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C-10068: NOVEL SIGMA-1 AGONIST FOR EPILEPSY AND NEUROPROTECTION

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Concert Pharmaceuticals is a clinical stage pharmaceutical company that applies its deuterated chemical entity (DCE Platform™) technology to create and develop differentiated new medicines based on known, proven drugs. Deuterium is a safe, naturally-occurring, non-radioactive relative of hydrogen that is obtained from sea water. In most cases, selective incorporation of deuterium will not alter the biochemical potency or selectivity of a drug, but in select cases it can enhance certain metabolic properties such as increasing half life, improving bioavailability, or reducing the formation of undesirable metabolites. By leveraging known activity and safety of existing drugs this approach reduces the time, risk and expense typically associated with drug research and development.

C-10068 is a new chemical entity in the morphinan class. It was derived from a compound that was first described in the literature in the 1990s as possessing anti-seizure properties with low toxicity, but that was limited in practical applications by rapid and extensive metabolism. Selective deuterium incorporation in key positions resulted in increased metabolic stability, demonstrating a more than three-fold increase in oral bioavailability with C-10068 compared to its non-deuterated analog.

The anti-convulsant properties of C-10068 appear to be a result of activity at the sigma-1 receptor¹, which is reported to have unique modulatory actions² on activated ion channels (Ca²⁺, K⁺) and neurotransmitters that are important in the control of epilepsy. In addition it has been reported that the sigma-1 receptor plays an important role in synapse formation in hippocampal neurons³ suggesting C-10068 may have neuroprotective effects as well.

Rodent studies were conducted in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) Anti-convulsant Screening Program headed by James Stables and contracted by the University of Utah. In the maximal electroshock model (MES) of tonic-clonic seizures, an experimental model that is predictive of efficacy, although not therapeutic margin in humans, C-10068 dosed ip had an ED₅₀ = 22 mg/kg and 18 mg/kg in mice and rats respectively. This is substantially below the dose which induced adverse effects in the rotarod test; TD₅₀ = 65 mg/kg and 45 mg/kg mice and rats respectively. C-10068 also showed anti-convulsant activity in the 6Hz model of complex partial seizures.

Further, *in vitro* neuroprotection tests (hippocampal slice model) showed that C-10068 inhibited cytotoxicity induced by NMDA and kainic acid. At a dose of 22 mg/kg in the formalin-induced plantar pain model, C-10068 also proved highly effective (73% reduction) in ameliorating chronic inflammatory pain.

In summary, C-10068 is a potential novel treatment for seizure disorders which incorporates deuterium to greatly improve the pharmacokinetic profile of the agent. Preclinical evaluation of C-10068 is continuing at Concert and NINDS as well as through collaboration with Walter Reed Army Institute of Research to investigate its potential as a treatment for the non-convulsive seizures following traumatic brain injury.

1 Chou et al. Brain Research (1999) 821, 516–519

2 Cobos et al. Current Neuropharmacology (2008), 6, 344-366

3 Tsai et al., PNAS (December 29, 2009), 106(52), 22468–22473