Summary ID# 6120

Clinical Study Summary: Study H7U-MC-IDAH

A Pivotal Long-Term, Open-Label, Parallel Study of the Efficacy and Safety of Human Insulin Inhalation Powder in Patients with Type 1 Diabetes Mellitus

Date summary approved by Lilly: 05 May 2009

Title of Study: A Pivotal Long-Term, Open-Label, Parallel Study of the Efficacy and Safety of Human Insulin Inhalation Powder in Patients with Type 1 Diabetes Mellitus	
Investigators: This multicenter study included 74 principal investigators.	
Study Centers: This study was conducted at 66 study centers in 6 countries.	
Publications Based on the Study: None at this time.	
Length of Study: Date first patient enrolled (Visit 3, assigned to therapy): 14 September 2005 Date last patient completed 24-month treatment period (Visit 11): 09 April 2008 Date last patient completed first safety follow-up period (Visit 14): 08 May 2008	**Phase of Development:** 2/3
Objectives: The primary objective of this study was to test the hypothesis that preprandial Human Insulin Inhalation Powder (HIIP) plus insulin glargine was noninferior to preprandial injectable insulin (regular human insulin or insulin lispro) plus insulin glargine with respect to mean change from baseline to endpoint in hemoglobin A_{1c} (HbA_{1c}) in patients with type 1 diabetes treated for approximately 24 months. A noninferiority margin of 0.4% for HbA_{1c} was used. The secondary objectives **for the initial treatment period** of the study were: 1) To compare preprandial HIIP with preprandial injectable insulin in patients with type 1 diabetes over a 24-month period with respect to the following: • forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and total lung capacity (TLC). • Diffusing capacity of the lung for carbon monoxide (DL_{CO}). • Safety as assessed by insulin antibody binding levels, adverse events (AEs), and episodes of hypoglycemia. • Safety using serial high-resolution computed tomography (HRCT) scans of the chest. • Safety as assessed by Six-Minute Walk Test (6MWT) with the Borg CR10 Scale to	

assess perceived exertion.

- Glycemic control as assessed by the 8-point self-monitored blood glucose (SMBG) profiles (blood glucose measurements before and 2 hours after the start of the morning, midday, and evening meals, and blood glucose measurements at bedtime and 3 a.m.).
- Proportion of patients who achieved or maintained an HbA_{1c} <7.0%.
- Insulin dose requirements (total, preprandial, and basal insulin).
- Patient-reported outcomes (PRO) questionnaires to assess psychological well-being, health status (EQ-5D reported separately), and insulin delivery system satisfaction.
- Resource utilization (for example, hospitalizations) (reported separately).

2) To assess inhaler reliability in patients randomized to treatment with HIIP.

3) To explore differences in cough and other pulmonary symptoms in patients treated with HIIP or preprandial injectable insulin using the Pulmonary Symptoms Questionnaire (PSQ).

The secondary objective **for the extension treatment period** of the study was:

4) To assess the safety and efficacy of chronic administration of preprandial HIIP compared with preprandial injectable insulin in patients with type 1 diabetes over approximately 36 months with respect to the following:

- FEV_1, FVC, and DL_{CO}.
- Safety as assessed by insulin antibody binding levels, AEs, and episodes of hypoglycemia.
- Safety using serial HRCT scans of the chest.
- HbA_{1c} (mean change from baseline at Visit 3).
- Glycemic control as assessed by the 8-point SMBG profiles (blood glucose measurements before and 2 hours after the start of the morning, midday, and evening meals, and blood glucose measurements at bedtime and 3 a.m.).
- Proportion of patients who achieved or maintained an HbA_{1c} <7.0%.
- Insulin dose requirements (total, preprandial, and basal insulin).
- PRO questionnaires to assess health status (EQ-5D reported separately).
- Resource utilization (for example, hospitalizations) (reported separately).

Study Design: This multicenter, open-label, randomized, active-comparator, parallel-arm study assessed the efficacy and safety of HIIP in 385 patients with type 1 diabetes for 24 months followed by a 2-month follow-up period, and a 12-month extension period. The study consisted of 6 periods: a screening period, a lead-in period, a treatment period lasting 24 months, an initial safety follow-up period lasting about 2 months, an extension period lasting 12 months, followed by a second 2-month safety follow-up period.

