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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BACKGROUND

- Fragile X syndrome (FXS) is a rare genetic disease caused by alterations of the *FMR1* gene and involving a range of developmental, neuropsychiatric, and behavioral symptoms[1]
- Patients with complete/nearly complete methylation of their *FMR1* gene are believed most likely to have silencing of their *FMR1* gene[1,2]
- Current standard of care (including behavioral and educational interventions, dietary modifications, and prescription therapies) has suboptimal efficacy and tolerability[1,3-6]
- Disruption in the endocannabinoid system is one of the proposed mechanisms for the symptoms observed in FXS,[7,8] and cannabidiol is a non-psychoactive agent that can regulate this system[9]
- ZYN002 (also known as Zygel™)is pharmaceutically produced cannabidiol (not from a plant) that has been uniquely formulated as a gel for transdermal delivery (absorbed through the skin)
- ZYN002 is in clinical development for the treatment of behavioral symptoms associated with FXS, ASD, and 22q11.2 deletion syndrome
- 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 with FXS aged 3-17 years[10]
- RECONNECT is designed based on learnings from CONNECT-FX (ZYN2-CL-016), a randomized, double-blind, Phase 3 trial completed in 212 patients with FXS during the SARS-CoV-2 (COVID-19) pandemic[11]

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

- The primary endpoint in CONNECT-FX was change in severity of Social Avoidance (SA) as measured by the SA subscale of the Aberrant Behavior Checklist-Community FXS (ABC-C_{FXS} SA)
- Secondary endpoints included Caregiver Clinical Global Impression of Change (CaGI-C) for Irritability/Disruptive behaviors and Social Interactions
- A pre-planned ad hoc analysis of patients having ≥90% methylation of the *FMR1* gene was conducted
- A post hoc analysis of patients with complete methylation (100%) of the *FMR1* gene was conducted
- The results and conduct of CONNECT-FX were reviewed to identify key learnings to design RECONNECT

RESULTS

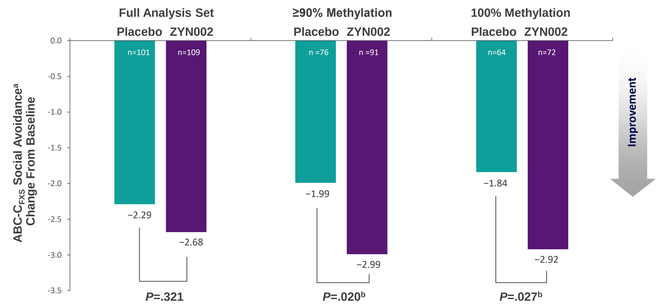
- In CONNECT-FX, improvements were seen in SA behaviors as measured by ABC-C_{FXS} SA in the full population but did not reach statistical significance
- Significant improvements were seen in patients with ≥90% or 100% methylation of their *FMR1* gene (**Figure 1A**)
- ZYN002 was superior to placebo in multiple analyses in the groups of patients with either ≥90% methylation or complete methylation (100%, **Figure 1B**) of their *FMR1* gene, which represented 80% and 65% of patients, respectively

Lessons Learned From CONNECT-FX

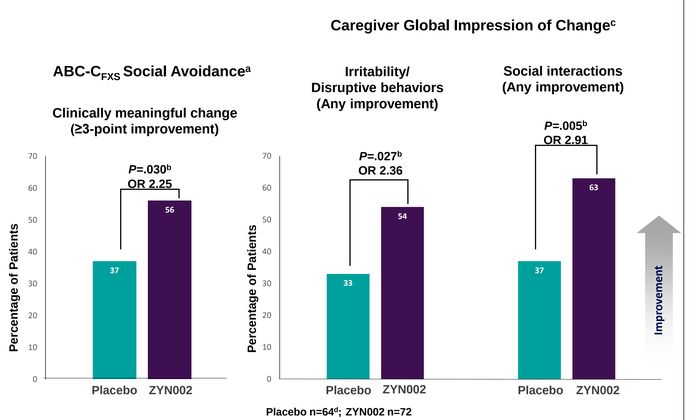
- Treatment response to ZYN002 was greatest in patients with ≥90% methylation of their *FMR1* gene
- Qualitative studies[12] support that the ABC-C_{FXS} is fit for purpose in FXS. Meaningful within-patient change thresholds (MCT) were estimated in CONNECT-FX for the SA , Irritability, and Socially Unresponsive/Lethargic subscales[13]
- Caregiver Global Impression of Severity/Change (CaGI-S/C) was responsive to change to treatment with ZYN002, with greatest change on the Social Interactions subscale
- Virtual visits were successfully incorporated as a result of COVID-19 restrictions

Figure 1. CONNECT-FX Efficacy Results That Informed the Design of RECONNECT

A. Significant Improvement in ABC-C_{FXS} SA in Patients With ≥90% or 100% Methylation of Their *FMR1* Gene



B. Improvement in Key Endpoints in Patients With 100% Methylation of Their *FMR1* Gene



[a]Primary endpoint. [b]Statistically significant. LS means. [c]Secondary endpoint.
[d]Placebo n=65, however, 1 patient did not have a post-baseline efficacy measure and was therefore not included in the efficacy analysis.

