METHODS

OBJECTIVES
• An FXS-specific domain structure of the ABC-C (henceforth the ABC-CFXS) was developed, which is more representative of the FXS phenotype, and has been established.
• The ABC-CFXS was utilized to measure the primary and key secondary endpoints in ZYN2-CL-016 (CONNECT-FX), a randomized, double-blind, placebo-controlled, multicenter clinical trial evaluating the efficacy and safety of ZYN002, a transdermal synthetic cannabidiol gel, for the treatment of behavioral symptoms associated with FXS in children and adolescent patients (NCT03814663).
• The FDA Clinical Outcomes Assessment Group determines clinical meaningfulness from the caregiver perspective using a mixed methods (qualitative and quantitative) approach.
• Thresholds for meaningful within-patient change were established using anchor-based methods with treatment benefit informed by interviews with caregivers of children with FXS.

RESULTS

CONNECT-FX Efficacy Results
• In the CONNECT-FX trial, in patients with ≥90% methylation of the FMR1 gene, ZYN002 was associated with a statistically significantly greater mean change from baseline in Social Avoidance vs placebo (p=0.0001; see SOBP poster by Berry-Kravis E, et al, entitled “A Pivotal Study of ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents With Fragile X Syndrome (CONNECT-FX [ZYN2-CL-016])”).

Anchor-Based Analyses
• Caregivers of children with FXS reported that even small improvements in their child’s behavior would be meaningful.
• Majority of caregivers (n=17; 68%) indicated that a 1-category change in their child’s behavior would be meaningful or important.
• In the analyses (n=193), the mean (SD) changes for the ABC-CFXS subscales in patients with a 1-category improvement on the CaGI-S DS and OB items were (Table 1)
  -3.9 (5.7) for ABC-CFXS SA
  -3.3 (5.0) for ABC-CFXS Irritability
  -3.0 (3.0) for ABC-CFXS SUL

In the CONNECT-FX trial, in patients with ≥90% methylation of the FMR1 gene, ZYN002 was associated with a statistically significantly greater mean change from baseline in Social Avoidance vs placebo (p=0.0001; see SOBP poster by Berry-Kravis E, et al, entitled “A Pivotal Study of ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents With Fragile X Syndrome (CONNECT-FX [ZYN2-CL-016])”).

Responder Threshold
• Triangulating the results from the anchor-based analyses, the visual plots, and the levels of meaningful change reported by caregivers in the cognitive interviews patients who experienced a reduction of 3 or more points on the ABC-CFXS SA subscale, 9 or more points on the ABC-CFXS Irritability subscale, and 5 or more points on the ABC-CFXS SUL subscale from Baseline to Week 12 in CONNECT-FX achieved a meaningful behavioral response to treatment.

Table 1. Mean Change Scores on the ABC-CFXS SA, Irritability, and SUL subscales by change in the CaGI-S DS and OB scores

<table>
<thead>
<tr>
<th>Anchor</th>
<th>ABC-CFXS SA</th>
<th>ABC-CFXS Irritability</th>
<th>ABC-CFXS SUL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-category</td>
<td>-3.9 (5.7)</td>
<td>-3.3 (5.0)</td>
<td>-3.0 (3.0)</td>
</tr>
<tr>
<td>2-category</td>
<td>-5.4 (6.46)</td>
<td>-5.2 (6.24)</td>
<td>-5.3 (6.69)</td>
</tr>
<tr>
<td>3-category</td>
<td>-7.2 (6.54)</td>
<td>-7.6 (6.92)</td>
<td>-7.9 (7.46)</td>
</tr>
</tbody>
</table>

Figure 1. Empirical cumulative distribution function curves of change in the ABC-CFXS SA, Irritability, and SUL subscale scores by change in the CaGI-S DS and OB scores.

Figure 2. Greater Percentages of Participants Achieved Meaningful Change in ABC-CFXS SA, Irritability, and SUL Subscales by Change in CaGI-S DS and OB Scores.

CONCLUSIONS
• The responder thresholds for meaningful within-patient behavioral change on key domains of the ABC-CFXS were determined using anchor-based methods based upon FDA guidance for caregiver-reported outcomes.
• The responder thresholds for meaningful within-patient behavioral change in CONNECT-FX corresponded to the following reductions
  - 3 or more points on the ABC-CFXS Social Avoidance subscale
  - 9 or more points on the ABC-CFXS Irritability subscale
  - 5 or more points on the ABC-CFXS Socially Unresponsive/Lethargic subscale

These thresholds serve as a basis for evaluating clinically meaningful treatment effects at the individual patient level in clinical trials of children and adolescents with FXS as demonstrated for ZYN002 in CONNECT-FX.

ZYN002 provided meaningful improvements in behavioral symptoms of FXS in patients with ≥90% methylation of the FMR1 gene.

REFERENCES AND ACKNOWLEDGMENTS

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