2. IOPW Synopsis

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Clinical Study Report Synopsis: Study F3Z-MC-IOPW

Title of Study: A Double-Blind, Randomized, Crossover Trial of CSII Reservoir In-use Comparing Insulin Lispro Formulation to Insulin Aspart in Patients with Type 1 Diabetes Mellitus

Number of Investigators: This multicenter study included 17 principal investigators.

Study Centers: This study was conducted at 17 study center(s) in 3 countries.

Publication(s) Based on the Study: None at this time.

Length of Study:
Date of first patient enrolled: 17 November 2010
Date of last patient completed entire study: 07 December 2011

Phase of Development: 3b/4

Objectives:

The primary objectives of this study were to determine that (using a gatekeeping strategy):

- Day 6 of 6 days of pump reservoir in-use of Humalog 6D was noninferior to day 6 of 6 days of pump reservoir in-use of Aspart 6D with regards to 7-point daily mean self-monitored blood glucose (SMBG; with a margin =0.6 mmol/L).
- Day 6 of 6 days of pump reservoir in-use of Humalog 6D was superior to Day 6 of 6 days of pump reservoir in-use of Aspart 6D with regards to 7-point daily mean SMBG.

The secondary objectives of the study were:

- Day 6 of Humalog 6D was noninferior to Day 2 of Humalog 6D with regards to mean SMBG (margin = 0.6 mmol/L).
- To compare Humalog 6D to Aspart 6D with respect to mean SMBG, hypoglycemic events, insulin dose, pump complications, hyperglycemic events, adverse events (AEs), and hemoglobin A_{1c} (HbA_{1c}).
- To compare Days 1 through 6 of Humalog 6D to Days 1 through 6 of Aspart 6D individually and cumulatively with respect to mean SMBG, insulin dose, hypoglycemic events, pump complications, and hyperglycemic events.
- To compare Days 1 through 3 with Days 4 through 6 individually and cumulatively of Humalog 6D and Aspart 6D between and within treatments with respect to mean SMBG, insulin dose, hypoglycemic events, pump complications, and hyperglycemic events.
- Compare Day 1, 2 with Day 4, 5 of Humalog 6D and Aspart 6D between and within treatments with respect to mean SMBG, insulin dose, hypoglycemic events, pump complications, and hyperglycemic events.

The exploratory objective of this study was to compare the Insulin Treatment Satisfaction Questionnaire (ITSQ) instrument between treatments.

Study Design: This study was a Phase 3b/4, 24-week, randomized, double-blind, 2-sequence, 2-treatment, 2-period (12 weeks each), cross-over design in continuous subcutaneous insulin infusion (CSII)-treated patients with type 1 diabetes.

Number of Patients:

Planned: 132 patients

Randomized: 133 patients (Humalog 6D/Aspart 6D sequence, n=67; Aspart 6D/Humalog 6D sequence, n=66)

Treated (at least 1 dose): 132 patients (Humalog 6D/Aspart 6D sequence, n=66; Aspart 6D/Humalog 6D sequence, n=66)

Completed: 118 patients (Humalog 6D/Aspart 6D sequence, n=57; Aspart 6D/Humalog 6D sequence, n=61)

Diagnosis and Main Criteria for Inclusion: Patients, aged 13 years or older and diagnosed with type 1 diabetes (World Health Organization [WHO] criteria) for at least 24 months, with HbA1c between 5% and 9% and BMI ≤35.0 kg/m2 at baseline. Patients must have used CSII therapy for at least the 6 months prior to Visit 1, with a mean total daily insulin dose for 3 days prior to Visit 1 of ≤46 units (U)/day using a 300-U reservoir, ≤30 U/day using a 200-U reservoir, or ≤26 U/day using a 180-U reservoir.

Patients were excluded from participation in the study if they have had: impaired renal function; legal blindness; an episode of hypoglycemia coma, seizures or disorientation, hypoglycemic unawareness, or emergency room visits or hospitalizations due to poor glucose control or pump-related infusion site abscess in the last 12 months prior to Visit 1; or a history of a staphylococcus aureus infection in the past 5 years.

Test Product, Dosage and Mode of Administration: Insulin lispro (100 U/mL) vials via insulin pump reservoir, replaced no more than every 6 days and changing the pump infusion set and site no more than every 3 days.

Reference Therapy, Dose and Mode of Administration: Insulin aspart (100 U/mL) vials via insulin pump reservoir, replaced no more than every 6 days and changing the pump infusion set and site no more than every 3 days.

