Arbaclofen produces clinically meaningful improvements in individuals with Fragile X

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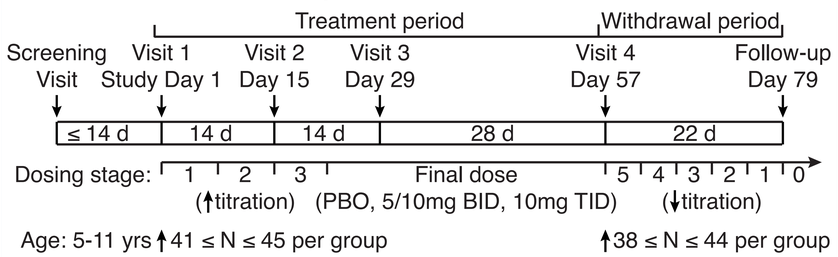
Overview:

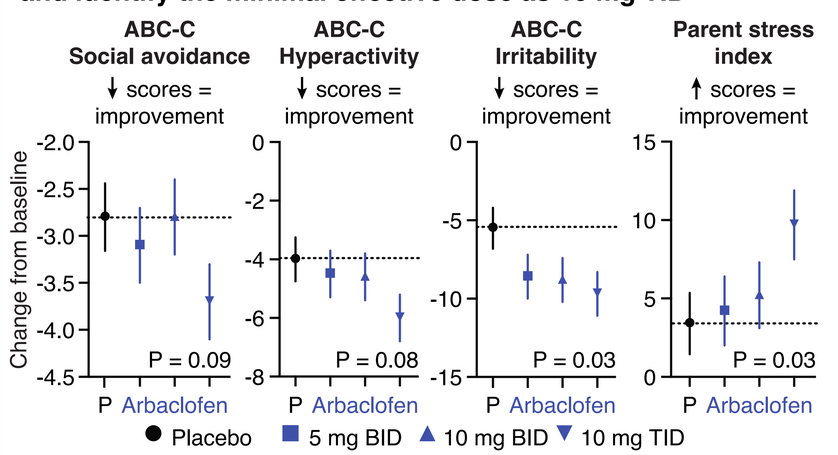
Arbaclofen is a GABA-B receptor agonist that has been shown in animal models of FXS to correct core disease phenotypes, including altered neuronal protein synthesis regulation, disrupted synaptic function and plasticity, and hyperexcitability. In clinical trials for both fragile X and autism, arbaclofen 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 of 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_{FX}-I), 3-points for the social avoidance (ABC_{FX}-SA), and 5 points for the socially unresponsive / lethargic (ABC_{FX}-SUL) subscales. 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 meaningful change threshold (MCT) on the ABC_{FX}-I. This study confirmed a significant interaction of treatment arm by responder level. Over 65% of subjects receiving the high dose of arbaclofen showed a response exceeding this MCT. Together, these analyses clearly demonstrate that arbaclofen produces clinically meaningful magnitudes of improvement in problem behaviors in children with FXS.

1). Berry-Kravis et al., 2017; PMID 28616094.
2). Merikle et al. Value in Health. 2021;24(Suppl. 1):S19

Seaside study 209FX302 experimental design (Berry-Kravis et al., 2017)



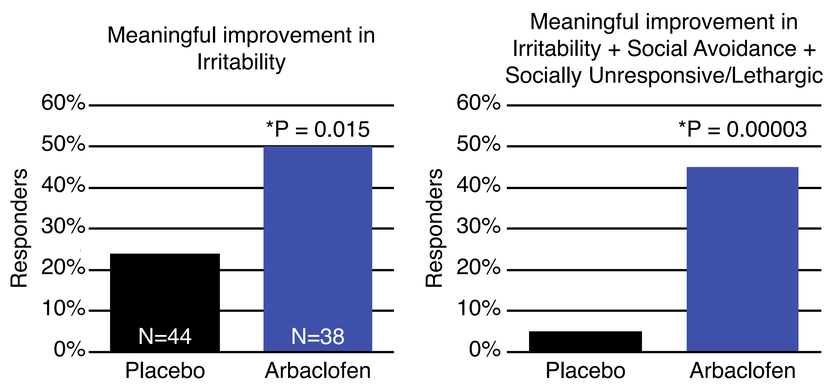
Group mean differences in prospectively defined clinical outcome assessments show a clear dose-response relationship and identify the minimal effective dose as 10 mg TID



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 (CaGI-C) and severity (CaGI-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 CaGI-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 treatment effects at the individual patient level in clinical trials of children and adolescents with FXS.

