TC-1734: An Orally Active Neuronal Nicotinic Acetylcholine Receptor Modulator with Antidepressant, Neuroprotective and Long-Lasting Cognitive Effects

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ABSTRACT

The development of selective ligands targeting neuronal nicotinic acetylcholine receptors to alleviate symptoms associated with neurodegenerative diseases presents the advantage of affecting multiple deficits that are the hallmarks of these pathologies. TC-1734 is an orally active novel neuronal nicotinic agonist with high selectivity for neuronal nicotinic receptors. Microdialysis studies indicate that TC-1734 enhances the release of acetylcholine from the cortex. TC-1734, by either acute or repeated administration, exhibits memory enhancing properties in rats and mice and is neuroprotective following excitotoxic insult in fetal rat brain in cultures and against alterations of synaptic transmission induced by deprivation of glucose and oxygen in hippocampal slices. At submaximal doses, TC-1734 produced additive cognitive effects when used in combination with tacrine or donepezil. Unlike (−)-nicotine, behavioral sensitization does not develop following repeated administration of TC-1734. Its pharmacokinetic (PK) profile (half-life of 2 h) contrasts with the long lasting improvement in working memory (18 h) demonstrating that cognitive improvement extends beyond the lifetime of the compound. The very low acute toxicity of TC-1734 and its receptor activity profile provides additional mechanistic basis for its suggested potential as a clinical candidate. TC-1734 was very well tolerated in acute and chronic oral toxicity studies in mice, rats and dogs. Phase I clinical trials demon-
strated TC-1734’s favorable pharmacokinetic and safety profile by acute oral administra-
tion at doses ranging from 2 to 320 mg.

The bioavailability, pharmacological, pharmacokinetic, and safety profile of TC-1734
provides an example of a safe, potent and efficacious neuronal nicotinic modulator
that holds promise for the management of the hallmark symptomatologies observed in
dementia.