



December 2018

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Zynerba Pharmaceuticals (NASDAQ: ZYNE)














A Rare/Near-Rare Neuropsychiatric Company

- Development efforts focused in rare and near rare neuropsych disorders
- Deep pipeline focused on high unmet medical needs; translating into multi-billion dollar market opportunity
 - Four clinical shots on goal: FXS, DEE, ASD, 22q
- Opportunities for efficient development and commercialization strategy
- Experienced team; proven development and commercialization track record in transdermal delivery, orphan diseases, neurology, psychiatry
- Well capitalized with cash runway expected into the second half of 2020
- Multiple expected near term milestones



Strong Clinical Pipeline



Indication	Preclinical	Phase 1	Phase 2	Pivotal	2019 Milestones
Fragile X Syndrome (FXS)*					
	 				<p>Top line CONNECT-FX data: 2H2019</p> <p>Additional long term data from FAB-C: 2019</p>
Developmental and Epileptic Encephalopathies (DEE)					
					<p>Top line BELIEVE 1 data: 3Q2019</p>
Autism Spectrum Disorder (ASD) in pediatric patients					
					<p>Initiate Phase 2 open label study: 1H2019</p>
22q Deletion Syndrome (22q)					
					<p>Initiate Phase 2 open label study: 1H2019</p>
Adult Refractory Focal Epilepsy					
					
Other neuropsychiatric conditions					
					<p>Assess other neuropsychiatric conditions: 2019</p>

*Orphan Drug Designation



ZYN002 Cannabidiol (CBD) Gel

Differentiated



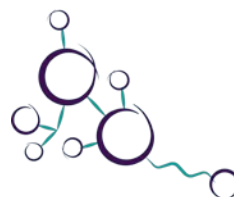
First & only patent-protected, permeation-enhanced, pharmaceutically-produced CBD gel

Transdermal

CBD

Formulation delivers CBD through the epidermis and into the circulatory system

Unique MOA



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

Neuropsych Indications



Potential utility in rare / near-rare neuropsychiatric conditions

Orphan Drug designation 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
 - ECs form 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
- Affects ~71K people in U.S.
- No approved drugs indicated for FXS



Fragile X Clinical Program



Recent ZYN002 Development Progress

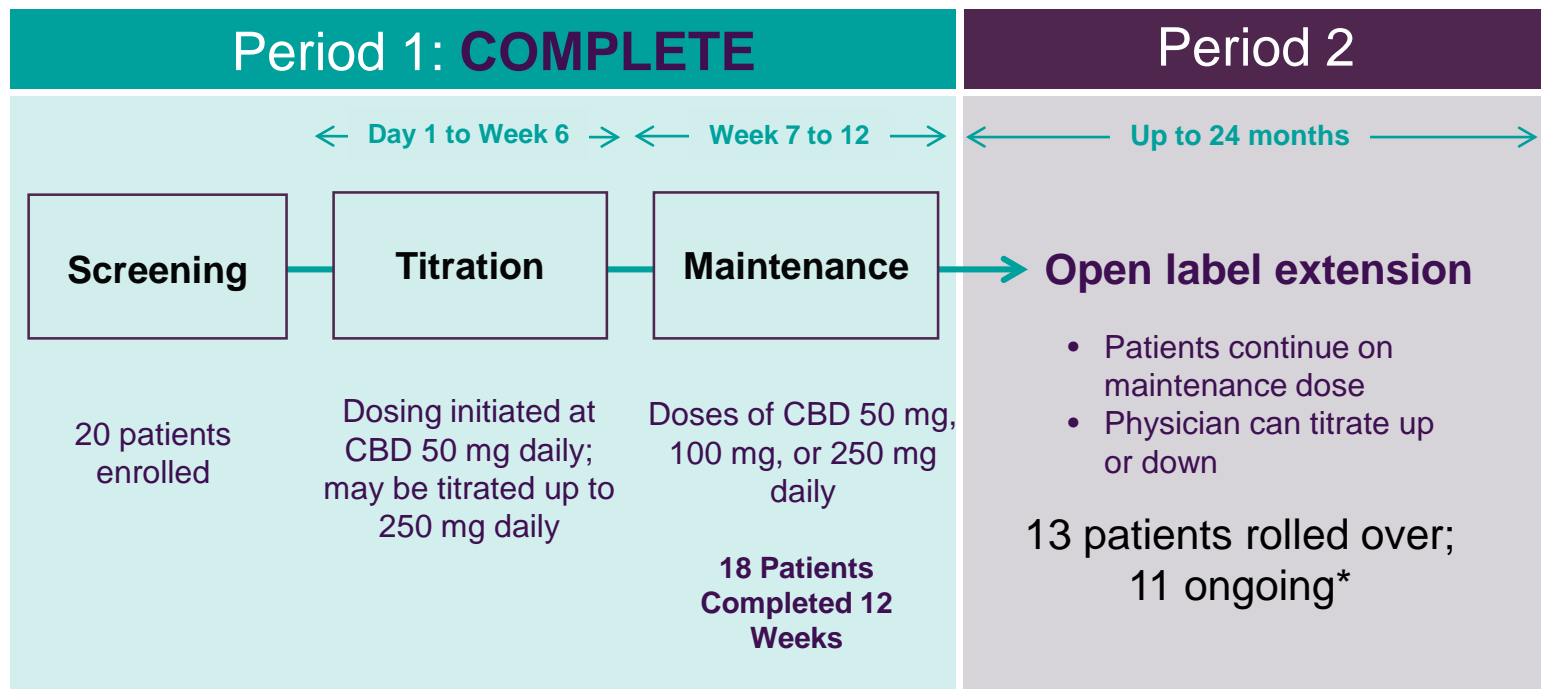
- Presented 12-month FAB-C open label Phase 2 data at American College of Neuropsychopharmacology meeting (ACNP; Dec. 2018)
 - Statistical improvement from baseline in FXS phenotypic behaviors including social avoidance, anxiety, and irritability
 - Three month improvements sustained through 12 months of treatment
 - Excellent tolerability profile
- Enrollment ongoing in CONNECT FX: a pivotal trial in pediatric and adolescent patients with FXS
 - Initiated July 2018
 - Top line results expected in 2H2019



