Corporate Overview

November 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: Cash runway expected to last until late in 4Q2021
- 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: Topline data released				Meet with FDA to discuss pivotal results in patients with a fully methylated *FMR1* gene in 4Q2020; outcome also expected in 4Q2020
Developmental and Epileptic Encephalopathies (DEE)					
	BELIEVE: Topline data released				Communicate specific DEE syndrome(s) for further clinical development around year-end 2020
Autism Spectrum Disorder (ASD)					
	BRIGHT: Topline data released				Discuss Phase 2 results and clinical path forward with FDA in 1H2021
22q Deletion Syndrome (22q)**					
	INSPIRE: Ongoing				Completion of enrollment once COVID-19 restrictions in Australia are eased

*Orphan Drug and Fast Track designation
**Orphan Drug designation

Zygel (ZYN002) Cannabidiol Gel

Differentiated

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

Transdermal

Formulation delivers Cannabidiol through the epidermis and into the circulatory system

Unique Mechanism of Action

Cannabidiol 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

Orphan Drug designation in 22q

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 system (ECS)
  - 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
- ~70K U.S. patients, of whom ~40K have a fully methylated *FMR1* gene (FMet)
- No approved drugs indicated for FXS

Fragile X Syndrome (FXS) Overview

Full Methylation (FMet) of *FMR1* Gene May be 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

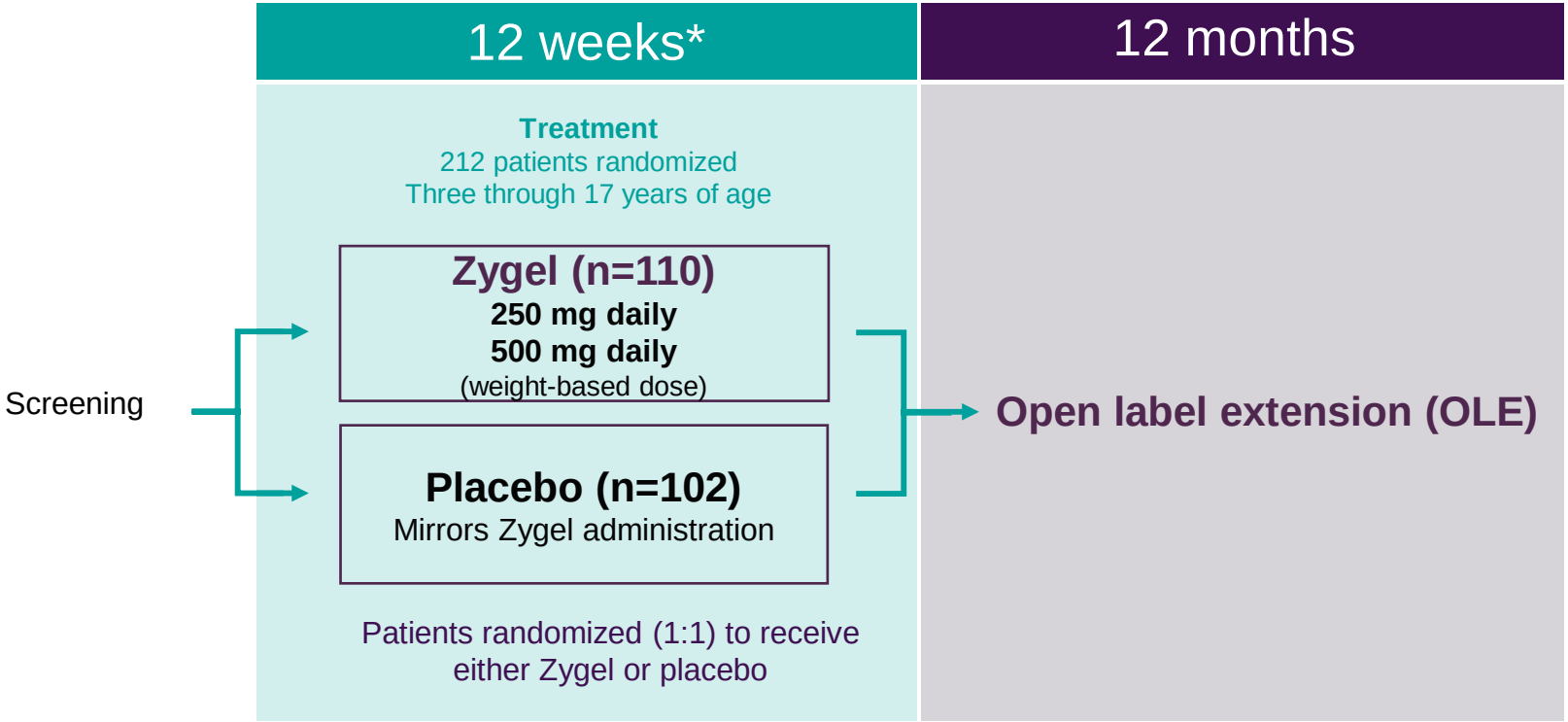
*FMR Protein; RNA-binding protein that helps regulate synaptic development and plasticity

