BACKGROUND

- ZYN002 is a pharmacologically manufactured transdermal cannabidiol gel in development for the treatment of behavioral symptoms in Fragile X syndrome (FXS).

- CONNECT-FX was a randomized, double-blind, multinational, 14-week pivotal study to evaluate the efficacy and safety of ZYN002 in children/adolescents with a full FMRI gene mutation (Figure 1).

- ZYN002 did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set.

- FXS is defined as full mutation of the FMR1 gene, which may require complete or near complete methylation of the FXS gene.

- Patients without silencing of the gene may represent a different biological population.

- A pre-planned ad hoc analysis of patients having at least 90% methylation of the FXS gene was performed.

OBJECTIVE

- To describe the results of the CONNECT-FX (ZYN2-CL-016) study in children/adolescents with FXS with complete or near complete methylation of their FXS gene.

METHODS

- Patients were randomized to 12-weeks of ZYN002 (250 mg or 500 mg daily [weight-based] or placebo, as add-on to standard of care.

- The primary endpoint was change in the Social Avoidance subscale of the Aberrant Behavior Checklist—Community FXS (ABC–CFX).

- Key secondary endpoints included change from baseline to end of treatment in ABC–CFX Social Avoidance and Irritability, Socially Unresponsive/Lethargic, and Sleep Behaviors, and multiple psychometric analyses (SOBP Poster by Merikle E. et al. entitled "Cannabidiol in Fragile X Syndrome (FXS): Proposed Mechanism of Action Translates Into Meaningful Clinical Benefits [CONNECT-FX]" [ZYN2-CL-016]).

RESULTS

BASELINE DEMOGRAPHICS

- The ≥90% methylation group represented 80% of the study population.

- Baseline characteristics are shown in Table 1.

EFFICACY RESULTS

- The ≥90% methylation group achieved statistically significant improvement in the primary endpoint of ABC–CFX Social Avoidance at Week 12 (p<0.002, Table 2 and Figure 2).

- The ≥90% methylation group achieved statistically significant improvements in Caregiver Global Impression-Change in Social Avoidance and Irritability, Discriminative Behaviors, and Social Interactions (p<0.038, p<0.028, and p<0.002) (Figure 4).

- The ≥90% methylation group did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set.

- The number needed to treat (NNT) for Social Avoidance was 5.7 (Cohen’s d of 0.52).

- Clinically meaningful within-subject change was determined by psychometric analyses (SOBP Poster by Merikle E. et al. entitled "Cannabidiol in Fragile X Syndrome (FXS): Proposed Mechanism of Action Translates Into Meaningful Clinical Benefits [CONNECT-FX]" [ZYN2-CL-016]).

- Significantly more ZYN002-treated patients in the ≥90% methylation group had a meaningful change in ABC–CFX subscales for Social Avoidance and Irritability (≥0.31 and ≥0.36, respectively) (Figure 3).

- There were no clinically significant changes to liver function tests.

- There were no clinically significant changes to laboratory values for chemistry and hematology, and electrocardiogram parameters were comparable between the placebo and ZYN002 treatment groups, and there were no clinically relevant abnormalities in either group.

SAFETY RESULTS

- ZYN002 was very well tolerated in CONNECT-FX.

- There were no serious or severe adverse events reported during the study.

- All treatment-emergent adverse events (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 electrocardiogram parameters were comparable between the placebo and ZYN002 treatment groups, and there were no clinically relevant abnormalities in either group.

CONCLUSIONS

- To our knowledge, CONNECT-FX is the largest controlled study ever performed in FXS.

- ZYN002 was well tolerated.

- In the ≥90% methylation group, ZYN002 was superior to placebo in multiple analyses.

- There was statistically significant mean change in Social Avoidance vs placebo.

- Proportion of patients attaining threshold of clinically meaningful change in Social Avoidance and Irritability.

- Caregiver reported improvements including Social Avoidance, Social Interaction, and Irritable behaviors.

- There was a data suggest that effective silencing of the FMR1 gene may have led to differences in treatment response in patients with ≥90% methylation of the FMR1 gene.

- These results may represent an important step forward in further understanding FXS and the importance of methylation of the FMR1 gene.

- A follow-up phase 3 study is being conducted to confirm these results.

REFERENCES


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