

## **FDA approves a Phase IIb clinical trial of ACR16 for HD patients**

NeuroSearch announced on July 10, 2008 that the United States' Food and Drug Administration (FDA) has approved the company's Investigational New Drug (IND) application for ACR16, a dopaminergic stabilizer and a novel drug candidate for the treatment of Huntington's disease (HD). The IND application approval allows NeuroSearch to initiate a planned US study, named HART (Huntington's disease ACR16 Randomized Trial). NeuroSearch expects that the HART study will begin in the second half of 2008.



Joakim Tedroff, M.D., Ph.D.,  
speaking about ACR16 at the  
2008 HDSA convention

ACR16 is a small molecule belonging to a pharmacological class called dopamine stabilizers. It can enhance or inhibit activity depending on the initial level. In other words, if dopamine activity levels are too high, ACR-16 can decrease them, but if activity is too low, ACR-16 can increase it. This contrasts with neuroleptics where a reduction in activity of this neurotransmitter occurs, regardless of initial level.

Dopamine is an important neurotransmitter which plays a role in cognition, mood, attention, learning, motor activity, sleep, and behavior, so targeting it needs to be done carefully. Dopamine appears to play a role in Huntington's Disease. Dopamine receptors are progressively reduced with the progression of the disease. In addition, there is some evidence that there is an abnormal sensitivity to dopamine in the medium spiny neurons affected in HD.

ACR-16 appears to work by strengthening cortical control of the basal ganglia. The striatum, which is part of the basal ganglia, is the brain's autopilot. Once we have learned a behavior, we need not give it our full attention. The striatum will control the activity while our cortex is thinking about something else. Once the striatum begins degenerating in HD, the cerebral cortex loses control of the basal ganglia. This is why HD patients have trouble with multitasking.

ACR16 was previously evaluated in four clinical Phase I/II studies with patients suffering from Huntington's disease, Parkinson's disease and psychoses, and demonstrated a good safety and tolerability profile. In a Phase II study with ACR16 in Huntington's disease, the results showed that 28 days' treatment with ACR16 resulted in a statistically significant improvement in the patients' voluntary movements including parkinsonism and gait function.

The HART study is planned as a randomized, double-blinded and placebo controlled study expected to include 220 patients. In the study, patients will receive daily doses of either 22.5 mg (QD), 45 mg (QD) or 45 mg (BID) ACR16 or placebo to evaluate the efficacy and safety of ACR16 over three months' treatment. The primary efficacy

endpoint of this study will be the effect of ACR16 on Huntington patients' voluntary motor function (parkinsonism, gait/balance, hand functionality, bradykinesia) measured by the modified Motor Score, mMS - a subscale of the Unified Huntington's Disease Rating Scale (UHDRS). Secondary endpoints include the overall clinical impression of the patients, their cognitive function, neuropsychiatric symptoms such as depression and anxiety. The efficacy endpoints in the HART study are the same as in the ongoing European MermaiHD study.

Both the EMEA (European Medicines Agency) and the FDA have granted ACR16 orphan drug status for the treatment of Huntington's disease.

ACR16 was discovered and is developed internally by NeuroSearch, which has the rights to develop and commercialise the compound for the treatment of Huntington's disease in the European Union, Norway, Switzerland and North America. All other rights to the compound have been outlicensed to Astellas Pharma Inc.

Flemming Pedersen, CEO of NeuroSearch, commented, "The FDA acceptance of our IND application for ACR16 and of the protocol for the US HART study is an important milestone for NeuroSearch. With the European Phase III MermaiHD (Multinational European Multicentre ACR16 study in Huntington's Disease) study ongoing, we now look forward to completing our international development program for ACR16 in the treatment of Huntington's disease. Currently, patients suffering from Huntington's disease have very limited treatment options. Bringing this promising novel treatment concept to the market to help alleviate the burden of a serious and very disabling disease would therefore be a highly valuable step forward for both patients and their relatives, as well as for NeuroSearch as a company."

### **References:**

Neurosearch Press Release

Dr. Joakim Tedroff's talk at the 2008 HDSA convention

Wikipedia on dopamine

Charvin, D. , Vanhoutte, P., Pages, C., Borelli, E., Caboche, J. "Unraveling a role for dopamine in Huntington's disease: The dual role of reactive oxygen species and D2 receptor stimulation." Proc Natl Acad Sci U S A. 2005 Aug 23;102(34):12218-23.

*Marsha L. Miller, Ph.D., July 10, 2008*