Zynerba®
PHARMACEUTICALS

Advancing Science. Improving Connections.

Next-Generation Transdermal Cannabinoid Therapeutics

August 2022

NASDAQ
ZYNE

Forward-Looking Statements

The statements in this presentation may include forward-looking statements within the meaning of the private securities litigation reform act of 1995. These statements, among other things relate to the future operations, opportunities or financial performance of Zynerba pharmaceuticals, inc. We may, in some cases, use terms such as “predicts,” “believes,” “potential,” “proposed,” “continue,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from the company’s current expectations, including the following: the company’s cash and cash equivalents may not be sufficient to support its operating plan for as long as anticipated; the results, cost and timing of the company’s clinical development programs, including any delays to such clinical trials relating to enrollment or site initiation; clinical results for the company’s product candidates may not be replicated or continue to occur in the company’s ongoing or planned clinical trials in FXS, 22q, or ASD, or in any additional trials, and may not otherwise support further development in a specified indication or at all; the company’s planned reconnect trial may not be determined to be sufficient to support a submission for regulatory approval, including an nda or maa; actions or advice of the U.S. Food and drug administration and foreign regulatory agencies may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional clinical trials; the company’s ability to obtain and maintain regulatory approval for its product candidates, and the labeling under any such approval; the company’s expectations regarding its ability to obtain and adequately maintain sufficient intellectual property protection for its product candidates. These and other risks are described in our filings with the securities and exchange commission, available at www.sec.gov. Any forward-looking statements that the company makes in this presentation speak only as of the date of this presentation. The company assumes no obligation to update forward-looking statements whether as a result of new information, future events or otherwise, after the date of this presentation.

A different and exciting approach to Cannabidiol

Zynerba®

PHARMACEUTICALS

An Orphan-Focused Neuropsychiatric, Biopharmaceutical Company

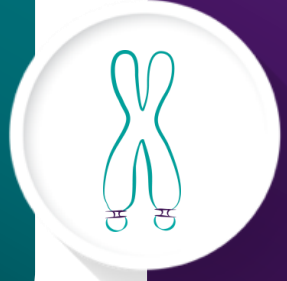
Zynerba

FIRST AND ONLY TRANSDERMAL CANNABIDIOL GEL

Permeation-enhanced

Patent-protected through 2038

Pharmaceutically manufactured; THC free



LATE-STAGE PIPELINE

One Phase 3 clinical program ongoing

Two additional indications are Phase 3 ready

POSITIONED FOR SUCCESS

Leadership expertise in transdermal delivery, rare diseases and specialty markets

Clean balance sheet and cash runway through end of 2023 / early 2024

A different and exciting approach to Cannabidiol

Benefits of Our Approach to Cannabidiol

PHARMACEUTICAL MANUFACTURING	
FDA regulated	✓
Consistency of production	✓
Purity of ingredients	✓
No THC – not a scheduled drug by U.S. 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 toxicity	✓
Lower risk for drug/drug interactions	✓
Avoids conversion to THC in stomach	✓

