator DLco which was realized by Week 1; however, by Week 4, the SC treatment group had experienced a similar decline. After Week 4, there did not appear to be noticeable treatment group differences. Results after Week 26 are based on a very small number of subjects and could potentially be influenced by fluctuations in lung function for a few subjects.

Post-Bronchodilator FEV_1 (L) and DLco (mL/min/mm Hg): Mean Baseline and Change From Baseline

	FEV_1 (L)				DLco (mL/min/mm Hg)			
	INH Insulin		SC Insulin		INH Insulin		SC Insulin	
	N	Mean (SD)	N	Mean (SD)	N		N	
Baseline	35	2.204 (0.477)	32	2.147 (0.514)	35	19.276 (4.427)	32	19.105 (4.027)
Δ Week 1	32	-0.054 (0.144)	29	-0.016 (0.126)	31	-0.437 (1.353)	29	-0.126 (0.910)
Δ Week 2	29	-0.032 (0.102)	30	-0.027 (0.114)	29	-0.402 (1.327)	29	-0.176 (1.023)
Δ Week 3	28	-0.034 (0.128)	30	-0.026 (0.131)	28	-0.427 (1.100)	30	-0.074 (1.151)
Δ Week 4	29	-0.035 (0.146)	30	-0.031 (0.163)	29	-0.435 (1.464)	30	-0.481 (1.302)
Δ Week 6	30	-0.066 (0.144)	27	-0.043 (0.161)	30	-0.572 (1.392)	27	-0.568 (1.139)
Δ Week 12	28	-0.047 (0.171)	29	0.026 (0.150)	28	-0.332 (1.590)	28	-0.394 (1.499)
Δ Week 18	29	-0.039 (0.162)	24	-0.015 (0.152)	28	-0.415 (1.167)	24	-0.170 (1.530)
Δ Week 26	26	-0.081 (0.170)	21	-0.033 (0.172)	26	-0.427 (1.681)	21	-0.664 (1.482)
Δ Week 39	21	-0.042 (0.202)	20	-0.023 (0.203)	21	-0.219 (1.359)	20	-0.907 (1.631)
Δ Week 52	13	-0.109 (0.217)	15	-0.082 (0.172)	13	0.095 (2.408)	15	-0.839 (1.655)

Conclusions: This study examined the efficacy and pulmonary safety of INH in subjects with COPD. The small numbers of subjects warrant caution with respect to conclusions. The trends in FEV_1, slightly favoring SC, observed in this interim analysis are similar to those observed in

other INH studies. The initial small decline in DLco in the INH group has also been observed in other studies; however, the magnitude of the present trend in DLco favoring INH after Week 18 has not been observed in other studies. The magnitudes of the pre-bronchodilator declines were generally not altered after bronchodilator treatment. The responsiveness of FEV_1 to bronchodilator therapy was little changed during 52 weeks of INH treatment. Adverse events were generally balanced between treatment groups, and glycemic control was maintained in both groups. There were 10 subjects with non-severe COPD exacerbations in the INH group and four in the SC group, resulting in an event rate of 0.05 in the INH group and 0.03 in the SC group. Thus, for this special population of subjects with COPD, there were no notable safety or efficacy concerns.