Biovitrum initiates Phase II study with its diabetes candidate drug BVT.3498

Stockholm, Sweden, 25 March 2003. Biovitrum today announced the initiation of a Phase II clinical trial of BVT.3498, its lead compound for type 2 diabetes. The primary endpoint of the study is improved glycaemia control. Safety, tolerability and several additional parameters related to the metabolic syndrome will be monitored as well. The placebo-controlled, double blind study will involve over 100 type 2 diabetes patients at centres in Finland and Sweden.

BVT.3498 is a proprietary compound discovered and developed by Biovitrum. It is a highly selective inhibitor of the enzyme 11betaHSD1, yielding reduced tissue levels of cortisol. The effectiveness of this novel concept has been demonstrated in several pre-clinical diabetes models. Phase I trials in 2002 involving 66 healthy volunteers showed very promising results including demonstrable effects on the target enzyme.

"BVT.3498 represents a novel method of treating type 2 diabetes, and we believe it may bring significant value to the treatment of this epidemic disease", says Terje Kalland, CSO at Biovitrum.

Unlike existing glucose-lowering drugs, BVT.3498 avoids the risk of hypoglycaemia during treatment and may also have positive effects on body composition, lipid profile, and other metabolic aberrations linked to insulin resistance.

Type 2-diabetes is a complex metabolic disorder in which genetic and environmental factors interact to disrupt the normal regulation of blood glucose levels. Whereas type 1-diabetes is characterized by a lack of insulin production, type 2 diabetes is usually associated with resistance to and lack of production of insulin.

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Notes to Editors:

Biovitrum is a biotech company active in the discovery and development of drugs to treat metabolic diseases, such as type 2 diabetes and obesity, and in the development of protein therapeutics, with metabolic diseases and oncology as targeted therapy areas. The company has a strong intellectual property and technology platform, with a number of compounds in pre-clinical and clinical development. Biovitrum is one of the largest biotech companies in Europe with more than 550 employees. Annual revenues, including royalties and contract service fees, finance the major part of the annual research budget.

11beta-HSD
Excess glucocorticoids such as cortisol produce visceral obesity and diabetes. 11beta-hydroxysteroid dehydrogenases (11beta-HSDs) are enzymes that play an important role in the interconversion of active glucocorticoids between its active and inactive forms. Two enzymes have been identified, 11beta-HSD1, and 11beta-HSD2. These 11beta-HSDs play a major role in the modulation of local cortisol levels and the access of active steroid to its receptors in the target tissues. Thereby, the 11beta-HSDs are also believed to have important roles in a number of common diseases, including obesity, type 2 diabetes and hypertension.

11beta-HSD2 is found primarily in tissues such as kidney, sweat glands and salivary glands. 11beta-HSD2 converts active glucocorticoids into inactive steroids and appears to act as an effective barrier to excess cortisol across a wide range of cortisol concentrations. However, in studies where the 11beta-HSD2-enzyme activity has been inhibited with liquorice this results in an excess of steroids that cause hypokalemia and hypertension.

11beta-HSD1 is present in tissues of importance for metabolism and insulin sensitivity such as the liver and the adipose tissue. Its activity can be altered by factors such as glucocorticoids, stress, sex steroids, growth hormone, cytokines and PPAR agonists. Under normal conditions, 11beta-HSD1 is believed to amplify local glucocorticoid concentrations in target tissues, in particular when the circulating plasma cortisol levels are low. However, in obese subjects the levels of 11beta-HSD1 are usually markedly increased, at least in adipose tissue. This observation is of importance in the light of a recently published rodent study in Science, demonstrating that animals with an increased 11beta-HSD1 activity (i.e., transgenic animals) have an excess of visceral fat and are insulin resistant, diabetic and dyslipidemic. Furthermore, in humans, pharmacological inhibition of 11beta-HSD1 with non-selective compounds has previously been shown to result in enhanced insulin sensitivity. This finding indicates that 11beta-HSD1 appears to play an important role in type 2 diabetes and the metabolic syndrome also in man, and that selective inhibitors 11beta-HSD1 could become a very useful tool in the treatment of this disorder.

Type 2 Diabetes (also known as non-insulin dependent, adult onset or type 2 diabetes mellitus)
Type 2 diabetes is a lifestyle disease with a strong hereditary component. Estimates of diabetes prevalence around the world have more than tripled since 1985. The current global prevalence is approximately 160 million people and has been

estimated to increase to 300 million people in 2025. Presently, approximately 6% of the population in the United States is diabetic. Of these patients, 90-95% are afflicted with different forms of type 2 diabetes, a condition that is expected to become increasingly widespread, due to the increasing number of elderly, a more sedentary lifestyle and rapidly growing incidence of obesity. The worldwide annual average mortality in diabetics (5.4%) is twice as high as in non-diabetics. Each year in the United States alone, about 200,000 deaths, 400,000 heart attacks, 130,000 strokes, 60,000 amputations, 10,000 new cases of kidney failure requiring dialysis or transplantation and 6,000 new cases of blindness result from type 2 diabetes. Type 2 diabetes also leads to other disabilities, especially nerve damage that could result in erectile dysfunction, numbness, intractable nausea, and diarrhea. Diabetes is currently the sixth leading cause of death by disease in the United States and is estimated to cost the US health care system 100 billion USD per year. It is estimated that by the year 2010, diabetes will exceed both heart disease and cancer as the leading cause of death through complications.

Type 2 diabetes is a progressive disease caused by a combination of decreased tissue sensitivity to insulin (insulin resistance) and an insufficient insulin secretion. The blood glucose control in type 2 diabetes usually deteriorates over time and, despite lifestyle intervention efforts, additional pharmacological treatment in many cases ultimately becomes necessary. Type 2 diabetes is frequently associated with obesity, dyslipidemia, hypertension, atherosclerosis, thrombosis and cardiovascular disease. In the treatment of diabetes it is important to address all these aspects of the disease. The unmet need for new, safe and effective treatment tools to prevent the progression of the type 2 diabetes, its serious complications and the associated over-mortality in this disease remains enormous.

Phase II clinical trials
Phase II clinical trials establish if a drug candidate has the desired initial efficacy in patients suffering from a specific disease or condition. If such efficacy can be demonstrated, *Proof of Concept* has been achieved for the drug candidate.

Double-blind placebo-controlled phase II study
In a *double-blind controlled study* neither the patients nor the clinicians involved in the study know if the patient belongs to the drug group or the placebo group. The clinician administers the trial and returns the results to the drug's innovator who then decodes which patients received the placebo and which received the drug. The majority of the placebo-controlled clinical trials are now conducted as double blind. This procedure enables the separation of 'placebo' effects, caused for instance by patient expectations and subsequent changes in lifestyle and behavior, from the true pharmacological effects of a drug candidate.