Fragile X Syndrome

FXS

22q Deletion Syndrome

22q

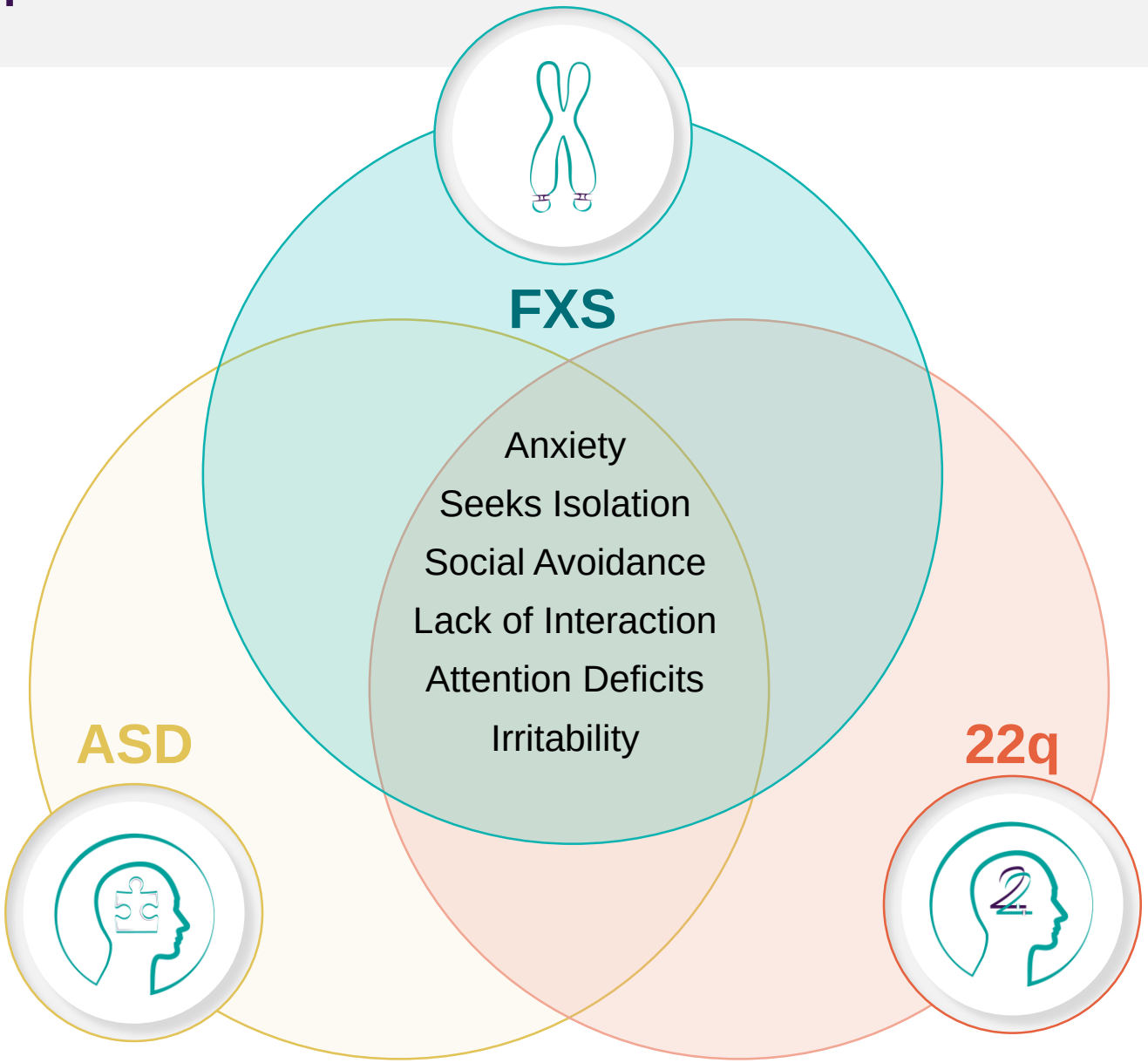
Autism Spectrum Disorder

ASD

Clinical Development Programs

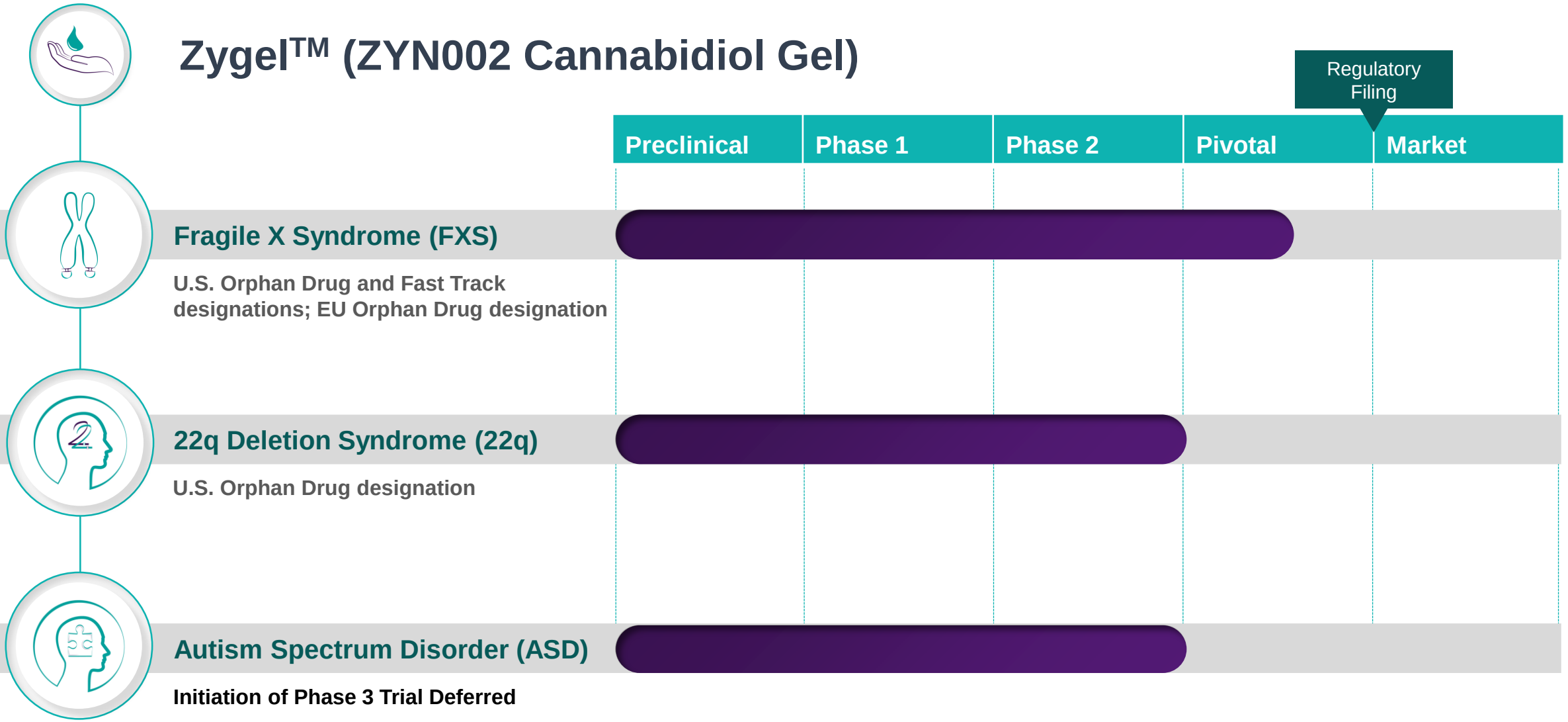
Zynerba®

Overlap of Symptoms Across Conditions



Focused Clinical Pipeline

Zygel™ (ZYN002 Cannabidiol Gel)



Fragile X Syndrome (FXS)

U.S. Orphan Drug and Fast Track designations; EU Orphan Drug designation

22q Deletion Syndrome (22q)

