Genzyme's Potential New Substrate Reduction Therapy

Genzyme Therapeutics is developing a potential new oral therapy for patients with Type 1 Gaucher disease writes David Meeker, President of LSD Therapeutics, Genzyme Therapeutics:

'Genz-112638 is an inhibitor of the enzyme glucosylceramide synthase (GS). GS is responsible for producing glucosylceramide, the fat that accumulates in the tissues of persons with Gaucher disease and leads to the symptoms of the disease. Genz-112638 was designed to mimic the structure of the lipid ceramide, making it different from miglustat (Zavesca®), which is an analog of the sugar glucose.

'In pre-clinical studies Genz-112638 had an acceptable safety profile and effectively reduced the accumulation of glucosylceramide in a mouse model of Gaucher disease. This animal model was developed by **Dr. Gregory Grabowski** at Children's Hospital Research Foundation in Cincinnati, Ohio.

'Further, in vitro studies have shown that Genz-112638 is very efficient at inhibiting GS, and has a reduced capacity to inhibit other enzymes that are not relevant to the symptoms of Gaucher disease. Thus, Genzyme believes that Genz-112638 may be more effective and have fewer side effects than the currently available oral therapy when used to treat Gaucher disease.

'To test this hypothesis, Genzyme has begun clinical testing of Genz-112638. Several Phase 1 clinical trials have involved over 120 healthy volunteers. The compound has demonstrated an acceptable safety profile at the expected efficacious dose.

'The results of these studies were presented at EWGGD meeting in Cambridge in July. The results of the pre-clinical studies will be submitted for publication in a peer-reviewed scientific journal in the next few months.

Phase II Trial

'A phase II clinical trial in Type 1 Gaucher patients is currently underway in Europe, Israel, the US and Latin America. The purpose of this open label study is to evaluate the safety and efficacy of Genz-112638 in Gaucher disease Type 1 patients over a period of one year.'

Amicus Therapeutics Continues to Explore a New Way to Treat Gaucher Disease

In the last edition of the Gauchers News, Dr Pedro Huertas, Chief Development Officer at Amicus Therapeutics, New Jersey, USA reported a potential new method to treat patients with Gaucher disease. Dr Huertas provides a further update:

'Certain types of mutations (changes) in the gene glucocerebrosidase, called missense mutations, allow the enzyme to be made but cannot fold properly. The misfolded enzyme is unstable and remains in the endoplasmic reticulum (ER) where it may accumulate, clump together and have damaging effects. Such damaging effects are thought to be in addition to the effects created by storage of the fatty substance in the lysosomes caused by the reduction or loss of the glucocerebrosidase enzyme.

'AT2101, Amicus' lead oral compound for Gaucher disease, is designed to selectively bind to the glucocerebrosidase enzyme and help it fold into its correct three-dimensional shape. This binding and stabilization helps increase the proper movement of the enzyme from the ER of the cell to the lysosomes, the compartments in the cell where it performs its intended biological function.

'In a study that recently appeared in the scientific journal, *Proceedings of the National Academy of Sciences* in the US, researchers performed several experiments with AT2101 on fibroblasts from an individual with Gaucher disease caused by the N370S mutation. N370S is a common disease-causing genetic mutation. After discovering that N370S glucocerebrosidase activity was increased in cells by as much as three-fold by AT2101 treatment for five days, researchers sought to understand in more detail the mechanisms by which AT2101 increased cellular glucocerebrosidase activity. Among the key findings:

- AT2101 facilitates proper folding, prevents premature degradation, and restores efficient transport of newly-synthesized N370S glucocerebrosidase to the lysosomes.
- AT2101 increases the total amount of N370S glucocerebrosidase in the lysosomes and leads to improved enzyme activity and lysosomal stability.

'Earlier this year Amicus filed an investigational new drug (IND) application for AT2101 with the United States' FDA. Phase I clinical trials are underway.

'Amicus are sponsoring an ex-vivo study (survey study) that will measure the change in glucocerebrosidase activity after human blood is treated in the laboratory with AT2101. The cells will be obtained from individuals with Gaucher disease and the goal is to collect response-data on a wide spectrum of genetic mutations known to cause Gaucher disease. Phase II clinical trials are being planned.'

