

Dedicated to the development of innovative  
pharmaceutically-produced transdermal  
cannabinoid therapies for rare and near-rare  
neuropsychiatric disorders

July 2018

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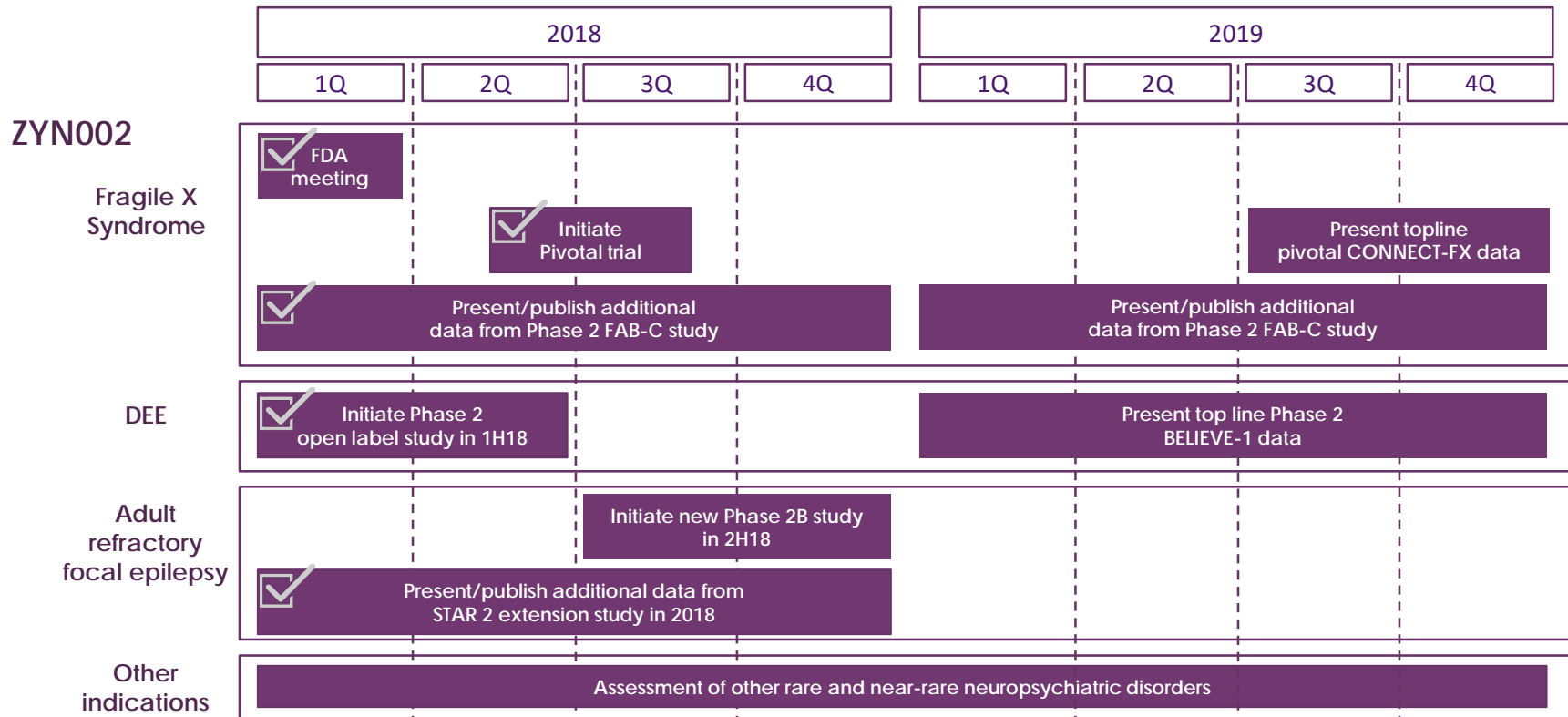


# Zynerba Pharmaceuticals

## A Rare/Near-Rare Neuropsychiatric Company

- Developing ZYN002 (CBD gel) in rare and near rare neuropsych disorders
- Focused on high unmet medical needs
  - Fragile X syndrome (FXS): ~71K U.S. patients; no approved products
  - Developmental and epileptic encephalopathies (DEE): ~45K U.S. patients
  - Adult refractory focal epilepsy: ~500K U.S. patients remain uncontrolled on existing AEDs
- Opportunities for efficient development and commercialization strategy
  - Orphan drug designation provides opportunity for rapid development/approval
  - Other regulatory designations available; if granted, can accelerate approval of drugs meeting criteria
  - Targeted physician audience = modest commercial investment
  - Potential for consistent orphan drug pricing across indications (>\$25K per patient per year for ZYN002)
- Experienced team with proven development and commercialization track record in transdermal delivery, orphan diseases, neurology, and psychiatry
- Well capitalized with cash runway into the second half of 2019
- Multiple expected near term milestones

# Expected 2018 and 2019 Milestones

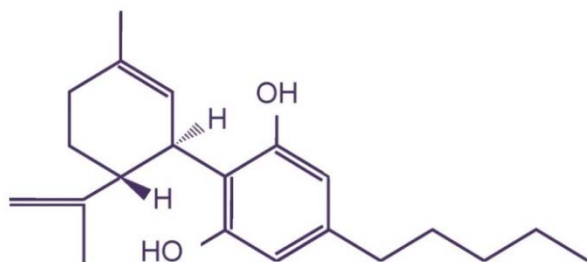


# ZYN002

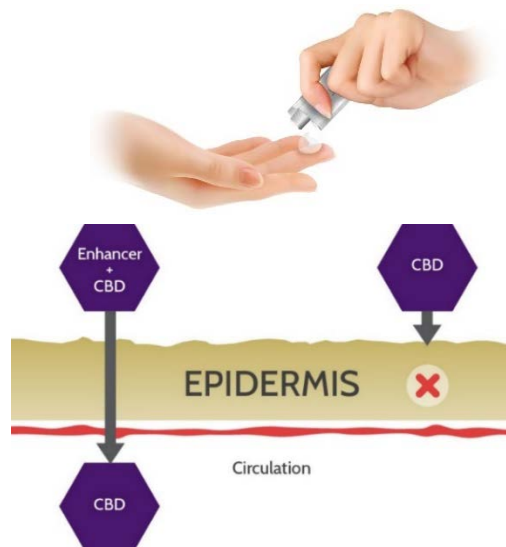
## Cannabidiol (CBD) Gel

- First and only patent-protected permeation-enhanced pharmaceutically-produced cannabidiol (CBD) gel formulated for transdermal delivery
  - CBD binds to multiple receptors and may mediate a number of pathways, including the endocannabinoid pathway
  - Patented formulation increases the delivery of CBD through the layers of the epidermis and into the circulatory system