Number of Patients:
Planned: 400 Actual: 385
Randomized: 193 preprandial HIIP, 192 preprandial injectable insulin
Completed (24-month treatment period): 157 preprandial HIIP, 154 preprandial injectable insulin

Diagnosis and Main Criteria for Inclusion: Male or female patients 18 years of age or older who had type 1 diabetes for at least 24 months' duration at study entry and met the disease diagnostic criteria as defined by the World Health Organization (WHO) and as confirmed by a C-peptide value <0.5 ng/mL

(165 pmol/L) at screening (Visit 1); who had an HbA_{1c} ≤11% at screening; who were not smokers; and who had acceptable pulmonary function test (PFT) results at baseline and a chest x-ray with no evidence of clinically significant pulmonary abnormalities.

Test Product, Dose, and Mode of Administration: HIIP administered to the deep lung by inhalation before meals using the commercial version of the Lilly/Alkermes insulin inhaler (AIR® Insulin Inhaler System) (specific dose was adjusted for individual patients), plus daily doses of insulin glargine.

Duration of Treatment: 1-month lead-in period, 24-month treatment period, initial 2-month follow-up period, 12-month treatment extension period, and a final 2-month follow-up period (41 months total).

Reference Therapy, Dose, and Mode of Administration: Injectable insulin (regular human insulin or insulin lispro) administered before meals, plus daily doses of insulin glargine.

Variables:

Efficacy: The primary efficacy measure was the HbA_{1c} change from baseline to the 24-month endpoint. The secondary measures of the study were: 8-point SMBG profiles; insulin dose requirements (total, preprandial, and basal insulin) for days when 8-point profiles were performed; and proportion of patients who achieved or maintained an HbA_{1c} <7.0% and ≤6.5%. In patients randomized to HIIP, insulin inhaler reliability was assessed by laboratory assessment of inhalers returned for patient complaint.

Safety measures: Insulin antibody binding levels, PFTs (FEV_1, FVC, and TLC), DL_{CO}, visual qualitative reading of HRCT scan of the chest, PSQ, 6MWT with Borg CR10 Scale, hypoglycemic episodes, "for cause" pulmonary evaluations, and adverse events. Additional safety measures included vital signs (including respiratory rate), body weight, general physical exam, and directed cardiopulmonary exam.

Health Outcomes: Patient-reported psychological well-being, health status, and insulin delivery system satisfaction were assessed using the Insulin Delivery System Questionnaire (IDSQ), respectively. Resource utilization data was also collected to examine costs of care between HIIP and preprandial injectable insulin.

Evaluation Methods:

The primary efficacy outcome was HbA_{1c} change from baseline to the endpoint during the initial 24-month treatment period. An analysis of covariance (ANCOVA) model was used to establish the noninferiority of HIIP to injected insulin. The model included randomization strata of previous prandial insulin type, country, and treatment as fixed effects and baseline HbA_{1c} as a continuous covariate and utilized all data from randomized patients with at least one measurement after baseline. In addition to the primary efficacy analysis of HbA_{1c} for noninferiority, the following outcomes were analyzed for efficacy: SMBG levels, daily insulin dose for days of the 8-point profiles, and the percentage of patients who reached or maintained HbA_{1c} <7% and ≤6.5%. For the SMBG levels and the daily insulin doses, a model similar to the ANCOVA model for the primary analysis was used, while a logistic regression analysis was utilized for the percentage of patients reaching or maintaining the HbA_{1c} goal of <7% and ≤6.5%. Descriptive statistics for each outcome were presented. Descriptive statistics were also presented for the unscheduled HIIP device return rate.

Summary:

A total of 791 patients signed informed consent for the study, all of whom completed Visit 1 and were included in the database. Of these 791 patients, 406 patients did not meet the entry criteria and 385 patients were randomly assigned to a treatment group (193 patients on preprandial HIIP and 192 patients on preprandial injectable insulin) at the randomization visit.

Although the study was designed to have a treatment phase of 24 months followed by a 2-month follow-up phase, the study was terminated early due to increasing uncertainties in the regulatory environment and after a thorough evaluation of the evolving commercial and clinical potential of the product compared with existing therapies. The decision was not a result of any observations during AIR Insulin trials relating to the safety of the product. The early termination did not have a major impact on the treatment phase as 80.8% of patients completed the 24-month visit. The follow-up phase was affected as only 43.1% of patients completed the full study (treatment plus follow-up phases). Trial participants had type 1 diabetes

with a mean age (mean±SD) of 39.2±12.8 years and a mean BMI of 25.82±4.18. The two treatment groups were similar with respect to their demographic and clinical characteristics at baseline.

