
# Corporate Overview

**January 2020**

# Forward-Looking Statements

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# Zynerba Pharmaceuticals (NASDAQ: ZYNE)

## A Rare/Near-Rare Neuropsychiatric Company

- Deep pipeline focused on high unmet medical needs; translating into multi-billion dollar market opportunity with Zygel™(CBD gel)
  - Four clinical shots on goal: FXS, DEE, ASD, 22q
  - Approaching enrollment target in pivotal CONNECT-FX FXS trial
  - Achieved target enrollment in Phase 2 BRIGHT ASD study
- Experienced team
  - Proven development and commercialization track record in transdermal delivery, orphan diseases, neurology, psychiatry
- Well capitalized
  - Cash runway expected into the second half of 2021 - beyond the expected NDA filing and potential approval in FXS
- Multiple expected near term milestones

# Deep Clinical Pipeline

**Zygel**
Cannabidiol Gel

| Indication | Preclinical | Phase 1 | Phase 2 | Pivotal | Expected Milestones |
|---|---|---|---|---|---|
| Fragile X Syndrome (FXS)* | | | | | |
| CONNECT-FX: Enrollment nearing completion | | | | | Topline pivotal data in 2Q2020 |
| Developmental and Epileptic Encephalopathies (DEE) | | | | | |
| BELIEVE 1: Complete | | | | | Meet with FDA in 1H2020 to discuss clinical path forward |
| Autism Spectrum Disorder (ASD) | | | | | |
| BRIGHT: Target enrollment achieved | | | | | Topline Phase 2 data in 2Q2020 |
| 22q Deletion Syndrome (22q) | | | | | |
| INSPIRE | | | | | Topline Phase 2 data in 2Q2020 |

*Orphan Drug Designation

# Zygel (ZYN002) Cannabidiol (CBD) Gel

**Differentiated**

First & only patent-protected, permeation-enhanced, pharmaceutically-produced CBD gel

**Transdermal**


Formulation delivers CBD through the epidermis and into the circulatory system

**Unique MOA**

CBD modulates multiple receptors and mediates numerous pathways, including the endocannabinoid pathway

**Neuropsych Indications**

Potential utility in rare / near-rare neuropsychiatric conditions

**FDA Fast Track and Orphan Drug designations in FXS**

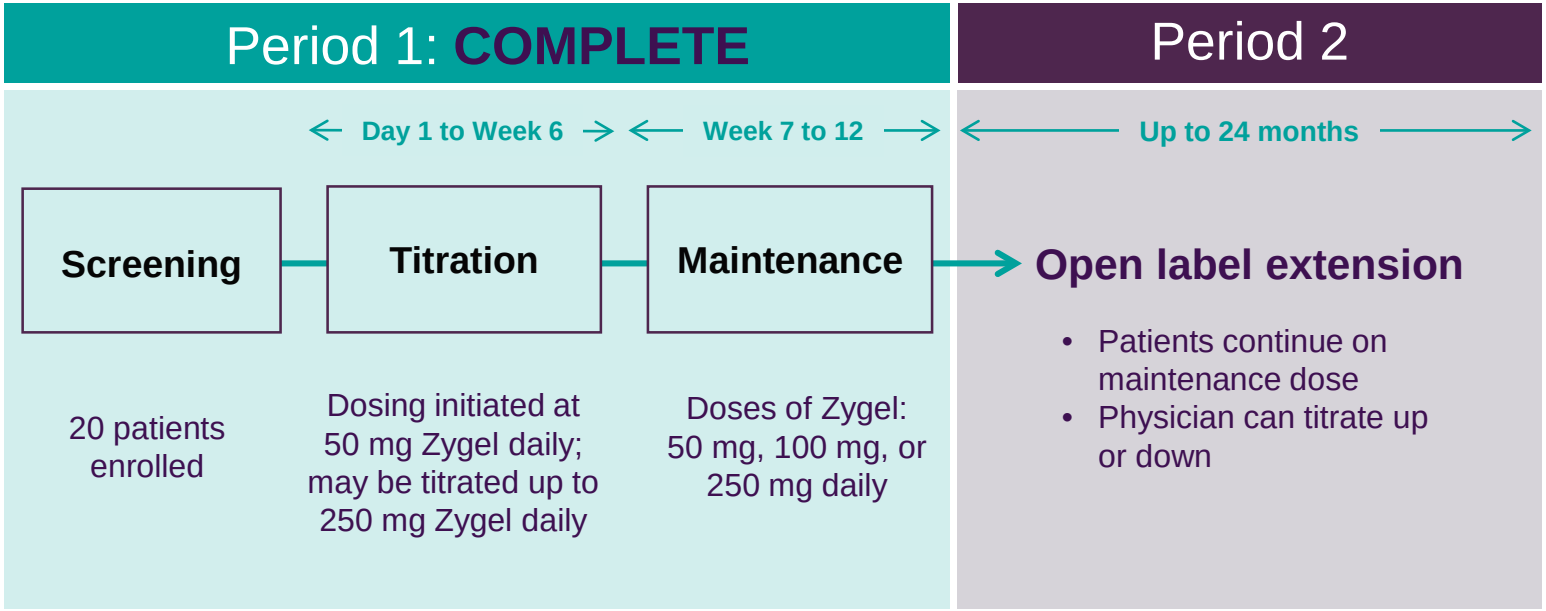
# Fragile X Syndrome (FXS)

# Fragile X Syndrome (FXS) Overview

- Rare genetic developmental disability
- Leading known cause of both inherited intellectual disability and autism spectrum disorder
- Symptoms linked to deficiencies in the endocannabinoid (EC) system
  - System of neurotransmitters regulating emotional responses, behavioral reactivity to context, social interaction
  - FMR1 mutation causes dysregulation of the EC system
  - Results in core cognitive, social, and behavioral symptoms of FXS
  - CBD may modulate EC system
    - Increases availability of endocannabinoids (anandamide, 2-AG) by inhibiting metabolism
- Affects ~71K people in U.S.
- No approved drugs indicated for FXS

