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Clinical Study Summary: Study H7U-MC-IDAU

A Phase 3, Open-Label, Parallel Group Study to Evaluate the Efficacy and Safety of Human Insulin Inhalation Powder (HIIP) Compared to Preprandial Injectable Insulin in Insulin-Naïve Patients with Type 2 Diabetes Mellitus

Date summary approved by Lilly: 01 May 2009

Title of Study: A Phase 3, Open-Label, Parallel Group Study to Evaluate the Efficacy and Safety of Human Insulin Inhalation Powder (HIIP) Compared to Preprandial Injectable Insulin in Insulin-Naïve Patients with Type 2 Diabetes Mellitus	
Investigator(s): This multicenter study included 58 principal investigators.	
Study Center(s): This study was conducted at 55 study centers in 10 countries.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date first patient enrolled: 6 July 2006 Date last patient completed: 3 June 2008	**Phase of Development:** 3

Objectives: The primary objective was to test the hypothesis that in insulin-naïve patients with type 2 diabetes not optimally controlled by oral anti-hyperglycemic medications, preprandial HIIP was noninferior to preprandial injectable insulin (insulin lispro) with respect to mean change from baseline to endpoint in HbA_{1c} at 6 months. A noninferiority margin of 0.4% for HbA_{1c} was used.

The secondary objectives of the study were as follows:

1) To test the hypothesis that preprandial HIIP is noninferior to preprandial injectable insulin with respect to mean change from baseline to endpoint in HbA_{1c} at 12 months and at 24 months.

2) To compare preprandial HIIP with preprandial injectable insulin in patients with type 2 diabetes who have been treated for approximately 6, 12, and 24 months with respect to the following:

- 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 am)
- proportion of patients who have an $HbA_{1c} \leq 6.5\%$ and $<7.0\%$
- insulin dose requirements (each mealtime, total mealtime, and total insulin)
- insulin antibody binding levels
- forced expiratory volume in one 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 adverse events, episodes of hypoglycemia (including nocturnal hypoglycemia), and chest x-rays
- differences in pulmonary symptoms using the Pulmonary Symptoms Questionnaire (PSQ)
- Six-Minute Walk Test (6MWT) and Borg CR10 scale
- body weight
- patient-reported outcomes questionnaires to assess psychological well-being, diabetes-related symptoms, diabetes treatment satisfaction, and insulin delivery system satisfaction.

3) To compare two dose titration methods at 6 months with respect to the following:

- HbA_{1c}
- 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 am)
- proportion of patients who have an $HbA_{1c} \leq 6.5\%$ and $<7.0\%$
- insulin dose requirements (each mealtime, total mealtime, total insulin)
- episodes of hypoglycemia and other blood glucose-related adverse events
- patient-reported outcomes questionnaires to assess insulin delivery system satisfaction.

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

5) To assess the pharmacokinetics of HIIP administered preprandially in a subgroup of patients.

The exploratory objectives were to assess the following in patients with type 2 diabetes who have been treated with preprandial HIIP or preprandial injectable insulin (insulin lispro) for approximately 6, 12, and 24 months:

- patient-reported outcomes questionnaire to assess health status (EQ-5D documented separately)
- resource utilization (for example, hospitalizations) (documented separately)
- proportion of patients who initiated rescue therapy, time-to-rescue therapy initiation, and insulin doses for patients who initiated rescue therapy
- secondhand smoking effects on clinical correlates.

Study Design: This was a Phase 3, open-label, randomized, active-comparator, two-arm, parallel-group study to assess the safety and efficacy of HIIP compared with injectable insulin in insulin-naïve patients with type 2 diabetes.

Number of Patients:
Planned: 420 Actual: 411
Randomized: 208 preprandial HIIP, 203 preprandial injectable insulin
Completed 6-month treatment period: 175 preprandial HIIP, 173 preprandial injectable insulin
Completed study: 0 preprandial HIIP, 0 preprandial injectable insulin

Diagnosis and Main Criteria for Inclusion: Male or female nonsmoking patients 18 years of age or older; who had type 2 diabetes mellitus for at least 6 months at study entry and were taking at least one oral anti-hyperglycemic medication for at least 3 months (stable for at least 6 weeks; thiazolidinedione [TZD] dose stable for at least 3 months), were insulin-naïve, had FEV_1/FVC > lower limit of normal and FEV_1 and DL_{CO} >70% predicted, and had an $HbA_{1c} \geq 6.5\%$ and $\leq 10.0\%$ at screening.

