RECONNECT (ZYN2-CL-033): Design of a Phase 3 Trial of ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents with Fragile X Syndrome Based Upon Learnings from CONNECT-FX (ZYN2-CL-016)

Joseph M. Palumbo, 1 Nancy Tich, 2 Thomas Dobbsina, 2,3 Elizabeth Merkile, 2 Stephen O’Quinn, 4 Chris Brady, 2 Terri Sebree 3
1 Zymeworks Pharmaceuticals, Devon, PA, USA; 2 The Griesser Group, Conshohocken, PA, USA; 3 Labcorp Drug Development, Gaithersburg, MD, USA; 4 Pﬁrsichs, Inc, Wake Forest, NC, USA; 5 VeraSci, Durham, NC, USA

BACKGROUND
• Fragile X syndrome (FXS) is a rare genetic condition involving a range of developmental, neuropsychiatric, and behavioral symptoms that are insufﬁciently managed by the current standard of care (including behavioral/educational interventions, dietary modiﬁcations, and olfactory prescription therapies) alone.

• Carbohydrate, the main nonneuronal component of the CNS, provides therapeutic beneﬁt in FXS through its effects on the endocannabinoid system, which is dysregulated in animal models of FXS.

• ZYN002 is a pharmaceutically produced cannabidiol transdermal gel in clinical development for the treatment of behavioral symptoms associated with FXS.

• RECONNECT (ZYN2-CL-033) is a pivotal, randomized, double-blind, Phase 3 trial to assess the efﬁcacy and safety of ZYN002 in children and adolescents aged 3 through 17 years with a full FMR1 gene mutation.

• The design of RECONNECT is based on learnings from CONNECT-FX (ZYN2-CL-016) Phase 3 trial, which was completed during the SARS-CoV-2 (COVID-19) pandemic. In patients with FXS who were dependent on caregivers for assessments and support.

OBJECTIVE
• To describe the learnings from CONNECT-FX, the ﬁrst randomized, double-blind, placebo-controlled trial of ZYN002 in the treatment of FXS, and how those learnings shaped the design of the follow-on trial, RECONNECT.

METHODS
CONNECT-FX
• CONNECT-FX was a randomized, double-blind, placebo-controlled, Phase 3 trial in children and adolescents with FXS (N=212) with a full FMR1 gene mutation.

• The primary endpoint was change in Social Avoidance/Isolation (SA) as measured by the 8A subscale of the Aberrant Behavior Checklist–Community FXS (ABC–C)

• A pre-planned ad hoc analysis of patients having at least 90% methylation of the FMR1 gene was performed.

• A post-hoc analysis of patients with complete methylation (100%) of the FMR1 gene was performed.

• Patients with complete/near complete methylation were believed to be most likely to have silencing of the FMR1 gene and may be a different biological population than the patients who did not have silencing.

RECONNECT
• The results and conduct of CONNECT-FX were reviewed to identify key learnings to design RECONNECT.

RESULTS
CONNECT-FX
• ZYN002 did not statistically signiﬁcantly separate from placebo on the primary or key secondary endpoints in the full analysis set, which included patients with <50% methylation.

• ZYN002 was superior to placebo in multiple analyses in the group of patients with either 20% methylation or complete methylation (100%) of their FMR1 gene, which represented the majority of patients in the trial (Figure 1).

• Leverage learnings from CONNECT-FX:

• Treatment response to ZYN002 was greatest in patients with 50% methylation of the FMR1 gene.

• Psychometric assessment determined that the ABC-C was ﬁt for purpose in processing within patient change in CONNECT-FX for the Social Avoidance/Isolation, and Socially Unresponsive/Lethargic subscales.

• Complete Global Improvement of Social Avoidance/Isolation and Socially Unresponsive/Lethargic symptoms (CGI-S/U) was responsive to change, with greater change in CGI-S over CGI-U.

• An FMS-speciﬁc Clinical Global Impression of Severity/Improvement (CGI-S/I) assessment was developed based upon outcomes in response to FDA guidance to use a disease-speciﬁc CGI.

• Virtual visits were successfully incorporated as a result of COVID-19.

RECONNECT Trial Design Considerations and Trial Design
Based on the learnings from the CONNECT-FX trial, several optimizations were made in the design of the RECONNECT trial (Figure 2).

The most common treatment that patients were treated with was a FMR1 gene mutation (100%) with partial methylation (<100%) to allow conﬁrmation of the impact of FMR1 gene methylation on treatment response.

Approximately 160 patients with complete methylation (100%) of FMR1 gene will be enrolled.

Approximately 40 patients with partial methylation (<100%) of FMR1 gene will be enrolled.

The duration of the trial was lengthened from 14 weeks in CONNECT to 18 weeks in RECONNECT to provide more time for data collection and elucidation of treatment effect.

Other subgroups in CONNECT were maintained, including the primary and key secondary endpoints.

The trial design for RECONNECT is shown in Figure 3.

CONSOLIDATED CLUB Fascinate/Confront (ZYN2-CL-016)
• The design of RECONNECT was optimized from learnings from CONNECT-FX and will provide key data to determine the effectiveness of ZYN002 in FXS, while reducing burden of participation in a clinical trial for families with children and adolescents with FXS.

• Results from RECONNECT, if successful, could serve as the basis for ZYN002 approval for use in patients with FXS.

REFERENCES

ACKNOWLEDGEMENTS AND DISCLOSURES
Acknowledgements
Medical writing support und the guidance of the authors was provided by p-values communications, and was funded by Zymeworks Pharmaceuticals, Devon, PA, USA.

Disclosures
JF, NT, and TS are employees of Zymeworks Pharmaceuticals. SJ is a consultant for Zymeworks Pharmaceuticals. RS is an employee of Covance by Labcorp, which has received research funding from Zymeworks. CB is an employee of VeraSci, which has received research funding from Zymeworks. This trial was funded by Zymeworks Pharmaceuticals.