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We hope this will show everyone that has supported us the fantastic results that we have already obtained. We currently have over 30 professionals involved in the Project Cure SMA network at multiple sites across North America. This would be a major endeavor and accomplishment even for a for-profit biotech company to pull off.

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1. Adults and children respond differently to medications, and so it will be difficult to generalize findings from the CARNI-VAL trial to our adult patients. Therefore, it is important to do a separate study to assess effectiveness in adult patients.

2. It is not clear that adult ambulatory SMA patients will require any Carnitine supplements, and determining this important information is a major goal of this new trial.

3. We need to document that our outcomes measures for assessing motor function, strength and quality of life in adult SMA patients are up to the task as new compounds become available for testing over the next couple of years. This is particularly crucial since there have been very few drug trials in adults with SMA.

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We continue our efforts to enroll pre-symptomatic SMA subjects at the University of Utah site. These are usually younger siblings of already diagnosed SMA children. They are eligible to participate in treatment with Phenytoin by as late as 2000 there was no means for specifically evaluating function in children with SMA, but the concept and need for such a scale was becoming apparent to the investigators who were to coalesce into Project Cure SMA. An accurate means of measuring function is, after all, essential to determining whether or not a drug works. For the last 5 years, clinicians of the Project Cure

CARNI-VAL Trial Enrollment Complete
Two New Trials Planned For 2007

by Kathryn J. Steege, M.D.
Associate Professor, Neurology, Adjunct Associate Professor, Pediatrics, University of Utah School of Medicine, Project Cure SMA-Principal Investigator

by Thomas Crawford, M.D.
Associate Professor of Neurology and Pediatrics, Johns Hopkins School of Medicine, Project Cure SMA, Principal Investigator

Functional Testing Scales for Use in SMA Clinical Trials

By as late as 2000 there was no means for specifically evaluating function in children with SMA, but the concept and need for such a scale was becoming apparent to the investigators who were to coalesce into Project Cure SMA. An accurate means of measuring function is, after all, essential to determining whether or not a drug works. For the last 5 years, clinicians of the Project Cure

continued on page 2
Clinical Trials Basics: The Drug Testing Process

Potential drugs to treat SMA fall into two different classes:

- Drugs approved by the FDA for other diseases (i.e., PPA (Phenylbutyrate), VPA (Valproic Acid), HU (Hydroxy Urea)) which are being repurposed for use in SMA.
- Novel drugs not yet approved by the FDA which are specifically designed for use in SMA (i.e. the SMN enhancing compound being developed at deCODE Chemistry).

For the latter class of compounds, not yet approved for use in humans for any purpose, the testing paradigm for FDA approval typically requires three stages of clinical trials, with each stage specifically designed to test different aspects of the drug:

- The first stage is often called a Phase I study, and is intended to test the safety of the drug, but generally it is not intended to evaluate whether or not it works.
- The second stage is the "Proof of Concept" study: Phase II (CARNIVAL or Phase II). It is used to demonstrate whether or not the drug has benefit, to further assess its safety and side effect profile, and to better define the best dose to be used in the final stage of clinical testing, which is called the Pivotal study.
- Phase III Pivotal studies are designed to determine definitively whether a drug has clinical benefit in a particular patient population.
- The time required for a full set of clinical trials can range from 5 to 8 years.

The typical drug testing process described above for FDA approval of new drugs can often be condensed into a more streamlined process if the drug is intended for use in an orphan disease like SMA where no effective treatment is presently available. For drugs that are already approved for use in humans, the series of required studies is also simpler.

continued from cover

SMA group have, with the support of FSMA, been active in developing, and further underscoring, a functional scale for this purpose. While not as "sexy" a process as working on genetic cell cultures to find out how we might make a drug that makes individuals with SMA stronger, it is just as important, as without such proof no drug can be approved.

The ideal scale for testing function for SMA should have several qualities:

- First, it needs to be reproducible, so that different investigators at different times in different places would assign the given patient the same or similar score.
- Another quality is that it has to be sensitive to change. For example, if a scale only scores one patient as having two grades of function, then very few patients could move from one grade to the other even if the drug had a powerful effect – though the reproducibility of those two measures would be good.
- So these two qualities – reliability and sensitivity to change – are in partial opposition to one another, where improvement in one dimension often degrades the other. Of course, with some clever work it is possible to get a little bit more of both.
- Another important quality is range of applicability. It would be best if a single scale were able to assess changes in power in the very weak, or the very strong, or those with multiple contractures, or otherwise ill individuals as well as it can accurately and reliably assess those who are stronger, older, supple and healthy.
- It is important that the scale itself be focused intensely on the areas that we think might be affected by a drug being tested.
- The scale needs to be easy to administer, not so esoteric that is held by only a few special "insiders," and documentable for future investigators.
- Finally, it has to be fun and easy for children with SMA to perform. "Buy-in" is essential to motivation, which is essential to performance, which is essential to success.

With all of these concerns in mind, the investigators of Project Cure SMA started looking at all of the scales available for assessment of motor function in children in 2001. One scale, developed by Marion Main and colleagues at the Hammarsmith Hospital in London and eventually published in 2003, was of particular interest as it was: the modified Hammersmith SMA scale for the purpose of defining a severity ranking, but it was validated for use by only a limited number of expert investigators within a single site. While not initially intended as an outcome measure scale, it had many of the above desired properties and was sensitive to items that matter to children with SMA.

