
# Corporate Overview

**May 27, 2020**

# 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 ADDITIONAL TRIALS AND MAY NOT OTHERWISE SUPPORT FURTHER DEVELOPMENT IN A SPECIFIED INDICATION OR AT ALL; 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; AND 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.

# 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
  - Positive results announced in BRIGHT trial in ASD including statistically significant and clinically meaningful improvements from baseline in all subscales of the ABC-C
  - Enrollment complete in pivotal CONNECT-FX trial in FXS with topline results expected in late June 2020
- 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

# COVID-19 Preparedness

- We believe we have made smart and actionable adjustments in response to COVID-19:
  - These include remote site monitoring and remote visits using telemedicine where needed
  - Our approach is consistent with FDA's Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic
- As of now, our timelines for delivery of top line results from all of our ongoing trials remain unchanged
  - Includes our expectation of results from our pivotal CONNECT-FX trial in FXS late in late June 2020

# Deep Clinical Pipeline

**Zygel**
Cannabidiol Gel

| Indication | Preclinical | Phase 1 | Phase 2 | Pivotal | Expected Milestones |
|---|---|---|---|---|---|
| Fragile X Syndrome (FXS)* | | | | | |
| CONNECT-FX: Enrollment complete | | | | | **Topline pivotal data in late June 2020** |
| Developmental and Epileptic Encephalopathies (DEE) | | | | | |
| BELIEVE: Positive data released | | | | | **Discussions with FDA in 1H2020 to define clinical path forward** |
| Autism Spectrum Disorder (ASD) | | | | | |
| BRIGHT: Positive data released | | | | | **Meet with FDA to discuss clinical path forward in 2H2020** |
| 22q Deletion Syndrome (22q) | | | | | |
| INSPIRE | | | | | **Topline Phase 2 data in 3Q2020** |

*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**

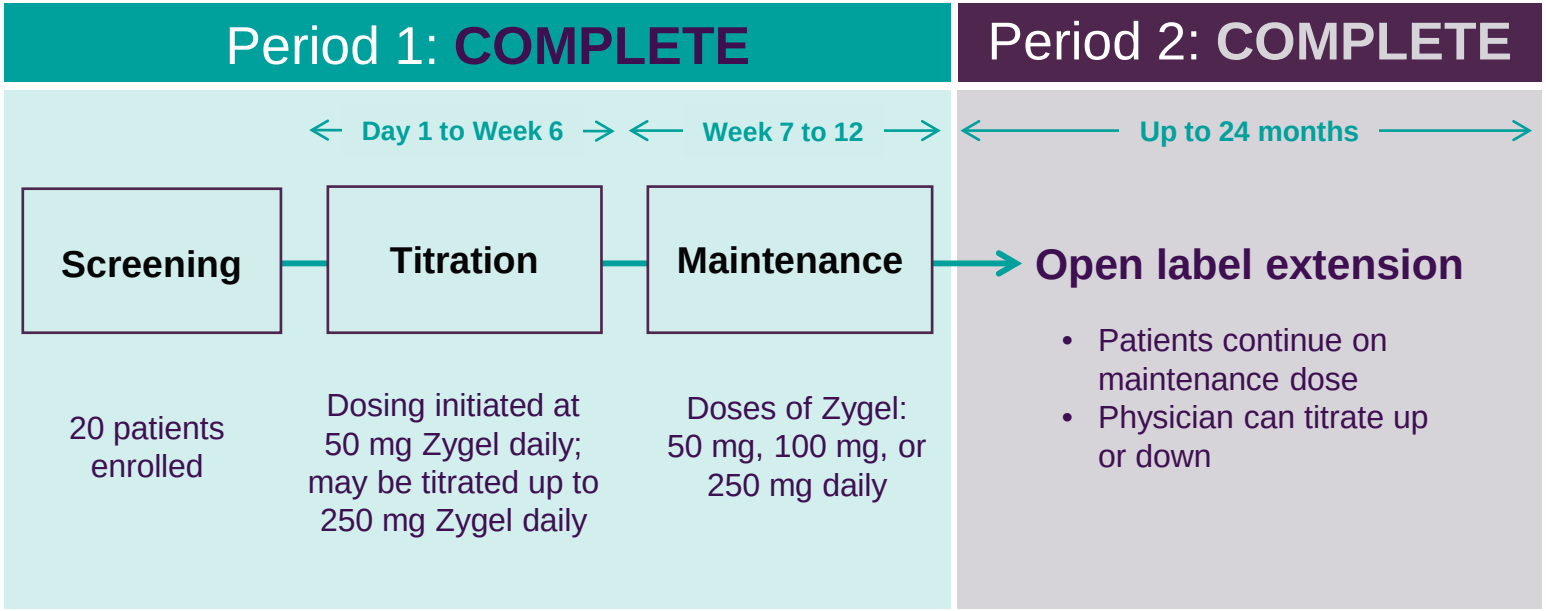
# Fragile X Syndrome (FXS)