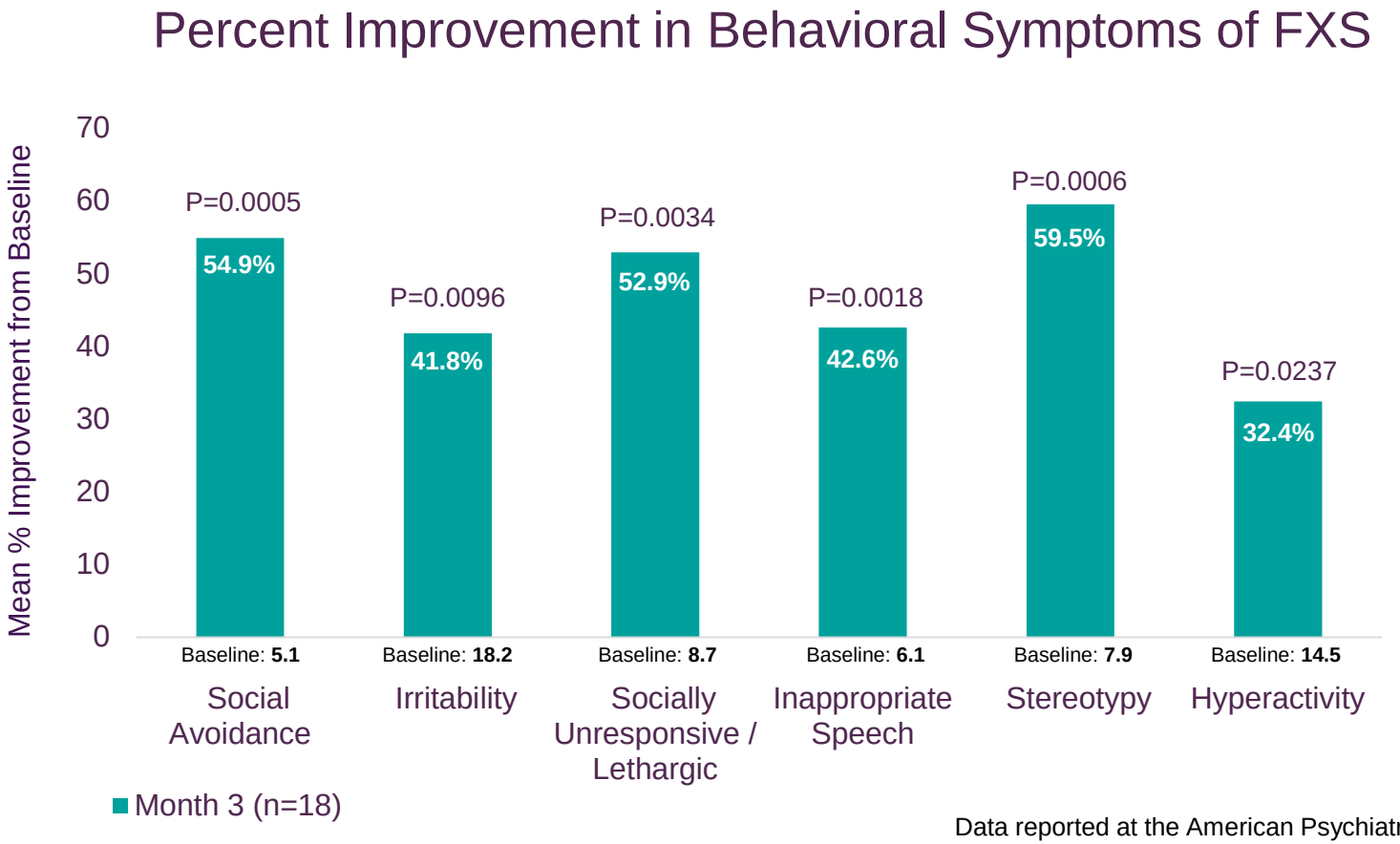
# FAB-C Open Label Phase 2 Trial Design

**Treatment of Fragile X Syndrome Anxiety and Behavioral Challenges with CBD**



# Data From Three Month FAB-C Phase 2 Trial

## Month Three: ABC-$C_{FXS}$ Mean Score

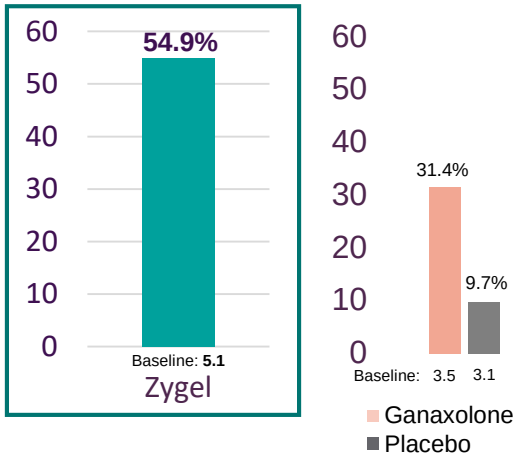



Data reported at the American Psychiatric Association (APA) meeting, May 2019

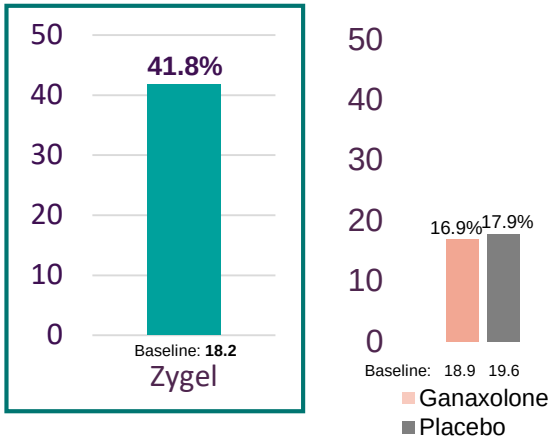
# FAB-C ABC-$C_{FXS}$ Subscales

## Third Party Data* Suggest PBO Rate of 10 to 18 Percent

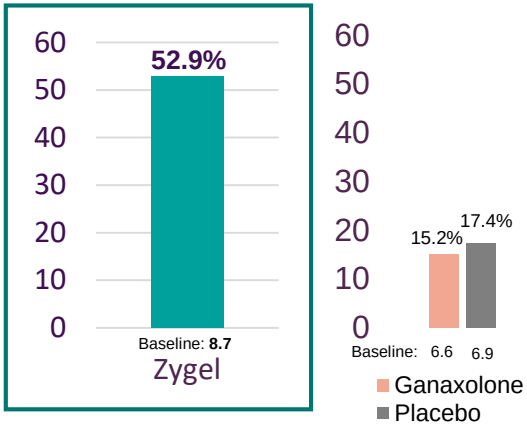
### Social Avoidance
*Seeks isolation*



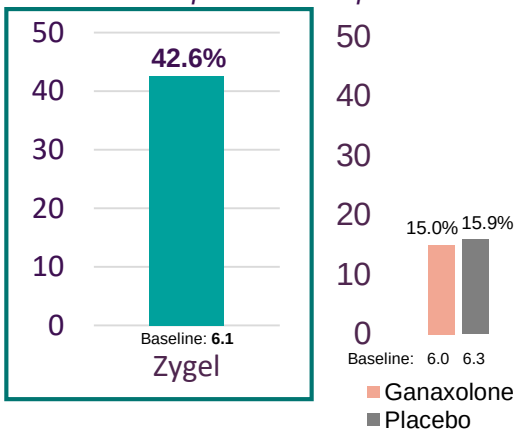

### Irritability
*Temper tantrums*



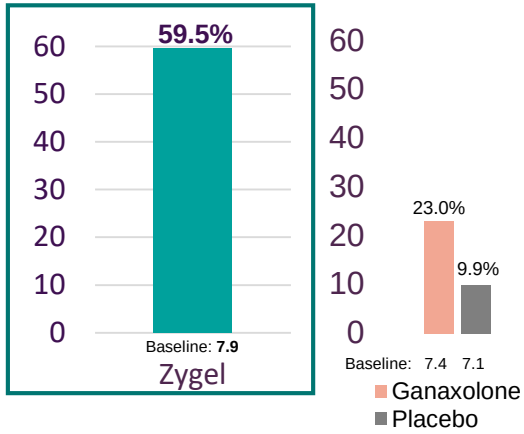

### Socially Unresponsive / Lethargic
*Does not pay attention*



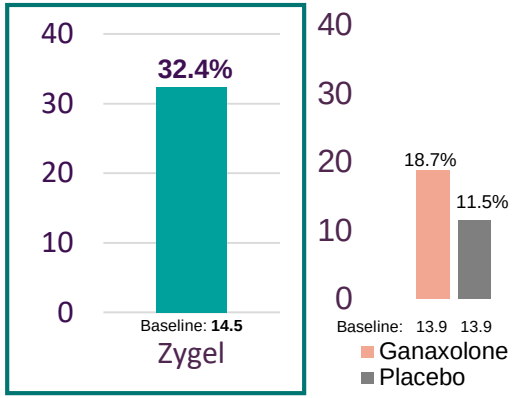