CBD



Transdermal gel delivery



# Fragile X Syndrome (FXS)

## The Endocannabinoid (EC) System is a Critical Pathway

- Rare genetic developmental disability; leading known cause of both inherited intellectual disability and autism spectrum disorder
- Symptoms linked to deficiencies in the endocannabinoid system
  - ECs form system of neurotransmitters regulating emotional responses, behavioral reactivity to context, social interaction
  - FMR1 mutation in FXS causes dysregulation of the EC system resulting in significant social, behavioral, and cognitive deficits
  - Modulation of EC system with CBD may have therapeutic potential in ameliorating some of those symptoms
  - Strong scientific rationale in FXS validated by Phase 2 FAB-C clinical data

U.S. Orphan Drug Designation for use of CBD as a treatment of Fragile X syndrome has been granted by the FDA (Feb. 2016)

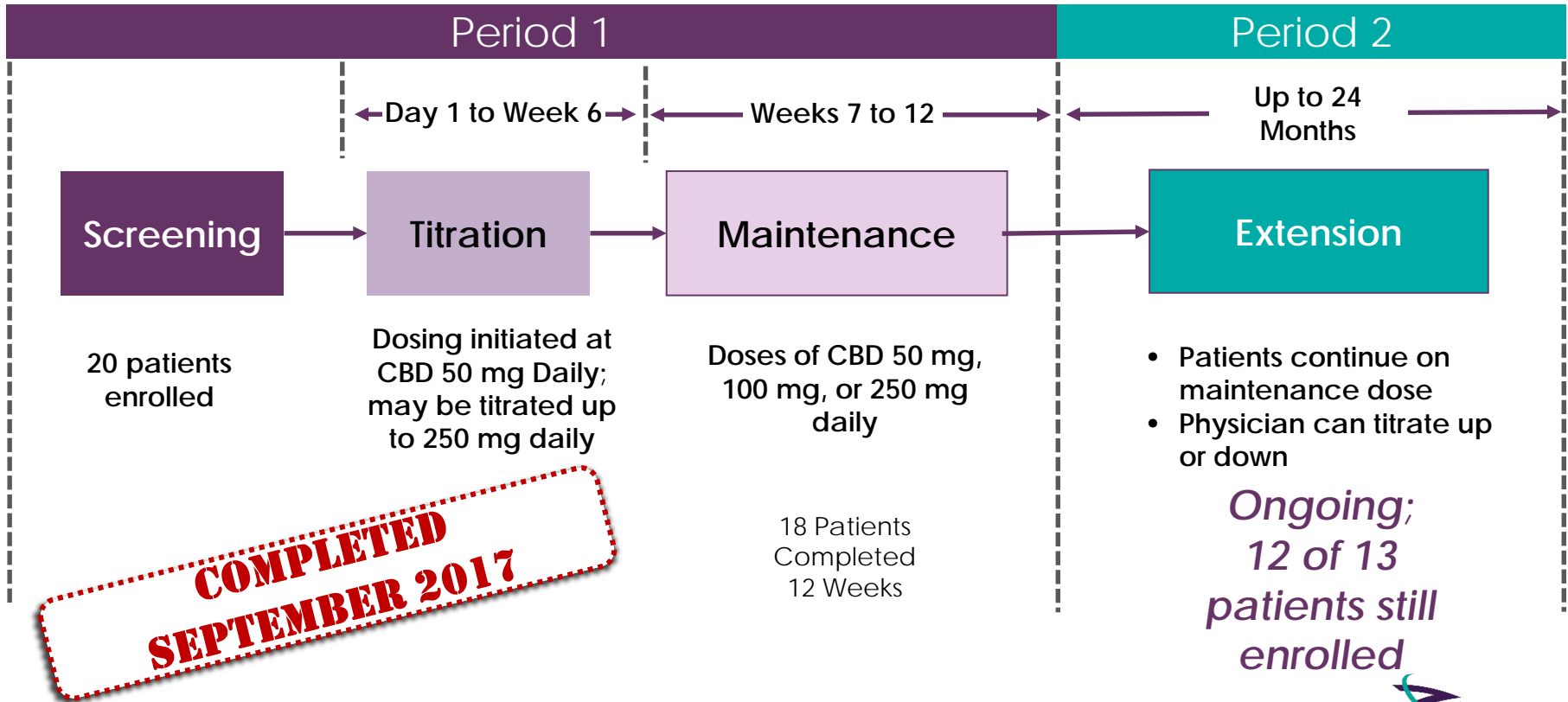
# Fragile X Syndrome (FXS) Overview

## FXS

- ~71,000 in U.S. patients with Fragile X
- Symptoms including significant behavioral, social, and cognitive deficits

- **CONNECT FX: a pivotal trial now underway in pediatric and adolescent FXS patients**
- **Initiated July 2018; results expected in 2H2019**
- **With positive results, will request FDA meeting to determine acceptability of data for NDA submission\***
- **Presented significant and sustained FAB-C open label Phase 2 efficacy data at the 16<sup>th</sup> NFXF International FXS Conference (July 2018)**
  - **Achieved primary and numerous secondary efficacy endpoints with statistical significance vs. baseline**
  - **Significant improvements at 12 weeks were sustained through 38 weeks of treatment with ZYN002**

# FAB-C Open Label Phase 2 (6 to 17 y.o.)





# FAB-C 12-Week Efficacy Data: ADAMS

Scale: ADAMS	Baseline (n=20)	Week 12 (n=18)	Week 12 % Improvement Group Mean	P-value vs baseline
<b>Total Score</b>	<b>33.4</b>	<b>18.1</b>	<b>45.8</b>	<b>&lt;0.0001</b>
General Anxiety	10.0	4.6	54.0	<0.0001
Social Avoidance	10.2	4.8	52.9	0.0002
Compulsive Behavior	2.8	1.4	50.0	0.0262
Manic/Hyperactive Behavior	9.4	6.1	35.1	0.0003
Depressed Mood	2.8	2.0	28.6	0.1417

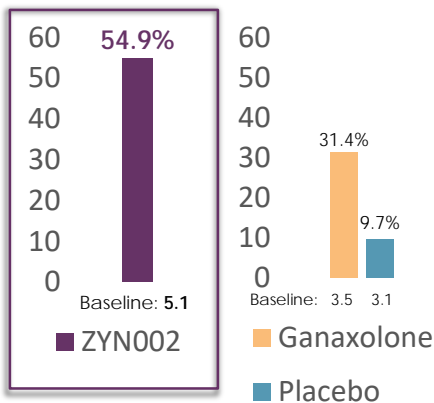
# FAB-C 12-Week Efficacy Data: ABC-C<sub>FXS</sub>

