ODM-208, a novel CYP11A1-inhibitor as a therapeutic approach for the treatment of castration-resistant prostate cancer

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Background: Androgen receptor (AR) plays a central role in prostate cancer and continues to be a key driver in castration-resistant prostate cancer (CRPC). Approximately half of the men with CRPC respond initially to abiraterone or enzalutamide, but most relapse within 1 to 2 years. Majority of the abiraterone and enzalutamide-resistant tumors have still high AR expression and persistent AR activity. As overexpressed AR can be activated by several steroids, a total block of steroid synthesis both in adrenal glands and de novo in tumours might be needed. CYP11A1 (cytochrome p450scc) is a mitochondrial enzyme catalysing the conversion of cholesterol to pregnenolone (Preg), which is the first rate-limiting step in steroid hormone biosynthesis. ODM-208 is a novel, oral, non-steroidal and selective inhibitor of CYP11A1 enzyme and suppresses the synthesis of all steroid hormones and their precursors.

Methods: The inhibition of CYP11A1 was measured in vitro by detecting the formation of radiolabelled isocapronic acid in a human adrenal cortex cell line (H295R), and further analysing Preg and testosterone (T) formation by ELISA. Inhibition of the adrenal and testicular hormone production in vivo was tested in the intact male rat assay by analysing plasma concentrations of progesterone (P), corticosterone (C) and T (with LS-MS/MS) after single oral dose of ODM-208. The tumor growth inhibition was studied by using androgen dependent VCaP cells, which were subcutaneously grafted to intact male nude mice. When tumor volumes reached on average 200 mm³, mice were castrated, and after regrowth of the tumors, the oral treatment of ODM-208 was started.

Results: ODM-208 potently inhibits CYP11A1 enzyme and formation of Preg and T with low nM concentrations in vitro. In male rats, clear decreases of P, C and T concentrations can be detected already after single oral administration of ODM-208. Further, in the murine VCaP CRPC xenograft model ODM-208 significantly inhibited tumor growth.

Conclusions: ODM-208 shows promising antitumor activity in preclinical CRPC models and suggests that ODM-208 may have the potential to be an effective treatment in CRPC. Clinical trial in patients with metastatic CRPC is under preparation.

Conflict of Interest: All other authors, but Huhtaniemi are employees of Orion Corporation Orion Pharma

Funding Acknowledgements: Studies were sponsored by Orion Corporation Orion Pharma