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Clinical Study Summary: Study H7U-MC-IDAZ

A Phase 3, Open-Label, Crossover Study to Evaluate the Efficacy and Safety of Human Insulin Inhalation Powder (HIIP) Compared with Once-Daily Insulin Glargine in Insulin-Naïve Patients with Type 2 Diabetes Mellitus on Oral Agents

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Title of Study: A Phase 3, Open-Label, Crossover Study to Evaluate the Efficacy and Safety of Human Insulin Inhalation Powder (HIIP) Compared with Once-Daily Insulin Glargine in Insulin-Naïve Patients with Type 2 Diabetes Mellitus on Oral Agents	
Investigators: This multicenter study included 21 principal investigators.	
Study Centers: This study was conducted at 20 study centers in 4 countries.	
Publication Based on the Study: None at this time.	
Length of Study: Date first patient enrolled: 13 March 2007 Date last patient completed: 22 May 2008	**Phase of Development:** 3
Objectives: The primary objective of this randomized, crossover study was to compare, in insulin-naïve patients with type 2 diabetes who had inadequate glycemic control on one or more oral antihyperglycemic medications (OAM), a regimen adding mealtime HIIP ("HIIP+orals") versus a regimen adding insulin glargine ("glargine+orals") with respect to change in HbA_{1c} from baseline (Visit 3) to endpoint. Superiority with respect to HbA_{1c} was concluded if the upper limit of the 95% confidence interval for the treatment difference ("HIIP+orals" minus "glargine+orals") was less than zero. Noninferiority was concluded if this upper limit was less than 0.4%, but greater than or equal to 0.0%. The secondary objectives of the study were: 1) To compare the "HIIP+orals" treatment versus "glargine+orals" treatment, with respect to the following after 24 weeks of treatment: • mean change in HbA_{1c} from baseline (measured at Visit 3) to various time points, • the proportion of patients who achieved HbA_{1c} <7% and, in a separate analysis, achieved $HbA_{1c} \leq 6.5\%$, • 8-point self-monitored blood glucose (SMBG) profiles obtained at baseline (Visit 3) and at the end of each study period (which elucidated changes in postprandial excursions),	

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- total insulin dose requirements,
- patient-reported preference, evaluation of insulin delivery system satisfaction, lifestyle impact of insulin delivery system, diabetes treatment satisfaction, energy, fatigue, cognitive distress symptoms, hyperglycemia symptoms, ease of dosing, positive well-being, negative well-being, and hypoglycemia symptoms,
- hypoglycemia (rate and incidence of total and nocturnal, and incidence of severe),
- changes in body weight,
- treatment-emergent adverse events (TEAEs),
- safety as assessed by total pulmonary function testing (PFT) (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}); and Pulmonary Symptoms Questionnaire (PSQ),
- standard fasting lipid profile (high-density lipoprotein cholesterol [HDL-C], total cholesterol, triglycerides, and low-density lipoprotein cholesterol [LDL-C]).

2) To assess inhaler reliability.

Exploratory objectives for this 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 compare the "HIIP+orals" treatment versus "glargine+orals" treatment, with respect to GlycoMark® values.

Study Design:
The study was stopped early due to the Sponsor's decision to terminate the development of the AIR Insulin program. The decision was made based on 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.

This randomized, multicenter, open-label, active-comparator, two-period crossover study with 143 patients assessed the efficacy of HIIP in patients with type 2 diabetes. After screening, patients who met study entry criteria participated in a pretreatment phase lasting approximately 4 weeks. During this period, patients continued their usual OAM therapy. Patients were administered baseline questionnaires and provided dietary counseling and instruction on blood glucose measurements. Pretreatment PFT and DL_{CO} data were collected, and patients performed SMBG checks. After the pretreatment phase, patients were randomized to one of the following treatment sequences:

Period 1: insulin glargine + continuation of OAM(s),
Period 2: HIIP + continuation of OAM(s) (the "glargine/HIIP" sequence);

OR

Period 1: HIIP + continuation of OAM(s),
Period 2: insulin glargine + continuation of OAM(s) (the "HIIP/glargine" sequence).

The duration of each period was 24 weeks. There was no washout period between Period 1 and Period 2. The total duration of the treatment phase of the study (Periods 1 and 2 combined) was 48 weeks. An 8-week follow-up period, during which HIIP was discontinued, was included at the end of the study to assess the reversibility of changes, if any, in PFTs, DL_{CO}, or pulmonary symptoms. Hemoglobin A_{1c} was

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used to assess overall glycemic efficacy. The primary efficacy endpoint was assessed at the end of each crossover period.