# 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

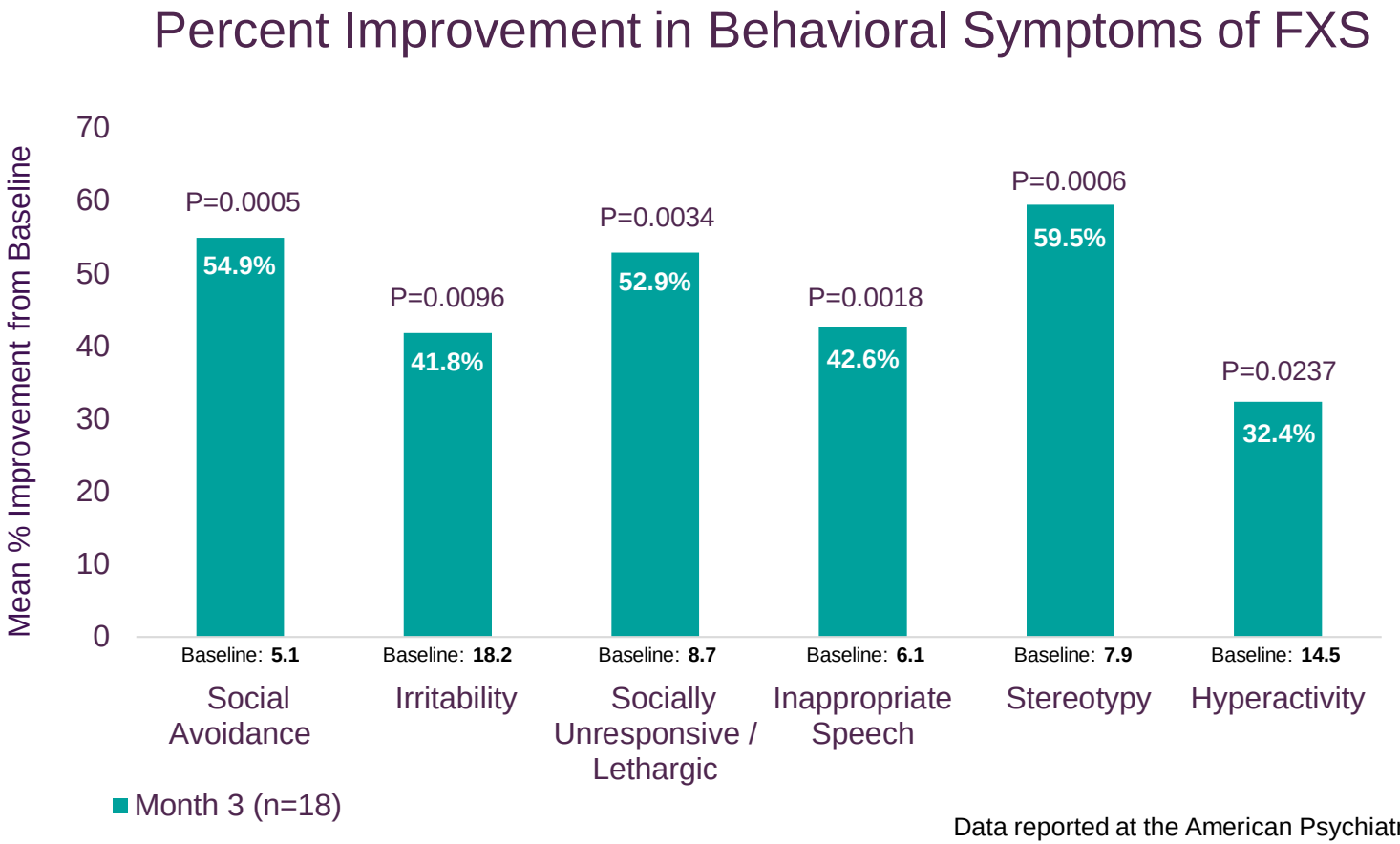
# FAB-C Open Label Phase 2 Trial Design

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



# Data From Three Month FAB-C Phase 2 Trial

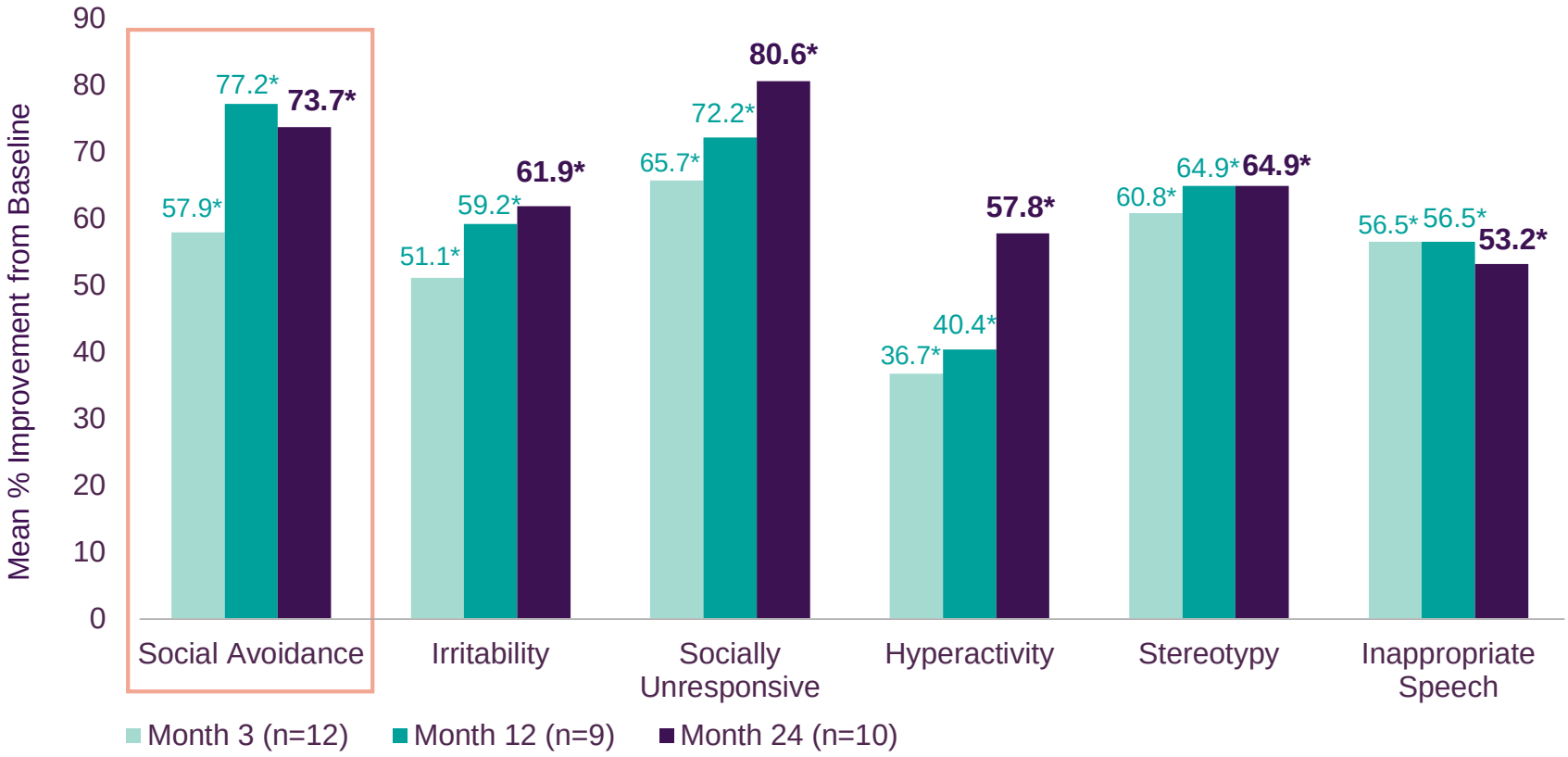
## Month Three: ABC-$C_{FXS}$ Mean Score




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

# Sustained Improvements in FXS Behavioral Symptoms Through Two Years of Treatment

## Improvements in Patients Completing 3, 12 and 24 Months




*P ≤ 0.05

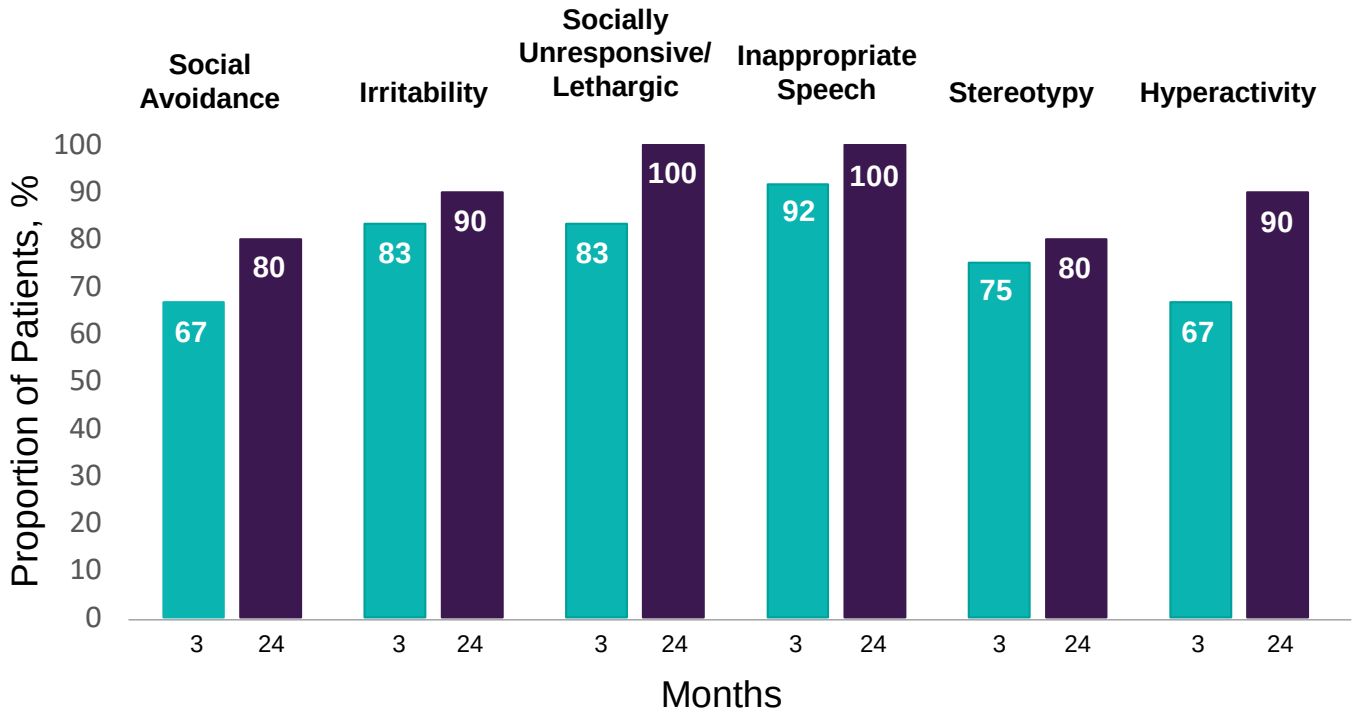
Data reported at the Data reported at the American Psychiatric Association (APA) meeting, May 2019; 2020 American Academy of Neurology (AAN) Science Highlights Virtual Session, May 2020

- Month 3 and 12 include patient completing 12 months
- Month 24 includes patients completing 24 months