Scale: ABC-C <sub>FXS</sub>	Baseline (n=20)	Week 12 (n=18)	Week 12 % Improvement Group Mean	P-value vs baseline
Stereotypy	7.9	3.2	59.5	0.0006
Social Avoidance	5.1	2.3	54.9	0.0005
Socially Unresponsive/Lethargic	8.7	4.1	52.9	0.0034
Inappropriate Speech	6.1	3.5	42.6	0.0018
Irritability	18.2	10.6	41.8	0.0096
Hyperactivity	14.5	9.8	32.4	0.0237

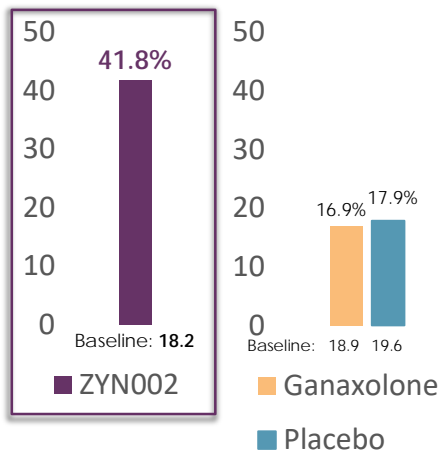
# FAB-C ABC-C<sub>FXS</sub> Subscales

## Week 12: Percent Improvement vs. 3<sup>rd</sup> Party Data\*

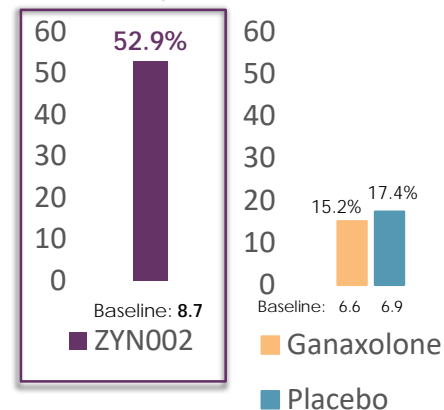
Social Avoidance  
Seeks Isolation



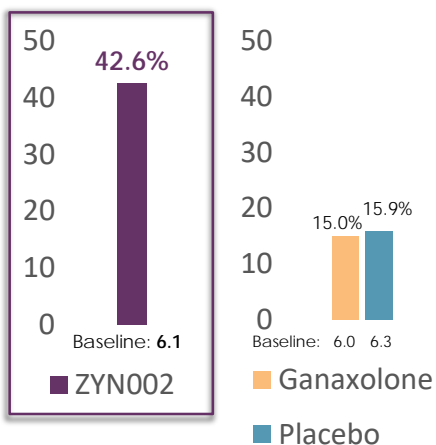
Irritability  
Temper Tantrums



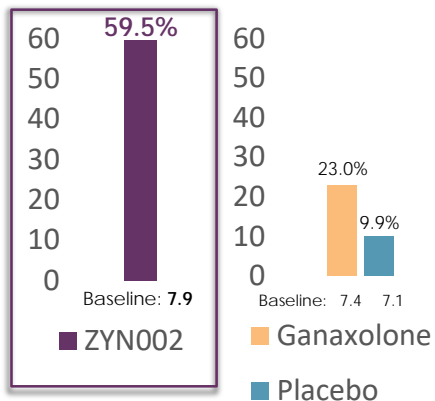
Socially Unresponsive / Lethargic  
Does Not Pay attention



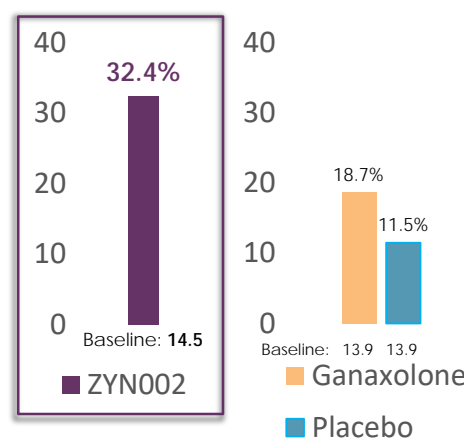
Inappropriate Speech  
Repeats Words / Phrases



Stereotypy  
Repetitive Movements



Hyperactivity  
Disrupts Group Activities



\* Ligsay, A., Van Djick, A., Nguyen, D. V., Lozano, R., Chen, Y., Bickel, E. S., et al. (2017). A randomized double-blind, placebo-controlled trial of ganaxolone in children and adolescents with fragile x syndrome. *Journal of Neurodevelopmental Disorders*, 9, 26.

# FAB-C Open Label Phase 2

## New Data Presented at NFXF International FX Conference

- Treatment with ZYN002 improved core behavioral symptoms of Fragile X syndrome with statistical significance versus baseline across multiple measures of efficacy at week 12
- Improvements sustained through 38 weeks of treatment
- ZYN002 is well tolerated
  - No serious adverse events were reported
  - No clinically meaningful trends in vital signs, ECG, or clinical safety laboratories, including liver function tests (LFTs) were observed
  - No THC detected in the plasma

