OBSERVATIONAL STUDY REPORT SYNOPSIS

KOMBIGLYZE XR (SAXAGLIPTIN + METFORMIN XR FIXED DOSE COMBINATION) REGULATORY POSTMARKETING SURVEILLANCE

Milestones:	First subject enrolled: 24 November 2012 Last subject last visit: 01 September 2016
Phase of development:	Not Applicable – Observational study
Sponsor:	AstraZeneca

Objectives:

As required by the Ministry of Food and Drug Safety (MFDS), this study is designed to evaluate the safety and effectiveness of Kombiglyze XR (saxagliptin + metformin extended release [XR]) used per approved indications in a large sample of Korean patients with type 2 diabetes mellitus (T2DM) treated under real life conditions.

The primary objectives are:

1. To evaluate known and unexpected adverse events, especially serious adverse events

2. To evaluate the incidence of adverse events under the routine drug use

3. To assess the effectiveness endpoints by assessing the change from baseline at Week 12 and up to Week 24 for patients that have a post Week 12 follow up visit(s) in HbA1c, FPG, and 2 hr PPG.

The secondary objectives are:

4. To evaluate factors (eg, gender, demographics etc) that may affect the safety of the drug

5. To evaluate factors (eg, gender, demographics etc) that may affect the effectiveness of the drug

6. To evaluate other safety information related to overdose, drug to drug interaction and laboratory abnormalities.

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 for at least 12 weeks and up to 24 weeks. The study will be continued for 4.5 years (until January 2017) after the date of product approval as determined by the MFDS regulation.

Each physician will sequentially enroll all patients who have received ≥ 1 dose of Kombiglyze XR for the first time until the target number of patients per center is reached. The eligibility of a patient and treatment protocol with Kombiglyze XR should comply with the Korean Kombiglyze XR prescribing information at the time of the patient's enrollment, as the local prescribing information may change over time.

Methods:
The study will measure and collect information of Kombiglyze XR use in the treatment of T2DM under the real world conditions. T2DM patients treated with Kombiglyze XR will be enrolled, and safety endpoints will be evaluated during Kombiglyze XR treatment until the 14 days after the end of study observation(the last effectiveness assessment day). However, if Kombiglyze XR is stopped before the end of study observation, then all adverse events that occur until the 6 days after the last dose will be evaluated. Effectiveness endpoints include change from baseline at Week 12 and up to Week 24 for patients that have a post Week 12 follow up visit(s) in HbA1c, FPG, and 2 hr PPG.

Participating sites: CRFs were retrieved from 763 subjects by 24 investigators at 22 hospitals from 12 Apr 2012 to 23 Jan 2017.

Study population:
Eligible patients will be ≥ 18 years of age with diagnosed T2DM who are initiating Kombiglyze XR treatment within the approved indications in Korea. Patients will be excluded if they are being treated for an indication not approved for the use of Kombiglyze XR in Korea or are contraindicated for the drug as described in the Korean label.

Inclusion Criteria:
- ≥ 18 years of age
- Have diagnosed with T2DM
- Are initiating Kombiglyze XR treatment within the approved Korean indications

Exclusion criteria:
- Being treated for an indication not approved for the use of Kombiglyze XR in Korea
- Is contraindicated for the use of Kombiglyze XR as described in the Korean label

Statistical methods:

Statistical analyses will be of explorative and descriptive nature. For this study there is no hypothesis being tested. All safety analyses will be performed for the total study population who will consist of all patients taking at least one dose of Kombiglyze XR. Effectiveness will be evaluated for patients who have received at least one dose of study drug and have at least 12 week effectiveness data.

Analysis methods of safety endpoints
The number of AEs and SAEs including unexpected adverse drug reactions by type will be calculated.

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 characteristics (eg, background variables such as gender, age etc, administration status of 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 (95% CI) determined.

If the occurrence probability of certain AE is 0.5% in the population, the expected number of occurrence in the sample size of 600 will be 3. The probability of an adverse event to be zero in the sample size of 600 of this investigation, when using Poisson distribution and assuming parameter to be 3, can be calculated.

Therefore, the probability to observe at least one adverse event out of subjects in the surveillance is 1 - 0.0498 = 0.9502.

Analysis methods of efficacy endpoints

The pre- and post dose assessment results based on laboratory values and overall effectiveness assessment will be analyzed. Changes in HbA1c, FPG, and 2 hr PPG from baseline to Week 12 and up to Week 24 for patients with post-week-12 clinic visits of Kombiglyze XR will be analyzed using a paired t test.

