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Clinical Study Summary: Study H7U-MC-IDAY

A Phase 3, Open-Label, Parallel-Group Study to Compare Two Dosing Algorithms for Preprandial Human Insulin Inhalation Powder (HIIP) in Insulin-Naïve Patients with Type 2 Diabetes Mellitus

Date summary approved by Lilly: 05 May 2009

Title of Study: A Phase 3, Open-Label, Parallel-Group Study to Compare Two Dosing Algorithms for Preprandial Human Insulin Inhalation Powder (HIIP) in Insulin-Naïve Patients with Type 2 Diabetes Mellitus	
Investigators: This multicenter study included 56 principal investigators.	
Study Centers: This study was conducted at 56 study centers in 9 countries.	
Publications Based on the Study: None at this time.	
Length of Study: 17 months Date first patient enrolled: 13 Dec 2006 Date last patient completed: 12 May 2008	**Phase of Development:** 3

Objectives: The primary objective of this study, in suboptimally-controlled insulin-naïve individuals with type 2 diabetes, was to demonstrate that a simple approach for adding HIIP to oral antihyperglycemic medication achieved, within 6 months, glycemic control similar to a more aggressive approach.

The two treatment algorithms (simplified [Algorithm A] versus intensive [Algorithm B] diabetes management regimen) were compared with respect to mean change in HbA_{1c} from baseline to endpoint (6 months). Noninferiority with respect to HbA_{1c} was concluded if the upper limit of the 95% confidence interval for the treatment difference (Algorithm A – Algorithm B) was less than 0.4%.

The secondary objectives of the study were:

1) To compare the two dose titration algorithm groups with respect to the following:

- mean change in HbA_{1c} from baseline to various timepoints (2 months, 3 months)
- daily insulin dose requirements (each mealtime, total mealtime)
- time to maximum dose; time to 90% maximum dose; and time to achievement of 75% of self-monitored blood glucose (SMBG) targets (defined as patient achieving target for three out of four measurements for a particular day)
- the proportion of patients achieving HbA_{1c} <7% and, in a separate analysis, achieving HbA_{1c} $\leq$6.5%
- 8-point SMBG profile (blood glucose measurements before the morning, midday, and evening

meals; 2 hours after the start of the morning, midday, and evening meals; at bedtime; and at 3 a.m.), 4-point SMBG profile (blood glucose measurements before the morning, midday, and evening meals and at bedtime), and total number of blood glucose measurements per week
- hypoglycemia (rate, incidence, nocturnal, severe)
- patient-reported energy; fatigue and cognitive distress symptoms; diabetes treatment satisfaction; and evaluation of the insulin delivery system
- treatment-emergent adverse events
- safety, as assessed by insulin antibody levels; pulmonary function testing (PFT) (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], and total lung capacity [TLC]) and diffusing capacity of the lung for carbon monoxide (DL_{CO}); Pulmonary Symptoms Questionnaire (PSQ); body weight.

2) To assess inhaler reliability.

The exploratory objectives of the study were:

1) To assess patient expectations regarding treatment with an insulin delivery system and insulin therapy at baseline and evaluate the extent to which these expectations were met at study endpoint.
2) To assess change in HbA_{1c} from baseline in subgroups defined by baseline oral antihyperglycemic medication.

Study Design: This Phase 3, randomized, multicenter, open-label, parallel-group study compared two dosing algorithms for HIIP with respect to mean changes in HbA_{1c} from baseline to endpoint (6 months) in insulin-naïve patients with type 2 diabetes.

Number of Patients:
Planned: 360 Actual: 382
Randomized: Algorithm A: 191, Algorithm B: 191
Completed: Algorithm A: 147, Algorithm B: 153

Diagnosis and Main Criteria for Inclusion: Male or female, insulin-naïve, 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 1 or more oral antihyperglycemic medications on a stable dose for at least 6 weeks prior to study entry (12 weeks for thiazolidinediones [TZDs]), had an FEV_1 and DL_{CO} >70% predicted, an FEV1/FVC of greater than the lower limit of normal (LLN) per local PFT Lab, and had an HbA_{1c} >7.0% and ≤10.5% at screening.

Test Product, Dose, and Mode of Administration: Algorithm A, defined as a simplified diabetes management regimen, started with a fixed dose of HIIP, titrated 2 times per week based on 2 times per week 4-point blood glucose values for the first month; then titrated 1 time per week based on once-weekly 4-point blood glucose values for the remainder of the study. Each dose may have been changed by 2U increments or total daily dose by a maximum of 6 U per day.

Algorithm B, defined as an intensive diabetes management regimen, started with an adjusted dose of HIIP, titrated 2 times per week based on daily 4-point blood glucose values, with sustained monitoring of dose and blood glucose throughout the study. Doses were changed 2 to 6 U, depending on the corresponding blood glucose, with a maximum of 8 U per day.

HIIP was delivered to the deep lung using the Lilly/Alkermes insulin inhaler (AIR® Insulin Inhaler System). Patients continued their prestudy oral antihyperglycemic medication without a change in dose throughout the study unless the patient's safety would be compromised by doing so.

