Families of SMA *Research. Support. Hope.*

CLINICAL TRIALS SUMMER 2008

COMPASS

A Publication Dedicated To Research Updates

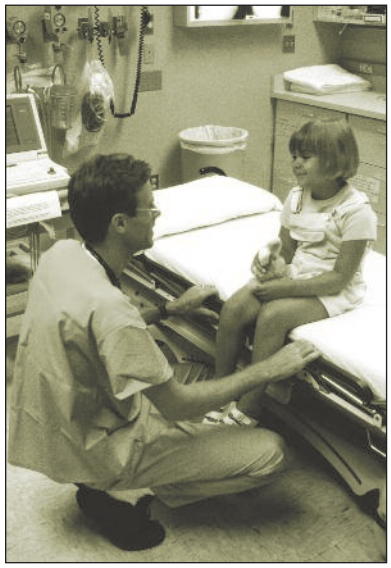
Dear Families and Friends

After three years of hard work, Families of SMA is pleased to have the first results from the Phase 2 CARNI-VAL Trial conducted by Project Cure SMA to test the safety and possible efficacy of valproic acid (VPA) and carnitine in children with SMA. This study involved the work of more than 30 professionals at 6 different clinical testing sites. 94 children and their families enrolled in the trial and participated in more than 450 site visits. Over a half million pieces of data are being analyzed. **In this letter, I am going to briefly summarize the first results from the Phase 2 trial and then discuss the implications for the new Type I trial.**

CARNI-VAL RESULTS

This issue of Compass includes a detailed report on the Phase 2 trial results for one sample group comprised of children with SMA Type II, ages 2-8 years. They were randomly given either the drug treatment of VPA and carnitine or a placebo for the first six months of the trial. Every child then received drug treatment for the second six-month period.

Overall, children who received the drug when compared to placebo over a six-month period showed no significant improvement in motor function as measured by the Modified Hammersmith Functional Motor Scale (MHFMS), the primary outcome we used for the study. A subgroup analysis on younger and lighter children, aged 2-3 years of age who



received a full year of drug treatment, demonstrated a significant probability of increased motor function when compared to the placebo group. *For more results, please see the detailed article.*

These results, like those from the open-label VPA study, suggest that responder and non-responder SMA patient populations to this drug may exist. Weight gain and age appear be significant factors in responding to the drug. Such a hypothesis would require additional formal testing to prove. In addition, the CARNI-VAL data indicate that increased fat mass is negatively related to an increase in motor function, suggesting that weight needs to be carefully monitored when administering this drug. At this point in the data analysis, drug-related weight gain is the main adverse effect in this population of children.

IMPLICATIONS FOR THE NEW CARNIVAL TYPE I TRIAL

I also want to discuss the implications of these results for the recently announced CARNI-VAL Type I trial designed to test the safety of VPA and carnitine in infants less than 9 months old. Although functional improvement was not demonstrated in older children, there are important reasons to study this drug combination in infants with severe SMA:

1) This drug is clearly associated with an increased risk of toxicity in children under two, and this may be similar or even worse in SMA infants. Given the severity of the disease in Type I infants and the lack of viable alternatives, VPA has increasingly been provided to such infants, often without consistent monitoring for toxicity as would be done in a clinical trial.

2) The CARNI-VAL trial in older children was designed to look for improvement in motor function, not the slowing of decline. It is almost impossible to test for the slowing of decline in children with Type II SMA, because this decline occurs over a relatively long time course, sometimes years. In contrast, infants with severe SMA often worsen in the early months of life, so a change in decline can more easily be measured during the timeline of a feasible clinical trial.

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3) These initial clinical trials are part of a long-term strategy to establish a clinical trial infrastructure. Each trial builds on the next and is a necessary stepping stone to progress. This new trial will guide us in designing future trials for Type I infants that include the assessment of efficacy in addition to safety. The trial for Type I infants is part of a broader plan to develop special clinical trial infrastructure to meet the needs of this extremely fragile and vulnerable patient population. It brings us closer to overcoming obstacles to the identification of therapies that have the potential to prolong survival, maintain and increase motor function, and enhance quality of life for this population. Reliable measures of motor function have not yet been established for infants with SMA. Thus, this new study will be broadly important to SMA clinical research.

While the overall results for this clinical trial were negative, the positive results in a sub-group of younger and lighter children at one year do warrant careful consideration for the next steps of testing this drug in Type II SMA patients. Several possibilities are outlined in the flowchart attached. These include: 1)focusing on a new candidate drug in these patients; 2)moving forward with a new trial in younger and lighter children; or 3)waiting for the data from the ongoing VALIANT trial in ambulatory adults with SMA to decide the best path forward. Importantly, choosing one of these three actions requires that we have the full data set from the CARNI-VAL Trial in hand, which is not yet available. In particular, we are waiting for analyzed data assessing motor unit function (cMAP), and all the results from cohort II that included non-ambulatory Type III children.

