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Roche to Commence Phase III Trials with Innovative Treatment Designed to Lower Cardiovascular Risk in Diabetes Patients with Recent Heart Attack

-- *SYNCHRONY Study Published in The Lancet Supports Cardio-Protective Potential of Aloglitazar* --

Roche today announced it will start Phase III clinical investigations for aloglitazar, its innovative PPAR co-agonist R1439 which is uniquely designed to reduce cardiovascular morbidity and mortality in high risk patients with type 2 diabetes. This decision is supported by data from the Phase II SYNCHRONY study published today in *The Lancet*¹ and announced at the American Diabetes Association meeting in New Orleans. The Phase III program is anticipated to start in the second half of 2009.

SYNCHRONY, a placebo-controlled dose ranging study in type 2 diabetes patients, showed that aloglitazar had a balanced synergistic effect on both lipid and glucose control with a good safety and tolerability profile in patients with type 2 diabetes.

Cardiovascular disease is currently the leading cause of death among those with type 2 diabetes, accounting for half of all deaths.² Despite guidelines recommending that cardiovascular risk in this patient group should be reduced by controlling factors such as dyslipidemia, blood pressure, body weight and hyperglycemia,^{3, 4} the majority of patients still do not achieve their treatment goals leaving them vulnerable to both initial and residual cardiovascular events.^{3, 5} Significantly, one in ten patients with an acute myocardial infarction died within a year.⁶

"Roche is confident that aloglitazar has the potential to reduce cardiovascular morbidity and mortality in this high-risk patient group and is therefore committed to pursuing its rapid development," said Jean-Jacques Garaud, Global Head of Development Pharmaceuticals Division of Roche.

The focused Phase III outcomes trial will investigate whether once daily 150 µg aloglitazar reduces the incidence of cardiovascular mortality, non-fatal myocardial infarction and stroke in patients with type 2 diabetes. The approach in this selected high-risk patient population will be unique as no drug has been demonstrated to reduce cardiovascular risk in type 2 diabetes patients following an ACS event.

Professor Robert Henry, SYNCHRONY Clinical Investigator and Chief VA Endocrinology & Metabolism and Professor of Medicine in Residence at the University of California at San Diego, commented: "The favorable balance in the safety and efficacy profile of aleglitazar seen in the SYNCHRONY study represents encouraging short-term clinical data for this agent and provides good evidence to enter Phase III investigation."

With the decision to move into Phase III, aleglitazar is Roche's third Phase III clinical trial program in the area of metabolism. The new Phase III study is a cardiovascular outcomes trial designed to assess the potential of once-daily 150 µg aleglitazar to reduce cardiovascular mortality, non-fatal myocardial infarction and stroke in type 2 diabetes patients with a recent ACS.

About the SYNCHRONY Study

SYNCHRONY was a multicenter, randomised, double-blind, placebo-controlled dose ranging study among 332 type 2 diabetes patients (either drug-naïve or pre-treated with ≤ 2 oral agents). Designed to determine the glucose-lowering and lipid-modifying effects, and safety profile of aleglitazar, the study confirmed the favorable safety and efficacy profile of the once daily 150 µg aleglitazar dose and supported commencement of the Phase III clinical investigation.

Patients underwent a single-blind 4- to 5-week placebo run-in period, then were randomized to receive 16 weeks treatment with either aleglitazar at one of four once daily doses (50, 150, 300 or 600 µg), placebo or 45 mg pioglitazone.

The primary endpoint of dose-dependent reductions from baseline HbA1c versus placebo was met and a range of responses observed from -0.36% (95% CI: 0.00 to -0.70, P=0.048) with 50 µg aleglitazar, to -1.35% (95% CI: -0.99 to -1.70, p<0.0001) with the 600 µg dose. Notably, the once daily 150 µg aleglitazar dose (currently in clinical trials) demonstrated numerically comparable reductions from baseline HbA1c to those observed with pioglitazone (-0.85%, 95% CI: -0.50 to -1.20, P<0.0001 vs. -0.71%, 95% CI: -0.36 to -1.06, P<0.0001).

The study's secondary clinical endpoints were changed from baseline in fasting plasma glucose and lipid profiles. Notably, significant dose-dependent reductions versus placebo were observed with aleglitazar for fasting plasma glucose (-1.0 mmol/L with 50 µg to -3.3 mmol/L with 600 µg), triglycerides (-27.8% with 50 µg to -51.6% with 600 µg), and LDL-C (-9.1% with 50 µg to -25.9% with 600 µg), as well as a significant dose-dependent increase in HDL-C (8.2% with 50 µg to 22.9% with 300 µg). Importantly, treatment with the once daily 150 µg aleglitazar dose produced a numerically superior effect on triglycerides, HDL-C, and LDL-C when compared with 45 mg pioglitazone.

Known PPAR- α (creatinine increase) and γ -related effects (edema, haemodilution, and weight gain) were seen in a dose-dependent manner of which the incidence of edema for the 150 µg aleglitazar dose was similar to placebo and numerically less than with pioglitazone, and body weight gain was numerically less than with pioglitazone.

About Aleglitazar

Aleglitazar is an innovative treatment designed to reduce the incidence and

impact of cardiovascular mortality, non-fatal myocardial infarction and stroke in patients with a recent ACS and type 2 diabetes.

It is a rationally designed molecule providing balanced dual PPAR α/β activation. Specifically, it combines the improvements in peripheral insulin sensitivity (and therefore glycemic control) associated with PPAR β activation, with improved management of dyslipidemia, which is commonly associated with PPAR α activation.

About Diabetes

Diabetes is a disease characterised by excess blood glucose due to a deficiency in insulin availability and/or resistance to its action. Type 2 diabetes accounts for 90 percent of all diabetes cases worldwide. Complications from diabetes, such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness, are resulting in increasing disability, reduced life expectancy and enormous health cost for virtually every society. According to current estimates by the World Health Organization, more than 180 million people worldwide have diabetes. This number is likely to more than double by 2030.

About Roche

Hoffmann-La Roche Inc. (Roche), based in Nutley, N.J., is the U.S. pharmaceuticals headquarters of the Roche Group, one of the world's leading research-oriented healthcare groups with core businesses in pharmaceuticals and diagnostics. For more than 100 years in the U.S., Roche has been committed to developing innovative products and services that address prevention, diagnosis and treatment of diseases, thus enhancing people's health and quality of life. For additional information about the U.S. pharmaceuticals business, visit our website <http://www.rocheusa.com>. Product and treatment information for U.S. healthcare professionals is available at www.RocheExchange.com.

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