First FARA Webinar

July 26, 2011

Repligen and its HDAC Inhibitors for FA

Summary

This was the first in what is to become a series of periodic FARA webinars designed to enhance up-to-the-minute communications between the FA patient community and FARA's scientific, pharmaceutical and advocacy partners regarding key aspects of the research effort aimed at treatments and a cure.

The Repligen participants were CEO Walter Herlihy, VP for Research and Development James Rusche and Medical Director David Jacoby. FARA Executive Director Jen Farmer moderated the webinar that included 25 participants.

Walt Herlihy began with an overview of Repligen's three-pronged business plan – pancreatic imaging, bio-processing, and drugs for rare neuro diseases (FA and SMA). The FDA assented to Repligen's proposal for a phase I clinical trial of its SMA drug (RG3039) and dosing of healthy volunteers began this month. Repligen filed with the FDA its FA submission for a clinical trial in May 2010 and was put on hold in June 2010 because of FDA concerns that the animal toxicology studies did not provide enough information to guide first dosing in man. Repligen had to repeat and extend the animal toxicology studies to show that the drug is safe for humans. Repligen believes that the data from the longer, repeated animal studies will address the FDA concerns by showing, for example, that the animal toxicity appeared at doses higher than those anticipated for humans and the toxic impact was reversed when dosing was halted. Analysis of all the additional data should be complete soon so that Repligen can submit its final response to the FDA this quarter and, if the FDA releases its hold, the phase I clinical trial of RG2833 in healthy volunteers could begin in the United States by year's end.

In the meantime, Repligen is pursuing RG2833 clinical trials in Europe. The European Medicines Agency (European Union's FDA equivalent) has assented to Repligen's proposal of a phase I clinical trial of RG2833 in FA patients – Repligen is now seeking the permission of the Italian government and the ethics committee at the Italian hospital where the trial is proposed. If that permission is granted, the phase I trial of RG2833 in FA patients should commence in Italy by year's end.

Walt Herlihy also told the group how Repligen has explained to its shareholders why all should be excited about the company's HDACI program in FA: 1) clear disease biology with evidence that increasing frataxin protein expression just two-fold could potentially arrest the disease; 2) significant orphan disease market (FA not ultra rare); 3) limited competition; 4) long-lasting patent protection; 5) favorable regulatory environment (should qualify for fast-track market

approval reviews and other FDA incentives); 6) strong relationships with and funding from non-profits such as FARA, MDA and GoFAR, and 7) unique approach (small molecules for protein replacement).

Walt Herlihy and Jim Rusche briefly reviewed the history of the HDACI program and hit just a few of the key aspects of all that has been accomplished in moving from licensing the initial discovery from The Scripps Research Institute and Joel Gottesfeld's lab in 2007 through all the medicinal chemistry required to identify and optimize a lead drug candidate, working out all the manufacturing requirements, conducting all the tests to determine pharmacokinetics and toxicology, developing a follow-on candidate, etc. Walt summarized the financial parameters of Repligen's FA HDACI program by saying the company has devoted about $13.4M in direct costs and a couple million dollars more in indirect costs to the program, which has been offset to some extent by grants from the non-profit partners (FARA, MDA, GoFAR, etc.).

Jim Rusche went on to highlight some of the key experiments that indicate to Repligen the significant promise of its HDACIs in FA. Chief among these experiments have been the often-repeated tests in the blood cells from FA patient families (thank you) that have demonstrated the consistent ability of the HDACIs to increase frataxin protein expression in the patient cells up to the levels in the cells from carriers. Jim also emphasized the importance of the fact that the FA mutation is not in a protein-coding region of the FA gene, so the protein that is expressed (and increased by the HDACI) is the normal ("wild type") frataxin protein that is in short supply in FA patients.

In the opening presentation and later in the Q&A portion, Jim Rusche explained the importance of the early phase clinical trials of RG2833 establishing "proof of principle." Early in the trials, we want to prove the principle that an HDACI administered to FA patients is effective in significantly increasing the expression of the frataxin protein. Later in the trials, of course, we will want to show that the significant increases in frataxin protein expression result in significant clinical benefits.

Walt Herlihy concluded the initial presentation by explaining Repligen's concept of drug development partnerships that will be needed to advance the HDACI through the later-stage clinical trials and, if successful, into the global market place. Repligen has developed a great deal of expertise and experience with FA and HDACIs but it does not have, in house, all the drug development and global marketing resources that will be needed to move the FA HDACI through all the steps of drug development and marketing. Repligen's plan, therefore, is to seek pharmaceutical partners who can fill the gaps in resources and capabilities at the appropriate junctures, while Repligen applies its own resources, expertise and experience to insure that the HDACI program receives all the quality time and attention needed to advance it promptly to the finish line. Discussions with potential partners have commenced but are in the very early stages.