Duration of Treatment: 24 weeks
Lead-in period: 2 weeks Treatment period: 24 weeks

Variables:

Efficacy:

Daily mean of the last six Day 6, 7-point SMBG profiles for Humalog 6D and Aspart 6D treatment periods. Mean SMBG for each day of reservoir use and cumulatively to Day 2, 3, 4, 5, and 6 and cumulatively from Day 4 to 5, 6 where possible, for each treatment. HbA1c at endpoint and change from baseline to endpoint of treatment period. Mean daily insulin dose (total, basal, and bolus) on interested day(s), at endpoint and change from baseline to endpoint. Percentage of patients achieving HbA1c <7.0%, ≤6.5% at endpoint. Intrasubject variability (coefficient of variation [CV]) of mean SMBG values for each day of reservoir use and cumulatively to Day 2, 3, 4, 5, and 6 and cumulatively from Day 4 to 5, 6, where possible, for each treatment.

Safety:

Event of infusion set occlusions/clogs (with and without alarms) not related to infusion set complications listed below:

- Event of infusion site/set complications.
- Infusion site (for example: skin abscess, erythema, induration, bleeding, or bruising at infusion site).
- Infusion set (for example: crimping, disconnection, or inadvertent removal).
- Hyperglycemic event (blood glucose [BG] >250 mg/dL (13.9 mmol/L) preprandially or >300 mg/dL (16.7 mmol/L) postprandially with and without ketonemia/ketonuria) overall and not explained by dietary indiscretion, rebound or treatment of hypoglycemia, empty reservoir, or infusion site/set complications.
- Event of premature change of infusion set and/or reservoir overall and that are related to occlusion/clogs, infusion site/set complications or empty reservoir.
- Occurrence of new subcutaneous nodule formation or lipoatrophy or lipohypertrophy.
- Hypoglycemic events (incidence and rate of overall, asymptomatic, documented, nocturnal, and severe).
- Absolute weight and weight gain at endpoint, and change from baseline to endpoint.
- Treatment-emergent adverse events (TEAEs).

Health Outcomes:

Overall insulin experience, as measured by the ITSQ administered at Visits 2, 5, 8, and early termination (ET).

Statistical Evaluation Methods:

Sample size:

The sample size was based on the primary efficacy variable of 7-point daily mean SMBG. Approximately 132 patients with type 1 diabetes were planned to be randomized into this study. Patients were randomized into 1 of 2 sequence groups in a 1:1 ratio (66 patients per sequence group) and randomization were stratified according to age (≤19 years and >19 years).

Assuming a 15% drop-out rate after randomization, the remaining 108 patients in the study provided sufficient power to assess noninferiority. An alpha level of 0.05 with 87% power, assuming a standard deviation of (within-subject difference) 2.0 mmol/L was used to determine statistical significance. A 95% confidence interval (CI) was calculated to test for no treatment difference, using the upper limit of the 2-sided interval and a noninferiority limit of 0.6 mmol/L. If the treatment difference was -0.6 (Humalog 6D – Aspart 6D), then this study has 87% power to show superiority.

All primary and secondary continuous efficacy variables were summarized and analyzed by treatment for the combined periods using the intent-to-treat (ITT) population. The ITT population included all randomized patients with at least 1 post-randomization visit.

Primary:

This study used a gatekeeping strategy on the primary outcome, daily mean SMBG of the last six Day 6, 7-point glucose profiles for each treatment period. The first test determined if Humalog 6D was noninferior to Aspart 6D using a crossover analysis on the ITT dataset, which included fixed effects (treatment, period, sequence, and age stratum), baseline HbA_{1c} as a covariate, and patient within-treatment sequence as a random effect (Grizzle 1965). Noninferiority was supported if the upper limit of a 2-sided 95% CI for the difference (Humalog 6D – Aspart 6D) is less than 0.6 mmol/L.

Second, the gatekeeping strategy tested if Humalog 6D was superior to Aspart 6D using the same model as in the first primary analysis. The superiority was supported if the upper limit of a 2-sided 95% CI for the difference (Humalog 6D – Aspart 6D) was less than zero. This study was considered to have achieved its primary objective if, at minimum, Humalog 6D was found to be noninferior to Aspart 6D. A robustness check will be made using the per-protocol dataset and applying the same procedures.

Secondary, Exploratory, and Safety: .

The continuous variables (HbA_{1c}, hypoglycemia rate) were analyzed using a model similar to the one used in the primary analysis. Mean SMBG for the secondary efficacy analysis was analyzed using an appropriate model and is described in detail in the Statistical Analysis Plan (SAP).

