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Clinical Study Summary: Study H7U-MC-IDAW

A Phase 3, Open-Label, Parallel Group Treatment Concordance Study to Compare Insulin Use and Its Effect on Glycemic Control in Patients with Type 2 Diabetes Mellitus: Two Populations with Different Insulin Treatment Options

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Title of Study: A Phase 3, Open-Label, Parallel Group Treatment Concordance Study to Compare Insulin Use and Its Effect on Glycemic Control in Patients with Type 2 Diabetes Mellitus: Two Populations with Different Treatment Options	
Investigator(s): This multicenter study included 86 principal investigator(s).	
Study Center(s): This study was conducted in 11 countries.	
Publication(s) Based on the Study (17 June 2008)**:** Bergenstal R, Leyk M, Muchmore D. 2008. Will patient choice of AIR® Inhaled Insulin among other treatments for type 2 diabetes affect their glycemic control? Concordance study design and patient baseline characteristics. Diabetes 57(Suppl 1): A563.	
Length of Study: 23 months Date first patient enrolled: 19 June 2006 Date last patient completed: 01 May 2008	**Phase of Development:** 3
Objectives: The primary objectives were to test the hypothesis that, for insulin-naïve patients whose type 2 diabetes was not optimally controlled by 2 or more oral anti-hyperglycemic medications (including patients who were taking only one oral agent, but were considered to be appropriate candidates for insulin therapy [for example, patients with contraindications to one or more of the oral agents]), patients whose diabetes care options included Human Insulin Inhalation Powder (HIIP) ("standard options + HIIP"), as compared with patients whose options did not include HIIP ("standard options"), achieved: • Superior acceptance of insulin therapy, as measured by the proportion of patients in each group who were using insulin at study endpoint. • Noninferior glycemic control, as measured by mean change in HbA_{1c} from baseline to study endpoint, with noninferiority margin of 0.3%. • Superior glycemic control, as measured by mean change in HbA_{1c} from baseline to study endpoint.	

These objectives were tested in the order listed above. This "gatekeeping" approach required all previous tests to demonstrate a statistically significant result at the 0.05 level before conducting the next test in the list. The study was considered to have achieved its primary objective(s) if at least the first of the objectives was achieved.

The secondary objectives of the study were as follows:

1) To compare the following in patients who were in the standard options group or standard options + HIIP group for different time(s) throughout the 9-month study period:
   - proportion of patients using insulin at intermediate time points during the study
   - mean change in HbA_{1c} from baseline to intermediate time points during the study
   - proportion of patients who had an HbA_{1c} ≤6.5% and, in separate analysis, <7.0% at intermediate time points and at study endpoint
   - time to insulin initiation
   - safety as assessed by adverse events
   - rate per 30 days and incidence of hypoglycemic episodes (total, severe, and nocturnal)
   - patient-reported outcomes measurements to assess general well-being, diabetes-related symptoms, and diabetes treatment satisfaction.
2) For patients who started any form of insulin, to assess the following:
   - type(s) of insulin therapy used and insulin dose requirements
   - insulin antibody levels
   - patient evaluation of insulin delivery system.
3) For patients who chose HIIP, to assess 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})
   - inhaler reliability.
4) To assess and/or compare for patients in the standard options and standard options + HIIP groups the average HbA_{1c} and proportion of patients taking each category of diabetes treatment (insulin, insulin secretagogue, metformin, thiazolidinedione [TZD], "other").

The exploratory objectives were economic endpoints (reported separately) including health status, hospitalizations, and emergency room visits.

Study Design: This Phase 3, randomized, multicenter, open-label, parallel group, treatment study compared insulin use and its effect on glycemic control in two populations of patients with type 2 diabetes mellitus who had different treatment options. Safety, efficacy, and health outcome measurements were assessed for up to 9 months.

Number of Patients:

Planned: 1000 Actual: 1021

Randomized: 516 Standard Options Group, 505 Standard Options + HIIP Group

Completed: 479 Standard Options Group, 438 Standard Options + HIIP Group

Diagnosis and Main Criteria for Inclusion: Male or female nonsmoking patients between 18 and 100 years of age; who had type 2 diabetes mellitus for at least 6 months at study entry and were taking at least 2 oral anti-hyperglycemic medications for at least 3 months (stable for at least 6 weeks; thiazolidinedione [TZD] dose stable for at least 3 months), were insulin-naïve, and had an HbA_{1c} ≥7.5% and ≤11.0% at screening.

Test Product, Dose, and Mode of Administration: For patients in the standard options + HIIP group, the investigator was able to prescribe from a representative selection of marketed pharmaceutical products from each of the major treatment classes indicated for the treatment of type 2 diabetes (excluding any other formulation of inhaled insulin) in accordance with local regulations, manufacturer's product labeling, and

local standards of care, with the additional possibility that the investigator could prescribe Human Insulin Inhalation Powder (HIIP) delivered to the deep lung using the commercial version of the Lilly/Alkermes insulin inhaler (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. Dosage was determined based on individual needs.

