

Avandia: The RECORD Trial

OVERVIEW

The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) was designed to compare cardiovascular outcomes of patients on Avandia (rosiglitazone) added to metformin or sulfonylurea to those on metformin and sulfonylurea.

The primary endpoint of the study, which was sponsored by GlaxoSmithKline and launched in 2001, evaluated the number of patients who died or were hospitalized as a result of cardiovascular events.

DATA

A total of 2,220 patients were randomized into the Avandia arm and 2,227 patients were randomized to receive metformin and sulfonylurea. Patients were followed for an average of 5.5 years. This makes RECORD the largest and longest prospective clinical trial examining Avandia's cardiovascular safety.

Primary Endpoint (cardiovascular death or cardiovascular hospitalization):

- 321 events (14.5%) in the Avandia group, 323 (14.5%) in the control group
- Hazard ratio=0.99 (non-inferiority $p=0.02$; 95% confidence interval=0.85 to 1.16)

Secondary Safety Endpoints:

- **All-Cause Death:** 136 (6.1%) in the Avandia group, 157 (7%) in the control group (non-significant)
 - Hazard ratio=0.86 (95 percent confidence interval=0.68 to 1.08)
- **Cardiovascular Death:** 60 (2.7%) in the Avandia group, 71 (3.2%) in the control group (non-significant)
 - Hazard ratio=0.84 (95 percent confidence interval=0.59 to 1.18)
- **MACE:** 154 (6.9%) in the Avandia group, 165 (7.4%) in the control group (non-significant)
 - Hazard ratio=0.93 (95 percent confidence interval=0.74 to 1.15)
- **Acute Myocardial Infarction (heart attack):** 64 (2.9%) in the Avandia group, 56 (2.5%) in the control group (non-significant)
 - Hazard ratio=1.14 (95 percent confidence interval=0.80 to 1.63)
- **Stroke:** 46 (2.1%) in the Avandia group, 63 (2.8%) in the control group (non-significant)
 - Hazard ratio=0.72 (95 percent confidence interval=0.49 to 1.06)
- **Congestive Heart Failure:** 61 (2.7%) in the Avandia group, 29 (1.3%) in the control group (significant)
 - Hazard ratio=2.10 (95 percent confidence interval=1.35 to 3.27)
- **Glycemic Control:**
 - Statistically significantly lower hemoglobin A1c levels at study's end

Other Findings:

Fracture: The group randomized to Avandia had increased bone fracture rates, mostly in the bones of the arm, hands, lower leg and feet, and predominantly in women.

Malignancy: RECORD showed no evidence of an increase in malignancies. There were fewer events of pancreatic cancer in patients taking Avandia although the numbers were small.

BURDEN OF DISEASE:

More than 18 million Americans have type 2 diabetes, according to the Centers for Disease Control and Prevention. Diabetes is the 7th largest cause of death in United States, and the disease contributes to more than 200,000 deaths annually. Diabetes is responsible for more than \$100 billion in direct medical costs each year.

Type 2 diabetes, which accounts for about 90 to 95 percent of diagnosed diabetes cases, is a chronic, progressive and serious disease that occurs either when the body does not produce enough insulin or when the body does not respond properly to its natural insulin. As a result, sugar builds up in the blood and over time, high levels of blood sugar can lead to a variety of other serious health problems including: heart disease, stroke, eye damage, kidney failure and foot problems that lead to amputations.

Important safety information for *Avandia*® (rosiglitazone maleate)

Prescription AVANDIA, along with diet and exercise, helps improve blood sugar control in adults with type 2 diabetes. Taking AVANDIA with insulin or nitrates is not recommended.

AVANDIA can cause or worsen heart failure. If you have severe heart failure (very poor pumping ability of the heart) you cannot be started on AVANDIA. AVANDIA is also not recommended if you have heart failure with symptoms (such as shortness of breath or swelling) even if these symptoms are not severe.

AVANDIA may increase your risk of other heart problems that occur when there is reduced blood flow to the heart, such as chest pain (angina) or heart attack (myocardial infarction). This risk appeared higher in patients taking medicines called nitrates or insulin.

If you have chest pain or a feeling of chest pressure, you should seek immediate medical attention, regardless of what diabetes medicines you are taking. If you take AVANDIA, tell your doctor right away if you: have swollen legs or ankles, a rapid increase in weight or difficulty breathing, or unusual tiredness; experience changes in vision; become pregnant.

Before taking AVANDIA, review your medical history and tell your doctor if you:

- Have heart failure or other heart problems, or are on any medicines for high blood pressure, high cholesterol or heart failure, or for prevention of heart disease or stroke.
- Take insulin or nitrate medicines.
- Have a type of diabetic eye disease called macular edema.
- Have liver problems or had liver problems while taking REZULIN® (troglitazone).
- Are pregnant or planning to become pregnant.
- Are breastfeeding or planning to breastfeed.

Women taking AVANDIA should know that AVANDIA may increase the risk of pregnancy. More fractures have been observed in women taking AVANDIA. Other possible side effects of AVANDIA include anemia and hypoglycaemia. Your doctor should do blood tests to check your liver before you start AVANDIA and during treatment as needed.

For more information about AVANDIA, please see Medication Guide or full Prescribing Information at www.AVANDIA.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.