FAB-C Open Label Phase 2 Trial Design



Treatment of **F**ragile X Syndrome **A**nxiety and **B**ehavioral **C**hallenges with CBD



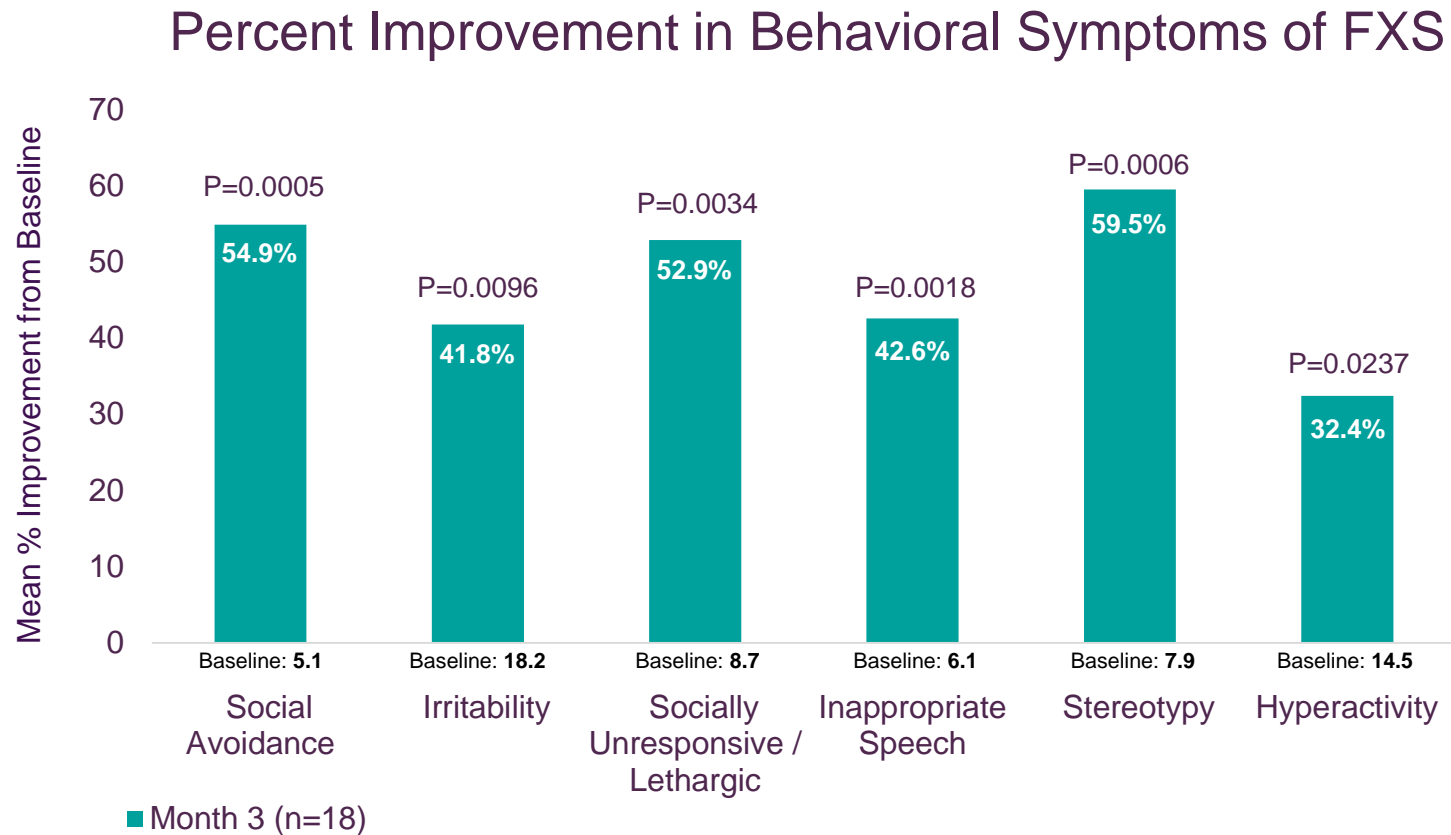
*As of November 2018





FAB-C Open Label Phase 2

Month Three: ABC-C_{FXS} Mean Score

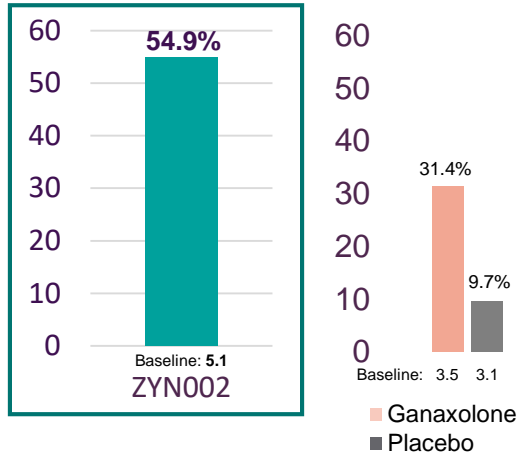




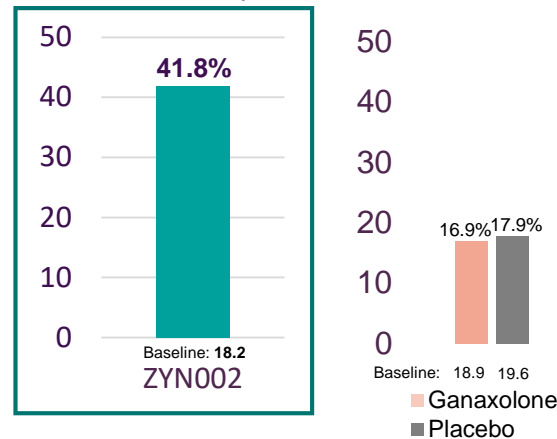
FAB-C ABC-C_{FXS} Subscales

