OBSERVATIONAL STUDY REPORT SYNOPSIS

ONGLYZA (SAXAGLIPTIN) REGULATORY POSTMARKETING SURVEILLANCE

Milestones:	First subject enrolled: 02 April 2012 Last subject last visit: 07 September 2016
Phase of development:	Not Applicable – Observational study
Sponsor:	AstraZeneca

Objectives:

This study is to identify the following problems and questions with respect to the safety and effectiveness of Onglyza® in patients with T2DM in a large sample of patients in the real-life conditions in its registered indication(s) as required by MFDS.

1. Known and unknown adverse reactions, especially serious adverse reactions
2. Incidence of adverse reactions under the routine drug use
3. Factors that may affect the safety of the drug
4. Factors that may affect the effectiveness of the drug
5. Other safety information related to overuse, drug interaction and laboratory abnormalities
6. Other adverse reactions

The secondary objective is to explore factors that are considered to affect the safety and efficacy of Onglyza® in order to analyze factors considered to influence on them.

Study design:

This study is a local, prospective, open-label, non-interventional, non-controlled, multicenter, observational study (Regulatory Postmarketing Surveillance Study). Each patient will be followed up to 24 weeks. The study will be continued for 6 years after the date of product approval, as determined by the MFDS regulation. Each physician will sequentially enroll all patients who have received at least one dose of Onglyza® for the first time until the target number of patients per center is reached. The treatment with Onglyza® should comply with the recommendations written in the local product information.

Methods:

Safety endpoints will be evaluated until the 14 days after the end of study observation(the last effectiveness assessment day). However if Onglyza® is stopped before the end of study

observation, all adverse events that occurs until the 6 days after the last dose will be evaluated. Efficacy endpoints include HbA1c, fasting plasma glucose, and 2-hr post-prandial glucose.

Participating sites: Between 24 Jan 2011 and 23 Jan 2017, 105 investigators from 90 sites collected CRFs from 3,446 subjects.

Study population:
Female and male patients ≥ 18 years of age with diagnosis of type 2 diabetes mellitus initiating Onglyza® treatment within the approved indications will be enrolled.

Inclusion Criteria:

1. Female and male patients who are at least 18 years of age

2. Patients with diagnosis of T2DM initiating Onglyza® treatment within the approved indications in Korea

Exclusion criteria:

1. Indication which is not approved for Onglyza® in Korea

2. Patients with contraindication for the use of Onglyza® (as clarified in Korean label)

Statistical methods:

Statistical analyses will be of explorative and descriptive nature. All analyses will be performed for the total study population who will consist of all patients taking at least one dose of Onglyza®.

Analysis methods of safety endpoints
The number of adverse events and serious adverse events including unexpected adverse drug reactions by type will be calculated: severity, causality, and outcome of adverse events will be analyzed.

In order to explore the factors which are considered to influence safety, the incidence rates of adverse events by the following background factors will be analyzed as necessary:

- Age
- Gender
- BMI (calculated with height and weight)
- Waist circumference
- Duration of diabetes mellitus
- Presence of diabetes complications
- Presence or type of concomitant medications

Severity, actions taken to the surveillance drug, outcome, and causal relationship of AE to the surveillance drug will be analyzed.

To identify the factors that potentially affect safety, a Chi-square test or Fisher's exact test will be used to analyze the incidence rate of adverse events by the subject's individual factor (eg,

background factor, administration status of the surveillance drug, presence of concomitant drug yes or no, type of concomitant drug). The study variables will be adjusted depending on the contents of the study data, study status, and significance.

At the time of the final reporting, the incidence rate of all the adverse events surveyed during the re-examination period will be analyzed, and 95% confidence interval will be presented.

Analysis methods of efficacy endpoints

Changes in HbA1c, FPG, and 2-hr PPG before and after administration of Onglyza® will be analyzed using a paired t test.

The pre- and post-dose assessment results based on laboratory values and overall efficacy assessment results according to the physician's judgment will be analyzed. Overall efficacy assessment will analyze changes in HbA1c, FPG, and 2-hr PPG levels before and after 24 weeks of Onglyza® administration. These measures will be compared and assessed, and the changes will be classified into four categories (improved, unchanged, worsened, and assessment impossible). Except for "assessment impossible," the efficacy assessment criteria will be re-classified from "improved" to "effective" and from "unchanged" and "worsened" to "ineffective" in order to determine the efficacy rate by each factor. The factors deemed to influence the efficacy rate will be analyzed using a categorical data analysis (Chi-square test or Fisher's exact test).

