Development of ZYN002 (Zygel™) for the Treatment of Behavioral Symptoms in Fragile X Syndrome:

Partnering to advance the care of children and adolescents with Fragile X Syndrome
Disclosures

• This presentation is intended to communicate scientific and medical information about data from clinical trials involving ZYN002 (Zygel™). ZYN002 is an experimental treatment which has not been approved by any government regulatory bodies, including the United States Food and Drug Administration (FDA), and has not been determined by the FDA to be a safe or effective treatment for any disease or condition. This presentation is not designed or intended to promote the use of ZYN002 or any other Company product in order to impact prescribing.

• Stephen O’Quinn is an employee of Zynerba Pharmaceuticals.

• The trials discussed were funded by Zynerba Pharmaceuticals.
Zygel™: Pharmaceutically Produced Cannabidiol Transdermal Gel

<table>
<thead>
<tr>
<th>PHARMACEUTICALLY PRODUCED</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA regulated</td>
</tr>
<tr>
<td>Consistency of production</td>
</tr>
<tr>
<td>Purity of ingredients</td>
</tr>
<tr>
<td>No THC – not a scheduled drug by US DEA</td>
</tr>
<tr>
<td>Scalable production process</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TRANSDERMAL DELIVERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of application for caregivers of patients with behavioral issues</td>
</tr>
<tr>
<td>Minimizes GI side effects and reduces risk for liver side effects</td>
</tr>
<tr>
<td>Lower risk for drug/drug interactions</td>
</tr>
<tr>
<td>Avoids conversion to THC in stomach</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; THC, tetrahydrocannabinol; US DEA, United States Drug Enforcement Agency.
# Focused Clinical Pipeline

## Zygel™ (ZYN002 Cannabidiol Gel)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fragile X Syndrome (FXS)</strong></td>
<td>Preclinical</td>
</tr>
<tr>
<td><strong>22q Deletion Syndrome (22q)</strong></td>
<td>Preclinical</td>
</tr>
<tr>
<td><strong>Autism Spectrum Disorder (ASD)</strong></td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

### Milestones
- **US Orphan Drug and Fast Track designations; EU Orphan Drug designation**
- **Regulatory Filing**
- **US Orphan Drug designation**
- **5**
Why Study Zygel™ in Fragile X Syndrome (FXS)?

- The Endocannabinoid System (ECS) does not function well in FXS because of changes in how the \textit{FMR1} gene functions in FXS
  - Changes in \textit{FMR1} result in absence of FMR protein (FMRP), an important protein for development; the lack of FMRP, in turn, affects the ECS\textsuperscript{1}
- The ECS plays an important role in the neuronal development and functions in helping the body maintain normal neuronal function\textsuperscript{2}
- Alterations in the ECS may impact cognition and behavior\textsuperscript{3,4}
- Cannabidiol is thought to act to help minimize some of the changes in the ECS seen in FXS\textsuperscript{3}
- Cannabidiol has also shown activity at serotonin (5HT\textsubscript{1A}),\textsuperscript{5} GABA\textsubscript{A},\textsuperscript{6} and dopamine receptors (D\textsubscript{2}, D\textsubscript{3})\textsuperscript{7,8}
- The combined effects may help to improve the balance in inhibitory and excitatory transmission and help restore neuronal function and synaptic plasticity in patients with FXS

The History of Zygel™
More Than 15 Years of Research, Dedication, and Expertise

The company was founded by a pharmacologist and transdermal experts at the University of Kentucky College of Pharmacy

FAB-C 1st Trial in FXS

Preclinical Program Begins

ZYN002 First-in-Human Clinical Trial

CONNECT-FX

Open-Label Extension Trial

FAB-C, Feelings, Attitudes, and Behaviors Scale for Children.
1. FAB-C in Australia
2. File US IND with FDA
3. Multiple Meetings with FDA
4. CONNECT-FX in US, AU & NZ
5. More Meetings with FDA
6. RECONNECT in US, AU, UK, Ireland
What Have We Learned Along the Road?
What Have We Learned Along the Road?

• You are a passionate and dedicated community

• Zygel™ has been well tolerated over the long term

• Zygel has shown the potential to provide clinically meaningful improvements in Fragile X-related behavioral symptoms
  • Methylation of the FMR1 gene may play an important role in determining response to Zygel
Passionate and Dedicated Community

Families, Participants, Advocacy Groups, Study Sites, Partnering Labs

- **NFXF**
  - >2000 Patient Visits
  - >5000 Caregiver Assessments + Skin Diaries
  - >100 Site Staff

- **FRAXA**
  - 5 Countries
  - 37 Trial Sites
  - Travel by Planes, Trains, & Automobiles

- **MIND INSTITUTE**
  - 10 Time zones
  - >300 Children & Adolescents Screened

- **UK Fragile X Society**
  - 28-Person Zynerba Team

- **Fragile X Association of Australia**

- **Asuragen**

Zynerba Pharmaceuticals | Advancing Science. Improving Connections.
Partnering With You Along the Way