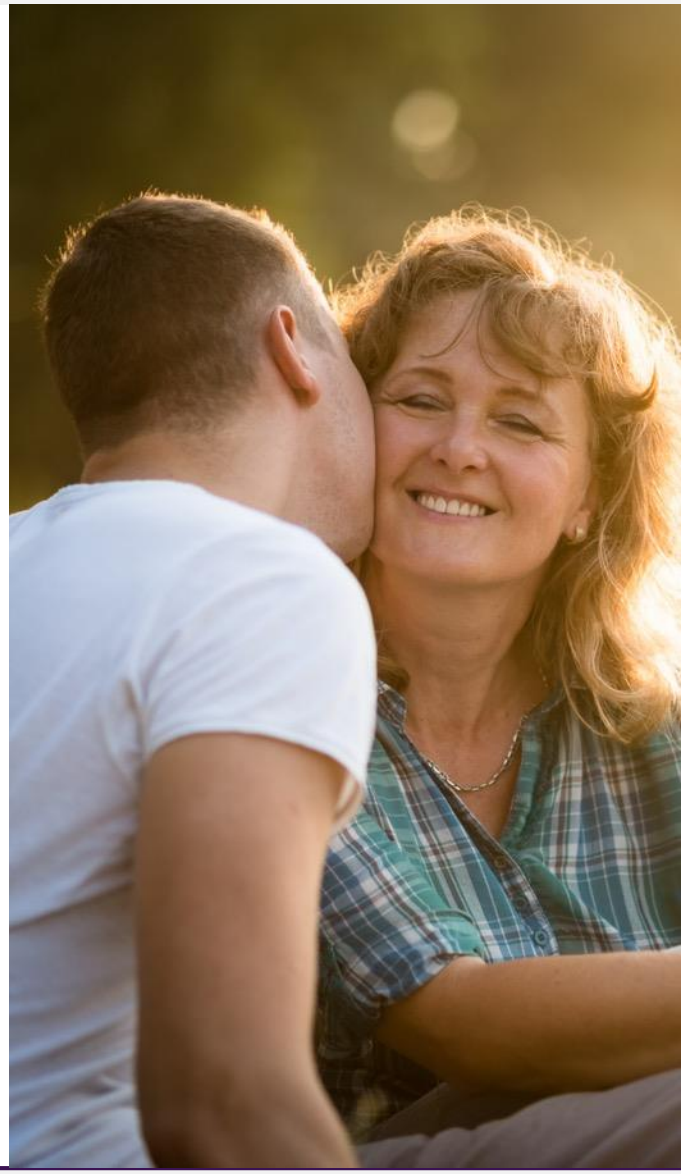
U.S. Orphan Drug designation

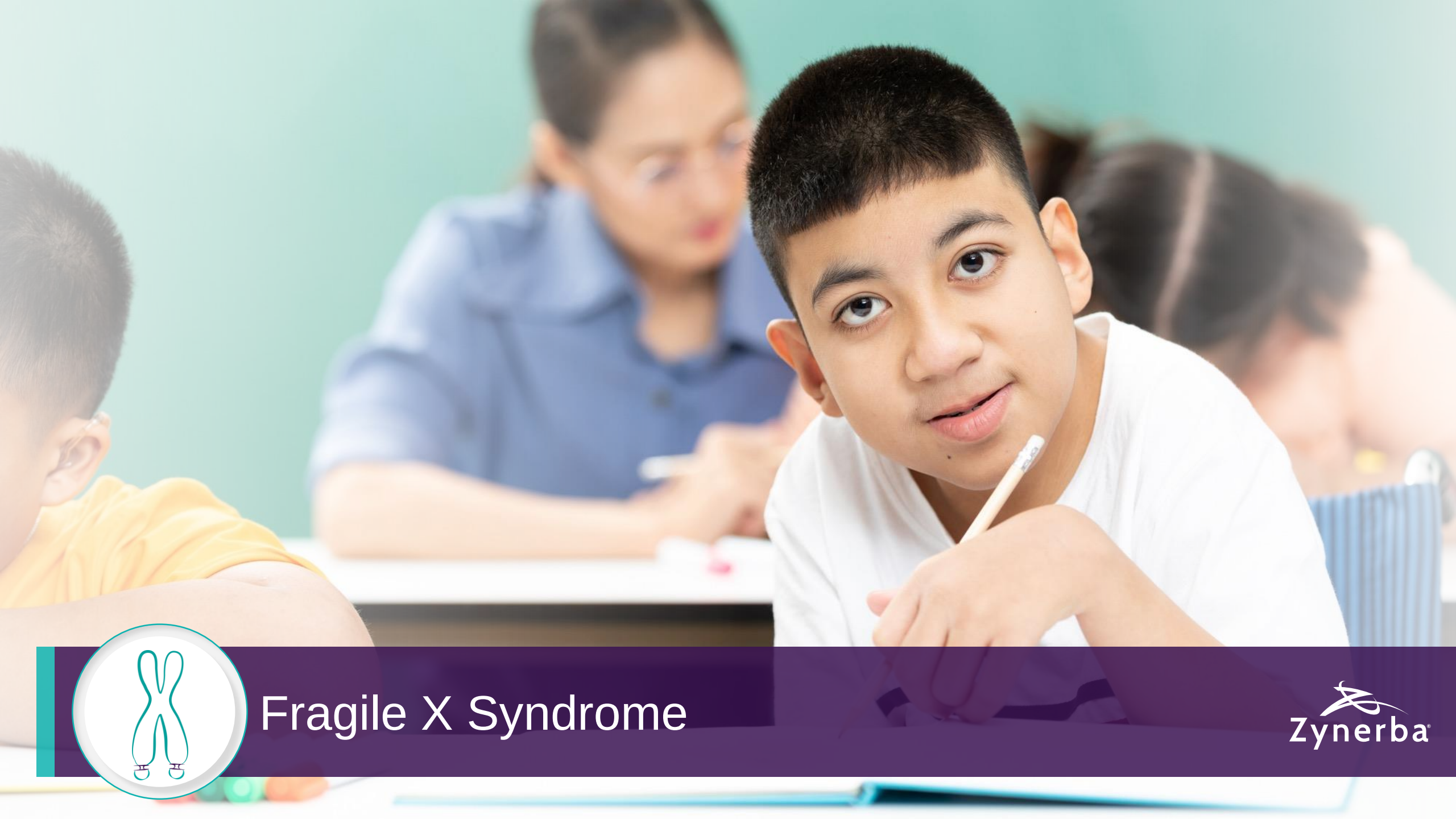
Autism Spectrum Disorder (ASD)

Initiation of Phase 3 Trial Deferred

Well-Tolerated Safety Profile

- Zygel safety database across all clinical studies includes data from over 900 volunteers and patients
- Majority of treatment-emergent AEs (TEAE) were mild or moderate
- Most common Zygel-related TEAE 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





Fragile X Syndrome

Zynerba

What is Fragile X Syndrome (FXS)

- Leading known cause of inherited intellectual disability and autism spectrum disorder
- Mutation of the *FMR1* gene causes endocannabinoid system (ECS) dysregulation
  - Easily identified mutation manifests as multiple CGG repeats on *FMR1* (full mutation >200 repeats)
  - Resulting in cognitive, social, and behavioral symptoms
- Behavioral Symptoms linked to deficiencies in the ECS

