AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Byetta
ACTIVE INGREDIENT: Exenatide

Study No: D5550C00001
Exenatide (Byetta subcutaneous injection) Specific Clinical Experience Investigation for long term use

Developmental Phase: post-marketing
Study Completion Date: October 2019
Date of Report: June 2020

OBJECTIVES:

To confirm the safety and efficacy of Byetta subcutaneous injection (hereinafter referred to as Byetta) in long-term use under actual drug use.

1.1. Primary objective

To confirm development of adverse events with administration of Byetta. Especially, development of acute pancreatitis and cardiovascular related events (MACE:Major Adverse Cardiovascular Events) should be focused on.

1.2. Secondary objective

As the secondary objective of this investigation, the following items are to be investigated.

- The safety and efficacy in patients with renal impairment
- ADR development related to hypoglycaemia, digestive symptoms, and malignant neoplasm
- Variation of HbA1c from the baseline
- Changes of weight, blood pressure, and blood lipid
- Change of satisfaction level with diabetes treatment
- Expression of exenatide antibody in cases of hypersensitivity

METHODS:

Observational Study

RESULTS:

Subject population

Regarding the 2632 patients whose CRF was collected, 55 patients in total (including overlapping data) were excluded from the safety analysis set: 32 for “compliance deviations”, 20 for “violation of enrolment”, 3 for “no revisit after the first visit” and 1 for “not receiving the investigation drug”; the remaining 2577 patients were considered to be the safety analysis set.

Among the 2577 patients of the safety analysis set, 145 patients "without efficacy data” were excluded, and the remaining 2432 were considered to be the efficacy analysis set.

Byetta administration

The duration of treatment with Byetta (mean ± SD) in the 2577 patients of the safety analysis set was 507.26 ± 411.235 days, with a maximum duration of treatment of 1732.0 days. As to maximum daily dose of Byetta, 10 mcg was most common in 1345 patients (52.2%), followed by 20 mcg in 1158 patients (44.9%). The daily frequency of administration (maximum) was “twice daily” in 2528 patients (98.1%). The mean dose per patient was 7317.1 mcg.

Summary of safety results

[1] Adverse drug reaction(ADR)/infection development

Adverse drug reactions were reported in 411 of 2577 patients of safety analysis set (15.95%). ADRs reported in 5 patients or more were Nausea (197 patients, 7.64%), Vomiting (42 patients, 1.63%), Hypoglycaemia (29 patients, 1.13%), Constipation (28 patients, 1.09%), Decreased appetite (26 patients, 1.01%), Abdominal discomfort (16 patients, 0.62%), Diarrhoea (11 patients, 0.43%), Diabetes mellitus inadequate control (9 patients, 0.35%), Hypoglycaemia, Taste disorder, Abdominal distension, Malaise, and Weight decreased (8 patients, 0.31% for each), and Dizziness, Headache, and Dyspepsia (5 patients, 0.19% for each).

Serious ADRs were reported in 17 patients (0.66%). The details were: Diabetic ketosis and Cholelithiasis (2 patients, 0.08% for each), and Gastroenteritis, Tuberculosis, Herpes zoster oticus, Gastric cancer, Diabetes mellitus inadequate control, Diabetic ketoacidosis, Hypoglycaemia, Decreased appetite, Nausea, Vomiting, Cholecystitis, Hepatic function abnormal, Acute kidney injury, Death, Malaise, and Sudden death (1 patient, 0.04% for each). Of these events, the followings were unexpected ADRs: Diabetic ketosis and Cholelithiasis (2 patients each), and Gastroenteritis, Tuberculosis, Herpes zoster oticus, Gastric cancer, Diabetes mellitus inadequate control, Diabetic ketoacidosis, Cholecystitis, Death and Sudden death (1 patient each). The outcome of serious ADR was reported as Death for 2 events (Death and Sudden death), Recovered with sequelae for 1 event (Herpes zoster oticus), Improved or Recovered for 16 events, and Unknown for 1 event.

Unexpected ADRs were reported in 57 patients (2.21%). The details were Diabetes mellitus inadequate control (9 patients, 0.35%), Hyperglycaemia (7 patients, 0.27%), Glycosylated haemoglobin increased (4 patients, 0.16%), Diabetes mellitus (3 patients, 0.12%), Gastroenteritis, Diabetic ketosis, Loss of consciousness, Palpitations, Hypertension, Cholelithiasis and Blood glucose increased (2 patients, 0.08% for each), and Tuberculosis, Herpes zoster oticus, Gastric cancer, Colon adenoma, Diabetic ketoacidosis,Hypertriglyceridaemia, Dyslipidaemia, Hyperlipidaemia, Duodenal ulcer, Gastric ulcer, Irritable bowel syndrome, Pancreatic enzyme abnormality, Dyschezia, Cholecystitis, Skin odour abnormal, Prostatitis, Death, Feeling hot, Hunger, Sudden death and Blood pressure increased (1 patient, 0.04% for each).

[2] Key investigation item:

Risk Management Plan (RMP) was not developed.

The following items were reviewed as safety specifications: "hypoglycaemia", "acute pancreatitis-related events", "acute renal failure-related events", “digestive symptoms-related events”, "hyperglycaemia associated with switching from insulin, including diabetic ketoacidosis”, “anaphylactic reaction/angioedema-related events”, “neoplasm malignant-related events”, “cardiovascular events (Major Adverse Cardiovascular Events: MACE)”, “weight decreased” and “development of anti-exenatide antibody in the cases of hypersensitivity and/or loss of control of blood sugar”.

