Betagenon

PRESSRELEASE

The Small molecule AMPK activator O304 acts as an oral PCSK9 inhibitor

Low-density lipoprotein cholesterol (LDL-C),"bad" cholesterol, is considered a risk factor for cardiovascular diseases like heart attacks. LDL-C is removed from the blood upon binding to the LDL receptor (LDLR) present on the surface of liver cells, which results in uptake of LDL-C into the cells. The enzyme PCSK9 binds to and degrades the LDLR, thereby inhibiting removal LDL-C from blood. In man, gene variants with reduced expression or activity of PCSK9 are associated with reduced circulating LDL-C levels, supporting the mechanism for PCSK9 in LDLR degradation and thereby circulating LDL-C levels. Thus, drugs which block or lower PCSK9 will reduce LDL-C and may also reduce the risk of cardiovascular disease. Currently, such drugs are limited to antibodies, which although they have shown significant reduction of LDL-C levels, have to be injected to block PCSK9 in the blood.

PCSK9 has both intra-cellular and extra-cellular functions, inducing degradation of the LDLR both before the receptor reaches the cell surface and at the cell surface. Gene variants linked to reduced levels of active PCSK9 affects both the intra-cellular and extra-cellular function of PCSK9. Antibodies act however mainly on extra-cellular PCSK9, indicating that clinical results obtained with anti-PCSK9 antibodies may not fully correlate with epidemiological findings in man. In contrast, a small molecule PCSK9 inhibitor has the potential to block both intra- and extra-cellular PSCK9 and to mimic findings with different human gene variants.

In human liver cells, the small molecule AMPK activator O304 reduces both the intra- and extra-cellular levels of PCSK9, and in addition increases the expression of LDLR. Consistently, oral administration of O304 to obese rats O304 reduces plasma levels of both PCSK9 and total cholesterol, as well as of triglycerides, providing evidence that;

O304 acts as an orally active PCSK9 inhibitor with dual beneficial effects on LDL receptor levels

O304 is in development for use in Type 2 diabetes and in Peripheral arterial disease. Phase 1a clinical studies with O304 at 100 to 2400 mg have been succesfully completed without any significant adverse effects and with the expected pharmacokinetics.

Together these results support the clinical development of O304 also as an oral anti-PCSK9 medicine to be used in treatment and prevention of cardiovascular diseases.

Betagenon AB is a privately owned Swedish Biotechnology company focused on the development of small molecule AMPK activators for multiple indications. The AMPK activator program is funded by **Baltic Bio AB,** a subsidiary of the investment company Fort Knox Forvaring AB, Umea, Sweden.

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