

Breaking News: In a Phase II trial, Dimebon was found to be safe and well tolerated with indications of effectiveness for HD patients

Medivation has been conducting a Phase II clinical trial of Dimebon in collaboration with the Huntington Study Group. Encouraging results were announced July 7 through a conference call, web cast, and press release.

Medivation, Inc. announced top-line results showing that its investigational drug Dimebon(TM) significantly improved cognitive function in patients with mild-to-moderate Huntington's disease (HD). Cognitive function was significantly improved over placebo ($p=0.03$) as measured by the Mini-Mental State Examination (MMSE), the cognition scale most widely used by clinicians to assess patients with neurodegenerative diseases. Dimebon-treated patients also demonstrated favorable results on the behavioral component of the United Huntington's Disease Rating Scale (UHDRS), a composite scale measuring several components of HD, but these results did not reach statistical significance.

Dimebon was very well tolerated in this trial. The overall incidence of adverse events was lower in the Dimebon group than in the placebo group, an unusual finding in a clinical study of any drug. This result is consistent with a similar finding from the first pivotal Alzheimer's disease trial in which Dimebon-treated patients had significantly fewer serious adverse events after one year of treatment.

Of particular note, Huntington's disease patients treated with Dimebon had fewer falls (9%), a common problem in this patient population that often results in injury and associated health care costs, than did patients on placebo (16%). The most common adverse event in the Dimebon group was headache, which occurred in 19% of treated patients compared to 7% of placebo patients. Headaches were generally mild in severity. Dry mouth and depressed mood were similar in both treated and placebo groups (4% and 7%, respectively).

Those who were randomized to the Dimebon group were more likely to complete the study than those who were randomized to the placebo. The Dimebon completion rate was 87 percent compared with 82 percent for the placebo group, again suggesting that the drug was well-tolerated.

The purpose of a Phase II drug is to ascertain whether a drug is safe and well-tolerated by those with the disease so these findings are very encouraging. However, Medivation also wanted to look for any indications that the drug might be effective. With only 90 patients, a short time frame of 90 days, and a disease that is slowly progressive, the study was not powered to demonstrate effectiveness, but any such finding would be very promising. The statistically significant difference between the Dimebon and placebo groups on cognition as measured by the MMSE generated much excitement on the conference call.

"To my knowledge, no other drug has resulted in statistically significant benefit in cognition in Huntington's disease patients in a randomized, well-controlled trial," said Karl Kieburtz, M.D., M.P.H., professor of neurology at the University of Rochester, director of the HSG Clinical Trials Coordination Center, and principal investigator in this trial. "Cognitive impairment is the most important therapeutic unmet need in Huntington's disease. I am pleased by this result and Dimebon's favorable safety profile, and believe that further development of this compound is warranted."

The randomized, double-blinded, placebo-controlled Phase 2 trial was conducted at 16 centers in the United States and the United Kingdom in collaboration with the Huntington Study Group (HSG), a network of more than 250 experienced clinical trial investigators, coordinators and consultants from more than 60 academic and research institutions throughout the United States, Canada, Europe and Australia dedicated to clinical research of Huntington's disease. The trial enrolled 90 HD patients, with half randomized to Dimebon and the other half to placebo for a three-month dosing period. The primary endpoint of the trial was safety and tolerability. The secondary endpoint was efficacy, as measured by the MMSE, the UHDRS and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), a cognition scale generally used in Alzheimer's disease clinical trials.

"We are very encouraged that Dimebon improved cognition and was well tolerated in both trials assessing efficacy that we have conducted to date -- this trial and our first pivotal trial in Alzheimer's disease. The consistency seen in the data between these two trials underscores the potential for this drug," said Lynn Seely, M.D., chief medical officer of Medivation. "These data are also important because they provide further support for our belief that Dimebon is exerting its benefits through a novel mechanism of action targeting mitochondrial dysfunction, a contributor to the loss of neuronal function in Huntington's disease. Medivation is committed to aggressively advancing development of Dimebon for patients and families devastated by Huntington's disease."

Full results from the Phase 2 study will be submitted for presentation at an upcoming scientific meeting.

The mechanism by which Dimebon is thought to work is through its effect on the mitochondria. The brain has a high need for energy. The mitochondria are like 'tiny gas stations' to provide fuel to cells so that they can carry out their normal function. The brain has about 100 billion brain cells and each of these has 1000 mitochondria. Dimebon appears to have a potent effect on mitochondria function. Medivation will present data later in July on Dimebon's effect on the mitochondria. However, work with animals continues and it is possible that there may be other helpful methods of action that are also operating.

Dimebon was developed in Russia as an antihistamine and it has been used safely for that purpose for more than two decades in that country. Russian scientists discovered that the drug has neurologic properties and identified it as a potential treatment for Alzheimer's Disease. Medivation licensed the drug and also began researching it as a potential

treatment for Alzheimer's disease; a Phase III trial for AD patients is ongoing. Medivation also decided to look at its potential for Huntington's Disease since both diseases involve progressive neurodegeneration and abnormal protein accumulation, and both have abnormal mitochondrial function. The results of a Phase I study in 2007 encouraged Medivation to conduct the Phase II study.

HDSA will continue to report on this drug as more information becomes available. Although conclusions cannot be drawn until there are results from a Phase III trial, it is encouraging to this drug advance another step in the treatment pipeline.

Marsha L. Miller, Ph.D., July 7, 2008