



Families of SMA *Research. Support. Hope.*

COMPASS

A Publication Dedicated To Research Updates

Dear Families and Friends

The clinical trial network Project Cure SMA was started by FSMA in 2001 as a collaborative initiative between our organization and clinical investigators. It was designed to facilitate the progress of promising new therapies toward clinical trials. Our specific aims were to:

- Test repurposed drug candidates for SMA
- Develop measurements for SMA clinical trials
- Improve our understanding of SMA natural history
- Develop experienced SMA trial sites across US
- Establish a patient registry for trial recruitment

Overall, this effort was designed to develop the needed infrastructure to conduct pivotal FDA clinical trials on novel SMA drugs, while initially conducting repurposed drug trials as these novel therapies were being developed.

To date, the Project Cure SMA network has conducted five clinical trials and helped develop multiple clinical trial endpoints, with over \$6 million in funding from FSMA. We have solely supported the network. Much of their progress and results are described within.

We have come a long way since 2001. We now have several promising candidate therapies specifically designed for SMA on the brink of starting the clinical trial process. Our current focus is on preparing for these novel therapy clinical trials. We need to be ready to conduct FDA registration trials by having validated endpoints, qualified biomarkers, established means for patient recruitment, and experienced clinical trial sites.

The US government, through a new initiative called “**The Network for Excellence in Neuroscience Clinical Trials - NEXT**”, will also support this type of work. This is a new clinical trials network designed by NINDS to promote clinical trials in neurological diseases. The first clinical trial will be to develop and qualify biomarkers for SMA. Dr. Elizabeth McNeil has written an article for this newsletter describing their project and its goals. FSMA is actively pursuing ways to synergize our ongoing efforts and funding to Project Cure SMA with the NINDS NEXT project.



John Kissel, MD, Professor of Neurology at OSU says “**Project Cure has proven to be a ‘game changer’ in terms of SMA clinical investigations. In addition to performing important drug trials and perfecting trial methodologies, the group has really set the stage for future clinical trials as well as collaborative projects with the NEXT initiative.**”

Sincerely,

Jill Jarecki, Ph.D., *Research Director, FSMA*

Clinical Trials Conducted by Project Cure SMA

1. Open-label Safety/Tolerability Study of Sodium Phenylbutyrate in Type II/III
2. Open-label Safety/Tolerability Study for Valproic acid in Type II/III
3. CARNI-VAL Placebo Controlled Phase II Trial in Type II/III
4. Valiant Placebo Controlled Phase II Trial in Ambulatory Adults with Type III
5. CARNI-VAL Open-label Study in Infants with Type I

See Funding Facts link on the FSMA website for details of our \$6,435,707 funding to Project Cure SMA.

Project Cure Is Making Progress Against SMA

Modified from a press release by University of Utah.

Kathryn J. Swoboda, MD, leads the team of University of Utah researchers investigating the disease and is the Principal Investigator for Project Cure SMA. “**Families of SMA made an early and astute commitment to the development of a clinical trials network that has paved the way to bring new therapies rapidly to the clinic. Now, as several novel therapies approach clinical trials, we are well prepared to prove or disprove their efficacy.**”

Project Cure SMA is a clinical trials network of seven sites located in the United States and Canada, fully funded by Families of SMA. Additional locations include Johns Hopkins University, led by Dr. Thomas Crawford; The Ohio State University, led by Dr. John Kissel; University of Wisconsin, led by Dr. Mary Schroth; Wayne State University, led by Dr. Gyula Acsadi; Duke University, led by Drs. Priya Kishnani and Edward Smith; and CRME du CHU Ste-Justine in Montreal, led by Dr. Guy D’Anjou.



