



Corporate Overview

August 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™ (Cannabidiol Gel)
- Currently pursuing four neuropsychiatric indications:
 - Fragile X syndrome (FXS) – pivotal trial complete
 - Developmental and epileptic encephalopathies (DEE) – Phase 2 complete
 - Autism spectrum disorder (ASD) – Phase 2 complete
 - 22q11.2 deletion syndrome (22q) – Phase 2 ongoing
- Experienced team
 - Proven development and commercialization track record in transdermal delivery, orphan diseases, neurology, and psychiatry
- Well capitalized with cash runway expected into 4Q2021
- Multiple expected near term milestones





Deep Clinical Pipeline

Indication	Preclinical	Phase 1	Phase 2	Pivotal	Expected Milestones
Fragile X Syndrome (FXS)*					<p>Discussions with FDA in 2H2020 to discuss pivotal results in FXS patients with full methylation</p> <p>Results of discussions with FDA on clinical path forward in 3Q2020</p> <p>Discuss clinical path forward with FDA in 2H2020</p> <p>Completion of enrollment once COVID-19 restrictions in Australia are eased</p>
	CONNECT-FX: Topline data released				
Developmental and Epileptic Encephalopathies (DEE)					
	BELIEVE: Topline data released				
Autism Spectrum Disorder (ASD)					
	BRIGHT: Topline data released				
22q Deletion Syndrome (22q)					
	INSPIRE: Ongoing				

*Orphan Drug Designation



Zygel (ZYN002) Cannabidiol (CBD) Gel

Differentiated



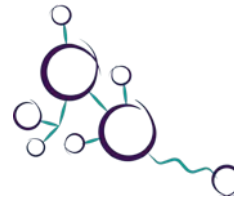
First & only patent-protected (2038), permeation-enhanced, pharmaceutically-produced CBD gel

Transdermal

CBD

Formulation delivers CBD through the epidermis and into the circulatory system

Unique Mechanism of Action



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 regulates emotional responses, behavioral reactivity to context, social interaction
 - Mutation in *FMR1* gene on the X chromosome causes dysregulation of the EC system and results in core cognitive, social, and behavioral symptoms of FXS
 - CBD modulates EC system
 - Increases availability of endocannabinoids (anandamide, 2-AG)
- Affects ~71K people in U.S.
- No approved drugs indicated for FXS



Fragile X Syndrome (FXS) Overview

Full Methylation (FMet) of *FMR1* Gene is a Biomarker for Disease Impact



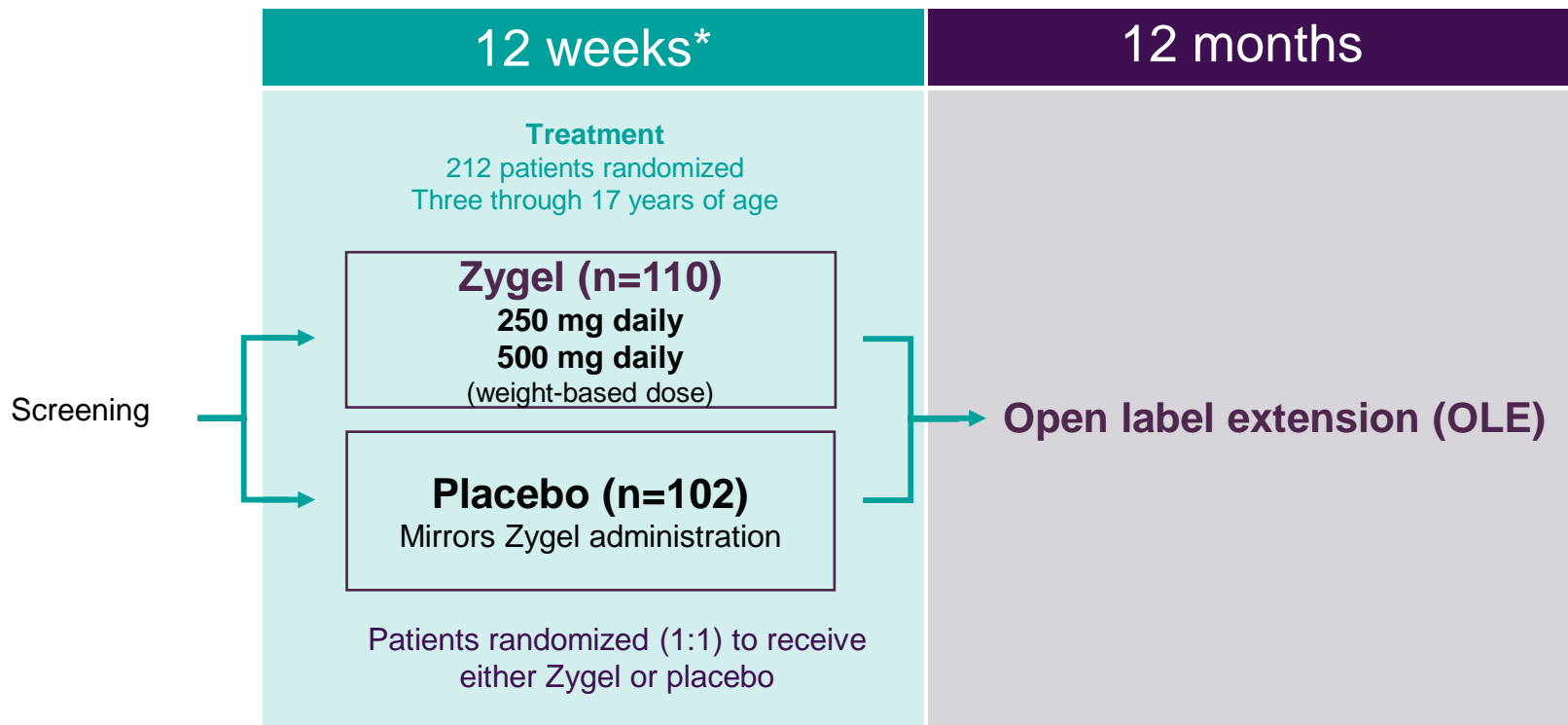
- *FMR1* gene codes for production of FMRP which is vital to synapse development
- Mutation manifests as multiple repeats of a DNA segment (CGG) in *FMR1*
 - No Fragile X: Segment repeats 5 to 40 times; normal production of FMRP
 - Premutation Fragile X: Segment repeats 50 to 200 times; reduced FMRP production
 - Full mutation FXS: Segment repeats >200 times; usually causes severely impacted or non-functional *FMR1* and leads to core FXS behaviors
- Methylation of *FMR1* also plays a role in determining functionality of the gene
 - At ≥90% methylation (“full methylation” or “FMet”), *FMR1* is silenced
 - No FMRP is produced: Systems and processes affected by FMRP become dysregulated
- Patients with full mutation FXS and full methylation of *FMR1* are generally the most severely impacted by the disorder: lower IQ, more impacted behaviors
 - ~60% of patients with full mutation FXS are believed to fall into this category



CONNECT-FX: A Pivotal Trial In FXS



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



*2 weeks placebo period, followed by 12 weeks treatment.