### Inappropriate Speech
*Repeats words / phrases*




### Stereotypy
*Repetitive movements*




### Hyperactivity
*Disrupts group activities*

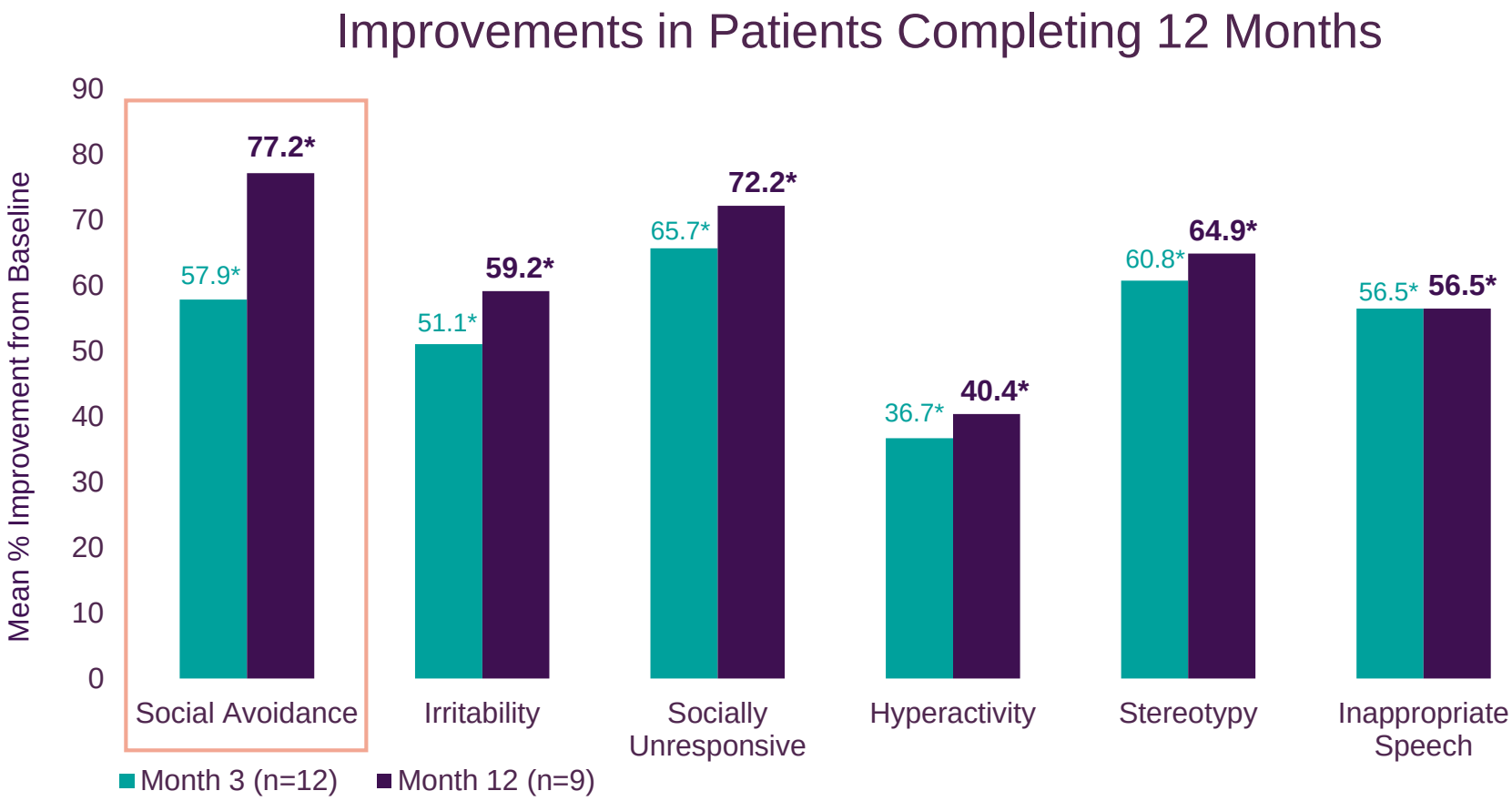





* Ligsay, A., Van Dijck, A., Nguyen, D. V., Lozano, R., Chen, Y., Bickel, E. S., et al. (2017). A randomized double-blind, placebo-controlled trial of ganaxolone in children and adolescents with fragile x syndrome. Journal of Neurodevelopmental Disorders, 9:26.

# Three Month FAB-C Data vs. 12 Months of Treatment

## Sustained Improvements in FXS Behavioral Symptoms Through 12 Months of Treatment




*P ≤ 0.05

Data reported at the American Psychiatric Association (APA) meeting, May 2019

# FAB-C Open Label Phase 2

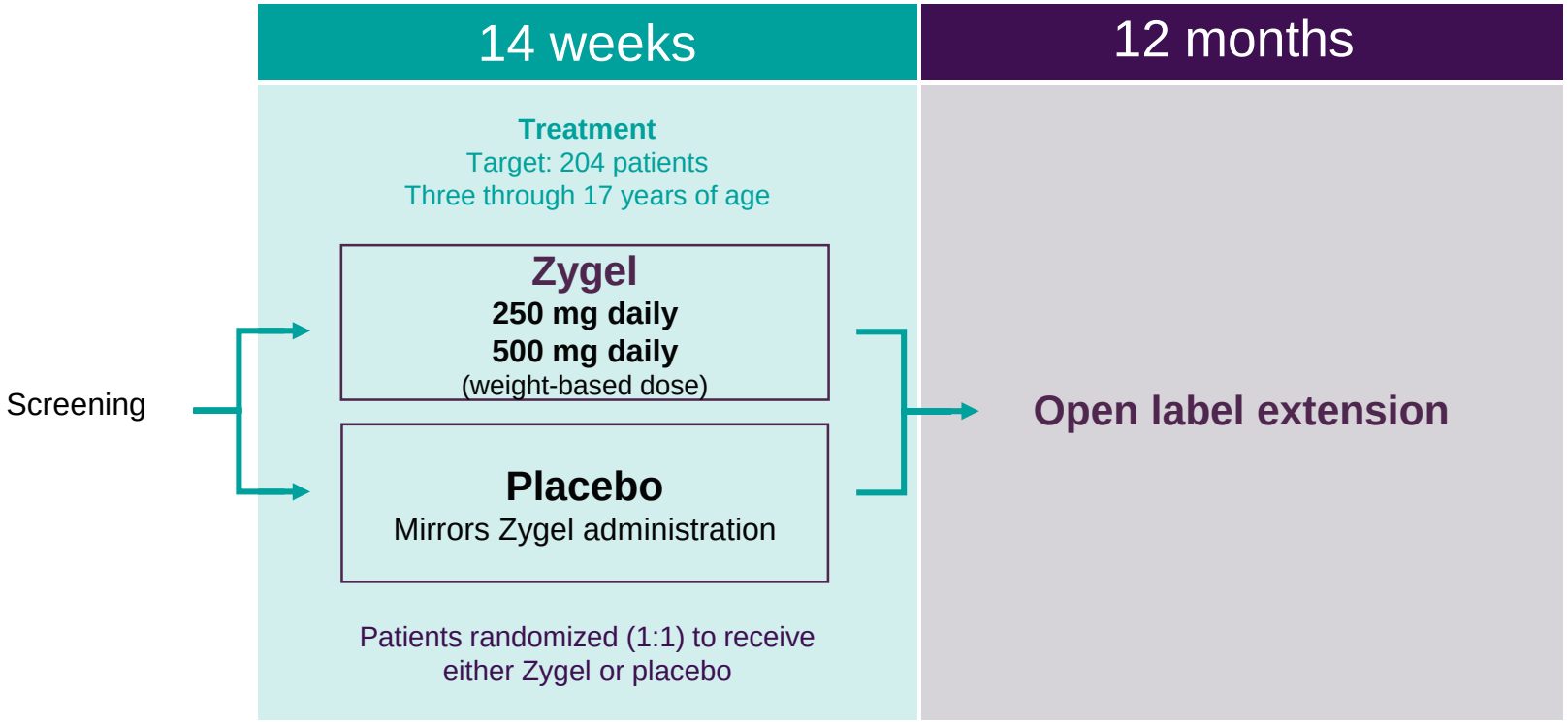
## Zygel Safety Summary Through 12 Months

