Cancer Risk Associated with Lorcaserin — The FDA's Review of the CAMELLIA-TIMI 61 Trial

John Sharretts, M.D., Ovidiu Galescu, M.D., Shanti Gomatam, Ph.D., Eugenio Andraca-Carrera, Ph.D., Christian Hampp, Ph.D., and Lisa Yanoff, M.D.

On February 13, 2020, the Food and Drug Administration (FDA) announced that it had requested that the manufacturer of Belviq and Belviq XR (lorcaserin and extended-release lorcaserin) voluntarily withdraw the products from the U.S. market. The agency's request was based on its assessment of lorcaserin's benefits and risks after review of a large postmarketing clinical trial that revealed a higher frequency of cancer diagnoses in the lorcaserin group than in the placebo group. The manufacturer, Eisai, complied with the FDA's request. Lorcaserin, a selective agonist of the serotonin (5-hydroxytryptamine) 2C receptor, was approved in the United States on June 27, 2012, as an adjunct to diet and physical activity for long-term weight management for adults who are obese or overweight and have coexisting conditions.

Obesity increases the risk of life-threatening diseases, including type 2 diabetes, cardiovascular disease, and cancer, and contributes to an estimated 300,000 U.S. deaths per year.[1] Weight reduction is associated with improvements in cardiovascular and metabolic parameters such as blood pressure, lipid levels, and insulin sensitivity; guidelines generally define clinically important weight loss as reduction in body weight of at least 5%.[2] Drugs indicated for weight management have generally been approved on the basis of their effects on weight, but clinical trials have not demonstrated improvements in survival or cardiovascular outcomes in patients who are obese or overweight.

The FDA did not approve the original marketing application for lorcaserin, submitted in December 2009, in part because nonclinical carcinogenicity studies revealed an increased incidence of several tumor types in rats exposed to the drug. In December 2011, Arena Pharmaceuticals, the original applicant, submitted additional nonclinical and clinical data addressing, among other issues, the relevance to humans of the findings in rats. In May 2012, an FDA public advisory committee voted 18 to 4 in favor of approval.[3]

In the clinical trials, lorcaserin met the regulatory standard for effectiveness: 47% of patients randomly assigned to the lorcaserin group achieved at least a 5% weight reduction after 1 year, as compared with 23% of those assigned to the placebo group. Median placebo-adjusted weight loss was approximately 3% of initial weight. No cancer-related safety signal emerged in 1-year trials involving more than 2400 patients treated with lorcaserin.[4]

As a condition of approval, the FDA required Arena to conduct a postmarketing study focused on cardiovascular safety. The FDA has required cardiovascular-safety studies for the new weight-management drugs since the withdrawal of sibutramine in 2010. The randomized, double-blind, placebo-controlled CAMELLIA-TIMI 61 trial, conducted from 2014 through 2018, evaluated lorcaserin's effect on the incidence of major adverse cardiovascular events (MACE) in 12,000 patients randomly assigned to lorcaserin or placebo in a 1:1 ratio. The trial was not powered for cancer end points. The median follow-up was 3.3 years. Among patients assigned to a treatment group, 96% completed the trial and 62% remained on their assigned treatment. These rates were similar between treatment groups. The trial met the primary safety objective to rule out a hazard ratio for MACE greater than 1.4 for lorcaserin as compared with placebo.[5] The published report identified no safety signal related to cancer.

The FDA's initial safety analyses of the CAMELLIA study report identified a potential signal of increased cancers and cancer-related mortality. In contrast to the published study, when assessing cancer incidence, the FDA considered all postrandomization adverse events, not just "on treatment" events (those that occurred within 30 days after drug discontinuation).[5] Including all postrandomization events in safety analyses limits the effect of attrition bias and permits consideration of long-latency outcomes that can occur after treatment discontinuation.

