Zynerba®
PHARMACEUTICALS

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

18th International Fragile X Conference | July 15, 2022

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

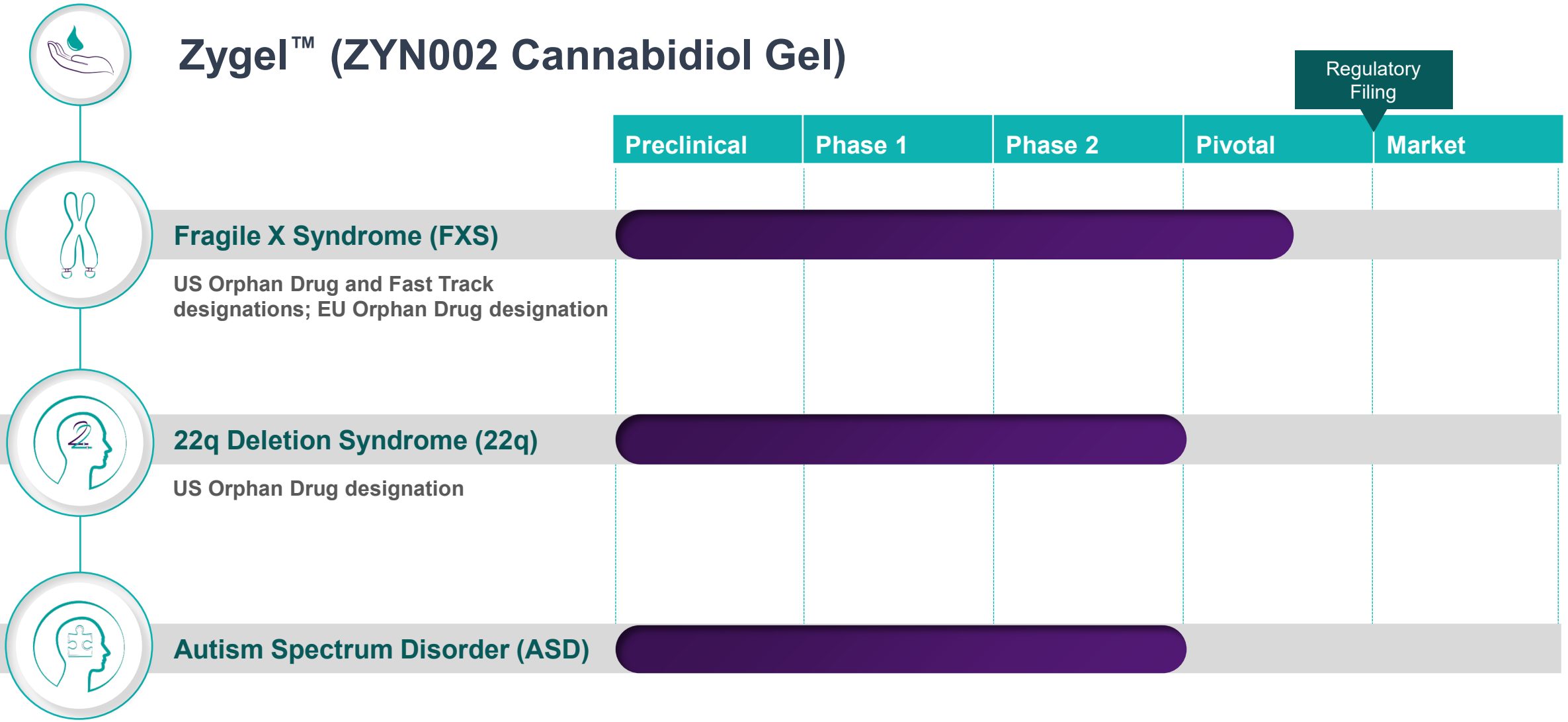
PHARMACEUTICALLY PRODUCED	
FDA regulated	✓
Consistency of production	✓
Purity of ingredients	✓
No THC – not a scheduled drug by US DEA	✓
Scalable production process	✓

TRANSDERMAL DELIVERY	
Ease of application for caregivers of patients with behavioral issues	✓
Minimizes GI side effects and reduces risk for liver side effects	✓
Lower risk for drug/drug interactions	✓
Avoids conversion to THC in stomach	✓

GI, gastrointestinal; THC, tetrahydrocannabinol; US DEA, United States Drug Enforcement Agency.