Month Three: Percent Improvement vs. 3rd Party Data*

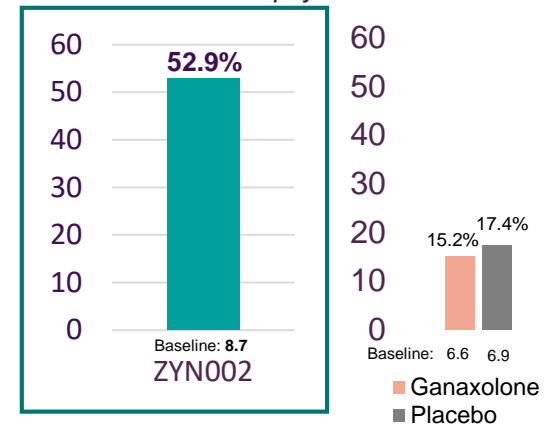
Social Avoidance
Seeks isolation



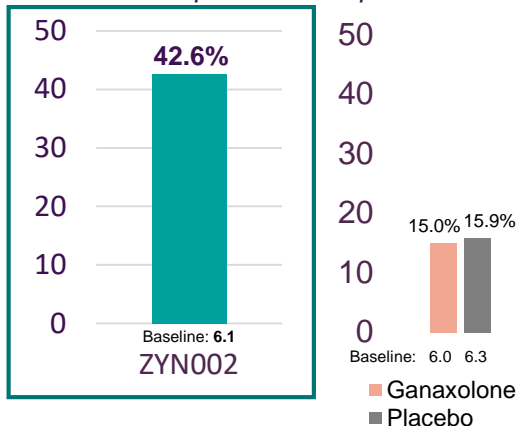
Irritability
Temper tantrums



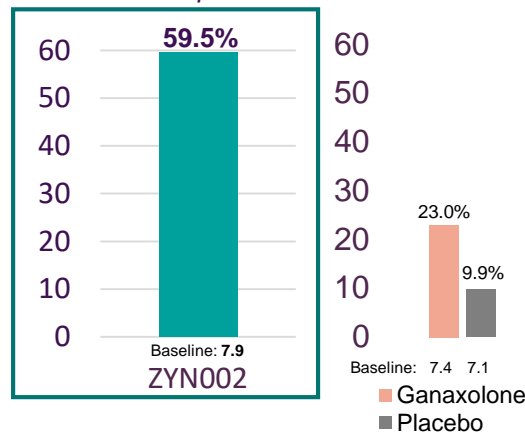
Socially Unresponsive / Lethargic
Does not pay attention



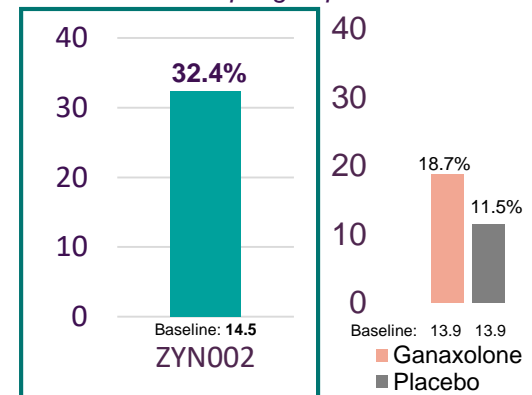
Inappropriate Speech
Repeats words / phrases