These measures will be compared and assessed, and the changes will be initially classified into 4 categories. Except for "not evaluable," the effectiveness assessment criteria will be re classified from "improved" to "effective" and from "unchanged" and "worsened" to "ineffective" in order to determine the effectiveness rate for each variable.

The factors deemed to influence the effectiveness rate will be analyzed using a categorical data analysis (Chi square test or Fischer's exact test).

Results:

Overall participation status

During the re-examination period, case report forms (CRFs) were collected from a total of 763 subjects. Among the subjects whose CRFs were collected, 2 subjects 'enrolled prior to contract', 23 subjects 'lost to follow-up (status of adverse events unknown), and 74 subjects with 'violation of inclusion/exclusion criteria' were excluded from the safety evaluation, and the remaining 664 subjects were evaluated for safety. Among those in the safety evaluation, 65 subjects who were 'unassessable/unclassifiable for final efficacy assessment after last visit' were excluded from the final efficacy assessment, and the remaining 599 subjects were included in the efficacy set.

Descriptive data

Among 664 subjects in the safety evaluation, 55.27% (367/664 subjects) were male and 44.73% (297/664 subjects) were female.

The average age of subjects was 59.61±11.20 years old. The age distribution was as follows: '50 years ~ 59 years' in 30.87% (205/664 subjects), '60 years ~ 69 years' in 30.42% (202/664 subjects), and '< 50 years' in 18.37% (122/664 subjects).

Pediatric aged < 18 years were not included in the study since use in this group is off label, Adolescents aged < 19 years, the re-examination criteria, were also not collected in this study.

When those '≥ 65 years' were classified as elderly group, 35.24% (234/664 subjects) of the study subjects belonged to this category.

There were no pregnant women among subjects.

The average height of subjects was 163.54±8.42 cm, ranging from 142.00 cm to 192.00 cm. The mean body weight was 67.82±11.20 kg, ranging from 39.00 kg to 138.10 kg.

The average of body mass index (BMI) was 25.25±2.97 kg/m2, ranging from 16.61 kg/m2 to 37.46 kg/m2.

The average of waist measurement was 88.44±7.67 cm, ranging from 68.00 cm to 108.00 cm.

The average disease duration was 728.70±1,348.58 days, including those who were newly diagnosed with the disease and those who had the disease for up to 9,571 days.

Distribution of disease duration was as follows: '< 3 months' in 52.80% (283/536 subjects), '≥ 1 year' in 35.45% (190/536 subjects), and '6 months ~ < 1 year' in 6.90% (37/536 subjects).

In total, 31.36% (159/507 subjects) of subjects had a family history of diabetes.

In total, 67.32% (447/664 subjects) of subjects had concurrent medical history. When analyzing concurrent diseases by allowing multiple counting, the most common concurrent diseases were 'Vascular disorders' in 68.90% (308/447 subjects), followed by 'Metabolism and nutrition disorders' in 63.09% (282/447 subjects) and 'Nervous system disorders' in 14.54% (65/447 subjects).

In total, 10.39% (69/664 subjects) of subjects had past medical history of any condition. By allowing multiple counting, the most common past medical history was 'Infections and infestations' in 24.64% (17/69 subjects), followed by 'Gastrointestinal disorders' in 23.19% (16/69 subjects) and 'Nervous system disorders' in 18.84% (13/69 subjects).

A total of 16.57% (110/664 subjects) had diabetic complications. Specifically, these included 'Atherosclerosis', 'Diabetic polyneuropathy', and 'Diabetic Neuropathy'. 0.75% (5/664 subjects) of subjects had nephropathy. Specifically, these included 'Diabetic nephropathy', 'Angiomyolipoma of right kidney', 'Rt. renal stone', and 'Uricosuria'.

A total of 1.66% (11/664 subjects) had hepatopathy. Specifically, these included 'Fatty liver', 'Elevated liver enzyme levels', 'Liver Cirrhosis', and 'Alcoholic fatty liver'.

The study drug included different amounts of saxagliptin and metformin. Therefore, it was analyzed for each ingredient. The mean total administration period of the study drug in subjects was 143.84±77.27 days, ranging from 1 day to 807 days. The distribution of total administration period of the study drug was '3 months ~ < 6 months' 68.07% (452/664 subjects), '≥ 6 months' 27.56% (183/664 subjects), and '< 3 months' 4.37% (29/664 subjects), respectively.