Focused Clinical Pipeline

Zygel™ (ZYN002 Cannabidiol Gel)



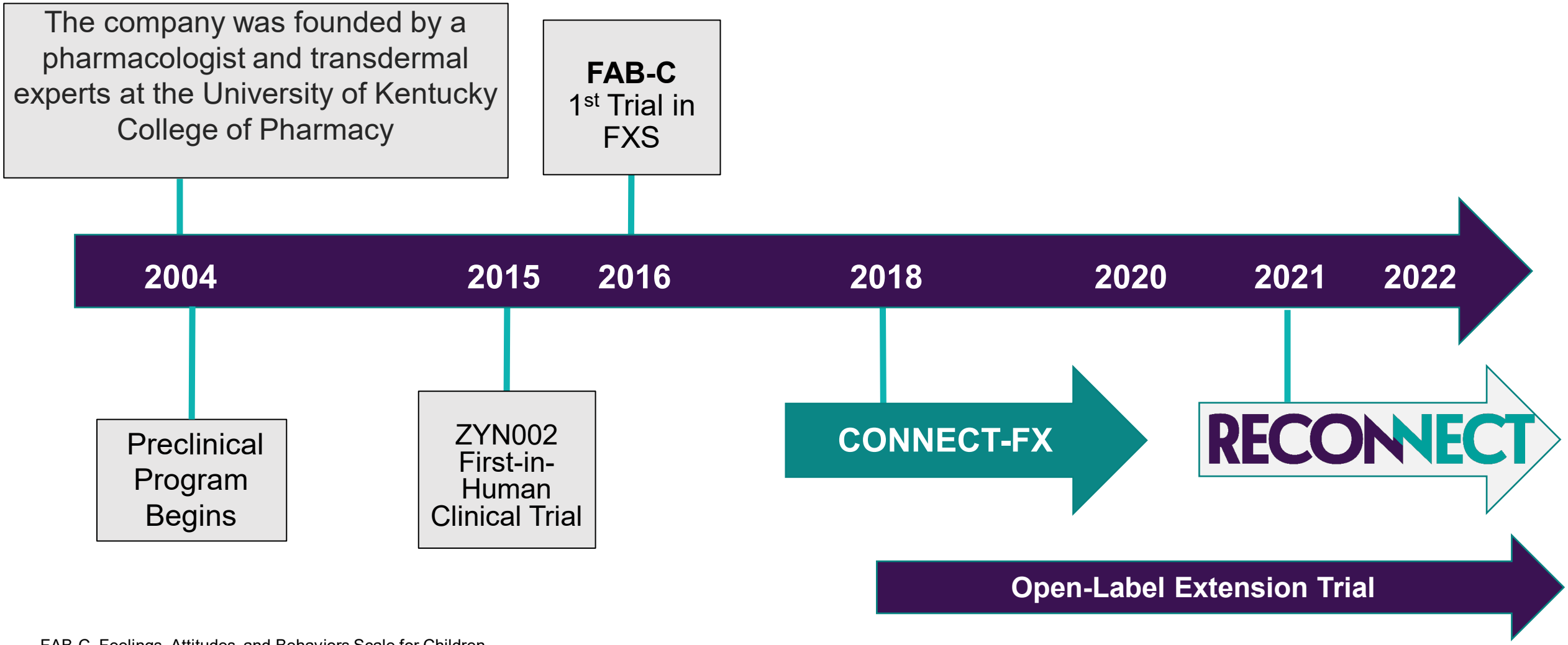
Why Study Zygel™ in Fragile X Syndrome (FXS)?