After 24 months (endpoint LOCF) of treatment the mean difference in HbA_{1c} between the treatment groups (HIIP – injectable insulin) was 0.44% (95% CI 0.24, 0.63; p<.001). Non-inferiority of HIIP to injectable insulin was not proven as the upper limit of the 95% CI was >0.4%. Patients in the injectable insulin group experienced significantly smaller increases in HbA_{1c} when compared with the preprandial HIIP group intent to treat (ITT) population and the per-protocol population. This difference occurred in spite of the HIIP group having a higher (by approximately 0.05 U/kg) total weight-adjusted preprandial insulin dose.

There were 12 inhalers returned for complaint with 2 inhalers being found faulty, yielding a 0.1% faulty device return rate.

There was 1 death during the study (injectable insulin group) due to hypoglycemic coma. A total of 74 patients experienced one or more SAEs, 45 patients in the HIIP group and 29 patients in the injectable group. One notable SAE (increased anti-insulin antibody level) was reported in the HIIP group during the study. A total of 4 patients in the HIIP group and 1 patient in the injectable insulin group had an AE that resulted in study discontinuation after randomization. One event of hypoglycemia (in the HIIP group) was considered to be related to study drug. All other AEs that resulted in discontinuation were not considered possibly study drug related.

Overall, 169 (87.6%) patients in the HIIP group and 157 (83.1%) patients in the injectable insulin group experienced at least one TEAE during the study. There was no statistically significant difference between the 2 groups in the percentage of patients reporting one or more TEAE. Table 1 shows the TEAEs reported by at least 2% of patients in the safety population. There were statistically significant differences between the 2 treatment groups for cough (p=.026) and tendonitis (p=.035). The increase in occurrence of cough as a TEAE in the HIIP group was corroborated by the findings from the PSQ that showed worsening in symptom severity scores at any time during the study for questions concerning the intensity and frequency of cough.

Pulmonary function test results showed a statistically significantly greater decrease in the mean change from baseline between the two treatment groups in corrected DL_{CO} measurements at various visits during the study and at endpoint (p=.006) with patients in the HIIP group having larger decreases in DL_{CO}. The statistically significant difference between treatment groups was no longer present at the 1-week follow-up visit. There were no significant differences between the treatment groups for FEV_1, FVC, and TLC. The 'for cause' process did not identify clinically significant differences among patients exposed to HIIP versus injectable insulin.

There were no statistically significant differences between the 2 treatment groups in the incidence or rate (per 30 days) of hypoglycemia (all types included). There was a statistically significantly higher percentage of patients in the HIIP group than in the injectable insulin group who had at least 1 nocturnal hypoglycemic episode during the study (p=.015). There was no statistically significant difference between the groups in the rate (per 30 days) of nocturnal hypoglycemia at study endpoint (p=.267). However, statistically significant differences occurred at various visits during the study with patients in the HIIP group having a higher rate.

Percent binding for anti-human insulin, anti-lispro insulin and cross-reactive insulin antibodies increased in the HIIP group from baseline to Visit 4 and endpoint. There were minimal changes in the injectable insulin group. The greatest differences between the 2 groups were seen in the cross-reactive insulin antibody assay. The differences between the groups for all 3 measures were statistically significant at LOCF

endpoint (p<.001) and remained statistically different for insulin-specific and cross-reactive (p=.002 and p<.001, respectively) but not for anti-lispro antibodies levels during the follow-up period despite a drop in anti-insulin antibody levels after discontinuation of HIIP. A plateau was reached within 6 months of exposure to HIIP.

Analysis of the study data led to the following conclusions:

- The study did not meet the primary objective of demonstrating non-inferiority between the preprandial HIIP and preprandial injectable insulin groups.
- Change from baseline to endpoint for overall blood glucose values and the percent of patients achieving HbA_{1c} levels of <7% or ≤6.5% were not different between groups.
- Change from baseline to endpoint in the weight-adjusted daily preprandial insulin dose was about 0.05 U/kg higher in the HIIP group.
- The risk of hypoglycemia did not differ between the treatment groups at endpoint. However, in the early months of the study, patients randomized to HIIP experienced more episodes of nocturnal hypoglycemia.
- Insulin antibody assays showed there were statistically significant higher antibody levels in the HIIP group at all timepoints during the study.
- The HIIP group had larger decreases in DL_{CO} (approximately 0.9 $mL \cdot min^{-1} \cdot torr^{-1}$) that reversed after one week of follow-up off HIIP. There were no significant differences between the 2 groups in FEV_1, FVC, and TLC.
- Significantly more patients in the HIIP group experienced worsening in pulmonary symptom severity as measured by PSQ questions related to cough, shortness of breath, and chest congestion.
- Patients in the HIIP group experienced statistically significantly less weight gain (approximately 1 kg) at study endpoint.
- None of the safety findings in this study changed the known safety profile of HIIP.