Test Product, Dose, and Mode of Administration: Human Insulin Inhalation Powder (HIIP) delivered to the deep lung using a version of the Lilly/Alkermes insulin inhaler; using combinations of two dose strengths, low (2U equivalent) and middle (6U equivalent) (dose as appropriate for individual patients); administered preprandially. Dosage was determined based on individual needs. After 6 months, for patients with HbA_{1c} >7.5% at 2 consecutive visits, a morning dose of subcutaneous insulin glargine (100 U/mL) may have been added as rescue therapy. Patients who were assigned to injectable insulin analog lispro may also have used Humalog Mix 25 ("Low Mix") instead of lispro and glargine, as their rescue therapy.

Duration of Treatment: 24 months

Reference Therapy, Dose, and Mode of Administration: Injectable insulin (subcutaneous insulin lispro, 100 U/mL) administered preprandially. Dosage was determined based on individual needs. After 6 months, for patients with HbA_{1C} >7.5% at 2 consecutive visits, a morning dose of subcutaneous insulin glargine (100 U/mL) may have been added as rescue therapy. Patients that qualified for rescue therapy may have switched to insulin lispro LM (75% insulin lispro protamine suspension, 25% insulin lispro) after 6 months if frequent injections were a major issue.

Variables:

Efficacy: The primary efficacy measure was the HbA_{1c} change from baseline to 6 months. The secondary measures were: HbA_{1c} change from baseline to 12 months and 24 months; 8-point SMBG profiles; daily insulin dose requirements for the days of the 8-point profiles; and in patients randomized to HIIP, insulin inhaler reliability as assessed by laboratory assessment of inhalers returned for patient complaint.

Safety Measures: Insulin antibody levels; change from baseline in pulmonary function tests (FEV_1, FVC, FEV_1/FVC, TLC, DL_{CO}); chest x-rays; hypoglycemic episodes; treatment-emergent adverse events; vital signs (body temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate); body weight; PSQ measures; the Borg CR10 Scale, 6MWT, and 'for cause' pulmonary evaluations.

Pharmacokinetic: Serum concentration of insulin as free immunoreactive insulin (IRI) in blood samples collected from a subgroup of patients in the HIIP treatment group after 3 and 6 months of treatment.

Health Outcomes: Patient-reported outcomes using the 12-item Well-Being Questionnaire (W-BQ12); the Cognitive Distress, Fatigue, Hyperglycemia, and Hypoglycemia Subscales of the Diabetes Symptom Checklist-Revised (DSC-R); the Diabetes Treatment Satisfaction Questionnaire Status Version ($DTSQ_s$); the Insulin Delivery System Questionnaire (IDSQ); and the EuroQol (EQ-5D) Instrument (documented separately), respectively.

Evaluation Methods:

This study planned to randomize 420 patients. With an estimated 10% of patients not having post-randomization data, intent-to-treat (ITT) analysis with 378 patients has 89% power to show that HIIP was noninferior to injectable insulin with respect to change from baseline to 6 months in HbA_{1C}.

Noninferiority would be demonstrated if the upper limit of the two-sided 95% confidence interval for the difference in HIIP mean HbA_{1c} and injectable insulin mean HbA_{1c} was no greater than 0.4%. This analysis used an ANCOVA model with covariates of treatment, dose titration method, insulin secretagogue usage, country, and baseline HbA_{1c}. Analyses of other continuous variables used similar models with slight modifications. For proportion of patients who had an HbA_{1C} $\leq$6.5% and <7.0%, a logistic regression analysis was utilized. A non-parametric test was performed on hypoglycemia rates. Analyses of categorical safety measures used the Fisher's exact test or Chi-square tests. All tests of treatment effects were conducted at a two-sided alpha level of 0.05 and/or two-sided 95% confidence intervals. No adjustments for multiplicity were performed, and no adjustments for missing data were performed; with the exception of last observation carried forward (LOCF) when earlier observations were available. Summary statistics were performed for all efficacy and safety measures.