Duration of Treatment: 9-month treatment period.

Reference Therapy, Dose, and Mode of Administration: For patients in the standard options group, the investigator was able to prescribe from a representative selection of marketed pharmaceutical products from each of the major treatment classes indicated for the treatment of type 2 diabetes (excluding any other formulation of inhaled insulin) in accordance with local regulations, manufacturer's product labeling, and local standards of care.

Variables:

Efficacy: Acceptance of insulin therapy was measured by the proportion of patients in each group who were using insulin at study endpoint. Glycemic control was assessed by measuring change in HbA_{1c} from baseline to study endpoint. The secondary measures included comparing the patients who were in the standard options group or standard options + HIIP group for (a) proportion of patients using insulin, (b) HbA_{1c} change from baseline, (c) proportion of patients who achieved or maintained an HbA_{1c} of ≤6.5% and <7.0%, (d) time from randomization to insulin initiation in days, (e) health outcomes, (f) proportion of patients taking each category of medication, and (g) HbA_{1c} of patients by category of medication. For patients who started insulin, the following were assessed: daily insulin doses, and evaluation of insulin delivery system. For patients who used HIIP, insulin inhaler reliability was measured by a laboratory assessment of inhalers returned for complaint.

Safety Measures: The primary safety measures were evaluated at study endpoint. All patients were evaluated for treatment-emergent adverse events (TEAEs), and hypoglycemic episodes. For patients who took insulin, insulin antibodies were assessed. For patients who took HIIP, the following were evaluated: mean change from baseline in the pulmonary function tests (FEV_1, FVC, TLC, DL_{CO}), PSQ measures, and 'for cause' pulmonary evaluations.

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 (DTSQs); the Insulin Delivery System Questionnaire (IDSQ); and the EuroQol (EQ-5D) Instrument.

Evaluation Methods:

Patients were randomized to one of two groups (standard options or standard options + HIIP) in a 1:1 ratio. This study used a gatekeeping strategy on the primary outcomes. First, it was tested if a greater proportion of patients in the standard options + HIIP treatment group than in the standard options group used insulin at study endpoint. Treatment group difference was tested using Cochran-Mantel-Haenszel (CMH) statistic with HbA_{1c} strata (<9.0% and ≥9.0%) and country at 0.05 level. Odds ratios were calculated using logistic regression with treatment group, country, and baseline HbA_{1c} as covariates. If there was significantly greater insulin use in the standard options + HIIP patients (based on CMH p-value), then better glycemic control was tested at 0.05 level by measuring change in HbA_{1c} from baseline to study endpoint. A 95% confidence interval was constructed for the treatment group difference (standard options + HIIP–standard options) for the change in HbA_{1c} from baseline to study endpoint using an analysis of covariance (ANCOVA) model with treatment group, country, and HbA_{1c} at baseline as covariates. Superiority with respect to change in HbA_{1c} was concluded if the upper limit of the 95% confidence interval for the treatment group difference (standard options + HIIP−standard options) was less than zero; noninferiority was concluded if this upper limit was less than 0.3%, but greater than or equal to 0.0%. The analyses for primary outcomes used the ITT analysis dataset with no imputations, with the exception of LOCF. For additional secondary efficacy variables (daily insulin dose), and for continuous safety measures (vital signs) collected in all patients, a similar ANCOVA model as for the primary analysis was performed for

treatment comparisons. A non-parametric test was performed on hypoglycemia rates. For proportion of patients who had an HbA_{1c} ≤6.5% and <7.0%, a logistic regression analysis was utilized. Time to insulin initiation was analyzed using a survival model with log-rank test. 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 missing data were performed with the exception of last observation carried forward (LOCF). Summary statistics were calculated for all efficacy and safety measures.

Summary:

Of 1554 patients who signed informed consent, 533 patients did not meet the study entry criteria. The remaining 1021 patients were randomly assigned to the standard options group (516 patients) or the standard options + HIIP group (505 patients). Approximately 75% of patients in the standard options + HIIP group who chose to use HIIP successfully qualified to take HIIP, based on their PFT scores. Of these randomized patients, 917 (89.8%) patients completed the study: 479 (92.8%) patients in the standard options group; 438 (86.7%) patients in the standard options + HIIP group, (p=.001). The most common reasons for early discontinuation in both groups were patient decision and lost to follow-up.

Of the 1014 randomized patients in the ITT population (randomized patients having at least one post-randomization visit after baseline), 472 (46.5%) were male and 542 (53.5%) were female; the majority of patients (51.4%) were Caucasian. The average age (mean±SD) was 56.7±10.3 years with a minimum age of 24 years and maximum age of 89 years. The average body weight was 84.10±21.62 kg and the average height was 164.19±10.30 cm. Of the 1014 randomized patients, 275 (27.1%) were past smokers with an average number of years smoked of 19.3±12.5 years. The average duration of diabetes was 10.00±6.55 years. The patient demographic data were similar between the 2 treatment groups.