Results:

Overall participation status

During the re-examination period, CRFs were collected from 3,446 subjects. Excluding 4 subjects who received Onglyza before the contract date, 5 subjects who did not receive Onglyza, 17 subjects who were lost to follow-up (unknown incidence of adverse event), 165 subjects who violated inclusion/exclusion criteria, and 35 subjects who violated dose/dosage, a total of 3,220 subjects were included in the safety evaluation. From the safety analysis set, 266 subjects who were unassessable in the final efficacy evaluation after the last visit and 40 subjects who received Onglyza for less than 12 weeks were excluded, and the remaining 2,914 subjects were included in the efficacy evaluation.

Descriptive data

Of 3,220 subjects in the safety analysis set, 54.91% (1,768/3,220 subjects) were males and 45.09% (1,452/3,220 subjects) were females.

The mean age of subjects was 59.04±11.88 years with '50 years ~ 59 years' group representing 31.77% (1,023/3,220 subjects), '60 years ~ 69 years' group representing 26.21% (844/3,220 subjects), and '≥ 70 years' group representing 21.37% (688/3,220 subjects), in decreasing order.

Pediatric subjects aged < 19 years were not included in this surveillance since use in this group is off label.

In total, 33.39% (1,075/3,220 subjects) were geriatrics, defined as those at or above 65 years of age.

There were no pregnant women among female subjects.

The mean height of subjects was 163.01±8.75 cm, ranging from minimum 138.50 cm to maximum 193.00 cm.

The mean body weight of subjects was 66.92±11.49 kg, ranging from minimum 34.00 kg to maximum 120.00 kg.

The mean BMI of subjects was 25.12±3.38 kg/m2, ranging from minimum 13.65 kg/m² to maximum 48.07 kg/m².

The mean waist circumference of male subjects was 88.57±7.37 cm, ranging from 70.00 cm to maximum 111.00 cm.

The mean waist circumference of female subjects was 86.73±8.92 cm, ranging from 58.00 cm to maximum 115.00 cm.

The mean duration of disease of subjects was 52.46±70.55 months, ranging from initial diagnosis to maximum 491 months. Duration of disease was '< 1 year' in 42.57% (1,370/3,218 subjects), '1 year ~ < 5 years' in 25.17% (810/3,218 subjects), and '5 years ~ < 10 years' in 16.31% (525/3,218 subjects), in decreasing order.

In total, 11.49% (370/3,220 subjects) of subjects had medical history. Medical history (multiple counting allowed) included 'Infections and infestations' in 18.92% (70/370 subjects), 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' in 18.11% (67/370 subjects), and 'Nervous system disorders' in 14.86% (55/370 subjects), in decreasing order.

In total, 72.24% (2,326/3,220 subjects) of subjects had concurrent disease. Concurrent disease (multiple counting allowed) included 'Vascular disorders' in 62.60% (1,456/2,326 subjects), 'Metabolism and nutrition disorders' in 58.34% (1,357/2,326 subjects), and ' Nervous system disorders' in 15.43% (359/2,326 subjects), in decreasing order.

In total, 34.45% (730/2,119 subjects) of subjects had family history of diabetes.

In total, 13.35% (430/3,220 subjects) of subjects had diabetes complication. Diabetes complications included 'Atherosclerosis', 'Diabetic retinopathy', 'Diabetic polyneuropathy', 'Diabetic neuropathy', 'Hyperlipidemia', 'Diabetic nephropathy', and etc.

In total, 2.58% (83/3,220 subjects) of subjects had renal impairment. Renal impairment included 'Diabetic nephropathy', 'Chronic kidney disease', 'Glomerular disorders in diabetes mellitus', 'Malignant neoplasm of kidney', 'Chronic renal failure', 'Proteinuria', and etc.

In total, 6.09% (196/3,220 subjects) of subjects had hepatic impairment. Hepatic impairment included 'Fatty liver', 'Hepatitis', 'Liver cell carcinoma', 'Liver cirrhosis', 'Alcoholic liver disease', and etc.

The mean total duration of treatment with Onglyza was 157.49±90.89 days, ranging from minimum 1 day to maximum 772 days. The total duration of treatment was '3 months ~ < 6 months' in 48.54% (1,563/3,220 subjects), '≥ 6 months' in 44.04% (1,418/3,220 subjects), and '< 3 months' in 7.42% (239/3,220 subjects), in decreasing order.

The mean total dose of treatment with Onglyza was 714.65±432.74 mg, ranging from minimum 2.50 mg to maximum 3,860.00 mg.

The mean daily dose of treatment with Onglyza was 4.56±0.94 mg, ranging from minimum 2.50 mg to maximum 5.00 mg. The daily dose of treatment was '5 mg' in 81.80% (2,634/3,220 subjects), '2.5 mg' in 16.27% (524/3,220 subjects), and '2.5 mg ~ 5 mg' in 1.93% (62/3,220 subjects), in decreasing order.