CONNECT-FX

Baseline Characteristics



	Placebo	Zygel	Total
n	102	110	212
Age (years)	9.8	9.6	9.7
Sex – Males, n (%)	78 (76%)	81 (74%)	159 (75%)
Weight (kg)			
Median	34.3	36.8	35.7
Range (Min, Max)	15.6, 104.7	14.6, 87.0	14.6, 104.7
>35kg, %	48%	56%	52%
Baseline psychoactive medications, %	66%	57%	62%

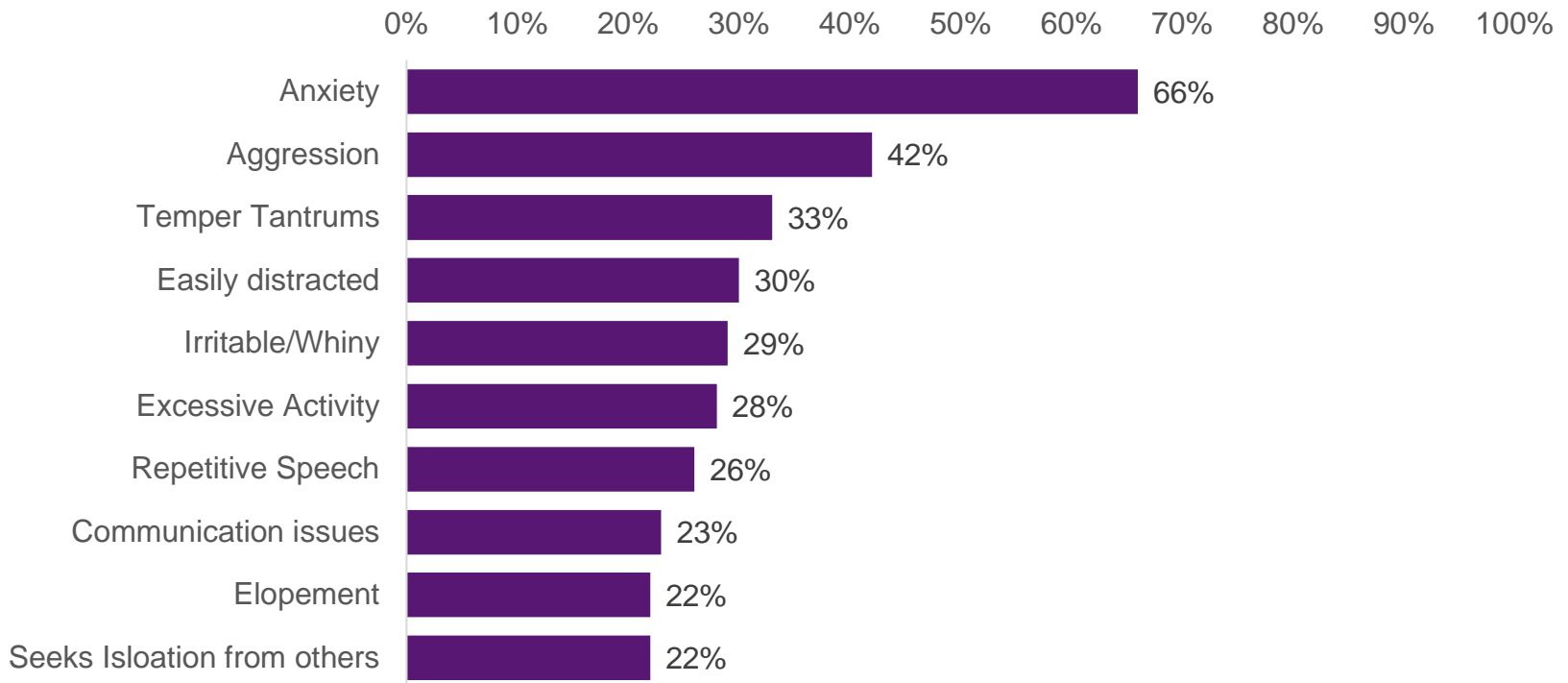


CONNECT-FX: Qualitative Caregiver Reported Behavioral Survey



Utilizing the Qualitative Caregiver Reported Behavioral Survey, caregivers were asked to describe their most important behavioral challenges at baseline

Top 10 Classifications of Behavioral Challenges



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
 - Captured qualitative data on clinical relevance of FXS behaviors

Zygel did not statistically significantly separate from placebo on the primary or key secondary endpoints in the full analysis set



CONNECT-FX: Rationale for Pre-Planned Ad Hoc Analysis

Building on the Scientific Evidence



Background

- Methylation of genes is considered to be important in numerous pathological disorders including FXS
- Methylation has been associated with the mechanism of mGluR5 in FXS
- Currently, treatment options are limited for many of these disorders
- The degree of methylation can influence the severity of FXS symptoms

CONNECT-FX

- Pre-planned analysis of the most severely impacted patients defined by patients having $\geq 90\%$ methylation (“full methylation” or “FMet”) of the impacted *FMR1* gene
 - 80% of the patients enrolled in CONNECT-FX were FMet
- Analysis to explore differences in two groups:
 - FMet group (n=167)
 - Non-FMet group (n=42)



CONNECT-FX



Full Data Set, FMet and Non-FMet

Patient Disposition: FMet Group Comprised 80% of Full Data Set Patients

Patients	Full Data Set	FMet Group	Non-FMet Group
Randomization (ITT)	212	169	42
Full Analysis set	210	167	42

- One patient did not receive study medication after randomization and one patient did not have post-baseline efficacy assessments resulting in 210 patients in Full Analysis set
- One patient with FMR1 gene deletion was not included in either the FMet or Non-FMet groups



CONNECT-FX: Demographics and Baseline Characteristics



Similar in the Full Data Set and FMet Group

	Full Data Set Group			FMet Group		
	Placebo	Zygel	Total	Placebo	Zygel	Total
n	102	110	212	77	92	169
Age (years)	9.8	9.6	9.7	9.6	9.2	9.4
Sex – Males (%)	78 (76%)	81 (74%)	159 (75%)	54 (70%)	65 (71%)	119 (70%)
Weight (kg)						
Median	34.3	36.8	35.7	33.9	35.7	35.0
Range (Min, Max)	15.6, 104.7	14.6, 87.0	14.6, 104.7	15.6, 104.7	14.6, 87.0	14.6, 104.7
>35kg, %	48%	56%	52%	46%	53%	50%
Baseline psychoactive medications, %	66%	57%	62%	65%	54%	59%



Pre-Planned Ad Hoc Results: Fmet Group



Zygel Achieved Statistical Significance on Social Avoidance: Changes From Baseline to Week 12 (ABC-C_{FXS})