Duration of Treatment: 6 months

Reference Therapy and Mode of Administration: Not applicable; no reference therapy was used.

Variables:
Efficacy: The primary efficacy measure was the HbA_{1c} change from baseline to 6 months. The secondary

measures of the study are: change in HbA_{1c} from baseline to various timepoints; daily insulin dose; proportion of patients who had an HbA_{1c} ≤6.5% and <7.0%; 4-point SMBG profiles; total number of blood glucose measurements per week; 8-point SMBG profiles; time to (maximum dose, 90% maximum dose, and achievement of 75% of SMBG targets).
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; "for cause" evaluations; treatment-emergent adverse events; vital signs (body temperature, systolic and diastolic blood pressure, pulse and respiratory rate); body weight.
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 ($DTSQ_S$); and the Insulin Delivery System Questionnaire (IDSQ).

Evaluation Methods:
This study planned to randomize 360 patients. Accounting for a 20% dropout rate, a study with 288 completers (144 patients per treatment) will have 80% power to show that Algorithm A is noninferior to Algorithm B with respect to HbA_{1c} if the upper limit of the two-sided 95% confidence interval (Algorithm A-Algorithm B) is less than 0.4%, assuming no true treatment difference. This analysis used an ANCOVA model with insulin secretagogue use, country, treatment, and HbA_{1c} at baseline as covariates using the intent-to-treat (ITT) analysis dataset for primary analysis and using the per-protocol data set as a supportive analysis. Analyses of other continuous variables used similar models with slight modifications. Summary of descriptive statistics was used for total number of blood glucose measurements per week. For the proportion of patients who had an HbA_{1c} ≤6.5% and <7.0%, logistic regression analysis was utilized. For time to event data (maximum dose, 90% maximum dose, achievement of 75% of SMBG targets) survival analysis was performed to compare the algorithms. Analyses of categorical safety measures used the Fisher's exact test or chi-square tests. No adjustments for multiplicity were performed, and no adjustments for missing data were performed, with the exception of last observation carried forward (LOCF). All tests of treatment effects were conducted at a two-sided alpha level of 0.05 and/or two-sided 95% confidence interval. Summary statistics were performed for each outcome and inhaler reliability.

Summary:
A total of 781 patients signed informed consent for the study, all of whom completed Visit 1. Of these 781 patients, 399 patients did not meet the entry criteria and 382 patients were randomly assigned to a treatment group (191 patients in Algorithm A and 191 patients Algorithm B) at the randomization visit (Visit 2). Of the 382 randomized patients, 300 (78.5%) patients completed this study (147 patients in the Algorithm A group; 153 patients in the Algorithm B group). The most common reasons for study discontinuation in both groups were patient decision and lost to follow-up.

Of the 381 randomized patients in the ITT population, 227 (59.6%) were male and 154 (40.4%) were female; the majority of randomized patients (66.9%) were Caucasian. The average age (mean±SD) was 57.4±9.6 years with a minimum age of 27 years and maximum age of 81 years. The average baseline body weight was 87.42±20.48 kg and the average baseline height was 166.88±10.77 cm. Of the 381 randomized patients, 141 (37.0%) were past smokers with an average number of years smoked of 18.9±12.1 years. The overall average duration of diabetes was 9.98±6.85 years. The patient demographic data were similar between the groups with the exception of some categories of tobacco use history such as number of years of tobacco use (p=.030) and number of cigarettes smoked daily (p=.013) with patients in Algorithm A having higher mean values.

The primary objective of this study, in suboptimally-controlled insulin-naïve individuals with type 2 diabetes, was to demonstrate that a simple approach (Algorithm A) for adding HIIP to oral antihyperglycemic medication can achieve, within 6 months, glycemic control similar to a more aggressive

approach (Algorithm B). The noninferiority of a simplified dosing regimen was not demonstrated. The overall difference (Algorithm A – Algorithm B) in the change in HbA_{1c} between algorithms was 0.24%.

Secondary efficacy measures in the study included HbA_{1c} at intermediate time points, 8-point SMBG profiles, 4-point SMBG profiles, measurements of insulin use including total number of daily doses, daily insulin use, and time to maximum dose, and concomitant medication use. Overall, patients in Algorithm B needed approximately 30-40% higher total daily insulin dose as measured in U/kg. Patients in the Algorithm B group were more consistently able to achieve HbA_{1c} values of <7.0% and ≤6.5% over the course of the study. There were statistically significant differences between the treatment algorithm groups during the study and overall (p=.005 and p=.022, respectively). There were some statistically but not clinically significant differences between the 2 treatment algorithm groups for the other parameters.

One unscheduled return of a faulty inhaler occurred.

No deaths were reported during the study. A total of 23 patients experienced one or more SAEs, 11 patients in the Algorithm A group and 12 patients in the Algorithm B group. A total of 6 patients in the Algorithm A group and no patients in the Algorithm B group had a TEAE that resulted in study discontinuation. One event of bronchiolitis, one event of grand mal convulsion, and one event of allergic dermatitis were considered to be related to study drug, study device, and/or study procedures. All other TEAEs that resulted in discontinuation were not considered possibly study drug related.

