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Clinical Study Summary: Study H7U-JE-IDBB

A Crossover Study to Evaluate the Efficacy and Safety of Preprandial Human Insulin Inhalation Powder (HIIP) Compared to Preprandial Injectable Insulin in Patients with Type 1 Diabetes Mellitus

Date summary approved by Lilly: 03 February 2009

Title of Study: A Crossover Study to Evaluate the Efficacy and Safety of Preprandial Human Insulin Inhalation Powder (HIIP) Compared to Preprandial Injectable Insulin in Patients with Type 1 Diabetes Mellitus	
Investigator(s): This multicenter study included 9 principal investigators.	
Study Center(s): This study was conducted at 9 study centers in two countries.	
Length of Study: Date of first patient visit: 19 April 2007 Date of last patient visit: 26 May 2008	Phase of Development: 2/3
<p>Objectives:</p> <p>The primary objective of this study was to test the hypothesis that preprandial HIIP plus insulin glargine is noninferior to preprandial injectable insulin (regular human insulin or insulin lispro) plus insulin glargine with respect to the change in HbA_{1c} from baseline to endpoint in patients with type 1 diabetes treated for approximately 12 weeks with each therapy. Noninferiority was to be accepted if the upper limit of 95% confidence interval for the treatment difference ("HIIP plus insulin glargine" minus "injectable insulin plus insulin glargine") was less than 0.4%.</p> <p>The secondary objectives of the study were as follows:</p> <ol style="list-style-type: none"> 1) To compare preprandial HIIP plus insulin glargine with preprandial injectable insulin (regular human insulin or insulin lispro) plus insulin glargine with respect to the following: <ul style="list-style-type: none"> • Proportion of patients with HbA_{1c} ≤6.5% and HbA_{1c} <7.0%; • Insulin dose requirements; • 8-point self-monitored blood glucose (SMBG) profiles; • Safety as assessed by pulmonary function tests (PFTs), the pulmonary symptoms questionnaire (PSQ), adverse events (AEs), and episodes of hypoglycemia; • Patient-reported outcomes (PRO) questionnaires to assess symptoms of diabetes, patient vitality, and patient satisfaction with the diabetes treatments. 2) To assess inhaler reliability as measured by unscheduled device return rate. 	
<p>Study Design:</p> <p>Study H7U-JE-IDBB was a Phase 2/3, multicountry, open-label, randomized, crossover study to assess the safety and efficacy of HIIP in patients with type 1 diabetes. Following screening and a 4-week lead-in period to stabilize daily insulin requirements, patients were randomly assigned to one of the following treatment sequences:</p> <ul style="list-style-type: none"> • Period I: HIIP (plus insulin glargine); Period II: injectable insulin (plus insulin glargine); • Period I: injectable insulin (plus insulin glargine); Period II: HIIP (plus insulin glargine). <p>Each treatment was administered for 12 weeks. During Period I, patients returned for scheduled visits at 2 weeks, 4 weeks, 8 weeks, and 12 weeks (endpoint visit for Period I, crossover to Period II). During Period II, patients returned for scheduled visits at 14 weeks, 16 weeks, 20 weeks, and 24 weeks (endpoint visit for Period II). A follow-up safety visit was scheduled 4 weeks following the endpoint visit for Period II.</p> <p>Patients who temporarily or permanently discontinued study medication were expected to attend all scheduled study visits and undergo all study procedures until the conclusion of the study. Patients who temporarily discontinued study medication were encouraged to restart if there were no safety concerns. Patients who discontinued the study early had early discontinuation procedures performed, including a follow-up safety visit 4 weeks following early discontinuation.</p>	
<p>Number of Patients:</p> <p>Planned: 100</p> <p>Randomized: 41 HIIP (Period I) followed by injectable insulin (Period II);</p>	