# FAB-C Open Label Phase 2 Trial

## ≥25% Responder Analyses for Patients Who Entered Period 2

**Proportion of Patients with a ≥25% Improvement from Baseline ABC-$C_{FXS}$ Subscales**

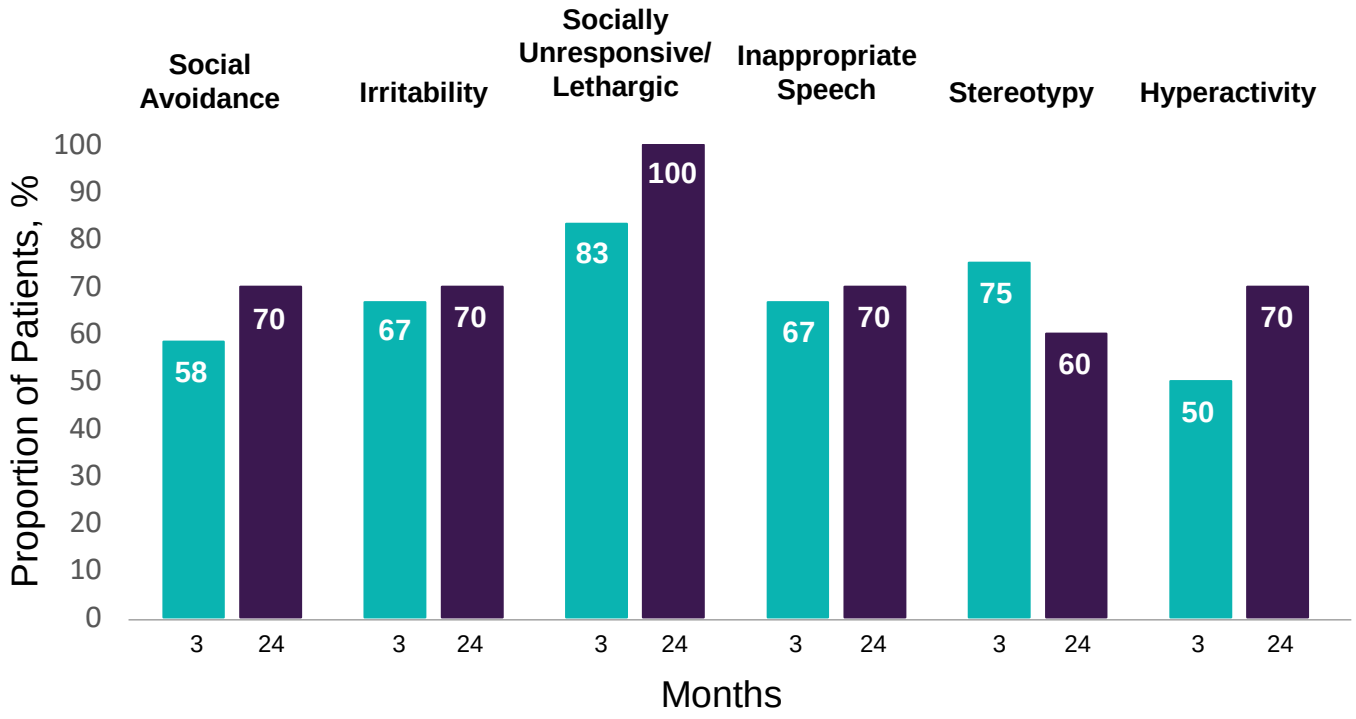



Data reported at the 2020 American Academy of Neurology (AAN) Science Highlights Virtual Session

# FAB-C Open Label Phase 2 Trial

## ≥50% Responder Analyses for Patients Who Entered Period 2

**Proportion of Patients with a ≥50% Improvement from Baseline ABC-$C_{FXS}$ Subscales**




Data reported at the 2020 American Academy of Neurology (AAN) Science Highlights Virtual Session

# FAB-C Open Label Phase 2 Trial

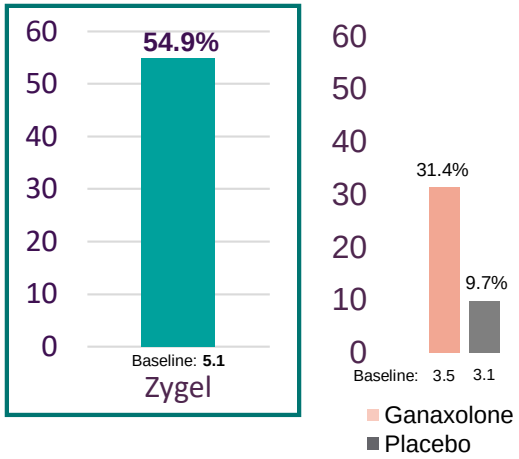
## Zygel Safety Summary Through 24 Months

- Well tolerated, consistent with previously reported data
- No drug-related SAEs
- 66 treatment-emergent adverse events (TEAE; all events, whether unrelated or related to study drug) reported in 19 patients
  - All were either mild (85%) or moderate (15%)
  - 91% were determined to be unrelated to treatment
- No treatment-related TEAEs occurred in more than one patient
- No clinically meaningful trends in vital signs, ECG, or clinical safety labs including LFTs; no THC detected in plasma