Jen and the Repligen speakers also emphasized the importance of all the FA patient community has done and continues to do to help advance the HDACI program and participate in clinical research generally. FARA, GoFAR and MDA have supported the HDACI program directly. The patient community has donated blood samples facilitated by FARA and GoFAR. FA patients are increasingly active in clinical research by participating in FARA's Collaborative Clinic Research Network in FA; enrolling in the FARA patient registry; providing blood, skin and cheek swab samples; and participating in efforts to develop biomarkers and clinical outcome measures. Jen also reminded patient families of the importance of fundraising to help support FA research. She also indicated that FARA is advocating for increased budgets for the NIH and FDA.

The Q&A portion of the webinar addressed questions submitted in advance as well as several asked live. Highlights were as follows:

Q1. Status and impact on FDA of the Italian trial?

A1. Repligen has assent of the appropriate committee of the EU's regulators (EMA) to conduct phase I trial in FA patients. Seeking assent of the appropriate Italian Government Ministry and the Ethics Committee (similar to Institutional Review Board in U.S.) of the local hospital in Turino. The FDA assures us that, if such a foreign trial is conducted to the same standards as in the U.S., the data from the Italian trial will be taken fully into account.

Q2. Has the response to FDA concerns taken so long because animal tests had to be extended to address FDA concerns about toxicity regarding spermatogenesis?

A2. Yes, the initial animal studies did show some toxicity in that regard as well as some mild atrophy of lymphoid tissue – neither of which is uncommon in such animal studies. What the additional animal studies seem to demonstrate is that these toxicities occurred at dosing levels higher than those we anticipate in humans and that the toxicities are largely reversed when dosing was discontinued. We believe the additional data will be sufficient to address the FDA concerns.

Q3. Do you expect the HDACI to stop progression or reverse it?

A3. Impossible to answer that question but, because the HDACI target is to increase expression of frataxin protein and because the HDACI gets across the blood-brain barrier and into key tissues such as heart and sensory nerves, etc., we are quite hopeful that the HDACI will result in considerable benefits.

Q4. Is there a possibility that the HDACI could lead to excessive frataxin protein that could be toxic? Have you seen the article from studies in an FA fly model that seemed to indicate such a possibility?

A4. We have conducted a large number of HDACI experiments in FA blood cells obtained in collaboration with FARA and GoFAR and have observed no evidence of such a problem. We should keep in mind that FA patients have frataxin protein levels ranging from around 10 percent of normal to 20 percent of normal and that we need, most likely, to increase those levels by a factor of two or three to be significantly therapeutic. So, we have a wide margin, here. In our experiments, the HDACI has increased frataxin protein levels as little as 20 percent and as much as 6-fold. In most cases, even a 6-fold increase would take the frataxin protein levels to only slightly above normal levels. Also, we know of no experiments in mammalian cells showing toxicity from excessive frataxin protein.

Q5. Status and timing for the follow-on compound?

A5. In an excellent three-way collaboration, Repligen, FARA and GoFAR have supported development of a follow-on drug candidate. We believe we have identified a promising follow-on HDACI compound and have begun testing it in animals to see if it might be somewhat better in crossing the blood-brain barrier and may be somewhat more stable in blood. No simple answer to question as to when you might want to shift gears from a lead candidate to a follow-on candidate, but we might want to show "proof of principle" in the lead candidate before considering such a shift. In other words, we might want to show in the early-phase trial of RG2833 in FA patients that it consistently and safely increases frataxin protein levels over time and, then, consider whether the program could be improved by a follow-on candidate with an even better safety profile resulting from better penetration of the blood-brain barrier and greater stability.

Q6. In the animal studies, you say you have shown that the toxicity was reversed when the dosing was halted. Because we will need to dose FA patients on a continuous basis, wouldn't such reversibility be irrelevant?

A.6. First, we are not sure that the impairment to fertility will occur because the toxicity did not develop in the animals until they were dosed at levels higher than we intend to use in humans. Also, it was important to show, even at the much higher dosing levels, that any toxicity could be resolved by ceasing administration of the drug.

Q7. What did you learn from your HDACI experiments in the blood cells from FA patients vs. the blood cells from controls who were clear (no FA mutation)?

A.7 We learned that the HDACI had no effect on the cells from clear controls and that, in most the cells from FA patients, the HDACI increased frataxin protein levels significantly. Now, we look forward to testing the HDACI in FA patients for the "proof of principle" that the HDACI will increase frataxin protein expression in patients.

Q8. On the business side, what kind of response regarding the HDACI program are you receiving from your investors?

A8. Over the 4 years of the program, Repligen has received a strong level of support for the program, resulting in consensus that we should move it forward at a rapid pace. Yes, we will need capable partners to help get this exciting program to the finish line, but we intend to support and protect the program so it continues to get the time, attention it needs to advance it fully and effectively.

This first FARA webinar got us off to a great start in this new program to enhance communications in the FA community. Our thanks to Walt Herlihy, Jim Rusche and Dave Jacoby of Repligen for their time and contributions to making this such a successful event and for all they are doing to develop such an exciting and promising candidate treatment for FA.