Project Cure SMA plans to publish these results in a scientific journal in the near future. Further results from the trial will be reported to you as they become available. Thank you for your continued support.

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

CARNI-VAL Trial: Overview of Results for the Randomized Placebo-Controlled Phase 2 Trial of Valproic Acid and Carnitine in Children with SMA Type II

Swoboda KJ, Scott CB, Acsadi G, Kissel JT, Krosschell KJ, LaSalle B, Crawford TO, D'Anjou G, Reyna SP, Schroth MK, Simard LR, Sorenson SL, for Project Cure SMA, fully funded by Families of SMA

The completion of the SMA CARNI-VAL Trial marks an important milestone in our goal to identify effective therapies for SMA patients. In this report, we focus on results for cohort 1 only, consisting of 61 Type II children ages 2-8 years. These children were randomly assigned to receive either treatment with valproic acid (VPA) and carnitine or a placebo for the first six months of the trial. Overall we were unable to demonstrate efficacy of this treatment in children with SMA Type II over a six-month treatment period. However, we gained valuable information about this particular treatment regimen and the frequency of adverse events in children with Type II, which will have important implications for the design of future trials. Below, we review the rationale for the initial trial design, the methods chosen, and our primary objectives for the SMA CARNI-VAL Trial. We then summarize the observed results and put them into context.

Rationale for Choosing VPA:

The rationale for choosing VPA for study in our first multi-center clinical trial was based on several factors:

1) Demonstrated up-regulation of SMN protein levels in cells taken via skin biopsy from SMA patients,

2) A large published clinical trials experience with VPA in a number of different neurological disorders, with a well-known range of potential side effects that we were prepared to monitor,

3) Data to support that the drug crosses the blood-brain-barrier, and hence could reach motor nerve cells in the spinal cord,

4) The availability of a dosage formulation that was acceptable for use in young children and for which levels could be tested in blood to help determine whether or not patients were taking the medication, and

5) The observation of possible benefit based on initial open label trial results, including improvement in scores on the Modified Hammersmith Functional Motor Scale (MHFMS), as well as improvement in the level of muscle responses to electrical stimulation.

Primary objectives of this trial included:

A) The assessment of potential efficacy of a combined regimen of L-carnitine and VPA in children with SMA Type II as compared to placebo, in a double-blind randomized placebo-controlled fashion,

B) The establishment of a multi-center clinical trials network to assess new therapies efficiently and effectively, and carefully determining safety and frequency of adverse events,

C) The implementation of clinical outcome measures that have been undergoing development and assessment for several years for children with SMA Types II and III.

In designing the study protocol, we identified a number of issues that might impact our ability to prove efficacy with VPA. The open label results suggested that it was not likely to be effective in older children, in those who demonstrated excessive weight gain, in those with the most severe motor neuron loss, or in those with severe joint contractures and scoliosis.

For this trial it seemed premature to limit participants to those younger than 5 years, even though in the open label study the youngest children demonstrated the greatest benefit. In addition in the open label trial, it appeared that

