An Interview with Lawrence Friedhoff

Chief Development Officer of Axovant Sciences

Discuss your involvement with the development of donepezil, the most widely used drug for the treatment of Alzheimer’s. What was the Alzheimer’s disease landscape when donepezil was being developed?

There was a lot of doubt about Alzheimer’s therapeutics when we first began developing donepezil. In fact, very few people even used the term ‘Alzheimer’s disease’ – the commonly used term was ‘Senile Dementia,’ and it was looked upon as an inevitable consequence of aging. Only a few people even considered the possibility that it was a disease that could be treated; there was only one other company developing a drug for Alzheimer’s. Even the very promising results of our initial Phase II clinical trial didn’t change things much. Eventually, Pfizer licensed some of the marketing rights, which gave us some external validation.

Tell us about your experience leading the development of donepezil.

I was hired by a mid-size pharmaceutical company to help them get their internally developed products approved for marketing. Until that time, they had only been marketing products discovered by other companies. Since they had quite a broad range of drug discovery projects, it took about a year to identify two products that I thought had significant potential to help patients. Both products had been in a few very early clinical trials so we had some basic information about them. I hired and worked with a remarkably talented small team of development experts to run the development programme, and we were also greatly assisted by a small group of academic experts, most of whom were young researchers at the time and are now leading AD experts.

The development programme was completed in just a little over five years; much faster than the industry average then, which was over 14 years. Starting as just a small group with an idea, turning that idea into a large and successful development organisation, and then knowing that we helped a lot of patients was very exciting and fulfilling for the entire team. I had that same experience with the other product I put into development at that company. It’s a treatment for gastro-esophageal reflux disease that’s used by millions of patients all over the world.

Unfortunately, there has been a nearly 12-year period when almost all clinical trials of Alzheimer’s disease therapeutics have failed. Two notable exceptions were a gamma secretase inhibitor study and a 5-HT6 receptor antagonist study conducted by GlaxoSmithKline. The gamma secretase inhibitor study showed very clearly that interfering with the production of beta amyloid protein by blocking the last step in its production actually made Alzheimer’s worse. Although I expect this was a disappointment to the study sponsor because they hoped their product would make patients better, it was, I believe, a very important result because until that time, interfering with production of beta amyloid was viewed as a very promising strategy by many researchers.

The GlaxoSmithKline 5-HT6 receptor antagonist study, a 684-subject multinational double-blind placebo-controlled trial, showed clear evidence that inhibition of the 5-HT6 receptor improves both cognition and activities of daily living in patients with mild to moderate Alzheimer’s disease. This was the first study in years to show such strong evidence of benefit. In addition, a study conducted on another 5-HT6 receptor antagonist showed similar but less statistically robust results. These studies, together with evidence from other clinical and preclinical trials, have convinced me that 5-HT6 antagonism is currently the most promising approach for the treatment of Alzheimer’s disease.

What’s your current involvement with Axovant and the RVT-101 compound – an adjunct therapy with donepezil?

I’m currently the Chief Development Officer at Axovant Sciences, Inc. We are a dementia solutions company, committed to addressing all aspects of dementia therapy. RVT-101 is the name of the 5-HT6 receptor antagonist previously in development by GlaxoSmithKline and currently being developed by Axovant. In the fourth quarter of this year, we plan to initiate a confirmatory Phase III study intended to replicate key results of the previous 684-patient study.

What drew you to work on it?

As I mentioned earlier, I think 5-HT6 antagonism is the most promising approach to the treatment of Alzheimer’s disease at the moment, and we have what appears to be the best-in-class 5-HT6 antagonist: RVT-101. In addition to the strong signals of potential efficacy, the drug has been dosed in over 1200 patients and was well tolerated. Thus far, no clear evidence of drug-related toxicity has been identified. One promising observation in the 684-patient study is that there were more falls in the placebo group than in the RVT-101 groups.

The opportunity to work on a product like this comes only once or twice in a professional lifetime.

What is the structure of the current trial?

We’ve announced that we expect to begin a final confirmatory Phase III trial of RVT-101 in the fourth quarter of this year. We believe that, if the results are positive, this will be the final pivotal efficacy trial needed to obtain marketing approval for RVT-101. The design will closely follow the design of the earlier GlaxoSmithKline 684-patient trial that had shown statistically significant benefit on both patients’ cognition and activities of daily living (or ‘function’). The two endpoints the FDA requires for approval of new Alzheimer’s drugs.
In our study, mild to moderate Alzheimer’s disease patients on a steady background of donepezil will be randomly assigned to once-daily treatment with either placebo or 35mg of RVT-101 for 24 weeks. Each arm of the study will have over 500 patients, so it will be very highly powered. Once the study is over, the data from cognition and activities of daily living tests will be examined and if there are statistically significant benefits of RVT-101 relative to placebo, we should have the final pivotal efficacy trial needed to submit an application to the FDA for approval.

Where are the trials taking place?

The Phase III efficacy trial will be conducted internationally including the United States and other countries throughout the world.

Why are clinical trials so important for those affected by Alzheimer’s?

Except in certain rare situations, animal study results seem to have almost no relationship to effects in Alzheimer’s patients. In general, the only way to determine the efficacy of a drug is through clinical studies of Alzheimer’s patients.

Participation in Alzheimer’s clinical trials helps patients and caregivers in general and may be beneficial for the individual patient participant. However, the risks and benefits of experimental medications vary substantially from one product and trial to another. My advice to patients and their caregivers would be to carefully consider clinical trial options. It is important to understand the evidence that suggests a product may be helpful and what kinds of toxicity have been observed in prior animal and human studies before volunteering to participate. When in doubt, ask questions of the study physician and/or your personal healthcare provider.

Lawrence Friedhoff, MD, PhD, FACP, is the Chief Development Officer of Axovant Sciences, Inc. and the Senior Vice President, Research & Development at Roivant Sciences, Inc. Dr. Friedhoff has led and managed teams that developed and obtained approval for six new drugs, including Aricept (donepezil), the most widely used drug for the treatment of Alzheimer’s, and Aciphex (rabeprazole) for the treatment of heartburn. Each are used by millions of patients around the world.

For more information about the study and Dr. Friedhoff visit: www.axovant.com.