Stereotypy
Repetitive movements



Hyperactivity
Disrupts group activities

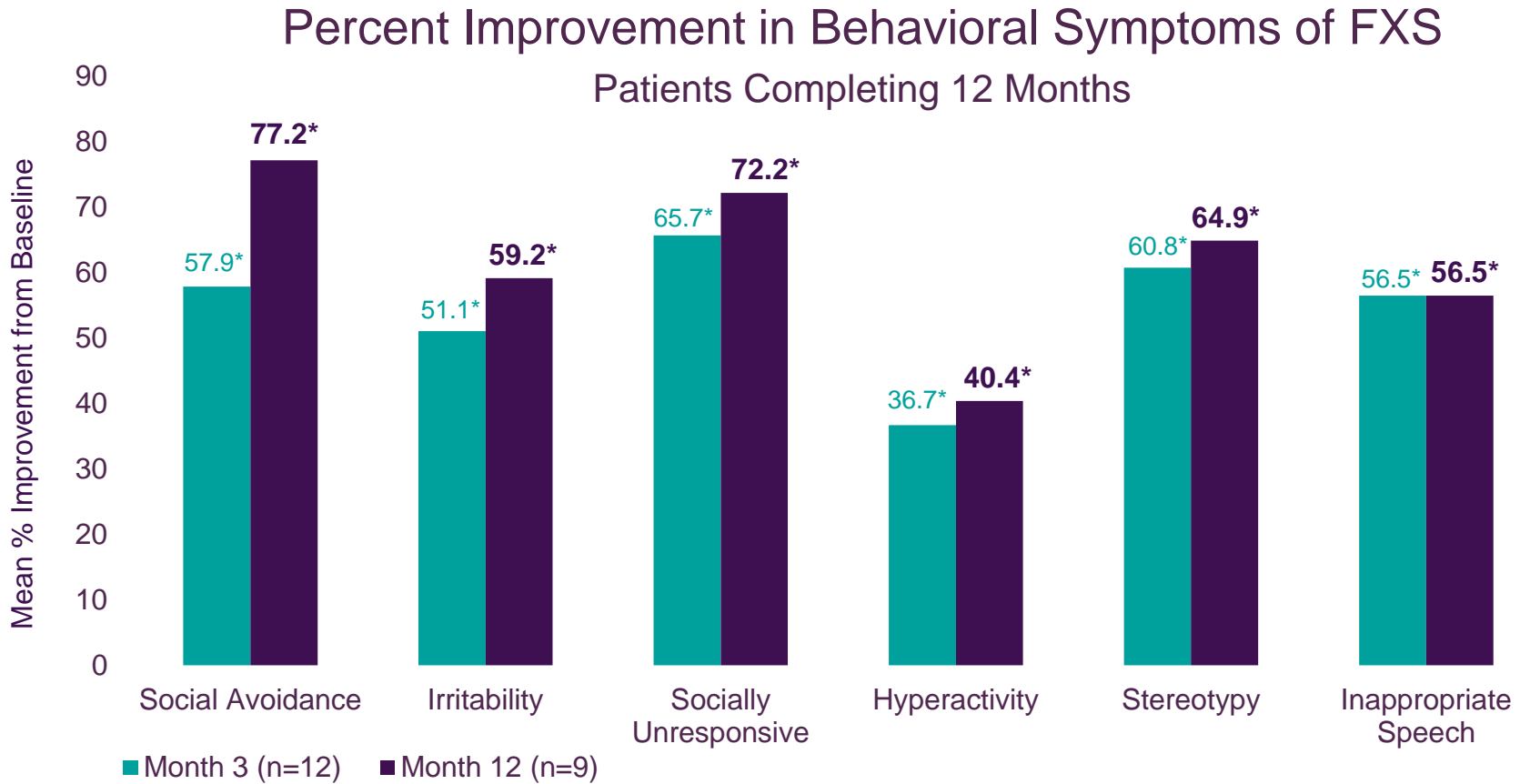


* Ligsay, A., Van Dijk, A., Nguyen, D. V., Lozano, R., Chen, Y., Bickel, E. S., et al. (2017). A randomized double-blind, placebo-controlled trial of ganaxolone in children and adolescents with fragile x syndrome. *Journal of Neurodevelopmental Disorders*, 9:26.



FAB-C Open Label Phase 2

Month 12: ABC-C_{FXS} Mean Score



*P ≤ 0.05

Data from American College of Neuropsychopharmacology (ACNP) meeting, December 2018





FAB-C Open Label Phase 2