CARNI-VAL Clinical Trial Results Published from Project Cure SMA Network



Multiple lines of evidence, including treatment of patient-derived cell lines, animal models and open-label pilot human trials, have suggested that valproic acid (VPA) might have a therapeutic benefit in patients with SMA. The SMA CARNIVAL TRIAL

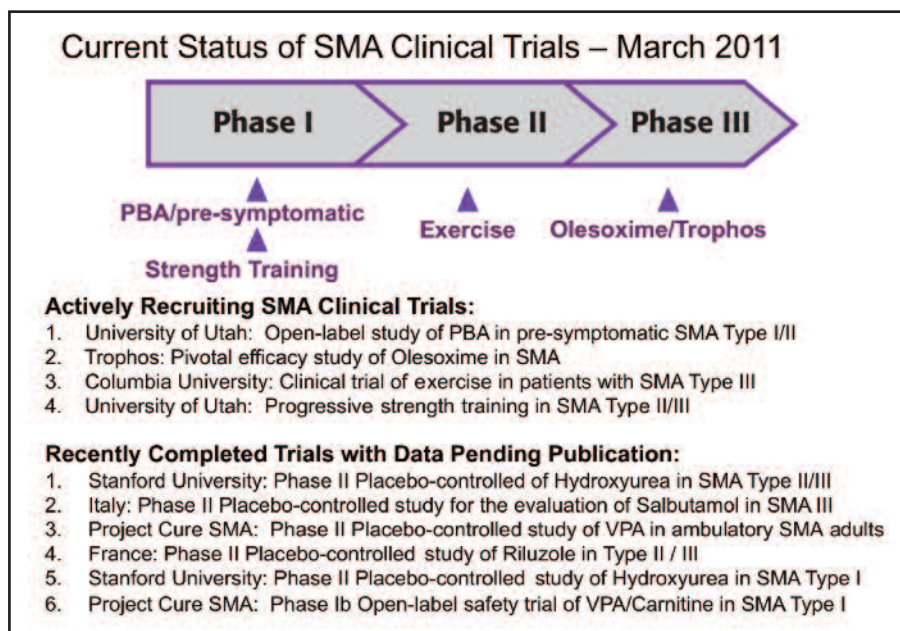
was designed to evaluate the effectiveness of combined oral VPA and L-Carnitine in two different groups of children with SMA. This clinical trial was fully funded by Families of SMA.

Results were recently published from the SMA CARNI-VAL Trial Part I: Double-Blind, randomized, placebo-controlled trial of L-Carnitine and Valproic Acid in SMA. The paper was published in the Journal PLoS ONE.

This paper presents results for the first group: non-ambulatory SMA subjects 2-8 years of age. Sixty-one subjects with SMA were enrolled in 6 centers as part of Project Cure SMA clinical trial network and randomly selected 1:1 to receive Valproic Acid (VPA) and L-Carnitine, or placebo treatment for the first six months; all subjects received active treatment the subsequent six months.

The primary objective of the study was to test the efficacy and safety of the drug. The secondary objectives were to assess the methods (endpoints/outcome measures) being used to assess drug efficacy in a multi-center setting. Essentially to ask, what are the best ways to evaluate this or any other drug for SMA?

Though the trial as designed failed to show that VPA is helpful for this SMA population, it did confirm the earlier open label trial that the combination with L-Carnitine VPA is safe for children with SMA, with one consideration. Excessive weight gain is a problem for children with SMA as they grow older, and treatment with VPA may exacerbate that tendency. It is possible that a trial with a different combination



of patient selection, duration, primary outcome variable, and with greater attention to weight gain, might have had a more favorable result. However, the use of VPA and L-Carnitine cannot be recommended at this time based upon this trial.

While the study did not demonstrate functional improvement after a six month treatment with VPA and L-Carnitine, it did yield critically important insights. “The first trials of any drug in a new field of medicine are difficult”, said one of the study authors, Dr. Tom Crawford. “The design of any trial requires assumptions about which patients will be most responsive, the best duration of treatment, what means of assessment are most able to show improvement, and other choices. Each is critical to a trial’s ability to demonstrate benefit of treatment. Although negative, from this trial the community has learned a lot that will make future trials much more powerful.”

Second Set of CARNI-VAL Clinical Trial Results From Group II Presented: A 12 Month Prospective, Open-label Trial of VPA and L-Carnitine in Ambulatory Children with SMA.

