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.

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

- Disruption in the endocannabinoid system is one of the proposed mechanistic pathways for the loss of synaptic plasticity and the deficits in emotional responsivity observed in FXS.

- Cannabidiol is a negative allosteric modulator at presynaptic cannabinoid CB1 receptors and a 5HT2A agonist. ZYN002 is a pharmaceutical produced cannabinoid transdermal gel in clinical development for the treatment of behavioral symptoms associated with FXS.

- RECONNECT (ZYN2-002) 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, 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/Social Interactions (S/I) measured on the CGI-I in patients aged 3 through 17 years with FXS (ABC-CDDA-SA).

- Secondary endpoints included Caregiver Clinical Global Impression of Change (CaGIC-C) for Intermittent/Dissipative behaviors and Social Interactions.

- A pre-planned ad hoc analysis of patients having ≥90% methylation of the FMR1 gene was conducted post hoc analysis of patients with ≥90% and ≥100% methylation 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-CDDA-SA in the full population and at not reach statistical significance.

- Significant improvements were seen in patients with ≥90% and ≥100% methylation of their FMR1 gene (Figure 1A).

- ZYN002 was superior to placebo in multiple analyses in the groups of patients with either ≥90% and ≥100% methylation of the 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 support the recommendations to use FMR1 genotyping to identify the cohort of patients with ≥90% and 65% of patients, respectively.

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

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

RECONNECT 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 stratified enrichment of the trial population by ensuring a primary cohort of patients with complete methylation (100%) of their FMR1 gene and a secondary cohort with partial methylation (≥60%) to allow confirmation of the impact of methylation status on treatment response for ZYN002.

  - Approximately 160 patients with complete methylation (100%) of FMR1 will be enrolled in the primary cohort.

  - Approximately 40 patients with partial methylation (<100%) of FMR1 will be enrolled in the secondary cohort.

  - 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.

ACKNOWLEDGMENTS

- 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 regulatory approval for the use of ZYN002 in children with FXS.

- RECONNECT will be conducted in 29 centers in the US, Australia, the UK, and Ireland.

- The US centers for RECONNECT include:

  - California
  - Minnesota
  - Oklahoma
  - Florida
  - Mississippi
  - Pennsylvania
  - Georgia
  - Arizona
  - South Carolina
  - Illinois
  - New York
  - Texas
  - Massachusetts
  - North Carolina
  - Utah
  - Michigan
  - Ohio
  - Washington DC

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

REFERENCES


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