41 injectable insulin (Period I) followed by HIIP (Period II).	
Completed Period I:	31 HIIP (Period I); 32 injectable insulin (Period I).
Completed Period II:	25 HIIP (Period I) followed by injectable insulin (Period II); 28 injectable insulin (Period I) followed by HIIP (Period II).
Diagnosis and Main Criteria for Inclusion: Male or female patients, at least 20 years of age, with type 1 diabetes mellitus of at least 24 months duration were enrolled in this study. All patients had been treated for at least 4 weeks prior to study entry using a basal/bolus regimen, including pre-prandial injections of insulin lispro, aspart or regular insulin (or mixtures) by injection pen or syringe (not insulin pump). Patients had HbA _{1c} <11.0%, were nonsmokers, and had no clinically significant pulmonary abnormality or pulmonary disease history. Patients were required to perform pulmonary function tests (PFTs) of acceptable quality (grade "C" or better) during the screening phase, and satisfy the following PFT criteria: DL _{CO} >70% of predicted; FEV ₁ /FVC > lower limit of normal and FEV ₁ >70% predicted; performance of at least three acceptable FEV ₁ , FVC, and two acceptable DL _{CO} maneuvers, two of which were reproducible.	
Study Drug, Dose, and Mode of Administration: HIIP, given three times daily by inhalation (Lilly/Alkermes insulin inhaler), 15 minutes before meals. HIIP was supplied as 2U (15% insulin by weight, equivalent to 2U of injected insulin) or 6U (30% insulin by weight, equivalent to 6U of injected insulin). The dose of insulin administered was dependent upon the individual requirements on the patient and could be adjusted at any time. <i>Required concomitant therapy:</i> Insuline glargine, given once daily by subcutaneous injection, before the morning meal. Insulin glargine was supplied as 10 mL vials (100 U/mL), for injection with syringe, 3 mL prefilled pens (100 U/mL), or 3 mL cartridges to be injected with a reusable pen. The dose of insulin administered was dependent upon the individual requirements on the patient and could be adjusted at any time.	
Comparator, Dose, and Mode of Administration: Insulin lispro or regular human insulin, given three times daily by subcutaneous injection. Insulin lispro was administered 15 minutes before meals; regular human insulin was administered 30 minutes before meals. Insulin lispro and regular human insulin were supplied as per insulin glargine. <i>Required concomitant therapy:</i> Insuline glargine, given once daily by subcutaneous injection, before the morning meal.	
Duration of Treatment: 24 weeks per patient: HIIP 12 weeks; injectable insulin 12 weeks.	

Variables:Efficacy (primary):

- Change in HbA_{1c} from baseline to endpoint of each treatment period

Efficacy (secondary):

- Proportion of patients who achieve an HbA_{1c} <7% and HbA_{1c} ≤6.5%
- Daily insulin dose requirements (preprandial and basal insulin)
- 8-point SMBG profiles
- Two-hour blood glucose excursions (based on 8-point SMBG data)

Safety:

- Pulmonary function tests (PFTs): FEV₁, FVC, FEV₁/FVC, TLC, and corrected DL_{CO}
- Pulmonary symptoms questionnaires (PSQ)
- Adverse events (AEs)
- Hypoglycemic episodes

Inhaler reliability:

- Laboratory assessment of inhalers returned due to patient complaint

Health Outcomes:

- Diabetes Treatment Satisfaction Questionnaire (DTSQs)
- Insulin Delivery System Questionnaire (IDSQ)
- Preference Questionnaire

Note: Due to program termination, only the primary efficacy endpoint and safety endpoints have been analyzed. Secondary efficacy endpoints, health outcomes endpoints, and inhaler reliability are not presented in this report.

Evaluation Methods:Primary Efficacy:

From approximately 100 patients, assuming a 20% dropout rate, a trial with 80 completers (40 per arm) had 90% power to demonstrate that HIIP plus glargine is noninferior to preprandial injectable insulin plus glargine with respect to the change in HbA_{1c} from baseline to endpoint. The endpoint was evaluated using the last observation carried forward (LOCF) technique within each treatment period. The power was calculated assuming no expected difference between the two treatments in change in HbA_{1c} from baseline, and intra-subject standard deviation of 0.77%.