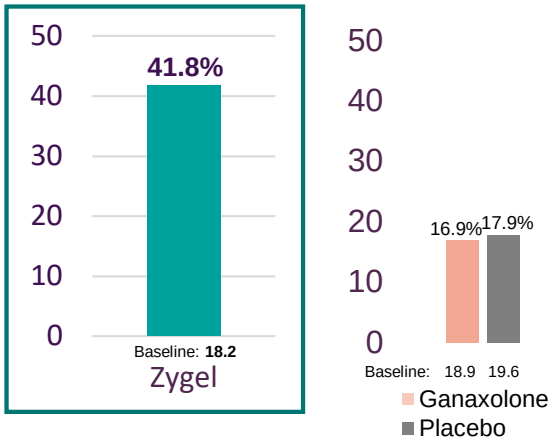
# FAB-C ABC-$C_{FXS}$ Subscales

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

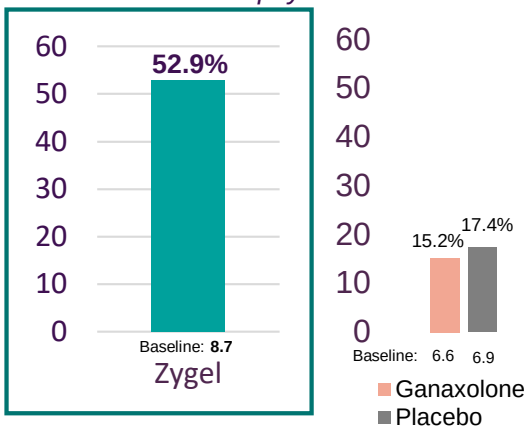
### Social Avoidance
*Seeks isolation*



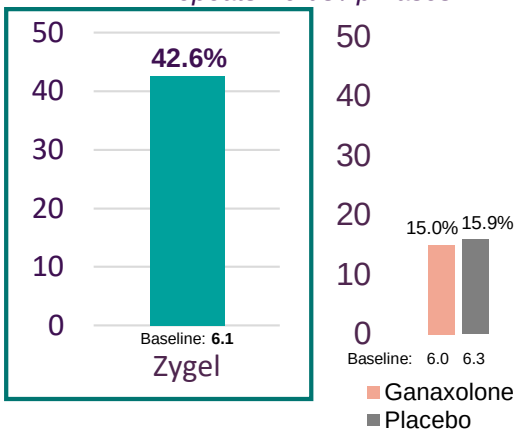

### Irritability
*Temper tantrums*



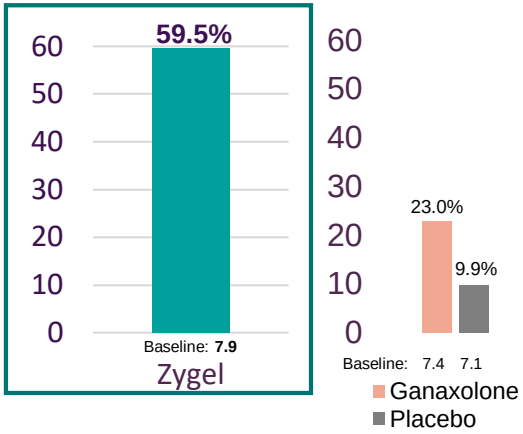

### Socially Unresponsive / Lethargic
*Does not pay attention*



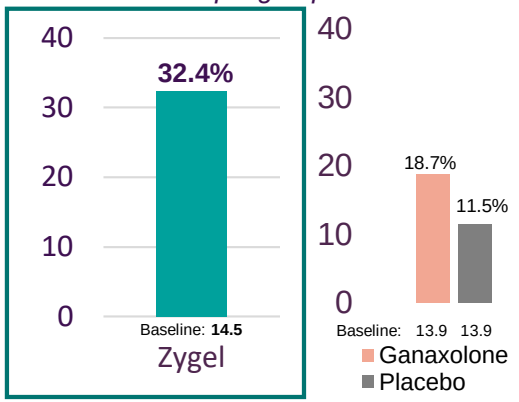

### Inappropriate Speech
*Repeats words / phrases*




### Stereotypy
*Repetitive movements*




### Hyperactivity
*Disrupts group activities*



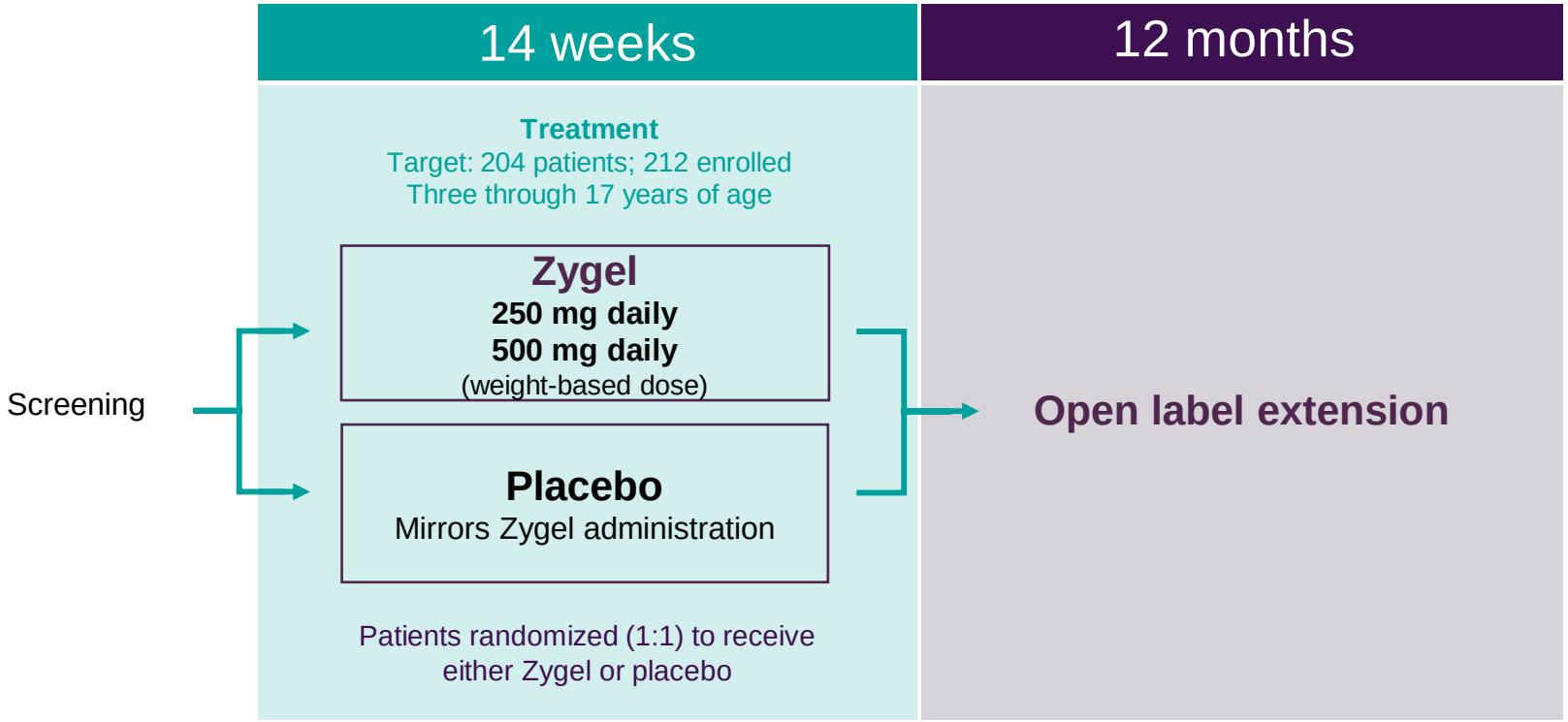



* Ligsay, A., Van Dijck, A., Nguyen, D. V., Lozano, R., Chen, Y., Bickel, E. S., et al. (2017). A randomized double-blind, placebo-controlled trial of ganaxolone in children and adolescents with fragile x syndrome. Journal of Neurodevelopmental Disorders, 9:26.

# CONNECT-FX: A Pivotal Trial In FXS

## Enrollment Complete; Topline Data Expected in Late 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 Clinical Global Impression (CGI-I) at end of treatment, anchored to FXS behaviors
- Aligned with FDA's 'Voice of the Patient' Guidance
  - Capturing qualitative data on clinical relevance of FXS behaviors
  - New data presented at ISCTM (February 2020) and ASENT (March 2020) further validate core FXS behaviors from the perspective of caregivers
- Top line results expected in late June 2020

# CONNECT-FX Demographics

| Patients | n |
|---|---|
| Randomization: Enrollment complete | 212 |
| Number of male patients | 159 (75%) |
| Mean age at randomization in study | 9.7 years |
| Completed 14-week Tx period (as of 5/8/2020) | 188 |
| Percent of completed patients enrolling in CONNECT-FX OLE | 96% |

# 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) | **18.4** | 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

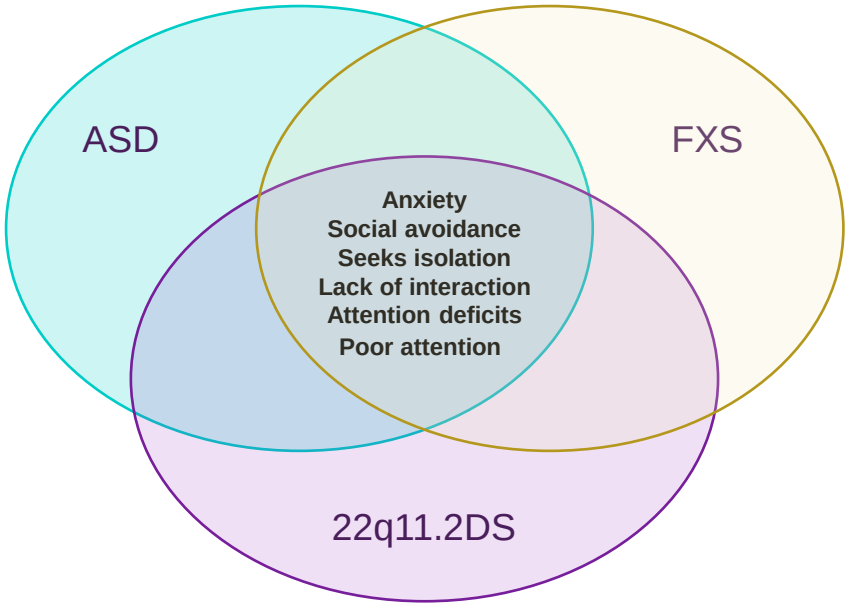
# CONNECT-FX

- 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 children and adolescents

# ASD in Pediatrics Overview

- Near-rare disorder affecting ~1MM pediatric and adolescent pts
- DSM-5 diagnosis
- Symptoms include
  - Irritability
  - 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