- The Endocannabinoid System (ECS) does not function well in FXS because of changes in how the *FMR1* gene functions in FXS
  - Changes in *FMR1* result in absence of FMR protein (FMRP), an important protein for development; the lack of FMRP, in turn, affects the ECS[1]
- The ECS plays an important role in the neuronal development and functions in helping the body maintain normal neuronal function[2]
- Alterations in the ECS may impact cognition and behavior[3,4]
- Cannabidiol is thought to act to help minimize some of the changes in the ECS seen in FXS[3]
- Cannabidiol has also shown activity at serotonin ($5HT_{1A}$),[5] $GABA_A$,[6] and dopamine receptors (D_2, D_3)[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

1. Laprairie RB, et al. *Br J Pharmacol.* 2015;172:4790-4805.
2. Katona I, Freund TF. *Annu Rev Neurosci.* 2012;35:529-558.
3. Jung KM, et al. *Nat Commun.* 2012;3:1080.
4. Castillo PE, et al. *Neuron.* 2012;76(1):70-81.
5. Russo EB, et al. *Neurochem Res*. 2005;30(8):1037-1043.
6. Bakas T, et al. *Pharmacol Res*. 2017;119:358-370.
7. McGuire P, et al. *Am J Psychiatry*. 2018;175(3):225-231.
8. Bian YM, et al. *Acta Pharmacol Sin*. 2019;40(3):374-386.

