

PYM50028 (Cogane™): A NOVEL, POTENTIALLY DISEASE MODIFYING TREATMENT FOR PARKINSON'S AND OTHER NEURODEGENERATIVE DISEASES OF THE CENTRAL NERVOUS SYSTEM

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Clinical studies involving the direct infusion of glial cell-derived neurotrophic factor (GDNF) and neurosurgical delivery of viral vectors containing GDNF and related molecules (e.g. neurturin) have demonstrated that the provision of neurotrophic factors, especially GDNF, represents a valid approach towards achieving beneficial neurorestorative and neuroprotective effects in patients with Parkinson's disease (PD). However, to date, in Phase II placebo-/sham-procedure-controlled clinical trials with these agents have been unsuccessful in meeting their primary endpoints. Additionally, the need to neurosurgically introduce material directly in to discrete regions in the brain limits the number of patients that can be treated. Cogane™, a steroidal sapogenin (molecular weight ca. 417), can be taken orally, readily crosses the blood brain barrier and stimulates the release of GDNF, thereby overcoming many of the challenges associated with neurosurgical delivery of GDNF or gene therapy modalities. Cogane™ has been shown to stimulate the release of neurotrophic factors and promotes neurite outgrowth *in vitro* and in *in vivo* preclinical models, Cogane™ elevates GDNF levels and reverses the loss of dopaminergic neurones. Specifically, in several studies in the MPTP-lesioned mouse model of PD, Cogane™ consistently protects against loss of dopaminergic neurones in the *substantia nigra* as well as dopaminergic functionality in the striatum (Visanji *et al.*, 2008). We have latterly reported data from an efficacy study in a non-human primate model of PD (Johnston *et al.*, 2009). In this study, oral administration of Cogane™ for 18 weeks to stably MPTP-lesioned macaques significantly reduced the mean parkinsonian disability by 43%, with statistically significant improvements in behavior in favour of Cogane™ occurring from Week 9 onwards and was still increasing at Week 18.

In a separate study in stably parkinsonian MPTP-lesioned macaques, the effects of Cogane™ in animals already receiving L-DOPA was investigated. In this study, macaques were administered (Madopar®, 20 mg/kg/day) twice daily for 19 weeks before commencing treatment with either L-DOPA+Cogane™ (20 mg/kg/day) or L-DOPA+vehicle for a further 18 weeks. Spontaneous activity of animals in this study was measured using Actical™ passive activity monitors. In this study MPTP administration significantly reduced the level of activity by ~80%. L-DOPA partially restored activity (to ~50-60% of "normal"), although this was still significantly lower than pre-MPTP levels. In macaques receiving L-DOPA+vehicle the level of activity at Weeks 20 and 37 was similar to L-DOPA alone at Week 18. In macaques receiving L-DOPA+Cogane™ the level of activity at Week 20 was similar to L-DOPA alone at Week 18 but then increased over time and by Week 37 was increased to ~80% of pre-MPTP levels and was not significantly different from pre-MPTP "normal" activity levels. These data suggest a potential role for Cogane™ as an adjunct therapy to L-DOPA in the treatment of advanced PD patients.

Cogane™ has also been shown to be neuroprotective and neurorestorative in a number of other neuronal cell types (e.g. cortical, sensory and spinal motor neurones) and in preclinical models of Alzheimer's disease (AD), Cogane™ has been shown to restore memory and learning deficits, suggesting a potentially wider role for Cogane™ in the treatment of neurodegenerative diseases generally.

A substantial preclinical data package is available to support long-term dosing with Cogane™ in clinical studies. Cogane™ has a good emerging safety profile and does not cause any significant effects in any of the standard battery of safety pharmacology studies conducted.

In the clinic, Cogane™ has been shown to be safe and well-tolerated across a number of clinical studies in healthy volunteers and in AD patients when taken for up to 12 weeks. In a recently reported Phase Ib, safety, tolerability and pharmacokinetic study in healthy volunteers and patients with mild-moderate PD, the current liquid formulation of Cogane™ was shown to be safe and well tolerated when taken for up to 28 days. There were no substantial differences in the pharmacokinetics of Cogane™ in healthy volunteers and PD patients in this study and importantly, on Day 28, plasma levels of Cogane™ in PD patients taking a daily dosage of 150 mg Cogane™ reached levels associated with efficacy in preclinical models of PD (Priestly *et al.* 2009).

A Phase II proof-of-concept and dose ranging clinical study to determine whether Cogane™ has potential clinical utility in the treatment of early stage (Hoehn and Yahr Stage 1 to 2.5, inclusive), untreated PD patients (aged between 35 and 75 years) who will take Cogane™ for 28 weeks, to be conducted at up to 70 sites across the United States, Canada and Western Europe. Four groups of ~100 subjects will be randomised to receive one of three dose levels of Cogane™ or placebo. is planned to commence imminently. The primary efficacy outcome measure will be the mean group change in the Unified Parkinson's Disease Rating Scale (UPDRS) parts II and III combined score, (from baseline to the end-of-treatment; Week 28 compared with placebo. A range of

secondary efficacy outcome measures will be employed to provide a broader understanding of the possible clinical utility of Cogane™ in this patient population, including the use of the SCOPA-COG rating scale to assess effects on cognition (Marinus *et al.*, 2003), the Parkinson's Disease Questionnaire-39 to assess effects on quality of life (Jenkinson *et al.*, 1997) and the Non-Motor Symptoms Scale (Chaudhuri *et al.*, 2004). Time to dopaminergic and/or other PD therapy will also be a secondary outcome measure. This clinical study, which is scheduled to commence enrolment towards the end of 2010, should provide a clear indication of Cogane™'s utility in the treatment of early stage PD and will pave the way for pivotal, Phase III clinical trials.