AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Exenatide
Study Code	D5554C00001/BCB119
Edition Number	01
Date	21 November 2014

Evaluation of the Single-Use Prefilled Autoinjector

Study dates: First subject enrolled: 11 February 2013
Last subject last visit: 10 December 2013

Phase of development: Phase 1

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

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Objectives and criteria for evaluation

The primary objective of this study was to determine the device-related injection failure rate of the single-use, prefilled autoinjector. The secondary objective of this study was to explore the device-related injection failure rate of alternate device configurations, as needed.

Table S1 Endpoints and outcome variables

Endpoints		Outcome Variable
Type	**Description**	**Description**
Primary efficacy	Determine device-related injection failure rate of the autoinjector	Device-related injection failure rate defined by the inability to deliver the full volume of study drug due to mechanical failure upon activation of the autoinjector
Secondary efficacy	Explore device-related injection failure rate of alternate device configuration	Device-related injection failure rate defined by the inability to deliver the full volume of study drug due to mechanical failure without replacement of the needle and repositioning of the syringe
Safety	Adverse events, clinical laboratory assessments (including calcitonin), physical examination, vital signs, and body weight	Subject incidence and event counts of AEs, deaths, SAEs, DAEs, hypoglycemia, and injection-site AEs by SOC and PT.
		Observed values and mean change from baseline in laboratory parameters and incidence of MAs of laboratory parameters of interest (ALT, AST, total bilirubin).
		Observed values and mean change from baseline in heart rate, and systolic and diastolic blood pressure.
		Change from baseline in body weight.

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; DAE Discontinuation due to adverse event; MA Marked abnormality; PK Pharmacokinetic; PT Preferred term; SAE Serious adverse event; SOC System organ class.

Study design

This Phase 1 study employed a flexible study design to accommodate multiple cohorts until an acceptable injection configuration for exenatide suspension was identified. Each cohort employed an open-label, single-arm, repeat-dose design. Initially, the study design utilized 2 cohorts but the number of cohorts was extended to 5, through study amendment, as the injection failure rate was unacceptable in Cohorts 1 and 2. Subsequent cohorts (Cohorts 3, 4, and 5) employed an identical study design as Cohorts 1 and 2. Adaptations in the injection configuration included variations in injection volume and dosage delivered (between 4.5 mg and 9 mg). Only 1 injection configuration was applied per cohort. Subsequent cohorts were conducted in parallel or sequentially.

Injection failure rates were continuously assessed. Injection failure was defined as the inability to deliver the full volume of study drug upon activation of the autoinjector (Cohort 1, Device Assessment Questionnaire) or without replacement of the needle and repositioning of the syringe (Cohorts 2, 3, 4, and 5, Injection Assessment Questionnaire).

The study began with Visit 1 (Screening) to obtain written informed consent and assess subject eligibility. Eligible subjects were invited to return to the study site within 21 days of Visit 1 (Screening) for Visit 2 (Day 1) when subjects completed eligibility criteria and eligible subjects were enrolled. At Visit 2 (Day 1), subjects began treatment with exenatide suspension (administered by trained study staff). Subjects returned to the study site at approximately 2-week intervals through Visit 5 (Week 6) for study treatment and assessments. Study site personnel contacted subjects via telephone at Week 8 to discuss any issues related to the study. Subjects returned to the study site for Study Termination procedures at Visit 6 (Week 10/Study Termination). All study site visits after Visit 2 (Day 1) occurred within ± 2 days of the scheduled interval, relative to Visit 2 (Day 1).

Observations made by the study staff member administering study drug were collected through the Device Assessment Questionnaire for Cohort 1 and the Injection Assessment Questionnaire for all other cohorts. For all cohorts, the Injection-Pain Assessment (11-point pain scale rating pain from 0-10) was administered by trained study staff following the first administration of exenatide suspension in that cohort (Visit 2). Blood samples to assess plasma exenatide concentrations and anti-exenatide antibody titer were collected before the first injection on Visit 2 and again on Visit 6. Safety was assessed throughout the study by examination of AEs, concomitant medications, clinical laboratory evaluations, vital signs, and physical examinations.

Target subject population and sample size

Healthy male or female subjects ≥18 years of age with no significant health issues were included in the study. The individual cohorts were comprised of at least 40% male subjects and at least 40% female subjects, at least 50% of subjects age ≥40 years, and 41% to 43% of subjects with body mass index (BMI) ≥30 kg/m^2.