# FAB-C Open Label Phase 2

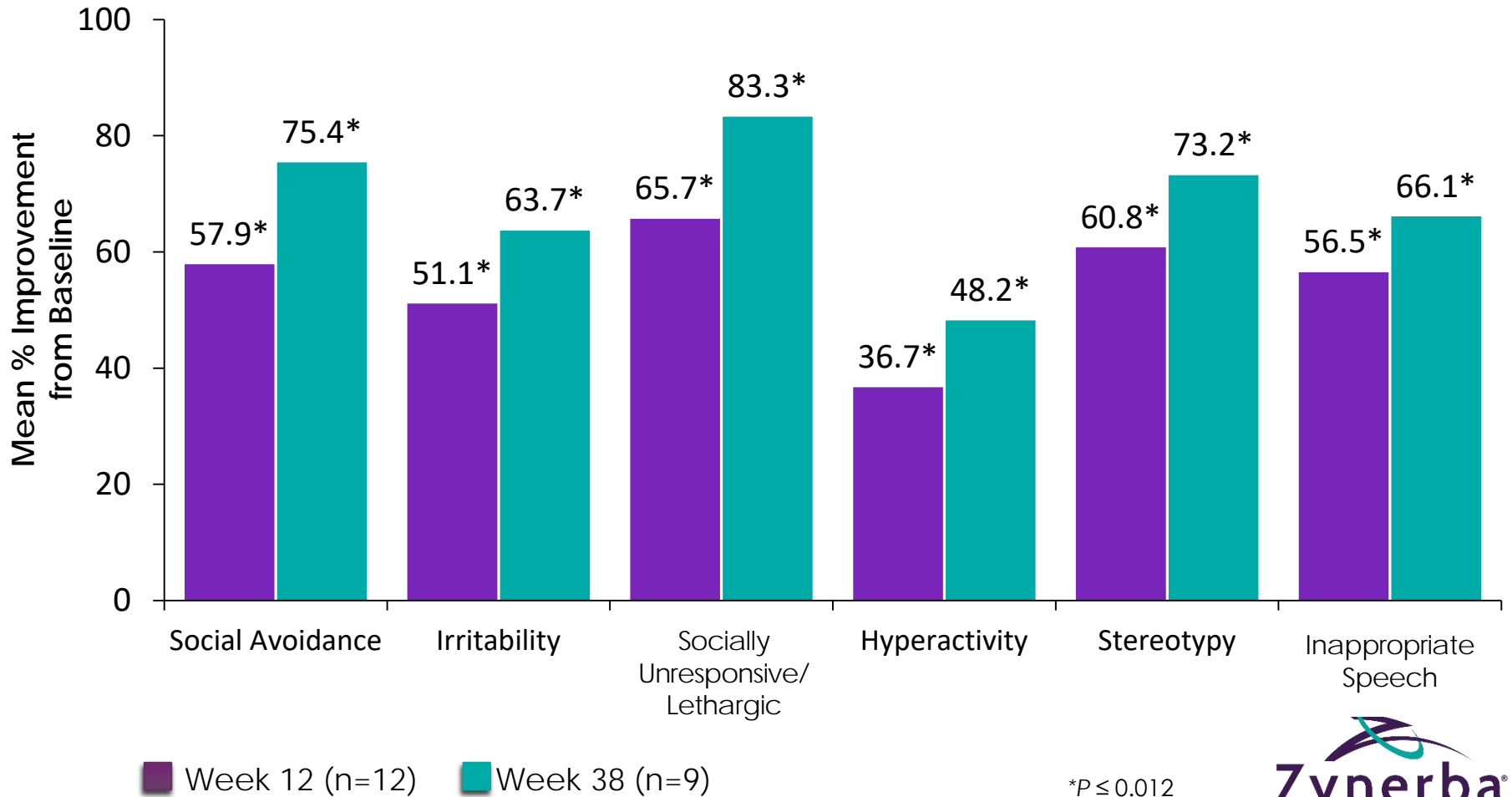
## Additional 12-Week Efficacy Data

Scale	Baseline (n=20)	Week 12 (n=18)	Week 12 % Improvement Group Mean	P-value vs baseline	Assessor
CGI Improvement (7 point scale)	n/a	2.5*	n/a	n/a	Clinician
Pediatric Anxiety Rating Scale – Revised (5-item used for Clinical Trials)	15.6	10.6	32.1	0.0006	Clinician
Pediatric Quality of Life Inventory: Total	57.3	67.7	18.2	0.0100	Caregiver
VAS Hyperactivity/Impulsivity	6.2	3.6	41.9	0.0002	Caregiver
VAS Tantrum/Mood Lability	5.0	3.2	36.0	0.0023	Caregiver
VAS Anxiety	6.2	3.8	38.7	0.0005	Caregiver
Vineland III: Overall Adaptive Behavior	48.3	48.9	1.2	0.0472	Clinician