The full analysis set (FAS) was used to assess primary outcome. The per protocol analysis set (PPS) was used for comparative purposes only. Data were analyzed with a mixed effects model for crossover design, which included treatment, period, sequence, prior insulin type (regular/lispro) and country as fixed effects, baseline HbA_{1c} as a covariate, and patient within treatment sequence as a random effect.

A two-sided 95% confidence interval of the least squares mean difference between the two treatments was constructed for testing noninferiority. Noninferiority was to be claimed if the upper limit of the 95% confidence interval for the treatment difference (HIIP minus injectable insulin) was less than 0.4%.

Safety:

The safety population included all randomized patients who received study drug, irrespective of whether it was assigned for that period.

The dataset for pulmonary function test (PFT) results consisted of tests that received acceptable quality scores. Between-treatment comparisons within each period were based on an ANCOVA model with treatment, gender, and country as fixed effects and baseline score, height, and age as continuous covariates. The Pulmonary Symptoms Questionnaire (PSQ) results were summarized separately for each question for baseline, endpoint by treatment for each period, and overall.

Treatment-emergent adverse events (TEAEs) considered possibly related to study medication or study procedure were presented by treatment for each period and overall. The incidences of hypoglycemic episodes (symptomatic or documented; nocturnal; severe) were presented for each visit (incidence between visits) and overall. Hypoglycemic incidence was analyzed using Fisher's exact test.

Summary:

On 08 March 2008, the sponsor decided on early termination of this study secondary to the termination of compound development. Only the primary efficacy endpoint and safety endpoints have been analyzed.

Patient Demographics and Disposition

Mean patient age was 35.9 years, 62.2% of patients were female, and all patients (100.0%) were of East Asian origin. Mean (\pm SD) BMI was 23.3 (\pm 3.3) kg/m², systolic and diastolic blood pressure were 119 (\pm 13) and 72 (\pm 10) mmHg respectively, pulse rate was 76 (\pm 13) beats per minute, and respiration rate was 17 (\pm 4) breaths per minute.

Of the 82 patients enrolled (Japan n=62; Taiwan n=20), 41 patients were randomized to the HIIP/injectable insulin sequence and 41 patients were randomized to the injectable insulin/HIIP treatment sequence. **This study was terminated early by the sponsor.** At that time, 53 patients (64.6%) had completed the study, 1 patient (1.2%) had discontinued early due to AE (during HIIP treatment [Period I]), and 2 patients (2.4%) had discontinued early due to patient decision (during injectable insulin treatment [Period I, Period II]). The remaining 26 patients (31.7%) were discontinued due to sponsor

decision upon termination of the study. Mean exposure to both HIIP and injectable insulin was 2.6 (± 0.5) months.

Primary Efficacy Measure

Table 1 summarizes the mean change in HbA_{1c} from baseline to endpoint for HIIP and injectable insulin treatment arms (combined periods). The adjusted mean change (\pm SE) in HbA_{1c} from baseline to endpoint was +0.04% (± 0.12) in the HIIP arm and -0.04% (± 0.12) in the injectable insulin arm, with an adjusted mean difference (HIIP-injectable insulin) of 0.08% (95% CI: -0.131, 0.288; $p=0.456$).

Analysis of HbA_{1c} using the per-protocol set ($N=53$) demonstrated an adjusted mean difference (HIIP-injectable insulin) of 0.07% (95% CI: -0.137, 0.285; $p=0.483$).

Note: Although the upper limit of the confidence interval was less than 0.4% (noninferiority margin), due to program termination and early discontinuation of the study the final sample size provided insufficient power to assess noninferiority.