Table 1. Summary of Treatment-Emergent Adverse Events Reported in at Least 2% of Patients by Decreasing Frequency Safety Population

Preferred Term	Treatment Group: Preprandial HIIP (N=193) n (%)	Treatment Group: Preprandial Injectable Insulin (N=189) n (%)	p-Value
Patients with >= 1 TEAE	169 (87.6)	157 (83.1)	.248
Patients with No TEAE	24 (12.4)	32 (16.9)	.248
NASOPHARYNGITIS	58 (30.1)	49 (25.9)	.425
COUGH	45 (23.3)	27 (14.3)	.026
UPPER RESPIRATORY TRACT INFECTION	42 (21.8)	33 (17.5)	.305
HEADACHE	29 (15.0)	21 (11.1)	.290
PHARYNGOLARYNGEAL PAIN	29 (15.0)	18 (9.5)	.120
VOMITING	18 (9.3)	15 (7.9)	.717
HYPOGLYCAEMIA	16 (8.3)	12 (6.3)	.557
PYREXIA	15 (7.8)	18 (9.5)	.588
NAUSEA	15 (7.8)	12 (6.3)	.691
DIARRHOEA	15 (7.8)	9 (4.8)	.292
SINUSITIS	13 (6.7)	14 (7.4)	.844
URINARY TRACT INFECTION	13 (6.7)	10 (5.3)	.668
BACK PAIN	12 (6.2)	19 (10.1)	.192
ARTHRALGIA	11 (5.7)	14 (7.4)	.540
BRONCHITIS	11 (5.7)	11 (5.8)	>.999
INFLUENZA	9 (4.7)	16 (8.5)	.151
FATIGUE	8 (4.1)	6 (3.2)	.787
CHEST PAIN	8 (4.1)	4 (2.1)	.380
GASTROENTERITIS VIRAL	7 (3.6)	9 (4.8)	.618
HYPERTENSION	7 (3.6)	8 (4.2)	.798
DYSMENORRHOEA	7 (3.6)	5 (2.6)	.771
DIABETIC RETINOPATHY	7 (3.6)	4 (2.1)	.543
NASAL CONGESTION	7 (3.6)	4 (2.1)	.543
TOOTHACHE	7 (3.6)	3 (1.6)	.337
DENTAL CARIES	6 (3.1)	9 (4.8)	.441
VIRAL INFECTION	6 (3.1)	7 (3.7)	.785
MYALGIA	6 (3.1)	6 (3.2)	>.999
GASTROENTERITIS	6 (3.1)	5 (2.6)	>.999
RASH	6 (3.1)	5 (2.6)	>.999
LOWER RESPIRATORY TRACT INFECTION	6 (3.1)	4 (2.1)	.751
RHINITIS	6 (3.1)	3 (1.6)	.503
PAIN IN EXTREMITY	5 (2.6)	11 (5.8)	.132
HYPOAESTHESIA	5 (2.6)	2 (1.1)	.449
SEASONAL ALLERGY	5 (2.6)	1 (0.5)	.215
TOOTH INFECTION	5 (2.6)	1 (0.5)	.215
ABDOMINAL PAIN	4 (2.1)	7 (3.7)	.376
DYSPEPSIA	4 (2.1)	5 (2.6)	.749
EOSINOPHILIA	4 (2.1)	5 (2.6)	.749
FEBRILE INFECTION	4 (2.1)	5 (2.6)	.749
NECK PAIN	4 (2.1)	5 (2.6)	.749
CYSTITIS	3 (1.6)	9 (4.8)	.084
PAIN	3 (1.6)	8 (4.2)	.137
RHINITIS ALLERGIC	3 (1.6)	7 (3.7)	.216
FALL	3 (1.6)	6 (3.2)	.333
DEPRESSION	3 (1.6)	5 (2.6)	.499
CARPAL TUNNEL SYNDROME	2 (1.0)	6 (3.2)	.171
OEDEMA PERIPHERAL	2 (1.0)	6 (3.2)	.171
FUNGAL INFECTION	2 (1.0)	5 (2.6)	.280
MUSCULOSKELETAL PAIN	2 (1.0)	5 (2.6)	.280
SKIN LACERATION	2 (1.0)	5 (2.6)	.280
TENDONITIS	1 (0.5)	7 (3.7)	.035
EYE INFECTION	1 (0.5)	6 (3.2)	.065

Abbreviations: HIIP = Human Insulin Inhalation Powder; N = number of patients; TEAE = treatment-emergent adverse event.