\* N=17 at week 12

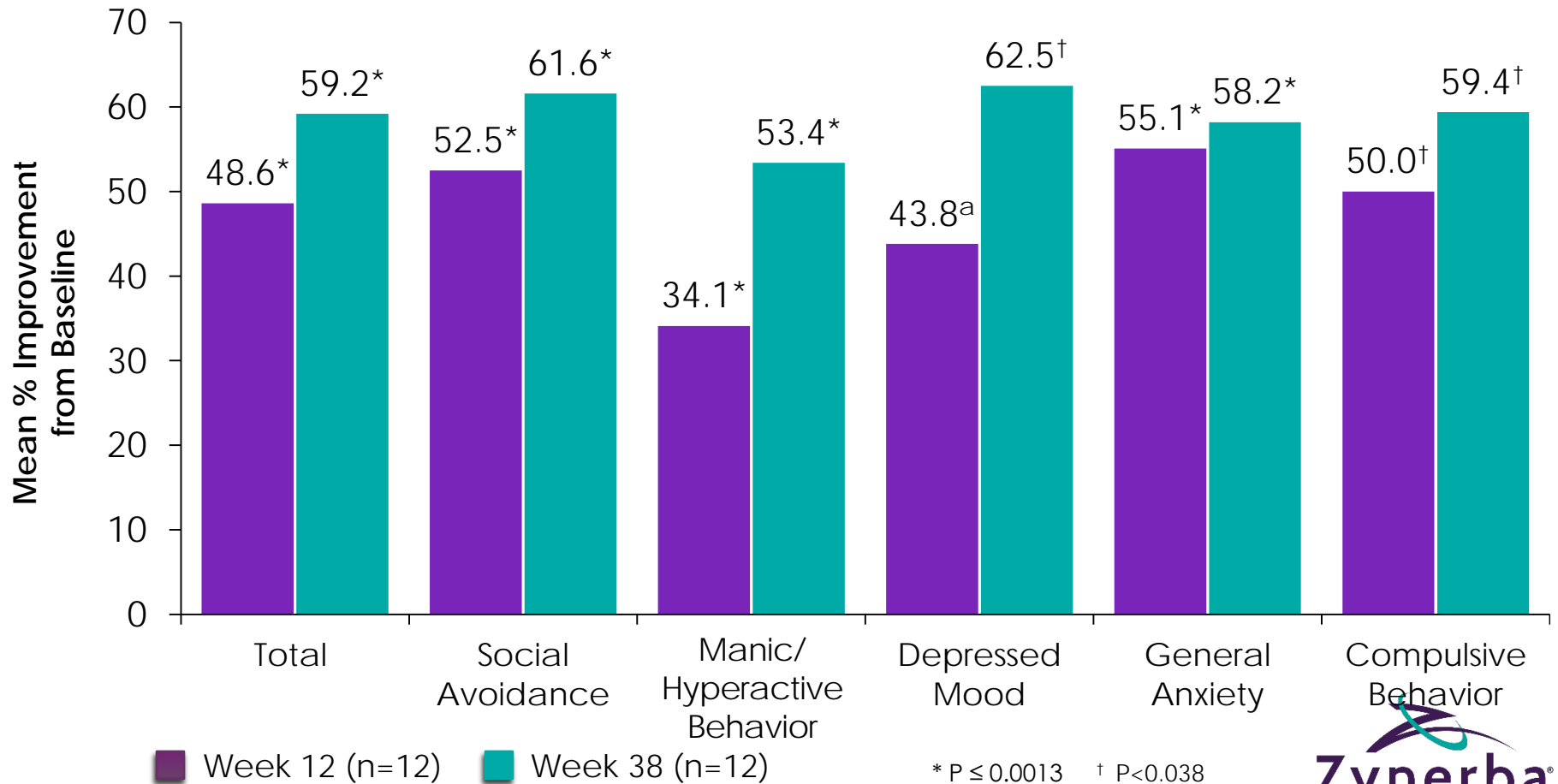
# FAB-C Open Label Phase 2

## ABC-C<sub>FXS</sub> Mean Score: 38 Weeks



# FAB-C Open Label Phase 2

## ADAMS Mean Score: Week 38



\* P ≤ 0.0013

† P < 0.038

<sup>a</sup> P = 0.083

# FAB-C Open Label Phase 2 Safety Summary

## ZYN002

- Overall safety database across all studies comprised of 570 volunteers and patients
  - Single dose to 24 months of exposure to ZYN002

## FAB-C (Through 38 Weeks)

- Well tolerated, consistent with previously reported clinical data; no SAEs
- No clinically meaningful trends in vital signs, ECG, or clinical safety laboratories, including liver function tests (LFTs)
- No THC was detected in the plasma
- Two sibling patients discontinued in Period 1 of study
  - One patient for worsening of pre-existing eczema (not considered treatment related)
  - One patient (sibling of the patient with eczema) discontinued due to administrative reasons
- Application site assessment scores showed little to no redness in most patients
  - One patient developed moderate application site rash, which resolved and did not recur; patient remains in the study



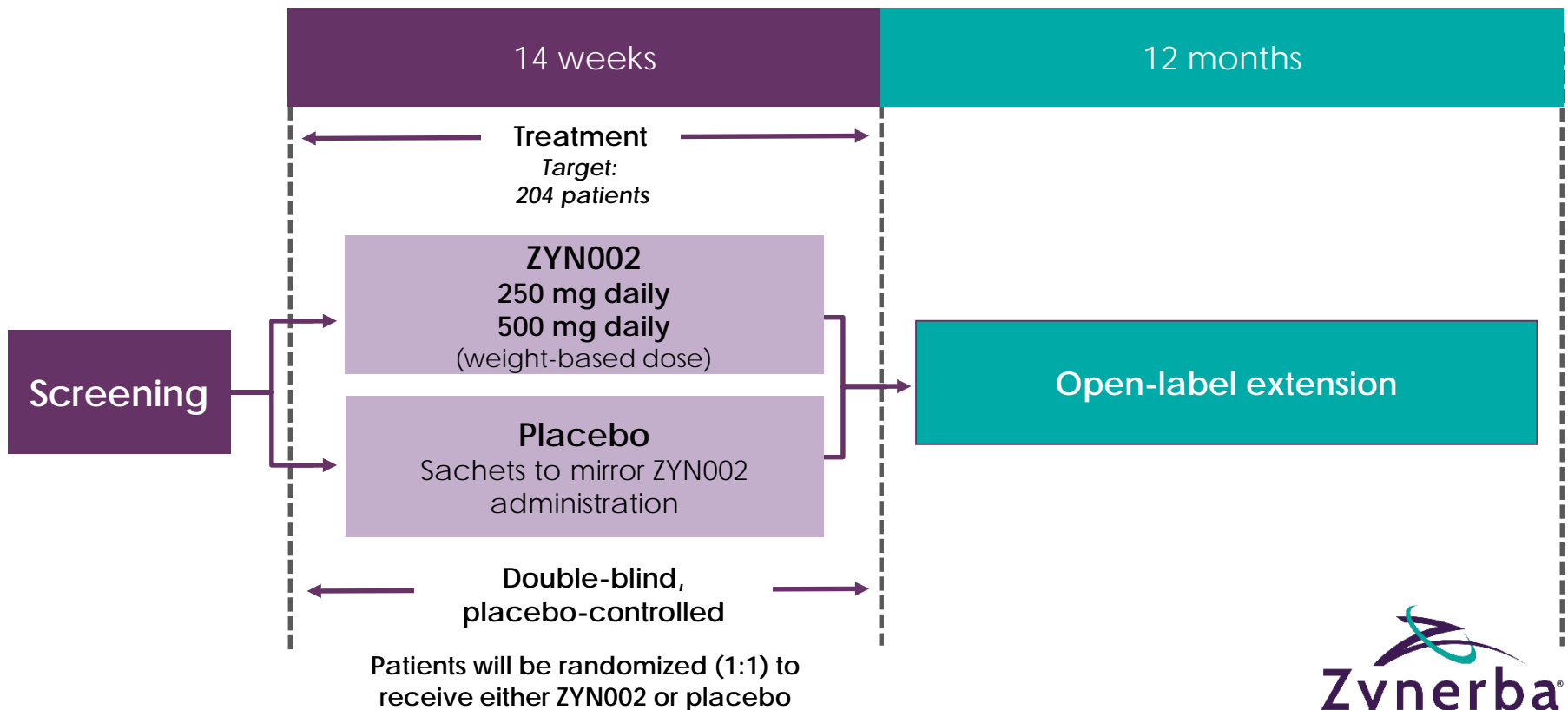
# FAB-C Open Label Phase 2

## Treatment-Emergent Adverse Events

- Through Week 38, patients have reported 43 treatment-emergent adverse events (TEAEs)
  - TEAEs were mild or moderate and most unrelated to treatment with CBD
- Most common TEAEs (all considered not related and resolved during study period):
  - Gastroenteritis (14%)
  - Upper respiratory tract infection (12%)
- One patient developed moderate application site rash – resolved

# CONNECT-FX: A Pivotal Trial in FXS Patients

Clinical study of Cannabidiol (CBD) in Children and Adolescents with Fragile X (CONNECT-FX)



# CONNECT-FX - Multi-national, randomized, double-blind, placebo-controlled, 14-week study

- 204 patients with FXS, three to 17 years of age
- Primary endpoint:
  - Change from baseline to end of treatment in ABC-C<sub>FXS</sub> Social avoidance subscale
- Key secondary endpoints:
  - Change from baseline to the end of the treatment period in
    - ABC-C<sub>FXS</sub> Irritability subscale score
    - ABC-C<sub>FXS</sub> Socially Unresponsive/Lethargic subscale score
  - Improvement in CGI-I at the end of the treatment period.
- Study will anchor the CGI-I to behavioral symptoms of FXS
- Additional qualitative data on the clinical relevance of FXS behaviors to caregivers and patients will be collected
  - Based on FDA's Voice of the Patient Guidance

