***Triheptanoin Clinical Trial Results and Reactions, October 2016***

In September 2016, Dr. Raphael Schiffmann presented the results of the Phase 11 APBD clinical trial for Triheptanoin (or C7) at the Society for the Study of Inborn Errors of Metabolism (SSIEM). Unfortunately in that SSIEM presentation (SSIEM link shown here), Dr. Schiffmann concluded that the “study failed to show the efficacy of Triheptanoin in APBD patients….”

Based on this SSIEM presentation, some members of the Foundation formulated nine questions for Dr. Schiffmann. The Foundation wrote a letter to Dr. Schiffmann posing these questions, and he graciously answered them.

Dear Dr. Schiffmann,

We are honored by the years of investigation that you have spent on studying APBD and appreciate the commitment of your supporters to your efforts.  We also really appreciate your presentation on the results of the Triheptanoin study.  It is especially significant because, as you well know, it is the only trial specifically on APBD. Thus we want to draw from it as many lessons as we can.  It is important that we help the community develop a realistic understanding about clinical trials.

***Q1***-What do you think is the most important accomplishment to come out of this trial?

***A1-***We identified and validated clinical outcome measures for APBD and studied them over time.

***Q2-***What would you-and we-say to the patients that are so disappointed by the results of the Triheptanion trial and the time it took to get results?

***A2***-Clinical trials are done to find out if a treatment works. Sometimes it does and sometimes it does not. That is normal.

***Q3***- Do you think that the lack of a sensitive and reliable clinical endpoint had any effect on the outcome of the trial?

***A3***- Possibly, [it was the choice of the endpoint]. More likely the treatment did not work. Note that we showed that these endpoints got significantly worse over time suggesting that they are OK to use. Maybe over a longer period of time such as a year [the results may have been different]; however, I did not think patients would accept that.

***Q4-***How do you account for the fact that some patients found Triheptanoin helpful?

***A4-***That happens with every intervention. It happens either because of a placebo effect or more rarely because of a true effect that occurs only in very few patients.



***Introduction to Q5***: Given the demonstrated heterogeneity of the APBD condition, this clinical trial correctly used a randomized and double-blind Crossover design to avoid potential selection bias in the evaluation of C7 efficacy. But we understand that it was difficult to recruit APBD patients for this trial, especially with five visits required in a year; baseline, walking test every three months, and placebo/oil given at six month intervals. Question 5 has multiple parts.

**Q5-** Concerning future APBD Crossover trials on new drugs, what would you recommend for reducing travel and other costs of participation to improve recruitment and retention of patients?

***A5***-[I am]not sure.

Limit visits to three per year: baseline, six months and 12 months?

***A5***-That all depends on the study. But that could be one solution for sure.

Establish more test sites around the country?

***A5***-Yes, that will help.

What are the minuses of teaming up with a drug company to help defray the costs of travel, drugs, and other clinical trial costs?

***A5***-Drug companies are in general good to work with since they have the most experience in developing medications/treatments and in general they pay for the whole study.

***Q6***- Why did you assume no washout period for this C7 trial when other rare disease investigators did otherwise in similar circumstances? Referring to ClinicalTrials.gov, current C7 Crossover trials show a washout period ranging from one week for GSD-V to one month for HEMIHEP. In 2009, Dr. McCue, M.E. and others applied C7 to horses and used a 26-day washout period for that Crossover trial.

***A6***-That depends on the disease, the drug and the study that is being contemplated. C7 oil has a short effect time in view of its metabolism and can provide energy only for a few hours. If that was the mechanism of a potential effect, it is very short and therefore no need for a washout period. There was also a practical reason to assume that in such a small study with patients coming from all over the country.

***Q7-***Why did you include trial patients less than 40 years of age when your presentation indicated that the onset of the disease is in the fourth and fifth decade of life? In the 2011 C7 patent in-use application, you cited that the 2007-2009 Phase 1 C7 study had been successful, and its APBD patients ranged in age from 51 to 66.

***A7***-There was one patient or two who were younger but showed a typical APBD in every way, and there was no justification to exclude them.

***Introduction to Q-8:*** This presentation raisesthe problem of false positives when testing multiple comparisons individually, one at a time. When doing so, the C7 clinical trial results could not be proven positive statistically.

By way of statistical explanation, suppose we consider the efficacy of a drug in terms of the reduction of any one of a number of disease symptoms. As more symptoms are considered one at a time, it becomes more likely that the drug will appear to be an improvement in terms of at least one symptom. Consequently, our confidence in the results will be weaker if it is observed as part of an analysis that involves multiple comparisons one at a time, rather than an analysis that involves only a single comparison. When compensating for this with the false discovery rate adjustment, Dr. Schiffmann found he could not prove the efficacy of C7 statistically.

***Q-8***-Did you consider using principal component analysis to combine certain results of the clinical trial to cut down on the number of multiple comparisons? For example, the primary and secondary endpoint data may be highly correlated with one another and benefit from an endpoint index that is developed with the first principal component. The endpoint index then is tested statistically, rather than the individual endpoints one at a time.

***A8***-The question is better addressed to statisticians. We shall have a detailed statistical report in our manuscript.

***Q9***-In April 2016, you said that you would publish the raw de-identified data for the Phase II C7 trial. When do you expect that these data will become available?

***A9***-Sure, eventually we have to put the data in clnicaltrials.gov. Again, it will all be in our publication. If beyond that someone has questions or request we shall happy to provide all appropriate data.