In total, 4.94% (159/3,220 subjects) of subjects discontinued treatment within 12 weeks from the first dose. The reason for discontinuation was 'stop visit' in 55.35% (88/159 subjects), 'others' in 36.48% (58/159 subjects), and 'adverse event' in 8.18% (13/159 subjects), in decreasing order. Others included 'Researcher resignation - early ternination', 'Withdraw a consent', 'Follow up less than 12 weeks', 'Arbitrary discontinuation', 'Change of treatment', and etc.

In total, 90.19% (2,904/3,220 subjects) of subjects received antihyperglycemic agent before and after Onglyza. Antihyperglycemic agents (multiple counting allowed) included 'Antidiabetic Agents' in 98.14% (2,850/2,904 subjects) and 'Insulin Preparations' in 3.99% (116/2,904 subjects). In total, 8.82% (284/3,220 subjects) of subjects received antihyperglycemic agent before Onglyza. Antihyperglycemic agents (multiple counting allowed) included 'Antidiabetic Agents' in 87.68% (249/284 subjects) and 'Insulin Preparations' in 13.73% (39/284 subjects). In total, 88.35% (2,845/3,220 subjects) of subjects received antihyperglycemic agent in combination with Onglyza. Antihyperglycemic agents (multiple counting allowed) included 'Antidiabetic Agents' in 97.93% (2,786/2,845 subjects) and 'Insulin Preparations′ in 3.94% (112/2,845 subjects).

In total, 71.43% (2,300/3,220 subjects) of subjects received concomitant medication other than antihyperglycemic agents. Concomitant medication (multiple counting allowed) included medication for 'Cardiovascular & Hematopoietic System' in 91.30% (2,100/2,300 subjects), medication for 'Gastrointestinal & Hepatobiliary System' in 23.09% (531/2,300 subjects), and medication for 'Central Nervous System' in 19.57% (450/2,300 subjects), in decreasing order.

In total, 44.04% (1,418/3,220 subjects) of subjects were long-term users, defined as those who received Onglyza for 24 weeks or longer.

Safety data

During this surveillance period, 249 adverse events were reported from 173 subjects (5.37%). The most common adverse events by system organ class (SOC) included 'Gastrointestinal disorders' in 1.46% (47/3,220 subjects), 'Respiratory system disorders' in 0.75% (24/3,220 subjects), and 'Body as a whole - general disorders' and 'Central & peripheral nervous system disorders' in 0.71% (23/3,220 subjects) each, in decreasing order. The most common adverse events by preferred term (PT) included 'DIZZINESS' and 'UPPER RESPIRATORY TRACT INFECTION' in 0.28% (9/3,220 subjects) each, 'DIARRHOEA' in 0.25% (8/3,220 subjects), and 'DYSPEPSIA' in 0.22% (7/3,220 subjects), in decreasing order.

In total, 33 events from 25 subjects (0.78%) were adverse drug reactions for which causal relationship to Onglyza could not be excluded. The most common adverse drug reactions by

SOC included ‘Gastrointestinal disorders’ in 0.37% (12/3,220 subjects), ‘Body as a whole - general disorders’, ‘Central & peripheral nervous system disorders’, and ‘Metabolic and nutritional disorders’ in 0.12% (4/3,220 subjects) each, and ‘Skin and appendages disorders’ in 0.09% (3/3,220 subjects), in decreasing order. The most common adverse drug reactions by PT included ‘DIARRHOEA’ in 0.12% (4/3,220 subjects), ‘DYSPEPSIA’ in 0.09% (3/3,220 subjects), and ‘CONSTIPATION’, ‘NAUSEA’, ‘DIZZINESS’, etc. in 0.06% (2/3,220 subjects) each, in decreasing order.

During this surveillance period, 29 serious adverse events were reported from 25 subjects (0.78%). The most common serious adverse events by SOC included ‘Neoplasms’ in 0.12% (4/3,220 subjects), ‘Myo-, endo-, pericardial & valve disorders’ in 0.09% (3/3,220 subjects), and ‘Gastrointestinal disorders’, ‘Respiratory system disorders’, ‘Metabolic and nutritional disorders’, etc. in 0.06% (2/3,220 subjects) each. The most common serious adverse events by PT included ‘MYOCARDIAL INFARCTION’ in 0.09% (3/3,220 subjects), ‘BONE METASTASES’ in 0.06% (2/3,220 subjects), and ‘ABDOMINAL PAIN’, ‘PANCREATITIS’, ‘NASAL POLYP’, etc. in 0.03% (1/3,220 subjects) each, in decreasing order. In total, 1 event from 1 subject (0.03%) was serious adverse drug reaction for which causal relationship to Onglyza could not be excluded: HYPERGLYCAEMIA in “Metabolic and nutritional disorders”.

