Clinical Study Report Synopsis	
Drug Substance	Exenatide
Study Code	MB001-078
Edition Number	1
Date	24 February 2015

Post-Marketing Surveillance Study: 12 To 24 Weeks Study On The Treatment Emergent Adverse Events In Patients With Type 2 Diabetes Taking Exenatide In Korea

Study dates: First subject enrolled: 23 February 2009
Last subject last visit: 16 March 2014

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

Objectives and criteria for evaluation

Primary objective of this study is to estimate the proportion of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in patients who are treated with exenatide for type 2 diabetes mellitus by physicians in the normal clinical practice setting over a period of 12 weeks, and 24 weeks for long-term surveillance.

Study design

This study is a single country, prospective, non-interventional, regulatory postmarketing surveillance study to assess the proportion of TEAEs in Korean type 2 diabetic patients treated with exenatide therapy. The healthcare provider′s decisions regarding the proper treatment and care of the patient will be made in the course of the normal clinical practice; without blinding or randomization to particular comparator arms or therapies.

Target subject population and sample size

The patient population for this study will consist of Korean patients who are at least 18 years old, diagnosed with type 2 diabetes and are treated with exenatide in an ambulatory care setting according to the approved label.

According to the MFDS requirement, this study will be conducted as a single arm. At least 1,050 patients will be analyzed and reported as safety evaluation population.

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

Exenatide 5μg / 10μg twice a day subcutaneous, Exenatide 2mg once a week subcutaneous

Statistical methods

The proportion of patients experiencing an AE during the 12 weeks will be calculated and 95% confidence intervals will be constructed. The event rates of TEAE and SAE will be summarized by patient demographics and other factors, and the result between different levels of the factor will be compared using Pearson′s chi-square test.

For those who agree to be on long-term follow-up, the method for the effectiveness measure will be based on MMRM analysis, with the change in the effectiveness measure from baseline to other study visits as dependent variable.

The mean change between different level of the factor will be compared using an ANCOVA model for each visit. Additionally, multivariate logistic regression models will be utilized to assess factors that might have an influence on change of effectiveness measure.

Subject population

Case report forms (CRFs) for 1,648 subjects have been collected during the re-examination period. 379 subjects (7 subjects ‘who enrolled before the date of contract’, 4 subjects ‘who did

not meet inclusion/exclusion criteria', 367 subjects 'who violated dose/dosage', 1 subject 'who did not receive study drug') were excluded, and remaining 1,269 subjects were included in safety evaluation. Among those included in safety evaluation, 270 subjects (193 subjects 'who did not have either pre- or post-dose efficacy outcome', 77 subjects 'who received this drug for less than 8 weeks (56 days)') were excluded, and remaining 999 subjects were included in efficacy evaluation.

When subjects who received the study drug for 20 weeks (24±4 weeks) or longer were classified as long-term subjects, 754 out of 1,269 routine safety subjects were considered as long-term users. 30 subjects 'who did not have either pre- or post-dose efficacy outcome' were excluded, and 724 subjects were included in long-term efficacy evaluation.

Because all subjects in this surveillance were administrated with Byetta pen injection, any subject with Bydureon injection was not included in the analysis.

Summary of safety results

During this re-examination period, 369 out of 1,269 subjects included in safety set experienced 532 adverse events. Thus, incidence of adverse events was 29.08%.

Adverse events included 'Nausea' in 16.63% (211/1,269 subjects, 224 events), 'Vomiting' in 4.65% (59/1,269 subjects, 61 events), and 'Hypoglycaemia' in 1.73% (22/1,269 subjects, 23 events), in decreasing frequencey.

During this re-examination period, 302 subjects (23.8%) reported 409 adverse drug reactions of which causal relationship to study drug could not be excuded.

Adverse drug reactions included 'Nausea' in 15.29% (194/1,269 subjects, 207 events), 'Vomiting' in 4.57% (58/1,269 subjects, 60 events), and 'Hypoglycaemia' in 1.65% (21/1,269 subjects, 21 events), in decreasing frequency.