Proposed MOA of Cannabidiol in patients with FXS and fully methylated FMR1 gene

- FMRP affects multiple intracellular processes
  - Endocannabinoid system
  - Glutamate and GABA feedback loops
- FMet patients
  - Males produce no FMRP
  - Females have significant reduction in FMRP
- Absence or loss of FMRP is correlated with behavioral and cognitive deficits
- Cannabidiol in FMet patients
  - Attenuates the disruption of the ECS by increasing the availability of the endocannabinoids (2-AG and anandamide)
  - Modulates the glutamate and GABA feedback loops

CONNECT-FX: A Pivotal Trial In FXS

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



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

CONNECT-FX

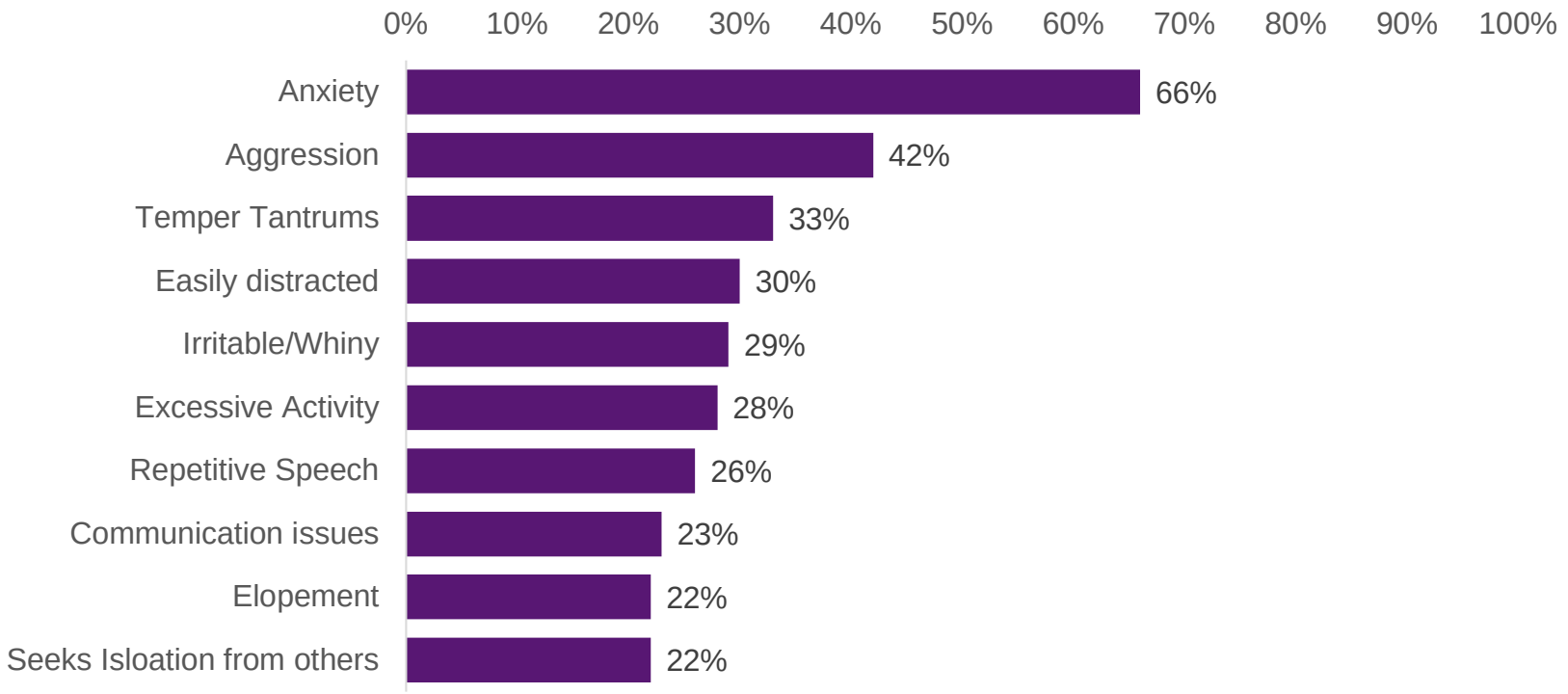
Baseline Characteristics

	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 ≥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 *p*-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

