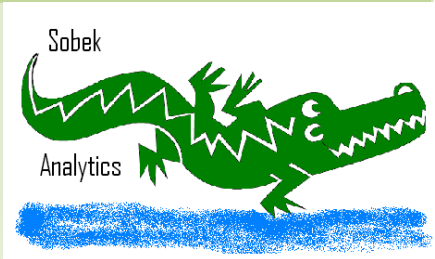

Amicus Therapeutics: Kowing When to FOLD Them

Rare Diseases Make Big Money

Genzyme (GENZ) developed a successful model of targeting rare diseases to make outsized profits. Amicus Therapeutics (FOLD) is attempting to follow this path by creating novel approaches to the treatment of rare diseases. This report focuses on Amicus' most advance program for the treatment of Fabry disease (FD), which is a rare X-linked (inherited), lysosomal storage disease. Amicus' lead compound (Amigal) targets the 50% of FD patients whose disease is caused by the mis-folding alpha-galactosidase-A. Essentially, Amigal acts as a pharmacological chaperone that allows the cell to maintain a proper level of alpha-galactosidase-A. This, in turn, normalizes the breakdown of lipids.

This differs from current therapy that simply adds new enzymes into the system. While this can help with the breakdown of lipids, it does not affect the enzymes produce within the cells. These remain defective. The pharmacological chaperone approach taken by Amicus has been successful in a phase II study and the company recently announced positive results from a long-term extension study. In addition, the 50% of FD patients whose disease are not causes by improper enzyme folding are not completely untreatable by Amigal. Amicus is currently testing Amigal in conjunction with enzyme replacement therapy, where it was found that a pharmacological chaperone can increase the ability of ERT to treat the disease.

Amicus Therapeutics also has a number of additional programs in the pipeline. It is trying to tackle two additional rare diseases (Pompe disease and Gaucher disease) where a pharmacological chaperone is used in conjunction with ERT. In addition, they have preclinical work that demonstrates pharmacological chaperones being useful in the treatment of Alzheimer's and Parkinson's diseases. This report, however, will focus on the use of Amigal as a monotherapy for the treatment of FD.

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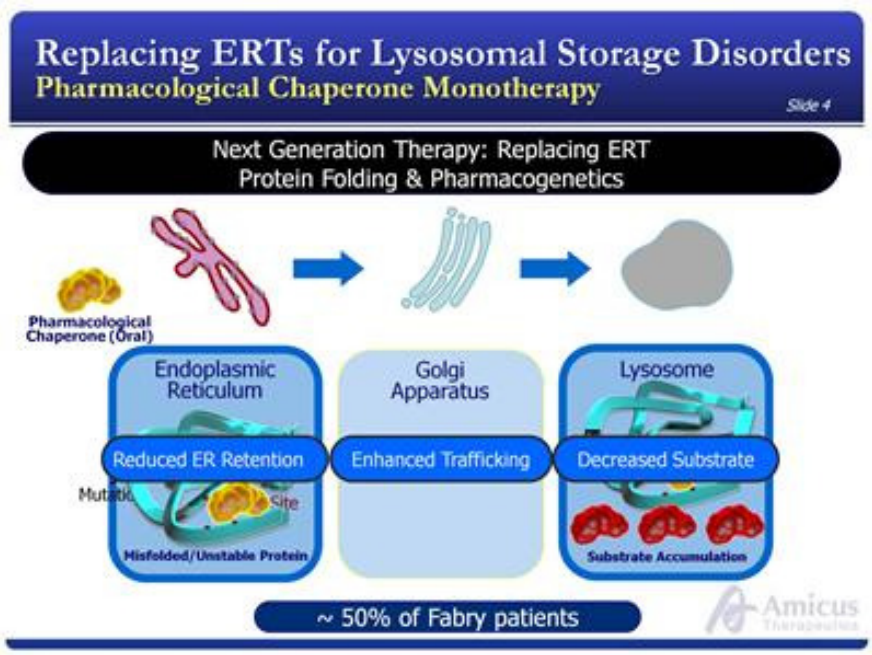
Fabry Diseases Basics

As noted above Fabry disease (FD), which is a rare X-linked (inherited), lysosomal storage disease. A mutation of alpha-galactosidase-A (a-GAL A) causes a glycolipid known as globotriaosylceramide (known as Gb3 or GL-3) to accumulate within blood vessels, tissues, and organs. It is the accumulation of Gb3 that causes the symptoms and not the mutation of a-GAL A. Problems of a-GAL A can derive from numerous mutations and often missense mutations (change in a single nucleotide) create subtle effects and problems. One of these can be the mis-folding of the enzyme.