		Placebo N=76			Zygel N=91					
Endpoints		Baseline Mean (SE)	Week 12 Mean (SE)	Week 12 Median Percent Change	Baseline Mean (SE)	Week 12 Mean (SE)	Week 12 Median Percent Change	Treatment Difference / Odds Ratio [†]	Treatment <i>p</i> -value	
Primary Endpoint	Social Avoidance	7.18 (0.32)	5.41 (0.42)	-21.1	7.12 (0.29)	4.32 (0.33)	-40.0	-1.00	0.020*	
	Secondary Endpoints	Irritability	28.0 (1.56)	24.11 (1.56)	-11.6	29.36 (1.37)	22.69 (1.42)	-24.3	-2.30	0.091
		Socially Unresponsive /Lethargic	13.17 (0.85)	10.29 (0.80)	-20.5	13.30 (0.68)	9.03 (0.67)	-30.8	-1.17	0.135
		CGI-I	-	35.7%		-	51.1%		1.88 [†]	0.056

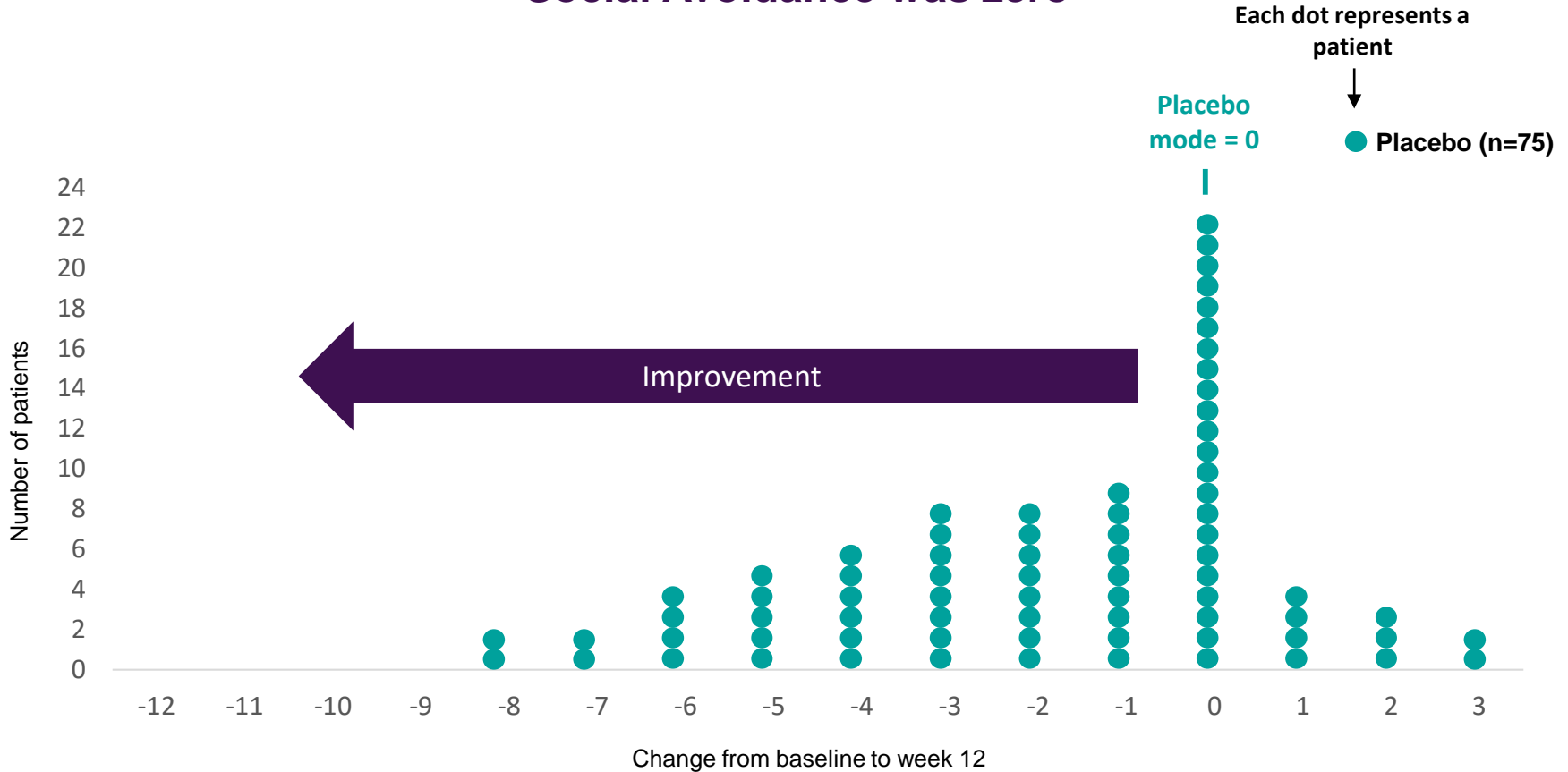
*Statistically significant



CONNECT-FX: ABC-C_{FXS} Social Avoidance Changes From Baseline to Week 12 in FMet Group



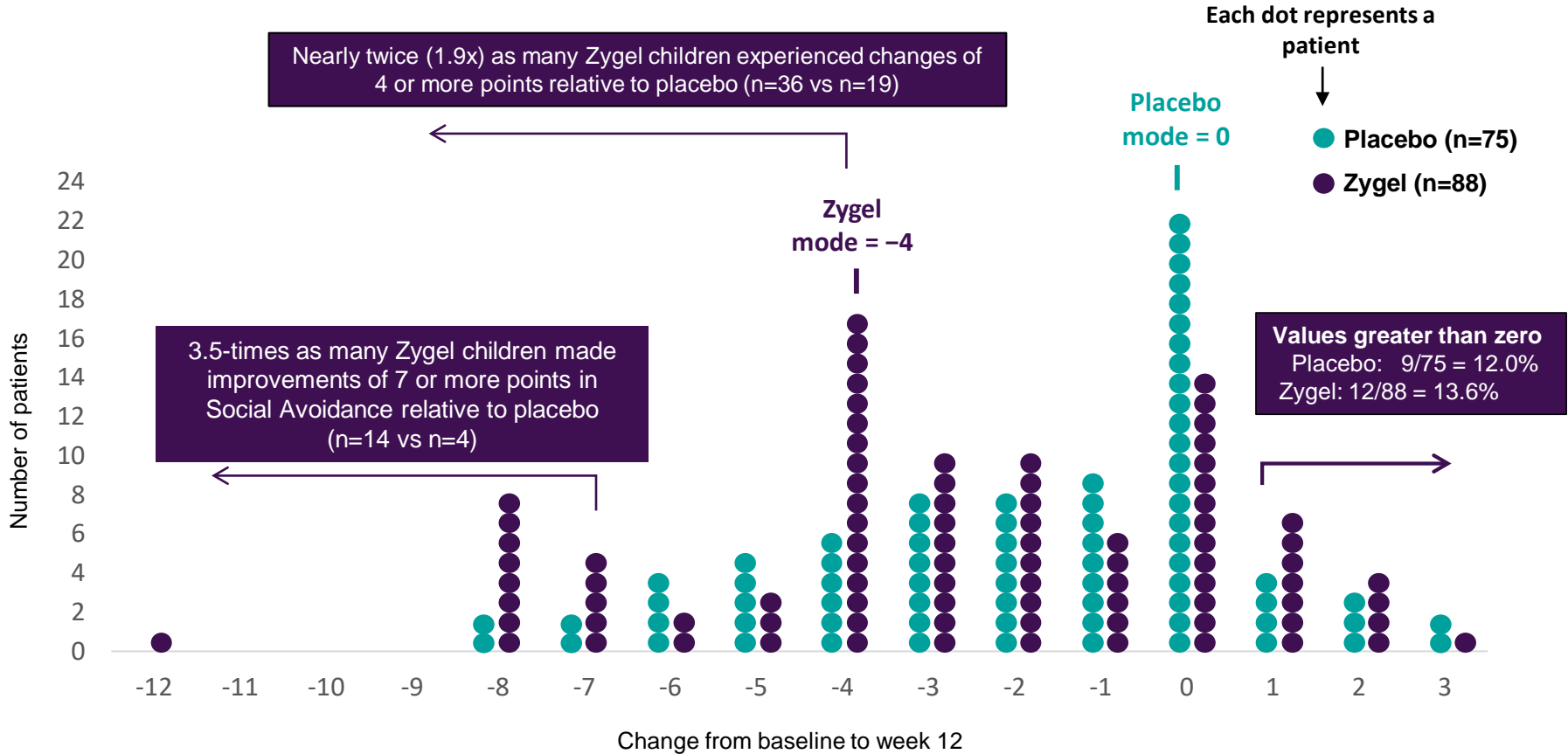
In placebo group, the most common change (mode) in Social Avoidance was zero



