NDC-1308, a small molecule with remyelinating activity for treatment of secondary progressive multiple sclerosis patients

Steven H. Nye and James G. Yarger, ENDECE Neural, LLC, Mequon, WI USA,

Abstract

Background: Current therapeutics for MS patients impact the immune mechanisms of the disease, rather than the axonal remyelination activity needed to repair the damaged myelin sheath. NDC-1308 is known to activate intracellular pathways for oligodendrocyte progenitor cell (OPC) differentiation. NDC-1308 induces mouse OPcs to differentiate into mature, myelinating oligodendrocytes in vitro and significantly increases remyelination of axons in vivo. These studies extend the in vitro remyelination results while addressing the safety and exposure of NDC-1308.

Objectives: A main goal was to correlate the ability of NDC-1308 to repair the damaged myelin sheath, in the cuprizone mouse model of demyelination, with a functional improvement. Intended outcomes also included an initial safety assessment for NDC-1308 and determining the dosing parameters for non-clinical ND-enabling studies.

Methods: Male mice were treated for 12-weeks with cuprizone and rapamycin to cause demyelination of white and gray matter regions of the brain. The demyelinated mice were administered NDC-1308 (8 mg/kg, i.p. q.d.) for up to 6 weeks. Blood was collected at termination for clinical chemistry analysis, along with reproductive tracts for pathology, and brain regions for assessing the level of NDC-1308 remyelination. The OPC population in different brain regions was evaluated by immunohistochemistry using P0/PLP antibodies. The degree of mutagenicity and genotoxicity of NDC-1308 was measured by a bacterial reverse mutation assay and a mammalian cell micronucleus screening assay, respectively.

Results: NDC-1308 rapidly crosses the blood brain barrier and is absorbed into CNS tissues in amounts sufficient for inducing OPcs to differentiate into mature, myelinating oligodendrocytes that can then repair the myelin sheath. NDC-1308 appears to be a potentially safe and effective therapeutic for treating SPMS patients. Non-clinical ND-enabling studies and a first-in-human Phase 1 study are planned.

Conclusions: These results suggest NDC-1308 can be delivered to the CNS tissues in amounts sufficient for inducing OPcs to differentiate into mature, myelinating oligodendrocytes that can then repair the myelin sheath. NDC-1308 appears to be a potentially safe and effective therapeutic for treating SPMS patients. Non-clinical ND-enabling studies and a first-in-human Phase 1 study are planned.

Enhanced CNS absorption of NDC-1308 in dog

Phase 1 trial design for NDC-1308

Conclusion

1. NDC-1308 has desirable qualities for an MS therapeutic. It is a small molecule that rapidly crosses the blood brain barrier and is absorbed into CNS tissues following systemic administration.
2. NDC-1308 has a potent activity in vitro to induce OPcs to differentiate into mature, myelinating oligodendrocytes.
3. In the cuprizone mouse model of demyelination, NDC-1308 induces significant remyelination of demyelinated axons in cortical and hippocampal regions.
4. The remyelinating activity of NDC-1308 is associated with a functional improvement in forelimb grip strength.
5. The biological activity of NDC-1308 is distinct from estradiol. NDC-1308 has gained the function of remyelination, but lost commonly associated side-effects of estradiol, such as estrogenicity.
6. NDC-1308 is being advanced to the clinic as a therapy for treating patients with Secondary Progressive MS.