ARBACLOFEN IN FRAGILE X SYNDROME: RESULTS OF PHASE 3 TRIALS AND FXCRC ANALYSIS OF ARBACLOFEN RESPONSES

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Arbaclofen reverses spine morphology, seizure, behavioral, and biochemical phenotypes in the *Fmr1* knockout mouse and showed safety and efficacy for social avoidance in a small phase 2 placebo-controlled crossover trial in fragile X syndrome (FXS). Two phase 3 placebo-controlled trials were conducted to demonstrate safety and efficacy of arbaclofen for social avoidance in FXS. These trials included a flexible dose trial in subjects with FXS age 12-50 (study FX301) and a 3-dose fixed dose trial in subjects age 5-11 (study FX302), both with dose titration over 4 weeks followed by 4 weeks of stable dosing. For both trials inclusion criteria required a score of $\geq$8 on the Social Withdrawal subscale of the Aberrant Behavior Checklist-Community Edition (ABC-C) and primary efficacy outcome was the Social Avoidance (SA) subscale on ABC-C refactored for FXS (ABC-FX). Secondary outcomes included other ABC-FX subscale scores, CGI-I, CGI-S, and Vineland Socialization subscore. Safety outcomes included adverse events (AEs) and standard chemistries, hematology, and EKGs. FX301 had 125 patients randomized and 119 completed (57 arbaclofen, 62 placebo); FX302 had 172 randomized and 159 completed (arbaclofen 5 BID:38; 10 BID:39; 10 TID:38; placebo:44). FX302 was stopped prematurely, short of the prospectively planned 50 subjects in each group, due to financial constraints. There were AEs in >5% of subjects, no serious AEs, and only two discontinuations due to an AE (both behavioral worsening). FX301 did not show benefit for arbaclofen over placebo for any measure, although there were large improvements on both drug and placebo. In FX302 the highest dose group showed benefit over placebo on the ABC-FX Irritability subscale (p=0.031, effect size 0.51) and the parent stress index (p=0.032, effect size 0.42) and a trend toward benefit on the ABC-FX SA (p=0.085, effect size 0.24) and Hyperactivity (p=0.081, effect size 0.44) subscales and CGI-I (p=0.119, effect size 0.43). Arbaclofen did not meet the pre-defined primary outcome of improved social avoidance in FXS in these studies, although given the strong trend toward benefit in the arbaclofen high dose group in FX302, use of a smaller sample size than projected to have power to detect drug effect on the ABC-FX SA likely limited the ability to achieve statistical significance on the primary outcome measure. Data from secondary measures and the long term treatment extension (improved Vineland Socialization) suggest some patients derive benefit from arbaclofen. The FXCRC fragile X clinics involved with the trials have gathered clinical data for subjects who responded to arbaclofen and not to placebo. This data suggests that additional outcome measures targeting language and other functional domains might have detected arbalcofen effects better. These studies illustrate the challenges of translating targeted treatments from an animal model to humans in FXS.