Fate of Dual-Action Diabetes Drug in Limbo

BY MIRIAM E. TUCKER
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It would take about 5 years to complete a trial to satisfy the Food and Drug Administration's concerns about the cardiovascular safety of the investigational diabetes drug muraglitazar, according to a statement issued by Bristol-Myers Squibb.

The company, which manufactures the dual-acting agent under the trade name Pargluva, has begun discussions with its marketing partner Merck to terminate their collaborative agreement.

At press time, Bristol-Myers Squibb was discussing a range of options with the FDA, including possible termination of muraglitazar's development.

The announcement came just 9 days after the FDA granted an "approval" letter for the combination peroxisome proliferator-activated receptor α and γ activator, in which the agency had also requested more data regarding the drug's safety profile.

Later that same week, an article by Steven E. Nissen, M.D., of the Cleveland Clinic Foundation and his associates outlined increased cardiovascular event rates among muraglitazar-treated patients in phase II and III clinical trials of the drug.

The primary outcome measure occurred in 1.47% of treated patients vs. 0.67% of controls who received either placebo or 30-mg pioglitazone.

The investigators recommended that the drug not be approved until its safety is documented in a dedicated cardiovascular (CV) events trial (JAMA 2005;294: [Epub doi:10.1001/jama.294.20.joc50147]).

Their analysis was based on data made public on the Food and Drug Administration's Web site on Sept. 8 and discussed in detail at a Sept. 9 meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee. At that time, the panel voted to recommend approval of the drug as monotherapy and in combination with metformin, but not with sulfonylureas (FAMILY PRACTICE NEWS, Oct. 1, 2005, p. 10).

For their analysis, Dr. Nissen, Eric J. Topol, M.D., and Kathy Wolski combined data from five clinical trials, limiting the analysis to diabetic patients given the 2.5-mg and 5-mg doses of muraglitazar for which the companies are seeking licensure.

The primary outcome measure—all-cause mortality, nonfatal MI, or nonfatal stroke—occurred in 1.47% (35) of 2,374 subjects versus 0.67% (9) of 1,351 control patients who received either placebo or 30-mg pioglitazone, for a relative risk (RR) of 2.23.

Substituting CV death for all-cause mortality, the combined end points occurred in 1.14% (27) of 2,374 muraglitazar-treated patients, versus 0.52% (7) of 1,351 controls (RR 2.21). When heart failure and transient ischemic attacks were added to the composite, the incidence rates were 2.11% for muraglitazar and 0.81% for controls (RR 2.62).

Relative risk was consistently higher for individual components of the primary end point in the muraglitazar-treated group versus controls. Rates ranged from 2.14 for fatal or nonfatal MI to 7.43 for adjudicated heart failure. However, the number of events was small and differences for individual components of the primary outcome measure were not statistically significant, the investigators reported.

These and other safety data were analyzed and presented in detail at the Sept. 9 hearing by Julie Golden, M.D., a medical officer in the FDA's Division of Metabolic and Endocrine Drug Products. She, too, had noted that the percentage of CV events in the muraglitazar groups was approximately twice that of comparators. However, when broken down by monotherapy (two studies) and combination therapy (three studies), the imbalance of CV adverse events was seen only in the combination studies, and in fact was mostly driven by one study in which muraglitazar or placebo was added to glyburide (11 vs. 0 events). At least two of these subjects had evidence of other causes for the event.

CV deaths occurred in 9 of 3,226 muraglitazar subjects, 1 of 591 placebo subjects, and none of 823 on pioglitazone, giving an overall death rate 1.5 times higher with muraglitazar than with the comparators. Overall deaths occurred in 19, 1, and 2 patients, respectively; the incidence was 2.5-3 times higher with muraglitazar, Dr. Golden said. However, "the rates in the comparator groups, based on exceedingly small numbers of events, are highly unstable, meaning that even one additional death in either group could impact the result," she said at the hearing.

Eight of the CV deaths were in subjects taking 2.5 or 5 mg of muraglitazar, and six were subjects from a single study in which 5-mg muraglitazar or 30-mg pioglitazone was added to metformin.

In that study, which had about 580 subjects per treatment arm, there was no marked difference in overall CV events. Moreover, no clear clinical or pathologic pattern could be identified for either deaths or CV events, and the pooled studies did not show a dose-response pattern, she noted.

For its part, Bristol-Myers Squibb had analyzed the data taking into account the duration of drug exposure. For CV events, there were 28.2/1,000 patient-years on muraglitazar, compared with 33.4/1,000 for placebo and 19.7/1,000 with pioglitazone—a nonsignificant difference, Rene Belder, M.D., vice president of global clinical research at Bristol-Myers Squibb, said at the hearing.

Similarly, for the CV deaths, the rates were 3/1,000 patient-years for placebo, compared with 2.6/1,000 with muraglitazar. "By taking into account the difference in patient exposure, the apparent imbalance in cardiovascular death is reversed," Dr. Belder said.

But that analysis was challenged by James M. Brophy, M.D. in an editorial accompanying the Dr. Nissen's report. He pointed out that the company's analysis included 495 patients who had received subtherapeutic doses of 2.5 mg or less in whom there were no CV events, thereby diluting the risk estimate. When the rates were recalculated to include only those patients receiving the proposed marketed doses of 2.5 or 5 mg, the muraglitazar group shows a 20% increase in events, compared with placebo, and a 67% increase, compared with the combined pioglitazone/placebo control group, said Dr. Brophy, of McGill University, Montreal, who also listed several other flaws in the analysis. ■

Acarbose Reduces MI Risk in Type 2 Diabetes By Nearly Two-Thirds in Metaanalysis

BY BRUCE JANCIN
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VANCOUVER, B.C. — Acarbose markedly reduces the risk of cardiovascular events in patients with type 2 diabetes, according to a metaanalysis of seven randomized trials, Dieter Petzinna, M.D., said at a meeting sponsored by the International Academy of Cardiology.

The trials, each double-blind, placebo-controlled, and of at least 1 year's duration, included 2,180 patients with type 2 diabetes mellitus. Roughly 60% of participants were on background intensive cardiovascular risk reduction therapy, including statins, ACE inhibitors, and antiplatelet agents.

The primary end point in the metaanalysis was the occurrence of any newly diagnosed cardiovascular event. The rate was 6.1% in the acarbose patients and 9.4% in the placebo patients, for a highly significant 35% relative risk reduction favoring acarbose, said Dr. Petzinna of Bayer HealthCare, Wuppertal, Germany.

The reduction in overall cardiovascular events was driven largely by a 64% decrease in the relative risk of MI. The incidence was 2.0% in the placebo arm and 0.7% in patients assigned to acarbose.

There was also a consistent but statistically nonsignificant trend for lower rates of new-onset heart failure, angina, stroke, peripheral vascular disease, revascularization procedures, and cardiovascular death in the acarbose group.

Treatment with acarbose significantly lowered triglyceride levels, body weight, and systolic blood pressure. It also significantly improved glycemic control. These metabolic benefits, as well as the reduction in cardiovascular events, are attributable to the drug's ability to curb postprandial blood glucose excursions, which are known to trigger a cascade of atherogenic events, he said. ■