Responders in arbaclofen high-dose group using Merikle et al. MCTs



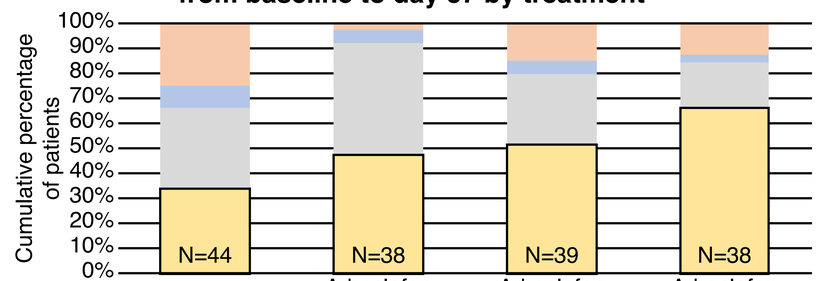
De novo statistical analysis of MCTs derived from phase 3 arbaclofen studies

- MCTs for the ABC-I were derived on blinded data from the 209FX301 and 209FX302 studies using anchor-based methods and supported with distribution-based methods. The MCTs were then applied to the 209FX302 data for responder analysis.
- For the anchor-based analysis to derive the MCT, CGI-S was used as an anchor and patients were classified into response groups depending on their level of change in CGI-S over the course of the study. Mean (SE) within patient change from baseline, along with min, max, 95% confidence intervals, and a p-value for the respective paired t-test was calculated for each of the uncollapsed and collapsed categories of CGI-S change from baseline. In the uncollapsed categories, patients were classified among all possible change categories (15 levels, ranging from -7 to 7 where negative changes scores indicate improvement). In the collapsed categories, patients were classified among four change categories.
- The standard effect size (SES) and 95% CI were calculated for the difference in mean change for the change categories compared to its adjacent anchor category.
- The final MCTs for the ABC-I were applied to the 209FX302 data in subsequent unblinded responder analysis. MCT categories were classified as 'improved', 'declined' or 'stable', based on whether a change in ABC-I met or exceeded the MCT.
- Chi square tests were used to test for differences in proportions of categorical change from baseline to day 28 between treatment and placebo for each score.
- Meaningful change above the mean/median for the no change group results suggests a threshold above 6.5 points is sufficient across all age ranges (data from ages ≥ 12 in study 209FX301 are not shown).
- A one category improvement (-1) is associated with a -11.1 point mean improvement in the ABC-I scale score at Day 28 compared to baseline, with a 95% CI: -13.727, -8.477; p < 0.0001; and a large SES = -1.215. The upper bound of the confidence interval, -8.47, differentiates from the mean of the no change group suggesting that this meaningful change may also be considered.

MCT derivation from arbaclofen study 209FX302

Change in ΔCGI-S Anchor	N	Mean ΔABC-I (SD)	Median Change	95% Confidence Interval	P-Value	Standardized Effect Size
Uncollapsed categories						
1	2	2.00 (5.66)	2	-48.825 , 52.825	0.7048	
0	96	-6.32 (8.05)	-5	-7.955 , -4.691	<.0001	-0.785
-1	49	-11.10 (9.14)	-10	-13.727 , -8.477	<.0001	-1.215
-2	10	-10.20 (13.55)	-4	-19.891 , -0.509	0.0412	-0.753
-3	1	-21.00 (.)	-21			
Collapsed categories						
Decline	2	2.00 (5.66)	2	-48.825 , 52.825	0.7048	
Stable	96	-6.32 (8.05)	-5	-7.955 , -4.691	<.0001	-0.785
Responder (ΔCGI-S = 1)	49	-11.10 (9.14)	-10	-13.727 , -8.477	<.0001	-1.215
Hyper-responder (ΔCGI-S > 1)	11	-11.18 (13.26)	-5	-20.088 , -2.275	0.0189	-0.843

Anchor-based MCT responder analysis for change from baseline to day 57 by treatment



ΔABC_{FX}-I	Placebo	Arbaclofen 5mg BID	Arbaclofen 10 mg BID	Arbaclofen 10 mg TID
Decline	25.0	2.6	15.4	13.2
Stable	9.1	5.3	5.1	2.6
Improve -1 to -6.5	31.8	44.7	28.2	18.4
Improve < -6.5	34.1	47.4	51.3	65.8

Interaction of treatment arm by responder level is statistically significant at p=0.0441 (chi-square)

Conclusions:

Clinical trials of arbaclofen demonstrated statistical 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 trial in children, aged 5-11. Using current FDA guidelines, 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 values measured in the phase 3 arbaclofen trials, and confirmed a significant effect of treatment with >65% 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 majority of those receiving 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-arousal. 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).