The History of Zygel™

More Than 15 Years of Research, Dedication, and Expertise



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

Fragile X Association of Australia

Asuragen®

10 Time zones

>5000 Caregiver Assessments + Skin Diaries

>100 Site Staff

>300 Children & Adolescents Screened

5 Countries

37 Trial Sites

28- Person Zynerba Team

MIND INSTITUTE

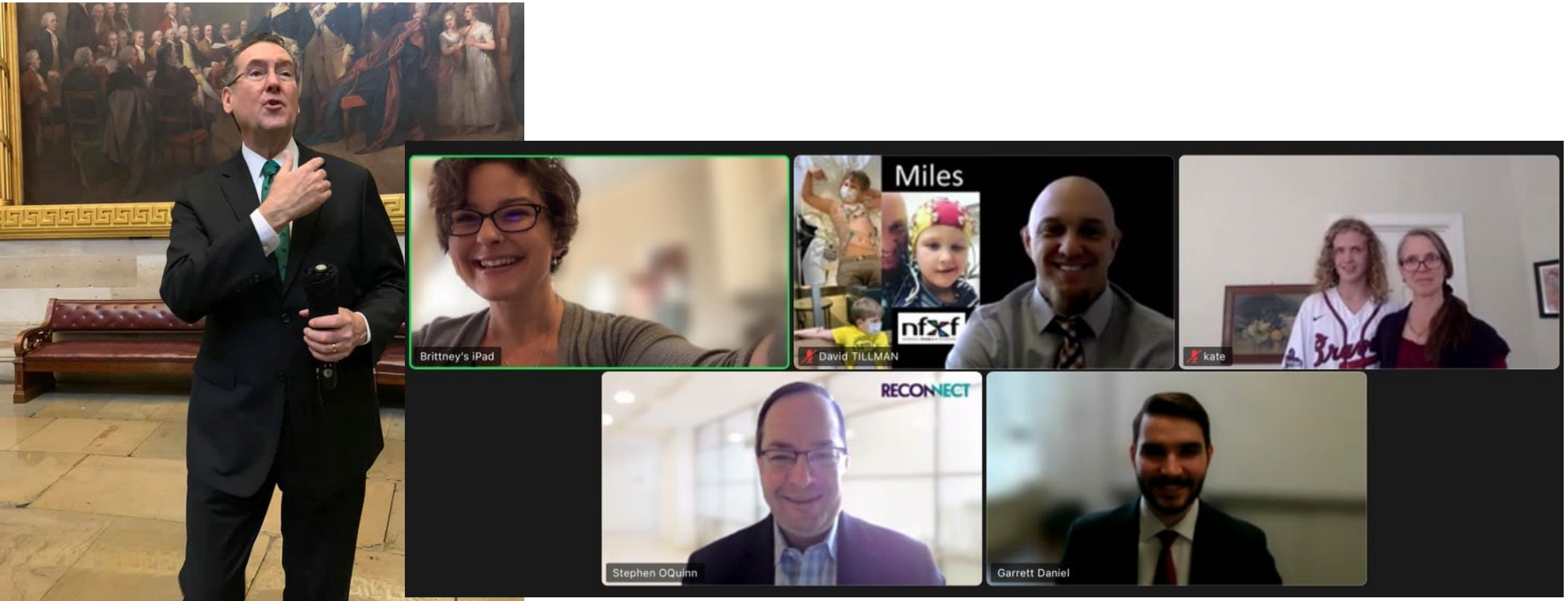
UK Fragile X Society

FRAXA

Travel by Planes, Trains, & Automobiles

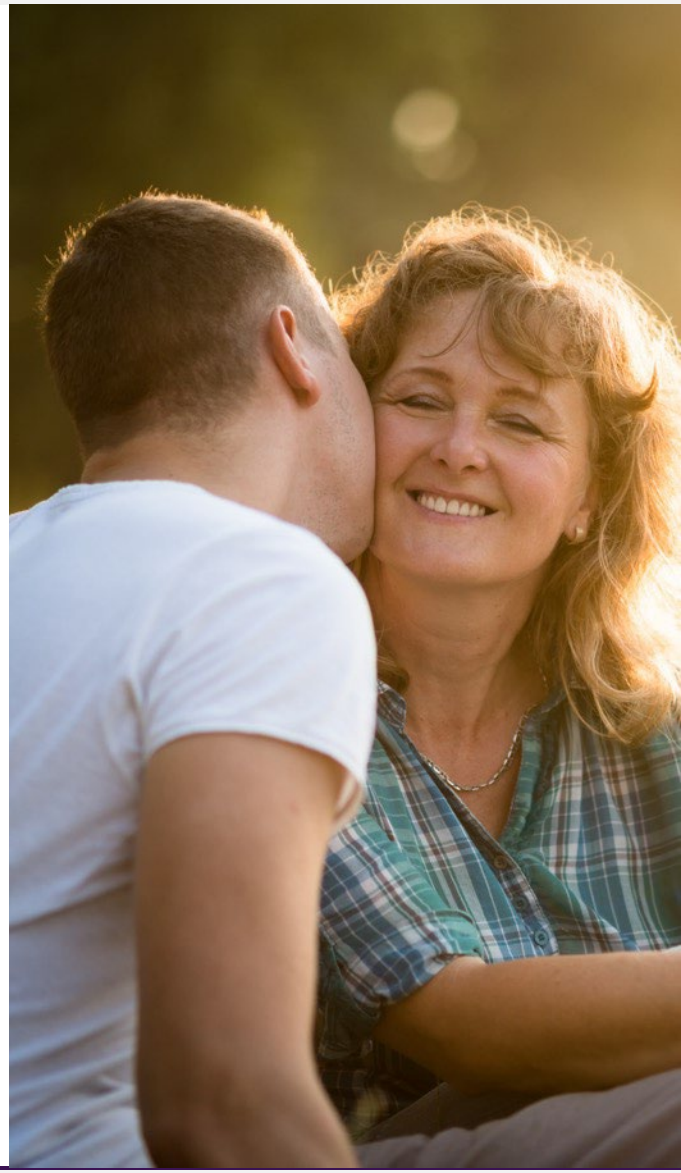
Partnering With You Along the Way

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

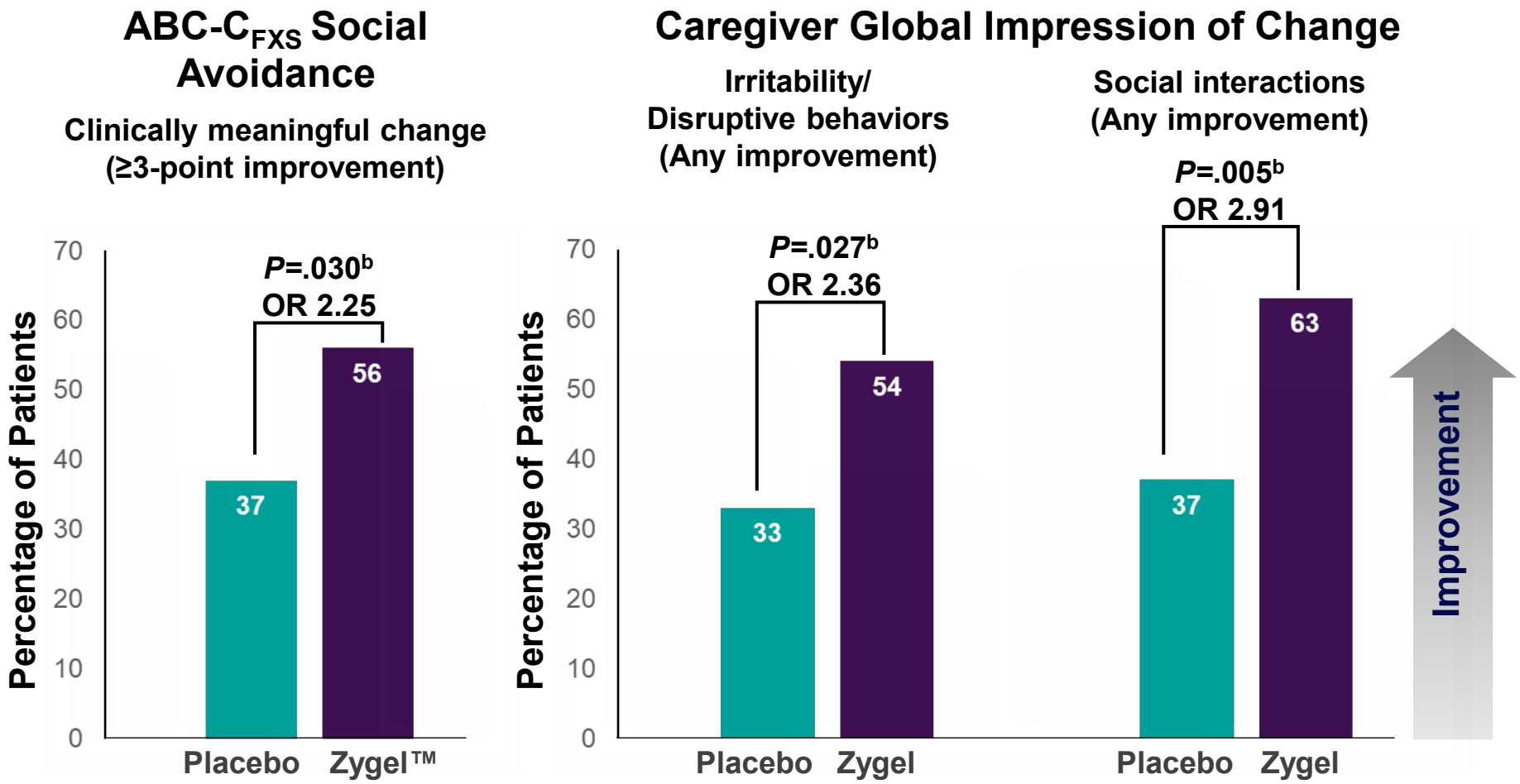
Open-label extension trial up to 38 months of treatment

