No.18-72

August 28, 2018
Eisai Co., Ltd.

LONG-TERM CARDIOVASCULAR OUTCOMES DATA FOR ANTI-OBESITY AGENT BELVIQ® PRESENTED AT THE EUROPEAN SOCIETY OF CARDIOLOGY AND PUBLISHED IN THE *NEW ENGLAND JOURNAL OF MEDICINE*

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") has announced that results from the Cardiovascular Outcomes Trial (CAMELLIA-TIMI 61) in patients treated with lorcaserin hydrochloride (generic name, product name in the U.S.: BELVIQ®, "BELVIQ") were highlighted in an oral presentation at the European Society of Cardiology (ESC) Congress 2018 held in Munich, Germany, and concurrently published in the *New England Journal of Medicine*, one of the world's most influential medical journals.[1] BELVIQ is the first ever weight loss medication approved for chronic weight management which has been proven to not increase the incidence of major cardiovascular (CV) events in a dedicated long-term cardiovascular outcome trial.

This study was conducted at over 400 sites in eight countries including the United States in collaboration with the Thrombolysis in Myocardial Infarction (TIMI) Study Group, and is the largest cardiovascular outcome trial conducted to date for a weight loss medication. As the primary safety objective, the study assessed the incidence of major adverse cardiovascular events (MACE: defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in 12,000 overweight and obese adults with existing cardiovascular disease or type 2 diabetes mellitus (T2DM) with cardiovascular risk factors who were administered BELVIQ 10 mg twice-daily (median 3.3 years). Overall, the median age of patients in the study was 64 and the median body mass index (BMI) was 35kg/m^2, with 57% of patients at baseline having T2DM, 90% with hypertension, 94% with hyperlipidemia and 20% with chronic kidney disease. Approximately 75% of patients had established atherosclerotic CV disease.

At the time of study completion, MACE occurred in 364 of 6,000 patients in the BELVIQ arm (2.0%/year) and 369 of 6,000 patients in the placebo arm (2.1%/year; hazard ratio, 0.99; 95% confidence interval (CI), 0.85-1.14; non-inferiority margin, 1.4). This demonstrated that BELVIQ did not increase the incidence of MACE, and therefore the primary safety objective of statistical non-inferiority was met. Since the primary safety objective was met, the primary efficacy outcome of incidence of CV death, myocardial infarction, stroke hospitalization for unstable angina, heart failure or any coronary revascularization (MACE+) was also assessed. From the results, MACE+ occurred in 707 of 6,000 patients (4.1%/year) in the BELVIQ arm and in 727 of 6,000 patients in the placebo arm (4.2%/year). Although statistical superiority was not observed (p=0.55), statistical non-inferiority was confirmed (hazard ratio, 0.97; 95% CI, 0.87-1.07; non-inferiority margin, 1.4).

In exploratory assessments of the efficacy of BELVIQ, at one year, significantly more patients treated with BELVIQ versus placebo lost greater than or equal to five percent of body weight (39% vs. 17%; nominal p-value<0.001) or greater than or equal to ten percent of body weight (15% vs. 5%; nominal p-value<0.001).

The average change in weight from baseline was -4.2 kg with BELVIQ and -1.4 kg with placebo, translating to a 2.8 kg greater net weight loss with BELVIQ (nominal p-value<0.001).

Furthermore, treatment with BELVIQ (for a period of one year), on top of standard of care for the respective comorbid conditions in CAMELLIA-TIMI 61, was associated with statistically significant improvements in systolic blood pressure (placebo-subtracted difference -0.9 mm Hg), diastolic blood pressure (-0.8 mm Hg), heart rate (-1.0 beat per minute), low-density lipoprotein cholesterol (-1.2 mg/dL), triglycerides (-11.7 mg/dL) and non-high-density lipoprotein cholesterol (-2.6 mg/dL).

BELVIQ also reduced hemoglobin A1C (HBA1c) in patients with T2DM at baseline (placebo-subtracted difference -0.3%) and reduced the rate of new onset diabetes in patients with pre-diabetes at baseline (3.1%/year with BELVIQ versus 3.8%/year with placebo).