Mis-folded enzyme are problematic because cells essentially have a quality control apparatus (the endoplasmic reticulum). Improperly folded enzyme will be prematurely degraded in the ER. In other words, the enzyme does not pass quality control and is destroyed. This means fewer enzymes reach the lysosome where they are needed to break up Gb3. Ultimately, then, Gb3 levels increase to the point that they causes the symptoms associated with FD. The key to treatment, then, becomes the normalization of Gb3 levels. As noted above, current treatments essentially add new enzymes (ERT) to the system, which help moderate Gb3 levels.



Pharmacological Chaperone Approach

Amicus Therapeutics attempts to reduce the levels of Gb3 by helping the mutated enzymes through the quality control of the endoplasmic reticulum. The pharmacological chaperones are designed to mimic part of the substrate of the target enzyme. These chaperones selective bind to the target enzyme and stabilize it and help with its proper folding. In addition, the chaperone can detach from the enzyme and allow it to properly degrade the substrate in the lysosome. The pharmacological chaperones are orally administered and small in size, which allows them to propagate widely within the body. In the endoplasmic reticulum, where the pH is relatively neutral, they are attracted to the enzymes and bind to it. The enzymes with the chaperone are now able to more easily pass the quality control of the cells and make it into the lysosome. Once in the lysosome the more acidic pH encourages the pharmacological chaperone to dissociate from the enzyme. This now frees the enzyme to degrade the accumulated substrate, thereby normalizing the Gb3 levels and alleviating the disease symptoms.

Effectiveness of Amigal

Currently Amigal is in a phase III study that will examine a total of 60 patients, where the primary endpoint is a greater than 50% reduction of kidney interstitial capillary Gb3 (as compared to placebo). There are 36 global site and enrollment is expected to be completed in the first half of 2011 with top-line data in the second half of 2011.

The phase II data of Amigal in FD was quite promising and bodes well for the phase III data. While the trials will all have small numbers given the rarity of the diseases, the phase II trial had 5 out of 9 patients show a greater than 50% reduction of kidney interstitial capillary Gb3 at the first post-treatment biopsy. This increased to 7 of 10 at the second post-treatment biopsy. In addition, the secondary surrogate (change in urine Gb3 from baseline to week 24) provided additional evidence of efficacy. The subjects with the responsive mutation had a 34% decrease and those who received 150 mg QOD had a 52% decrease.

The success of the phase II study allowed the company to extend it to examine the long term efficacy and safety of Amigal. At this point 23 subjects have been treated with Amigal for over 3 years and 7 for over 4 years. The drug has maintain a clean safety profile with no serious adverse events. In addition, the drug continues to show efficacy. In fact, the estimated glomerular filtration rate (eGFR) remained stabile out to the 3 and 4 years of the study. Those identified as responders to Amigal had an annual eGFR change of +1.6 mL/min/1.73m2 compared to an expected decline of 2.93 for males, and 1.02 ml/min/1.73 m2/year for females.

In general, then, the phase II data and its extension were quite positive and bode well for the phase III trial that will finish this year. One caveat, however, is that these trials are all small (again because this is a rare disease). With small numbers comes greater variation. This means that results are more likely to change than if the trials were based on larger numbers. This does not mean that one should not believe the phase II results but that one should realize the added risk given the size of these trials.

Chaperones and ERT

The current phase III trial of Amigal essentially targets only half of the FD population. These responders are those who have a missense mutation that causes of mid-folding of the enzyme. There are other causes of FD that are not related to the proper folding of the enzyme and these patients do not respond to Amigal monotherapy. While Amigal is co-administered with ERT, however, the effectives of the ERT is enhanced. Pre-clinical studies of this approach showed that Amigal significantly increased Fabrazyme tissue uptake and reduced GL-3 levels in the kidney.

Amicus is moving forward with this approach for the treatment of Pompe disease. In fact, Amicus recently announces an agreement with the FDA to Commence Phase 2 Study of AT2220 Co-administered with Enzyme Replacement Therapy for Pompe Disease. In addition, Amicus has early pre-clinical work on the combination of a pharmacological chaperone and ERT for the treatment of Gaucher disease.

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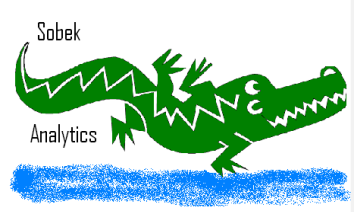

Disclaimer

I am not a certified financial analyst. All the information provided in this report is my interpretation and may contain errors. Please, do not invest based solely on my opinions as it is critical for all investors to conduct their own due diligence and invest in ways that best fit their own needs. In addition, I own shares of FOLD.