BACKGROUND AND OBJECTIVES

Background

- Fragile X syndrome (FXS) is a rare genetic disorder, which is a common cause of intellectual disability.
- The Aberrant Behavior Checklist-Community (ABC-C) is an observer-reported outcome (ObsRO) measure that has been validated in individuals with intellectual disabilities.
- An FXS-specific domain of the ABC-C (henceforth the ABC-CFXS), which is more representative of the FXS phenotype, has been established.

- The ABC-CFXS was utilized to measure the primary and key secondary endpoints in 2N-DL-016 (CONNECT-FX), a randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of ZYN002, a transdermal synthetic cannabidiol (CBD) gel, for the treatment of behavioral symptoms associated with FXS in children and adolescent patients (NCT03614663).

- The FDA Clinical Outcomes Assessment Group recommends determining 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.

Objectives

- To derive responder thresholds (RTs) representing individual patient-level change indicative of meaningful treatment benefit for the ABC-CFXS Social Aviance (SA), Irritability, and Soially Unresponsive/Lethargic (SUL) subscales.

METHODS

- Anchor-based methods supplemented with visual plots were used to estimate RTs for change from Baseline to Week 12 in the ABC-CFXS SA, Irritability, and SUL subscales.
- SA: primary endpoint, score range 0 to 12
- Irritability: key secondary endpoint, score range 0 to 54
- SUL: key secondary endpoint, score range 0 to 39
- Higher subscale scores represented higher severity of aberrant behavior
- Primary anchors were domain-specific (DS) behavioral problems and overall behavior (OB) of the Caregiver Global Impression of Severity (CGi-S). Problems experienced by a child were rated on a 4-point scale (0=no problems to 3=severe problems). A significant change in the CGi-S would be meaningful or important.
- Anchor-based analyses were performed on key ABC-CFXS subscales in patients with a 1-category change on the CGi-S DS and OB items (Table 1).

RESULTS

Anchor-Based Analyses

- Caregivers of children with FXS reported that even small improvements in their child’s behavior would be meaningful.
- Major anchors were caregivers (n=17; 68%) indicated that a 1-category change on the CGi-S 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 CGi-S DS and OB items were (Table 1):
  - 3.0 (3.9) and 3.6 (2.94) for ABC-CFXS SA
  - 1.0 (0.70) and 0.8 (0.42) for ABC-CFXS Irritability
  - −5.4 (6.46) and −6.8 (6.92) for ABC-CFXS SUL

- 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 Aviance subscale
  - 9 or more points on the ABC-CFXS Irritability subscale
  - 5 or more points on the ABC-CFXS Soially 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.

Table 1. Mean Change Scores on the ABC-CFXS SA, Irritability, and SUL Subscales by Domain-Specific (DS) Behaviors and Overall Behavior (OB) in CBC-CFXS Change Categories

<table>
<thead>
<tr>
<th>Change Category</th>
<th>DS</th>
<th>OB</th>
</tr>
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<tbody>
<tr>
<td>No change</td>
<td>68.0</td>
<td>16.9</td>
</tr>
<tr>
<td>−1</td>
<td>9.8</td>
<td>27.6</td>
</tr>
<tr>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>−2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>+2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>−3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>+3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Higher subscale scores represented higher severity of aberrant behavior.
- Most caregivers indicated that a 1-category change on the CGi-S DS and OB items would be meaningful or important.
- Caregivers of children with FXS reported that even small improvements in their child’s behavior would be meaningful.

Visual Plots

- Empirical cumulative distribution function curves of change in the ABC-CFXS SA, Irritability, and SUL subscale scores from Baseline to Week 12 by change in the CaGI-S DS and OB scores, the primary anchors in this study, supported responder thresholds identified in the anchor-based analyses (Figure 1).

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 Aviance subscale
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REFERENCES AND ACKNOWLEDGMENTS

REFERENCES


Acknowledgments

Editorial/medical writing support under the guidance of the authors was provided by bE Creative Communications, and was funded by Zynerba Pharmaceuticals, Devcon, PA, USA, in accordance with Good Publication Practice (GPP3) guidelines (Ann Intern Med. 2015;163:461-464).

DISCLOSURES

NT, TS, and JP are employees of Zynerba Pharmaceuticals. TD and JG are contractors for Zynerba Pharmaceuticals. EM and VPP are employees of Covance by Labcorp which has received research funding from Zynerba. RH has received research support from Zynerba Pharmaceuticals. The study was funded by Zynerba Pharmaceuticals.