- Well tolerated, consistent with previously reported data; no SAEs
- No clinically meaningful trends in vital signs, ECG, or clinical safety labs including LFTs; no THC detected in plasma
- Discontinuations
  - Two siblings discontinued in Period 1
    - One for worsening of pre-existing eczema (not considered Tx-related)
    - One due to administrative reasons
  - Three patients discontinued in Period 2 (administrative reasons; non-compliance)
- Little to no redness at application site
  - One patient developed moderate application site rash (resolved, did not recur); remains in the study
- TEAEs mild or moderate
  - Most common: Gastroenteritis (14%), URTI (12%)
  - All resolved during study period

# CONNECT-FX: A Pivotal Trial In FXS

## Enrollment Nearing Completion; Topline Data Expected in 2Q2020

### Clinical study Of CaNNabidiol (CBD) in ChildrEn and AdolesCenTs with Fragile X (CONNECT-FX)



# CONNECT-FX: A Pivotal Trial In FXS

- Primary endpoint:
  - Change from baseline to end of treatment in ABC-$C_{FXS}$ Social Avoidance subscale
- Key secondary endpoints:
  - Change from baseline to end of the treatment in
    - ABC-$C_{FXS}$ Irritability subscale score
    - ABC-$C_{FXS}$ Socially Unresponsive/Lethargic subscale score
  - Improvement in CGI-I (anchored to FXS behaviors) at end of treatment
- Aligned with FDA's 'Voice of the Patient' Guidance
  - Capturing qualitative data on clinical relevance of FXS behaviors
  - New data presented at SSBP (September 2019) further validate core FXS behaviors from the perspective of caregivers
- Top line results expected in 2Q2020

# CONNECT-FX Enrollment Status and Demographics

## Screening Expected to Complete by End of January 2020

| Patients | n* |
|---|---|
| Randomized (target=204) | 178 |
| Screened but not yet randomized | 15 |
| Completed 14-week Tx period | 141 |
| Percent of completed patients enrolling in CONNECT-FX OLE | 96% |

*As of January 10, 2020

| Demographic data in 178 enrolled pts | |
|---|---|
| Number of male patients | 135 (76%) |
| Mean age in study | 9.6 years |

# Baseline Behavior Severity: CONNECT-FX vs Ph2 FAB-C

Prospective inclusion criteria expected to provide a more severely impacted population which we believe should enhance ability to demonstrate a strong signal of activity and minimize response variability

| ABC-$C_{FXS}$ Subscale | CONNECT-FX baseline score | Phase 2 FAB-C baseline score |
|---|---|---|
| Social Avoidance (12 point scale) | **7.2** | 5.1 |
| Irritability (54 point scale) | **28.1** | 18.2 |
| Socially Unresponsive / Lethargic (39 point scale) | **13.2** | 8.7 |
| Hyperactivity (30 point scale) | **18.5** | 14.5 |
| Stereotypy (18 point scale) | **9.4** | 7.9 |
| Inappropriate Speech (12 point scale) | **6.9** | 6.1 |

**Note**: Higher baseline scores denote more severe behaviors

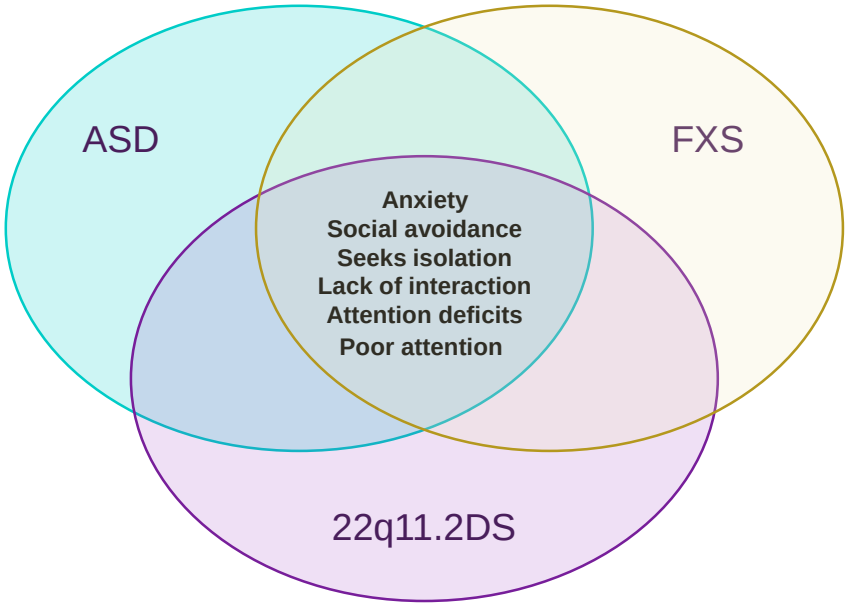
# CONNECT-FX

- With positive results in pivotal trial, Zynerba intends to request a meeting with the FDA to:
  - Determine acceptability of data as basis for NDA filing by YE 2020
  - Seek advice on marketing authorization preparation
- Potential approval by mid-year 2021
- Zynerba believes the indication may be the treatment of behavioral symptoms associated with FXS

# Improvements in Behavior May Provide a Read-Through to Other Zygel Studies

- Presented data at SSBP* showing constellation of shared socio-behavioral symptoms in ASD, FXS, and 22q11.2DS
- These include anxiety leading to:
  - Isolation and social avoidant behaviors
  - Irritability
  - Attention deficits
  - Poor communication

Common behavioral Features of ASD, FXS, and 22q11.2DS*




**Common Behavioral Features of Autism, Fragile X Syndrome, and 22q11.2 Deletion Syndrome*, Society for the Study of Behavioural Phenotypes (SSBP), 2019