Shire Human Genetic Therapies - Emerging New Enzyme Treatment

In the last edition of Gauchers News, Prof Ari Zimran, Director of the Gaucher Clinic at Shaare Zedek Medical Center in Israel reported on the 9-month Phase I/II results for a new enzyme preparation for patients with Type 1 Gaucher disease, produced by Shire Human Genetic Therapies. Prof Zimran provides a further update on the preliminary results at 24 months :

'Shire Human Genetic Therapies Inc's enzyme preparation known as GA-GCB is a human glucocerebrosidase which is produced in a continuous human cell line using proprietary Gene-Activated technology. GA-GCB has an identical amino acid sequence to the naturally occurring human enzyme.

'The preliminary results show significant increases in hemoglobin from baseline (mean increase of 2.44g/dL from baseline; mean percent increase of 21.5% from baseline) and in platelet counts (mean increase of 69.9x10^3/mm^3 from baseline; mean percent increase of 119.8% from baseline) and also significant decreases in spleen and liver volume (by 70.9% and 26.9% from baseline, respectively). Similarly, there were significant decreases in the biomarkers chitotriosidase (by 79.7% from baseline) and CCL18 (by 51.2% from baseline).

'Improvements in some parameters were apparent as early as three months after the start of the therapy and patients continue to improve over time." In terms of safety, as of 24 months on treatment, there have been no drug related serious adverse events nor the need for pre-infusion medication. In addition, no patient has developed antibodies to GA-GCB to date.

'Following the results of the Phase I/II trial in adult patients, two global, multi-center Phase III clinical trials to determine the safety and efficacy of GA-GCB in children and adults will take place. One study will be for untreated patients and the other study will be for those patients who are currently on enzyme replacement therapy. These Phase III studies will start in the UK and the rest of Europe in the early Spring of 2007. In the UK, Prof Cox at Addenbrooke's Hospital, Cambridge and Dr. Mehta of the Royal Free Hospital, London have expressed an interest in these studies.'

Phase III trial on new Enzyme Replacement Therapy from Plant Cells begins 2007

In the last edition of Gauchers News, Dr Einat Almon, Vice President Product Development, Protalix Biotherapeutics reported on a new enzyme replacement therapy produced in plant cells for patients with Type 1 Gaucher disease. Dr Almon provides a further update:

'Protalix Biotherapeutics has developed a novel plant-cell culture system for the production of active biopharmaceutical proteins. Glucocerebrosidase for enzyme replacement therapy (prGCD) on Gaucher disease is the first Protalix product entering Phase III clinical trial in the beginning of 2007.

'prGCD is a recombinant human glucocerebrosidase expressed and purified in Protalix's bioreactor system from a transformed carrot plant cell line free of animal derived factors.

'In July 2006 at the European Working Group on Gauchers Disease (EWGGD) meeting at Cambridge University, Prof Ari Zimran presented the results of a Phase I trial designed to evaluate safety and pharmacokinetic profile of prGCD. The study was performed in accordance with FDA requirements on healthy volunteers.

Dr Raul Chertkoff (left) and Dr Einat Almon at the EWGGD meeting in Cambridge 2006

Results showed that prGCD was well tolerated; no significant adverse reactions were observed showing safety together with a promising pharmacokinetic profile. Prof Anthony Futerman of the Weizmann Institute of Science, presented data demonstrating that the three dimensional structures of prGCD and Cerezyme were practically identical, as were other biochemical parameters.

'A world wide Phase III clinical trial to assess the safety and efficacy of prGCD will be conducted according to FDA guidelines and will be initiated at the beginning of 2007. Leading medical experts of the Gaucher field from EU, UK, USA and other countries will participate in this study coordinated by Prof Ari Zimran from Shaare Zedek Medical Center, Jerusalem, Israel. **Dr Raul Chertkoff,** former chairman of the Israel Gaucher Association and now Medical Director of Protalix will play an active role in the trial.

'Protalix advances in production of active glucocerebrosidase enzyme (prGCD) in plant cells culture may offer several advantages in safety, efficacy and cost.'