Most events related to conditions commonly reported in children and adolescents

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

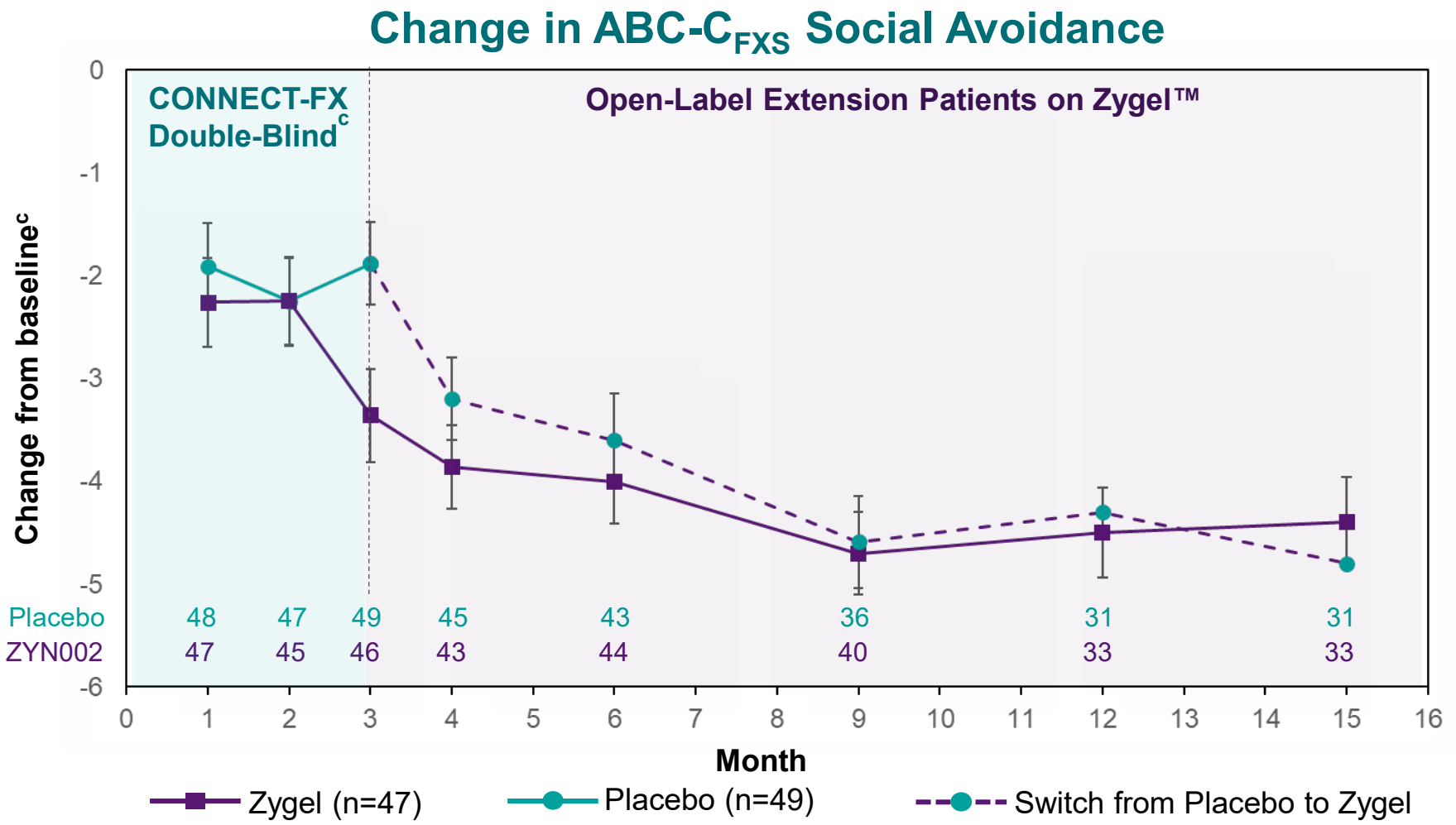
[a]TEAE, whether related or unrelated to study drug.

Clinically Meaningful Improvements in FXS-Related Behavioral Symptoms: CONNECT-FX Patients With Complete Methylation of *FMR1*[a]



[a]Data in patients with 100% *FMR1* gene methylation. [b]Statistically significant. LS means.
[c]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.