Full review required accurately identifying cancer diagnoses and related deaths. As is typical for large cardiovascular-outcomes tri-

als, no specific methods had been used to collect data on cancer-related adverse events. The FDA's review process involved identifying, whenever possible, the cause of death from written case summaries, pathology reports, or other data sources when the cause was classified in the company's database as undetermined, and assessing nonspecific diagnoses, such as adrenal neoplasm or renal tumor, which could reflect benign or malignant tumors. In some instances, it was unclear whether multiple adverse-event reports for a single patient reflected one cancer case (an initial cancer and metastatic disease) or more than one primary cancer. The FDA therefore requested additional information from the company during the review process.

Demographic characteristics and clinical covariates of interest, such as rates of smoking and prior cancer diagnoses, were balanced between the treatment groups at baseline and throughout the study. From 2000 reports of neoplasms, the FDA identified 990 cancer diagnoses in 885 patients. In the lorcaserin group, there were more total cancers, more patients with cancer, more cancer deaths, more patients with multiple primary tumors, and more patients with metastatic disease than in the placebo group (Table 1). Overall, 7.7% of participants in the lorcaserin group and 7.1% in the placebo group were diagnosed with cancer. The proportions of participants in each group who died from cancer were 0.9% and 0.6%, respectively.

Table 2 summarizes cancer diagnoses by type. Rates were notably higher in the lorcaserin group than in the placebo group for colorectal cancer, pancreatic cancer, and lung cancer. Overall, incidence was higher in the placebo group for 5 cancer types and higher in the lorcaserin group for 13 cancer types. The overall rate ratio (for lorcaserin vs. placebo) for any cancer was 1.09 (95% confidence interval [CI], 0.96 to 1.24). The rate ratio for malignant neoplasms, excluding common skin cancers, was

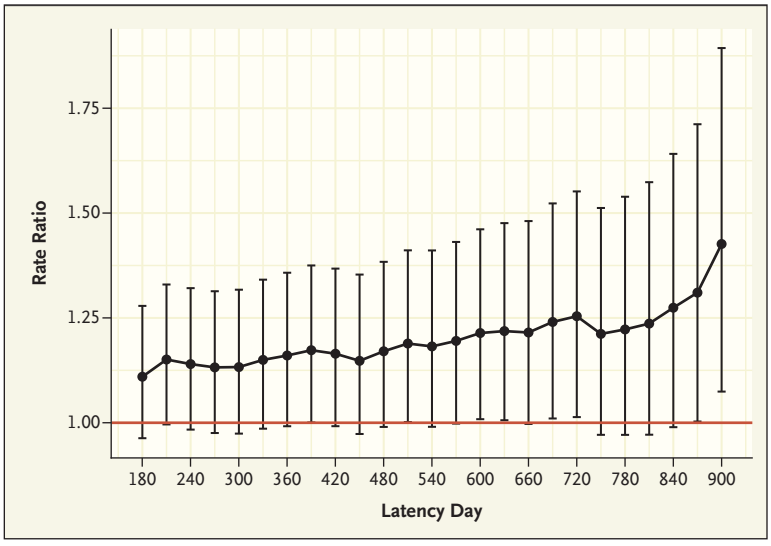
Table 1. Number of Cancers by Treatment Group in the CAMELLIA-TIMI 61 Trial, Full Analysis Set.*

Variable	Lorcaserin (N = 6000)	Placebo (N = 6000)	Total (N = 12,000)
Cancers	520	470	990
Patients with cancers	462	423	885
Deaths from cancer	52	33	85
Patients with multiple primary lesions	20	8	28
Metastases	34	19	53

* Some patients had multiple cancers or multiple metastases.

Table 2. Number of Cancers by Type and Treatment Group, Full Analysis Set.

