Neflamapimod

Neflamapimod (previously code-named VX-745) is a clinical phase 2b-ready highly specific inhibitor of the intracellular enzyme p38 mitogen-activated protein kinases alpha (“p38α”) that is being developed as a disease-modifying drug for Alzheimer's disease (AD) that acts via targeting synaptic dysfunction. Neflamapimod was discovered through a proprietary structure-based drug discovery platform at Vertex Pharmaceuticals and developed previously by Vertex through to phase 2a in rheumatoid arthritis. EIP Pharma licensed the compound in 2014 for development and commercialization as a treatment of central nervous system (CNS) disorders. Neflamapimod is the most advanced in the clinic drug that targets specific molecular mechanisms within neurons that leads to synaptic dysfunction, the pathogenic process that is now considered to be a major driver of the development of memory deficits and disease progression in the early stages of AD. Based on the scientific rationale of targeting synaptic dysfunction and the preclinical data, neflamapimod has the potential to both reverse memory deficits and slow disease progression. Phase 2a clinical data in patients with early-stage AD (MMSE 20-28, biomarker positive) provides evidence that the preclinical science may be translatable to human Alzheimer's, as 6- to 12 weeks of neflamapimod treatment led to significant improvement in episodic memory, the best clinical measure of synaptic dysfunction in AD. A phase 2b six-month placebo-controlled 150-patient clinical study is anticipated to start by end of 2017. This study is designed to definitively demonstrate that neflamapimod reverses memory deficits, and also to provide preliminary evidence that the drug slows disease progression [1].

Neflamapimod is a small molecule drug that specifically targets p38α with excellent blood-brain barrier (BBB) permeability.

NEF blocked TMZ-responsive PDIA3P1 upregulation and produced synergistic effects when combined with Temozolomide at specific concentrations. The combination of TMZ and NEF exhibited excellent synergistic antitumor effects both in vitro and in vivo [2].

1)
Alam J, Blackburn K, Patrick D. Neflamapimod: Clinical Phase 2b-Ready Oral Small Molecule Inhibitor of p38α to Reverse Synaptic Dysfunction in Early Alzheimer's Disease. J Prev Alzheimers Dis. 2017;4(4):273-278. doi: 10.14283/jpad.2017.41. PMID: 29181493.
2)
Gao Z, Xu J, Fan Y, Qi Y, Wang S, Zhao S, Guo X, Xue H, Deng L, Zhao R, Sun C, Zhang P, Li G. PDIA3P1 promotes Temozolomide resistance in glioblastoma by inhibiting C/EBPβ degradation to facilitate proneural-to-mesenchymal transition. J Exp Clin Cancer Res. 2022 Jul 15;41(1):223. doi: 10.1186/s13046-022-02431-0. PMID: 35836243.