# CONNECT-FX

## Top Line Results Expected in 2H2019

- With positive results from this trial, Zynerba intends to request a meeting with the FDA to:
  - Determine the acceptability of these data as the basis for an NDA filing
  - Seek advice on preparation of our marketing authorization
- We believe ZYN002 indication may include the treatment of behavioral symptoms associated with Fragile X syndrome
- Evaluating opportunities for FDA fast-track, breakthrough status, and/or priority review

ZYN002  
CBD Gel Clinical Program

*Developmental Epileptic  
Encephalopathies (DEE)*

# Developmental and Epileptic Encephalopathies

## DEE category includes:

Doose Syndrome

Dravet Syndrome

Early Myoclonic Encephalopathy

Epilepsy of Infancy With Migrating Focal Seizures

Epilepsy with Generalized Tonic-Clonic Seizures alone (EGTCS)

Juvenile Myoclonic Epilepsy (JME)

Landau-Kleffner Syndrome

Lennox-Gastaut Syndrome

Ohtahara Syndrome (Early Infantile Epileptic Encephalopathy)

West Syndrome / Infantile Spasms

- Heterogeneous group of rare and ultra rare epilepsy syndromes associated with severe cognitive impairment and behavioral disturbances
- ~45,000 U.S. children and adolescents with DEE
- Syndromes involve:
  - Significant developmental impairment (*developmental encephalopathies*)
  - Regression of developmental progress (*epileptic encephalopathies*)
- Often progressive; highly resistant to treatment
- Improved seizure control may have a positive impact on development and quality of life

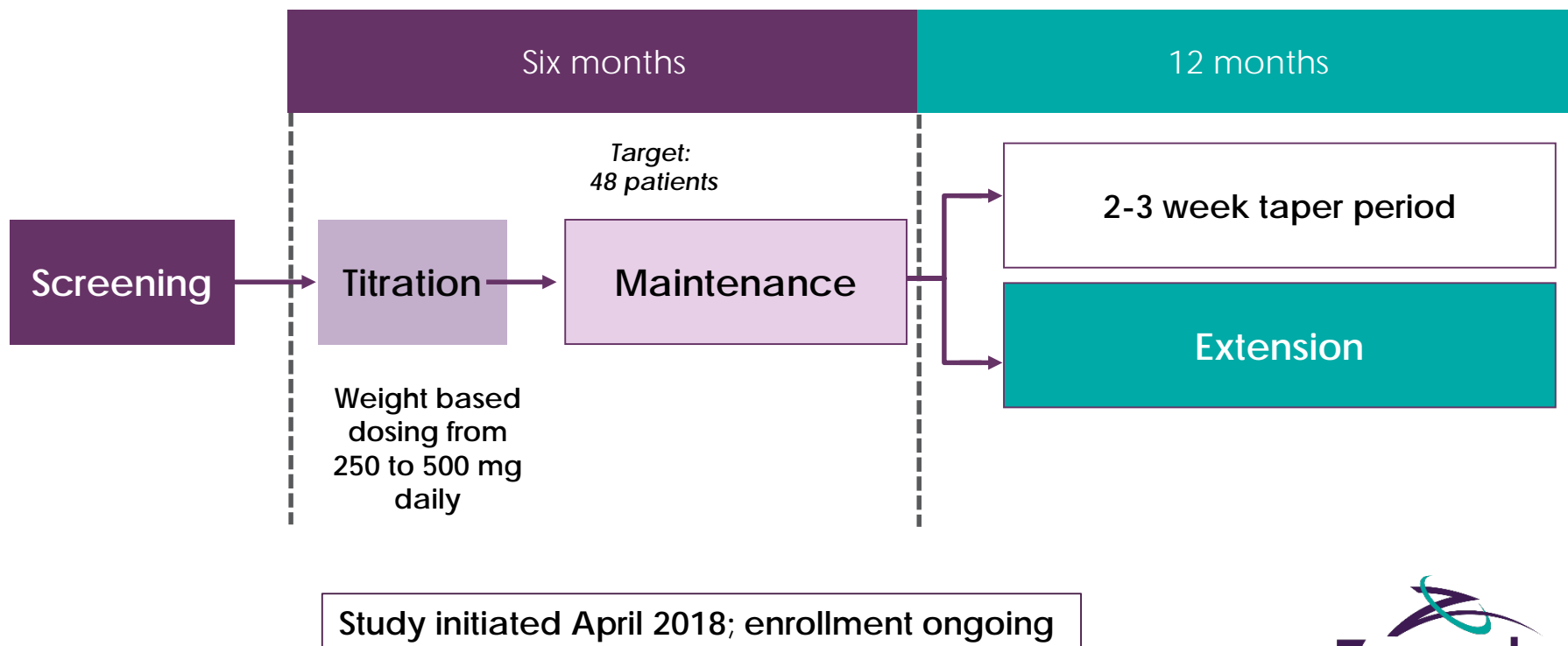
# Developmental & Epileptic Encephalopathies

## BELIEVE 1 New Phase 2 Program Initiated April 2018

- Third party clinical data show impact of CBD on seizures and behavioral issues in children
- DEE classified by the International League Against Epilepsy (ILAE) (Scheffer et al. 2017)
- Patient enrollment in BELIEVE 1 Phase 2 study underway
  - Six month multi-dose study in ~50 DEE patients (3 to <18 years)
  - Approximately half may have either Dravet or Lennox-Gastaut syndrome
  - Primary efficacy assessment: change in seizure frequency
- Results expected in 2019

# BELIEVE 1 DEE Open Label Phase 2 Study Results Expected in 2019

Open Label Study to Assess the Safety and Efficacy of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with Developmental and Epileptic Encephalopathy