Summary:

Of 880 patients who signed informed consent for the study, 411 patients were randomly assigned to either HIIP treatment (208 patients) or injectable insulin treatment (203 patients). Of these 411 randomized patients, 348 patients completed the 6-month primary analysis treatment period (175 patients, HIIP group; 173 patients, injectable insulin group) Subsequently, 274 patients completed the 12-month treatment period (141 patients, HIIP; 133 patients, injectable insulin), and one patient completed 24 months of treatment. Because the study was terminated early due to termination of the clinical development program, no patient from either treatment group had the intended follow-up visit after 24 months. The most common reasons for early patient discontinuations were sponsor decision and patient decision.

Of the 408 randomized patients in the ITT population (randomized patients having baseline and at least one postbaseline observation), 222 (54.4%) were male and 186 (45.6%) were female; the majority (57.4%) were Caucasian. The average age (mean±SD) was 56.5±9.7 years with a minimum age of 25 years and maximum age of 84 years. The average baseline body weight was 83.3±18.7 kg and the average baseline height was 165.2±10.1 cm. One hundred patients (24.6%) were past smokers, with an average number of years smoked of 19.4±13.4 years. There was a statistically significant difference (p=.019) between the 2 treatment groups for years of smoking with patients in the HIIP group having a longer duration of smoking, and for mean number of years since quitting (p=.041) with patients in the injectable insulin group having more years since quitting.

At the 6 month primary analysis endpoint, the LOCF LsMean difference (HIIP – injectable insulin) in HbA_{1c} change between the two groups was 0.058% (95% CI -.12, .24 %, p=.514). This confirmed the hypothesis that preprandial HIIP is noninferior to preprandial injectable insulin in insulin-naïve patients with type 2 diabetes, since the upper limit of the 95% CI was less than 0.4%. Similar analysis using the per-protocol population confirmed the result.

Other aspects of glycemic control (percentage of patients achieving the HbA_{1c} goal of <7.0% or ≤6.5%, 8-point SMBG profiles, insulin doses, body weight change and incidence and rate of hypoglycemia) were similar in the two groups at the 6-month LOCF endpoint. Due to early study termination, the analysis of the data at the 12-month and 24-month was limited, and it was not possible to address the long-term secondary objectives described by the protocol.

The change in DTSQ treatment satisfaction score and the IDSQ overall insulin delivery satisfaction score at 6-month endpoint was higher among patients in the HIIP group (higher satisfaction) compared with the injectable insulin group; however, these differences were not significant after adjusting the alpha level based on the pre-specified Hochberg's method to control for multiplicity with health outcomes endpoints. None of the inhalers dispensed during the study was found to be faulty.

Four deaths were reported during this study: 2 acute myocardial infarction (HIIP group); 1 suicide (injectable insulin group); and 1 aphasia and hemiparesis (HIIP group). A total of 42 patients experienced one or more SAEs, 23 patients in the HIIP group and 19 patients in the injectable group. Four patients in the HIIP group and 4 patients in the injectable insulin group had an AE that resulted in study discontinuation after randomization. One discontinuation event of severe hypoglycemia was considered to be related to study procedure. All other AEs that resulted in discontinuation were not considered possibly study drug related.

Overall, 150 (73.2%) patients in the HIIP group and 133 (66.8%) patients in the injectable insulin group experienced at least one TEAE during the study. There was no statistically significant difference between the treatment 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 6 reports of lung neoplasm (4 HIIP group, 2 injectable insulin group). All were pulmonary nodules found on radiologic examination. None were biopsied for histologic diagnosis.

Statistically significant differences between the two treatment groups were observed for cough (p=.002), pain in extremity (p=.030) dizziness (p=.004), and pneumonia (p=.028). The increased incidence of cough in the HIIP group was consistent with the findings from the PSQ, which showed worsening in symptom severity scores from baseline to endpoint in the HIIP group for questions relating to coughing frequency and severity.

The assessment of lung function in the trial showed that FEV_1 and FVC decreased in both treatment groups. For FEV_1, differences between the treatment groups in changes from baseline were statistically significant at the 12-month LOCF endpoint (p=.031), and at the 24-month LOCF endpoint (p=.016). For FVC, differences between the 2 treatment groups in changes from baseline were statistically significant at 12-month LOCF endpoint (p=.041) and at the 24-month LOCF endpoint (p=.020). There were no significant differences between the treatment groups for DL_{CO}, FEV_1/FVC, or TLC. The 'for cause' process did not identify clinically significant differences in pulmonary abnormalities among patients exposed to HIIP versus injectable insulin.

