Disappointing results in a Phase III clinical trial of Dimebon in Alzheimer's Disease (AD).

The AD Results:

Medivation and Pfizer have announced that a Phase III trial of Dimebon for Alzheimer's patients has failed to achieve success in primary or secondary endpoints. The HDSA is disappointed for the AD community but remains hopeful that the ongoing Phase III study in Huntington's Disease (HD) will be successful.

The Alzheimer's trial, called CONNECTION, was a multi-national, double-blind, placebo-controlled safety and efficacy trial involving 598 patients with mild-to-moderate AD at 63 sites in North America, Europe, and South America. Patients were randomly assigned to one of three groups. One group received dimebon 20 mg three times a day (TID) one received 5 mg of dimebon TID, or one received a placebo TID for six months.

There were no statistically significant improvements for the 20 mg TID or 5 mg TID groups compared to the placebo group. There were two primary endpoints. One was cognition as measured by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). The other primary endpoint was independently-rated global function over the course of the six-month trial, as measured by the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus; p=0.81).

There were no statistically significant improvements achieved on secondary endpoints either. One endpoint was change in the activities of daily living as measured by the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL). Neither the Dimebon groups nor the placebo group improved from baseline. Another endpoint was behavior as measured by the Neuropsychiatric Inventory (NPI). The 20 mg TID group did improve compared to the placebo group but the difference was not statistically significant (p = .17).

On the Mini Mental State Examination (MMSE), another measure of cognition, both groups improved significantly over baseline (dimebon 0.7; placebo 1.2). The difference favoring placebo was not significant (p=0.10). Results for the dimebon 5 mg TID dose were similar to dimebon 20 mg and placebo, although they were numerically lower.

In contrast, in the Phase II clinical trial with Huntington's patients, there was a statistically significant improvement in MMSE compared to the placebo group.

"The results from the CONNECTION study are unexpected, and we are disappointed for the Alzheimer's community," said Dr. David Hung, president and chief executive officer of Medivation. "We are working with our colleagues at Pfizer to better understand the CONNECTION data and we plan to present these data at an upcoming medical meeting."

Encouragingly, Dimebon was shown to be well tolerated in a separate multi-center placebo controlled Phase III safety and tolerability study which enrolled 742 participants.

This was true whether it was given alone or in combination with a variety of other medications often prescribed in Alzheimer's. One of these drugs, memantine, is also in clinical trials for HD so this would be good news should both drugs prove to be effective in Huntington's patients.

What Does this Mean for the HORIZON study?

HORIZON, the Phase III Dimebon trial for HD is moving full speed ahead. Dr. Karl Kieburtz, principal investigator for the Phase III clinical trial of Dimebon in HD, says that we need to take a broad perspective and wait for the results of further research:

> One study in AD showed benefit and now another one has not. That happens in studies of drugs that eventually are shown to work in many diseases of the brain including AD, depression and pain. These results do not diminish the DIMOND results either. Also very importantly there was excellent safety in both studies announced today. I feel very strongly that now is the time to push ahead with HORIZON and learn if it does work in HD. I also hope that the other studies of dimebon in AD will show benefit in the future, for the sake of those patients and families. In every struggle there are ups and downs, and today had a down, but I hope we can get back up and continue the struggle to find treatments for HD.

Mechanistic studies:

Is there any information about the mechanism by which Dimebon is thought to improve cognition that would predict that the results in HD would be different from those in AD? The latest study from Medivation, conducted by Dr. Andrew Protter and colleagues, looked at cognition enhancement in normal rats to see this occurs and if so, if they could identify the mechanism. Of course, this is not a model for Alzheimer's or Huntington's but such a study can provide some insight about mechanism. They administered Dimebon and found that the animals had improved performance on the novel object recognition task, a standard measure of memory.

Dr. Protter then investigated various possible methods of action. It does not work through the inhibition of acetylcholinesterase as donezepil (Aricept) does nor by blockage of NMDA receptors as memantine does. It does not prevent calcium influx. There is a high affinity with the histamine 1 receptor, which one would expect since Dimebon was originally developed as an antihistamine. However, this receptor is not associated with memory.

Others have suggested that Dimebon may work by affecting 5-HT6 receptors. This study could not rule that out but the researchers point out that it's unclear as to whether the doses used in their study would have been sufficient to affect the receptors. In addition, they note that other researchers have suggested that 5-HT6 antagonists improve memory by raising levels of extracellular Ach and glutamate but that did not happen in this study.

One possibility is that Dimebon could work by affecting alpha adrenoceptors since it binds to several subtypes but more work would need to be done to determine this. This would seem to be a promising area for further investigation since a recent study of transgenic HD rats found that adrenergic alpha(2)-receptor densities in these regions were significantly altered in the hippocampus and basal forebrain in a transgenic HD rat model.

The authors remind us of earlier studies where mitochondrial function was enhanced and neurite outrgrowth was promoted in a cell model. This could certainly be helpful in Huntington's where the mitochondria are not managed properly and energy levels are reduced. However, the mechanism by which Dimebon did this was not clear.

Further mechanistic studies as well as ongoing and future clinical trials will clarify the issues raised by current research. Participants in the HORIZON trial can be encouraged by the good safety profile demonstrated in the Alzheimer study.

References:

Medivation Press Release

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- *Marsha L. Miller, Ph.D., March 4, 2010*