NFXF Advocacy Days
Zygel™ Has a Well-Tolerated Safety Profile

- Safety database across all clinical studies includes data from over 900 volunteers and patients
- Over 5 years of experience in children and adolescents with Fragile X syndrome
- Majority of treatment-emergent AEs (TEAEs) were mild or moderate
- Most common Zygel-related TEAEs are application site events, the majority of which were mild and transient
- No clinically significant changes in vital signs or ECGs
- No Zygel-related clinically significant changes in laboratory values, including liver function tests

ECG, electrocardiogram.
Zygel™ Has Been Well Tolerated Over the Long Term
Open-label extension trial up to 38 months of treatment

Most events related to conditions commonly reported in children and adolescents

<table>
<thead>
<tr>
<th>Adverse Event Type</th>
<th>Patients (n = 240) or Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Emergent Adverse Events (TEAEs)a</td>
<td>62.9%</td>
</tr>
<tr>
<td>Mild-to-moderate TEAEs</td>
<td>97.6% (events)</td>
</tr>
<tr>
<td>TEAEs (≥3% of patients)</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>15.8%</td>
</tr>
<tr>
<td>Application-site pain</td>
<td>6.7%</td>
</tr>
<tr>
<td>Pyrexia (fever)</td>
<td>5.4%</td>
</tr>
<tr>
<td>Nasopharyngitis (common cold symptoms)</td>
<td>5.0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.2%</td>
</tr>
<tr>
<td>Ear infection</td>
<td>4.2%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.8%</td>
</tr>
<tr>
<td>Cough</td>
<td>3.3%</td>
</tr>
<tr>
<td>Influenza</td>
<td>3.3%</td>
</tr>
<tr>
<td>Discontinuations due to TEAEs</td>
<td>2.5% (6 patients)</td>
</tr>
<tr>
<td>Serious AEs (all non-treatment-related)</td>
<td>10 events in 7 patients</td>
</tr>
<tr>
<td>Treatment-Related AEs</td>
<td>12.9%</td>
</tr>
<tr>
<td>Most common treatment-related AE (≥3% of patients)</td>
<td>6.7%</td>
</tr>
<tr>
<td>Application-site pain (transient; mild in 15 and moderate in 1 patient)</td>
<td></td>
</tr>
</tbody>
</table>

*aTEAE, whether related or unrelated to study drug.*
Clinically Meaningful Improvements in FXS-Related Behavioral Symptoms: CONNECT-FX Patients With Complete Methylation of $FMR1^a$

<table>
<thead>
<tr>
<th>ABC-C$_{FXS}$ Social Avoidance</th>
<th>Caregiver Global Impression of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically meaningful change (≥3-point improvement)</td>
<td>Irritability/Disruptive behaviors (Any improvement)</td>
</tr>
</tbody>
</table>

- Placebo $n=64$; Zygel $n=72$
- $P=0.030^b$ OR 2.25
- $P=0.027^b$ OR 2.36
- $P=0.005^b$ OR 2.91

- Data in patients with 100% $FMR1$ gene methylation.
- Statistically significant. LS means.
- Placebo $n=65$, 1 patient did not have a post-baseline efficacy measure.
- ABC-C$_{FXS}$ Aberrant Behavior Checklist-Community Fragile X Syndrome; OR, odds ratio.
Sustained Improvement in Patients With Complete Methylation of FMR1

- Patients matching primary efficacy population in RECONNECT.
- ZYN2-CL-016 (CONNECT-FX).

Least square mean ± SE; reduction equals improvement.

<table>
<thead>
<tr>
<th>Change from baseline</th>
<th>Placebo (n=49)</th>
<th>Zygel (n=47)</th>
<th>Switch from Placebo to Zygel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>48 47 45 46 49 45 43 44 36 40 31 33 31</td>
<td>47 45 46 43 44 43 44 43 36 40 31 33 31</td>
<td></td>
</tr>
</tbody>
</table>

CONNECT-FX Double-Blind

Open-Label Extension Patients on Zygel™

a. Patients matching primary efficacy population in RECONNECT.
b. ZYN2-CL-016 (CONNECT-FX).
c. Least square mean ± SE; reduction equals improvement.
Clinically Meaningful Change$^a$ Achieved and Maintained in Patients With Complete Methylation of $FMR1$ Gene$^b$

Change in ABC-C$_{FXS}$ Social Avoidance

- **CONNECT-FX Double-Blind**
- **Open-Label Extension Patients on Zygel™**

$a$. Meaningful change in Social Avoidance: ≥3-point improvement from baseline; maintained for ≥2 consecutive visits.

$b$. Patients matching primary efficacy population in RECONNECT.

$c$. ZYN2-CL-016 (CONNECT-FX).

Cumulative Percentage of Patients

\[ \begin{align*}
\text{Zygel (n=47)} & \quad \text{Placebo (n=49)} \quad \text{Switch from Placebo to Zygel}
\end{align*} \]
What’s Next?
Confirmatory Trial – Complete Enrollment

Patients will be enrolled regardless of the degree of methylation of their FMR1 gene.