CONNECT-FX: ABC-C_{FXS} Social Avoidance Changes From Baseline to Week 12 in FMet Group



Zygel group demonstrated greater improvement versus placebo



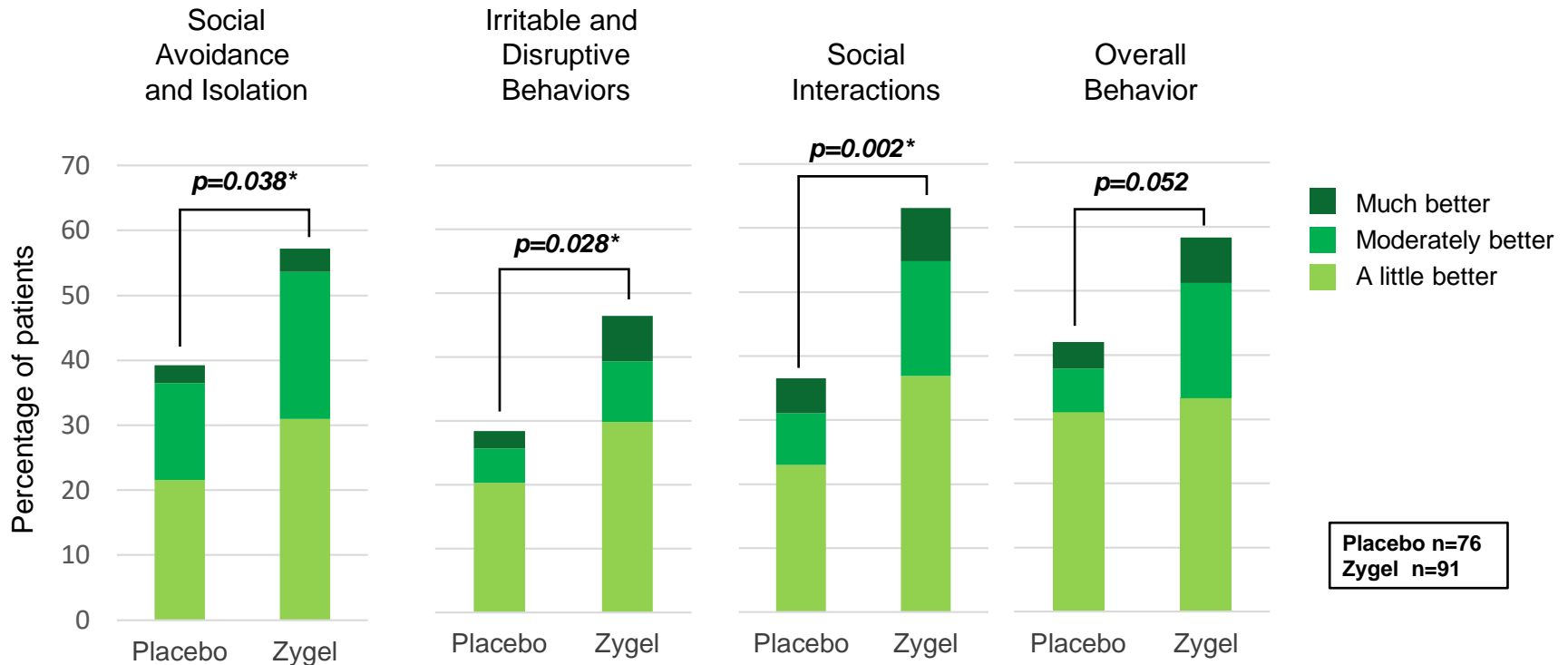
Data represent observed cases: 4 patients did not have Week-12 ABC-C_{FXS} assessment



CONNECT-FX: Caregiver Global Impression-Change: FMet Group



Change from Baseline to Week 12: Broad Shifts Towards Global Improvement



*Statistically significant

P-values indicate "betterment" on Zygel vs "betterment" on placebo



Zygel Advantages Observed in Social Avoidance Are Supported by Caregiver and Clinical Global Impression Improvements in FMet Group



Primary Endpoint: ABC-C_{FXS} Social Avoidance Subscale

- Statistically significant improvement vs. placebo ($p=0.020^*$)

Caregiver Global Impression – Change at Week 12 (Four Domains)

- Statistically significant improvement vs. placebo in Social Interactions ($p=0.002^*$)
- Statistically significant improvement vs. placebo in Irritable & Disruptive Behaviors ($p=0.028^*$)
- Statistically significant improvement vs. placebo in Social Avoidance & Isolation ($p=0.038^*$)
- Trend toward statistical significance in improvement in Overall Behavior vs. placebo ($p=0.052$)

Clinical Global Impression - Improvement** (anchored to FXS behaviors; clinician rated)

- Trend toward statistical significance vs. placebo ($p=0.056$)