Approximately 265 subjects were enrolled into each cohort, with each subject receiving up to 4 injections. With an assumption of 5% early withdrawal rate, a maximum of approximately 1000 injections were expected to be administered by Study Termination for each cohort. An intra-subject correlation of 0.1 was assumed based on results from Study BCB111 where repeated injections were given to the same subject. Using the correlated binary data analysis method, a total of 1000 injections were supposed to have 95% power to distinguish a failure rate of 4% from a failure rate of 2% (to rule out a failure rate of 4% or above if the true rate is 2%, or vice versa, to rule out a failure rate of 2% or below if the true rate is 4%), at a 1-sided alpha level of 0.05.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Exenatide suspension dosing

	Exenatide suspension				
Cohort	Dose (mg)	Injection volume (mL)	Concentration (mg/mL)	Delivery device	Delivery route
1	9	0.85	211	Prefilled autoinjector	SC injection
2	9	0.85	211	Syringe	SC injection
3	4.5	1.1	82	Syringe	SC injection
4	9	1.1	164	Syringe	SC injection
5	9	1.5	120	Syringe	SC injection

SC Subcutaneous.

Exenatide suspension (AC2993-F38) consists of exenatide microspheres (exenatide encapsulated within biodegradable poly-D, L lactide co-glycolide microspheres [PLG], 5% exenatide by mass) compounded in a vehicle of MCT. Batch nos: AVLF05-121046 (suspension pen kit); AVLF05 (suspension cartridge kit); 1-FIN-0646 (myglyol vials).

Duration of treatment

In each of the 5 cohorts, subjects received a single subcutaneous (SC) injection of exenatide suspension by trained study staff every 2 weeks for up to 6 weeks (maximum 4 injections per subject), followed by a 4-week follow up period.

Statistical methods

The primary efficacy endpoint of the injection failure rate for the single-use, prefilled autoinjector was calculated as the number of failed injections specific to the device divided by the number of total injections given to all subjects in study Cohort 1. Each cohort was analyzed separately in a similar way. Correlation-adjusted Wilson score type confidence intervals (CI) were provided for failure rates. Intra-subject correlation coefficient was estimated using all subjects available at the time of the analysis. Subjects were analyzed as

treated, based on a subject level treatment assignment. However, a sensitivity analysis was run to analyze subjects as treated at the visit level.

The device-related injection failure rate of alternate device configurations (secondary efficacy endpoint) was analyzed similarly to the analyses conducted for the primary endpoint. Similarities between Cohort 1 and Cohort 2 were explored. In addition, all types of injection failures were summarized descriptively and by subgroup. Subgroups of interest included: age (<40, ≥40), gender, sex, injection site quadrant, BMI, site, and diabetes risk status (≥40 years, BMI ≥30).

The Injection-Pain Assessment results were summarized descriptively and by subgroup.

For PK analysis, observed exenatide concentrations were summarized for each study cohort.

The primary safety and tolerability endpoint was the incidence of AEs. Other safety and tolerability endpoints included physical examinations, clinical laboratory measurements, and vital signs measurements. AEs were summarized using frequency counts and percentages. Hypoglycemia events were summarized separately. All hematology, clinical chemistry, and urinalysis results were listed by treatment, subject, and visit including scheduled and unscheduled/repeat measurements. Laboratory assessments that were outside of normal ranges were flagged. Baseline values, the values at each subsequent visit, and changes from baseline were summarized for applicable laboratory assessments by treatment. Post-hoc analyses of marked abnormalities included: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 3, 5, 10, and 20 x upper limit of normal (ULN), total bilirubin 1.5 and 2 x ULN, creatine kinase (CK) 5 and 10 x ULN, creatinine >1.5 x pre-treatment values, and phosphate <1.8 mg/dL and >5.6 mg/dL. Observed values and changes from baseline in heart rate, and systolic and diastolic blood pressures, as well as in weight and BMI, were summarized descriptively by treatment. Physical exam findings were listed.

Subject population

Approximately 265 subjects were randomized and treated in each cohort (265 subjects each in Cohorts 1 and 2, 263 subjects in Cohort 3, and 266 subjects each in Cohorts 4 and 5). Across all cohorts, 92.5% to 97.7% of subjects completed the study. Overall, the most common reason for discontinuation from treatment or discontinuation from the study was due to AEs (1.1% to 5.3% across all cohorts).

Overall, the demographic characteristics were balanced across the 5 cohorts. There were more female subjects than male subjects (54.0% to 60.1% female vs 39.9% to 46.0% male). Most subjects were between 18 and <65 years of age (97.0% to 98.5%) with a mean age ranging from 39.4 to 39.7 across cohorts. Most subjects were White (84.9% to 91.3%) and the majority of subjects were of non-Hispanic or Latino ethnicity (55.1% to 63.5%).

Summary of efficacy results

The injection failure rates were low in all cohorts, but were higher in Cohorts 1 and 2 (4.5% and 3.5%, respectively) than in Cohorts 3, 4, and 5 (0.4%, 1.6%, and 1.2%, respectively).

Most injection failures (approximately 90%) were attributed to tissue failure and not to needle clog.

Although the number of injection failures within the individual subgroups were small, differences in injection failure rates were observed for subgroups by gender (higher in males than females), by quadrant (higher for upper abdomen Q1 and Q2 than lower abdomen Q3 and Q4), and by site (higher for subjects at the Lincoln site than the Phoenix site). No patterns were observed for other subgroups.