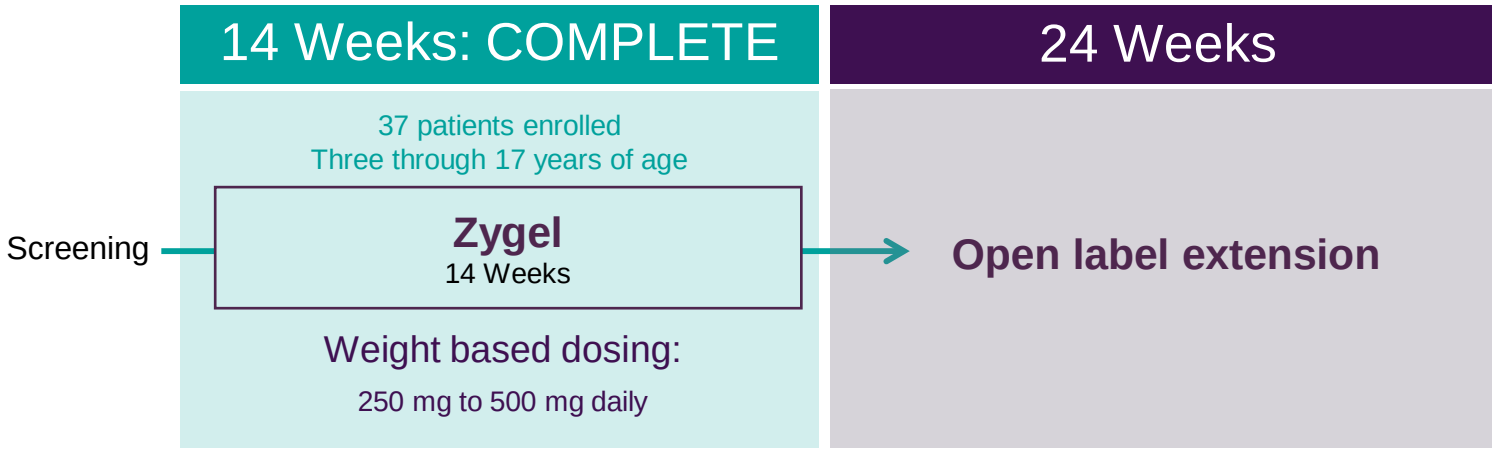
# Developing Zygel in ASD

- 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
- Children dosed with CBD displayed clinical and anecdotal data improvement in social avoidance and anxiety
  - CBD may modulate the EC system and improve certain autism-related behaviors
- Two recent US patents directed to methods of treating ASD by transdermally administering synthetic or purified cannabidiol, respectively, provide IP protection to 2038

# BRIGHT Phase 2 Trial in ASD

## Positive Topline Data Reported on May 27, 2020

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




Efficacy assessments (primary efficacy assessment = week 14 vs baseline) :

- Aberrant Behavior Checklist (ABC-C)
- Parent Rated Anxiety Scale – Autism Spectrum Disorder (PRAS-ASD)
- Autism Parenting Stress Index
- Autism Impact Measure (AIM)
- Clinical Global Impression – Improvement (CGI-I) and Severity (CGI-S)
- Qualitative Caregiver Reported Behavioral Problems Survey

# BRIGHT Trial Patient Populations

| Baseline Patient Population: BRIGHT | |
|---|---|
| Patients enrolled | N = 37 |
| Included in safety analysis | 37 |
| Included in efficacy analyses | 36* |
| Discontinuations | 9 |
| Patients completing 14-week trial | 28 |

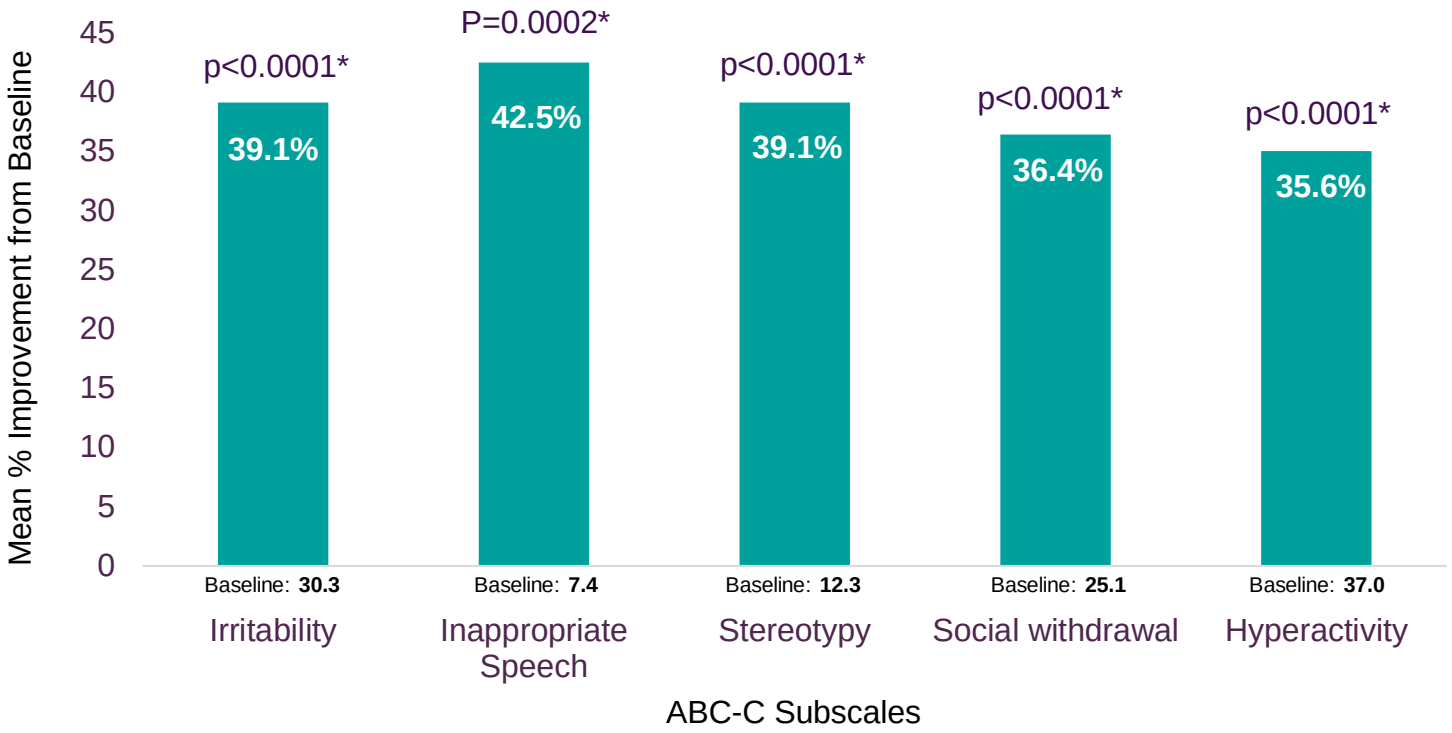
* One patient was lost to follow up and did not have post-dosing efficacy assessments

# BRIGHT Trial Patient Demographics

| Baseline Patient Demographics | |
|---|---|
| Patients enrolled, n | 37 |
| Age, years | |
| Mean (range) | 9.2 (3-16) |
| Sex, n (%) | |
| Male | 34 (91.9) |
| Female | 3 (8.1) |
| Race, % | |
| White | 70.3 |
| Asian | 8.1 |
| Native Hawaiian or other Pacific Island | 2.7 |
| Other | 18.9 |
| Time to diagnosis, years | 5.4 |
| Underlying medication, % | |
| Subjects entering with ≥1 underlying medication | 92 |
| Subjects entering with ≥1 underlying psychotropic medication (includes anti-depressants, anxiolytics and antipsychotics) | 65 |