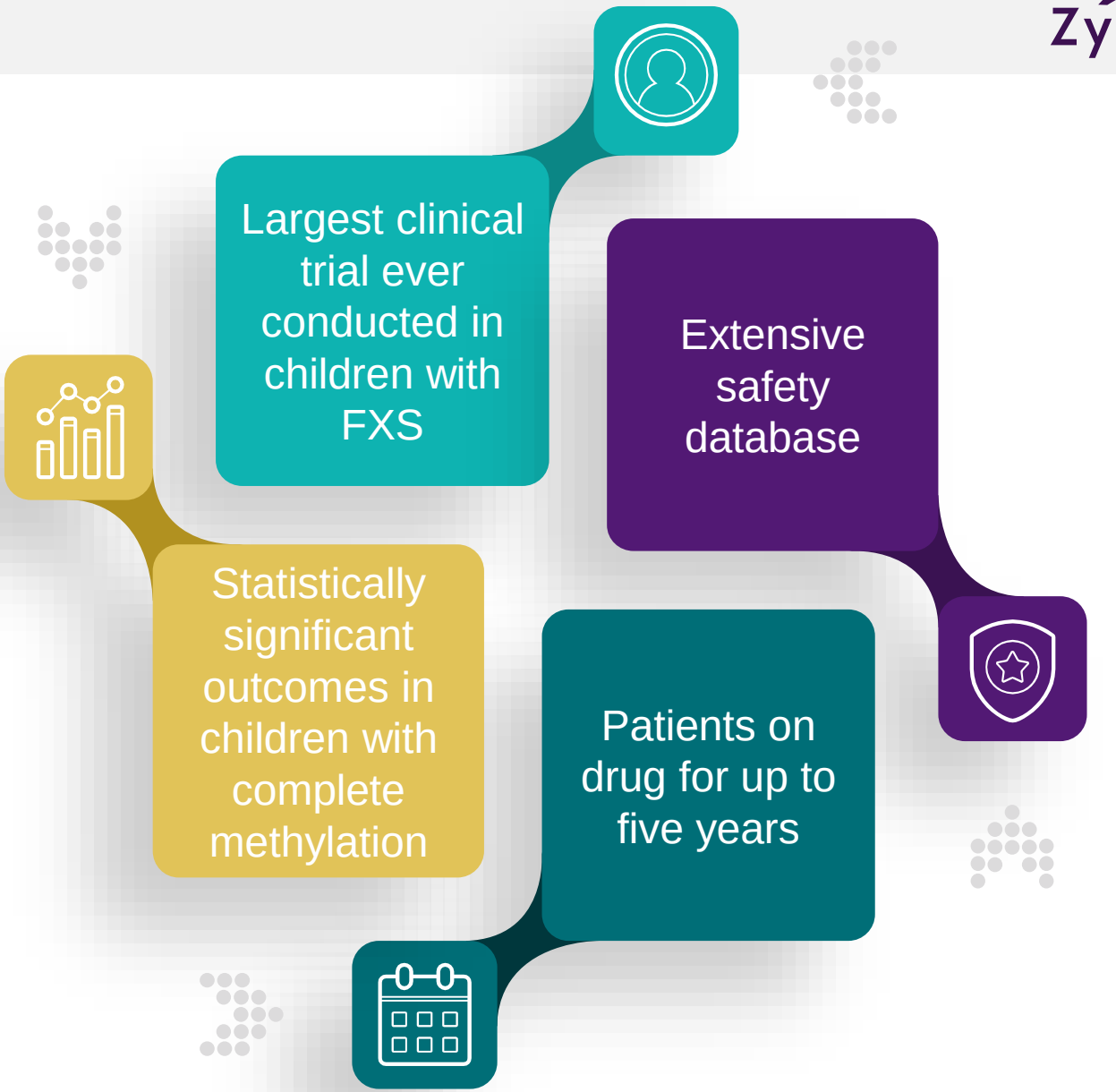
~78K
U.S. PATIENTS

~121K
EU/UK PATIENTS

WITH FXS

Poised for Success in FXS

Lessons Learned from Previous Trials Improve Probability of Success in **RECONNECT** Pivotal Trial



Role of *FMR1* Methylation in FXS

- *FMR1* gene codes for production of FMRP* which is vital to synapse development
- Methylation of the *FMR1* gene plays a role in determining gene function
  - When methylation of the *FMR1* gene silences the gene, no FMRP is produced:
  - Systems and processes affected by FMRP become dysregulated
- ~60% of FXS patients are believed to be completely methylated
- Completely methylated patients are the most severely impacted

~47K
U.S. PATIENTS

~73K
EU/UK PATIENTS

WITH COMPLETE METHYLATION

**RNA-binding protein that helps regulate synaptic development and plasticity*

CONNECT-FX Trial Key Learning: Results with complete methylation of *FMR1* gene

Consistent Improvements Observed with Zygel vs. Placebo in Patients with Complete Methylation

PRIMARY ENDPOINT

ABC-C_{FXS} Social Avoidance Subscale

40% median percent improvement in socially avoidant behaviors
(*p*=0.027*)

CAREGIVER REPORTED BEHAVIOR CHANGE

Caregiver Global Impression of Change (ZYGEL vs Placebo)

SOCIAL INTERACTION
63% vs 37%
(*p*=0.005*)

IRRITABLE/DISRUPTIVE BEHAVIORS
54% vs 33%
(*p*=0.027*)

SOCIAL AVOIDANCE/ISOLATION
58% vs 46%
(*p*=0.195)

OVERALL BEHAVIOR
61% vs 46%
(*p*=0.100)

CLINICIAN REPORTED BEHAVIOR IMPROVEMENTS

Clinical Global Impression of Improvement (anchored)**

ANY IMPROVEMENT
Zygel vs placebo 50% vs 36%
(*p*=0.128)

CLINICALLY MEANINGFUL BEHAVIOR IMPROVEMENTS

More Patients Achieved Meaningful Change (ZYGEL vs Placebo)

