Meaningful Change Thresholds for the Aberrant Behavior Checklist-Community Fragile X Syndrome (ABC-C_{FXS}) in Children and Adolescents With FXS

Elizabeth Merikle,[1] Vanessa Perez Patel,[1] Thomas Dobbins,[2] Jim Griesser,[2] Nancy Tich,[3] Terri Sebree,[3] Randi Hagerman,[4] Joseph M. Palumbo[3]

[1]Covance by Labcorp., Gaithersburg, MD, USA; [2]The Griesser Group, West Conshohocken, PA, USA; [3]Zynerba Pharmaceuticals Inc., Devon, PA, USA; [4]The Mind Institute, University of California Davis, Sacramento CA, USA

BACKGROUND AND OBJECTIVES

Background

- Fragile X syndrome (FXS) is a rare genetic disorder, which is a common cause of intellectual disability[1]
- The Aberrant Behavior Checklist-Community (ABC-C) is an observer-reported outcome (ObsRO) measure that has been validated in individuals with intellectual disabilities[2]
- An FXS-specific domain structure of the ABC-C (henceforth the ABC-C_{FXS}), which is more representative of the FXS phenotype, has been established[3]
- The ABC-C_{FXS} was utilized to measure the primary and key secondary endpoints in ZYN2-CL-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[4]
- 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-C_{FXS} Social Avoidance (SA), Irritability, and Socially 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-C_{FXS} 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 (CaGI-S). Problems experienced by a child were rated on a 4-point scale (0=no problems to 3=severe problems). CaGI-S change was categorized on a 5-point scale (−2=much better to +2=much worse)
- Caregiver Global Impression of Change (CaGI-C) DS and OB were supportive anchors. Changes in problems experienced by a child were rated on a 7-point scale (−3=much worse to +3=much better)
- Identification of the point change on the CaGI-S/C representing meaningful change was informed by semi-structured cognitive interviews with 25 caregivers of children with FXS

RESULTS

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 on the CaGI-S would be meaningful or important
- In the analyses (n=193), the mean (SD) changes for the ABC-C_{FXS} subscales in patients with a 1-category improvement on the CaGI-S DS and OB items were (**Table 1)**
  - −3.0 (3.0) and −3.6 (2.64) for ABC-C_{FXS} SA
  - −9.8 (9.70) and −8.9 (9.43) for ABC-C_{FXS} Irritability
  - −5.4 (6.46) and −6.8 (6.92) for ABC-C_{FXS} SUL

Table 1. Mean Change Scores on the ABC-C_{FXS} SA, Irritability, and SUL Subscales for Domain-Specific (DS) Behaviors and Overall Behavior (OB) by CaGI-S Change Categories

ABC-C_{FXS}	CaGI-S Change Category[a]				
	Much better (−2)	Better (−1)	No change (0)	Worse (+1)	Much worse (+2)
Social Avoidance					
DS	−5.6 (3.06) (n=17)	−3.0 (3.0) (n=60)	−1.5 (2.44) (n=96)	−0.2 (1.91) (n=20)	N/A (n=0)
OB	−3.3 (4.85) (n=9)	−3.6 (2.64) (n=47)	−1.8 (2.85) (n=110)	−0.9 (2.22) (n=27)	N/A (n=0)
Irritability					
DS	−13.8 (11.73) (n=15)	−9.8 (9.7) (n=55)	−2.5 (6.34) (n=90)	1.2 (6.85) (n=29)	−3.8 (6.19) (n=4)
OB	−10.1 (17.06) (n=9)	−8.9 (9.43) (n=47)	−3.9 (8.01) (n=110)	−0.4 (4.14) (n=27)	N/A (n=0)
Socially Unresponsive/Lethargic					
DS	−7.2 (5.48) (n=13)	−5.4 (6.46) (n=55)	−2.3 (5.01) (n=98)	−1.7 (4.14) (n=23)	−5.5 (2.08) (n=4)
OB	−3.9 (5.69) (n=9)	−6.8 (6.92) (n=47)	−2.7 (4.76) (n=110)	−0.9 (3.55) (n=27)	N/A (n=0)

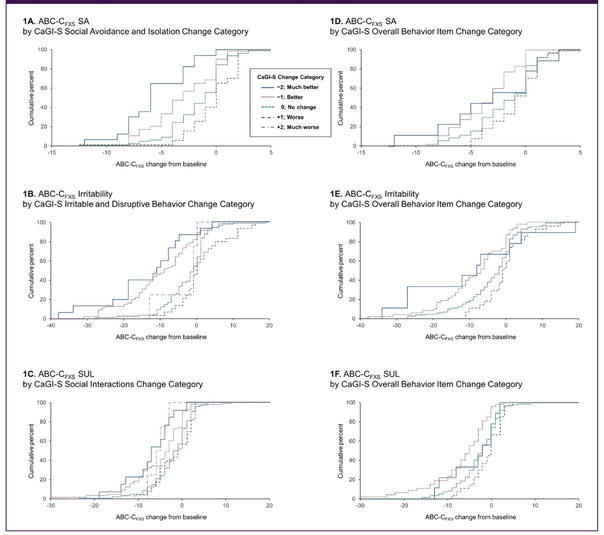
N/A, not applicable.
[a]Data are mean change from Baseline (Visit 3, randomization) to Week 12 (Visit 6) (standard deviation).

- A similar pattern of mean change on the ABC-C_{FXS} SA, Irritability and SUL subscales was observed for the CaGI-C DS and OB items
- Patients rated as a little better (+1) on the CaGI-C DS and OB items had mean (SD) changes for the ABC-C_{FXS} subscales listed below
  - −2.6 (3.47) and −2.9 (2.95) for ABC-C_{FXS} SA
  - −9.0 (9.62) and −8.6 (9.71) for ABC-C_{FXS} Irritability
  - −5.1(6.00) and −5.4 (5.65) for ABC-C_{FXS} SUL

Visual Plots

- Empirical cumulative distribution function curves of change in the ABC-C_{FXS} 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, support the responder thresholds identified in the anchor-based analyses (**Figure 1**)

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



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 interview study, patients who experienced a reduction of 3 or more points on the ABC-C_{FXS} SA subscale, 9 or more points on the ABC-C_{FXS} Irritability subscale, and 5 or more points on the ABC-C_{FXS} SUL subscale from Baseline to Week 12 in CONNECT-FX achieved a meaningful behavioral response to treatment
- More patients with ≥90% methylation of their *FMR1* gene treated with ZYN002 than placebo met the responder threshold at Week 12 for SA (odds ratio 2.04, p=.031) and Irritability (odds ratio 2.17, p=.036)

CONCLUSIONS

- Responder thresholds for meaningful within-patient behavioral change on key domains of the ABC-C_{FXS} 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-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 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

REFERENCES AND ACKNOWLEDGMENTS

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