During this re-examination period, 18 subjects (1.42%) reported 24 serious adverse events.

Serious adverse events included 'Nausea' in 0.24% (3/1,269 subjects, 3 events), and 'Vomiting', 'Diabetic ulcer', 'Pneumonia', and 'Pyelonephritis' in 0.16% (2/1,269 subjects, 2 events) each, in decreasing frequency.

During this re-examination period, 3 subjects (0.24%) reported 5 serious adverse drug reactions of which causal relationship to study drug could not be excuded.

Serious adverse drug reactions included 'Nausea' in 0.24% (3/1,269 subjects, 3 events) and 'Vomiting' in 0.16% (2/1,269 subjects, 2 events).

During this re-examination period, 89 subjects (7.01%) reported 120 unexpected adverse events regardless of causal relationship to study drug.

Unexpected adverse events included 'Gastro-intestinal disorder nos' in 0.71% (9/1,269 subjects, 9 events), 'Neuropathy' in 0.55% (7/1,269 subjects, 7 events), and 'Hyperglycaemia' in 0.47% (6/1,269 subjects, 6 events), in decreasing frequencey.

During this re-examination period, 38 subjects (2.99%) reported 40 unexpected adverse drug reactions of which causal relationship to study drug could not be excuded.

Unexpected adverse drug reactions included 'Gastro-intestinal disorder nos' in 0.71% (9/1,269 subjects, 9 events), 'Hyperglycaemia' in 0.32% (4/1,269 subjects, 4 events), and 'Depression', 'Sweat gland disorder', and 'Dyspnoea' in 0.16% (2/1,269 subjects, 2 events), in decreasing frequency.

There was no unexpected adverse drug reaction of which incidence was ≥ 1% and causal relationship to study drug could not be excuded. Unexpected adverse drug reactions of which incidences were < 1% are shown below.

- Gastro-intestinal system disorders: Gastro-intestinal disorder nos, Gastritis
- Central & peripheral nervous system disorders: Neuropathy
- Metabolic and nutritional disorders: Hyperglycaemia, Hypercholesterolaemia
- Psychiatric disorders: Sleep disorder, Depression, Emotional lability, Apathy, Insomnia, Nervousness
- Skin and appendages disorders: Sweat gland disorder, Dermographia
- Body as a whole - general disorders: Fatigue, Temperature changed sensation, Rigors
- Musculo-skeletal system disorders: Myalgia, Arthralgia
- Respiratory system disorders: Dyspnoea
- Vision disorders: Cataract, Sunken eyes
- Heart rate and rhythm disorders: Palpitation
- Hearing and vestibular disorders: Tinnitus
- Myo-, endo-, pericardial & valve disorders: Angina pectoris

Severity of adverse events was classified into three categories of 'Mild', 'Moderate' and 'Severe' for analysis. 'Mild' represented 57.33% (305/532 events), 'Moderate' represented 34.59% (184/532 events), and 'Severe' represented 8.08% (43/532 events).

Causal relationship of adverse event to study drug was categorized into five categories of 'Probably not', 'Possibly', 'Probably', 'Definitely', and 'Unknown' for evaluation. 'Probably'

represented 32.52% (173/532 events), 'Probably not' represented 23.12% (123/532 events), and 'Possibly' represented 22.37% (173/532 events), in decreasing frequency.

Summary of efficacy results

Efficacy evaluation was based on the level of improvement of main diagnosis assessed by study doctor at the end of the study. Results were categorized into five categories of 'Improved', 'Slightly improved', 'Unchaged', 'Aggravated', and 'Unable to evaluate' for analysis. 'Slightly improved' represented 46.25% (462/999 subjects), 'Improved' represented 21.32% (213/999 subjects), 'Unchanged' represented 20.52% (205/999 subjects), 'Aggravated' represented 8.31% (83/999 subjects), and 'Unable to evaluate' represented 3.6% (36/999 subjects), in decreasing frequency.