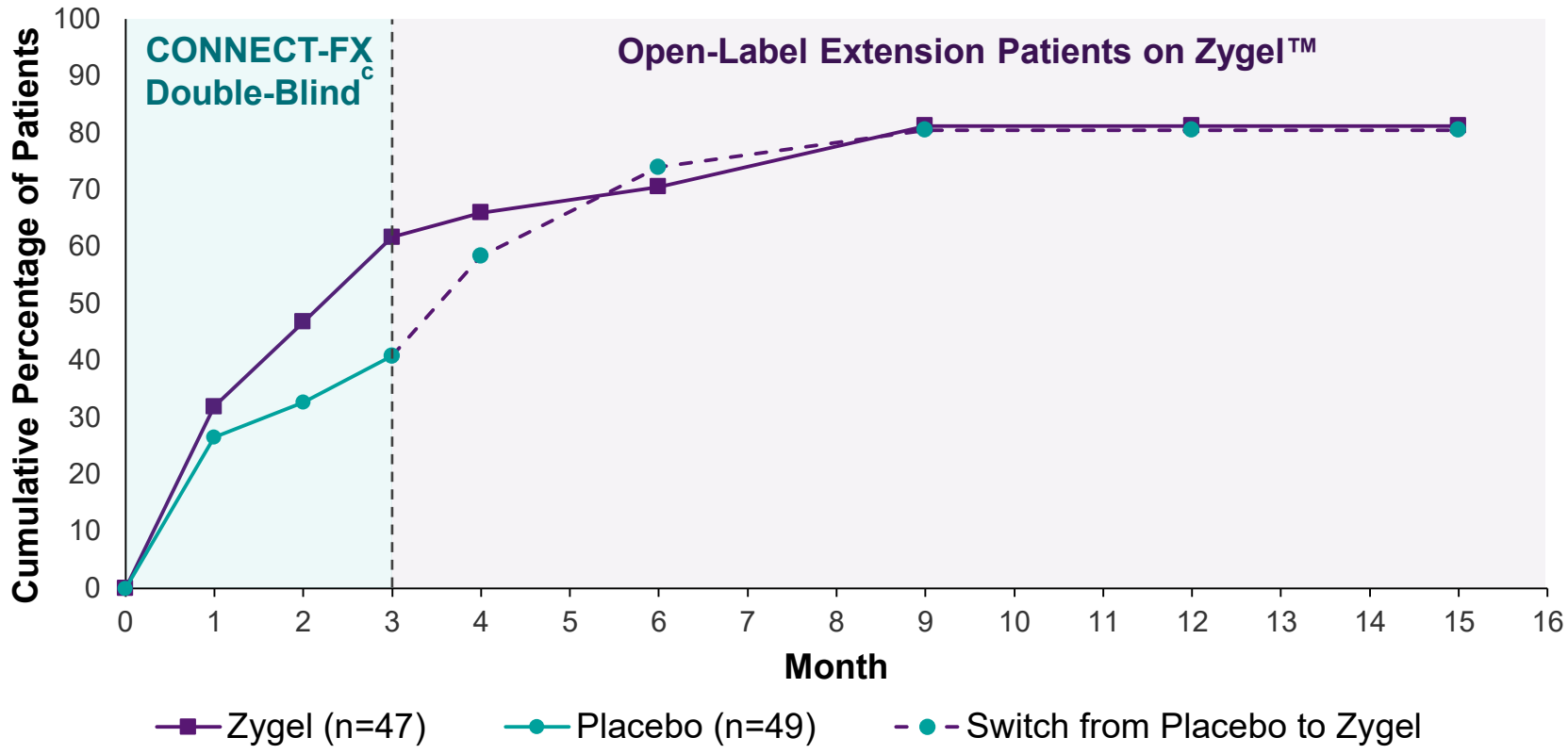
Sustained Improvement in Patients With Complete Methylation of *FMR1*[a]



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



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).

What's Next?

RECONNECT 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[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[a])

Mirrors Zygel administration

Open-Label Extension (OLE): Ongoing

24 months

All patients receive Zygel

[a]Patients with complete methylation of *FMR1* gene.

RECONNECT "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

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Week -3	Day 1	Week 2	Week 4	Week 6	Week 10	Week 14	Week 18
In-office	In-office	In-office	Virtual	Virtual	Virtual	Virtual	In-office
• 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]						
	Confirm OK to continue						

a. Caregiver and Clinician questionnaries 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?