For the proportion of patients in the ITT population with HbA_{1c} ≤6.5% and <7.0%, a logistic regression was conducted with prespecified fixed effects (treatment, etc.). For hypoglycemia rates, a negative binomial test was performed. For both the logistic regression and negative binomial test, repeated adjustments were specified on patients to account for the multiple measurements. For categorical variables (AEs, incidence of hypoglycemia), the Gart test was used.

Health Outcomes:

Total score and each of the 5 domain subscale scores of the ITSQ were calculated for each treatment arm for Visits 2, 5, 8, and endpoint for the ITT set. The ITSQ subscales were analyzed on the ITT population using a model similar to the one used in the primary analysis, with the addition of baseline ITSQ total score and subscale scores as appropriate.

Summary:
This was a Phase 3b/4, multicenter, randomized, double-blind, crossover trial with 2 study periods comparing Humalog 6D to Aspart 6D in patients with type 1 diabetes mellitus (T1DM). This study was designed to determine noninferiority and/or superiority, using a gatekeeping strategy, for 7-point daily mean SMBG of Humalog 6D to Aspart 6D using CSII pumps. To be included in the study, patients had to be 13 years or older, diagnosed with T1DM WHO criteria for at least 24 months with HbA1c between 5% and 9% and BMI ≤35.0 kg/m2 at baseline. Patients had to be using CSII therapy for at least the 6 months prior to Visit 1 with mean total daily insulin dose for 3 days prior to Visit 1 of ≤46 units (U)/day using a 300-U reservoir, ≤30 U/day using a 200 U reservoir or ≤26 U/day using 180-U reservoir. Patients were excluded from participation in the study if they have had impaired renal function; legal blindness; or had an episode of hypoglycemic coma, seizures or disorientation or hypoglycemic unawareness; emergency room visits or hospitalizations due to poor glucose control; or pump-related infusion site abscess in the 12 months prior to Visit 1; or a history of a *staphylococcus aureus* infection in the past 5 years.

Of the 162 patients who entered the study, 133 were randomly assigned to treatment. Following randomization, 1 patient discontinued prior to receiving any study drug leaving 132 patients in the study receiving at least 1 dose of study drug. There were 118 (88.7%) patients who completed the study and 15 (11.3%) patients did not complete the study. The most common reason for early discontinuation was patient decision (n=9). One patient in the Humalog 6D/Aspart 6D Sequence Group discontinued from the study due to an adverse event of hypersensitivity during the Humalog 6D sequence of the study.

The mean patient age was 42.9 years with no patients ≤19 years, 127 (96.2%) patients >19 to <65 years, and 5 (3.8%) patients ≥65 years. All patients were white (100.0%); 69.7% were female and 30.3% were male. The mean body weight at baseline was 68.7 kg, and the mean BMI was 24.5 kg/m^2. The mean duration of diabetes for patients was 23.2 years. Mean HbA1c for patients at baseline was 7.5% with the majority of patients (90.9%) having an HbA1c <8.5% at baseline. The baseline mean total insulin dose was 28.0 units/day with mean daily basal insulin dose of 15.7 units/day and mean daily bolus insulin dose of 14.6 units/day. Patients were also asked at baseline about prior site complication history in regard to lipoatrophy (percentage of patients with a history of lipoatrophy: 0.8%). No patients had a prior site complication history of skin abscess, subcutaneous nodules, or lipohypertrophy. At baseline, there were statistically significant differences between the sequence groups in systolic blood pressure (Humalog 6D/Aspart 6D, 121.1 mmHg versus Aspart 6D/Humalog 6D, 125.7 mmHg; p=0.042) and heart rate (Humalog 6D/Aspart 6D, 76.7 bpm versus Aspart 6D/Humalog 6D, 72.1 bpm; p=0.014).

Unless otherwise specified, all reported results focus on comparisons between Days 1-6 of reservoir in-use cycles for Humalog 6D versus Aspart 6D:

