BACKGROUND

- Fragile X syndrome (FXS) is a rare genetic disease caused by alterations of the FMR1 gene and involving a range of developmental, neurocognitive, and behavioral disorders.

- Patients with complete/nearly complete methylation of their FMR1 gene are believed most likely to have silencing of their FMR1 gene.

- Current standard of care (including behavioral and educational interventions, dietary modifications, and prescription therapies) has suboptimal efficacy and tolerability.

- Disruption in the endocannabinoid system is one of the proposed mechanisms for the symptoms observed in FXS, and cannabidiol is a non-psychoactive agent that can regulate this system.

RESULTS

- In CONNECT-FX, improvements were seen in SA behaviors as measured by ABC-0.3 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%, respectively.

- Lessons Learned From CONNECT-FX

  - Treatment response to ZYN002 was greatest in patients with ≥90% methylation of their FMR1 gene.

  - Qualitative studies support that the ABC-0.3 SA 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.

  - Caregiver Global Impression of Severity/Change (CaG-I/C) was responsive to changes in treatment with ZYN002, with greatest change on the Social Interactions subscale.

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

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-0.3 SA).

- Secondary endpoints included Caregiver Global Impression of Change (CaG-I/C) for Irritability/Disruptive behaviors and Social Interactions.

- A preplanned 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.

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 on 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.

- Addion of a third weight-based dose and, in response to FDA guidance, addition of a disease-specific CGI.

- The data cutoff 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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Primary endpoint</th>
<th>Key secondary endpoints</th>
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<tr>
<td></td>
<td>Change from baseline in the ABC-0.3 SA subscale at week 18 in patients with complete methylation (100%) of their FMR1 gene</td>
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<td>Complete methylation (100%) population</td>
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<td></td>
<td>Change from baseline in ABC-0.3 SA subscale</td>
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<td>Improvement in CaG-I/C Social Interactions</td>
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<td>Improvement in FXS-specific CGI</td>
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<td>Change from baseline in ABC-0.3 SA in the full population (complete and partial methylation)</td>
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REFERENCES