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 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 noneuphoric 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

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 (SA) as measured by the SA subscale of the Aberrant Behavior Checklist–Community FXS (ABC-C_{FXS})
- A pre-planned ad hoc analysis of patients having at least 90% methylation of the *FMR1* gene[a] was performed
- A post-hoc analysis of patients with complete methylation (100%) of the *FMR1* gene was performed
- Patients with complete/near complete methylation are believed to be most likely to have silencing of the *FMR1* gene and may be a different biologic population than the patients without silencing[1,8]

RECONNECT

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

[a]*FMR1* methylation status was determined using Southern blot analysis.

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 <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 the majority of patients in the trial (**Figure 1**)
- Lessons learned from CONNECT-FX:
  1. Treatment response for ZYN002 was greatest in patients with ≥90% methylation of the *FMR1* gene
  2. Psychometric assessments[9] 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[10]
  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

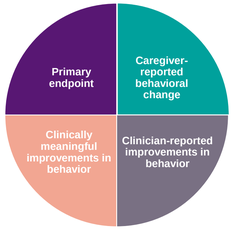
Figure 1. CONNECT-FX Efficacy Results

Consistent Improvements Observed With ZYN002 vs Placebo

Results in the population with ≥90% *FMR1* methylation (n=169[a]; 80% of total population)

ABC-C_{FXS} Social Avoidance subscale

40% median improvement in socially avoidant behaviors (p=0.020)



Caregiver Global Impression of Change

Any Improvement
ZYN002 vs placebo

Social interaction
66% vs 41% (p=0.002)

Irritable/Disruptive Behaviors
53% vs 35% (p=0.028)

Social Avoidance/Isolation
60% vs 43% (p=0.038)

Overall behavior
63% vs 48% (p=0.052)

Clinically meaningful improvement

Significantly more patients achieved a clinically meaningful change
ZYN002 vs placebo

Social Avoidance (≥3 points)
58% vs 41% OR=2.04 (p=0.031)

Irritability (≥9 points)
40% vs 24% OR=2.17 (p=0.036)

Clinical Global Impression of Improvement (anchored)[b]

Any Improvement
ZYN002 vs placebo
51% vs 36%
Trend toward statistical significance (p=0.056)

[a]2 subjects were not included; 1 subject did not receive study medication after randomization and 1 subject did not have post-baseline efficacy assessments.
[b]Not specific to Social Avoidance. OR=odds ratio.

Results in the population with complete methylation (100%) of *FMR1* (n=137; 65% of total population)

Endpoint 12 weeks post baseline	ZYN002 n = 72	Placebo[c] n = 64	Treatment Difference / Odds Ratio	p value
ABC-C_{FXS} Social Avoidance **Mean change**	−2.92	−1.84	−1.08	0.027*
% change (median)	−40%	−20%		
Meaningful Change (≥3 points) ***Social avoidance / isolation***	56%	37%	2.25	0.030*
Caregiver global impression-Change (any improvement) ***Social interactions***	63%	37%	2.91	0.005*
Caregiver global impression-Change (any improvement) ***Irritable / disruptive behaviors***	54%	33%	2.36	0.027*

*Statistically significant
[c]Placebo N = 65, however, 1 patient did not have a post-baseline efficacy measure and was therefore not included in the efficacy analysis.

CONNECT-FX Safety (full analysis set, N=212)

- ZYN002 was very well tolerated in CONNECT-FX
- There were no serious or severe adverse events reported during the trial
- TEAEs (any event, whether unrelated or related to study drug) were mild or moderate
  - The most common treatment-related TEAE was application site pain (ZYN002: 6.4%; placebo: 1.0%)
- Laboratory values for chemistry and hematology, and ECG parameters were comparable between the placebo and ZYN002 treatment groups, and there were no clinically relevant abnormalities in either group
  - There were no clinically significant changes to liver function tests

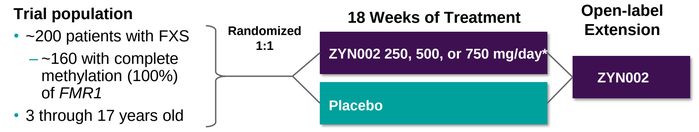
RECONNECT Trial Design Considerations and Trial Design

- Based on the learnings from the CONNECT-FX trial, several optimizations were made in the design of the RECONNECT trial (**Figure 2**)
- 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
  - 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 data collection and elucidation of treatment effect
- Other key elements of RECONNECT were maintained, including the primary and several key secondary end points
- The trial design for RECONNECT is shown in **Figure 3**

Figure 2. 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 CGI-S/I**: anchored on 3 core behavioral symptoms of FXS: Social avoidance/isolation, Social interactions, and Irritability
- **Longer trial duration:** 18 weeks double-blind treatment vs 14 weeks in CONNECT-FX
- **Trial visits:** both on-site and face-to-face virtual visits to reduce burden for families

Figure 3. RECONNECT Trial Design



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

End Points

Primary end point

- Change from baseline in the ABC–C_{FXS} 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-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} Social Avoidance in the full population (complete and partial methylation)

CONCLUSIONS

CONNECT-FX:

- 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 the majority of patients in the trial
- 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 well tolerated

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

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Disclosures
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