Safety Summary Through 12 Months

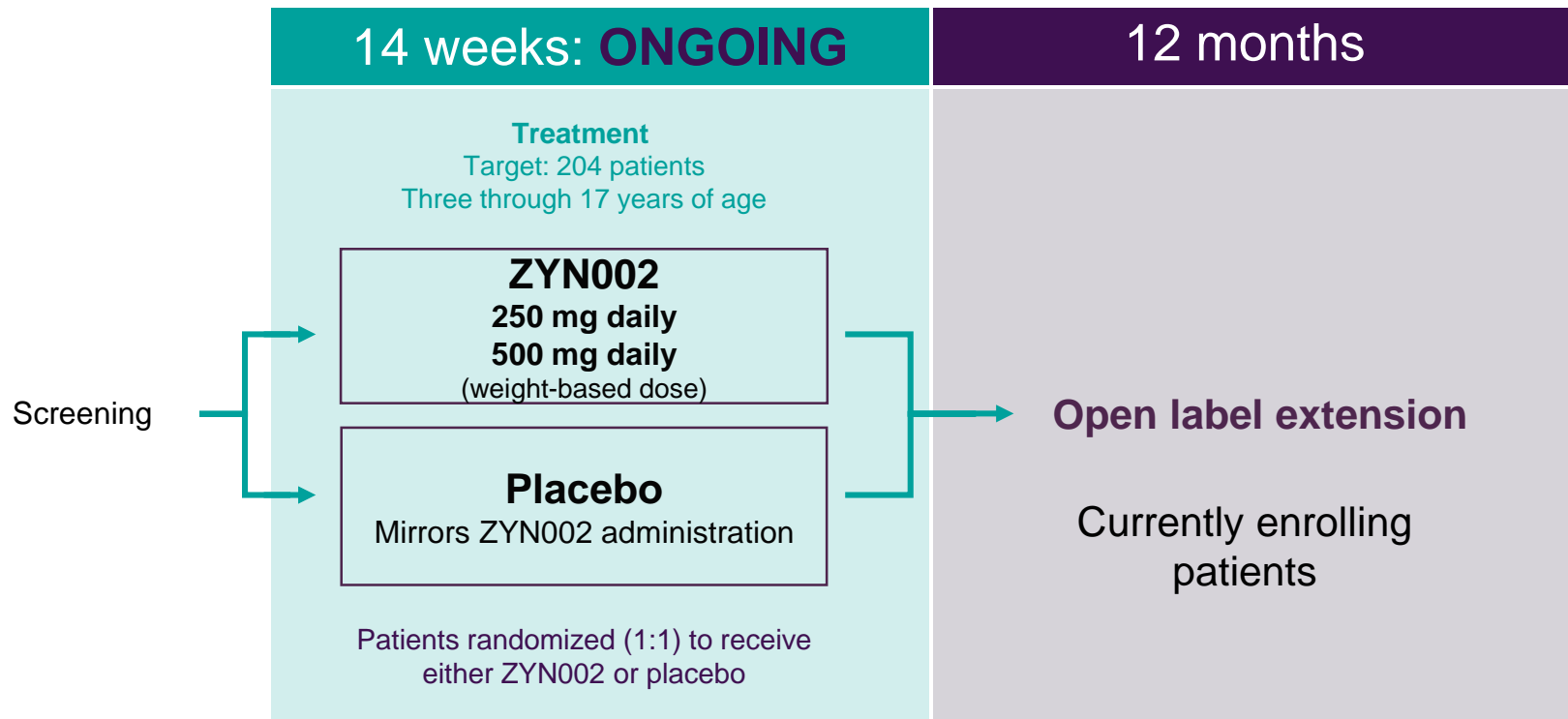
- Well tolerated, consistent with previously reported data; no SAEs
- No clinically meaningful trends in vital signs, ECG, or clinical safety labs including LFTs; no THC detected in plasma
- Discontinuations
 - Two siblings discontinued in Period 1
 - One for worsening of pre-existing eczema (not considered Tx-related)
 - One due to administrative reasons
 - One patient discontinued in Period 2 for administrative reasons
- 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



