

COMPASS

A Publication Dedicated To Research Updates



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



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It has been a year of increasing momentum and excitement for Project Cure SMA. We began enrolling our first participants in the CARNI-VAL trial last fall, and we are pleased to announce that we have achieved our goal of enrolling all of the required ninety patients. Enrollment in CARNI-VAL was certainly spurred on by the positive results in our open label Valproic Acid trial. Over the next few months the first patients that were enrolled in CARNI-VAL will finish treatments. We expect all participants to finish the trial by Fall 2007, with results to be released as soon as possible afterwards.

We have been in the planning phases for additional clinical trials. **The first of these proposed trials would be a single-site study targeting ambulatory adult SMA patients.** It will be designed as a placebo-controlled trial of Valproic acid. Subjects will be enrolled for a total of one year, receiving either six months of placebo followed by six months of medication or six months of medication followed by six months of placebo (i.e. all patients will get drug for six months). Neither the clinical investigators nor the patients will know which group they are in until the completion of the entire trial. This is an important effort for several reasons:

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 outcome 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.

We are planning an additional trial for 2007 that will enroll Type I SMA children.

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 treatments 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.



A Project Cure SMA team member works with a patient during the SMA CARNI-VAL Trial.

Functional Testing Scales for Use in SMA Clinical Trials



by Thomas Crawford,
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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

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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. PBA (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 (CARNI-VAL is a Phase II study). 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.

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SMA group have, with the support of FSMA, been active in developing, and further modifying, a functional scale for this purpose. While not as “sexy” a process as working on genes and 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 a given patient the same or similar score.
- Another quality is that it has to be sensitive to change. For example, if a scale only scored a 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 young, 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 intently on the areas that we think might be affected by a drug being tested.
- The scale needs to be easy to administer, not tied to special expertise 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, as “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 Hammersmith Hospital in London and

eventually published in 2003, was of particular interest. It assessed children with SMA for the purpose of defining a severity ranking, but it was validated for use by only a limited number of experts within a single site. While not initially intended as an outcome measure scale, it had many of the above desired properties and a real focus on the 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 “Modified Hammersmith” development team are active in the International Coordinating Committee (ICC) for SMA subcommittee 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 CARNI-VAL is an important goal.

Do you want to participate in clinical trials?

To learn more see the Indiana registry ad in the Fall 2006 Directions or visit the FSMA website www.curesma.org

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 necessary clinical 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 CARNI-VAL 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 we have now reached full enrollment of 90 SMA patients in the CARNI-VAL 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.

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 measure 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 CARNI-VAL 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 trial sites 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 babies, for whom travel is especially challenging.

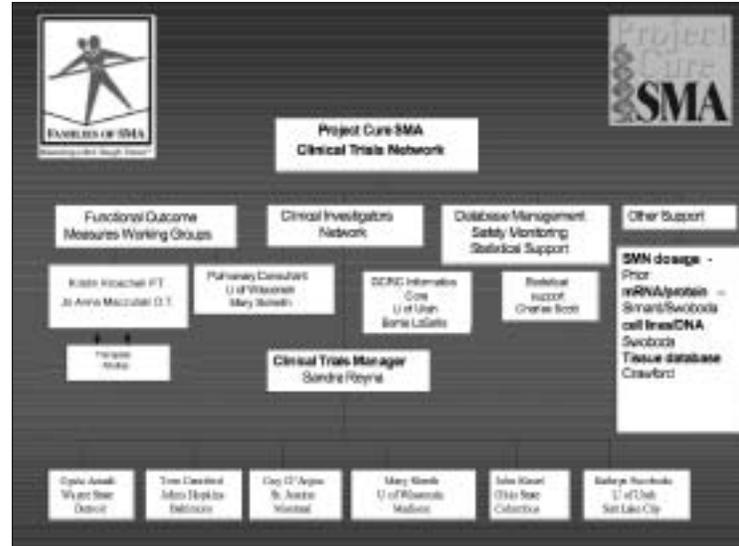
Finally, we anticipate that the clinical testing of novel therapeutics (non-FDA

approved drugs) will commence for SMA in the next 2 years. Hopefully our primary drug discovery program with deCODE will enter Phase I 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 CARNI-VAL 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



FSMA Donation Form

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Dear Supporters,

Clinical trials are really where all of our past efforts and results in academic research and testing in the laboratory finally start to reach patients with practical applications. This is by no means the end of the road, but it is the final stage that we need to go through before we can say we have developed a treatment for this disease.

I hope that this edition of *Compass* will provide you with valuable information on the great results that we have already obtained from our funding of Project Cure SMA, and also with details on our plans and goals for the future.

This edition is the first publication that we have sent out to the entire "FSMA Community", including all of our supporters – over 50,000 families and organizations in all! We hope this will show everyone that has supported us the fantastic results that we have produced, and will continue to produce in the future, using your kind and generous donations.

As described by Jill Jarecki, our Research Director, and shown in the graph, the infrastructure involved with running clinical trials is sub-

stantial. 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.

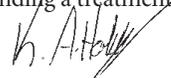
In 2003, FSMA funded just under \$150,000 in clinical work for SMA. This past fiscal year we funded over \$1.4 Million for clinical trials. This growth is primarily a result of the success of our earlier programs in producing new opportunities to test drug treatments in patients.

These demands will increase over the next few years as we increase the range of types of SMA patients that are enrolled in trials, as we expand the number of clinical sites to allow easier travel,

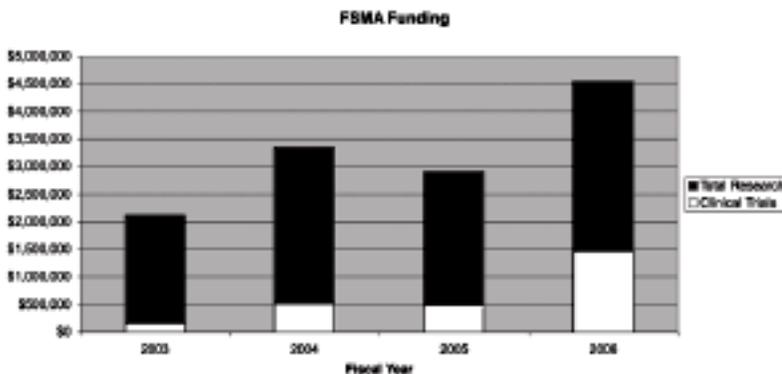
and especially as we begin to test additional drugs including novel therapies designed specifically to treat SMA. Your support is critical.

The opportunities that are now available to us will require significant levels of funding. ***Our goals are to fund \$3.4 Million over the next two years for clinical trials.*** These are exciting and important times for the SMA community.

Thank you for your support of our goal in finding a treatment for SMA.



Kenneth Hobby
Executive Director, FSMA



Did you know: FSMA has funded over \$25 Million to date for research, including \$1.4 Million for clinical trials last year. FSMA is leading the way in advancing research and supporting families. FSMA funds clinical trials, drug discovery and research that helps to expand knowledge of SMA and bring us closer to a treatment and a cure.

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