Group II of the study involved an ambulatory group of 33 genetically proven SMA “standers and walkers” (type III), between the ages 3-17 years. Twenty-nine patients completed the 12 month open label study. VPA and carnitine were generally well tolerated, with only 1 patient developing a serious adverse event (dehydration) during the study. **In group 2, excessive weight gain and abdominal pain were the most frequent drug-related adverse events.**

There was no significant change in any of the primary outcome measures at six or 12 months. There were some changes in secondary measurements. Some pulmonary function measures showed improvement at one year as expected with normal growth. CMAP amplitude did significantly improve at six and 12 months, suggesting a possible modest biologic effect directly on motor neurons, but that change was not clinically meaningful in improving participant function.

The results of this analysis, coupled with the data from the Group I, indicate that VPA at the doses used in these studies is not effective in improving strength or function in children with SMA. The results also demonstrate that the out-

See website
for full articles
www.curesma.org

come measures implemented in this study are feasible, well-tolerated and reliable, and can be employed in future clinical trials in ambulatory children with SMA.

“While we are obviously disappointed in the negative results of the trial, through this study we have gained valuable insights in performing clinical trials in young children with SMA,” said Dr. John Kissel, Director of the SMA Clinic at Nationwide Children’s Hospital/The Ohio State University and Project Cure investigator. **“These insights will help us more efficiently and effectively evaluate future therapeutic agents. We also learned a great deal about the importance of controlling for certain variables, especially weight gain, when testing any agent in SMA.”**

Randomized, Double-blind, Placebo-controlled Trial of Hydroxyurea in SMA

In December Dr. Jong and colleagues at the Kaohsiung Medical University Hospital, Kaohsiung, Taiwan published results in the journal Neurology.

The purpose of the study was to evaluate the safety and efficacy of hydroxyurea (HU) in SMA in a randomized, double-blind, placebo-controlled trial. Twenty-eight patients with type II SMA and 29 patients with type III SMA were randomly assigned (2:1) to receive HU or matching placebo for 18 months.

Fifty-five patients completed this trial, which lasted from March 2007 to June 2009. Except for neutropenia, no differences were found in adverse events between the 2 groups.

Under the current regimen and schedule, HU brought about no improvement in patients with type II and III SMA, and its main side effect was neutropenia. This trial provides Class I evidence that HU 20 mg/kg/day does not effectively treat SMA.

Importance of Clinical Endpoints and Outcome Measures: Project Cure SMA Publishes New Results in Two Papers in the Journal “Muscle and Nerve”

The Project Cure SMA Clinical Trial Network Recently Published a Paper Entitled “Compound Muscle Action Potential and Motor Function in Children with SMA”.

Reliable tests to determine if a new therapy is working are needed for future clinical trials in SMA. In this study, the authors evaluated one potential such test, a test of a nerve that moves the pinky finger. The specific nerve study is called the “maximum ulnar compound muscle action potential”, or CMAP for short.

“This paper is important because it offers another way to measure SMA. If it can make clinical trials more efficient, we can show the benefit of a therapy with fewer patients in a shorter time.”, says Tom Crawford MD, Principle Investigator of the Project Cure SMA Baltimore site.

Families of SMA Funded Clinical Research Study Titled “Reliability of the Modified Hammersmith Functional Motor Scale in Young Children with SMA”.

The paper published by lead author Kristin Krosschell extends the reliability of the Hammersmith Functional Motor Scale (MHFMS) to children under 30 months, allowing younger children to participate in future SMA clinical trials. Several years ago Project Cure SMA, published work showing the reliability of Modified Hammersmith Functional Motor Scale (MHFMS), which estimates motor function in SMA. This current study extends the usability of this test to children under 30 months.

Natural History data (or data collected over years from SMA patients) supports the continued loss of functional motor units with increasing age. It also shows an increased rate of secondary complications, including contractures and scoliosis. This can complicate clinical trials and testing of new therapies. Currently a limited number of tests for clinical trials (functional outcome measures) are available to measure motor function in those with SMA Type II, younger than 2½ years. Most tests that are available are not disease specific.