# Autism Spectrum Disorder (ASD)
## in pediatric patients

# ASD in Pediatrics Overview

- Near-rare disorder affecting ~1MM pediatric and adolescent pts
- DSM-5 diagnosis
  - Includes Autistic disorder, Asperger's syndrome, and Pervasive Development Disorder-not otherwise specified (PDD-NOS)
- Symptoms include
  - Anxiety
  - Restricted, repetitive patterns of behavior
  - Impairments in social communication
  - Deficits in verbal and non-verbal communication
  - Deficits in developing, understanding and maintaining relationships
- Most diagnosed after age 4; can be diagnosed as early as age 2
- Significant unmet medical need
  - Accelerating rate of diagnosis but only two FDA approved products
    - Both atypical antipsychotics have significant side effect profile
    - Neither approved to address the key symptoms of social impairment and anxiety

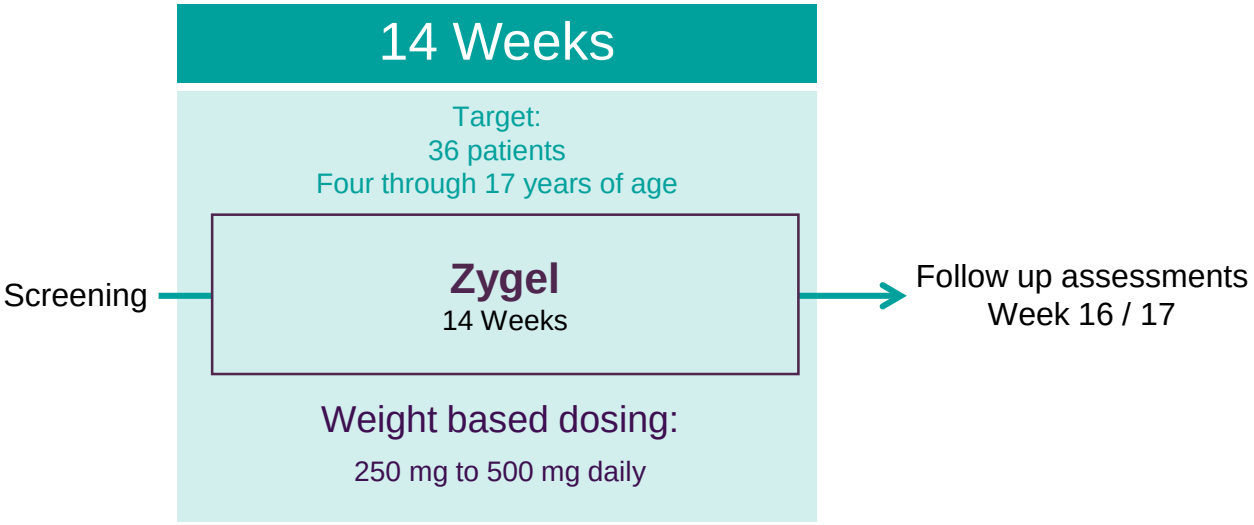
# Developing Zygel in ASD

- Newer studies suggest ASD is linked to disruption in the EC system
  - Altered anandamide signaling may contribute to ASD-related social and communication impairments
  - EC system modulates many cellular functions and molecular pathways altered in ASD: imbalanced GABAergic, glutamatergic transmission, oxidative stress, immune dysregulation and altered energy metabolism
- Clinical and anecdotal data show improvement in social avoidance and anxiety in children with CBD
  - CBD may modulate the EC system and improve certain autism-related behaviors
- Recent US patent directed to methods of treating ASD with synthetic cannabidiol provides IP protection to 2038
- Target enrollment achieved in Phase 2 study in pediatric and adolescent patients with ASD
- Top line results expected in 2Q2020

# BRIGHT Phase 2 Trial in ASD

## Target Enrollment Achieved; Topline Data Expected in 2Q2020

**Open-LaBel ToleRabIlity and Efficacy Study of ZYN002 Administered as a Transdermal Gel to CHildren and AdolescenTs with Autism Spectrum Disorder**



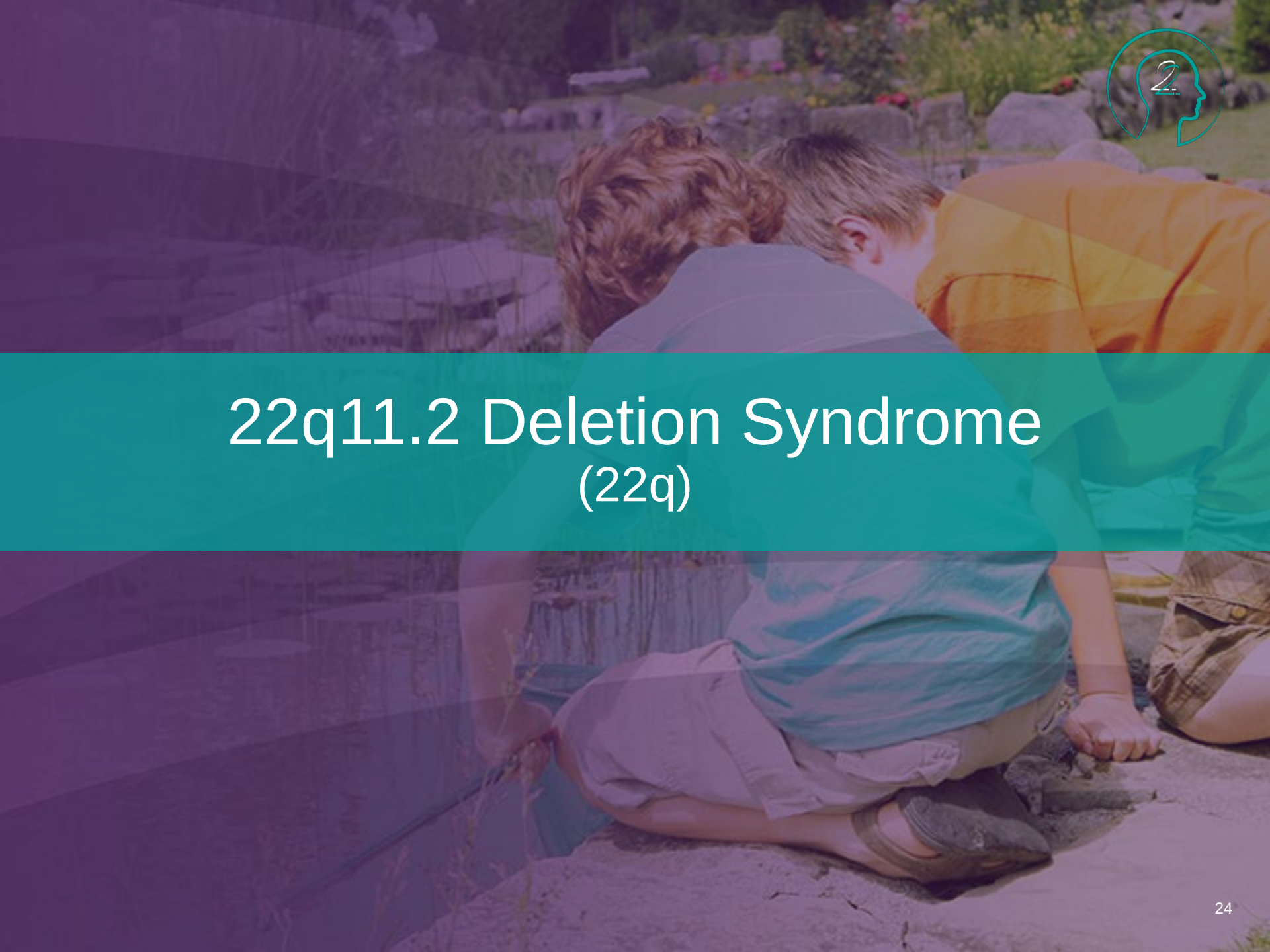

Efficacy assessments (week 14 vs baseline) include:

