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Clinical Study Summary: Study H7U-MC-IDAV

A Phase 3, Open-Label, Parallel Group Study to Evaluate the Efficacy of Preprandial Human Insulin Inhalation Powder (HIIP) Compared to Preprandial Injectable Insulin in Patients with Type 1 Diabetes Mellitus

Date summary approved by Lilly: 05 May 2009

Title of Study: A Phase 3, Open-Label, Parallel-Group Study to Evaluate the Efficacy of Preprandial Human Insulin Inhalation Powder (HIIP) Compared to Preprandial Injectable Insulin in Patients with Type 1 Diabetes Mellitus	
Investigators: This multicenter study included 49 principal investigators.	
Study Centers: This study was conducted at 49 study centers in 9 countries/regions.	
Publication Based on the Study: None at this time.	
Length of Study: Date first patient enrolled: 19 September 2006 Date last patient completed: 27 May 2008	**Phase of Development:** 3

Objectives: The primary objective of this study was to test the hypothesis that preprandial HIIP is noninferior to preprandial injectable insulin (insulin lispro) with respect to mean change in HbA1c from baseline to endpoint of 6 months in patients with type 1 diabetes. A noninferiority margin of 0.4% for HbA1c was used.

The secondary objectives of the study were:
1) To compare preprandial HIIP with preprandial injectable insulin (insulin lispro) in patients with type 1 diabetes who have been treated for 6 months with respect to the following:

- nocturnal hypoglycemia rate, overall hypoglycemia rate, and severe hypoglycemia rate as well as incidences,
- 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 had an HbA1c ≤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}),
- pulmonary symptoms using the Pulmonary Symptoms Questionnaire (PSQ),

- safety as assessed by adverse events,
- body weight,
- patient-reported outcomes questionnaires to assess psychological well-being, diabetes-related symptoms, diabetes treatment satisfaction, and insulin delivery system satisfaction.

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

3) To assess the pharmacokinetics (PK) of HIIP administered preprandially in a subgroup of patients.

The exploratory objective of this study was to explore the secondhand smoking effects on clinical correlates.

Study Design: This randomized, multicenter, open-label, active-comparator, two-arm, parallel group 6 month study with 500 patients assessed the efficacy of HIIP in patients with type 1 diabetes. Following a lead-in period with preprandial insulin lispro and insulin glargine to optimize daily insulin treatment, patients were assigned randomly to receive one of the following treatments: 1) preprandial HIIP plus insulin glargine, or 2) preprandial injectable insulin (insulin lispro) plus insulin glargine, for 6 months. Hemoglobin A_{1c} was used to assess overall glycemic efficacy. The primary efficacy endpoint was assessed at 6 months.

Number of Patients:
Planned: 520; Actual enrolled: 500
Randomized: 249 preprandial HIIP, 251 preprandial injectable insulin (insulin lispro)
Completed: 192 preprandial HIIP, 217 preprandial injectable insulin (insulin lispro)

Diagnosis and Main Criteria for Inclusion: Male or female nonsmoking patients, 18 years of age or older who had type 1 diabetes mellitus for at least 24 months at study entry and were taking at least 2 injections of insulin per day for at least 2 months, had FEV_1 and DL_{CO} >70% predicted and FEV_1/FVC >lower limit of normal, and had an HbA_{1c} ≤11.0% at screening.

Test Product, Dose, and Mode of Administration: Human Insulin Inhalation Powder (HIIP) delivered to the deep lungs using the Lilly/Alkermes AIR® Insulin Inhaler system; using combinations of two dose strengths, low (2U equivalent) and middle (6U equivalent) (dose as appropriate for individual patients); administered preprandially in combination with injectable insulin glargine (of recombinant DNA origin, 100U/mL) administered once a day. Dosage was determined based on individual needs.

Duration of Treatment: 6-month treatment period.

Reference Therapy, Dose, and Mode of Administration: Injectable insulin (subcutaneous insulin lispro, 100 U/mL) administered preprandially in combination with injectable insulin glargine (of recombinant DNA origin, 100U/mL) administered once daily. Dosage was determined based on individual needs.

Variables:
Efficacy: The primary efficacy measure was the HbA_{1c} change from baseline to 6 months endpoint (LOCF). The secondary measures of the study are: 8-point SBGM profiles; proportion of patients who had an HbA_{1c} ≤6.5% and <7.0%; daily insulin dose.
HIIP Delivery System: Insulin inhaler reliability (inhalers returned for complaint/inhalers dispensed).
Safety Measures: Insulin antibody levels (% binding); change from baseline in FEV_1, FVC, TLC, $DL_{CO,}$ and PSQ measures; hypoglycemia; treatment-emergent adverse events and serious adverse events; 'for cause' evaluations; laboratory tests; vital signs (body temperature, systolic and diastolic blood pressure, pulse and respiratory rate); body weight. Exploratory measures included second-hand smoking questions. Continuous blood glucose monitoring was done in a subgroup of patients to further assess risk of nocturnal hypoglycemia. Due to data quality issues, the continuous blood glucose monitoring data were not analyzed.
Pharmacokinetic: Free immunoreactive insulin (IRI) concentrations in serum of up to 5 samples collected from a subgroup of approximately 120 patients in the HIIP treatment group at Visits 5 and 6. Visit 5 includes the consumption of a standard meal. Results of the PK analysis will be reported separately.