* Statistically significant

** Not specific to Social Avoidance



CONNECT-FX: Safety

Zygel Was Very Well Tolerated in FXS Patients



- Zygel was very well tolerated
 - Safety profile consistent with previously released data from all other Zygel trials
 - No safety signal identified
- No serious or severe adverse events reported during the study
- All treatment-emergent adverse events (TEAEs; any event, whether unrelated or related to study drug) were mild or moderate
 - Most common treatment-related TEAE: application site pain
 - Zygel: 6.4%; placebo: 1.0%
 - Seven total psychiatric disorder TEAEs; 5 were in placebo group
- Laboratory values for chemistry and hematology comparable between placebo and Zygel groups; no clinically relevant abnormalities in either group
 - No clinically significant changes to liver function tests



Next Steps in Fragile X Program



- Discuss CONNECT-FX data and the pathway for submitting a New Drug Application (NDA) with FDA
- Pivotal data to be published and presented at upcoming medical meetings





Autism Spectrum Disorder (ASD) in children and adolescents



ASD in Pediatrics Overview

- Near-rare disorder affecting ~1MM pediatric and adolescent patients
- 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



Rationale for 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 demonstrate that children dosed with CBD displayed an 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

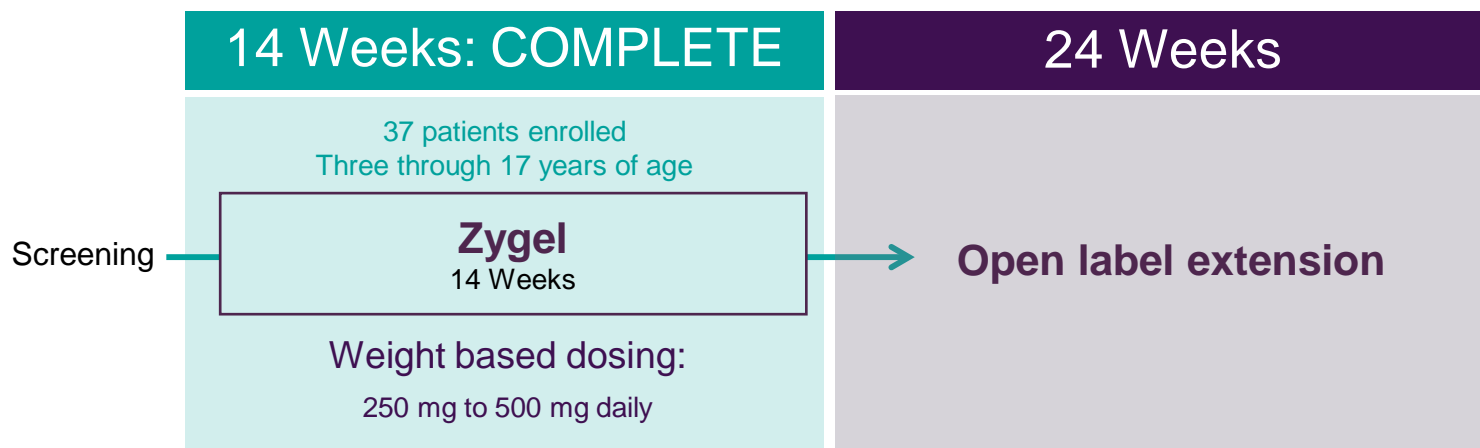




BRIGHT Phase 2 Trial in ASD

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 Female	34 (91.9%) 3 (8.1%)
Race, % White Asian Native Hawaiian or other Pacific Island Other	70.3% 8.1% 2.7% 18.9%
Time to diagnosis, years	5.4
Underlying medication, % Subjects entering with ≥ 1 underlying medication Subjects entering with ≥ 1 underlying psychotropic medication (includes anti- depressants, anxiolytics and antipsychotics)	92% 65%



Strong Safety and Tolerability Profile in BRIGHT Trial in ASD



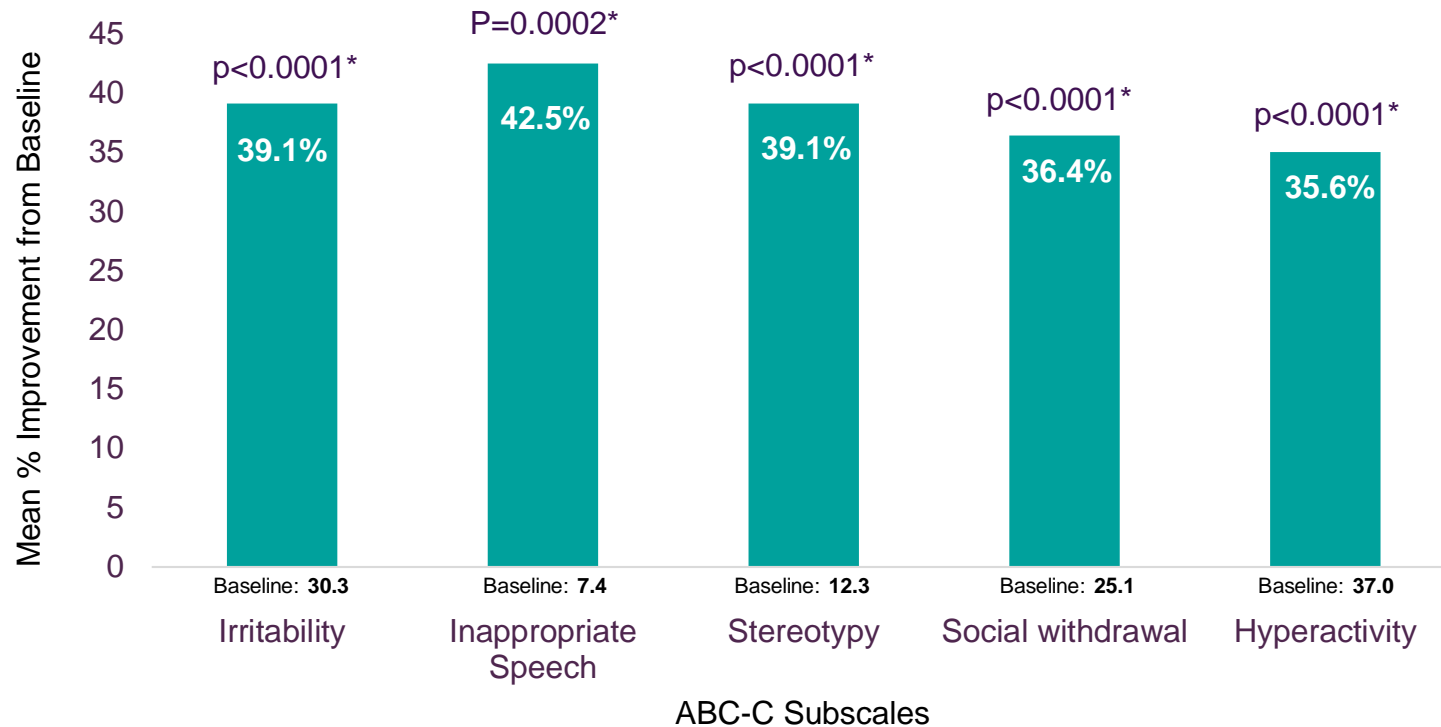
- Well tolerated; consistent with previously released data
- Fewer than half of patients experienced an adverse event (AE); most were mild and transient
- Only 14% of patients experienced a treatment-related AE
 - All application site-related
- No severe or serious AEs reported during the study.