**Table 1. Analysis of Hemoglobin A1c (HbA_{1c}) (percent)
Change from Baseline to Endpoint for Combined Periods
Full Analysis Set**

	HIIP	Injectable Insulin
Patients Reporting, N	57	53
(baseline plus at least one postbaseline measurement)		
Baseline		
Mean (SD)	7.6 (0.94)	7.6 (0.94)
Median (Min – Max)	7.6 (6.0 – 10.0)	7.6 (6.0 – 10.0)
Endpoint		
Mean (SD)	7.7 (1.13)	7.6 (0.98)
Median (Min – Max)	7.4 (6.1 – 11.4)	7.4 (6.3 – 11.9)
Change		
LS Mean (SE)	0.04 (0.12)	-0.04 (0.12)
Treatment Difference		
LS Mean (95% Confidence Interval)	0.08 (-0.131, 0.288)	
p-Value	$p=0.456$	

Abbreviations: HIIP = human insulin inhalation powder; LS Mean = least squares mean.

Change from baseline treatment comparison was tested using a crossover model including treatment, period, country, prior insulin type (regular/lispro), and sequence as fixed effects, baseline HbA_{1c} as a covariate, and patient within sequence as a random effect.

Safety Measures

Pulmonary Function Tests (PFTs)

Table 2 summarizes the PFT results for each period. There was a statistically significant difference in change from baseline between the 2 treatment groups in FEV₁/FVC and DL_{CO} measurements during the first treatment period; the HIIP group had larger

decreases in FEV_1/FVC and DL_{CO} than the injectable insulin group. These differences were not observed during the second treatment period.

Table 2. Pulmonary Function Tests
Change from Baseline to Endpoint for Each Period
Safety Population

	Baseline		Period I		Period II	
	HIIP	Inj. Insulin	HIIP	Inj. Insulin	HIIP	Inj. Insulin
FEV₁ (L)						
N	41	41	41	41	28	29
Mean (SD)	3.0 (0.63)	3.0 (0.75)	3.0 (0.63)	3.0 (0.75)	3.1 (0.79)	3.0 (0.56)
Change, LS Mean (SE)			-0.05 (0.02)	-0.01 (0.02)	0.02 (0.02)	0.02 (0.02)
Treatment Difference, LS Mean (95% CI)			-0.05 (-0.09, 0.00), p=.062		0.00 (-0.06, 0.06), p=.909	
FVC (L)						
N	41	41	41	41	28	29
Mean (SD)	3.5 (0.80)	3.6 (0.85)	3.5 (0.77)	3.6 (0.87)	3.7 (0.88)	3.6 (0.77)
Change, LS Mean (SE)			-0.04 (0.02)	-0.05 (0.02)	0.01 (0.02)	0.05 (0.02)
Treatment Difference, LS Mean (95% CI)			0.01 (-0.04, 0.06), p=.701		-0.04 (-0.10, 0.02), p=.149	
FEV₁/FVC						
N	41	41	41	41	28	29
Mean (SD)	0.9 (0.05)	0.8 (0.07)	0.8 (0.05)	0.8 (0.07)	0.8 (0.06)	0.8 (0.06)
Change, LS Mean (SE)			-0.01 (0.00)	0.01 (0.00)	0.00 (0.00)	-0.01 (0.00)
Treatment Difference, LS Mean (95% CI)			-0.02 (-0.03, -0.01), p=.002		0.01 (-0.00, 0.02), p=.135	
TLC (L)						
N	40	41	40	41	28	29
Mean (SD)	5.0 (1.06)	5.1 (1.14)	6.3 (7.42)	5.2 (1.13)	5.3 (1.27)	5.1 (1.13)
Change, LS Mean (SE)			1.20 (0.92)	-0.51 (0.91)	0.32 (0.08)	0.04 (0.08)
Treatment Difference, LS Mean (95% CI)			1.71 (-0.58, 4.00), p=.141		0.28 (0.07, 0.49), p=.010	
Corrected DL_{CO} (mL.min⁻¹torr⁻¹)						
N	41	41	29	28	28	25
Mean (SD)	22.0 (4.83)	23.1 (4.64)	20.6 (5.02)	22.9 (4.12)	22.3 (4.06)	21.2 (4.86)
Change, LS Mean (SE)			-0.89 (0.35)	0.30 (0.36)	-0.33 (0.42)	-0.21 (0.43)
Treatment Difference, LS Mean (95% CI)			-1.19 (-2.17, -0.21), p=.019		-0.12 (-1.27, 1.04), p=.841	