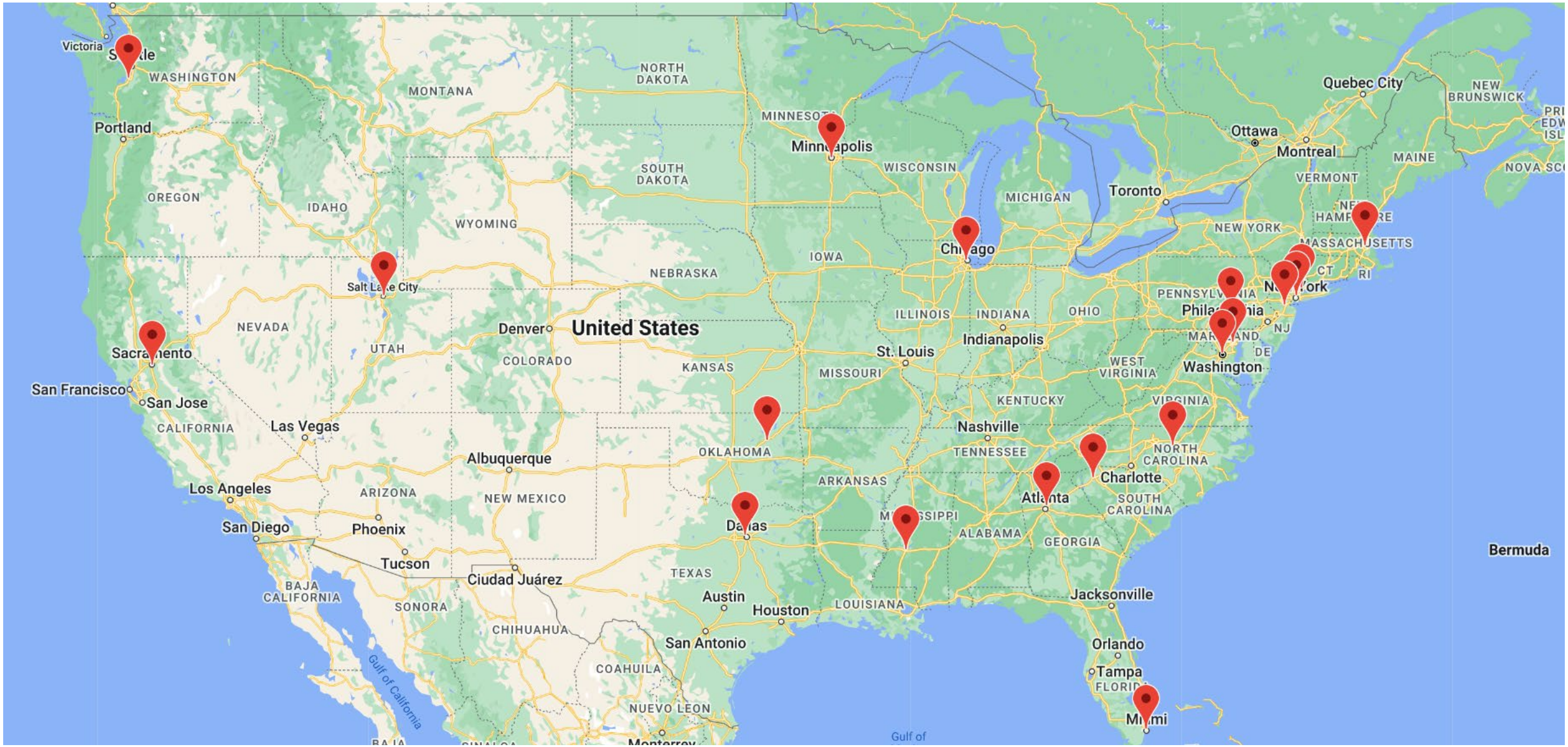
- RECONNECT
  - Complete enrollment
  - Analyze and report the topline results of the trial in 2H 2023
- Seek approval from the FDA (pending positive results from RECONNECT)
- Upon approval, Zygel™ would become available in the US
- Seek approval in other countries

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	Minnesota	Oklahoma
Florida	Mississippi	Pennsylvania
Georgia	New Jersey	South Carolina
Illinois	New York	Texas
Maryland	North Carolina	Utah
Massachusetts	Ohio	Washington
		Washington, DC

RECONNECT US Clinical Trial Sites



We are in this together!

We need YOU!

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