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

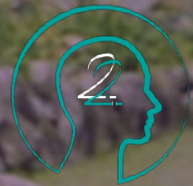


Results of other efficacy assessments support the results demonstrated in the ABC-C, including:

- 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
- Zynserba intends to present additional data at future medical meetings

Next steps: Meet with FDA in 2H2020 to discuss clinical path forward





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 quality of life, 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 currently approved drugs indicated for 22q



Rationale for 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
- Enrollment delayed due to COVID-19 travel restrictions in Australia; topline results timeline to be announced following lifting of restrictions

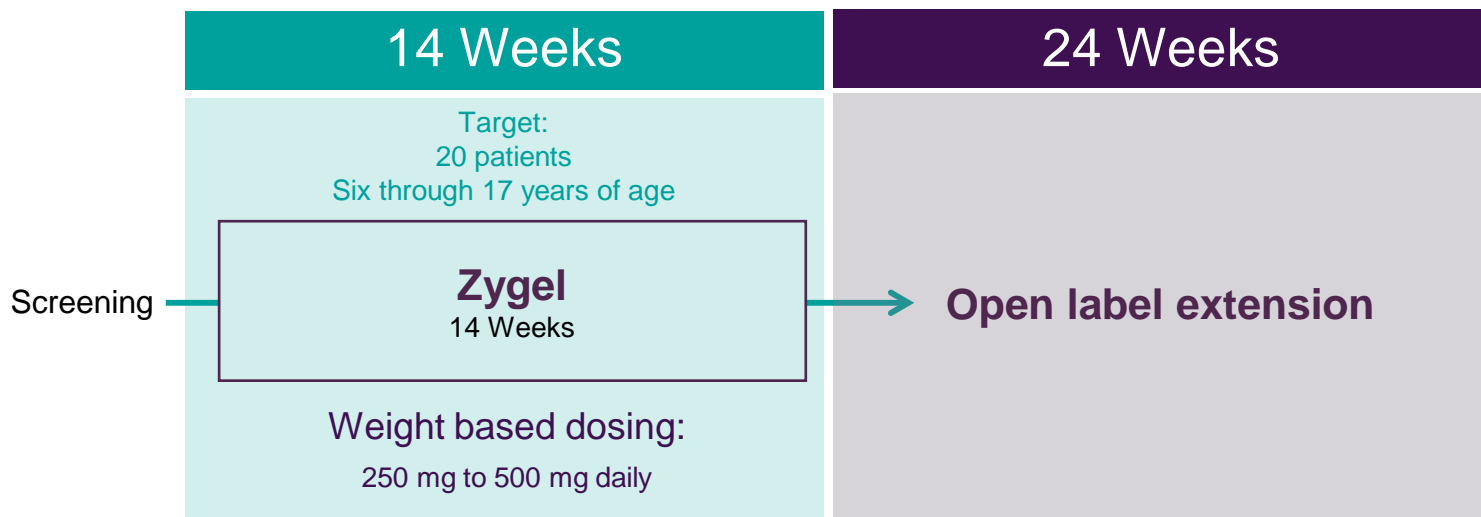




INSPIRE Phase 2 Trial in 22q

Enrollment Ongoing

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
 - Includes wheelchair bound individuals 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 (TCS) – commonly known as convulsive seizures (CS)

