Press Release

GlaxoSmithKline

**GSK's ROSIGLITAZONE MALEATE (AVANDIA®) REDUCES RISK OF PROGRESSION FROM PRE-DIABETES TO TYPE 2 DIABETES BY 62 PERCENT IN LARGEST-EVER DIABETES PREVENTION TRIAL[1]**

***Pre-diabetes Estimated to Affect 300 Million People Globally[2]***

**New Delhi – 18 September, 2006 –** In the largest diabetes-prevention trial ever conducted, Avandia® (rosiglitazone maleate) reduced the risk of developing type 2 diabetes by 62 percent relative to placebo among people at high risk of developing type 2 diabetes. This highly statistically significant reduction of 62 percent ($p<0.0001$) was additive to standard counselling on healthy eating and exercise. The results of the landmark study was reported both in *The Lancet* and at the 42nd annual meeting of the European Association for the Study of Diabetes (EASD) on Friday night.[1]

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial evaluated the likelihood of progression to type 2 diabetes over a three-year median follow-up period among 5,269 people with a condition known as "pre-diabetes."[1] In pre-diabetes, blood sugar levels are higher than normal, but not yet high enough for a diagnosis of type 2 diabetes.[3] Patients included in the study were randomized to rosiglitazone (8 mg daily) or placebo and to ramipril (15 mg daily) or placebo and were assessed every six months for three to five years to determine if rosiglitazone or ramipril can reduce the risk of developing type 2 diabetes in pre-diabetic patients, when added to healthy eating and exercise counseling.[1] The DREAM study was not designed as a direct comparison between rosiglitazone and ramipril. Results from the ramipril arm of the study, which increased regression to normoglycemia but did not reduce the risk of diabetes or death, are also being reported at EASD and published separately in the *New England Journal of Medicine*.[4]

In this study, designed and conducted by the Population Health Research Institute at McMaster University, 10.6 percent of people receiving rosiglitazone progressed to type 2 diabetes versus 25 percent of people treated with placebo.[1] In the composite primary endpoint of development of diabetes or death from any cause, rosiglitazone demonstrated a 60 percent risk reduction relative to placebo ($p<0.0001$).[1]

"The DREAM findings are particularly significant as we are in the midst of an epidemic of type 2 diabetes with global implications. It is also noteworthy that the damaging complications of type 2 diabetes can often precede the diagnosis of this condition by several years," said Dr. Bernard Zinman, DREAM Steering Committee Member, director

of the Diabetes Centre, Mount Sinai Hospital and professor of medicine, University of Toronto, Canada. "By demonstrating that rosiglitazone significantly reduced the risk of developing type 2 diabetes, these data provide important evidence that it may be possible to alter the course of rising blood sugar levels and its consequences."

Over the three-year median follow-up period of the trial, 51 percent of the people receiving rosiglitazone returned to normal blood sugar levels compared to 30 percent of people receiving placebo; thus, people taking rosiglitazone were about 70 percent ($p<0.0001$) more likely than those taking placebo to return to normal blood sugar levels. As might be expected, people in the placebo group with higher Body Mass Index (BMI), an indicator of obesity, were more likely than those with lower BMI to progress to diabetes. However, the risk of developing diabetes did not increase with BMI in the group randomized to rosiglitazone. These findings suggest that rosiglitazone may reduce the increased risk of developing diabetes that is attributable to obesity.[1]

“The DREAM study is the largest diabetes prevention trial conducted to date, involving over 5000 patients at high risk of developing diabetes (those with impaired fasting glucose or impaired glucose tolerance). This study provides the first evidence that rosiglitazone can reduce the risk of progression from pre-diabetes to Type 2 diabetes. In my opinion, with such impressive results, rosiglitazone has the potential to treat “dysglycemia”, the way statins treat “dyslipidemia”. Regulatory approvals will be required before rosiglitazone can be used to manage pre-diabetes,” said Dr. Sadhna Joglekar, Vice President, Medical & Clinical Research, GlaxoSmithKline Pharmaceuticals Ltd.