SOCIAL AVOIDANCE (≥ 3 POINTS)
56% vs 37%
(*p*=0.030*)

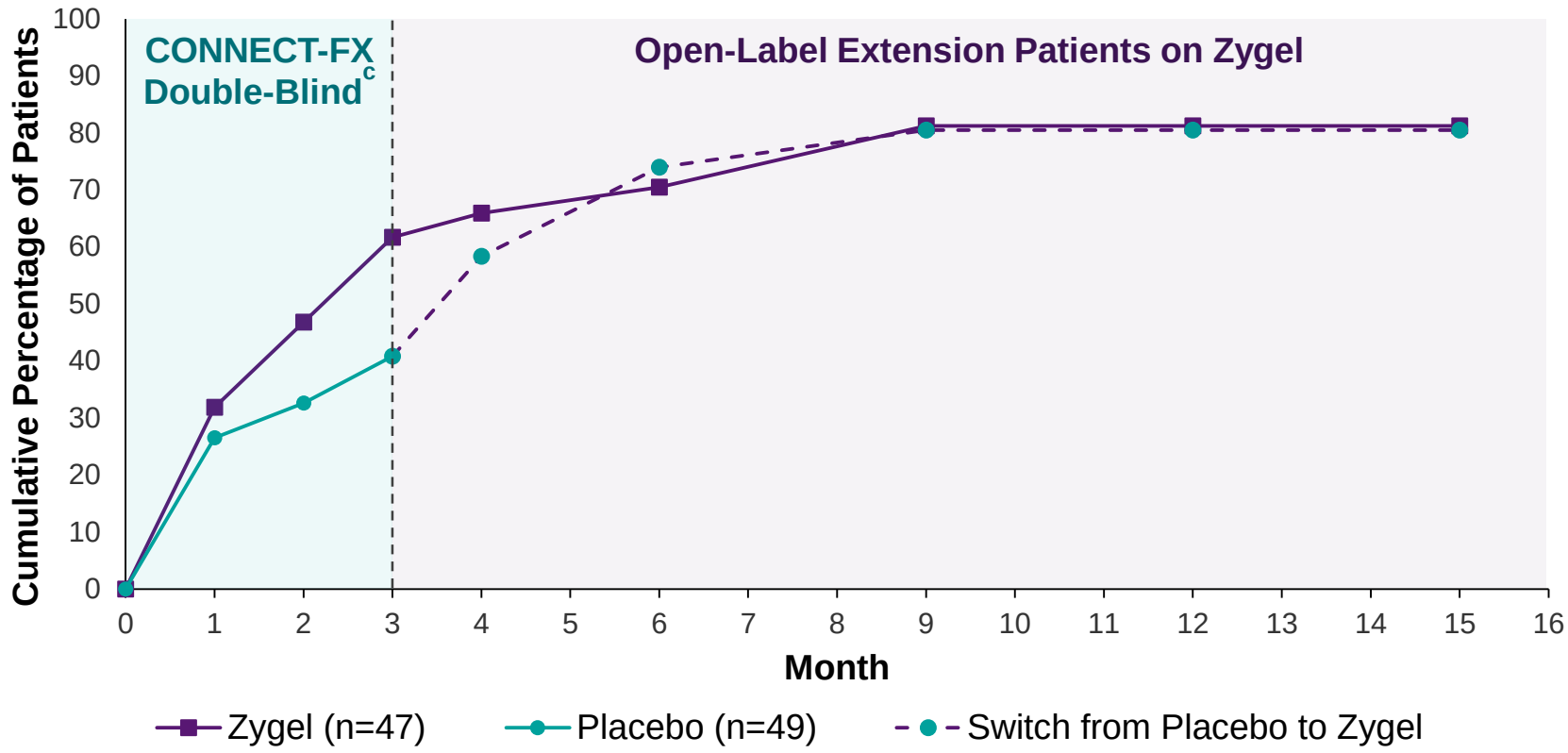
IRRITABILITY (≥ 9 POINTS)
37% vs 26%
(*p*=0.232)

*Statistically significant , **Not specific to Social Avoidance

Ad hoc analysis of 136 patients with complete methylation

Clinically Meaningful Change[a] Achieved and Maintained in Patients with Complete Methylation of *FMR1* Gene[b]