Overall, 118 (61.8%) patients in the Algorithm A group and 120 (63.2%) patients in the Algorithm B 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 algorithms in the SOC psychiatric disorders (p=.037) with 1 patient in the Algorithm A group reporting seasonal affective disorder versus a total of 7 patients in the Algorithm B group reporting events for this SOC with 3 patients reporting anxiety, 2 reporting depression, and 2 reporting insomnia.

Insulin antibody tests showed there were no statistically significant differences between treatment groups for percent binding.

There were consistent, small, mean decreases from baseline in FEV_1 and FVC and no appreciable change from baseline in DL_{CO}. There were no significant differences between the treatment groups for any of the PFT components. Interpretation of the magnitude of the baseline to endpoint changes was limited by the absence of data from a comparator group.

There was no statistically significant difference between Algorithm A and Algorithm B patients in body weight at study endpoint. However, statistically significant differences between the 2 groups occurred at various visits with patients in Algorithm A having less (by about 0.5-1.0 kg) weight gain. Differences between the 2 treatment groups were not significant at follow-up.

No significant difference was observed between treatment groups in the DTSQ treatment satisfaction scale score at baseline or in change from baseline at endpoint. No significant differences were observed between treatment groups in any of the IDSQ domain scores at any visit or at endpoint.

The rate of hypoglycemia per 30 days was significantly greater in the Algorithm B group from randomization through endpoint (p<.001). There were statistically significant differences between the treatment groups at many time points during the study for rate or incidence of both hypoglycemia and nocturnal hypoglycemia. The incidence of severe hypoglycemic episodes was 8.7% in the Algorithm A

group and 14.4% in the Algorithm B group; however, the difference between groups did not meet the threshold for statistical significance (p=.105).

Analysis of the study data led to the following conclusions

- The study did not meet the primary objective of demonstrating non-inferiority between the simplified and intensive algorithms in the ITT population.
- The decrease in HbA_{1C} from baseline was significantly greater in the intensively managed population, starting at month 2, and continuing to endpoint (month 6). The overall difference in the change in HbA_{1C} between algorithms was 0.24%.
- A greater proportion of patients in the intensive algorithm achieved an HbA_{1C} <7%, and in a separate analysis, ≤6.5%.
- The intensive algorithm led to a higher weight-adjusted insulin dose.
- The intensive algorithm produced a slightly greater increase in body weight through the 3-month visit.
- The intensive algorithm led to a higher rate of hypoglycemia.
- There were no differences between treatment algorithms in DTSQ and IDSQ scores.
- None of the safety findings in this study changed the known safety profile of HIIP.

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

Preferred Term	Treatment Group: Algorithm A (N=191) n (%)	Treatment Group: Algorithm B (N=190) n (%)	p-Value
Patients with >= 1 TEAE	118 (61.8)	120 (63.2)	.833
Patients with No TEAE	73 (38.2)	70 (36.8)	.833
COUGH	27 (14.1)	28 (14.7)	.885
NASOPHARYNGITIS	22 (11.5)	18 (9.5)	.617
INFLUENZA	14 (7.3)	17 (8.9)	.580
HEADACHE	12 (6.3)	19 (10.0)	.195
PAIN IN EXTREMITY	9 (4.7)	12 (6.3)	.511
BACK PAIN	11 (5.8)	9 (4.7)	.819
PHARYNGOLARYNGEAL PAIN	10 (5.2)	6 (3.2)	.445
PYREXIA	5 (2.6)	9 (4.7)	.292
DIARRHOEA	9 (4.7)	4 (2.1)	.259
ARTHRALGIA	8 (4.2)	4 (2.1)	.380
UPPER RESPIRATORY TRACT INFECTION	6 (3.1)	5 (2.6)	>.999
PHARYNGITIS	8 (4.2)	2 (1.1)	.105
BRONCHITIS	6 (3.1)	4 (2.1)	.751
HYPERTENSION	6 (3.1)	3 (1.6)	.503
SINUSITIS	5 (2.6)	4 (2.1)	>.999
OEDEMA PERIPHERAL	4 (2.1)	5 (2.6)	.751
GASTRITIS	3 (1.6)	6 (3.2)	.337
MUSCULOSKELETAL PAIN	3 (1.6)	6 (3.2)	.337
MUSCLE SPASMS	4 (2.1)	3 (1.6)	NA
WEIGHT INCREASED	4 (2.1)	3 (1.6)	NA
FATIGUE	3 (1.6)	4 (2.1)	NA
MYALGIA	2 (1.0)	5 (2.6)	.284
VOMITING	5 (2.6)	1 (0.5)	.215
ASTHENIA	4 (2.1)	2 (1.1)	NA
GASTROENTERITIS	4 (2.1)	2 (1.1)	NA
DYSPNOEA	2 (1.0)	4 (2.1)	NA
PARAESTHESIA	2 (1.0)	4 (2.1)	NA
ABDOMINAL PAIN UPPER	1 (0.5)	5 (2.6)	.122

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