ZYN002  
CBD Gel Clinical Program

*Adult Refractory Focal Epilepsy*

# Adult Refractory Focal Epilepsy

## Phase 2B Study Initiation Anticipated in 2H2018

### Adult Refractory Focal Seizures

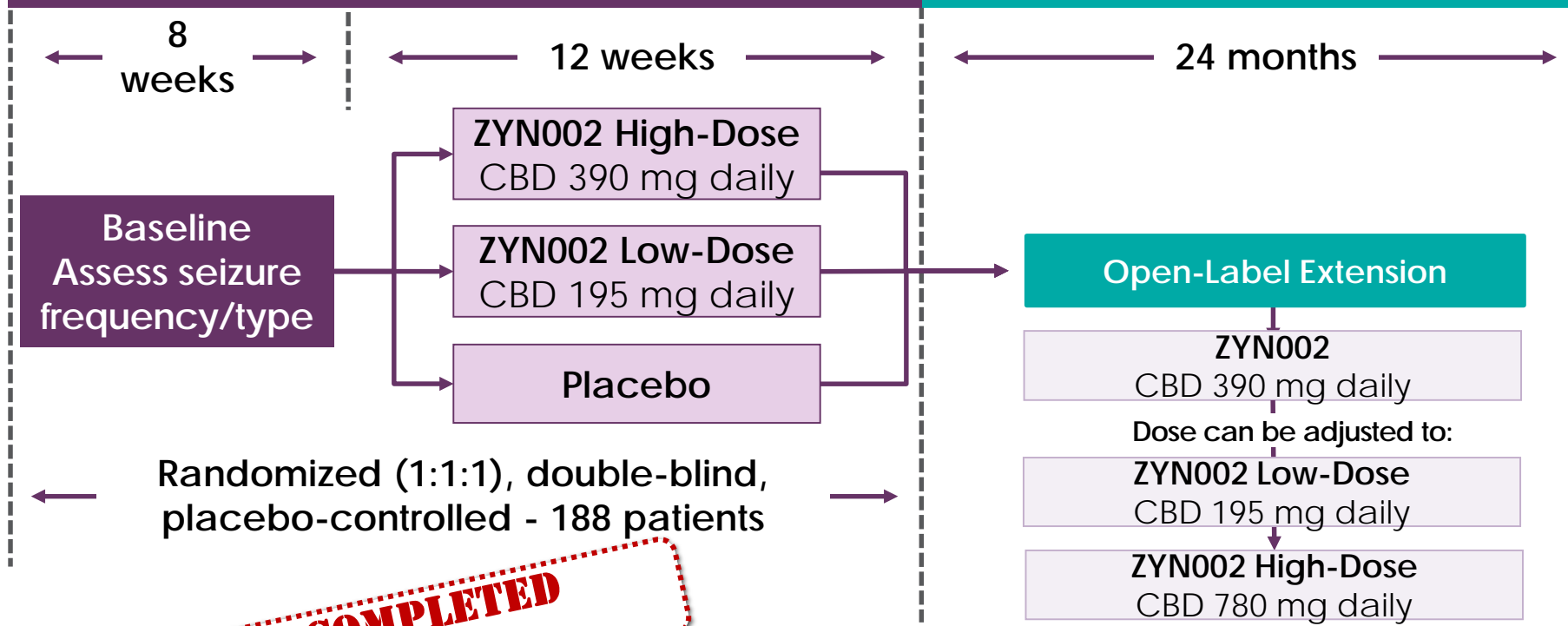
- Focal seizures are the most common epilepsy in adults
  - Substantial U.S. market
    - ~500,000 refractory patients
  - New treatment options with improved quality of life (safety and efficacy) needed
- STAR 2 data suggest continued improvement in seizure control in adult refractory focal seizure patients receiving ZYN002 through 12 months of open label exposure
    - Presented in Late Breaking poster session at 2018 AAN (April 25, 2018)
  - Learnings from Phase 2 STAR 1 study and open label STAR 2 extension provide input into Phase 2b trial design
    - Planned modifications include increased baseline seizure frequency, patient count, and trial duration
  - Expect to initiate ~300 patient double blind placebo controlled study in 2H2018

# Epilepsy Phase 2 Clinical Study Trial Design

## Synthetic Transdermal Cannabidiol for the Treatment of Epilepsy

### STAR 1 Trial

### STAR 2 Trial



**COMPLETED  
AUGUST 2017**

*Ongoing*

# Epilepsy Phase 2 Clinical Study

## Demographics and Baseline Characteristics

STAR 1 patients	Placebo	195 mg ZYN002	390 mg ZYN002	Total
Pts Randomized	63	63	62	188
Sex	43% male 57% female	51% male 49% female	42% male 58% female	45% male 55% female
Pts Analyzed for efficacy	63	62	61	186
Pts completing study	62	57	55	174
Patients continuing into STAR 2				171
Baseline median seizure rate	10.5	14.0	10.1	10.6 (3-335)
AEDs				Median: 3.0 Mean: 2.5
Primary endpoint: Percent reduction in baseline seizures	8.7%	18.4%	14.0%	

# Epilepsy Phase 2 Clinical Study

## STAR 1 and STAR 2 Results

### STAR 1

- Company believes study missed primary endpoint due to bimodal distribution of placebo patient responses :
  - >50% reductions in focal seizures in ~¼ of placebo patients
  - 13 of these 15 patients were female
- Strong separation from placebo seen at >15 baseline seizures
- Excellent tolerability

### STAR 2

- 98 patients have reached 9 mo. of total drug exposure; 84 have reached 12 months\*
- Excellent tolerability
- Data suggest continued improvement in seizure control with longer term use

Learnings provide input into revised Phase 2B clinical trial design

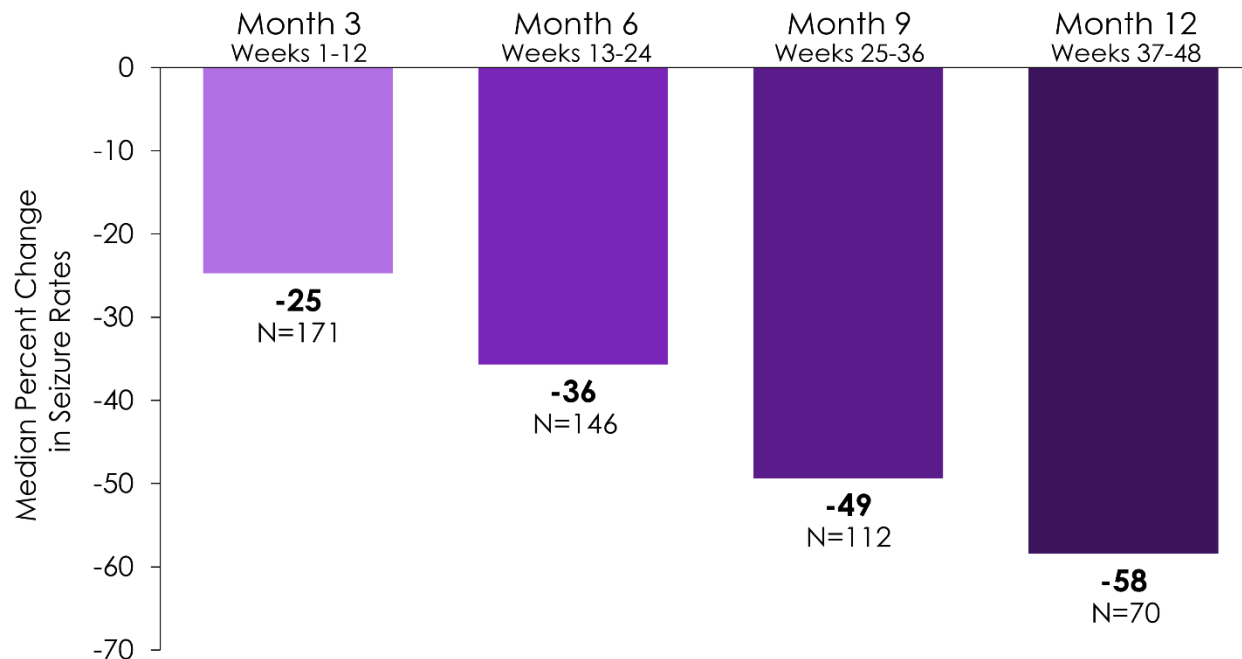
Twelve Month STAR 2 data presented during Emerging Science (Late Breaker) poster session at the 2018 American Academy of Neurology (AAN) meeting

