CTAD Highlights November 14, 2013

San Diego, California. The sixth annual Clinical Trials in Alzheimer's Disease (CTAD) conference opened today with the presentation of the first ever CTAD Lifetime Achievement Award in Alzheimer's Disease Therapeutic Research to Dr. Russell Katz, the recently retired director of the Food and Drug Administration's (FDA) Division of Neurology Products.

Paul Aisen, M.D., Director of the Alzheimer's Disease Cooperative Study and Professor of Neurosciences at the University of California, San Diego, introduced Dr. Katz as "our tireless friend and leader at the FDA," noting that under Dr. Katz's leadership, the FDA has become an active partner with academia and industry in the AD drug development effort. "The optimism that many of us feel today is due in good part to our collaborative relationship with the FDA that has allowed the field to evolve towards effective therapy," said Dr. Aisen.

"I have always thought that the best way to win this fight is for all relevant parties to get together," said Dr. Katz. The award, he said, acknowledges the fact that the FDA is a pivotal partner in this fight. "The Agency's commitment to winning this fight is rock solid," he added.

A decade of frustration

Dr. Aisen followed the award presentation with a keynote address describing the challenges the field has faced over the past 10 years and the recent developments that he believes will lead to future success. "It's been a difficult and frustrating decade," said Dr. Aisen. No new drugs have been approved during this period for the treatment of AD despite hundreds of trials. One reason for these repeated failures is that the field has moved away from treating symptoms in late stage dementia towards trying to modify the underlying disease process in earlier stages of the disease such as a pre-dementia stage known as Mild Cognitive Impairment (MCI). Proving that a drug is effective in patients with MCI is complicated by the heterogeneous nature and gradual progression of the disorder, which results in a need for long studies and huge number of subjects.

However, recent proposed changes in the way the FDA will evaluate clinical trials should make it possible to design trials that can demonstrate efficacy in earlier stages of the disease. "We are confident that we are more likely to succeed because of these changes in the clinical trials approach," said Dr. Aisen. "We even look to move earlier – to the asymptomatic or preclinical AD stage. Ultimately, our eye is on primary prevention."

One of the essential elements of a preclinical AD trial will be the inclusion of biomarkers that will enable the classification of people with MCI according to how likely it is that they are on the AD trajectory. Ronald Petersen, M.D., Ph.D., Director of the Mayo Alzheimer's Disease Research Center described studies done both in research and community settings that support the notion that markers of amyloid deposition and neurodegeneration can differentiate people with MCI into four groups according to the likelihood (high, intermediate, uncertain, or unlikely) that their cognitive impairment is

due to Alzheimer's pathology. Although there are several different sets of criteria that have been proposed for the diagnosis of preclinical AD, Dr. Petersen said that there is more consistency between them that disagreement. All of these criteria rely to some extent on the use biomarkers, and recent studies from several research groups corroborate that the staging system proposed in these different criteria seem to be working. Moreover, recent data also indicate that there are clinical changes that can be detected in the preclinical stage. "Even in the normal aging stage there are data indicating subtle clinical changes," he said, echoing a point made by Dr. Aisen earlier that cognition may be the best biomarker of Alzheimer's pathology.

Other biomarkers have also recently emerged that seem to provide additional insight into the pathological process that underlies AD and other forms of dementia. One that has generated intense interest is tau imaging. Tau is the protein that forms the neurofibrillary tangles that are seen at autopsy in the AD brain. At CTAD, researchers from Japan and the United States reported progress in developing a class of agents that are used with positron emission tomography (PET) scanning to visualize tau in the brain. Although the results are still considered very preliminary, investigators expressed optimism that these agents could lead to a better understanding of the neurodegenerative process in the AD brain. Importantly, these early results indicate that tau imaging may be able to track progression over time and even possibly treatment effects.

The next generation of clinical trials

Eric Reiman, M.D., Chief Executive Officer of Banner Research said, in another keynote address, that the time has come to establish a new era in AD prevention research. Dr. Reiman leads the Alzheimer's Prevention Initiative (API), one of four large prevention studies getting underway in 2013. API and the other three studies: the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), the Anti-Amyloid treatment of Asymptomatic AD (A4), and the TOMMorrow trials are all selecting populations with a high likelihood of developing the disease during the trial period. Testing people close to this transition point is seen as the best way to assess whether a treatment slows the disease.

All of these studies are incorporating a treatment trial with extensive biomarker assessments in order to learn more about how biomarker behave as well as how they relate to clinical outcomes. And in order to ensure that findings from the studies can be compared and shared, API, DIAN and A4 have joined forces under the umbrella of the Collaboration for Alzheimer's Prevention (CAP).

"We are in uncharted territory," said Dr. Reiman. "I would argue that these complementary trials are truly complementary and greater than the sum of the parts."