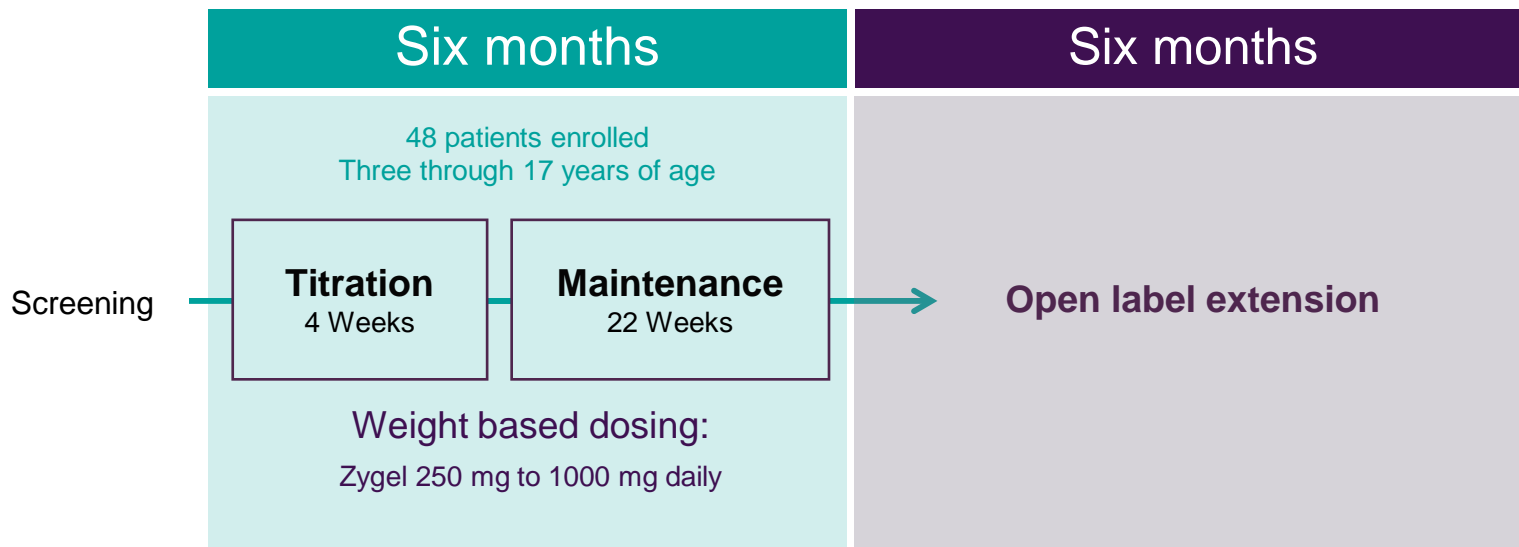




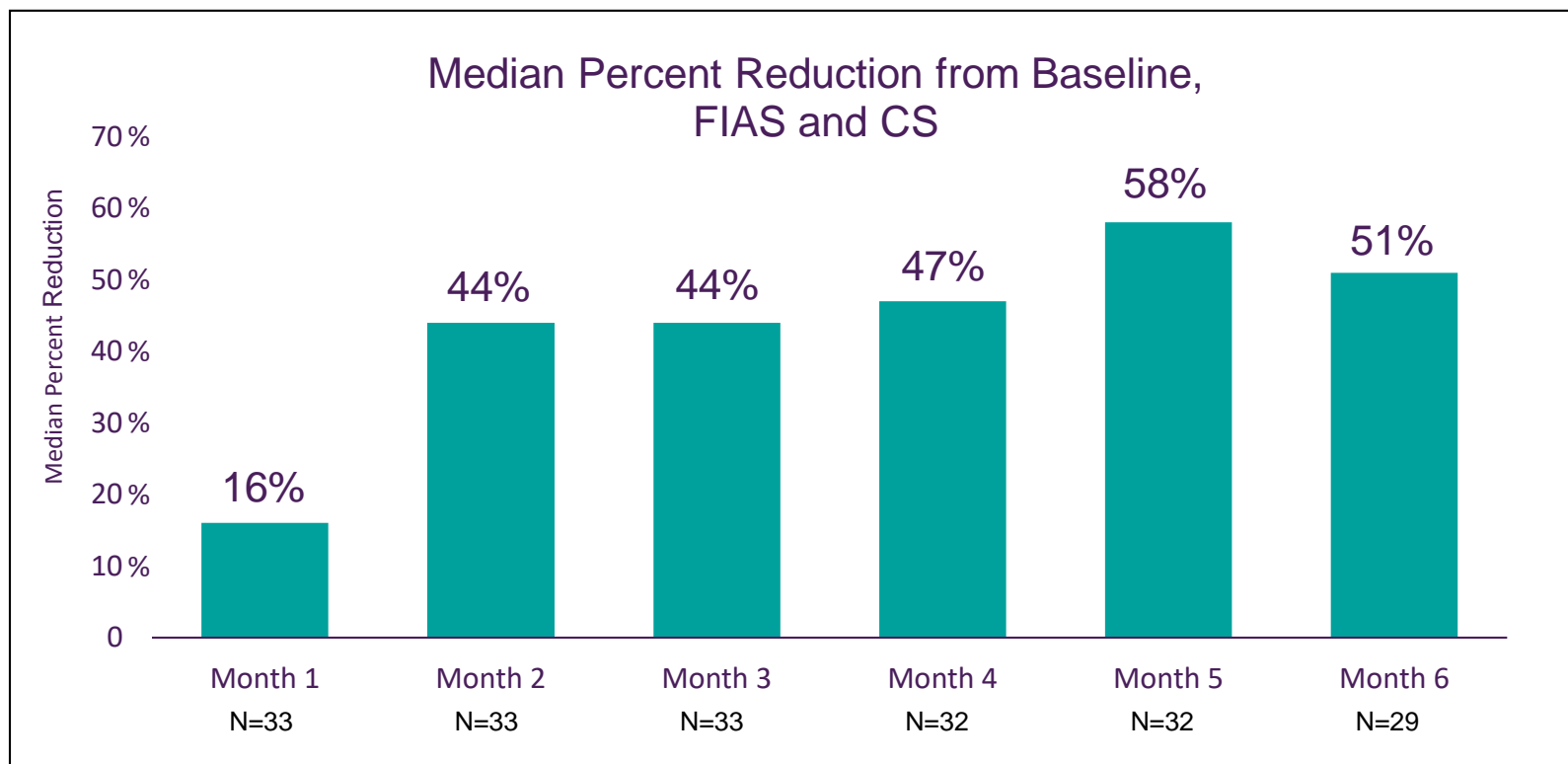
BELIEVE Phase 2 Trial in DEE

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

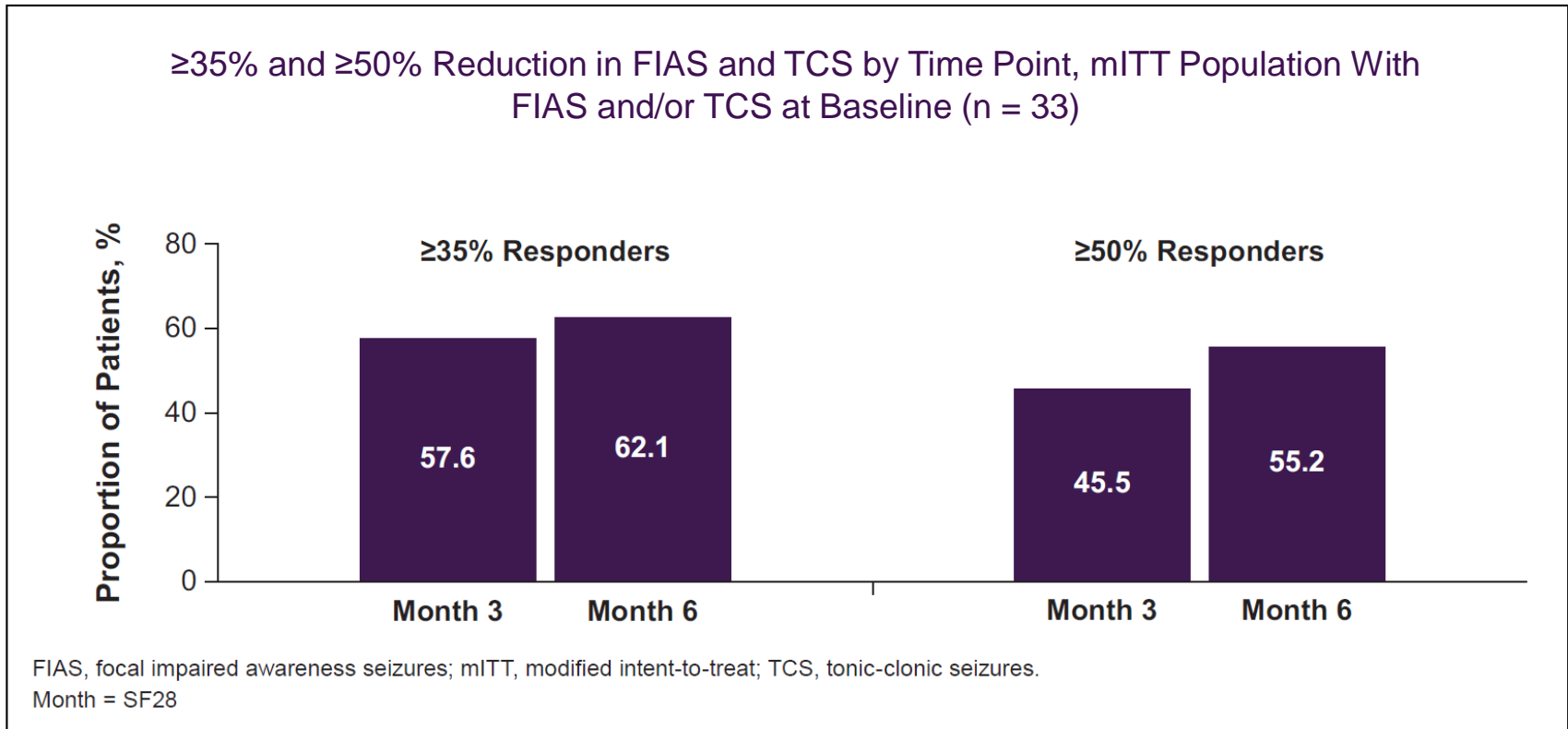
Open LaBel Study to Assess the Safety and Efficacy of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with Developmental and Epileptic Encephalopathy