# Data Presented at 2018 AAN

## STAR 2 Efficacy Data

Median Percent Change in Seizure Rates at  
Months 3, 6, 9, and 12

All ZYN002-Treated Patients in STAR 2



STAR 2 results based on data collected through mid-December 2017 and in patients who reported seizure frequency data during the respective time period.

# Proposed Phase 2b Study

## Adult Refractory Focal Epilepsy

### Trial design\*

- ~300 patient double-blind placebo controlled study
- To be conducted in U.S., Australia and New Zealand
- Primary endpoint: reduction from baseline in focal seizures
- 1:1:1 ratio (195 mg: 780 mg: placebo)

### Planned modifications

Learnings from STAR 1 and STAR 2 experience include:

- Stratified randomization by baseline seizure rate and gender
- Increase in patient count
- Increase trial duration
- Increase in baseline seizure frequency
  - Median seizure target: >15/month vs 10.6 in STAR 1

Expect to initiate study in 2H2018

*Open label extension to follow*

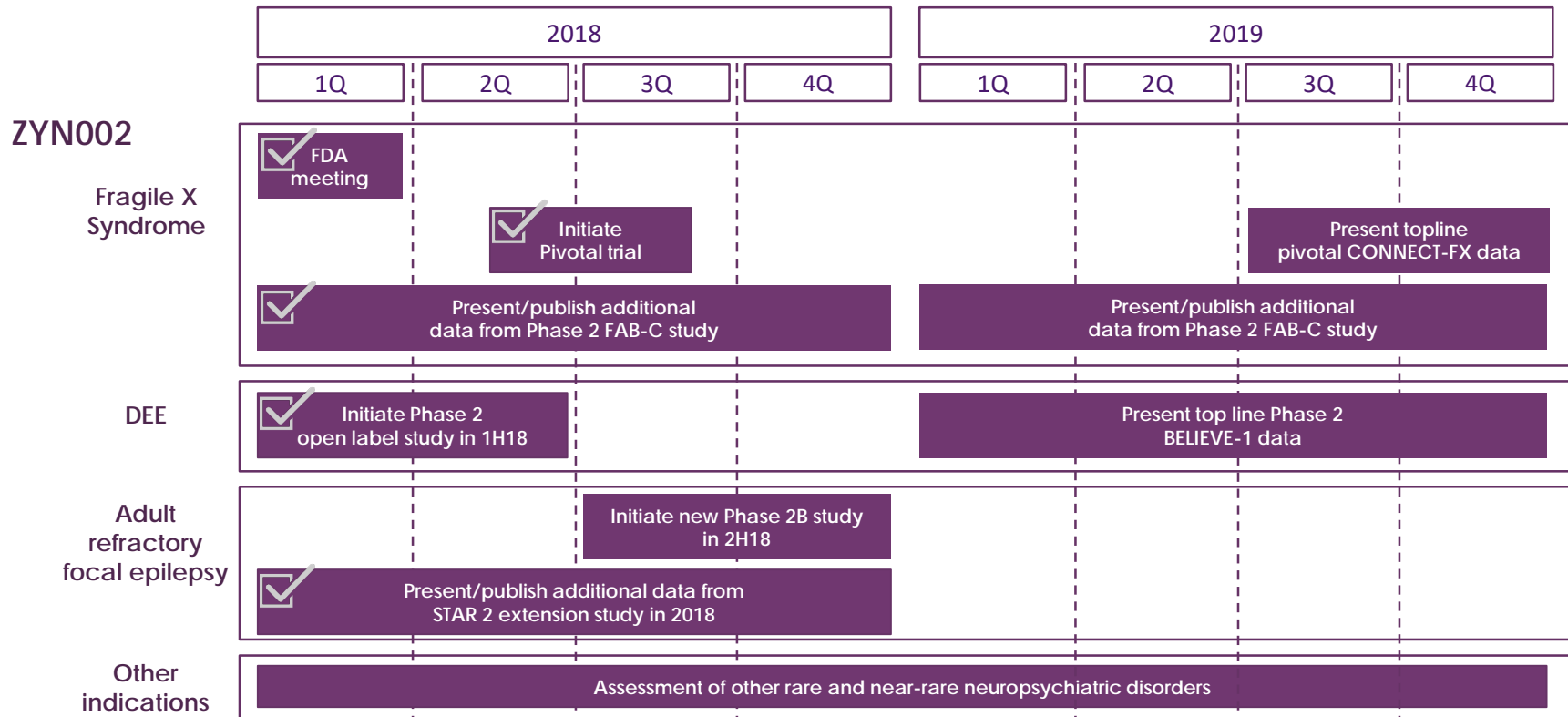
# Financial Strength

## As of March 31, 2018

- Cash and cash equivalent position of \$52.1 million
- Well capitalized, expect cash to fund operations into 2H2019



# Expected 2018 and 2019 Milestones



# Scientific Advisory Board

Elizabeth M. Berry-Kravis, MD, PhD	Professor, Department of Pediatrics, Rush Medical College
Craig A. Erikson, MD	Associate Professor, Department of Psychiatry and Behavioral Neuroscience, Cincinnati Children's Hospital
Randi J. Hagerman, MD	Medical Director, UC Davis MIND Institute, Distinguished Professor, Endowed Chair in Fragile X Research, Department of Pediatrics, UC Davis School of Medicine
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Michael Rogawski, MD, PhD	Professor of Neurology, UC Davis Center for Neuroscience



Fragile X Syndrome



Epilepsy

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Seaport Global: Corey Davis

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Zynerba



Dedicated to the development of innovative  
pharmaceutically-produced transdermal  
cannabinoid therapies for rare and near-rare  
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