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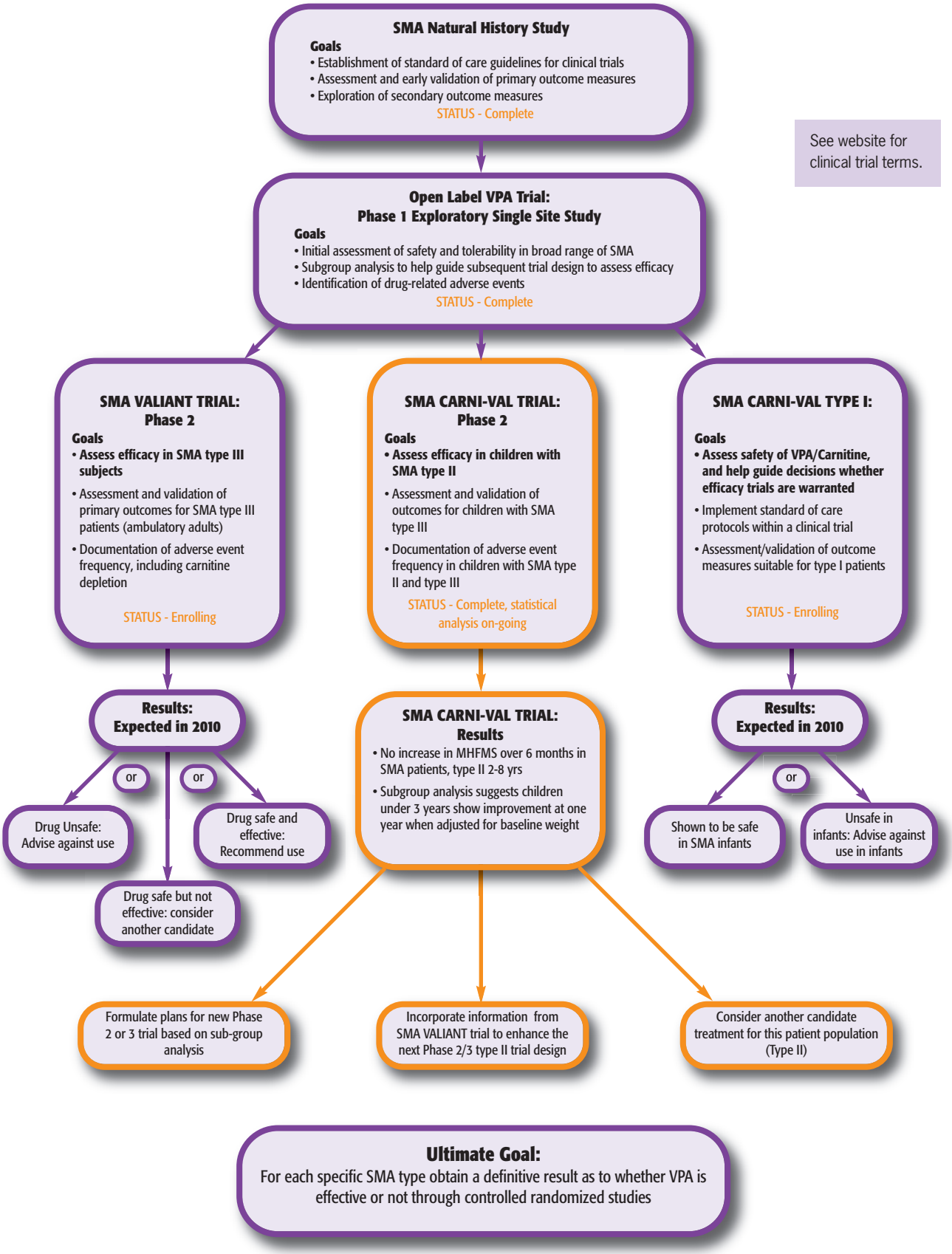
Clinical Testing Plan for VPA in SMA



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children who "responded" to VPA demonstrated nearly twice the improvement following a full year of treatment as compared to six months. Again we had to consider whether parents would accept a full year of possible "non-drug" treatment in a placebo-controlled trial. Both of these considerations impacted the trial design.

Main Conclusions:

Safety was determined by changes in laboratory values and the frequency of adverse events, which we categorized as likely or unlikely to be related to drug treatment. Although adverse events occurred in 80% of subjects, aside from excessive weight gain, they were not clearly treatment related, and mostly consisted of events expected in children with SMA. Pneumonia and other respiratory infections or symptoms, gastrointestinal symptoms, fever and fractures were common, and considered unlikely to be related to study medication. However, the rate of weight gain was clearly higher in the treatment group.

One of the most important observations from the CARNI-VAL trial, supporting the initial open label trial experience, is that excessive weight gain, particularly in an already weak SMA Type II child, is an adverse event that can be anticipated with VPA, and thus monitored closely. Not every child demonstrates this tendency to gain weight excessively, and this issue appears much less likely to affect the youngest children. Thus, results from this trial should prove helpful in guiding physicians who may be considering use of VPA in their patients, an increasing occurrence given the lack of any currently proven therapies.

Efficacy was assessed by comparing change in the MHFMS score in the treatment group as compared to the placebo group over a six-month period. However, no change in the MHFMS scores from baseline were noted in either the treatment or placebo group. A subgroup of children, those under age 3 years at the time of enrollment, showed significant improvement over a one year period of treatment compared to the placebo group when adjusted for baseline weight. Baseline weight and age had a significant influence on change in MHFMS scores; heavier and older children performed worse than younger and lighter children. Increased fat mass during the six month treatment period was negatively correlated with change in MHFMS scores. An analysis of age alone, independent of other factors, demonstrated that younger age is a significant factor in achieving an improved MHFMS score.

Whether or not phase 3 trials are justified for VPA is a point for ongoing discussion and consideration, pending final analysis of the results of the SMA Type III group in this trial, as well as in the ongoing VALIANT trial. An overriding goal for our community also has been to develop the necessary framework and tools to try to accurately determine safety and efficacy of potential treatments. Thus, while the study results with regard to efficacy for improved motor function in type II children are "negative", we remain optimistic that in completing this trial, we have made substantial progress towards our goal to establish the foundation necessary to identify treatments that will ultimately benefit individuals with SMA.

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