Change in ABC-C_{FXS} Social Avoidance

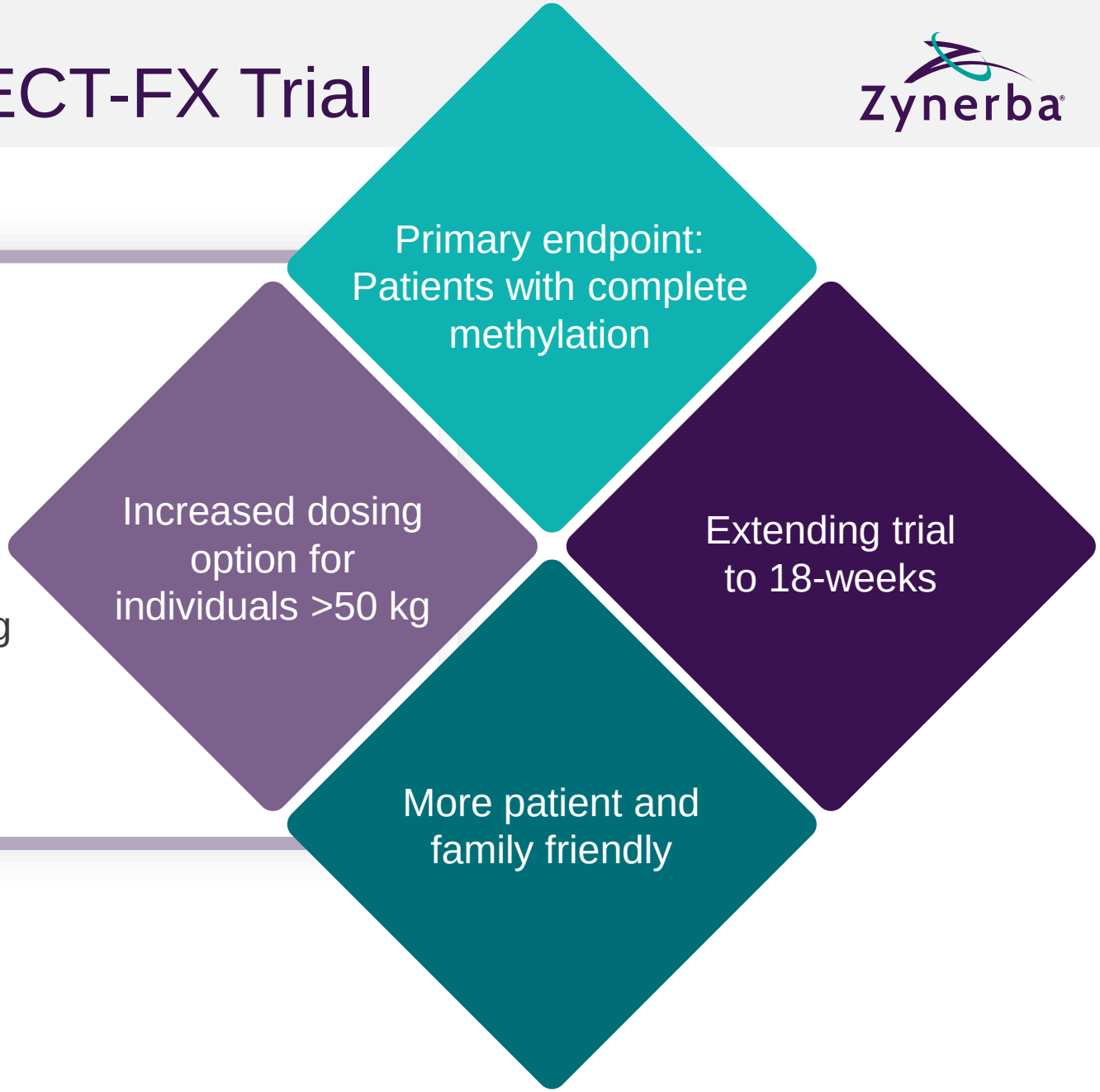


a. Meaningful change in Social Avoidance: ≥3-point improvement from baseline; maintained for ≥ 2 consecutive visits
b. Patients matching primary efficacy population in RECONNECT
c. ZYN2-CL-016 (CONNECT-FX)

Design Optimized from CONNECT-FX Trial

RECONNECT

Successful completion of Phase 3 pivotal trial expected to satisfy requirements for an NDA submission in the U.S. and a marketing authorization application in the EU.



RECONNECT Confirmatory Pivotal Trial Design

Double-Blind, Placebo-Controlled Study: Initiated

18 weeks

3 to 17 years old
Moderate-to-Severe FXS

Zygel
(n~100; 80*)

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

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

Placebo
(n~100; 80*)

Mirrors Zygel administration

Open Label Extension (OLE): Ongoing

24 months

All patients receive Zygel

*Patients with complete methylation of *FMR1* gene

RECONNECT Trial Objectives

PRIMARY ENDPOINT

Change from baseline to end of treatment in ABC-C_{FXS} Social Avoidance subscale in patients who have complete (100%) methylation of their *FMR1* gene

SECONDARY ENDPOINTS

- Change from baseline to end of treatment in:
  - ABC-C_{FXS} Irritability subscale in patients who have complete methylation
  - ABC-C_{FXS} Social Avoidance subscale among all randomized patients (complete and partial methylation)
- Percent of patients:
  - Any improvement on the Caregiver Global Impression of Change (CaGI-C) for Social Interactions among patients with complete methylation
  - Rated as improved on the Clinical Global Impression-Improvement (CGI-I) scale among patients with complete methylation

Next Steps in FXS

Continued **RECONNECT** pivotal trial enrollment

Topline results expected in 2H 2023

Eliza, living with 22q11.2 deletion syndrome

22q11.2 Deletion Syndrome (22q)

Zynerba

What is 22q11.2 Deletion Syndrome (22q)?

- Rare disorder and second most common genetic disorder, behind Down syndrome
- Midline condition with abnormalities affecting palate, face, heart and other organs; surgically corrected in infancy
- Neuropsychiatric illnesses and learning disabilities common
  - Early onset of neuropsychiatric symptoms disrupts development and quality of life, and heightens risk of later psychotic disorders
- No drugs currently approved

~83K

U.S. PATIENTS

WITH 22q

Rationale for Zygel in 22q

- Overlapping symptoms with FXS and ASD
  - Associated with increased anxiety, irritability, social withdrawal and social interaction problems
- Cannabidiol may treat neuropsychiatric symptoms due to activity as:
  - Modulator of ECS
  - Agonist at serotonin$_{1A}$ receptors
  - Antagonist at GPR55 receptors

U.S. ORPHAN DRUG

DESIGNATION GRANTED FOR TREATMENT OF 22q

INSPIRE Phase 2 Trial Design

Period 1: Completed

14 weeks

4 to 15 years old
With 22q11.2 Deletion Syndrome

Zygel
(n = 20)

250 mg daily (≤35kg)
500 mg daily (>35kg)
(weight-based dose)

Period 2: Ongoing

24 weeks

(n = 13 of 17 Completers)

Efficacy assessments include:
(week 14 vs baseline)

- **Anxiety, Depression and Mood Scale (ADAMS)**
- **Aberrant Behavior Checklist-Community (ABC-C)**
- **Pediatric Anxiety Rating Scale-Revised (PARS-R)**
- **Clinical Global Impression — Severity and Improvement**

Positive Topline Results from INSPIRE Trial

- Statistically significant improvements at 14 weeks of treatment compared to baseline for multiple efficacy assessments:
  - The total score and all five subscales of the Anxiety, Depression and Mood Scale (ADAMS)
  - All five subscales of the Aberrant Behavior Checklist – Community (ABC-C)
  - Pediatric Anxiety Rating Scale - Revised (PARS – R)