Double-Blind, Placebo-Controlled Study: Initiated

- **18 weeks**
- **3 to 17 years old**
- **Moderate-to-Severe FXS**

**Zygel™**
(n~100; 80\textsuperscript{a})

- 250 mg daily (≤30 kg)
- 500 mg daily (>30 kg)
- 750 mg daily (>50 kg)
  (weight-based dose)

Patients randomized (1:1) to receive either Zygel or placebo

**Placebo**
(n~100; 80\textsuperscript{a})

- Mirrors Zygel administration

Open-Label Extension (OLE): Ongoing

- **24 months**
- All patients receive Zygel

\textsuperscript{a}Patients with complete methylation of FMR1 gene.
**“In-office” and “Virtual at-Home” Visits**

- 4 visits at the doctor’s office and 4 virtual visits from home
- Visit 1 to confirm eligibility followed by 7 visits over 18 weeks

<table>
<thead>
<tr>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7</th>
<th>Visit 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week -3</td>
<td>Day 1</td>
<td>Week 2</td>
<td>Week 4</td>
<td>Week 6</td>
<td>Week 10</td>
<td>Week 14</td>
<td>Week 18</td>
</tr>
<tr>
<td>In-office</td>
<td>In-office</td>
<td>In-office</td>
<td>Virtual</td>
<td>Virtual</td>
<td>Virtual</td>
<td>Virtual</td>
<td>In-office</td>
</tr>
</tbody>
</table>

- Informed consent
- Medical history
- Physical exam
- Labs
- ECG
- Labs (some patients)\(^d\)
- Physical exam
- Labs
- ECG

**FXS Assessments**\(^a\)

- Blinded study medicine\(^b\) and daily skin diary\(^c\)

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\(^a\) Caregiver and Clinician questionnaires to assess symptoms of Fragile X syndrome.
\(^b\) Apply blinded study medication 2 times daily to upper arms/shoulders (morning/evening).
\(^c\) Complete daily skin diary (every evening).
\(^d\) Only participants on antiseizure or antipsychotic medicines (ie, risperidone) have labs at Visit 6.
What’s Next?

- RECONNECT
  - Complete enrollment
  - Analyze and report the topline results of the trial in 2H 2023
- Seek approval from the FDA (pending positive results from RECONNECT)
- Upon approval, Zygel™ would become available in the US
- Seek approval in other countries
Where Can I Get More Information?

- Visit the RECONNECT (#14) or Zynerba Booths (#3)
- FRAGILEXHELP.COM
- Scan the QR code
- Call 833-680-1155
- 29 study sites in the US, Australia, the UK, and Ireland

  - US RECONNECT study site locations are in:
    - California
    - Florida
    - Georgia
    - Illinois
    - Maryland
    - Massachusetts
    - Minnesota
    - Mississippi
    - New Jersey
    - New York
    - North Carolina
    - Ohio
    - Oklahoma
    - Pennsylvania
    - South Carolina
    - Texas
    - Utah
    - Washington
    - Washington, DC
RECONNECT US Clinical Trial Sites
We are in this together!

We need YOU!
Thank you to all Investigators and Staff

- Darius Adams - Jacobs Levy
  Personalized Genomic Medicine & Research Program
- Julian Barwell - Leicester Royal Infirmary
- Elizabeth Berry-Kravis - Rush University Medical Center
- Catherine Breen - Manchester Centre for Genomic Medicine
- Caroline Buchanan - Greenwood Genetic Center
- Dejan Budimirovic - Kennedy Krieger Institute
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- Aedin Collins - Trinity College Dublin
- Barbara Jane Coffey - University of Miami Miller School of Medicine
- Jonathan Cohen - Genetics Clinics Australia
- Craig Erickson - Cincinnati Children’s Hospital Medical Center
- Amy Esler - Masonic Institute for the Developing Brain
- Patricia Evans - UT Southwestern Medical Center
- Richard Frye - Phoenix Children's Hospital
- Patricia Gordon - Penn State Hershey Medical Center
- Andrea Gropman - Children’s National Medical Center
- Randi Hagerman - UC Davis Health System, MIND Institute
- Shivkumar Hatti - Suburban Research Associates
- Honey Heussler - Queensland Childrens’ Hospital
- Brad Ingram - University of Mississippi
- Soo-Jeung Kim - University of Washington
- Sarah Land - Central States Research, LLC
- Reymundo Lozano - Icahn School of Medicine at Mount Sinai
- Andrew Marshall - Wellington Hospital
- Nora McNamara - University Hospitals Cleveland Medical Center
- Raun Melmed - Southwest Autism Research & Resource Center
- Han Phan - Rare Disease Research, LLC
- Lisa Prock - Boston Children’s Hospital
- Michael Raff - MultiCare Neuroscience Center of Washington
- Natalie Silove - Westmead Children's Hospital
- Andrew Stanfield - University of Edinburgh
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