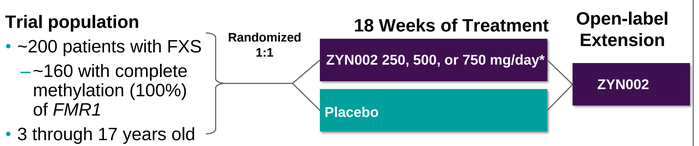
RECONNECT Trial Design Considerations and Trial Design

- Based on learnings from the CONNECT-FX trial, several optimizations were made in the design of the RECONNECT trial (**Table 1** and **Figure 2**)
- Strategic enrichment of the trial population by enrolling a primary group of patients with complete methylation (100%) of their *FMR1* gene and a secondary group with partial methylation (<100%) to confirm the impact of *FMR1* methylation on treatment response based upon the data from CONNECT-FX and input from the FDA
  - Approximately 160 patients with complete methylation (100%) of *FMR1* will be enrolled
  - Approximately 40 patients with partial methylation (<100%) of *FMR1* will be enrolled
- Addition of a third weight-based dose and, in response to FDA guidance, addition of a disease-specific CGI
- The duration of the trial was lengthened from 14 weeks in CONNECT-FX to 18 weeks in RECONNECT to provide more time for assessment of treatment effect
- Other key elements of CONNECT-FX were maintained, including the primary and several key secondary endpoints

Table 1. RECONNECT Trial Design Optimizations

- **Population enrichment:** Patients with complete methylation (100%) of their *FMR1* gene as the primary analysis population; patients with partial methylation (<100%) as a secondary group
- **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 Clinical Global Impression of Severity/Change (CGI-S/I)**: Anchored on 3 core behavioral symptoms of FXS: Social Avoidance/Isolation, Social Interactions, and Irritability
- **Longer trial duration:** 18 weeks of treatment vs 14 weeks in CONNECT-FX
- **Virtual visits:** Virtual visits incorporated (4 of 8) to reduce burden for families and provide flexibility in the event of ongoing challenges with COVID-19

Figure 2. RECONNECT Trial Design



*Weight-based dosing: ≤30 kg=250 mg/day; >30-50 kg=500 mg/day; >50 kg=750 mg/day.

Endpoints

Primary endpoint

- Change from baseline in the ABC-C_{FXS} SA subscale at week 18 in patients with complete methylation (100%) of their *FMR1* gene

Key secondary endpoints

Complete methylation (100%) population

- Change from baseline in ABC-C_{FXS} Irritability subscale
- Improvement in CaGI-C Social Interactions
- Improvement in FXS-specific CGI-I
- Change from baseline in ABC-C_{FXS} SA in the full population (complete and partial methylation)

CONCLUSIONS

- 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
- RECONNECT is being conducted in 29 centers in the US, Australia, the UK, and Ireland
- US RECONNECT study locations include:

California	Minnesota	Oklahoma
Florida	Mississippi	Pennsylvania
Georgia	New Jersey	South Carolina
Illinois	New York	Texas
Maryland	North Carolina	Utah
Massachusetts	Ohio	Washington
		Washington, D.C.

- **For more information on RECONNECT, visit www.fragilexhelp.com**

REFERENCES

1. Hagerman RJ, et al. *Nat Rev Dis Primers*. 2017;3:17065.
2. Schneider A, et al. *Transl Psychiatry*. 2020;10(1):205.
3. Crawford DC, et al. *Genet Med*. 2001;3(5):359-371.
4. Lozano R, et al. *Intractable Rare Dis Res*. 2016;5(3):145-157.
5. Tartaglia N, et al. *Cannabis Cannabinoid Res*. 2019;4(1):3-9.
6. Heussler H, et al. *J Neurodev Disord*. 2019;11(1):15.
7. Jung KM, et al. *Nat Commun*. 2012;3:1080.
8. Busquets-Garcia A, et al. *Nat Med*. 2013;19(5):603-607.
9. Cheung KAK, et al. *Front Psychiatry.* 2021;12:643442.
10. ClinicalTrials.gov. Clinical Study of Cannabidiol in Children and Adolescents With Fragile X Syndrome (RECONNECT). NCT04977986. Updated September 16, 2021. Accessed September 18, 2021. https://clinicaltrials.gov/ct2/show/NCT04977986
11. ClinicalTrials.gov. Clinical Study Of caNNabidiol in childrEn and adolesCenTs With Fragile X (CONNECT-FX). NCT03614663. Updated July 20, 2020. Accessed September 18, 2021. https://clinicaltrials.gov/ct2/show/NCT03614663
12. Merikle E, et al. Virtual International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2021 Meeting; May 17-20, 2021.
13. Merikle E, et al. Society of Biological Psychiatry (SOBP) 2021 Virtual Meeting; April 21-May 1, 2021.

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