Press Release

PIRAMAL'S NCE RESEARCH SHARED PRECLINICAL EFFICACY DATA FOR TWO PROMISING MOLECULES AT THE AMERICAN DIABETES ASSOCIATION'S 74TH SCIENTIFIC SESSIONS

Mumbai, June 18, 2014: Piramal Life Sciences - NCE Research, a division of Piramal Enterprises Ltd (PEL), made poster presentations for drugs in early clinical development for metabolic disorders in two different sessions of the 74th Scientific Session of the American Diabetes Association (ADA) in San Francisco, California, USA. The presentations covered Piramal's clinical stage GRP40 agonist, P11187 and Piramal's clinical stage DGAT1 inhibitor P7435.

P11187 (GPR40 agonist)

The P11187 presentation covered the preclinical pharmacological data in support of efficacy for a novel synthetic oral GPR40 partial agonist, P11187, which stimulates glucose-dependent insulin secretion.

The primary objective of the study was to evaluate the efficacy of P11187 to potentiate glucose-dependent insulin secretion. P11187 orally administered to both normal and diabetic mice and rats showed significant reduction in blood glucose levels. P11187 treatment in normal rats in the hyperglycemic clamp model results in considerable increase in glucose infusion rate and glucose-stimulated insulin secretion.

P11187 has been found to be a highly selective and potent partial agonist for these GPR40 receptors in humans, mice and rats. It is being developed for the management of Type II diabetes.

Overall, P11187 has demonstrated glucose-stimulated insulin secretion and anti-hyperglycemic potential in rodent models of type 2 diabetes with excellent safety profile. The drug is currently being tested in Phase I trial in the USA.

Dr. Owe Orwar, President – Piramal Life Sciences-NCE Research, stated, "P11187 is an intelligent oral anti-diabetic investigational drug that evokes insulin release in a glucose and Free Fatty Acid (FFA) dependent fashion. This means, the higher the glucose and free fatty acid concentration in the plasma, the better it may work. For glucose control, this has been corroborated by the Phase III study in type-II Diabetes mellitus with the investigational drug, Fasiligam (TAK-875), which was the leading molecule in the class until it failed due to hepatotoxicity in December 2013. We have done extensive work to de-risk our asset for this liability, and will shortly be initiating our Multiple Ascending Dose (MAD) portion of our Phase- I trial in type-II diabetics."

P7435 (DGAT1 inhibitor)

The P7435 presentation covered the preclinical data in support of efficacy for P7435, a novel, potent and selective, small molecule DGAT1 inhibitor in rodent models of hyperlipidemia and obesity. It also discussed the clinical results from a Phase I, randomized, double-blind, placebo-controlled study of single ascending doses (SAD) of P7435 in healthy male volunteers conducted in India.

The Phase I trial showed that P7435 was safe and well-tolerated when given in single doses from 10mg to 300mg to healthy male volunteers. The only adverse effect of the treatment seen was vomiting. The PK profile revealed that the increase in exposure from 10mg to 300mg of P7435 was dose-linear although less than dose-proportional.

In vivo data suggested that acute treatment with P7435 resulted in significant reduction in plasma triglyceride levels, and an increase in GLP-1 levels in the plasma along with sitagliptin. An overall reduction was observed in the body weight, food intake, cholesterol, epididymal fat pad weight, plasma glucose, plasma triglyceride, insulin, Steatorrhea and liver triglycerides of High Fat Diet (HFD) fed hamsters, ob/ob mice and SD rats when given a chronic treatment with P7435. On the whole, P7435 showed significant efficacy in rodent models of hyperlipidemia. The investigational drug is currently moving quickly through a Phase I trial in the US.

Dr. Owe Orwar, President – Piramal Life Sciences NCE Research, stated, "P7435 appears to be one of the safest DGAT1 inhibitors thus far, showing potent triglyceride-lowering potential. We are well on our way to concluding a Phase I in trial in the US the next few months and are looking forward to evaluating this molecule further in clinic and exploit its potential in hypertriglyceridemia, and combined dyslipidemia as well as in type 2 diabetes.

About Type 2 Diabetes Mellitus and Dyslipidemia:

Diabetes mellitus type 2 is a metabolic disorder that is characterized by hyperglycemia (high blood sugar) in the context of insulin resistance and relative lack of insulin. Type 2 diabetes makes up about 90% of cases of diabetes, with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. Type 2 diabetes is a chronic disorder wherein maintaining glycaemic control as diabetes progresses, is an ongoing problem as patients fear initiating new therapies that may increase the risk of side effects such as weight gain and hypoglycaemia chronic condition.

Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, the "bad" low-density lipoprotein (LDL) cholesterol and the triglyceride concentrations, and a decrease in the "good" high-density lipoprotein (HDL) cholesterol concentration in the blood. Dyslipidemia comes under consideration in many situations including diabetes, a common cause of lipidemia.

About GPR40 and DGAT:

GPR40 is a G-protein coupled receptor highly expressed in pancreatic beta cells of humans and rodents. It stimulates insulin-secretion when activated by a free fatty acid under elevated glucose concentrations in the blood.

Diacylglycerol acyltransferase (DGAT) is an enzyme catalyzes the final step of triglyceride formation from diacylglycerol and Acyl-CoA. A surplus accumulation of triglycerides in tissues and blood can lead to a range of medical conditions such as severe obesity, insulin resistance, hepatic steatosis, and cardiovascular disease. Therefore, inhibition of triglyceride synthesis has a strong therapeutic rational for treatment of such disorders. P7435 is a potent, selective oral DGAT1 inhibitor, aimed at fulfilling unmet medical needs in hypertriglyceridemia, and combined dyslipidemia.

About Piramal Enterprises Limited:

Piramal Enterprises Limited (PEL) is one of India's largest diversified companies, with a presence in pharmaceuticals, healthcare information management and financial services. PEL's consolidated revenues were ~$ 750 million in FY2014. In the pharmaceutical space, PEL is one of leading custom manufacturing player globally, has presence in the global critical care segment with a portfolio of inhalation and injectable anesthetics and its OTC business is ranked no. 7 in India. PEL is also engaged in drug discovery & research and has strong pipeline of development products. PEL's information management business, Decision Resources Group, is a leading provider of information based services to the healthcare industry. In the financial services space, PEL, through Piramal Fund Management, provides comprehensive financing solutions to real estate companies. Its Structured Investments Group provides mezzanine funding to corporates in various sectors, including infrastructure. PEL has also made long term equity investments in the Shriram Group, a leading financial conglomerate.

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