Clinical study Of CaNNabidiol (CBD) in ChildrEn and AdolesCentTs 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



CONNECT-FX



Top Line Results Expected in 2H2019

- With positive results, Zynerba intends to request a meeting with the FDA to:
 - Determine acceptability of data as basis for NDA filing
 - Seek advice on marketing authorization preparation
- Zynerba believes indication may include the treatment of behavioral symptoms associated with FXS
- Evaluating opportunities for FDA fast-track, breakthrough status, and/or priority review





DEE

Developmental and Epileptic Encephalopathies



DEE Overview

- Heterogeneous group of rare / ultra rare epilepsy syndromes
- Severe cognitive impairment and behavioral disturbances
- Affects ~45K U.S. children & adolescents
- Syndromes involve:
 - Impaired development (developmental encephalopathies)
 - Regression of developmental progress (epileptic encephalopathies)
- Often progressive; highly resistant to treatment
- Improved seizure control may positively impact development and quality of life

DEE includes syndromes such as:

Doose Syndrome
Dravet Syndrome
Early Myoclonic Encephalopathy
Juvenile Myoclonic Epilepsy (JME)
Landau-Kleffner Syndrome
Lennox-Gastaut Syndrome (LGS)
Ohtahara Syndrome
West Syndrome / Infantile Spasms