- Aberrant Behavior Checklist
- Parent Rated Anxiety Scale – Autism Spectrum Disorder
- Autism Impact Measure
- Clinical Global Impression – Severity and Improvement

# BRIGHT Trial Patient Demographics

36 patients enrolled in the BRIGHT trial:

- 94% of patients have moderate to severe symptoms of ASD at baseline as measured by the Autism Diagnostic Observation Schedule (ADOS-2)
- Mean baseline ABC-C Irritability subscale: 30.0
- 33 (92%) are male
- Mean age: 9.3 years



# 22q11.2 Deletion Syndrome
## (22q)

# 22q Overview

- Most common contiguous gene deletion syndrome
- Rare disorder: ~81K patients in US
- Midline condition with abnormalities affecting palate, face, heart and other organs; surgically corrected in infancy
- Neuropsychiatric illnesses (anxiety disorders, ASD) and learning disabilities common and impactful
  - 22q associated with increased anxiety, withdrawn behavior and social interaction problems
  - Early onset of neuropsychiatric symptoms disrupts development and QOL, and heightens risk of later psychotic disorders
    - 25-fold increased risk of developing schizophrenia vs. 1% lifetime risk in general population

# 22q Patient Management

- Two primary stages of 22q patient management:
  - During infancy, doctors address acute physical concerns, such as anomalies of heart and palate, with surgery
  - Once the physical concerns are stabilized, focus shifts to managing neuropsychiatric symptoms, such as anxiety and autistic behaviors
- No approved drugs indicated for 22q

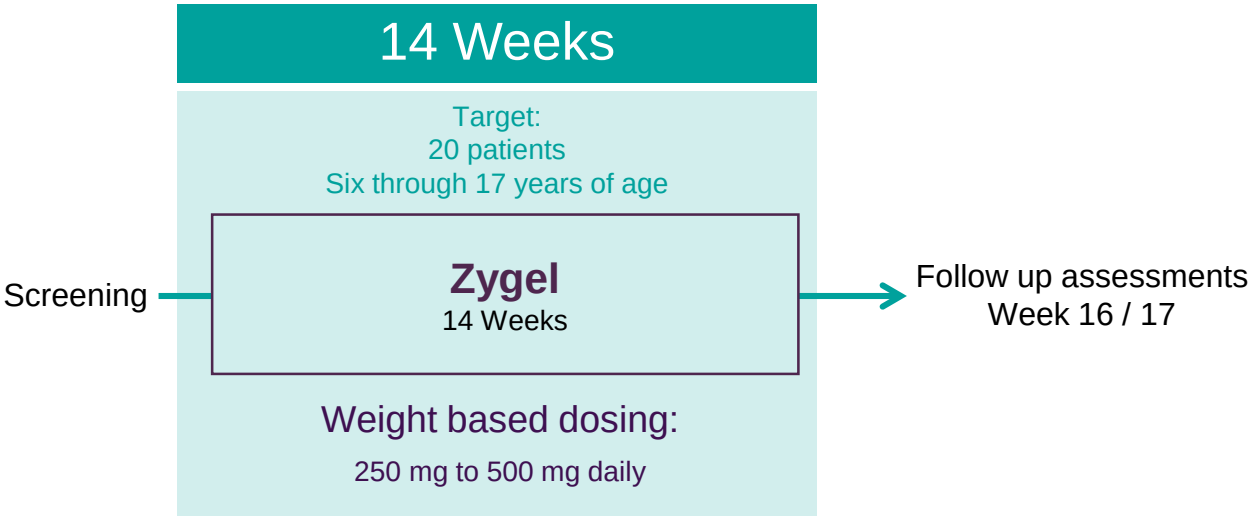
# Developing Zygel in 22q

- CBD may treat neuropsychiatric symptoms in 22q due to activity as:
  - Modulator of endocannabinoid system
  - Agonist at serotonin$_{1A}$ receptors
  - Antagonist at GPR55 receptors
- Early control of anxiety may delay the development of psychosis
- Phase 2 study underway in pediatric and adolescent patients with 22q
- Top line results expected in 2Q2020

# INSPIRE Phase 2 Trial in 22q

## Enrollment Ongoing; Topline Data Expected in 2Q2020

### Assessing the Impact of Zygel (Transdermal CBD Gel) on Pediatric Behavioral and Emotional Symptoms of 22q11.2 Deletion Syndrome




Efficacy assessments (week 14 vs baseline) include:

- Aberrant Behavior Checklist-Community (ABC-C)
- Anxiety, Depression and Mood Scale (ADAMS)
- Qualitative Caregiver Reported Behavioral Problem Survey
- Clinical Global Impression – Severity and Improvement

