

Tay-Sachs Gene Therapy Consortium
Progress Update
July, 2012

The following summarizes progress by the TSGT consortium toward initiating a human clinical trial for Tay-Sachs disease (TSD).

A number of positive results have been achieved in the last year and all research activities are progressing very well, albeit with some delays that have forced us to revise the clinical trial start date to March 2013. The following are the highlights of our progress:

1. Experiments in all GM2 mice, cats and sheep continued to show excellent results, and in many instances surpassed considerably our initial expectations.
2. The surgical approach to be used in humans has been refined using advanced imaging systems to ensure accuracy of the injections, and initial tests in monkeys show that the procedure is safe and can be performed with minimal surgical risk. Studies are ongoing to test the short-term and long-term safety of the gene therapy.
3. The UC Davis GMP facility has successfully established the method for producing AAV vectors in a very short time through hard work from an excellent team. The mouse vectors to be used in the formal GLP toxicity studies have been manufactured and the team is ready to start producing the human clinical grade material necessary for the clinical trial. Contract negotiations are currently ongoing.
4. The protocol for the formal toxicity studies has been finalized and the studies will start in the next few weeks.
5. A draft of the clinical protocol has been written and is being reviewed by clinical trial specialists at the Massachusetts General Hospital where we plan to conduct clinical studies.

We have made excellent progress successfully accomplishing numerous goals on the path toward the clinical trial due to the hard work of a very large team of researchers working collaboratively. We still have to follow FDA requirements and complete a number of studies before the entering the clinical trial phase.

Please see detailed description of the latest results below.

1. Experiments in GM2 cats

GM2 cats treated by the standard route and dosage have lived an average of 17.9 months, or 4 times longer than untreated GM2 cats, which die at ~ 4.5 months of age. **Two AAV-treated GM2 cats are still alive at 29.2 and 26.0 months of age, a remarkable outcome that surpasses our initial expectations.** As reported in the previous update, few of the AAV-treated cats died of typical neurological disease progression. Most treated cats succumbed to other problems such as heart disease or bladder and bowel dysfunction. It is important to note that

peripheral organs are thought to be more severely affected in Sandhoff disease (modeled by the cat studies) than Tay-Sachs disease. For this reason, peripheral organ dysfunction may be less problematic in the Tay-Sachs clinical trial than predicted from the cat studies. Nevertheless, clinical trial patients will be closely monitored for signs of disease in both brain and peripheral organs.

2. Alternative routes

To develop the safest surgical procedure possible, GM2 mice, cats and sheep were treated by alternative routes of delivery such as injection of the thalamus and lateral ventricle. The lateral ventricle contains cerebrospinal fluid, which acts as a cushion by bathing the brain and spinal cord, after which it is absorbed into the bloodstream. Because it circulates through the nervous system and eventually becomes part of the blood, cerebrospinal fluid may be an effective way to treat both the brain and peripheral organs. Though it is too soon to draw firm conclusions from ongoing experiments, the results are encouraging. For example, treated mice have lived twice as long as untreated mice and appear to be normal when observed in their home cages. Treated cats have lived an average of 17.4 months, with survival and disease progression similar to those treated by the standard therapy using cerebellum injections. Results in Tay-Sachs sheep have also been encouraging, with HexA enzyme activity above normal throughout the brain after treatment.

3. Feasibility and safety study in monkeys

Performing studies in monkeys is critical to perfect the surgical technique to be used in humans and test the safety of the gene therapy in a species more closely related to humans. For this study we assembled a multidisciplinary team composed of human neurosurgeons with research experience in monkeys, imaging specialists and veterinarians, in addition to an operating room with advanced imaging capabilities identical to those to be used in the human trial. Approximately 100 monkeys had to be screened by rigorous criteria to select the 11 animals used for this study. The injections in monkeys, and ultimately in humans, require the use of advanced imaging systems to accurately target the desired structures in the brain. In the process of establishing the injection procedure we determined that commonly used instruments interfered with the quality of imaging in monkeys and thus targeting accuracy. To address this issue we had to develop a new instrument with minimal imaging interference. This new instrument has allowed for excellent accuracy in placing the needles in the desired structures in the brain. Importantly all animals injected to date by the thalamus + cerebrospinal fluid route are doing very well, with no adverse side effects noted. Animals will be closely monitored for 30 or 90 days, when detailed analysis of the brain and spinal cord will be conducted to ensure that the gene therapy treatment is safe. Though initiation of these studies was delayed due to recruitment of the new investigators with the required expertise and development of a new instrument, the delay was necessary to ensure the feasibility of this crucial project, accuracy of the injection procedure and integrity of the results. Demonstrating safety of the procedure and gene therapy agent is critical to final approval of the clinical trial by the U.S. Food & Drug Administration.

4. Production of clinical grade AAV vectors for clinical trial

AAV vectors for human clinical trials must be produced by rigorous “good manufacturing practice (GMP)” standards. We contracted with a new, state-of-the-art GMP facility at the University of California-Davis for pilot-scale production of GMP-grade vector, which passed quality assurance standards required by the U.S. FDA for use in humans. Establishment of the AAV

production method at UC Davis was only possible due to the exceptional dedication and hard work of their team.

In addition to stocks for the actual clinical trial, AAV produced by identical methods is required by the FDA for rigorous safety/toxicity studies in mice. Mouse studies are the most commonly accepted type of toxicity assay and will complement the monkey experiments to ensure that the human clinical trial is as safe as possible. The AAV vectors necessary for the formal toxicity studies in mice have been successfully made and ready to be used.

Finally, **production of the actual AAV vector stocks for the first clinical trial is ready to begin.**

5. Approval of regulatory bodies for clinical trial

Numerous regulatory steps must be met before the clinical trial can begin, such as filing an “investigational new drug (IND)” application with the FDA and receiving approval from the “institutional review board (IRB)” at the Massachusetts General Hospital where we are planning to conduct the clinical trial. The path to IND approval is a 3-step process, and we completed the second step (a “pre-IND” meeting) early in 2012 after submission of a 182-page document to the FDA. Submission of the IND itself is the final step, after which FDA has 30 days to comment before the clinical trial can begin. The clinical protocol is being prepared for submission to the IRB at the Massachusetts General Hospital. Based on the clinical protocol a budget to conduct the clinical trial at the Massachusetts General Hospital is being prepared as well.

We are entering the final stages of our program towards the clinical trial, and all activities are proceeding well and on schedule for the revised start of the clinical trial in March 2013.