- In the ITT population, the Humalog 6D treatment demonstrated a higher mean 7-point SMBG for the last six Day 6 measurements compared to the Aspart 6D treatment (LS mean difference 0.36 mmol/L; 95% CI [0.06, 0.66]). Since the upper limit of the 95% CI (0.66) was higher than the prespecified noninferiority margin (0.6 mmol/L), Humalog 6D did not achieve noninferiority to Aspart 6D on Day 6 of reservoir use using a 7-point profile to measure SMBG. Similar results were shown when the primary efficacy analysis was analyzed using the per-protocol population.
- In the ITT population, Humalog 6D, Days 1-6 was noninferior to Aspart 6D, Days 1-6 for overall mean SMBG since the upper limit of 95% was lower (LS Mean difference 0.18; 95% CI: -0.10, 0.47) than the prespecified noninferiority margin (0.6 mmol/L).
- For overall mean SMBG, day to day comparisons (Humalog 6D versus Aspart 6D):
    - Humalog 6D, Day 1 was noninferior to Aspart 6D, Day 1 (95% CI: -0.15, 0.47).
    - Humalog 6D, Day 2 was noninferior to Aspart 6D, Day 2 (95% CI: -0.20, 0.42).
    - Humalog 6D, Day 3 was noninferior to Aspart 6D, Day 3 (95% CI: -0.06, 0.53).
    - Humalog 6D, Day 4 was noninferior to Aspart 6D, Day 4 (95% CI: -0.12, 0.50).
    - Humalog 6D, Day 5 was noninferior to Aspart 6D, Day 5 (95% CI: -0.07, 0.54).
    - Humalog 6D, Day 6 did not achieve noninferiority to Aspart 6D, Day 6. (95% CI: 0.02, 0.64).

- Humalog 6D, Days 1-2 was noninferior to Aspart 6D, Days 1-2 (95% CI: -0.15, 0.43).
- Humalog 6D, Days 1-3 was noninferior to Aspart 6D, Days 1-3 (95% CI: -0.12, 0.45).
- Humalog 6D, Days 1-4 was noninferior to Aspart 6D, Days 1-4 (95% CI: -0.11, 0.45).
- Humalog 6D, Days 1-5 was noninferior to Aspart 6D, Days 1-5 (95% CI: -0.12, 0.44).
- Humalog 6D, Days 4-5 was noninferior to Aspart 6D, Days 4-5 (95% CI: -0.11, 0.47).
- Humalog 6D, Days 4-6 was noninferior to Aspart 6D, Days 4-6 (95% CI: -0.07, 0.51).
- Humalog 6D, Days 1-2 was noninferior to Aspart 6D, Days 4-5 (95% CI: -0.27, 0.31).
- Humalog 6D, Days 4-5 was noninferior to Aspart 6D, Days 1-2 (95% CI: 0.00, 0.58).

- For overall mean SMBG, day to day comparisons (Humalog 6D, Day 6 versus Day 2):
  - Humalog 6D, Day 6 was noninferior to Day 2 (LS Mean difference of 0.42 mmol/L; 95% CI: 0.25, 0.58).
- Mean HbA1c at endpoint and change from baseline for HbA1c were significantly different between treatments ($p<0.001$) with patients in Aspart 6D treatment having a greater change from baseline compared to Humalog 6D (LS Mean difference of 0.16 mmol/L; 95% CI: 0.08, 0.24).
- For insulin dose: The total daily insulin dose, the total daily bolus dose and the daily basal rate were not significantly different between treatments.
- For hypoglycemia:
  - Patients in the Humalog 6D treatment demonstrated a significantly lower episode rate per 30 days compared to Aspart 6D for documented ($p=0.012$) and all reported hypoglycemia ($p<0.001$).
  - Asymptomatic and nocturnal hypoglycemic episode rates per 30 days were not significantly different between treatments.
  - During Humalog 6D treatment, 2 patients (2 events) reported at least 1 serious adverse event of severe hypoglycemia compared to 7 patients (4 events) in Aspart 6D. These differences were not statistically significant.
- For hyperglycemia:
  - Overall hyperglycemia and pump-related hyperglycemia episode rates per 30 days were not significantly different between Humalog 6D, Days 1-6 and Aspart 6D, Days 1-6.
  - Patients in the Humalog 6D, Days 1-6 treatment demonstrated a statistically significantly higher rate of non-explained hyperglycemia compared to patients in the Aspart 6D, Days 1-6 treatment ($p=0.003$).
  - Overall and pump-related hyperglycemia episode rates per 30 days were not significantly different between Humalog 6D, Days 1-2 and Aspart 6D, Days 1-2.
  - Patients in the Humalog 6D, Days 1-2 treatment demonstrated a significantly higher rate of non-explained hyperglycemia episode rate per 30 days compared to patients in Aspart 6D, Days 1-2 treatment ($p=0.005$).
  - Pump-related hyperglycemia episode rates per 30 days were not significantly different between Humalog 6D, Days 1-3 and Aspart 6D, Days 1-3.
  - Patients in the Humalog 6D, Days 1-3 treatment demonstrated a significantly higher rate of overall hyperglycemia ($p=0.034$) and non-explained hyperglycemia ($p=0.001$) episode rates per 30 days compared to patients in the Aspart 6D, Days 1-3 treatment.
  - Overall and pump-related hyperglycemia episode rates per 30 days were not significantly different between Humalog 6D, Days 4-6 and Aspart 6D, Days 4-6.
  - Patients in the Humalog 6D, Days 4-6 treatment demonstrated a significantly higher rate of non-explained hyperglycemia episode rate per 30 days compared to patients in Aspart 6D, Days 4-6 treatment ($p=0.022$).
- Infusion set complications:
  - The episode rate per 30 days for patients having premature reservoir or premature infusion set changes associated with infusion set complications showed no significant differences between treatments.

