AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Pramlintide

ACTIVE INGREDIENT: Pramlintide

Study No: D5570C00001/ABA163
A Phase 1, Randomized, Placebo-Controlled, Single-Blind, Dose-Ranging, 4-Way Crossover Study to Evaluate the Effect of Different Fixed Pramlintide:Insulin Dose Ratios on Postprandial Glycemic Control in Subjects With Type 1 Diabetes Mellitus

Developmental Phase: Phase I

Study Completion Date: Last subject last visit 05-Sep-2013

Date of Report: 27-Aug-2014

OBJECTIVES:

Primary:

To examine the effects of different fixed pramlintide:insulin dose ratios in subjects with type 1 diabetes on postprandial plasma glucose concentrations

Secondary:

To examine the plasma concentration profiles of glucose, glucagon, and pramlintide in subjects with type 1 diabetes administered different fixed pramlintide:insulin dose ratios

To examine the effects of different fixed pramlintide:insulin dose ratios in subjects with type 1 diabetes on postprandial plasma glucagon concentrations

To quantify and summarize the exposure of pramlintide after different fixed pramlintide:insulin dose ratios in patients with type 1 diabetes.

Safety:

To assess the safety and tolerability (specifically hypoglycemia and nausea) of different fixed pramlintide:insulin dose ratios in subjects with type 1 diabetes

Exploratory:

To assess the 3-hour glucose profile using continuous glucose monitoring

METHODS:

The primary efficacy endpoint, consisting of the incremental $AUC_{(0\text{-}3\ h)}$ of plasma glucose concentrations, was summarized descriptively by treatment and by period for the ITT analysis set. The incremental $AUC_{(0\text{-}3\ h)}$ of plasma glucose concentrations was assessed using the mixed-effects model with repeated measures (MMRM) for the ITT analysis set (all randomized subjects who received an injection of study medication). Factors for randomized treatment sequence, period, and treatment were included as fixed main effects. A random effect for subject was included in the model as well. Period was a repeated effect blocked by subject (within sequence). Using the final fit of the model, least-squares (LS) means and corresponding 2-sided 95% confidence intervals (CIs) were produced for the mean incremental $AUC_{(0\text{-}3\ h)}$ of plasma glucose concentrations for each treatment. The LS means and corresponding 2-sided 95% CIs for the difference between treatments B and A, C and A, D and A were also calculated.

Secondary pharmacodynamic endpoints were analyzed using similar methods as the primary endpoint.

The pharmacokinetic (PK) variables were descriptively summarized.

Treatment emergent adverse events (TEAEs) were summarized using frequency counts and percentages by treatment. On-treatment hypoglycemia events and all protocol-defined hypoglycemia events were summarized separately by treatment. Hypoglycemia AEs which occurred on- and off- medication (treatment) were listed.

All hematology, clinical chemistry, and urinalysis results were listed. Observed values and changes from baseline in heart rate, systolic, and diastolic blood pressures were summarized descriptively by treatment. Physical exam findings and ECG results were also listed.

RESULTS:

Summary of efficacy results

Each individual received a constant insulin study dose across the treatment periods.

The primary objective of this study was to evaluate the effects of different fixed pramlintide:insulin dose ratios in subjects with T1DM on the postprandial plasma glucose concentrations. The glucose incremental $AUC_{(0\text{-}3\ h)}$ expressed as mg*h/dL was LS mean 343.08 (95% CI: 283.19, 402.98) with placebo/U insulin, LS mean 137.11 (95% CI: 75.42, 198.79) with 6 mcg pramlintide/U insulin dose ratio, LS mean 143.15 (95% CI: 80.97, 205.33) with 9 mcg pramlintide/U insulin dose ratio, and LS mean 96.48 (95% CI: 36.54, 156.42) with 12 mcg pramlintide/U insulin dose ratio. The decrease in glucose incremental $AUC_{(0\text{-}3\ h)}$ for all pramlintide:insulin dose ratios was statistically significant when compared to placebo/U insulin ($p < 0.001$).

The first secondary objective of the study was to describe the plasma profiles of glucose, glucagon, and pramlintide in subjects with T1DM. A statistically significant decrease in incremental $AUC_{(0\text{-}3\ h)}$ for glucagon was observed for all 3 pramlintide:insulin dose ratios compared to placebo/U insulin. A decrease was observed for glucose total AUC, C_{max}, and C_{ave}, and the difference was statistically significant from placebo/U insulin in all 3 dose ratios, and the delay in glucose T_{max} induced by pramlintide was also statistically significant with all dose ratios when compared to placebo/U insulin.

The other secondary objective was to evaluate the effects on postprandial plasma glucagon concentrations. A statistically significant reduction of glucagon total AUC and glucagon C_{max} was observed in all of the pramlintide:insulin dose ratios compared to placebo/U insulin. With regard to glucagon C_{ave}, only the 6 mcg pramlintide/U insulin dose ratio did not achieve a statistically significant reduction. Glucagon T_{max} was

delayed by all pramlintide:insulin dose ratios in a statistically significant manner compared to placebo/U insulin.
In general, the differences in efficacy between the pramlintide:insulin dose ratios were small.

Summary of pharmacokinetic results
The pramlintide plasma profile was characterized by a rapid absorption after injection with a median T_{max} of 15 minutes across the 3 pramlintide:insulin dose ratios tested and a rapid decline. The $t_{1/2}$ was approximately one hour.
The median $AUC_{(0-t)}$ was 194, 328, and 503 pg*h/mL for 6, 9, and 12 mcg pramlintide/U insulin dose ratios, respectively. The median C_{max} was 206, 288, and 328 pg/mL for 6, 9, and 12 mcg pramlintide/U insulin dose ratios, respectively.

Summary of safety results
Only 5 TEAEs were reported by 2 out of 19 subjects during this study. Nausea was reported by one subject after receiving 6, 9, and 12 mcg pramlintide/U insulin dose ratios; these events were mild in intensity and were drug-related according to the investigator. Diarrhea and abdominal pain of severe intensity were reported by one subject with the 9 mcg pramlintide/U insulin dose ratio; these AEs were not deemed related to the treatment.

No AEs of hypoglycemia were observed in the 24-hour period following study drug administration ("on-study medication"). Two subjects reported 3 AEs of hypoglycemia, classified as mild and minor, which occurred several days following study drug administration.