Developing ZYN002 in DEE

Enrollment Complete in BELIEVE 1 Trial

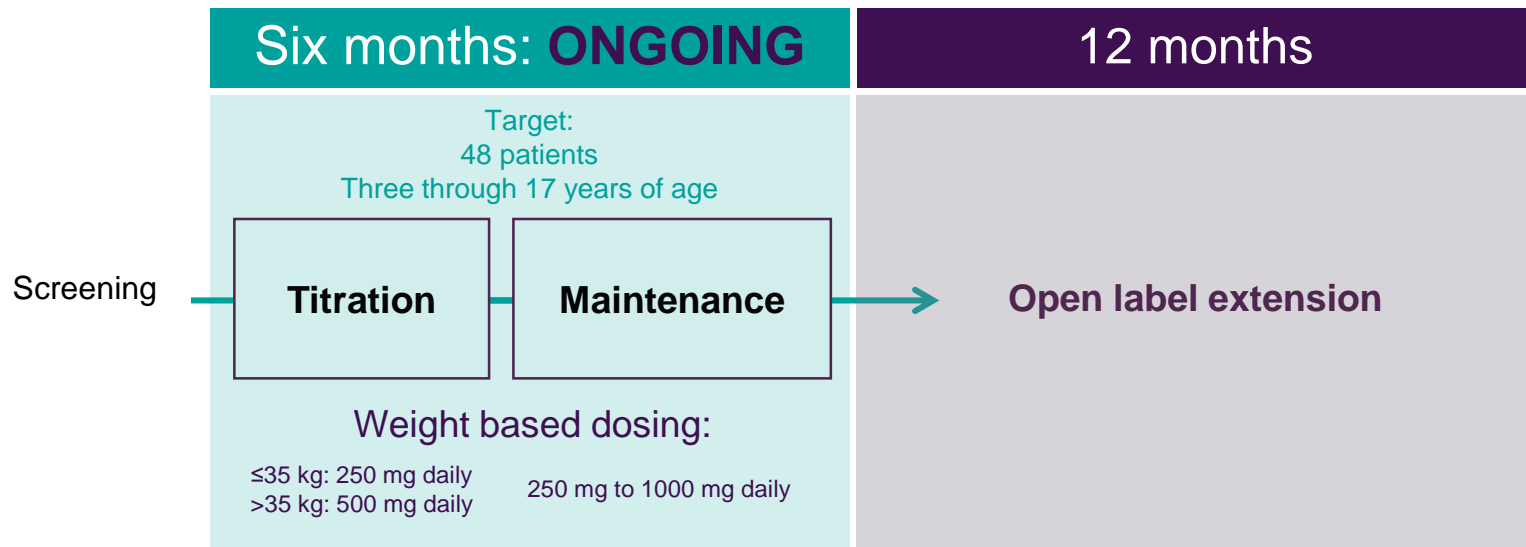
- Compelling rationale for utility of CBD in DEE
 - Third party clinical data show impact of CBD on seizures and behavioral issues in children
- Patient enrollment in BELIEVE 1 Phase 2 study complete
 - Six month multi-dose study in DEE patients (3 through 17 years)
 - Being conducted in Australia and New Zealand
 - Up to half may have Dravet or LGS
 - Primary efficacy assessment: change in seizure frequency
- Results expected in 3Q2019



BELIEVE 1 Phase 2 Trial in DEE



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





Autism Spectrum Disorder (ASD) in pediatric patients



ASD in Pediatrics Overview

- Near-rare disorder affecting <1MM pediatric and adolescent pts
- DSM-5 diagnosis including Autistic, Asperger's, Rhett's disorders
- 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