In the study, rosiglitazone was generally well tolerated. There was no significant difference between the rosiglitazone and placebo groups in withdrawal from study medication before study end, or in the secondary composite endpoint of cardiovascular (CV) events that included myocardial infarction, stroke, CV death, confirmed heart failure, new angina and revascularization procedures (2.9 percent in the rosiglitazone group [75 events]; 2.1 percent in the placebo group [55 events], $p=0.15$). There was a low number of deaths in the trial and no significant difference between the two groups (1.1 percent in the rosiglitazone group [30 deaths] versus 1.3 percent in the placebo group [33 deaths], $p=0.7$). The most commonly reported CV event in the study was revascularization procedures. More events of confirmed heart failure were reported in people who received rosiglitazone as compared to those who received placebo (0.5 percent in people randomized to rosiglitazone [14 events] versus 0.1 percent in people randomized to placebo [2 events], $p=0.01$). Data presented by McMaster University showed that all cases of heart failure were treated effectively during the trial. Information about the potential for heart failure can be found in rosiglitazone prescribing

information. At the conclusion of the study, mean bodyweight in the rosiglitazone group had increased slightly (2.2 kg) more than the placebo group.[1,5]

Rosiglitazone belongs to the thiazolidinedione class of drugs and is an approved treatment for type 2 diabetes that improves blood sugar control, enabling people to reach recommended blood sugar levels. No agent including rosiglitazone is currently approved for the treatment of pre-diabetes.[5]

## Notes to Editors

**Rosiglitazone maleate is marketed as Windia by GSK India**

**About the DREAM Study**

DREAM is an international, multi-center, randomized, double-blind, 2x2 factorial trial involving 5,269 patients from 21 countries with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), also known as pre-diabetes, who are therefore at high risk of developing type 2 diabetes. The DREAM study was conducted by the Population Health Research Institute at the Michael G. DeGroote School of Medicine at McMaster University and Hamilton Health Sciences in Hamilton, Ontario. DREAM was funded by a peer-reviewed grant from the Canadian Institutes of Health Research (CIHR) via the CIHR/Rx&D Collaborative Research Program as well as by GlaxoSmithKline, sanofi-aventis and King Pharmaceuticals.[1]

**About Pre-diabetes and Type 2 Diabetes**

The International Diabetes Federation (IDF) estimates a potential increase in pre-diabetes from 300 million people worldwide in 2003 to approximately 500 million by 2025.[2] While not everyone with pre-diabetes develops type 2 diabetes, large clinical outcomes trials have demonstrated that without intervention between 29 and 55 percent of people with pre-diabetes develop type 2 diabetes over the course of three years.[6-8] As type 2 diabetes naturally progresses, the combined effects of core defects of the disease, namely insulin resistance and beta-cell dysfunction, can make it increasingly difficult for physicians to help patients control blood sugar levels.[9]

Pre-diabetes is considered a key stage in the development of type 2 diabetes – a chronic, progressive illness often linked to premature death that affects approximately 230 million individuals worldwide and is expected to affect 350 million people globally by 2025.[3,10] Complications from diabetes can include eye disease, kidney disease, nerve damage, heart disease, stroke and peripheral vascular disease.[11-14] In fact, more than three million people die from diabetes-related causes each year – one death every 10 seconds.[15]

**Important Information for Windia (rosiglitazone maleate)**

Rosiglitazone, along with diet and exercise, helps improve blood sugar control. It may be taken alone by diabetic patients who cannot take metformin, in combination with metformin or a sulphonylurea, or with both metformin and a sulphonylurea.

Rosiglitazone is also contraindicated for patients with severe cardiac failure and may cause fluid retention. Patients with sudden rapid increase in weight, increasing edema or shortness of breath should consult their doctor.

Patients with liver impairment should not take rosiglitazone. Blood tests should be used to check for liver problems before starting treatment, and periodically after that according to clinical appropriateness.

Caution is advised when using rosiglitazone in patients with significant renal impairment.

When used in combination therapy, particularly with sulphonylurea, hypoglycaemia may occur. Dose reduction of concomitant diabetes therapy may be required.

Rosiglitazone may increase the likelihood of pregnancy. Where appropriate, patients should seek contraceptive advice from their doctor prior to commencing therapy.

Rosiglitazone is contraindicated while breast feeding.

For full prescribing information please consult the current rosiglitazone summary of product characteristics.

**About GlaxoSmithKline**

GlaxoSmithKline – one of the world's leading research-based pharmaceutical and healthcare companies – is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For company information, visit http://www.gsk.com.

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