No significant differences were seen in the overall incidence of serious adverse events between BELVIQ and placebo (31% vs. 32%), and the overall safety profile for BELVIQ in CAMELLIA-TIMI 61 was consistent with that of the approved label. Dizziness, fatigue, headache, nausea and diarrhea were the most commonly reported adverse events in CAMELLIA-TIMI 61. Adverse events possibly leading to study discontinuation were more frequent with BELVIQ versus placebo (7.2% vs. 3.7%), with the most commonly reported adverse events in this category for BELVIQ being dizziness, fatigue, headache, diarrhea and nausea.

Further results of analyses of the study will be presented on October 4 at the European Association for Study of Diabetes (EASD) Annual Meeting held in Berlin, Germany.

By continuing to provide additional clinical and scientific information regarding BELVIQ, Eisai continues to make further contributions to address unmet medical needs and increase the benefits for patients and their families.

Media Inquiries:
Public Relations Department,
Eisai Co., Ltd.
+81-(0)3-3817-5120

[Notes to editors]

1. About lorcaserin hydrochloride (U.S. brand name: BELVIQ, once daily formulation U.S. brand name: BELVIQ XR)

Discovered and developed by Arena Pharmaceuticals, Inc. (Headquarters: California, United States, President and CEO: Amit D. Munshi), lorcaserin is a novel chemical entity that is believed to decrease food consumption and promote satiety by selectively activating serotonin 2C receptors in the brain. Activation of these receptors may help a person eat less and feel full after eating smaller amounts of food. Lorcaserin was approved in June 2012 by the FDA as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition, and was launched in the United States under the brand name BELVIQ in June 2013 after receiving a final scheduling designation from the U.S. Drug Enforcement Administration (DEA). In addition, lorcaserin has been made available in South Korea via a third-party distributor from 2015. Lorcaserin was approved in Mexico in July 2016 and in Brazil in December 2016, with the same indication as for the United States.

Furthermore, BELVIQ XR, a once-daily formulation of lorcaserin aiming to increase convenience of administration for patients, was approved in the United States in July 2016.

In January 2017, Eisai acquired all of Arena's rights to develop and market BELVIQ.

The most common adverse reactions observed in multiple Phase III clinical studies on lorcaserin were headache, dizziness, fatigue, nausea, dry mouth and constipation in patients without diabetes, and hypoglycemia, headache, back pain, cough and fatigue in patients with diabetes. For further information on lorcaserin in the United States, including Important Safety Information (ISI), please visit the BELVIQ product website (http://www.belviq.com).

2. About the Cardiovascular Outcomes Trial, CAMELLIA-TIMI61 Study

The CAMELLIA (Cardiovascular And Metabolic Effects of Lorcaserin In Overweight And Obese Patients) TIMI 61 study was the largest double-blind, placebo-controlled, parallel-group Phase IIIB/IV study among weight loss medications. The primary safety objective was to evaluate the incidence of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction or stroke. If the primary safety objective was met, the efficacy objective was to evaluate the impact of lorcaserin on the incidence of MACE+, defined as MACE or hospitalization due to unstable angina or heart failure, or any coronary revascularization. Secondary objectives included evaluation for the potential to delay or prevent conversion to T2DM in patients with pre-diabetes or no diabetes at baseline and improvement of glycemic control in patients with T2DM.

3. About the TIMI Study Group

The TIMI Study Group is an Academic Research Organization based at Brigham and Women's Hospital that has been leading practice-changing cardiovascular clinical trials for 30 years.

4. About The *New England Journal of Medicine*

The *New England Journal of Medicine* (NEJM) is the world's leading medical journal and website, published continuously for over 200 years. NEJM has the highest Journal Impact Factor of all general medical journals (2017 *Journal Citation Reports*®, Clarivate Analytics, 2018).

[1] Bohula, E. A., Cardiovascular Safety of Lorcaserin in Overweight and Obese Patients, The *New England Journal of Medicine*, 2018.