# DEE
## Developmental and Epileptic Encephalopathies

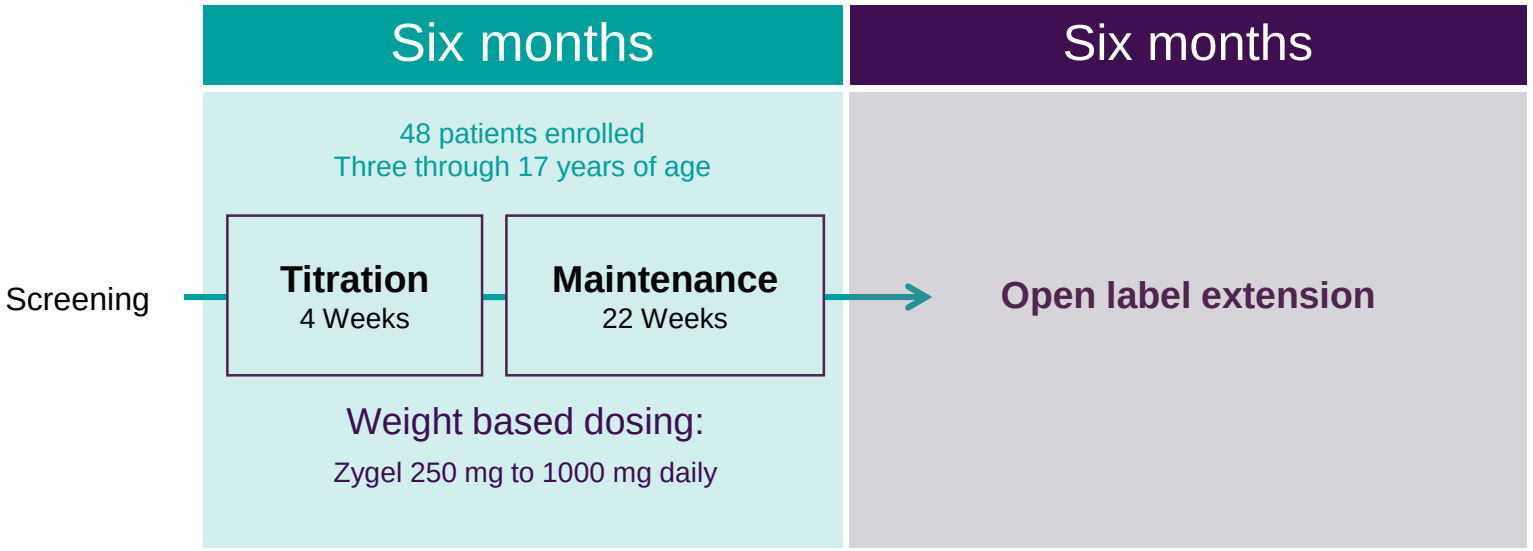
# DEE Patients are Medically Fragile

- Group of rare / ultra rare childhood-onset epilepsies with impaired or regressed developmental progress
- Cognitive impairment, psychiatric problems, and behavioral disturbances are phenotypic
- Medically fragile population
  - Comorbidities include cerebral palsy, chronic respiratory infections, gait disturbances, movement disorders, scoliosis, and feeding problems
  - Many wheelchair bound with feeding tubes
- Most common and debilitating seizure types in DEEs are:
  - Focal impaired-awareness seizures (FIAS) – formerly known as complex partial
  - Focal to bilateral tonic-clonic and generalized tonic-clonic seizures – commonly known as convulsive seizures (CS)

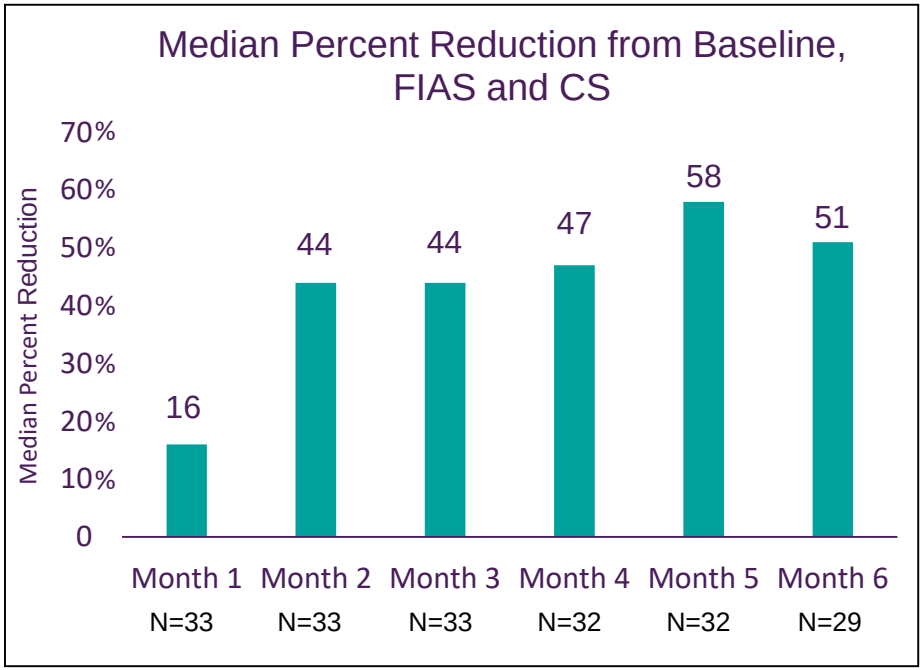
# BELIEVE 1 Phase 2 Trial in DEE

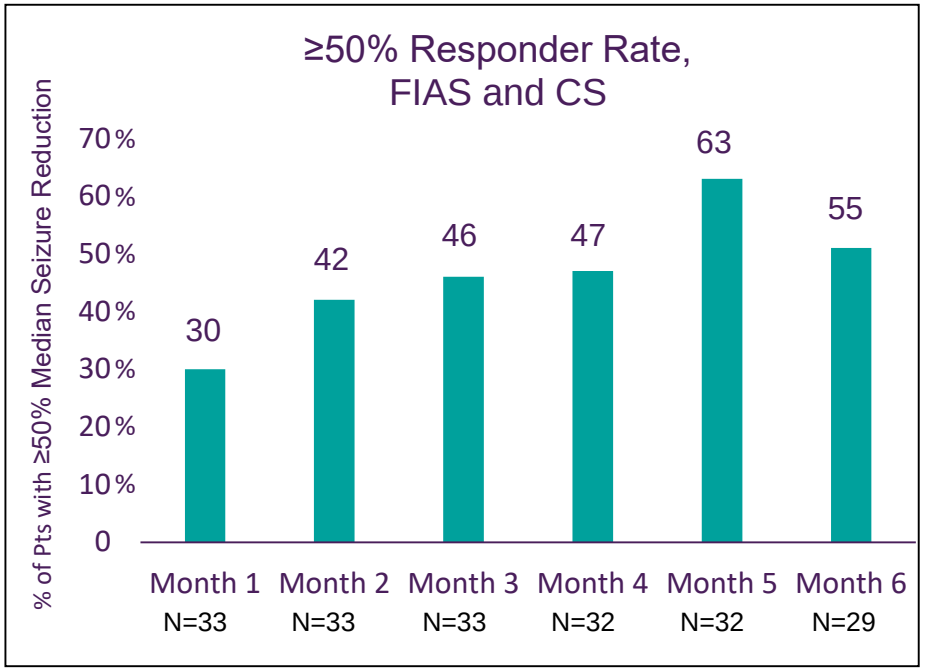
**Completed; Reported Positive Topline Results on 9/18/19**

**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**



# BELIEVE 1: Clinically Meaningful Seizure Reductions from Baseline and Sustained through Six Months in DEE



# BELIEVE 1 Safety

## Well Tolerated in this Six Month Trial

- All events in six month period, whether unrelated or related to study, drug are reported as adverse events (AEs) (e.g.: influenza, runny nose, ingrown toenail, scrapes, etc.)
- AEs common in this medically fragile population, and expected in a six-month trial
  - As a result, most patients experienced an AE
    - Most were mild and transient
    - Only one patient discontinued due to an AE (application site reaction)
  - Low rate of serious adverse events (SAE)
    - Only two SAEs deemed possibly drug-related (LRTI and status epilepticus)
    - No drug-related hepatic, gastrointestinal, or lethargy-related SAEs
- Tolerability profile consistent with the safety database for Zygel
  - May compare favorably to tolerability profiles of reported safety data from oral CBD solution[1] and other currently available AEDs[2]

[1]Devinsky - *Lancet Neurol* 2016

[2]Moavero – *Expert Opin Drug Saf*, 2018

# BELIEVE 1: Qualitative Assessments of Behavioral and Cognitive Improvements

- Parents and caregivers provided qualitative assessment on their child's overall experiences with Zygel
- Improvements were seen in seizure intensity and duration, and socio-behavioral and cognitive impairments
- Improvements in >25% of children:
  - 58% reported improved vitality (e.g. alertness / awareness, energy)
  - 51% reported improvement in seizures
  - 47% reported improved cognition and concentration
  - 44% reported improved socially avoidant behaviors
  - 28% reported that their child attended school on time / more often
- Improvements in socio-behavioral and cognitive impairments provide additional confidence in design of FXS, ASD and 22q11.2DS (22q) studies

