Development of VU0652957 for the treatment of Parkinsons disease (PD)

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USA

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1

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Research Abstract
PROJECT SUMMARY The primary pathological change underlying the motor symptoms associated with Parkinson’s disease (PD) is death of dopamine neurons in the substantia nigra pars compacta (SNc) of the basal ganglia (BG). Traditionally, therapeutic strategies for improving motor function in PD patients have relied on replacement of lost dopamine; recently, increasing efforts have focused on developing non-dopaminergic drug treatments for PD. The mGlu4 subtype of metabotropic glutamate (mGlu) receptor has emerged as a promising new target for potential therapeutic agents to normalize activity in BG motor circuits. mGlu4 is highly expressed on presynaptic GABAergic terminals within the “indirect pathway” of the BG, and

agonists and positive allosteric modulators (PAMs) of mGlu4 reduce transmission of indirect pathway neurons projecting from the striatum to the external segment of the globus pallidus. Numerous mGlu4 PAMs from international labs have consistently shown efficacy in inducing antiparkinsonian activity in multiple preclinical Parkinson's models. In addition, increasing evidence suggests that activation or potentiation of mGlu4 may also have neuroprotective effects. We have developed a first-in-class, highly selective, optimized PAM of mGlu4 termed VU0652597. VU0652957 exhibits good functional potency and efficacy at rodent and human mGlu4 and is highly selective among the mGlus as well as a panel of other clinically relevant receptors, including cardiac ion channels. An Ames test with VU0652957, both with and without S9 hepatic fractions, was negative, indicating a low risk of parent or metabolite mutagenicity. VU0652957 is also at low risk for CYP-mediated drug-drug interactions and displays a favorable unbound fraction in plasma proteins and brain homogenates. Pharmacokinetic studies in rats, dogs, and cynomolgus monkeys have demonstrated that VU0652957 is a moderately cleared compound with >30% oral bioavailability in all species examined. VU0652957 exhibits robust activity in a haloperidol- induced catalepsy model and reversal of catalepsy correlates closely with CSF concentrations that reach or exceed the in vitro potency at rat mGlu4, indicating a good pharmacokinetic:pharmacodynamic relationship that could be eventually used as a biomarker to set dose for clinical trials. A four step synthesis of VU0652957 was developed at VCNDD and is currently being optimized and executed on 200 gram scale. During the UH2 preparatory phase, we propose to perform formulation work, dose range finding studies in rats and dogs, and synthesis of VU0652957 for good laboratory practice (GLP) toxicology studies. Proposed plans for the UH3 phase include GLP analytical method development and validation, safety pharmacology, genetic toxicology, and rat and dog toxicology studies. It is anticipated that the completion of IND-enabling studies through the BPN initiative will position VU0652957 for testing in clinical populations of PD patients.

Further information available at:

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