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) Completed During SARS-COV-2 Pandemic

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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]
- Patients with complete/near complete methylation of their *FMR1* gene are believed to be most likely to have silencing of the *FMR1* gene[1,6]
- Disruption in the endocannabinoid system is one of the proposed mechanisms for the loss of synaptic plasticity and the deficits in emotional responsivity observed in FXS[7,8]
- Cannabidiol is a negative allosteric modulator at presynaptic CB_1 receptors, a $5HT_{1A}$ agonist, and a D_2 partial agonist[9-11]
- 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 with FXS aged 3 through 17 years
- RECONNECT is designed based on learnings from CONNECT-FX (ZYN2-CL-016), a randomized, double-blind Phase 3 trial, which was completed during the SARS-CoV-2 (COVID-19) pandemic, in 212 patients with FXS[13]

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[a] was conducted
- A post hoc analysis of patients with complete methylation (100%) of the *FMR1* gene[a] was conducted
- The results and conduct of CONNECT-FX were reviewed to identify key learnings to design RECONNECT

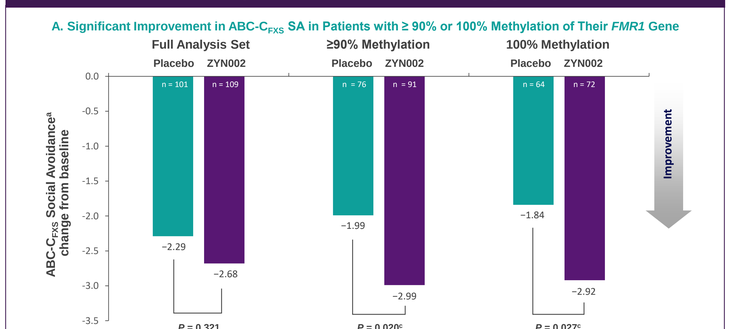
RESULTS

- 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 the *FMR1* gene
- Qualitative studies[14] 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[15]
- 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]Primary endpoint. [b]Secondary endpoint. [c]Statistically significant. LS means.
[d]Placebo n = 65, however, 1 patient did not have a post-baseline efficacy measure and was therefore not included in the efficacy analysis.

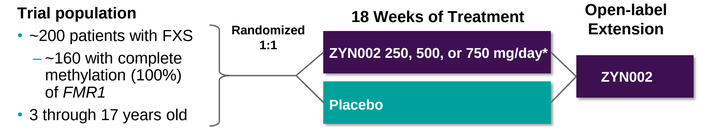
RECONNECT Trial Design Considerations and Trial Design

- Based on the learnings from the CONNECT-FX trial, several optimizations were made in the design of the RECONNECT trial (**Table 1**)
- These optimizations included a strategic enrichment of the trial population by enrolling a primary cohort of patients with complete methylation (100%) of their *FMR1* gene and a secondary cohort with partial methylation (<100%) to allow confirmation of 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
- The duration of the trial was lengthened from 14 weeks in CONNECT-FX to 18 weeks in RECONNECT to provide more time for elucidation of treatment effect
- Other key elements of CONNECT-FX were maintained, including the primary and several key secondary endpoints
- The trial design for RECONNECT is shown in **Figure 2**

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 cohort
- **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 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 the *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

Total population

- 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 will be 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 DC

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

REFERENCES

1. Hagerman RJ et al. *Nat Rev Dis Primers*. 2017;3:17065.
2. Crawford DC et al. *Genet Med*. 2001;3(5):359-371.
3. Lozano R et al. *Intractable Rare Dis Res*. 2016;5(3):145-157.
4. Tartaglia N et al. *Cannabis Cannabinoid Res*. 2019;4(1):3-9.
5. Heussler H et al. *J Neurodev Disord*. 2019;11(1):15.
6. Schneider A et al. *Transl Psychiatry*. 2020;10(1):205.
7. Jung KM et al. *Nat Commun*. 2012;3:1080.
8. Busquets-Garcia A et al. *Nat Med*. 2013;19(5):603-607.
9. Laprairie RB et al. *Br J Pharmacol*. 2015;172(20):4790-4805.
10. Russo EB et al. *Neurochem Res*. 2005;30(8):1037-1043.
11. McGuire P et al. *Am J Psychiatry*. 2018;175(3):225-231.
12. 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
13. 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
14. Merikle E et al. Virtual International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2021 Meeting; May 17-20, 2021.
15. Merikle E et al. Society of Biological Psychiatry (SOBP) 2021 Virtual Meeting; April 21-May 1, 2021.

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