MICA- Evaluation of AZD1080 (GSK-3 inhibitor) in a preclinical mouse model of motor neuron disease (MND)

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Country

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MICA- Evaluation of AZD1080 (GSK-3 inhibitor) in a preclinical mouse model of motor neuron disease (MND)

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MRC

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15/05/2013

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2

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Research Abstract
Motor neurone disease (MND) is a devastating neurodegenerative disorder with rapid progression to death from neuromuscular respiratory failure in the majority of afflicted individuals. There is an urgent need for improved approaches to achieve neuroprotection in ALS. Aberrant over-expression and activation of glycogen synthase kinase 3 (GSK-3) is implicated in neurodegeneration in MND and several studies in animal models suggest inhibition

of this pathway may be beneficial, however the compounds used are unselective and associated with side effects (lithium) or the studies were sub-optimal and so do not give a true reflection of the therapeutic potential of GSK-3 inhibitors in MND. The AstraZeneca compound, AZD1080 is a CNS-penetrating, potent and selective reversible inhibitor of GSK-3 which has been tested in 224 healthy volunteers in Phase I studies and shows PK profile commensurate with exposures observed in preclinical models of inhibition of Tau phosphorylation in the hippocampus. We have developed a preclinical mouse model and screening approach for candidate MND therapeutics which can provide rigorous, high quality data on a variety of readouts of motor neuron degeneration. We will use AZD1080 and our preclinical model to provide definitive information on the therapeutic potential of GSK-3 inhibition in MND with a view to further clinical development of AZD1080 in the human disease. In addition, recent in vitro data has shown that GSK-3 can promote degradation of Nrf2, a key regulator of cellular oxidative stress responses. We have identified compounds which activate this transcription factor, providing protection for motor neurones from oxidative stress. We will probe, in vivo, the importance of GSK-3 in regulating this pathway in our MND model using one of our Nrf2 activating molecules with AZD1080 to determine whether a combination of these compounds leads to a greater improvement in motor function than we have already achieved.

Further information available at:

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