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Eisai Co., Ltd.

NEW DATA ON EFFECT OF ANTI-OBESITY AGENT BELVIQ® ON PREVENTION AND REMISSION OF TYPE 2 DIABETES PRESENTED AT THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES AND PUBLISHED IN *THE LANCET*

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") has announced that new data on prevention and remission of type 2 diabetes mellitus (T2DM) from the long-term Cardiovascular Outcomes Trial (CAMELLIA-TIMI61) in patients treated with lorcaserin hydrochloride (generic name, product name in the U.S.: BELVIQ®, "BELVIQ") were presented at the 54th Annual Meeting of the European Association for the Study of Diabetes (EASD) 2018 held in Berlin, Germany, and concurrently published in *The Lancet*,[1] which is one of the world's most prestigious medical journals. This new analysis assessed metabolic effects on enrolled patients with T2DM or pre-diabetes (higher than normal blood sugar levels prior to incidence of diabetes) at baseline, as well as patients with normoglycemia.
At baseline, the study enrolled 3,991 patients with pre-diabetes (33%), 6,816 patients with T2DM (57%) and 1,193 patients with normoglycemia (10%).

From the results of this analysis, treatment with BELVIQ compared to placebo in patients with pre-diabetes reduced the risk of incident T2DM by 19% (BELVIQ 8.5% vs. placebo 10.3%; hazard ratio [HR] 0.81; 95% confidence interval [CI]: 0.66-0.99; nominal p-value=0.038) and tended to increase the rate of achievement of normoglycemia (9.2% vs 7.6%, HR:1.20, 95% CI: 0.97-1.49, nominal p-value=0.093).
In patients with T2DM at baseline, treatment with BELVIQ increased the rate of remission of hyperglycemia compared to placebo (7.1% vs 6.0%; HR 1.21; 95% CI: 1.00-1.45; nominal p-value=0.049) as well as reduced hemoglobin A1C (HBA1c, placebo-subtracted difference -0.3%). Furthermore, in patients with a baseline HBA1c greater than 8%, BELVIQ resulted in a net reduction in HBA1c of 0.5% at 1 year.
Additionally, treatment with BELVIQ reduced the risk of a composite of microvascular events of incident microalbuminuria, diabetic retinopathy or diabetic neuropathy by 21% in patients with T2DM (10.1% vs. 12.4%; HR 0.79; 95% CI: 0.69-0.92; nominal p-value=0.001).

After one year, net weight loss was greater with BELVIQ compared with placebo for patients with pre-diabetes (difference in mean change in body weight between BELVIQ and placebo at 1 year: -2.8 kg [95% CI: -3.2, -2.5], nominal p-value<0.0001), T2DM (-2.6 kg [-2.9, -2.3], nominal p-value<0.0001) and normoglycemia (-3.3 kg [-4.0, -2.6], nominal p-value<0.0001). At 1 year, a higher proportion of patients randomized to BELVIQ versus placebo achieved a 5% or greater decrease in body weight in each subgroup: pre-diabetes (40% vs 18%, nominal p-value<0.0001), T2DM (37% vs 17%, nominal p-value<0.0001) and normoglycemia (42% vs 17%, nominal p-value<0.0001). The between-treatment group weight loss remained within each glycemic subgroup over the duration of the study.

As previously announced in August 2018, this study was conducted as a post-marketing trial primarily

evaluating safety 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. 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 T2DM with cardiovascular risk factors who were administered BELVIQ 10 mg twice-daily. The study met its primary safety objective, finding that long-term treatment with BELVIQ did not increase the incidence of MACE.[2]

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-TIMI61 was consistent with that of the approved label. Adverse events attributed to study drug and leading to drug discontinuation were more frequent with BELVIQ versus placebo (7.2% vs. 3.7%, respectively), with the most commonly reported adverse events in this category for BELVIQ being dizziness, fatigue, headache, diarrhea and nausea. Additionally, in patients with diabetes at baseline, hypoglycemia occurred in 6.6% of patients treated with BELVIQ versus 5.8% in those treated with placebo (nominal p-value=0.18), with most (>85%) events occurring in patients on either insulin or a sulfonylurea at baseline. Severe hypoglycemia with serious complications was rare, but more common with BELVIQ versus placebo (0.4% vs. 0.1%, respectively).

With the data on BELVIQ gained through this study, 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) TIMI61 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. From the results of the study, it was confirmed that BELVIQ did not increase the incidence of MACE compared to placebo, and therefore the primary safety objective was met. In addition, regarding the incidence of MACE+, although statistical superiority was not observed for BELVIQ compared to placebo, statistical non-inferiority was confirmed.

Furthermore, 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.

At baseline, the study enrolled 3,991 patients with pre-diabetes (33%), 6,816 patients with T2DM (57%) and 1,193 patients with normoglycemia (10%). Patients were screened for T2DM via a hemoglobin A1c of <10% at screening and a stable clinical and treatment course of T2DM in the preceding three months with no hospitalizations for hypo- or hyperglycemia. In the absence of prevalent T2DM, pre-diabetes was defined as a hemoglobin ≥5.7%-<6.5% or a fasting plasma glucose of 100-125mg/dL.

The primary metabolic efficacy outcome was the time to incident T2DM among patients with pre-diabetes at baseline. Based on the American Diabetes Association guidelines[3], the primary definition for incident diabetes required either a single occurrence of a random plasma glucose of ≥200mg/dL with symptoms of hyperglycemia, or another abnormal glycemic parameter (i.e. HbA1c≥6.5%, fasting plasma glucose≥126mg/dL or a 2-hour plasma glucose of ≥200mg/dL

during an oral glucose tolerance test) that was confirmed on simultaneous or consecutive testing or with initiation of glucose-lowering medications. In addition, assessments of the efficacy of BELVIQ on change in weight from baseline and metabolic profiles of patients treated with BELVIQ were also observed in exploratory endpoints.

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 Lancet*

First published in 1823 and with a history spanning over 190 years, *The Lancet* is an influential medical journal that is highly regarded worldwide.

[1] Bohula E.A. et al, "Effect of Lorcaserin on Prevention and Remission of Type 2 Diabetes in CAMELLIA-TIMI61, a Randomized Trial in Overweight and Obese Patients", *The Lancet, 2018*

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

[3] American Heart Association. Cardiovascular Disease and Diabetes. Accessed at: http://www.heart.org/en/health-topics/diabetes/why-diabetes-matters/cardiovascular-disease--diabetes