# Percent Improvement in ABC-C Subscale Scores at Week 14 vs. Baseline

## Statistical Significance Achieved in All Subscales




* Statistically significant

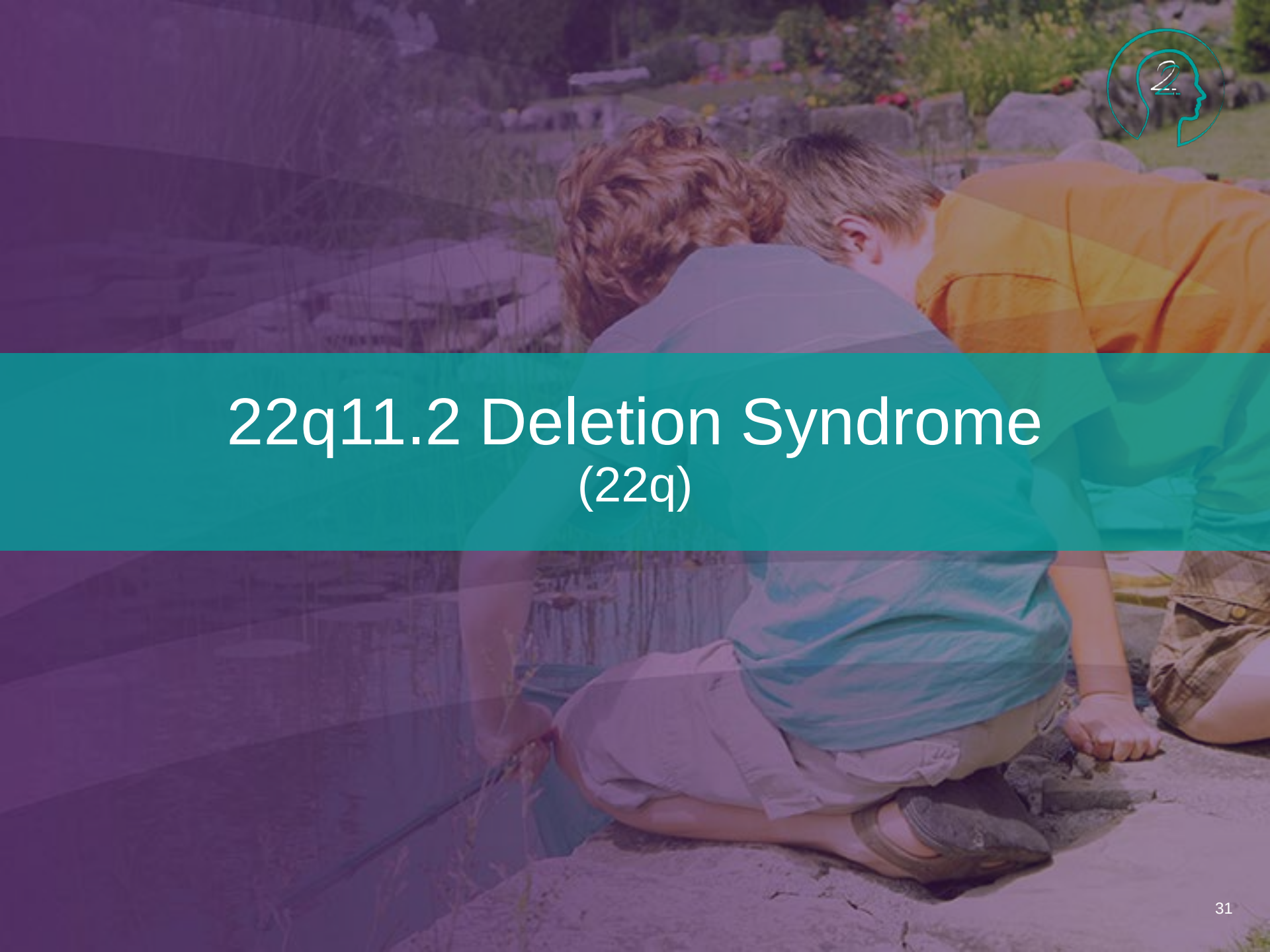
# ABC-C Responses Supported by Other Efficacy Assessments

Results of other efficacy assessments support the results demonstrated in the ABC-C, including:

- Parent Rated Anxiety Scale - Autism Spectrum Disorder (PRAS-ASD):
  - Mean improvement of 46% at week 14 from baseline ($p<0.0001$)
- Clinical Global Impression - Improvement (CGI-I)
  - 57% of patients were rated by clinician as Very Much or Much Improved at week 14
- Zynerba intends to present additional data at future medical meetings

# Strong Safety and Tolerability Profile in BRIGHT Trial in ASD

- Well tolerated; consistent with previously released data
- Fewer than half of patients experienced an AE; most were mild and transient
- Only 14% of patients experienced a treatment-related AE
  - All application site-related
- No severe or serious adverse events reported during the study.



# 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

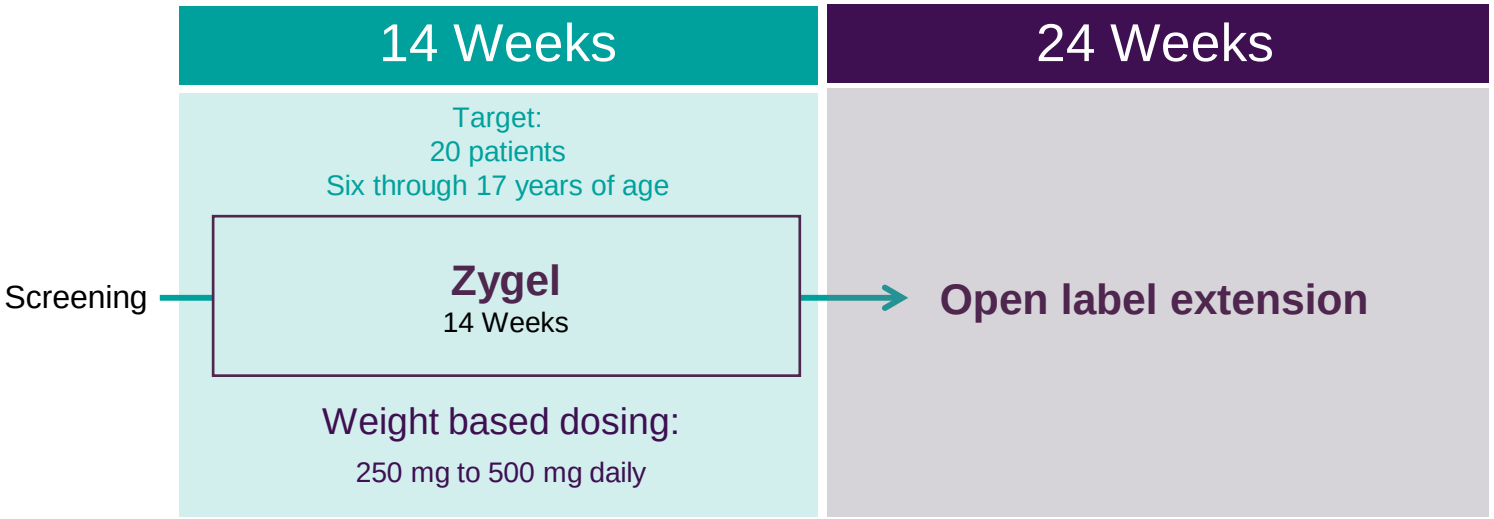
# Developing Zygel in 22q

- 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 3Q2020

# INSPIRE Phase 2 Trial in 22q

## Enrollment Ongoing; Topline Data Expected in 3Q2020

### 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

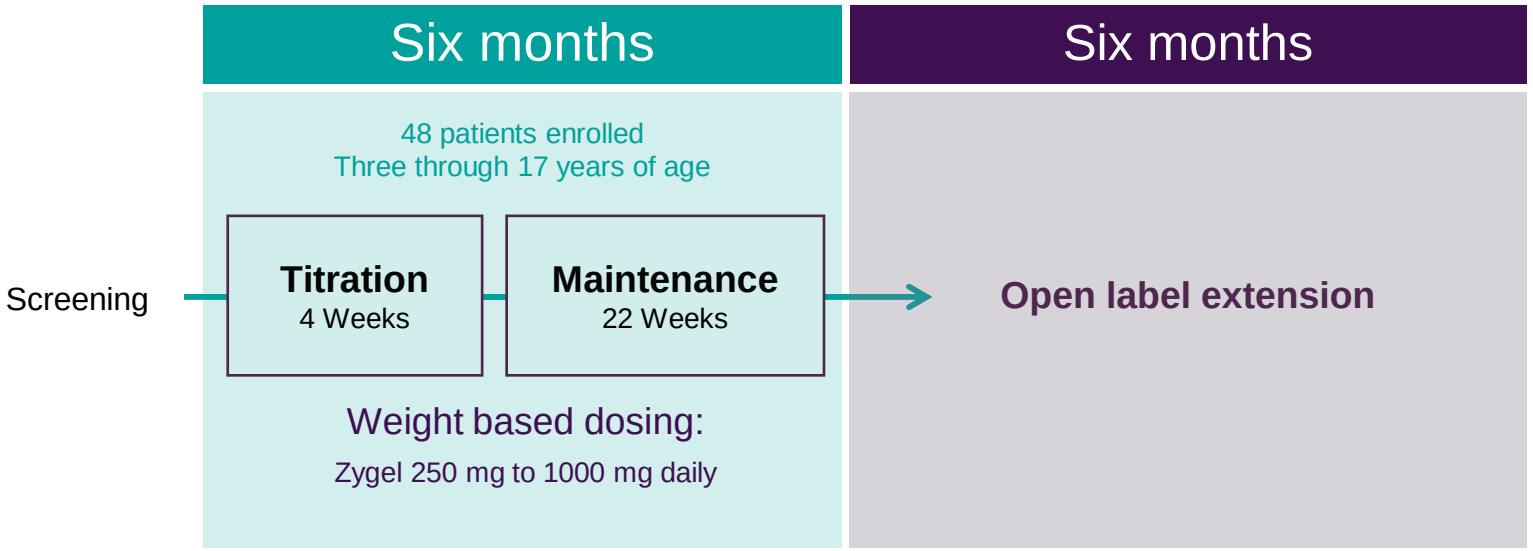
# DEE Patients are Medically Fragile

- 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)

