Conclusions: Cellestia Biotech’s drug development program has led to the discovery and development of a novel chemical series of pharmacological inhibitors of the NOTCH pathway for which the current Development Candidate is CB-103. Our studies demonstrate that CB-103 inhibits NOTCH signaling through a unique mechanism of action. CB-103 blocks NOTCH signaling downstream of S3 cleavage of NOTCH receptors by directly targeting NOTCH transcription complex.

Non clinical pharmacology, pharmacokinetics and safety profiling of CB-103: A novel first-in-class small molecule inhibitor of the NOTCH pathway

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Abstract: NOTCH signaling is a developmental pathway known to play critical roles in the regulation of self-renewing tissues. aberrant activation of NOTCH signaling leads to deregulation of the self-renewal process resulting in sustained proliferation, evasion of cell death, loss of differentiation capacity, invasion and metastasis, all of which are hallmarks of cancer. Over activation of NOTCH in human cancers can be a consequence of over expression of NOTCH ligands/receptors, GOF mutations in NOTCH receptors as well as chromosomal translocations leading to constitutive activation of the pathway. Activation of NOTCH and its oncogenic role in various cancers is prognostically relevant with shorter survival seen in patients harbouring these genetic alterations. Given the importance of Notch signaling in human cancers, several therapeutic approaches have been utilized to block NOTCH signaling. Two of these strategies are; a) the use of monoclonal blocking antibodies (mAbs) against NOTCH ligands and receptors and b) the use of small molecule γ-secretase inhibitors (GSIs). In human cancers harbouring NOTCH gene fusion due to chromosomal translocations, the use of mAbs GSIs will have very limited clinical benefits. Here we report discovery and characterization of CB-103, a novel first-in-class orally-active small molecule inhibitor of the NOTCH pathway. CB-103 inhibits NOTCH signaling by targeting the NOTCH transcriptional activation complex in the nucleus. In a GSI/mAb resistant xenograft models of human triple negative breast cancer, human T-ALL and mouse mammary tumor, CB-103 has demonstrated excellent anti-tumor efficacy. In this study we present additional pharmacology, PK data and provide an overview of the good safety and tolerability seen with CB-103 in the non-clinical studies. Based on these findings CB-103 has been selected as clinical candidate to be investigated in a FIM, phase II/III clinical study in advanced cancer patients.