For premature reservoir changes:

- Infusion site/set complications (other than clogging) and overall reservoir change episode rates per 30 days were not significantly different between Humalog 6D, Days 1-6 and Aspart 6D, Days 1-6. The incidence was low for infusion set clogging between Humalog 6D, Days 1-6 and Aspart 6D, Days 1-6, therefore, statistical significance could not be assessed.
- The incidence was low for infusion set clogging, infusion site/set complications (other than clogging), and overall reservoir change episode rates per 30 days between Humalog 6D, Days 1-2 and Aspart 6D, Days 1-2, therefore, statistical significance could not be assessed.
- The incidence was low for infusion set clogging, infusion site/set complications (other than clogging), and overall reservoir change episode rates per 30 days between Humalog 6D, Days 1-3 and Aspart 6D, Days 1-3, therefore, statistical significance could not be assessed.
- Infusion site/set complications (other than clogging), and overall reservoir change episode rates per 30 days were not significantly different between Humalog 6D, Days 4-6 and Aspart 6D, Days 4-6. The incidence was low for infusion set clogging between Humalog 6D, Days 4-6 and Aspart 6D, Days 4-6, therefore, statistical significance could not be assessed.

For premature infusion set changes:

- Infusion set clogging, infusion site/set complications (other than clogging), and overall infusion set change episode rates per 30 days were not significantly different between Humalog 6D, Days 1-6 and Aspart 6D, Days 1-6.
- Infusion site/set complications (other than clogging), and overall infusion set change episode rates per 30 days were not significantly different between Humalog 6D, Days 1-2 and Aspart 6D, Days 1-2. The incidence was low for infusion set clogging between Humalog 6D, Days 1-2 and Aspart 6D, Days 1-2, therefore, statistical significance could not be assessed.
- Overall infusion set change episode rates per 30 days were not significantly different between Humalog 6D, Days 1-3 and Aspart 6D, Days 1-3. The incidence was low for infusion set clogging between Humalog 6D, Days 1-3 and Aspart 6D, Days 1-3, therefore, statistical significance could not be assessed.
- Patients in the Humalog 6D, Days 1-3 treatment demonstrated a significantly lower rate of infusion site/set complications (other than clogging) compared to Aspart 6D, Days 1-3 treatment (p=0.010).
- Infusion set clogging, infusion site/set complications (other than clogging), and overall infusion set change episode rates per 30 days were not significantly different between Humalog 6D, Days 4-6 and Aspart 6D, Days 4-6.

- Safety:
  - The number of TEAEs reported (by system organ class or preferred term) during the study was not significantly different between treatments.
  - One patient in the Humalog 6D/Aspart 6D sequence group discontinued from the study due to an adverse event of hypersensitivity. This event was identified as mild in event severity and in the opinion of the investigator, was not related to study drug, procedure, device or disease.

Conclusions:

- Humalog 6D was not noninferior to Aspart 6D for the primary endpoint: the last six Day 6 mean SMBG measurements using a 7-point profile. During Humalog 6D treatment, patients demonstrated a significantly higher mean compared to Aspart 6D treatment.
- Humalog 6D was noninferior to Aspart 6D for overall mean SMBG measurements over Days 1-6 of treatment.
- Humalog 6D was noninferior to Aspart 6D for overall mean SMBG measurements on Day 1, Day 2, Day 3, Day 4, and Day 5.
- Humalog 6D, Day 6 was noninferior to Humalog 6D, Day 2 for overall mean SMBG measurements.
- The hypoglycemia rate for Humalog 6D was significantly lower than Aspart 6D for documented and all reported hypoglycemia.
- The non-explained hyperglycemia event rate for Humalog 6D, Days 1-6 was significantly higher compared to Aspart 6D, Days 1-6. The overall and pump-related hyperglycemia event rates were not significantly different.

- The premature reservoir and premature infusion set change rate associated with infusion set complications were not significantly different between Humalog 6D, Days 1-6 and Aspart 6D, Days 1-6.