Arbaclofen produces clinically meaningful improvements in individuals with Fragile X
Randall L. Carpenter (1), Mads E. Matthiesen (1), David C. Stoppel (2), Stacie Hudgens (3), Mark F. Bear (1,2)

1. Allos Pharma 2. The Picower Institute for Learning and Memory, Massachusetts Institute of Technology 3. Clinical Outcome Solutions

Overview:
Arbaclofen is a GABA-B receptor agonist that has been shown in animal models of FXS to correct core disease phenotypes, including altered neuronal protein synthesis, disrupted synaptic function and plasticity, and hyperexcitability. In clinical trials for both fragile X and autism, arbaclofen was shown to be safe and well tolerated. Arbaclofen also improved core behavioral problems measured by the FXS-specific Aberrant Behavior Checklist (ABC-FX) in controlled clinical trials. Most impressive was the treatment response in the phase 3 trial conducted in children aged 5-11 (1). The critical question arises whether the observed group-mean differences between drug and placebo are clinically meaningful. To address this issue, we first applied thresholds for “clinical meaningfulness” established for three subscales in a recent study by another group (2). These thresholds are a 9-point improvement in the irritability (ABC-I) subscale, with 5 points for the socially unresponsive or lethargic (SUL) subscale. When the phase 3 arbaclofen data were analyzed using these 3 thresholds, we find that 45% of 5-11-year-old subjects on the high dose had clinically meaningful improvements on all three scales, compared with 4% of those on placebo (p=0.00003). In a separate de novo analysis we used changes in the clinical global impression severity scale (CGI-S) in the arbaclofen trials as an anchor to establish the within-subject responders analysis.

Identifying Meaningful Change Thresholds (MCTs) (Merikle et al., 2021)

• Anchor-based methods were used to estimate MCTs for change from Baseline to Week 12 in the ABC-C FXS social avoidance (SA), irritability, and socially unresponsive or lethargic (SUL) subscales.
• Identification of the point change on the Caregiver Global Impression of Change (CGI-C) and severity (CGI-S) representing meaningful change was informed by semi-structured cognitive interviews with 25 caregivers of children with FXS.
• Majority of caregivers indicated that a 1-category change on the CGI-S would be meaningful or important.
• The responder thresholds for meaningful within-patient behavioral change (n = 123) over a 12-week period corresponded to the following reductions:
  - 3 or more points on the ABC-C FXS Social Avoidance subscale
  - 9 or more points on the ABC-C FXS Irritability subscale
  - 5 or more points on the ABC-C FXS Socially Unresponsive/Lethargic subscale
• These thresholds are a basis for evaluating clinically meaningful efficacy effects at the individual patient level in clinical trials of children and adolescents with FXS.

Conclusions:
Clinical trials of arbaclofen demonstrated statistically significant improvements in behavior, but the clinical relevance of the numerical improvements remained to be established. We applied clinically meaningful thresholds for improvement on three subscales of the ABC: irritability, Social Avoidance and Socially Unresponsive/Lethargic to assess efficacy in the phase 3 trials in children, aged 5-11. Using current accepted arbaclofen doses, clinically meaningful magnitudes of improvement were observed on all three ABC subscales for 45% of individuals receiving the high dose of arbaclofen vs 4% of those treated with placebo, clearly demonstrating the efficacy of arbaclofen in individuals with FXS. Further analysis established the MCT for the ABC-I vs measured in the phase 3 arbaclofen trials, and confirmed a significant effect of treatment with MCT exceeding the MCT in the high dose group.

These findings comport remarkably well with experiences reported by clinicians involved in the clinical trials, who reported that a major (≥11-point) change in arbaclofen showed clear and substantial improvements, mainly in the area of being able to better cope with typical life activities that are associated with anxiety and over-avoidal. Improved coping resulted in a decrease in a range of dysfunctional behaviors, such as aggression, avoidance, or hyperactive and escape behaviors (Dr. Elizabeth Berry-Kravis, personal communication).