A novel therapy for Huntington's disease

Huntington's disease (HD) is a devastating progressive disorder. Delaying disease onset requires novel targeted interventions early on in life.

HD is an autosomal dominant neurodegenerative disorder that gives rise to progressive neuronal dysfunction and cell death. It is caused by alterations in the N-terminal part of the HD gene product huntingtin (HTT). Currently, there is no therapy available for HD, only symptomatic treatment of the associated chorea and psychiatric problems.

SEN0014196, also known as selisistat, is a novel and selective SirT1 inhibitor with neuroprotective activity against toxicity induced by the mutant HTT. It has previously shown promising pre-clinical efficacy in treating HD in cellular and in vivo models. Selisistat has been granted orphan drug status in both Europe and the United States, and has proven to be safe in healthy volunteers.

The EU-funded PADDINGTON project was a continuation of the above clinical studies, wishing to extend the efficacy of selisistat in HD patients. Among the primary objectives of the study was to establish a battery of pharmacological assays that could be used to 'read' the disease-modification effect of selisistat.

During PADDINGTON, two trials were performed: one exploratory study in HD patients and one observational study aimed at identifying and evaluating neuroimaging biomarkers of disease progression. In the first trial, 55 early-stage HD patients who received different doses of selisistat over 14 days demonstrated the safety of the drug with no adverse effects.

In the observational study, a large cohort of patients and healthy volunteers underwent neuroimaging, clinical, laboratory and cognitive assessments over a period of 15 months. Analysis of this data led to the discovery of a number of biomarkers for disease state and progression.

In light of the devastating social impact of HD, a disease-modifying intervention such as selisistat is expected to improve the life of sufferers and their families. However, although the activities of the PADDINGTON study have established a clinical safety profile for the compound, pivotal efficacy studies are required to conclusively validate its ameliorating effect on disease symptoms.

Related information

Report Summary

Final Report Summary - PADDINGTON (Pharmacodynamic Approaches to Demonstration of Disease-Modification in Huntington's Disease by SEN0014196)