The primary efficacy analysis was based on a three-part gatekeeping strategy. The first goal of the primary endpoint was not met with 273 (53.4%) patients in the standard options group and 292 (58.9%) patients in the standard options + HIIP group using insulin at study endpoint. The difference was not statistically significant. There were no statistically significant differences between treatment options groups for change from baseline to endpoint in HbA_{1c}.

Secondary efficacy measures in the study included HbA_{1c} at intermediate time points, time from randomization to insulin initiation, patterns of use of antidiabetic medication, inhaler reliability, and awareness of HIIP availability in patients not randomized to the standard options +HIIP group. Most secondary efficacy measures were similar between the standard options and standard options + HIIP groups, although there was slightly decreased use of certain oral agents when HIIP was available. There was not a statistically significant difference in the percentage of patients in both treatment options groups that were able to achieve an HbA_{1c} of <7.0% or ≤6.5% at the 9-month LOCF endpoint. The faulty inhaler return rate was 0%.

Three deaths were reported during the study; 1 abdominal bleed, 1 sudden death, and 1 cardiopulmonary arrest. None of the patients who died had taken HIIP during the study. A total of 51 patients experienced one or more SAEs; 24 patients in the standard options group and 27 patients in the standard options + HIIP group. Two patients in the standard options group and 5 patients in the standard options + HIIP group had an AE that resulted in study discontinuation. One event of bronchitis and one event of flatulence were considered to be related to study drug, study device, and/or study procedures. All other AEs that resulted in discontinuation were not considered possibly study drug related.

Overall, 269 (52.1%) patients in the standard options group and 262 (51.9%) patients in the standard options + HIIP group experienced at least one TEAE during the study. There was no statistically

significant difference between the standard options and the standard options + HIIP groups in the overall percentage of patients reporting one or more TEAE. Table 1 shows the TEAEs reported by at least 2% of patients in the safety population. Statistically significant differences between the two groups were observed for cough (p=<.001), dizziness (p=.045), gastroenteritis (p=.020), and diarrhea (p=.015).

Insulin antibody binding percentages were measured; however, interpretation was limited by the lack of data from a comparator group.

During the study, scores were recorded for FEV_1, FVC, FEV_1/FVC, DL_{CO} and TLC for those patients in the standard options + HIIP group who qualified to use HIIP. Based on summary statistics, there were consistent, small, mean decreases in FEV_1, FVC, and DL_{CO}. However, interpretation was limited by the lack of data from a comparator group. There were no apparent changes in FEV_1/FVC or TLC.

There was no statistically significant difference between the standard options and standard options + HIIP groups in the incidence or the rate of overall hypoglycemic episodes or nocturnal episodes. The incidence of severe hypoglycemic episodes was low in both groups and did not meet the threshold for statistical significance.

No significant differences were observed between treatment groups on the IDSQ overall insulin delivery satisfaction and no further statistical comparisons on health outcomes endpoints were described.

Analysis of the study data led to the following conclusions:

- The study failed to demonstrate that the availability of inhaled insulin as a treatment option would either increase the acceptance of insulin therapy or improve glycemic control.
- The need for PFT qualification in this study may have altered the overall acceptance of insulin in the standard options + HIIP group since approximately 25% of patients who expressed interest in taking HIIP did not qualify.
- Health outcomes measures failed to show any differences between the groups in treatment satisfaction, well-being, or diabetes symptoms.
- 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: Standard Options (N=516) n (%)	Treatment Group: Standard Options + HIIP (N=505) n (%)	p-Value
Patients with >= 1 TEAE	269 (52.1)	262 (51.9)	.950
Patients with No TEAE	247 (47.9)	243 (48.1)	.950
COUGH	15 (2.9)	52 (10.3)	<.001
NASOPHARYNGITIS	26 (5.0)	30 (5.9)	.583
UPPER RESPIRATORY TRACT INFECTION	25 (4.8)	22 (4.4)	.766
INFLUENZA	24 (4.7)	22 (4.4)	.881
HEADACHE	19 (3.7)	19 (3.8)	>.999
HYPERTENSION	19 (3.7)	16 (3.2)	.732
ARTHRALGIA	9 (1.7)	15 (3.0)	.220
BACK PAIN	7 (1.4)	14 (2.8)	.126
NAUSEA	13 (2.5)	12 (2.4)	>.999
DIZZINESS	4 (0.8)	12 (2.4)	.045
DYSPEPSIA	6 (1.2)	11 (2.2)	.229
OEDEMA PERIPHERAL	15 (2.9)	10 (2.0)	.419
GASTROENTERITIS	2 (0.4)	10 (2.0)	.020
DIARRHOEA	22 (4.3)	8 (1.6)	.015
PAIN IN EXTREMITY	12 (2.3)	8 (1.6)	.500

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