- The majority of patients showed clinically meaningful improvements at week 14 as demonstrated by the Clinical Global Impression – Improvement (CGI-I)
  - Seventy-five percent of patients were rated by the clinicians as “improved”, “much improved” or “very much improved”
  - Nearly two-thirds (62.5%) of the patients being “much improved” or “very much improved”

- Zygel was shown to be well tolerated, and the safety profile was consistent with previously released data from other Zygel clinical trials
  - Three patients reported treatment related adverse events which were all mild application site adverse events
  - One patient discontinued treatment due to adverse events not related to Zygel

ADAMS and ABC-C Results

	Subscale	Baseline	Week 14	Change from Baseline	Mean % Improvement	p Value	Median % Improvement
ADAMS	**Total Score**	**36.1**	**17.7**	**-18.4**	**45.3%**	**0.0005**	**43.0%**
	General Anxiety	10.4	5.1	-5.4	43.6%	0.0005	48.8%
	Depressed Mood	7.6	3.4	-4.3	50.3%	0.0033	52.8%
	Social Avoidance	8.7	4.3	-4.4	41.3%	0.0084	50.5%
	Obsessive / Compulsive Behavior	3.0	1.1	-1.9	64.0%	0.0037	66.7%
	Manic / Hyperactive Behavior	7.6	4.4	-3.1	38.2%	0.0032	27.4%

	Subscale	Baseline	Week 14	Change from Baseline	Mean % Improvement	p Value	Median % Improvement
ABC-C	Social Withdrawal	14.4	7.9	-6.4	27.6%	0.0110	46.4%
	Inappropriate Speech	4.2	2.4	-1.8	18.3%	0.0166	50.0%
	Stereotypic Behavior	3.9	1.6	-2.3	52.1%	0.0155	58.3%
	Irritability	18.4	10.0	-8.4	36.3%	0.0055	39.6%
	Hyperactivity	18.1	10.4	-7.6	16.5%	0.0091	38.1%

Next Steps in 22q

Discuss regulatory pathway with FDA

Initiate Phase 3 program after FDA discussions and RECONNECT topline results

Autism Spectrum Disorder

Zynerba

Rationale for Zygel in Autism Spectrum Disorder (ASD)

- Results from FXS trials suggested spectrum of activity against behaviors also seen in ASD: irritability, social avoidance and anxiety

- Studies suggested ASD is linked to disruption of the ECS
  - Altered anandamide* signaling may contribute to ASD-related social and communication impairments
  - The ECS modulates many cellular functions and molecular pathways altered in ASD
  - Cannabidiol may modulate the ECS and improve certain autism-related behaviors

* Anandamide is one of two primary endocannabinoids

BRIGHT Open-label Phase 2 Trial Design

Period 1

14 weeks

3 to 16 years old
Moderate-to-Severe ASD

Zygel
(n = 37)

250 mg daily (≤35kg)
500 mg daily (>35kg)
(weight-based dose)

Period 2

24 weeks

18 Patients
with ≥ 35% improvement
in Irritability at week 14
continued on Zygel

BRIGHT Phase 2 Trial Results: Period 1

Statistically Significant Results at Week 14 Compared to Baseline (Completers in Efficacy Population n=28†)

Aberrant Behavior Checklist — Community (ABC-C) subscales % improvement

Irritability: 39%
(*p*<0.0001*)

Inappropriate Speech: 43%
(*p*=0.0002*)

Stereotypy: 39%
(*p*<0.0001*)

Social Withdrawal: 36%
(*p*<0.0001*)

Hyperactivity: 36%
(*p*<0.0001*)

Autism Impact Measure (AIM) % improvement

Atypical behavior: 34%
(*p*<0.001*)

Communication: 20%
(*p*<0.001*)

Peer interaction: 20%
(*p*<0.001*)

Repetitive behavior: 33%
(*p*<0.001*)

Social reciprocity: 11%
(*p*=0.0053*)

Autism Parenting Stress Index

Mean improvement:39%
(*p*<0.0001*)

Qualitative Caregiver Behavioral Problems Survey % improvements

Behavioral: 69% improved

Social: 63% improved

Emotional: 72% improved

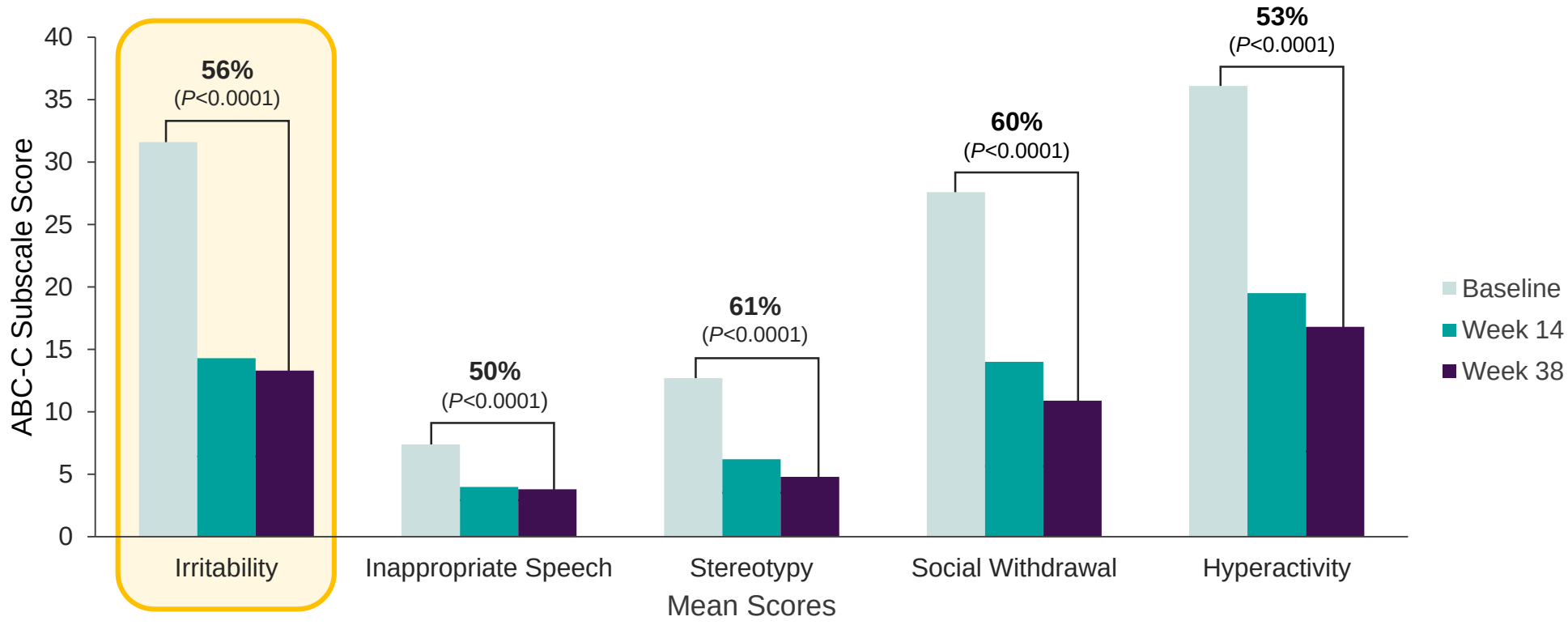
Parent Rated Anxiety Scale for ASD (PRAS-ASD)