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



BELIEVE: Percentage of Patients with $\geq 35\%$ and $\geq 50\%$ Reduction in FIAS and TCS



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



BELIEVE Safety



Zygel 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 AEs (e.g.: influenza, runny nose, 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 (SAEs)
 - 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)

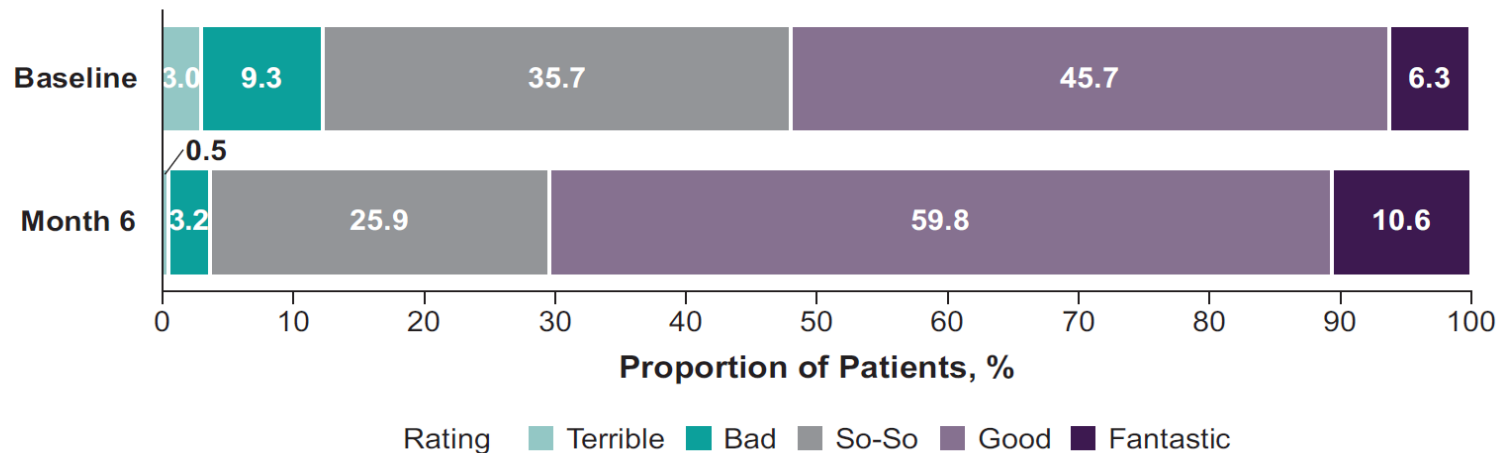
Data reported at the 2020 American Academy of Neurology (AAN) Science Highlights Virtual Session



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 Potential Pathway to Pivotal Trials



Results of FDA Discussions Regarding Clinical Path Forward Expected in 3Q2020

- 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

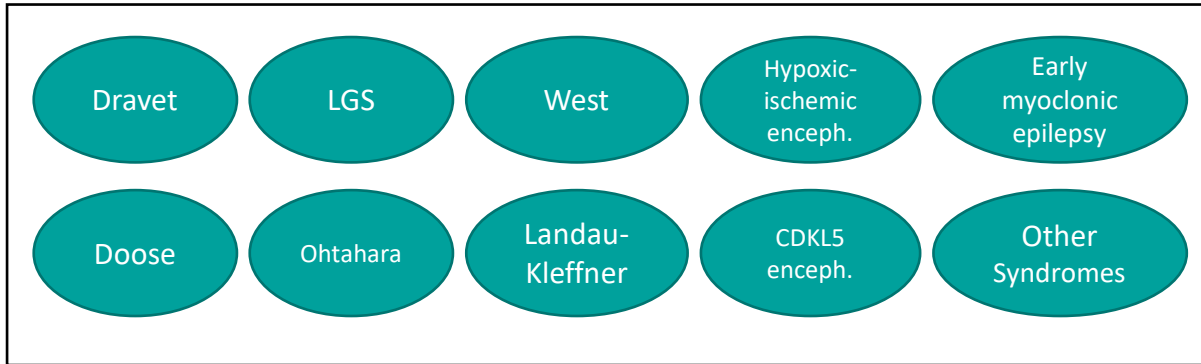


Planned Approach to FDA

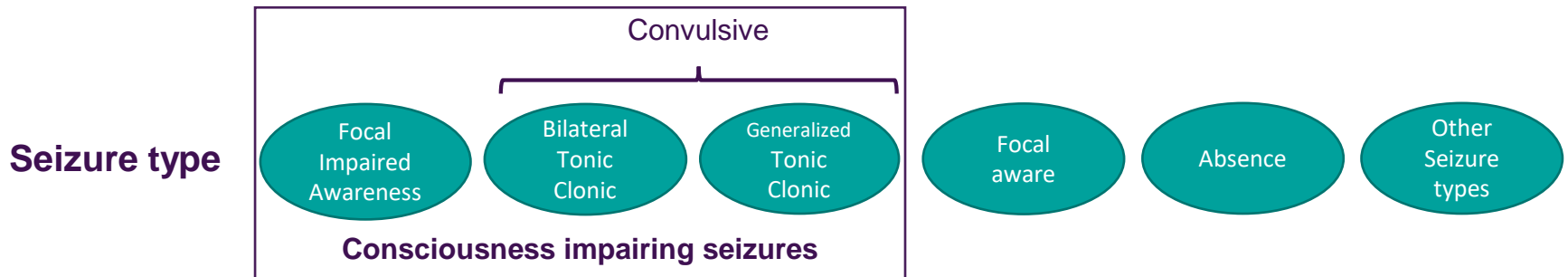


All DEE Patients with Consciousness Impairing Seizures

Syndromes and encephalopathies



Zynerba Planned Approach







Financial Strength

- Clean balance sheet
 - No debt, 29.3 M shares outstanding (as of August 6, 2020)
- Cash and cash equivalent position of \$77.0M as of June 30, 2020
- Cash runway expected to be sufficient to fund operations and capital requirements into the fourth quarter of 2021



Expected Clinical Milestones in 2020

	1Q 2020	2Q 2020	3Q 2020	4Q 2020
 FXS		<input checked="" type="checkbox"/> Report pivotal CONNECT-FX topline results	Discuss results in fully-methylated FMR1 FXS with FDA	
 DEE			Results of FDA discussions on clinical path	
 ASD		<input checked="" type="checkbox"/> Report Ph. 2 BRIGHT topline results	Discuss clinical path forward in ASD with FDA	
 22q	Enrollment delayed due to COVID-19 travel restrictions in Australia. Topline results timeline to be determined following lifting of restrictions			





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August 2020