Pain scores (injection pain and injection site pain) were very low at the time of injection and at 5 minutes post injection for all cohorts (mean injection pain scores ranged from 0.71 to 0.85; mean injection site pain scores ranged from 0.13 to 0.18).

Summary of pharmacokinetic results

Cohorts 1, 3, 4, and 5 showed similar dose-normalized plasma exenatide concentrations, suggesting no meaningful exenatide exposure differences based on delivery device, dose, or injection volume.

Summary of safety results

The proportions of subjects with at least 1 AE during the study was generally similar across all cohorts, with the lowest in Cohort 3 (55.1%) and rates of 66.8% to 71.8% in the remaining cohorts. This could potentially be explained by the lower dosage of IP administered to Cohort 3 patients (4.5 mg versus 9 mg) compared with other cohorts. The most frequently reported AEs were decreased weight (8.0% in Cohort 3 and 21.8% to 22.6% in the remaining cohorts) and nausea (12.9% in Cohort 3 and 16.2% to 21.9% in the remaining cohorts). A total of 41.1% of subjects in Cohort 3 and 56.6% to 60.5% in the remaining cohorts had AEs considered to be related to IP. The most common related AEs were decreased weight and nausea. The proportions of subjects with AEs leading to discontinuation of IP were low across all 5 cohorts (1.1% to 5.3%). The number of subjects with SAEs was low in all cohorts (≤1.5%). A total of 8 subjects experienced at least 1 SAE, 3 of which led to discontinuation of study treatment and none of which were considered by the investigator to be related to IP. There was 1 death (anoxic encephalopathy), considered by the investigator not to be related to IP.

Gastrointestinal-related events observed in this study were consistent with the mechanism of action of GLP-1 analogues in slowing the rate of gastric emptying. The proportion of patients with nausea-related AEs (nausea, vomiting, diarrhea, dyspepsia, and constipation) was highest in Cohorts 1, 2, and 4 (30.6%, 32.1%, and 29.3%, respectively) and lowest in Cohort 3 and 5 (18.3% and 23.7%, respectively).

With respect to injection site reactions, the overall rate was highest in Cohort 4 and 5 compared to Cohorts 1, 2, or 3 (24.1% and 25.9% in Cohorts 4 and 5, respectively, vs. 18.1%, 18.9%, and 18.3% in Cohorts 1, 2, and 3, respectively). No clear association was observed between injection site reactions and exenatide dose, volume of suspension, or

exenatide/suspension concentration. No consistent trends were observed for injection site reactions based on antibody status.

No trends were observed in mean changes from baseline in haematology parameters; changes were minimal or small across all cohorts.

Mean increases from baseline in CK were observed at Visit 6/Week 10 across all cohorts (range, 1.79 to 84.83 IU/L). This increase was mainly attributed to 5 subjects with marked abnormalities of CK >5 × ULN, 3 of which had CK values >10 × ULN. An ad hoc analysis of the change from baseline in CK was performed excluding these marked abnormalities. The results continued to show small mean increases in CK at Visit 6/Week 10, although decreased in magnitude (1.79 to 14.59 IU/L). Increases in median values ranged from 0 to 4 IU/L. Rhabdomyolysis was not reported in any patient.

Few subjects had marked abnormalities for any liver function test (2 subjects had AST values >3 × ULN, one of which was >5 × ULN) and no trends were observed in mean changes over time for these parameters. No subject had ALT/AST >3 × ULN combined with bilirubin >2 × ULN.

The number of subjects with positive antibody status on treatment were 78/100 (78.0%) in Cohort 1, 79/103 (76.7%) in Cohort 3, 81/105 (77.1%) in Cohort 4, and 73/103 (70.9%) in Cohort 5. For those subjects with positive antibody status, maximum antibody titers of 25, 125, 625, 3125, and 15625 were observed in 31.6%, 41.1%, 21.5%, 4.5%, and 1.4% of subjects, respectively. In all cohorts, subjects with positive antibody titers, the majority of which had exenatide antibody titers <625, were more likely to have AEs (mainly injection site reactions) than subjects who were antibody-negative. In all cohorts, approximately 75% of antibody-positive subjects with AEs had titers <625.

Minimal changes were observed in vital signs over time with small mean decreases in blood pressure (range, -1.50 to 0.31 mmHg for diastolic blood pressure and -4.74 to 0.53 mmHg for systolic blood pressure) and small mean increases in heart rate (from 1.41 to 4.25 bpm) observed in all cohorts. Decreases in body weight and BMI were observed across all cohorts (mean changes from baseline ranging from -1.07 to -2.23 kg for weight and from -0.81 to -0.39 kg/m^2 for BMI across the 5 cohorts). Weight loss >5% was to be reported as an AE and was the most frequently reported AE in this study. The rate was lowest in Cohort 3 (8.0%) but was otherwise similar across the remaining cohorts (21.8% to 22.6%). This was consistent with that observed for AEs of decreased appetite and gastrointestinal disorders of nausea, vomiting, dyspepsia, and diarrhea where Cohort 3 also had the lowest rates.