“This study is important as it demonstrates that a disease specific scale measuring motor function, called the MHFMS, can be reliably used in children with SMA younger than 2.5 years of age.”, said Kristin J Krosschell, PT, MA, PCS, PT Principle Investigator for Project Cure SMA and Assistant Professor, Feinberg School of Medicine at Northwestern University.

In addition to testing the safety and efficacy of repurposed drugs, conducting clinical trials like the CARNI-VAL Trial allows the SMA community to validate and test new outcome measures that will make future clinical trials more efficient and sensitive to effects of the drugs being studied.



What are Biomarkers and Clinical Endpoints?

Clinical Endpoints: Sometimes referred to as clinical trial outcome measures, are the overall outcomes of an intervention that the clinical trial is designed to evaluate. Common endpoints are severe toxicity or disease progression.

Primary Endpoints or Outcome Measures: The key measurements or observations used to measure the effect of experimental variables in a study. Having reliable primary endpoints is critical for FDA registration (pivotal) trials.

Secondary Endpoints or Outcome Measures: Additional measures utilized to help evaluate therapeutic interventions, often used as go/no-go decision points early in the clinical development process, rather than as the key endpoints in FDA registration trials.

Biomarker: A measure that can be used as an indicator of a particular disease state or some other physiological state. It is a characteristic that when objectively measured is an indicator of a biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarkers are often used in early drug development studies to help assess whether later larger more expensive trials are warranted.

NeuroNEXT- Network for Excellence in Neuroscience Clinical Trials

A New Network Initiative to Promote Clinical Trials in Neurological Diseases



By Elizabeth McNeil, MD MSc, NINDS Office of Clinical Research

The National Institute of Neurological Disorders and Stroke (NINDS) has initiated NeuroNEXT to support clinical trials for neurological diseases. NeuroNEXT will have multiple clinical sites throughout the US. The goal of this new network is to facilitate the implementation of Phase II clinical trials, or “exploratory” trials. Before researchers and patients embark on a “confirmatory” or Phase III trial which may take years and involve several hundred patients, they often want to answer some preliminary questions, for example: What is the best dose? Is there at least some signal that the new treatment works? Because a limited number of Phase III trials can be done at any given time, those should be focused on what appears to be the most promising path based on “exploratory” or Phase II trial findings.

While many areas may be explored in Phase II trials, two areas of particular relevance to SMA are biomarkers and clinical outcomes.

While researchers have discussed and begun investigations of biomarkers for SMA, there are no qualified 'biomarkers' of SMA disease progression, disease stabilization or disease ameliorization.

NeuroNEXT aims to support a “Biomarker” study for SMA. Some patients have already participated in a biomarker study and may ask why another one is needed. The reason is that we need a biomarker that not only looks promising, but one that we know works, and one that can potentially be useful to the FDA as they evaluate a new treatment. By collaborating with FDA, Neu-

roNEXT will hopefully identify a biomarker which meets regulatory approval. Biomarker studies typically have no treatment aspect to them. Participating in a biomarker study is therefore a true act of altruism because there is no potential to directly benefit. However, the potential future benefit to all patients with SMA is great, if a biomarker is found that can accelerate the evaluation of new treatments.

Deciding which outcome measure to use is another challenge in clinical trials. A clinical outcome measure is a means to test how a patient functions or feels. Several outcome measures have been used in SMA research, but there is not yet one generally agreed-upon outcome measure for clinical trials. SMA is a chronically progressive condition so changes may take a while to be evident. It is still not fully known what specific changes should best be monitored nor how much of a change should be considered ‘meaningful.’ Phase II studies can give insight into clinical outcome measures best suited for use in Phase III trials. Additionally, biomarker studies often measure a clinical outcome along with the biomarker to evaluate the possible association.

The road from ‘bench to bedside’ is long and fraught with pitfalls but careful planning, partnerships, and close attention to choosing most promising paths increase the chances of reaching the desired destination.

NeuroNEXT aims to encourage private-public partnerships so that the most promising treatments can be tested, regardless of whether they come from academic, foundation or industry investigators.

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**FSMA has Established
a Clinical Trials Network with
6 Sites Across the US.**