Cancer Type	Lorcaserin (N = 6000)	Placebo (N = 6000)	Total (N = 12,000)
Skin neoplasms	223	222	445
Malignant melanoma	29	25	54
Prostate neoplasms	61	70	131
Gastrointestinal neoplasms	58	30	88
Colorectal cancer	26	14	40
Pancreatic cancer	16	2	18
Respiratory and mediastinal neoplasms	45	28	73
Lung cancer	40	25	65
Breast neoplasms	28	27	55
Renal and urinary tract neoplasms	23	30	53
Bladder cancer	7	13	20
Female reproductive neoplasms	10	18	28
Endometrial cancer	6	13	19
Lymphomas	12	13	25
Miscellaneous cancers	11	8	19
Leukemias	12	6	18
Hepatobiliary neoplasms	10	4	14
Endocrine neoplasms	7	6	13
Nervous system neoplasms	7	3	10
Plasma-cell neoplasms	7	1	8
Soft-tissue neoplasms	2	1	3
Ocular neoplasms	2	1	3
Skeletal neoplasms	1	2	3
Mesotheliomas	1	0	1
All	520	470	990



Cancer Rate Ratios by Latency.

For each latency day, the graph shows the rate ratio for all cancers observed after that study day for lorcaserin versus placebo. I bars are 95% confidence intervals.

1.16 (95% CI, 0.98 to 1.36). Estimates of rate ratios and hazard ratios were similar. Because of the lack of systematic, prospective cancer surveillance, however, dates of many cancer diagnoses were unknown, making measures based on time-to-event analyses less interpretable.

Because it's unlikely that drug-related cancers would manifest quickly, the FDA analyzed cancer rates for latency periods in 60-day intervals after randomization (see graph). The rate for each period includes events reported from a specific latency day forward. The number of patients with a new cancer diagnosis was similar in the lorcaserin (76) and placebo (77) groups within the first 180 days. For periods ranging from 180 to 900 days (approximately 6 months to 2.5 years) after randomization, point estimates for cancer rate ratios were consistently greater than 1.0, in keeping with a drug effect manifested after a latency period. Among cancers that occurred more frequently in the placebo group, imbalances attenuated (for renal and urinary cancers) or disappeared (for female reproductive cancers) over time.

The cancer-related safety signal from nonclinical studies supports the plausibility of an excess cancer risk from lorcaserin, and the consistency of cancer findings in CAMELLIA-TIMI 61 and the robustness of sensitivity analyses further support a causative effect. The increased risk of various cancer types associated with lorcaserin in the clinical study reflects the pattern seen in nonclinical studies. In keeping with a long-latency safety signal, cancer risk was elevated among patients in the lorcaserin group for all latency periods beyond 180 days. The higher incidence of cancer-related death in the lorcaserin group is also troubling. Although we cannot exclude the possibility that the observed imbalances are due to chance, conducting another trial to confirm or refute the signal isn't feasible.

The FDA weighed the evidence of excess cancer risk associated with lorcaserin use against the drug's benefits. The agency recognizes the importance of weight-loss therapies, but the magnitude of clinical benefit associated with modest weight reduction is uncertain, and this benefit may manifest only after years of sustained weight loss. Cancer risk may also be higher among patients using lorcaserin over the long term. We recognize that the observed excess cancer risk in the trial was not large. Balancing the clinical importance of cancer and the difficulty of mitigating this risk against the uncertain clinical benefit of lorcaserin, however, we conclude that the therapy's benefits do not outweigh the risks for any identifiable patient population.

Disclosure forms provided by the authors are available at NEJM.org.

From the Food and Drug Administration, Silver Spring, MD.

1. The Surgeon General's call to action to prevent and decrease overweight and obesity. Rockville, MD: Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001 (https://www.ncbi.nlm.nih.gov/books/NBK44210/#A13).
2. Blackburn G. Effect of degree of weight loss on health benefits. Obes Res 1995;3:Suppl 2:211s-216s.
3. Food and Drug Administration. Summary minutes of the Endocrinologic and Metabolic Drugs Advisory Committee meeting. May 10, 2012 (http://wayback.archive-it.org/7993/20170113053036/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM309521.pdf).
4. Colman E, Golden J, Roberts M, Egan A, Weaver J, Rosebraugh C. The FDA's assessment of two drugs for chronic weight management. N Engl J Med 2012;367:1577-9.
5. Bohula EA, Wiviott SD, McGuire DK, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. N Engl J Med 2018;379:1107-17.

DOI: 10.1056/NEJMp2003873