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)

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Disclosures
JP, NT, and TS are employees of Zynerba Pharmaceuticals. SO is a consultant for Zynerba Pharmaceuticals. TD is a contractor for Zynerba Pharmaceuticals. EM is an employee of Covance by Labcorp, which has received research funding from Zynerba. CB is an employee of VeraSci, which has received research funding from Zynerba. The trial was funded by Zynerba Pharmaceuticals.
Disclaimers

• This presentation is intended to communicate scientific and medical information about data from clinical trials involving ZYN002. ZYN002 is an experimental treatment which has not been approved by any government regulatory bodies, including the United States Food and Drug Administration (FDA), and has not been determined by the FDA to be a safe or effective treatment for any disease or condition. This presentation is not designed or intended to promote the use of ZYN002 or any other Company product in order to impact prescribing.

• This slide presentation is based on an abstract submitted and accepted for presentation at the 2021 annual meeting of the American Academy of Child and Adolescent Psychiatry.
Background and Objective

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 and educational interventions, dietary modifications, and off-label prescription therapies)\(^1\)-\(^5\)

- Cannabidiol, the main non-euphoric component of the Cannabis plant, may provide therapeutic benefit in FXS through its effects on the endocannabinoid system, which is dysregulated in animal models of FXS\(^4\)

- ZYN002 is a pharmaceutically produced cannabidiol transdermal gel in clinical development for the treatment of behavioral symptoms associated with FXS\(^5\)

- 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\(^6\)

- RECONNECT is designed based on learnings from the 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 upon caregivers for assessments and support\(^7\)

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

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CONNECT-FX: Clinical study Of CaNNabidiol (CBD) in ChildrEn and AdoleCenTs with Fragile X

- CONNECT-FX was a randomized, double-blind, multinational, 14-week pivotal study to evaluate the efficacy and safety of ZYN002 in children/adolescents aged 3 through 17 years with a full FMR1 gene mutation

- ZYN002 did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set

- Building on current scientific evidence, a pre-planned ad hoc analysis of patients having at least 90% methylation of the impacted FMR1 gene was performed

- The results suggested that ZYN002 may have benefit in patients with ≥90% methylation of the FMR1 gene

- ZYN002 was very well tolerated. All adverse events (AEs) were mild or moderate in severity and no serious AEs were reported

- Most common treatment-related AE was application site pain (ZYN002: 6.4%; placebo: 1.0%)

- Laboratory values and ECG parameters were comparable between the placebo and ZYN002 treatment groups and there were no clinically significant changes in liver function tests or other laboratories

\(^a\)FMR1 methylation status was determined by using Southern blot analysis.
In Patients With ≥90% Methylation or Complete Methylation (100%) of \( FMR1 \), Statistical Significance Was Achieved on Social Avoidance at Week 12 (ABC-C\(_{\text{FXS}}\))

*Negative numbers represent an improvement.
Greater Percentages of Patients Achieved Meaningful Change in ABC-C_FXS Social Avoidance and Irritability With ZYN002 vs Placebo

Meaningful within-subject change in ≥90% methylation group

Social Avoidance (Change ≥ 3)  Irritability (Change ≥ 9)  Socially Unresponsive/Lethargic (Change ≥ 5)

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=76</th>
<th>ZYN002 n=91</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients</td>
<td>Placebo</td>
<td>ZYN002</td>
</tr>
<tr>
<td>Social Avoidance</td>
<td>40.6%</td>
<td>58.2%</td>
</tr>
<tr>
<td>Irritability</td>
<td>23.8%</td>
<td>40.3%</td>
</tr>
<tr>
<td>Socially Unresponsive/Lethargic</td>
<td>31.7%</td>
<td>42.1%</td>
</tr>
</tbody>
</table>

P=0.031* OR 2.04  P=0.036* OR 2.17  P=0.184 OR 1.57

OR= odds ratio  *Statistically significant. LS Means  Data on File.
Patients Achieved and Maintained Meaningful Change in ABC-CFXS Social Avoidance With ZYN002 and Placebo Patients Switched to Open-Label ZYN002 Demonstrated a Similar Response

100% methylation group meeting entry criteria for RECONNECT and ≥ 2 consecutive visits with meaningful change*

*Meaningful Change in Social Avoidance: ≥ 3 point improvement from baseline
CONNECT-FX: Summary and Lessons Learned

- ZYN002 did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set, which included patients with <90% methylation.
- ZYN002 was superior to placebo in multiple analyses in the groups of patients with either ≥90% methylation or complete methylation (100%) of their FMR1 gene, which represented 80% and 65% of patients in the trial, respectively.
- Lessons learned from CONNECT-FX:
  1. Treatment response for ZYN002 was greatest in patients with ≥90% methylation of the FMR1 gene.
  2. Psychometric assessments\(^1\) determined that the ABC–C\(_{FXS}\) was fit for purpose in FXS and meaningful within-patient change was determined in CONNECT-FX for the Social Avoidance, Irritability, and Socially Unresponsive/Lethargic subscales\(^2\).
  3. Caregiver Global Impression of Severity/Change (CaGI-S/C) was responsive to change, with greatest change on the Social Interactions.
  4. An FXS-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.
  5. Virtual visits were successfully incorporated as a result of COVID-19.

\(^1\) Merikle et al. Value in Health 2021. 23:S241-242
\(^2\) Merikle et al. Value in Health 2021. 24:S197
RECONNECT Trial Design

**Trial population**
- ~200 patients with FXS
  - ~160 with complete methylation (100%) of FMR1 gene
- 3 through 17 years old

**18 Weeks of Treatment**
- Randomized 1:1
- ZYN002 250, 500, or 750 mg/day
- Placebo

**Open-Label Extension**
- ZYN002

**Endpoints**

**Primary end point**
- Change from baseline in the ABC-CFXS Social Avoidance subscale at week 18 in patients with complete methylation (100%) of the FMR1 gene

**Key secondary end points**
- Complete methylation (100%) population
  - Change from baseline in ABC-CFXS Irritability subscale
  - Improvement in CaGI-C Social Interactions
  - Improvement in FXS-specific CGI-I

**Total population**
- Change from baseline in ABC-CFXS Social Avoidance in the full population (complete and partial methylation)

*Weight-based dosing: ≤30 kg = 250 mg/day; >30 kg = 500 mg/day; >50 kg = 750 mg/day*
RECONNECT Trial Design Optimization

Study Population:
• Patients with complete methylation (100%) of their \textit{FMR1} gene as the primary analysis population; patients with partial methylation (<100%) as a secondary cohort

Hybrid Trial Design:
• Half of all visits are virtual/remote visits to reduce burden for families

Dosing:
• 3 vs 2 weight-based dose strata (250, 500 and 750 mg/day vs 250 and 500 mg/day) incorporated, with the highest dose of 750 mg/day for patients >50 kg to optimize dosing across weight strata

FXS-anchored CGI-S/I:
• Anchored on 3 core behavioral symptoms of FXS: Social avoidance/isolation, Social interactions, and Irritability

Longer trial duration:
• 18-week treatment period vs 14 weeks in CONNECT-FX
Conclusions

CONNECT-FX

• Patients with complete/near complete methylation are believed to be most likely to have silencing of the \textit{FMR1} gene and may be a different biologic population than the patients without silencing\textsuperscript{1,2}

• ZYN002 was superior to placebo in multiple analyses in the groups of patients with either $\geq$90\% methylation or complete methylation (100\%) of their \textit{FMR1} gene, which represented the majority of patients in the trial

RECONNECT

• 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