Abbreviations: DL_{CO} = diffusion capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; HIIP = human insulin inhalation powder; Inj. Insulin = injectable insulin; LS Mean = least squares mean; TLC = total lung capacity.

Between group comparisons within each period are based in the ANCOVA model including treatment, country, and sex as fixed effects and baseline score, height, and age as continuous covariates.

Pulmonary Symptoms Questionnaire (PSQ)

The patient-reported PSQ assessed changes in pulmonary signs or symptoms, such as cough, shortness of breath, chest congestion, and wheezing.

Of the patients who responded to the questionnaire (N=69 for both treatment groups), the majority of patients were not troubled by a cough during treatment with either HIIP (n=50 [72.5%]) or injectable insulin (n=56 [81.2%]). “Mildly” troubling (HIIP: n=16 [23.2%]; injectable insulin: n=11 [15.9%]) and “moderately” troubling (HIIP: n=3 [4.3%]; injectable insulin: n=2 [2.9%]) coughs were reported; however, no patients reported a “severely” or “very severely” troubling cough. Patients most frequently coughed 1-5 times per day, and had a cough lasting less than 10 seconds, irrespective of treatment.

For those patients reporting a cough during HIIP treatment (N=19), 7 patients (36.8%) experienced cough around the time of insulin inhalation, 9 patients (47.4%) experienced cough not during the time of insulin inhalation, and 3 patients (15.8%) experienced cough around the time of inhalation as well as other times.

Less than 12% of patients were troubled by chest congestion (“Not at All” for combined periods; HIIP: n=61 [88.4%]; injectable insulin: n=68 [98.6%]), shortness of breath (HIIP: n=68 [98.6%]; injectable insulin: n=66 [95.7%]), or wheezing attacks/chest tightness (HIIP: n=67 [97.1%]; injectable insulin: n=67 [97.1%]).

Adverse Events

Overall, 5 TEAEs considered possibly related to study drug were reported (anti-insulin antibody, fall, headache, hypoglycemia x2). In addition, 1 patient reported a TEAE considered possibly related to study procedure (upper respiratory tract infection during HIIP treatment).

Three AEs were serious; 2 occurred during HIIP treatment (hypoglycemia requiring hospitalization, increased anti-insulin antibody) and 1 occurred during injectable insulin treatment (hypoglycemia requiring hospitalization). One patient discontinued due to adverse event (hypoglycemia requiring hospitalization during HIIP treatment). There were no deaths during the study.

Hypoglycemia

At least one hypoglycemic episode (symptomatic or documented) was experienced by 40 patients (97.6%) in the HIIP arm and 39 patients (95.1%) in the injectable insulin arm during Period I (p=1.000), and by 28 patients (100.0%) in the HIIP arm and 27 patients (93.1%) in the injectable insulin arm during Period II (p=.491).

At least one *nocturnal* hypoglycemic episode was experienced by 35 patients (85.4%) in the HIIP arm and 27 patients (65.9%) in the injectable insulin arm during Period I

($p=.070$), and by 25 patients (89.3%) in the HIIP arm and 19 patients (65.5%) in the injectable insulin arm during Period II ($p=.056$).

At least one *severe* hypoglycemic episode was experienced by 12 patients (29.3%) in the HIIP arm and 11 patients (26.8%) in the injectable insulin arm during Period I ($p=1.000$), and by 0 patients in the HIIP arm and 1 patient (3.4%) in the injectable insulin arm during Period II ($p=1.000$).