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NEWS RELEASE

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CLINICAL TRIAL TESTING SAFETY OF OBESITY DRUG CONTRAVE HALTED; 50 PERCENT INTERIM DATA RELEASED BY THE STUDY'S EXECUTIVE COMMITTEE

Unauthorized Release of Data Compromised Integrity of Study

TUESDAY, MAY 12, 2015, CLEVELAND: Following premature disclosure of interim study results, the 9,000-patient Light Trial – designed to study the cardiovascular safety of the obesity drug Contrave (buproprion-naltrexone) – has been halted by the trial's executive steering committee, led by Cleveland Clinic. The discontinuation of the study was announced earlier today by Orexigen Therapeutics Inc. and Takeda Pharmaceuticals, the drug's developers.

The Light Study was designed to meet the U.S. Food and Drug Administration's requirement for Orexigen to assess the cardiovascular safety of Contrave in overweight and obese patients, who are at a high risk of cardiovascular events due to diabetes and other health factors.

The primary endpoint in the Light Study is the composite of major adverse cardiovascular events (MACE) that included death, non-fatal stroke and non-fatal myocardial infarction (MI). Orexigen was permitted to file for approval of Contrave with a pre-specified interim analysis after approximately 25 percent of MACE had occurred in the Light Study, if the results ruled out a doubling of cardiovascular risk for patients taking Contrave. The results of this interim analysis, which were intended to remain confidential, demonstrated that Contrave met this criterion, and the FDA approved Contrave on September 10, 2014.

At the time of approval of Contrave, the FDA determined that Orexigen had violated the terms of a data access agreement by revealing the 25 percent interim results to both a wide group of individuals within the company and external business partners. The FDA also stated that this breach of confidentiality had sufficiently undermined its confidence in the ongoing trial; a new trial would be required to determine whether a 40 percent increase in cardiovascular risk could be ruled out.

Subsequently, in March 2015, Orexigen publicly disclosed the confidential 25 percent interim analysis of the Light Study as part of a patent and securities filing, without the authorization

of the study's academic leadership. At the time of this disclosure, the study's executive steering committee strongly cautioned against any potential misinterpretation of the preliminary 25 percent interim data inappropriately released in this disclosure by Orexigen. As a large number of MACE events are necessary to determine effect in a cardiovascular outcome trial, the 25 percent interim data are not conclusive in establishing either benefit or risk of Contrave on cardiovascular risk.

The data obtained after 50 percent completion of the trial with a total of 192 events, demonstrate that 102 primary endpoints (cardiovascular death, stroke, myocardial infarction) occurred in the placebo group compared with 90 in the Contrave group (HR=0.88, 95 percent CI 0.66 – 1.17). As previously reported, during the first 25 percent of the Light Study, 59 cardiovascular events occurred in the placebo treatment group and 35 events in the Contrave group, an estimated hazard ratio (HR) of 0.59. During the second 25 percent of the Light Study, 43 events occurred in the placebo group and 55 events occurred in the Contrave group. When non-cardiovascular deaths (Contrave 26, placebo 17) are included in the primary composite endpoint with stroke and MI, the results at the 50 percent time point include 114 events in the placebo group vs. 119 in the Contrave group (HR=0.95, 95 percent CI 0.74 – 1.23).

"These results do not confirm cardiovascular benefits of Contrave claimed by Orexigen in the patent application based on the data obtained at the 25 percent time point in the trial," said Steven Nissen, M.D., chair of the study's executive steering committee and chair of cardiovascular medicine at Cleveland Clinic.

"These results show neither benefit nor harm for patients taking the drug, but are consistent with the requirement by the FDA that the Light Trial demonstrate an absence of a doubling of cardiovascular risk for patients taking the drug," Dr. Nissen added. "The inconsistency of effects on cardiovascular outcomes between the first 25 percent and the second 25 percent of the Light Study clearly illustrates the risks inherent in pre-judgment of clinical trial results based upon an interim analysis and demonstrate why interim results should remain confidential during any ongoing trial."

The executive steering committee expects to report the final Light Study data in a scientific forum after all of the cardiovascular events in the Light Study have been collected and properly adjudicated.

About Cleveland Clinic

Cleveland Clinic is a nonprofit multispecialty academic medical center that integrates clinical and hospital care with research and education. Located in Cleveland, Ohio, it was founded in 1921 by four renowned physicians with a vision of providing outstanding patient care based upon the principles of cooperation, compassion and innovation. Cleveland Clinic has pioneered many medical breakthroughs, including coronary artery bypass surgery and the first face transplant in the United States. *U.S.News & World Report* consistently names Cleveland Clinic as one of the nation's best hospitals in its annual "America's Best Hospitals" survey. More than 3,000 full-time salaried physicians and researchers and 11,000 nurses represent 120 medical specialties and subspecialties. The Cleveland Clinic health system includes a main campus near downtown Cleveland, eight community hospitals, more than 75 Northern Ohio outpatient locations, including 16 full-service Family Health Centers, Cleveland Clinic Florida, the Lou Ruvo Center

for Brain Health in Las Vegas, Cleveland Clinic Canada, and, scheduled to begin seeing patients in 2015, Cleveland Clinic Abu Dhabi. In 2013, there were 5.5 million outpatient visits throughout the Cleveland Clinic health system and 157,000 hospital admissions. Patients came for treatment from every state and from more than 130 countries. Visit us at www.clevelandclinic.org. Follow us at www.twitter.com/ClevelandClinic.

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