This was the beginning of a long process of testing and retesting, validation and revalidation, by a team led by Kristin Krosschell of Project Cure SMA. The process involved hundreds of evaluations, consisting of visits by SMA families to team members, who then circulated video-tapes of the sessions for blinded cross-evaluation. The "Modified Hammersmith" scale was published in the same prestigious journal as the original scale. It is validated for multi-center use, by investigators with minimal "special" knowledge, has excellent reliability, and appears to be sensitive to the functions that matter in SMA and that change over time. A full manual and CD of the test explaining each of the test items and scoring in detail has been produced.

Members of the "Modifed Hammersmith" development team are active in the International CARNIVAL committee (funded by FSMA) for SMA subgroup on outcome measures.

This is not the end of the process for outcome measures, however. There are clearly areas for improvement. The Modified Hammersmith focuses on children within a certain range of function. We are working now to extend this scale to the larger range of children with SMA. With the assistance of Dr Finkel at CHOP, with funding by FSMA, development of scale items that will be reliable and sensitive to change in infants with SMA I is a major goal. In addition, the potential for including some of those individuals excluded in the Project Cure SMA study CARNIVAL is a very exciting time, as the trial will move to completion during the next year, and we are all anticipating the results.

Currently, our clinical network (www.projectcuresma.org) consists of six clinical testing sites and the entire supporting infrastructure. The support includes a full-time clinical trials manager (who runs the daily operations), a central pharmacy, a group for statistical analysis of data, an informatics core for data collection, and an outcome measurement development group (please see the chart for further details).

Now that an efficient drug-testing infrastructure has been established, which has been shown to be effective during the course of the CARNIVAL trial, we are poised to expand and begin several new projects. With a fully operational clinical network in place, new trials can be initiated faster, more cheaply, and more effectively. Therefore, this is the ideal opportunity to leverage our previous investment and to expand our clinical work in three main ways:

- Initiate trials in a broader population of SMA patients.
- Add clinical testing sites in North America.
- Prepare to test novel SMA drugs not yet approved by the FDA.

First, we want to conduct clinical trials that enroll a broader range of people with SMA, including both babies and adults. In order to make this happen, Kristin Krosschell, Principal Investigator of the "Functional Outcome Measure Working Group", has been developing and validating new clinical measurements in concert with the rest of the Project Cure SMA team. Our goals are to initiate trials in both SMA Type I babies and in adults with SMA Type III in 2007, if the necessary funding is available.

We also want to expand the number of clinical trials across North America. This will enable greater patient access to clinical trials, as well as reduce the amount of travel required for participation. Increasing the number of testing sites will also be critical for the success of a Type I trial in SMA Type I babies, for whom travel is especially challenging.

Finally, we anticipate that the clinical testing of novel therapeutics (non-FDA approved drugs) will commence for SMA in the next 2 years. Hopefully our primary drug discovery program with deCODE will Phase II trials in 2007. Having a fully functional clinical network with a sufficient number of sites to conduct a pivotal SMA drug trial will help attract and encourage biotech and pharmaceutical companies to invest in SMA drug development. Without a drug testing infrastructure already in place, companies can question the feasibility of conducting clinical trials in the SMA patient population.

It is important to all of us at Families of SMA to identify treatments for every person with SMA. We feel it is essential to use the momentum generated by the CARNIVAL trial to expand the number of people who can participate in clinical trials through Project Cure SMA.

With your help we can make this happen.

Jill Jarecki, Ph.D.
Research Director, Families of SMA

Dear Families and Friends,

This issue of Compass focuses on the achievements of the Project Cure SMA clinical trial network over the past year and our goals for the future. Project Cure SMA is a clinical trials network, developed with financial assistance from Families of SMA. The network has focused first on developing the trial infrastructure and drug testing protocols needed to assess candidate drugs for SMA, and then more recently, actually conducting a clinical trial.

During the last twelve months, the Project Cure SMA team has been conducting the Phase II CARNIVAL clinical trial to test the combined efficacy of Carnitine and Valproic acid. As was highlighted in this issue, Project Cure SMA reached an important milestone in May when we have now reached full enrollment of 90 SMA patients in the CARNIVAL trial. This is a very exciting time, as the trial will move to completion during the next year, and we are all anticipating the results.

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Research Director Update

FALL 2006

Did you know that FSMA will fund over $5 Million in research this year? Every dollar brings us closer to finding a cure!

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Project Cure SMA
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Skeletal Muscular Atrophy

Families for SMA
Type II, Childhood-Onset
Skeletal Muscular Atrophy

Families for SMA
Type III, Adulthood Onset
Skeletal Muscular Atrophy

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Type IV, Aging
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FSMA Donation Form
SMO 2006

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Carni-Val Trial Enrollment Complete
Two New Trials Planned For 2007

by Kathryn J. Scrobbia, M.D.
Associate Professor, Neurology, Adjunct Associate Professor, Pediatrics, University of Utah School of Medicine, Project Cure SMA-Principal Investigator

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We continue our efforts to enroll pre-symptomatic SMA subjects at the University of Utah site. These are usually younger siblings of already diagnosed SMA children. They are eligible to participate in treatment with Phenylbutyrate from as early as the newborn period. We have enrolled several such children to date, and all have received medication starting in early infancy. Obviously this is a challenging and long-term project, but helps support our goal to identify safe and effective treatment that can be given as early as possible following a diagnosis of SMA. In the future, we hope that newborn screening at birth will help to identify children at risk, thus giving them the best possible chance to beat this disease.

Kenneth Hobby
Executive Director, FSMA

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by Thomas Crawford, M.D.
Associate Professor of Neurology and Pediatrics, Johns Hopkins School of Medicine Project Cure SMA, Principal Investigator

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