Health Outcomes: Patient-reported outcomes using the 12-item Well-Being Questionnaire (W-BQ12); Subscales of the Diabetes Symptom Checklist-Revised (DSC-R); the Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs); and the Insulin Delivery System Questionnaire (IDSQ).
Evaluation Methods: This study planned to randomize 520 patients. Accounting for 15% dropout, a trial with 442 completers (221 patients per group) would have 96% power to show the primary objective that HIIP is noninferior to injectable insulin with respect to HbA_{1C} if the upper limit of a two-sided 95% confidence interval (HIIP – injectable) is no greater than 0.4%. This analysis used an ANCOVA model with country, treatment, and HbA_{1c} at baseline as covariates using the ITT analysis dataset. Analyses of other continuous variables used similar models with slight modifications. For the proportion of patients who had an HbA_{1C} ≤6.5% and <7.0%, logistic regression analysis was utilized. 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; with the exception of Hochberg's method for health outcome endpoints. Summary statistics were performed for all efficacy and safety measures.

Summary:

A total of 807 patients signed informed consent document for the study, all of whom completed Visit 1. Of these 807 patients, 307 patients did not meet the entry criteria and 500 patients were randomly assigned to a treatment group (249 patients, HIIP group; and 251 patients, injectable insulin group). Of the 500 randomized patients, 409 (81.8%) patients completed this study (192 [77.1%] patients,HIIP group; 217 [86.5%] patients, injectable group; p=.008). The most common reasons for study discontinuation in both groups were patient decision and lost to follow-up.

Of the 500 randomized patients, 285 (57.0%) were male and the majority (62.4%) were Caucasian. The participants in this trial were representative of the population of individuals with type 1 diabetes based on their age (39.2±13.2 years), mean BMI (25.24±4.48, and duration of diabetes (16.88±10.97 years). Patient demographic and clinical characteristics were similar.

After 6 months of treatment, the mean difference in HbA_{1c} between the treatment groups (HIIP – injectable insulin) was 0.27% (95% CI 0.11, 0.43; 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 had greater improvement in HbA_{1c} over the course of the study. The same analysis using the per-protocol population showed similar differences. There were no statistically significant differences between the treatment groups with respect to the percent of patients achieving HbA_{1c} levels of <7% or ≤6.5% at any visit or endpoint.

Treatment with HIIP was associated with statistically significantly greater baseline to endpoint improvement in morning preprandial blood glucose. Treatment with injectable insulin lispro was associated with statistically significantly greater improvement in 2-hour postprandial blood glucose after each main meal and overall, as well as at bedtime. Differences at other timepoints were not statistically significant. Overall blood glucose values were not different between the groups. Weight-adjusted daily insulin doses, at baseline and by visit through endpoint were not different between the 2 treatment groups. At 3 months, total prandial insulin daily dose was higher in the HIIP group (p=.014), but total daily dose was similar.

Nine inhalers were returned for complaint with no inhalers being found faulty, yielding a 0% faulty device return rate.

The change from baseline in the DTSQ score at endpoint was significantly higher in the HIIP group (p=.004), indicating greater satisfaction with diabetes treatment in that group. The change from baseline in the IDSQ overall insulin delivery satisfaction score at endpoint was significantly higher in the HIIP group (p=.009), indicating greater satisfaction with insulin delivery device.

One death due to cerebral infarction occurred during the study lead-in phase and before randomization to study drug. No deaths occurred during study treatment phase. A total of 29 patients experienced one or more SAEs, 10 patients in the HIIP group and 19 patients in the injectable insulin group. Two notable SAE were reported in the HIIP group during the study, one of allergic alveolitis (reported adverse event that was not confirmed by histological evaluation) and one of incorrect route of drug administration. A total of 1 patient in the HIIP group and 2 patients in the injectable insulin group had an AE that resulted in study discontinuation. The AEs that resulted in discontinuation were not considered study drug-related.

Overall, 182 (73.1%) patients in the HIIP group and 163 (64.9%) patients in the injectable insulin group experienced at least one TEAE during the study. The difference between the 2 groups in the percentage of patients reporting one or more TEAE was not statistically significant. 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 in the system organ class of respiratory, thoracic and mediastinal disorders (p=.009) resulting from differences in cough (p=.024) and dyspnea (p=.030). A statistically significantly greater percentage of patients in the HIIP group had a worsening in symptom severity scores from baseline to endpoint for PSQ questions related to the frequency and intensity of cough.

The difference between the groups in mean change from baseline in corrected DL_{CO} was statistically significant at LOCF endpoint (p=.020). The observed difference between the groups remained at the follow-up visit (p=.011). There were no significant differences between the treatment groups for FEV_1, FVC, and TLC. The 'for cause' evaluation process did not identify clinically significant differences in pulmonary abnormalities among patients exposed to HIIP versus injectable insulin.

