

Seviterenol Demonstrates Selective CYP17A1 Lyase Inhibition with Reduced Off-Target Activity and Minimal Ferroptotic Effects in Prostate Cancer Models

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Abstract

Castration-resistant prostate cancer (CRPC) remains largely driven by persistent androgen receptor (AR) signalling, making CYP17A1 inhibition a validated therapeutic strategy. However, first-generation inhibitors such as abiraterone lack enzymatic selectivity, suppressing both 17 α -hydroxylase and 17,20-lyase activities and leading to off-target endocrine disturbances. Seviterenol (VT-464) is a novel CYP17A1 inhibitor designed to preferentially target 17,20-lyase activity while sparing hydroxylase function.

Using prostate cancer cell lines (LNCaP, 22Rv1, PC3) and benign RWPE-1 cells, seviterenol selectively inhibited proliferation in AR-dependent LNCaP cells with minimal effects on non-malignant cells. In NCI-H295R steroidogenic cells, radiolabeled substrate assays and LC-MS analysis confirmed potent suppression of androgen biosynthesis with significantly greater lyase selectivity than abiraterone. The mean IC₅₀ for CYP17A1 hydroxylase inhibition was 6.74 μ M for seviterenol versus 0.07 μ M for abiraterone, consistent with relative sparing of the hydroxylase.

Given emerging links between AR signalling and ferroptosis, we explored ferroptotic responses following CYP17A1 inhibition. Seviterenol did not significantly induce ferroptosis nor alter intracellular iron levels under the conditions tested.

Currently evaluated in Phase II trials for metastatic CRPC, seviterenol represents a clinically relevant, next-generation CYP17A1 inhibitor with improved enzymatic selectivity, reduced off-target effects, and minimal ferroptotic perturbation, supporting its therapeutic potential in advanced prostate cancer.