

## **A Prospective, Randomized Controlled Trial of Valproic Acid in Ambulant Adults with SMA: The VALIANT Trial**

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**Objective:** To report the results of a twelve month prospective, randomized, double-blind, placebo-controlled trial of valproic acid (VPA) in ambulatory adults with spinal muscular atrophy (SMA).

**Background:** Multiple lines of evidence suggest that VPA, a histone deacetylase inhibitor, might benefit patients with SMA by modulating *SMN2* splicing to increase production of full-length SMN transcript from *SMN2*. Four open-label trials of VPA in humans showed a benefit in strength, motor function, or both. These results led us to perform a clinical trial of VPA in a large cohort of ambulatory adults with SMA, a group that might be expected to respond to VPA because of increased *SMN2* copy number.

**Design/Methods:** This was a prospective, randomized, double blind, 12 month study in genetically confirmed subjects with SMA over 18 years old. Subjects underwent two baseline assessments and then were placed on VPA or placebo in a blinded fashion. After six months, the patients were crossed over to the other group (i.e. VPA or placebo). Patients were evaluated at 3, 6, and 12 months. The primary outcome was the change at six months in strength as assessed by maximum voluntary isometric contraction testing (MVICT). Secondary outcomes included safety and adverse event profiles, and changes in ulnar compound motor action potential amplitude (CMAP) and motor unit number estimation (MUNE), strength assessed by handheld dynamometry, endurance measured by a 6 minute walk test, pulmonary function studies, function assessed using a modified adult SMA Functional Rating scale (SMAFRS), and a quality of life assessment. Genetic and biochemical assays of *SMN2* copy number, mRNA levels, and SMN protein levels were performed in all subjects.

**Results:** Thirty-three subjects were enrolled at one center (OSU) meeting target enrollment. There were 20 males and 13 females (mean age 37.1); 16 patients were initially placed on VPA and 17 on placebo. Three patients did not complete the study; two due to adverse events not clearly related to VPA and one simply withdrew. There were no significant adverse events recorded. There was no significant change in the primary or secondary outcome after six months of treatment.

**Conclusions:** These data indicate that VPA at the doses used in this study, although safe and well tolerated, did not improve strength or function in ambulatory adults with SMA. Coupled with the earlier PC-SMA negative studies of VPA children (CARNI-VAL Trials parts 1 & 2) this information further suggests that VPA is not effective in improving motor function with the dosage tested over a six month period. The PC-SMA group is currently analyzing data from an open label studies in infants with Type 1 that should provide additional important information on VPA and its effect on biomarkers.

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