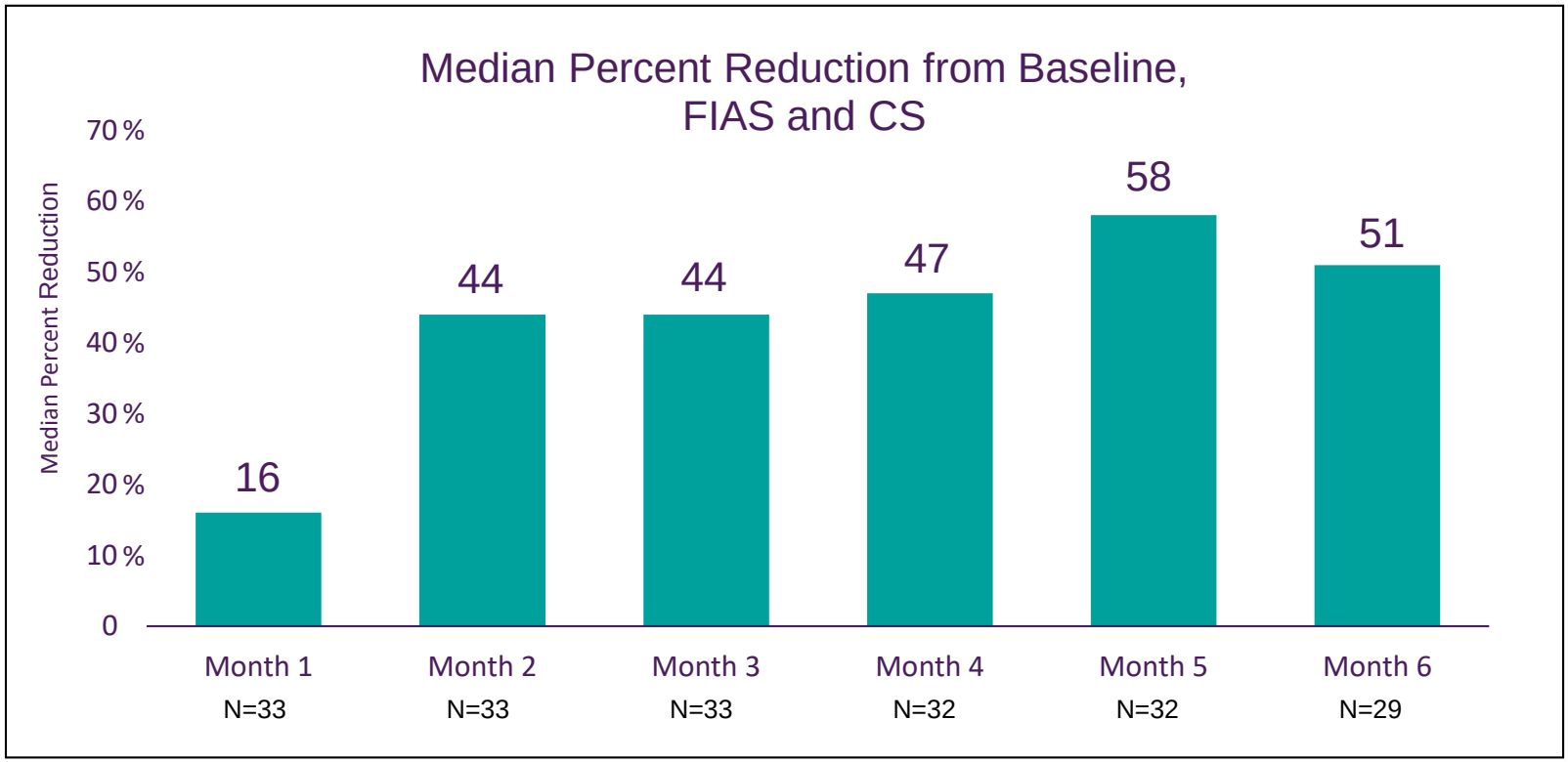
# BELIEVE Phase 2 Trial in DEE

**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**

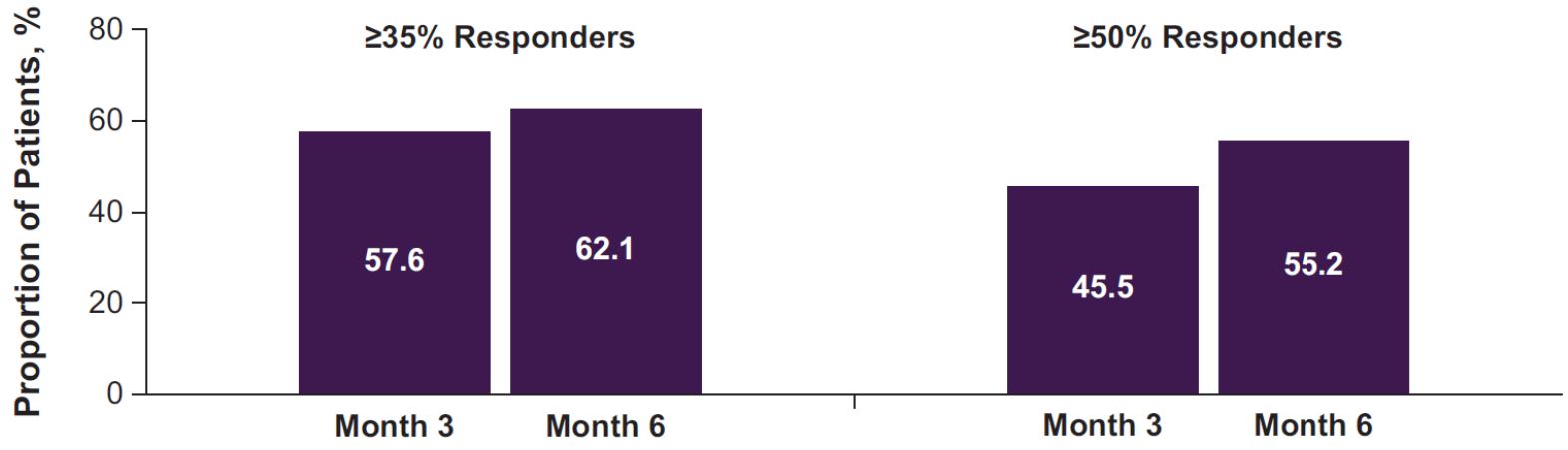


# BELIEVE: Clinically Meaningful Seizure Reductions from Baseline and Sustained through Six Months in DEE



# BELIEVE: Percentage of Patients with ≥35% and ≥50% Reduction in FIAS and TCS

≥35% and ≥50% Reduction in FIAS and TCS by Time Point, mITT Population With FIAS and/or TCS at Baseline (n = 33)




FIAS, focal impaired awareness seizures; mITT, modified intent-to-treat; TCS, tonic-clonic seizures.
Month = SF28

Data reported at the 2020 American Academy of Neurology (AAN) Science Highlights Virtual Session