The mean total dose of saxagliptin was 719.22±386.37 mg, ranging from 5 mg to 4,035 mg. The mean total dose of metformin was 101,806.48±64,868.79 mg, ranging from 500 mg to 807,000 mg.

The mean daily dose of saxagliptin was 5 mg in all subjects. The mean daily dose of metformin was 707.84±245.59 mg, ranging from 500 mg to 1,000 mg. The distribution of the mean daily dose of metformin was '500 mg' 57.83% (384/664 subjects), '1,000 mg' 40.66% (270/664 subjects), and '500mg ~ < 1,000 mg' 1.51% (10/664 subjects), respectively.

As a result of analysis depending on administration before or together with the study drug, 51.20% (340/664 subjects) had taken or were taking anti-hyperglycemic agents. By allowing multiple counting, the most common concomitant anti-hyperglycemic agents were 'Antidiabetic Agents' in 100.00% (340/340 subjects), followed by 'Insulin Preparations' in 3.24% (11/340 subjects).

In total, 68.07% (452/664 subjects) of subjects had concomitant medications other than anti-hyperglycemic agents. By allowing multiple counting, the most common concomitant medications were 'Dyslipidaemic Agents' in 57.52% (260/452 subjects), followed by 'Anticoagulants, Antiplatelets & Fibrinolytics (Thrombolytics)' in 41.59% (188/452 subjects) and 'Other Antihypertensives' in 22.79% (103/452 subjects).

When subjects who received the study drug for 24 weeks or longer were classified as long-term users, 27.56% (183/664 subjects) were long-term users.

The number of subjects who dropped out was 4.22% (28/664 subjects) and the reasons were 'visit discontinued' 53.57% (15/28 subjects), 'other' 35.71% (10/28 subjects), and 'adverse events' 10.71% (3/28 subjects).

Safety data

Among 664 subjects in safety analysis, 56 adverse events were occurred from 37 subjects, and the incidence of adverse event was reported to be 5.57% during the re-examination period.

No SAEs were reported during the re-examination period.

A total of 42 events reported in 31 subjects (4.67%) during the re-examination period were unexpected adverse events. When unexpected adverse events were classified based on system organ class (SOC), 'Metabolic and nutritional disorders' were reported in 0.75% (5/664 subjects, 6 events), followed by 'Body as a whole - general disorders' and 'Musculo-skeletal system disorders' in 0.60% each (4/664 subjects, 4 events) and 'Gastro-intestinal system disorders', 'Central & peripheral nervous system disorders', 'Urinary system disorders', 'Respiratory system disorders', and 'Liver and biliary system disorders' in 0.45% each (3/664 subjects, 3, 3, 3, and 5 events, respectively). When unexpected adverse events were evaluated by detailed symptoms, 'HYPERGLYCAEMIA' and 'SGPT INCREASED' were reported in 0.45% each (3/664 subjects, 3 events), 'VITAMIN D DEFICIENCY', 'MEDICINE INEFFECTIVE', 'MICTURITION FREQUENCY', and 'SGOT INCREASED' in 0.30% each (2/664 subjects, 2 events), and others in 0.15% (1/664 subjects, 1 event). Of those, 7 events in 7 subjects (1.05%) were reported as unexpected adverse drug reactions of which causal relationship to the study drug cannot be ruled out.

When unexpected adverse drug reactions were classified based on SOC, ‘Body as a whole - general disorders’ were reported in 0.45% (3/664 subjects, 3 events), followed by ‘Gastro-intestinal system disorders’, ‘Metabolic and nutritional disorders’, ‘Central & peripheral nervous system disorders’, and ‘Cardiovascular disorders, general’ in 0.15% each (1/664 subjects, 1 event). When unexpected adverse drug reactions were evaluated by detailed symptoms, ‘MEDICINE INEFFECTIVE’ were reported in 0.30% (2/664 subjects, 2 events), and ‘DYSPEPSIA’, ‘HYPERGLYCAEMIA’, ‘DIABETIC NEUROPATHY’, ‘ASTHENIA’, and ‘CARDIAC FAILURE’ in 0.15% each (1/664 subjects, 1 event).

