AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: BYDUREON
ACTIVE INGREDIENT: Exenatide

Study No: D5551C00001
Bydureon subcutaneous injection 2 mg and Bydureon SC Pen 2 mg Specific Clinical Experience Investigation for long term use

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

OBJECTIVES:

To confirm the safety and efficacy of Bydureon subcutaneous injection 2 mg and Bydureon SC Pen 2 mg (hereinafter referred to as Bydureon) in long-term use in Japanese patients with type 2 diabetes mellitus under actual drug use.

(1) Primary Objective

To confirm the safety profile in Japanese patients with type 2 diabetes mellitus receiving Bydureon under daily practices.

(2) Secondary objective

As the secondary objective of this S-CEI, the following items are to be investigated.

- Frequencies of AEs related to cardiovascular events, hypoglycaemia, digestive symptoms, and injection site reaction.
- Development of pancreatitis, renal impairment (especially acute renal failure), hypersensitivity reaction, and malignant tumour (especially thyroid tumour and pancreatic malignancy)
- Safety in patients with mild or moderate renal impairment
- Changes of weight, blood pressure, pulse rate, fasting blood sugar, fasting insulin, HbA1c, and blood lipids
- Bydureon administration under daily practices focusing on the patient's demographics and clinical characteristics of diabetes mellitus (duration of diabetes mellitus, treatment duration, complications, Bydureon administration, etc)
- Anti-exenatide antibody titer in AE cases (hypersensitivity, loss of control of blood sugar)

METHODS:

Observational Study

RESULTS:

Subject population

The number of enrolled patients was 1137 by the end of the registration period, and CRFs of 1069 patients were collected from 237 sites by the end of this investigation. Regarding the 1069 patients whose CRF was collected, 15 patients were excluded from the safety analysis set (8 for “no revisit after the first visit”, 6 for “violation of enrolment”, and 1 for “not receiving the investigation drug”; the remaining 1054 patients were considered to be the safety analysis set. Among the 1054 patients of the safety analysis set, 44 patients "without efficacy data” were excluded, and the remaining 1010 patients were considered to be the efficacy analysis set.

Bydureon administration

Of the 1054 patients of the safety analysis set, 735 patients (69.7%) discontinued Bydureon during the observation period. The details by discontinuation timing were "< 6 months” in 291 of 1052 patients (27.7%), ">/= 6 months, < 12 months” in 168 of 761 patients (22.1%), ">/= 12 months, < 24 months” in 173 of 586 patients (29.5%), ">/= 24 months, < 36 months” in 99 of 384 patients (25.8%), and ">/= 36 months” in 4 of 240 patients (1.7%).

The most common reason for discontinuation of treatment in the 735 patients was “Others (patient’s request, etc.)” in 266 patients, followed by "adverse events" in 167 patients, “no revisit (transferred to other hospital, change of address, etc.) in 161 patients, and “lack of effect” in 141 patients.

Summary of safety results

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

Adverse drug reactions were reported in 255 of 1054 patients of safety analysis set (24.2%). ADRs reported in 5 patients or more were Injection site induration (58 patients, 5.5%), Nausea (53 patients, 5.0%), Decreased appetite (31 patients, 2.9%), Vomiting (30 patients, 2.8%), Diarrhoea (24 patients, 2.3%), Constipation (13 patients, 1.2%), Injection site pain (11 patients, 1.0%), Hypoglycaemia (9 patients, 0.9%), Injection site pruritus (8 patients, 0.8%), Dizziness, Malaise and Weight decreased (6 patients, 0.6% for each), and Diabetes mellitus, Abdominal discomfort, Abdominal pain, Pruritus and Rash (5 patients, 0.5% for each).

Thirty-five events of serious ADRs were reported in 27 patients (2.6%): Hyperglycaemia, Decreased appetite, and Death (2 patients, 0.2% for each), and Appendicitis, Pancreatic carcinoma, Breast cancer female, Lung neoplasm malignant, Pancreatic neuroendocrine tumour, Hepatic cancer, Dehydration, Hypoglycaemia, Cerebral haemorrhage, Cerebral infarction, Embolic stroke, Atrial fibrillation, Cardiac failure, Myocardial infarction, Hypertension, Pneumonia aspiration, Abdominal mass, Colitis ischaemic, Constipation, Duodenal ulcer, Ileus, Intestinal obstruction, Liver disorder, Renal failure, Prerenal failure, Pyrexia, Sudden death, Weight decreased, and Fall (1 patient, 0.1% for each). The outcome of serious ADR was reported as death for 4 events (Death 2, Sudden death 1, and Pancreatic carcinoma 1), recovered with sequelae for 1 event (Embolic stroke), not

recovered for 3 events (Pancreatic neuroendocrine tumour 1, Atrial fibrillation 1, and Liver disorder 1), and improved/recovered for 22 events.
Unexpected ADRs were reported in 62 patients (5.9%). Of these, the unexpected ADRs reported in 2 patients or more were Diabetes mellitus (5 patients, 0.5%), Diabetes mellitus inadequate control (4 patients, 0.4%), Hyperglycaemia, Palpitations and Abdominal mass (3 patients, 0.3% for each), and Pharyngitis, Depression, Sinus tachycardia, Hypertension, Death, Pyrexia, Blood glucose increased and Weight increased (2 patients, 0.2% for each).

Safety was examined for children, elderly, pregnant and parturient women, patients with hepatic function disorder, and patients with renal impairment. As a result, no notable issue was recognised.