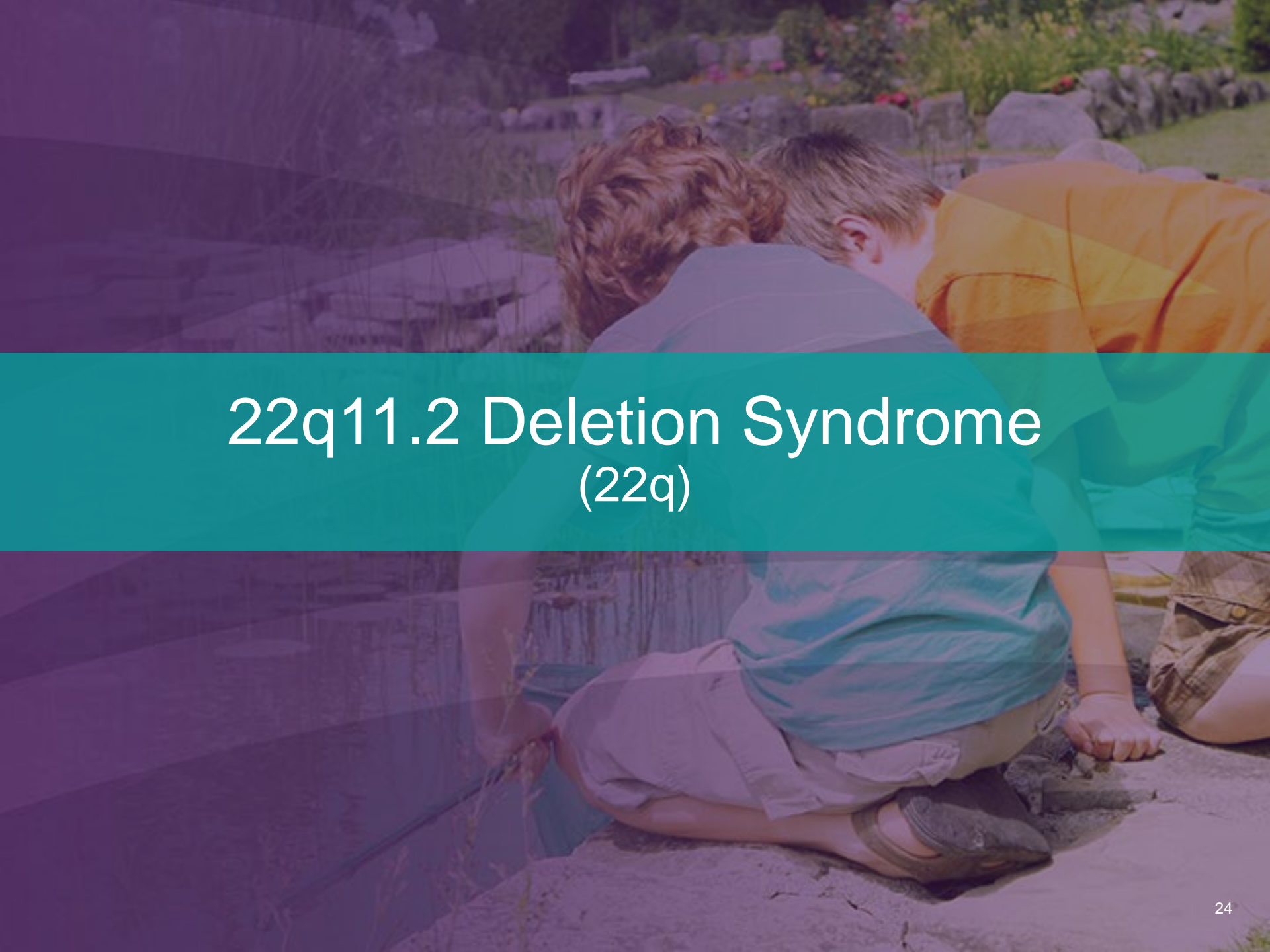


Developing ZYN002 in ASD



- Newer studies suggest ASD is linked to disruption in the endocannabinoid system
- Clinical and anecdotal data show improvement in social avoidance and anxiety in children with CBD
 - Exogenous CBD may modulate the endocannabinoid system and improve certain autism-related behaviors
- Expect to initiate Phase 2 study in pediatric patients with ASD in 1H2019
- Top line results expected in 1H2020





22q11.2 Deletion Syndrome (22q)



22q Overview

- Most common contiguous gene deletion syndrome
- Rare disorder: ~81K patients in US
 - Likely underdiagnosed
- 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 ZYN002 in 22q

- CBD may treat neuropsychiatric symptoms in 22q due to activity as:
 - Agonist at serotonin 1A receptors
 - Antagonist at GRP55 receptors
 - Modulator of endocannabinoid system
- Anxiety may predict adaptive functioning, and is thought to heighten the risk of later development of psychotic disorders
 - Early control of anxiety may delay the development of psychosis
- Expect to initiate Phase 2 study in 22q in 1H2019
- Top line results expected in 1H2020



ZYN002 in Adult Refractory Focal Epilepsy

Delaying Initiation of Phase 2B

- Delaying until after readout of four childhood neuropsych studies
- Provides additional time to better understand ZYN002 responders
 - Data at 2018 American Epilepsy Society meeting demonstrated strong, sustained response in patients (n=63) in STAR 2 for 18 months or more
 - Median seizure reductions of ~50% or greater
 - Long-term data collection continues; will evaluate the substantial data set to better define ZYN002 responders and design an appropriate study to maximize the likelihood of success
- Should extend cash runway into 2H2020
 - Beyond FXS, DEE, ASD and 22q clinical readouts








Financial Strength

- Cash and cash equivalent position of \$66.2 million as of September 30, 2018
- Expected to be sufficient to fund operations and capital requirements into 2H2020



Expected Milestones into 2020

	2018				2019				2020	
	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q
 FXS	<input checked="" type="checkbox"/> FDA meeting	<input checked="" type="checkbox"/> Initiate Pivotal trial <input checked="" type="checkbox"/> Present add'l Phase 2 FAB-C data		<input checked="" type="checkbox"/> FAB-C data		Present/publish additional data from Phase 2 FAB-C study		Topline pivotal CONNECT-FX data	NDA submission	
 DEE	<input checked="" type="checkbox"/> Initiate Phase 2 open label study							DEE Ph2 data		
 ASD (pediatric)					Initiate Phase 2 open label study				Present Phase 2 topline results	
 22q					Initiate Phase 2 open label study				Present Phase 2 topline results	
 Adult refractory focal epilepsy	<input checked="" type="checkbox"/> Present add'l STAR 2 extension data			<input checked="" type="checkbox"/> STAR-2 data						
Other indications				<input checked="" type="checkbox"/> ASD, 22q	Assessment of other rare and near-rare neuropsychiatric disorders					





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