Thirty-six events of “Hypoglycaemia” were reported in 32 of 2577 patients of safety analysis set (1.24%). Of these events, 32 events in 29 patients (1.1%) were ADRs. One of the ADR events was serious with the outcome of recovery. There was no event with fatal outcome.

Three events of “acute pancreatitis-related events” were reported in 3 patients(0.12%). The details were Pancreatitis acute, Amylase increased, and Lipase increased (1 patient each), for all of which, the causality with Byetta was ruled out. The event of Pancreatitis acute was serious with the outcome of improvement. There was no event with fatal outcome.

Twenty-six events of “acute renal failure-related events” were reported in 26 patients(1.01%). The details were Renal impairment (10 events), Chronic kidney disease, Blood creatinine increased and Blood urea increased (4 events each), Acute kidney injury (3 events), and Renal failure (1 event). Of these events, the causal relationship between the event and Byetta was ruled out for Renal impairment (7 events), Chronic kidney disease (3 events), Blood creatinine increased (3 events), Acute kidney injury (2 events), Blood urea increased (2 events), and Renal failure (1 event). Two events of Acute kidney injury were serious. The outcome was “recovered” for both events. For 1 event of Chronic kidney disease, the outcome was “not recovered”. There was no event with fatal outcome.

A total of 434 events of “digestive symptoms-related events” were reported in 352 patients (13.66%), and of these, 363 events in 310 patients (12.0%) were ADRs. The severity was mild for 316 AE events in 245 patients and 258 ADR events in 213 patients. The major adverse events (>/= 10 events) were Nausea (212 events), Vomiting (46 events), Constipation (37 events), Decreased appetite (30 events), Diarrhoea (19 events), and Abdominal discomfort (17 events). Decreased appetite, Gastric ulcer haemorrhage, Nausea, Oesophageal varices haemorrhage, Pancreatitis acute and Vomiting (1 event each) were reported as SAEs. Regarding these SAE events, the outcome was recovery or improvement for all of them, and the causal relationship with Byetta was ruled out for Gastric ulcer haemorrhage, Oesophageal varices haemorrhage and Pancreatitis acute. In addition, 1 event of Ileus was reported in 1 patient (0.04%). The event was non-serious with the outcome of recovery. There was no event with fatal outcome.

Regarding “hyperglycaemia associated with switching from insulin, including diabetic ketoacidosis”, a serious event of Diabetic ketoacidosis was reported in 1 patient. In this patient, combination treatment with an insulin product and metformin was switched to Byetta (in combination treatment with metformin and glimepiride), and 40 days later, diabetic ketoacidosis developed. The outcome was reported as recovery.

There was no reported case of ”anaphylactic reaction/angioedema-related events”.

Fourteen events of "neoplasm malignant-related events" were reported in 14 patients(0.54%). The details were Colon cancer (4 evens), Uterine cancer and Hepatic cancer (2 events each), and Gastric cancer, Myelodysplastic syndrome, Pancreatic carcinoma, Colon adenoma, Lung neoplasm malignant, and Renal cell carcinoma (1 event each). There was no reported case of Thyroid neoplasm. All of these events except Colon adenoma were serious. A causal relationship with Byetta was not ruled out only for the event of Gastric cancer among the serious events, and the outcome of the event was recovery.
Fourteen events of "MACE-related events" were reported in 14 patients (0.54%). The details were Angina pectoris (6 events), Acute myocardial infarction (3 events), Blood creatine phosphokinase increased (2 events), and Arteriosclerosis coronary artery, Myocardial infarction, and Myocardial ischaemia (1 event each). A causal relationship with Byetta was ruled out for all of these events. Angina pectoris (3 events), Acute myocardial infarction (2 events), Arteriosclerosis coronary artery (1 event) and Myocardial infarction (1 event) were serious. There was no event with the outcome of death except for the event of Myocardial infarction.
Ten events of "Weight decreased" were reported in 10 patients (0.39%). For 2 of these events, a causal relationship with Byetta was ruled out. All of 10 events were non-serious.
Among the 2577 patients of safety analysis set, there was no patient for whom the causality between an AE (hypersensitivity) and antibody production was suspected and the investigator decided the need of measurement of the antibody levels.

Summary of efficacy results
HbA1c, body weight, fasting blood sugar, blood lipid (total cholesterol, HDL-C, LDL-C, and triglyceride) and fasting insulin (HOMA-beta and HOMA-R) were summarised. NGSP was used for HbA1c.
The mean HbA1c decreased over time from the start of Byetta to 4 months after the start, and then remained at a steady level until 36 months after the start. HbA1c values were summarised at each time point by blood glucose control target value. As a result, the proportion of patients with HbA1c of 8.0% or more decreased numerically at each time point after the start of Byetta compared to that at the start of Byetta. In relation to this, the proportion of patients with HbA1c < 7.0% increased numerically at almost all time points after the start of Byetta.
The mean body weight decreased over time after the start of Byetta.
The mean fasting blood sugar decreased at each time point after the start of Byetta compared to that before the start of Byetta.
Regarding total cholesterol, HDL-C, LDL-C, and triglyceride, there were no clinically significant changes in the measured values and variations from the baseline at each time point throughout the observation period.
The measured values and variations from the baseline at each time point were reviewed for HOMA-beta and HOMA-R. As to HOMA-beta, the clinical significance was unknown because the number of patients for the data summary was small and no particular trend was recognised over the period from the baseline to 36 months after the start of Byetta. HOMA-R decreased generally from the baseline, indicating improvement of insulin resistance.