There were no statistically significant differences between the 2 treatment groups in the incidence or rate of hypoglycemic episodes at endpoint. The rate of overall hypoglycemia was increased in the HIIP group at 1 month (p=.012) and that of nocturnal hypoglycemia at 1 month (p<.001) and at 3 months (p=.009). There were no other observed differences between the treatment groups with respect to risk of hypoglycemia.

Statistically significant differences between the 2 treatment groups for systolic blood pressure occurred with patients in the HIIP group having a slight increase from baseline at the 6-month LOCF endpoint (p=.012). The difference was not significant at the follow-up visit. There were no significant differences at endpoint between the treatment groups for diastolic blood pressure, heart rate, respiratory rate, or body temperature. A statistically significant difference in mean body weight change from baseline between the 2 treatment groups was observed at endpoint (p<.001) with the injectable insulin group having an increase relative to the HIIP group.

The change from baseline in the DTSQ score (p=.004) and IDSQ overall insulin delivery satisfaction score (p=.009) were significantly higher in the HIIP group at endpoint, indicating greater satisfaction with diabetes treatment and insulin delivery device.

Percent binding for anti-human insulin, anti-lispro insulin and cross-reactive insulin antibodies increased in the HIIP group from baseline to the 6-month LOCF endpoint. There were minimal changes in the injectable insulin group. The difference between the groups was statistically significant at endpoint (p<.001). Percent binding for the insulin antibodies decreased during the follow up in the HIIP groups, but

the difference between the groups remained statistically significant for all antibody types at the end of follow up period.

Analysis of the study data led to the following conclusions:

- The study did not meet the primary objective of demonstrating non-inferiority between preprandial HIIP and preprandial injectable insulin.
- Overall blood glucose values, the percent of patients achieving HbA_{1c} levels of <7% or ≤6.5%, and the weight-adjusted total daily insulin dose were not different between groups.
- The risk of hypoglycemia did not differ between the treatment groups at endpoint.
- There was a significant increase in the percentage of insulin antibodies binding in the HIIP group, which declined during the follow-up period.
- There was a significantly greater decrease in DL_{CO} in the HIIP group beginning at 1 month that remained significantly lower throughout the study. There were no significant differences between the 2 groups in FEV_1, FVC, and TLC.
- Significantly more patients experienced worsening in pulmonary symptom severity as measured by PSQ in the HIIP group for cough, shortness of breath, and chest congestion.
- There was a significant difference between the 2 groups for body weight with the HIIP group experiencing a small decrease and the injectable insulin group experiencing a small increase.
- None of the safety findings in this study changed the known safety profile of HIIP.
- There was greater satisfaction with diabetes treatment and the insulin delivery device in the HIIP group.

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=249) n (%)	Treatment Group: Injectable Insulin (N=251) n (%)	p-Value
Patients with >= 1 TEAE	182 (73.1)	163 (64.9)	.053
Patients with No TEAE	67 (26.9)	88 (35.1)	.053
HEADACHE	34 (13.7)	28 (11.2)	.418
NASOPHARYNGITIS	33 (13.3)	27 (10.8)	.412
COUGH	28 (11.2)	14 (5.6)	.024
PHARYNGOLARYNGEAL PAIN	20 (8.0)	16 (6.4)	.494
PAIN IN EXTREMITY	12 (4.8)	14 (5.6)	.841
INFLUENZA	11 (4.4)	17 (6.8)	.331
UPPER RESPIRATORY TRACT INFECTION	11 (4.4)	10 (4.0)	.828
BACK PAIN	11 (4.4)	9 (3.6)	.656
NAUSEA	9 (3.6)	5 (2.0)	.293
DYSMENORRHOEA	8 (3.2)	9 (3.6)	>.999
DIARRHOEA	7 (2.8)	8 (3.2)	>.999
PYREXIA	7 (2.8)	4 (1.6)	.381
VOMITING	6 (2.4)	8 (3.2)	.788
HYPOGLYCAEMIA	6 (2.4)	7 (2.8)	>.999
URINARY TRACT INFECTION	5 (2.0)	10 (4.0)	.294
MUSCULOSKELETAL PAIN	5 (2.0)	8 (3.2)	.576
GASTROENTERITIS VIRAL	5 (2.0)	5 (2.0)	>.999
SINUSITIS	5 (2.0)	5 (2.0)	>.999
ABDOMINAL PAIN UPPER	5 (2.0)	4 (1.6)	.751
GASTROENTERITIS	5 (2.0)	3 (1.2)	.503
RASH	5 (2.0)	3 (1.2)	.503
TOOTHACHE	5 (2.0)	3 (1.2)	.503
RHINORRHOEA	5 (2.0)	1 (0.4)	.122
DYSPNOEA	5 (2.0)	0	.030
BRONCHITIS	4 (1.6)	7 (2.8)	.544
RHINITIS	4 (1.6)	6 (2.4)	.751
ARTHRALGIA	4 (1.6)	5 (2.0)	>.999
MYALGIA	3 (1.2)	5 (2.0)	.724

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