# Compelling Results Suggest a Pathway to Pivotal Trials

## Anticipate Meeting with FDA in 1H2020

- Efficacy results:
  - Clinically meaningful reductions in seizures beginning in month two and sustained through six months
  - Suggest improvements on important behavioral symptoms
- Safety results:
  - Zygel was well tolerated
  - Consistent with previously reported Zygel studies
  - May compare favorably to tolerability profiles of reported safety data from oral CBD solution[1] and other currently available AEDs[2]
- Zynerba approach to FDA approval will likely focus on most common and disabling seizure types in DEE, rather than patient syndromes

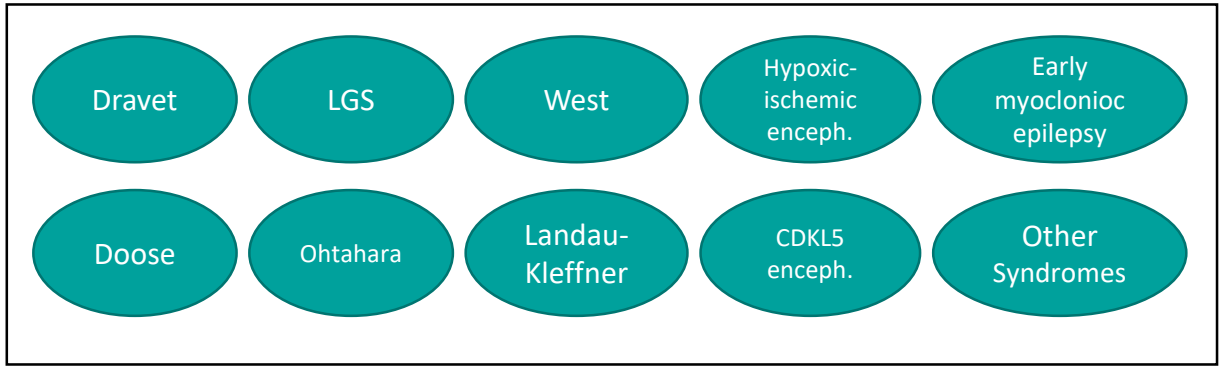
[1]Devinsky - *Lancet Neurol* 2016

[2]Moavero – *Expert Opin Drug Saf*, 2018

# Planned Approach to FDA

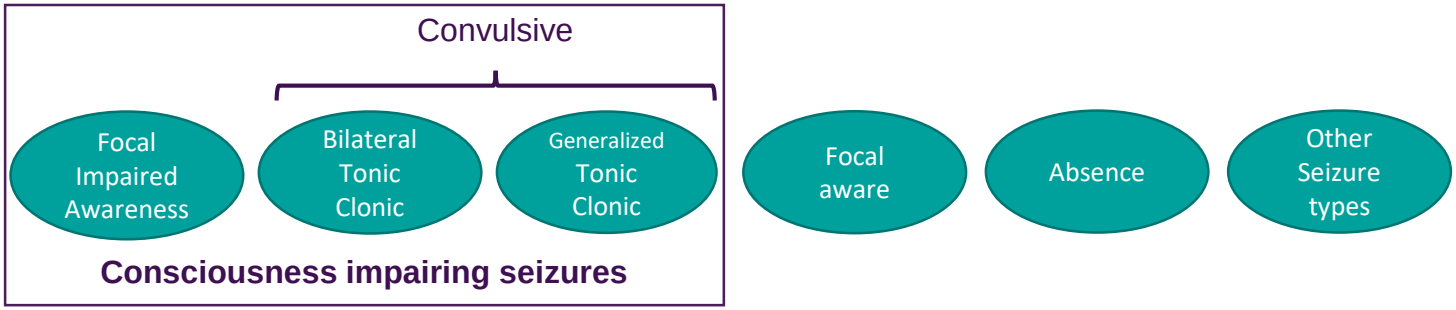
## All DEE Patients with Consciousness Impairing Seizures

### Syndromes and encephalopathies




### Zynerba Planned Approach

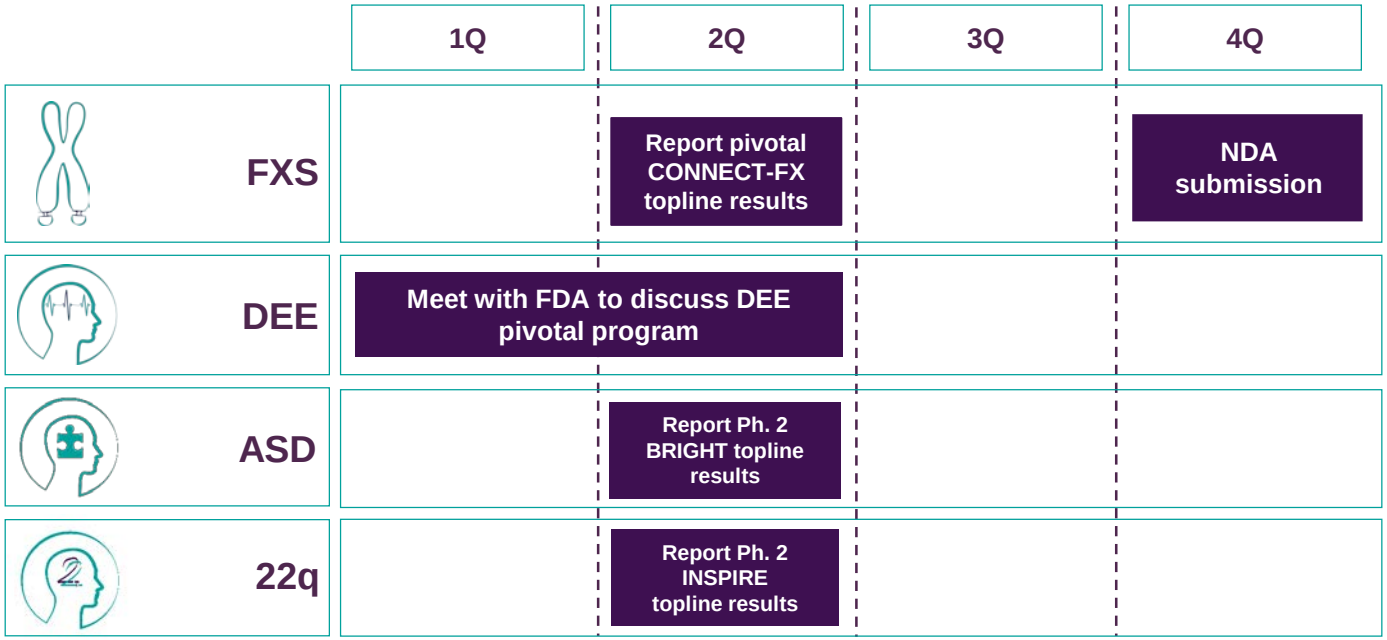
**Seizure type**



# Financial Strength

- Clean balance sheet
  - No debt, 23.2M shares outstanding (as of November 1, 2019)
- Cash and cash equivalent position of $77.5M as of September 30, 2019
- Cash expected to be sufficient to fund operations and capital requirements into the second half of 2021
  - Beyond the expected NDA submission and potential approval in FXS

# Expected Clinical Milestones in 2020

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