Number of Patients:
Planned: 132 Actual: 143
Randomized: 70 glargine/HIIP, 73 HIIP/glargine
Completed: Period 1: 71 (40 HIIP/glargine, 31 glargine/HIIP)
Period 2: 5 (2 HIIP/glargine, 3 glargine/HIIP)

Diagnosis and Main Criteria for Inclusion: Male or female nonsmoking insulin-naïve 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 OAMs on a stable dose for at least 6 weeks (12 weeks for thiazolidinediones [TZDs]), had FEV_1 and DL_{CO} >70% predicted, and had an HbA_{1c} ≥8.0% and ≤10.5% at screening.

Test Product, Dose, and Mode of Administration: Human Insulin Inhalation Powder (HIIP) was delivered to the deep lung using the Lilly/Alkermes insulin inhaler (AIR® Insulin Inhaler System). Patients continued their prestudy OAM(s) without a change in dose throughout the study unless the patient's safety would be compromised by doing so.

Duration of Treatment: Due to early study termination, the overall mean exposure time to study medication was 4.69±1.57 months for HIIP and 4.63±1.64 months for glargine.

Reference Therapy, Dose, and Mode of Administration: Injectable insulin glargine (subcutaneous insulin glargine of recombinant DNA origin, 100 U/mL) administered at bedtime in combination with 1 or more OAM(s). Dosage was determined based on individual needs.

Variables:
Efficacy: The primary efficacy measure was the HbA_{1c} change from baseline to the end of each crossover period. The secondary measures of the study were as follows: the proportion of patients who achieved an HbA_{1c} <7% and, in a separate analysis, achieved an HbA_{1c} ≤6.5%; 8-point SMBG; 2-hour blood glucose excursions for the morning, midday, and evening meals (based on 8-point SMBG data); daily insulin dose requirements (total, preprandial, and basal insulin); fasting lipid, total cholesterol, triglycerides, and low-density lipoprotein cholesterol [LDL-C]); and inhaler reliability. Exploratory measures included mean change in GlycoMark from baseline to the end of each treatment period and patient reported outcomes questionnaires assessing patient expectations about insulin therapy and experience with insulin therapy.
HIIP Delivery System: Insulin inhaler reliability.
Safety Measures: Change from baseline in pulmonary function tests (FEV_1, FVC, TLC, DL_{CO}); change from baseline in cough and other pulmonary symptoms using the PSQ; hypoglycemic episodes; treatment-emergent adverse events (TEAE); laboratory tests; "for cause" pulmonary evaluations, vital signs ; and body weight.
Health Outcomes: Patient-reported outcomes using the Well-Being Questionnaire (W-BQ12), the Diabetes Symptom Checklist-Revised (DSC-R), Diabetes Treatment Satisfaction Questionnaire ($DTSQ_S$), and the Insulin Delivery System Questionnaire (IDSQ).;The Patient Preference Questionnaire .

Evaluation Methods:
A total of 143 patients were randomized to one of two treatment sequences (73 in the HIIP/glargine arm and 70 in the glargine/HIIP arm). Due to the early termination of the trial, only 5 patients completed the entire treatment period. Therefore, the planned crossover analyses were not performed because of insufficient numbers of completers. Analyses of the safety measures were instead performed treating period 1 and period 2 separately. Analyses of the efficacy measures were not performed because of the lack of power when analyzed as parallel design study.

For some continuous safety measures (laboratory measures and vital signs), an ANCOVA model was performed for the treatment comparison included terms of treatment, insulin secretagogue use, baseline HbA1c stratum, country, and baseline values of the safety measures (laboratory measures and vital signs). For pulmonary function test (PFT) variables, an ANCOVA model was performed for the treatment

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comparison included terms of treatment, country, baseline HbA_{1c} stratum, insulin secretagogue use, and some other potential correlated covariates. Hypoglycemia rate was analyzed with a non-parametric model including factors for treatment, insulin secretagogue use, baseline HbA_{1c} stratum, and country. Analyses of categorical safety measures used the Pearson chi-square test or Fisher's exact test. Covariates such as patient demographics were tested between sequences for significance on parameters of interest. 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 calculated for all safety measures.