When adverse events were classified based on SOC, ‘Gastro-intestinal system disorders’ were reported in 1.20% (8/664 subjects, 9 events), followed by ‘Metabolic and nutritional disorders’ and ‘Central & peripheral nervous system disorders’ in 1.05% each (7/664 subjects, 9 and 7 events, respectively) and ‘Body as a whole - general disorders’ and ‘Musculo-skeletal system disorders’ in 0.60% each (4/664 subjects, 4 events). When adverse events were evaluated by detailed symptoms, ‘HEADACHE’ was reported in 0.60% (4/664 subjects, 4 events), ‘HYPERGLYCAEMIA’ and ‘SGPT INCREASED’ were reported in 0.45% each (3/664 subjects, 3 events), and ‘NAUSEA’, ‘VITAMIN D DEFICIENCY’, ‘HYPOGLYCAEMIA’, ‘MEDICINE INEFFECTIVE’, ‘MICTURITION FREQUENCY’, and ‘SGOT INCREASED’ were reported in 0.30% each (2/664 subjects, 2 events). Of those, 12 events in 11 subjects (1.66%) were reported as adverse drug reactions of which causal relationship to the study drug cannot be ruled out.

When adverse drug reactions were classified based on SOC, ‘Gastro-intestinal system disorders’, ‘Metabolic and nutritional disorders’, and ‘Body as a whole - general disorders’ were reported in 0.45% each (3/664 subjects, 3 events), followed by ‘Central & peripheral nervous system disorders’ were reported in 0.30% (2/664 subjects, 2 events). When adverse drug reactions were evaluated by detailed symptoms, ‘NAUSEA’, ‘HYPOGLYCAEMIA’, and ‘MEDICINE INEFFECTIVE’ were reported in 0.30% each (2/664 subjects, 2 events) and ‘DYSPEPSIA’, ‘HYPERGLYCAEMIA’, ‘HEADACHE’, ‘DIABETIC NEUROPATHY’, ‘ASTHENIA’, and ‘CARDIAC FAILURE’ were reported in 0.15% each (1/664 subjects, 1 event).

Efficacy data

Among 664 subjects in the safety evaluation, 65 subjects who were ‘“unassessable/unclassifiable” for final efficacy assessment after last visit’ were excluded from the final efficacy assessment, and the remaining 599 subjects were included in the efficacy set.

Overall efficacy was assessed based on change in HbA1c, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (2hr-PPG) at Weeks 12 to 24 from baseline in subjects who had a baseline visit and a follow-up visit at Week 12 or thereafter of study treatment.

For HbA1c, there was a mean decrease of 1.20±1.36% from mean 7.90±1.16% at baseline to mean 6.70±0.85% after treatment. The change in HbA1c after treatment from baseline was statistically significant ($p<0.0001$).

For FPG, there was a mean decrease of 34.45±40.12 mg/dL from mean 159.62±37.23 mg/dL at baseline to mean 125.16±25.53 mg/dL after treatment. The change in FPG after treatment from baseline was statistically significant ($p<0.0001$).

For 2hr-PPG, there was a mean decrease of 52.95±52.46 mg/dL from mean 234.26±56.83 mg/dL at baseline to mean 181.31±39.23 mg/dL after treatment. The change in 2hr-PPG after treatment from baseline was statistically significant ($p<0.0001$).

When the change in efficacy analysis was analysed comparatively and classified into 'Improved', 'No change', 'Worsened', or 'Unassessable', the results were as follows. 'Unassessable' was excluded from the analysis. As a result of assessment, 78.13% (468/599 subjects) were 'Improved', 13.52% (81/599 subjects) were 'No change', and 8.35% (50/599 subjects) were 'Worsened'. When those assessed as 'Improved' were regarded as 'Effective' and those assessed as 'No change' and 'Worsened' as 'Ineffective', except for subjects assessed as 'Unassessable', the results were as follows: 'Effective' in 78.13% (468/599 subjects) and 'Ineffective' in 21.87% (131/599 subject).

Conclusion:

In conclusion, regarding safety, the safety profile of Kombiglyze® XR reported herein is similar to that in the controlled clinical trials database, and 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, Kombiglyze® XR is an effective agent, leading to clinically important reductions in HbA1c, FPG, and PPG. Concomitant disease, the presence of diabetes/renal complications was associated with slightly less efficacy than individuals not possessing these characteristics. In the future, incidence of adverse events with the study drug and their causal relationships will continue to be monitored through spontaneous reports and other safety related reports.