[2] Key investigation item:

The following items were reviewed as safety specifications included in the Risk Management Plan (RMP): "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”, “injection site reaction-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”.
Thirteen events of “Hypoglycaemia” were reported in 10 of 1054 patients of safety analysis set (0.9%). Of these, one event was considered serious, and one event was assessed as not related to Bydureon. The outcome was recovery or improvement for all of the events. Regarding the serious event, the causality with Bydureon was not excluded.
Two events of “acute pancreatitis-related events” were reported in 2 patients(0.2%). The reported events were Hyperamylasaemia in one patient and Amylase increased in another patient. The both events were non-serious, and the outcome was unknown for Hyperamylasaemia and improvement for Amylase increased. The causal relationship with Bydureon was not ruled out for both events.
Ten events of “acute renal failure-related events” were reported in 10 patients(0.9%). The reported events were Blood creatinine increased and Blood urea increased (2 patients each), and Lupus nephritis, Renal failure, Postrenal failure, Renal impairment, Acute kidney injury, and Prerenal failure (1 patient each). Of these events, Lupus nephritis, Renal failure, Postrenal failure, and Prerenal failure (1 event each) were reported as serious. The events for which causal relationship with Bydureon was not ruled out were Renal failure, Acute kidney injury, Prerenal failure, and Blood creatinine increased (1 event each). There was no event with fatal outcome.
A total of 215 events of “digestive symptoms-related events” were reported in 157 patients (14.9%), and the causal relationship with Bydureon was not ruled out for 182 events. The major adverse events (>/= 10 events) were Nausea (54 events), Decreased appetite (35 events), Vomiting (31 events), Diarrhoea (29 events), and Constipation (18 events). The events reported as serious were Decreased appetite (3 events), Gastric cancer (2 events), and Gastroenteritis, Oesophageal carcinoma, Constipation, Abdominal mass, Colitis ischaemic, Duodenal ulcer, Dysphagia, ileus and Intestinal obstruction (1 event each). There was no event with fatal outcome.
There was no reported case of “hyperglycaemia associated with switching from insulin, including diabetic ketoacidosis” or ”anaphylactic reaction/angioedema-related events”.

Ninety events of “injection site reaction-related events” were reported in 68 patients(6.5%). The details (>/= 5 events) were Injection site induration (58 events), Injection site pain (12 events), Injection site pruritus (8 events), and Injection site erythema (5 events). All of the events were non-serious, and the causal relationship between each event and Bydureon was not ruled out.
Twenty-one events of “neoplasm malignant-related events” were reported in 21 patients(2.0%). The details were Gastric cancer, Pancreatic carcinoma, Breast cancer female, Lung neoplasm malignant, and Hepatic cancer (2 events each), and Bile duct cancer, Bladder cancer, Colon cancer, Lymphoma, Meningioma, Oesophageal carcinoma, Gastric adenoma, Neoplasm of orbit, Pancreatic neuroendocrine tumour, Gingival cancer and Renal cell carcinoma (1 event each). All of them were serious except Gastric adenoma and Neoplasm of orbit. There was no reported case of Thyroid neoplasm. The causal relationship with Bydureon was not ruled out for Pancreatic carcinoma, Breast cancer female, Lung neoplasm malignant, Hepatic cancer, Gastric adenoma, Neoplasm of orbit, and Pancreatic neuroendocrine tumour (1 event each). The events with fatal outcome were Pancreatic carcinoma, Bile duct cancer, Colon cancer, Lymphoma and Gingival cancer (1 event each).
Twenty events of “MACE-related events” were reported in 18 patients (1.7%). The details were Cerebral infarction (3 events), Atrial fibrillation and Myocardial ischaemia (2 events each), and Cerebral haemorrhage, Embolic stroke, Acute myocardial infarction, Angina pectoris, Arteriosclerosis coronary artery, Atrial flutter, Atrioventricular block first degree, Cardiac failure, Myocardial infarction, Sinus node dysfunction, Hypertrophic cardiomyopathy, Electrocardiogram change, and Subdural haematoma (1 event each). All events were serious except Myocardial ischaemia, Angina pectoris, Atrial flutter, Atrioventricular block first degree, and Electrocardiogram change (1 event each). The causal relationship between the event and Bydureon was not ruled out for Cerebral infarction, Cerebral haemorrhage, Embolic stroke, Atrial fibrillation, Myocardial ischaemia, Cardiac failure, and Myocardial infarction (1 event each). There was no event with fatal outcome.
Seven events of “Weight decreased” were reported in 7 patients (0.7%). Of these events, one was considered serious, and one was assessed as not related to Bydureon. The outcome of the serious event was “recovered”.
Among the 1054 patients of safety analysis set, there was no patient for whom the causality between an AE (hypersensitivity and loss of control of blood sugar) 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 Bydureon 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 Bydureon compared to that at the start of Bydureon. In relation to this, the proportion of patients with HbA1c < 7.0% increased numerically at almost all time points after the start of Bydureon.

The mean body weight continued to decrease gradually from 2 months to 36 months after the start of Bydureon.
The mean fasting blood sugar decreased significantly 2 months after the start of Bydureon and continued to decrease gradually until 36 months after the start of the drug.
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, useful interpretation was difficult and the clinical significance was unknown because the patients for the data summary were in a small number and included those with hypoglycaermia. HOMA-R decreased generally from the baseline, except the time point when the number of patients was small for the data summary, indicating improvement of insulin resistance.