Summary:

Of the 143 randomized patients, 142 patients were included in the ITT population consisting of 83 (58.5%) males and 59 (41.5%) females; the majority of randomized patients (59 patients, 41.5%) were Caucasian. The average age (mean±SD) was 54.2±9.0 years with a minimum age of 34 years and maximum age of 78 years. The average baseline body weight was 83.78±19.76 kg and the average baseline height was 164.96±9.51 cm. Of the 142 randomized patients, 37 (26.1%) were past smokers with an average number of years smoked of 17.6±12.2 years. The patient demographic data were similar between the 2 groups.

Of 143 randomized patients, 5 patients completed both treatment periods for this study, 2 patients in the HIIP/glargine group and 3 patients in the glargine/HIIP group. There were 40 (54.8%) patients in the HIIP/glargine group and 31 (44.3%) patients in the glargine/HIIP group that completed the treatment period 1 before the crossover. The most common reasons for study discontinuation were sponsor decision, patient decision, and lost to follow-up.

The planned crossover analyses were not performed because there were insufficient numbers of completers in the second period. Analyses of the efficacy measures were not performed because of the lack of power when analyzed as parallel design study. There were no inhalers returned for complaint.

There were no statistically significant differences in any of the PFTs at baseline or the period 1 LOCF endpoint. The only statistically significant difference observed during period 2 was for FVC at the LOCF endpoint. The distribution of PFT quality scores was similar between the treatment periods. The 'for cause' process did not identify clinically significant differences in pulmonary abnormalities among patients exposed to HIIP versus injectable insulin.

During period 1, 50 (68.5%) patients in the HIIP group and 37 (52.9%) patients in the glargine group reported 1 or more treatment-emergent adverse event (TEAE). The difference between the groups was not statistically significant. The TEAEs reported by at least 10% of patients during exposure to HIIP were nasopharyngitis (12.3%) and cough (11.0%) during exposure to HIIP. There were no TEAEs reported in >10% of patients during exposure to glargine. During period 1, there was a statistically significant difference in the percentage of patients with a worsening from baseline to the point of maximum severity in response to questions concerning the intensity and frequency of coughing.

During period 2, 15 (51.7%) patients in the HIIP group and 18 (47.4%) patients in the glargine group reported 1 or more TEAE. The difference between the groups was not statistically significant. There was a statistically significant difference between the groups in the number of patients reporting at least one event within the system organ class of respiratory, thoracic, and mediastinal disorders (p=.017) with 7 patients (24.1%) in the HIIP group and 1 patient (2.6%) in the glargine group reporting at least one event. The TEAE reported by at least 10% of patients during exposure to HIIP was cough (17.2%) and during exposure to glargine was nasopharyngitis (13.2%).

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During this study, 1 patient in the glargine group died from sudden death and 1 patient in the HIIP group died from complications due to organophosphate poisoning. Ten patients reported a total of 16 serious adverse events (SAEs). There were no patients in either treatment period that discontinued from the study due to an adverse event (AE).

There were no statistically significant differences in the overall incidence or rate of hypoglycemic episodes, confirmed hypoglycemic episodes or nocturnal hypoglycemic episodes at any LOCF endpoint. There were some statistically significant differences at individual visits with the glargine group having higher incidence and/or rate of hypoglycemic episodes, confirmed hypoglycemic episodes and nocturnal hypoglycemic episodes.

There were no statistically significant differences between treatment groups for systolic blood pressure, diastolic blood pressure, heart rate, or respiratory rate. There was a statistically significant difference in the change from baseline in body temperature with patients in the glargine group having a decrease in body temperature compared with the HIIP group which had a slight increase in body temperature. There was a statistically significant difference in the change from baseline in body weight at Visits 6 and 8 but not at the period 1 LOCF endpoint, with patients in the HIIP group having a greater increase in body weight.

Analysis of the study data led to the following conclusions:

- The study primary objective and all secondary efficacy objectives were not analyzed due to the early termination of the study and inadequate power.
- There were no statistically significant differences between treatment groups in pulmonary function tests except for FVC at the Period 2 LOCF endpoint where the HIIP group had a decline relative to the glargine group.
- There were no statistically significant differences between the treatment groups for hypoglycemia at any LOCF endpoint. There were some statistically significant differences at individual visits with the glargine group having higher incidence and/or rate.

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