Percent binding for anti-human insulin and cross-reactive insulin antibodies increased in the HIIP group after baseline, reaching a plateau between 6 and 9 months of HIIP exposure and remaining statistically significantly different at the 12- and 24-month LOCF endpoints. There were minimal changes in the injectable insulin group. The greatest differences between the two groups were seen in the cross-reactive insulin antibody assay.

There were no statistically significant differences between the HIIP group and the injectable insulin group in the incidence or rate of overall and nocturnal hypoglycemia, or the incidence of severe hypoglycemia at any LOCF endpoint.

Analysis of the study data led to the following conclusions:

- The study met the primary objective, demonstrating that, in insulin-naïve patients with type 2 diabetes, preprandial HIIP is noninferior to preprandial injectable insulin with respect to glycemic control as measured by change in HbA_{1c} after 6 months of treatment.
- The two treatment groups were not different with respect to blood glucose values, the percentage of patients achieving HbA_{1c} levels of <7% or ≤6.5%, and the weight-adjusted insulin dose.
- The risk of hypoglycemia did not differ between the treatment groups.
- There was a significantly greater decrease in FEV_1 and FVC in the HIIP group at the 12- and 24-month LOCF endpoints but not in DL_{CO}, FEV_1/FVC, or TLC.
- 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: HIIP (N=205) n (%)	Treatment Group: Injectable Insulin (N=199) n (%)	p-Value
Patients with >= 1 TEAE	150 (73.2)	133 (66.8)	.192
Patients with No TEAE	55 (26.8)	66 (33.2)	
COUGH	42 (20.5)	19 (9.5)	.002
NASOPHARYNGITIS	29 (14.1)	21 (10.6)	.293
HEADACHE	19 (9.3)	15 (7.5)	.593
INFLUENZA	19 (9.3)	14 (7.0)	.470
PAIN IN EXTREMITY	17 (8.3)	6 (3.0)	.030
UPPER RESPIRATORY TRACT INFECTION	13 (6.3)	15 (7.5)	.698
BACK PAIN	12 (5.9)	19 (9.5)	.192
ARTHRALGIA	11 (5.4)	17 (8.5)	.242
PHARYNGOLARYNGEAL PAIN	11 (5.4)	10 (5.0)	>.999
URINARY TRACT INFECTION	10 (4.9)	5 (2.5)	.293
BRONCHITIS	9 (4.4)	7 (3.5)	.800
HYPERTENSION	9 (4.4)	7 (3.5)	.800
TOOTHACHE	9 (4.4)	3 (1.5)	.141
DIZZINESS	9 (4.4)	0	.004
DIARRHOEA	8 (3.9)	12 (6.0)	.365
PHARYNGITIS	8 (3.9)	7 (3.5)	>.999
MUSCULOSKELETAL PAIN	7 (3.4)	6 (3.0)	>.999
MYALGIA	7 (3.4)	5 (2.5)	.771
SINUSITIS	6 (2.9)	8 (4.0)	.596
PYREXIA	6 (2.9)	6 (3.0)	>.999
NAUSEA	6 (2.9)	4 (2.0)	.751
CELLULITIS	5 (2.4)	2 (1.0)	.449
NEPHROLITHIASIS	5 (2.4)	2 (1.0)	.449
LARYNGITIS	5 (2.4)	0	.061
OEDEMA PERIPHERAL	4 (2.0)	7 (3.5)	.375
HERPES ZOSTER	4 (2.0)	5 (2.5)	.748
LUNG NEOPLASM	4 (2.0)	2 (1.0)	NA
RESPIRATORY TRACT INFECTION	3 (1.5)	6 (3.0)	.332
DIABETIC NEUROPATHY	2 (1.0)	6 (3.0)	.170
ANAEMIA	2 (1.0)	5 (2.5)	.278
FATIGUE	2 (1.0)	5 (2.5)	.278
MUSCLE SPASMS	1 (0.5)	5 (2.5)	.117
PNEUMONIA	0	5 (2.5)	.028

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