During this surveillance period, 211 unexpected adverse events were reported from 150 subjects (4.66%). The most common unexpected adverse events by SOC included ‘Gastrointestinal disorders’ in 1.34% (43/3,220 subjects), ‘Body as a whole - general disorders’ in 0.65% (21/3,220 subjects), and ‘Nervous system disorders’ in 0.62% (20/3,220 subjects), in decreasing order. The most common unexpected adverse events by PT included ‘DIZZINESS’ in 0.28% (9/3,220 subjects), ‘DIARRHOEA’ in 0.25% (8/3,220 subjects), and ‘DYSPEPSIA’ in 0.22% (7/3,220 subjects), in decreasing order. In total, 25 events from 21 subjects (0.65%) were unexpected adverse drug reactions for which causal relationship to Onglyza could not be excluded. The most common unexpected adverse drug reactions by SOC included ‘Gastrointestinal disorders’ in 0.37% (12/3,220 subjects), ‘Body as a whole - general disorders’ in 0.12% (4/3,220 subjects), and ‘Nervous system disorders’ in 0.09% (3/3,220 subjects), in decreasing order. The most common unexpected adverse drug reactions by PT included ‘DIARRHOEA’ in 0.12% (4/3,220 subjects), ‘DYSPEPSIA’ in 0.09% (3/3,220 subjects), and ‘CONSTIPATION’, ‘NAUSEA’, ‘DIZZINESS’, etc. in 0.06% (2/3,220 subjects) each, in decreasing order.

During this surveillance period, 26 unexpected serious adverse events were reported from 22 subjects (0.68%). The most common unexpected serious adverse events by SOC included ‘Neoplasms’ in 0.12% (4/3,220 subjects), ‘Myo-, endo-, pericardial & valve disorders’ in 0.09% (3/3,220 subjects), and ‘Respiratory system disorders’, ‘Metabolic and nutritional disorders’, ‘ Urinary system disorders’, etc. in 0.06% (2/3,220 subjects) each, in decreasing order. The most common unexpected serious adverse events by PT included ‘MYOCARDIAL INFARCTION’ in 0.09% (3/3,220 subjects), ‘BONE METASTASES’ in 0.06% (2/3,220 subjects), and

'NASAL POLYP', 'VERTIGO', and 'DYSPNOEA' in 0.03% (1/3,220 subjects) each, in decreasing order. In total, 1 event from 1 subject (0.03%) was unexpected serious adverse drug reaction for which causal relationship to Onglyza could not be excluded: 'HYPERGLYCAEMIA' in "Metabolic and nutritional disorders".

Efficacy data

From 3,220 subjects in the safety analysis set, 266 subjects who were unassessable in the final efficacy evaluation after the last visit and 40 subjects who received Onglyza for less than 12 weeks were excluded, and the remaining 2,914 subjects were included in the efficacy evaluation.

Final efficacy evaluation was performed before treatment, after maximum 24 weeks post-visit, and upon treatment discontinuation or at the end of observation period (whichever is earlier). Changes in HbA1c, fasting plasma glucose (FPG), and 2-hr post-prandial glucose (PPG) from pre-dose to 12 - 24 weeks post-dose were analyzed.

The mean HbA1c decreased by 1.01±1.31% from 7.93±1.30% pre-dose to 6.93±0.95% post-dose, which was statistically significant ($p<0.0001$).

The mean FPG decreased by 25.43±43.28 mg/dL from 157.62±44.17 mg/dL pre-dose to 132.36±30.97 mg/dL post-dose, which was statistically significant ($p<0.0001$).

The mean 2hr-PPG decreased by 57.47±71.38mg/dL from 234.83±68.43 mg/dL pre-dose to 175.98±54.17 mg/dL post-dose, which was statistically significant ($p<0.0001$).

Results of final efficacy evaluation were categorized into 'Improved', 'Unchanged', 'Worsened', and 'Assessment impossible' according to overall improvement as determined by the investigator at the end of surveillance. Subjects considered 'Assessment impossible' were excluded from the efficacy evaluation. Results of final efficacy evaluation in subjects included in the efficacy analysis set were 'Improved' in 80.34% (2,341/2,914 subjects), 'Unchanged' in 13.93% (406/2,914 subjects), and 'Worsened' in 5.73% (167/2,914 subjects).

Conclusion:

In conclusion, regarding safety, the safety profile of Onglyza® reported herein is similar to that in the controlled clinical trials database, and age, concomitant disease, and the presence of diabetes/renal complications was associated with higher rates of AE reporting. However, these findings are similar to anti-diabetes therapy in general. Regarding efficacy, Onglyza® is an effective agent, leading to clinically important reductions in HbA1c, FPG, and PPG. Age, concomitant disease, the presence of diabetes/renal complications was associated with slightly less efficacy than individuals not possessing these characteristics; also that greater efficacy was seen with the 5 mg dose Therefore, administration of Onglyza® in patients with type 2 diabetes mellitus is considered safe and effective. Onglyza will be continuously monitored via spontaneous reports or adverse event reports from studies.