# BELIEVE Safety

## Well Tolerated in this Six Month Trial: No Safety Signal Identified

- All events in six month period, whether unrelated or related to study, drug reported as adverse events (AEs) (e.g.: influenza, runny nose, ingrown toenail, scrapes, etc.)
- As a result and as anticipated, most patients experienced an AE
  - Most were mild and transient
  - Only one patient discontinued due to an AE (application site reaction)
- Most common treatment-related adverse events occurred in only four patients each:
  - application site dryness, application site pain, and somnolence (all four patients exhibiting somnolence were taking concomitant clobazam)
- 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

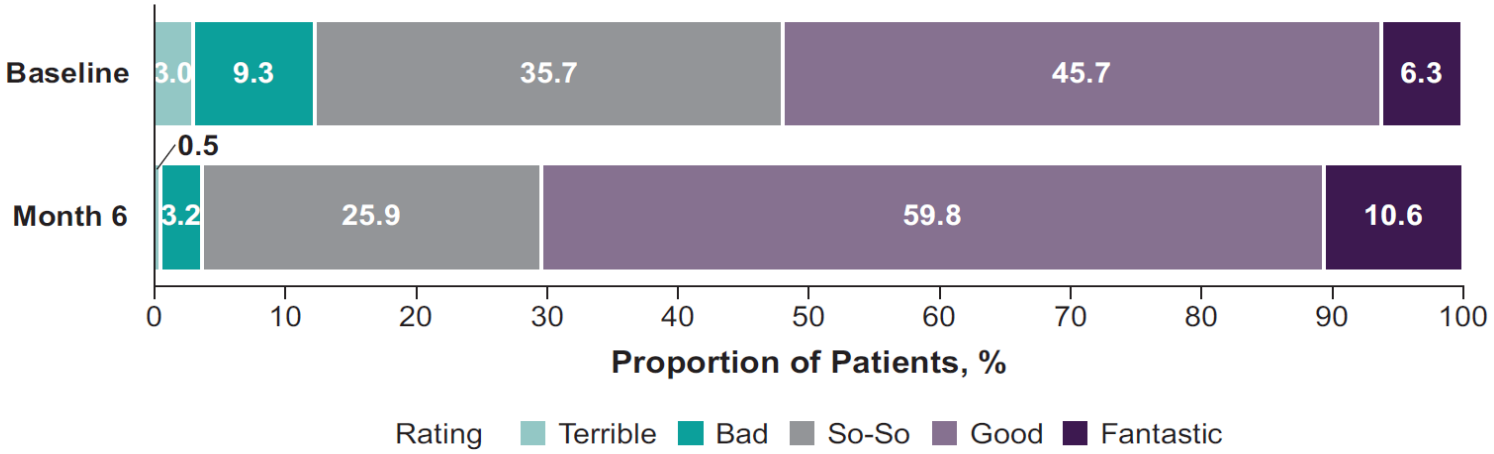
# BELIEVE: Qualitative Assessments of Behavioral and Cognitive Improvements

- Epilepsy and Learning Disabilities Quality of Life (ELDQOL) scale
  - Statistically significant reductions from baseline in subscale scores for seizure severity, behavior, and mood observed at month 6 ($p<0.01$)
- Qualitative caregiver feedback on improvements included:
  - Any improvement: 84% (n = 36)
  - Improved vitality: 58% (n = 25)
  - Improvement in seizures: 51% (n = 22)
  - Improved cognition/concentration: 47% (n = 20)
  - Improved socially avoidant behaviors: 44% (n = 19)
  - Improvement in irritability: 33% (n = 14)
  - School improvement: 28% (n = 12)
  - Medical improvement: 14% (n = 6)

Data reported at the 2020 American Academy of Neurology (AAN) Science Highlights Virtual Session

# BELIEVE: Qualitative Assessments of Behavioral and Cognitive Improvements

- Good Day/Bad Day comparing baseline to month six:
  - “Good day” and “fantastic day” reports increased from 52% to 70%
  - “Terrible day” and “bad day” reports decreased from 12% to 4%




Data reported at the 2020 American Academy of Neurology (AAN) Science Highlights Virtual Session

# Compelling Results Suggest a Pathway to Pivotal Trials

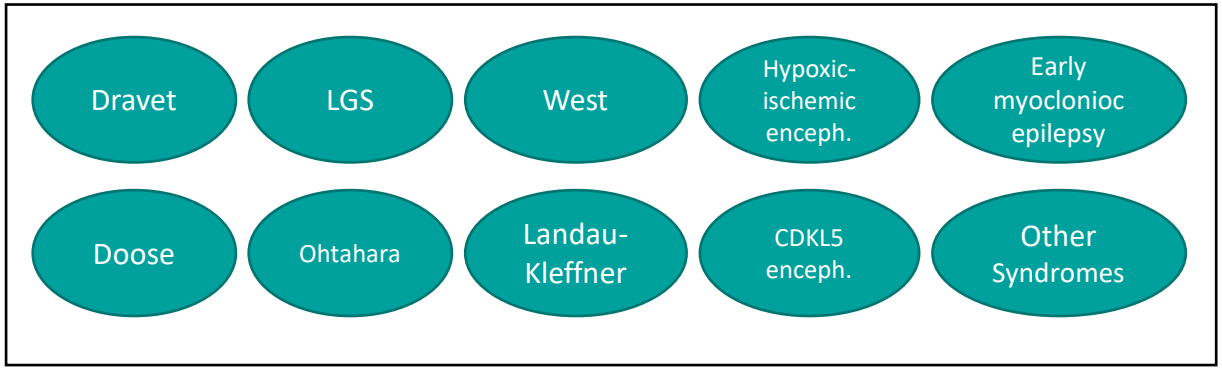
## Discussions with FDA in 1H2020 to Define Clinical Path Forward

- Zynerba engaging with FDA on next clinical steps
- 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
- Zynerba approach to FDA approval will likely focus on most common and disabling seizure types in DEE, rather than patient syndromes

# Planned Approach to FDA

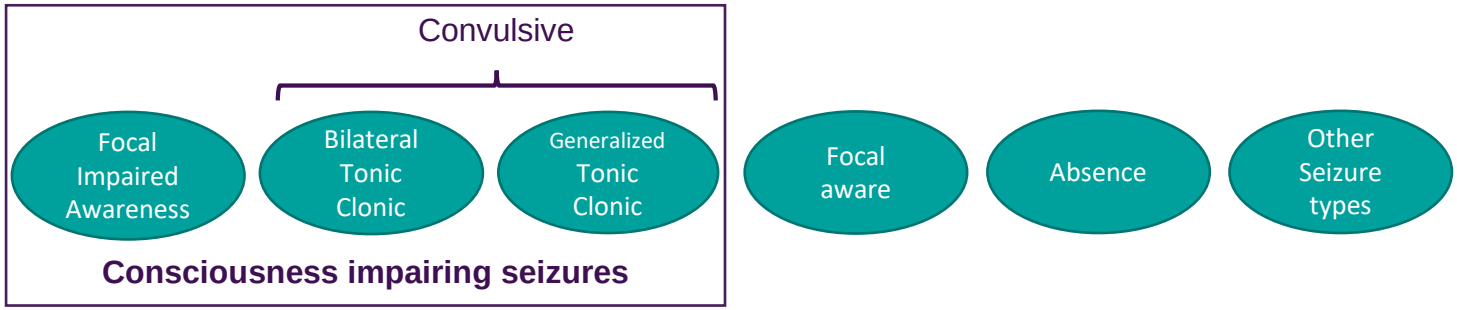
## All DEE Patients with Consciousness Impairing Seizures

### Syndromes and encephalopathies




### Zynerba Planned Approach

**Seizure type**



# Financial Strength

- Clean balance sheet
  - No debt, 25.0M shares outstanding (as of May 7, 2020)
- Cash and cash equivalent position of $60.6M as of March 31, 2020
- Cash runway 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

| | 1Q 2020 | 2Q 2020 | 3Q 2020 | 4Q 2020 |
|---|---|---|---|---|
| FXS | | Report pivotal CONNECT-FX topline results | | NDA submission |
| DEE | Discussions with FDA to define clinical path forward | | | |
| ASD | | Report Ph. 2 BRIGHT topline results | Meet with FDA to discuss clinical path forward | |
| 22q | | | Report Ph. 2 INSPIRE topline results | |


# Corporate Overview

**May 27, 2020**