Mean improvement: 46%
(*p*<0.0001*)

† n=26 for ABC-C inappropriate speech; *Statistically significant; Full data available in May 26, 2020 and October 15, 2020 press releases

ABC-C Irritability: Primary Endpoint to Support NDA Filing

BRIGHT Period 2 Results: Statistically Significant Improvements from Baseline Sustained through Week 38[1]



n=18

Lower values reflect improvement in each ABC-C subscale.

*Same primary endpoint utilized in pivotal trials for two existing FDA approved ASD treatments

[1]18 of 27 patients that completed week 14 demonstrated ≥35% improvement in the ABC-C at week 14 and were allowed to continue treatment for additional 24 weeks.

Next Steps in ASD

Submit Investigational New Drug (IND) application specific to ASD with finalized clinical protocol

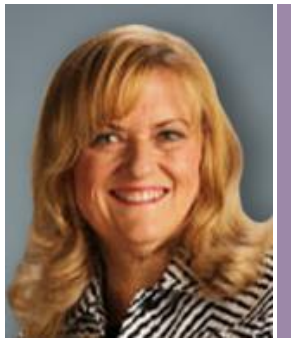
ASD is now third in priority and initiation of Phase 3 program is deferred at this time

Positioned for Success

Zynerba®

Leadership

Armando Anido
Chairman of the Board and CEO



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VP, Human Resources

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CFO and VP, Corporate Development

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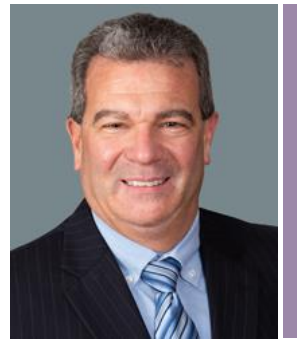
GM, Zynerba Pharmaceuticals Pty Ltd (Australia)



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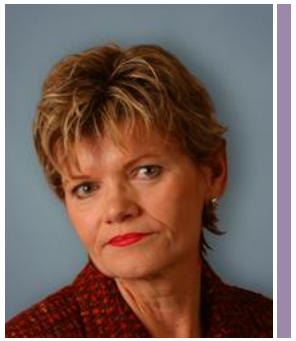

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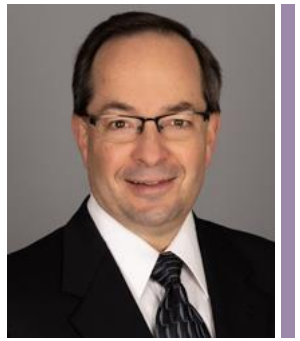


Stephen O'Quinn, PharmD
VP, Medical Affairs

Albert P. Parker
Chief Legal Officer

Brian Rosenberger
VP, Commercial and Business Development

Nancy Tich, Ph.D.
VP, Clinical

Financial Strength

CLEAN

BALANCE SHEET

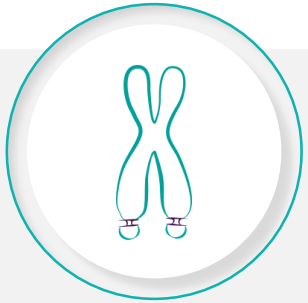
No debt, 45.8M
shares outstanding
(as of August 8, 2022)

$62.5M

CASH AND CASH EQUIVALENTS

as of June 30, 2022;
expected to be sufficient to fund
operations and capital requirements
through the end of 2023/early 2024

A Year of Clinical Progress Ahead



Fragile X Syndrome (FXS)

Pivotal trial results expected in 2H 2023

U.S. Orphan Drug and Fast Track designations;
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22q Deletion Syndrome (22q)

Finalize regulatory pathway with FDA; Initiate Phase 3 after RECONNECT topline results

U.S. Orphan Drug designation

Autism Spectrum Disorder (ASD)

Submit IND with finalized clinical protocol; initiation of Phase 3 program deferred

Zynerba Vision for Future Growth

Zynerba Today…

- Leaders in transdermal cannabidiol delivery
- Late-stage clinical company with multiple CNS programs, all in areas of high unmet need

…in 2025

- Launch Zygel for FXS into a $1.9B+ U.S. market opportunity
- Establish a fully integrated organization with U.S. commercial presence
- Prepare for EU approval in FXS
- Advance 22q Ph3 program towards completion

…and Beyond

- Launch Zygel in FXS via strategic partners in EU and other Territories
- Launch Zygel into additional multi-billion $ market of 22q
- Optimize Zygel growth with additional synergistic indications
- Accelerate further growth through complimentary asset licensing and acquisition

A different and exciting approach to Cannabidiol

Zynerba®

PHARMACEUTICALS

Zynerba®
PHARMACEUTICALS

Thank you!

NASDAQ
ZYNE