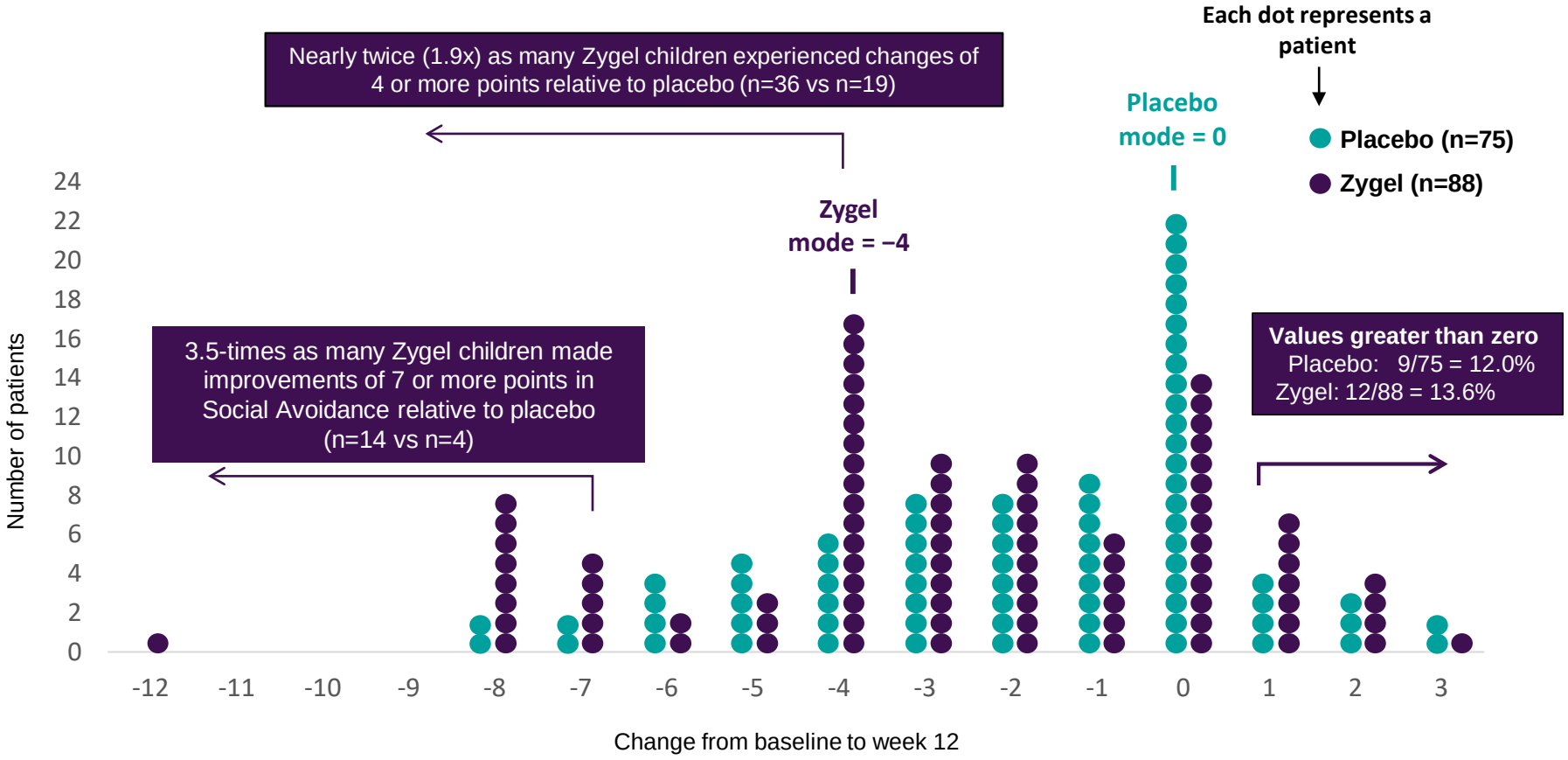
*Statistically significant

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

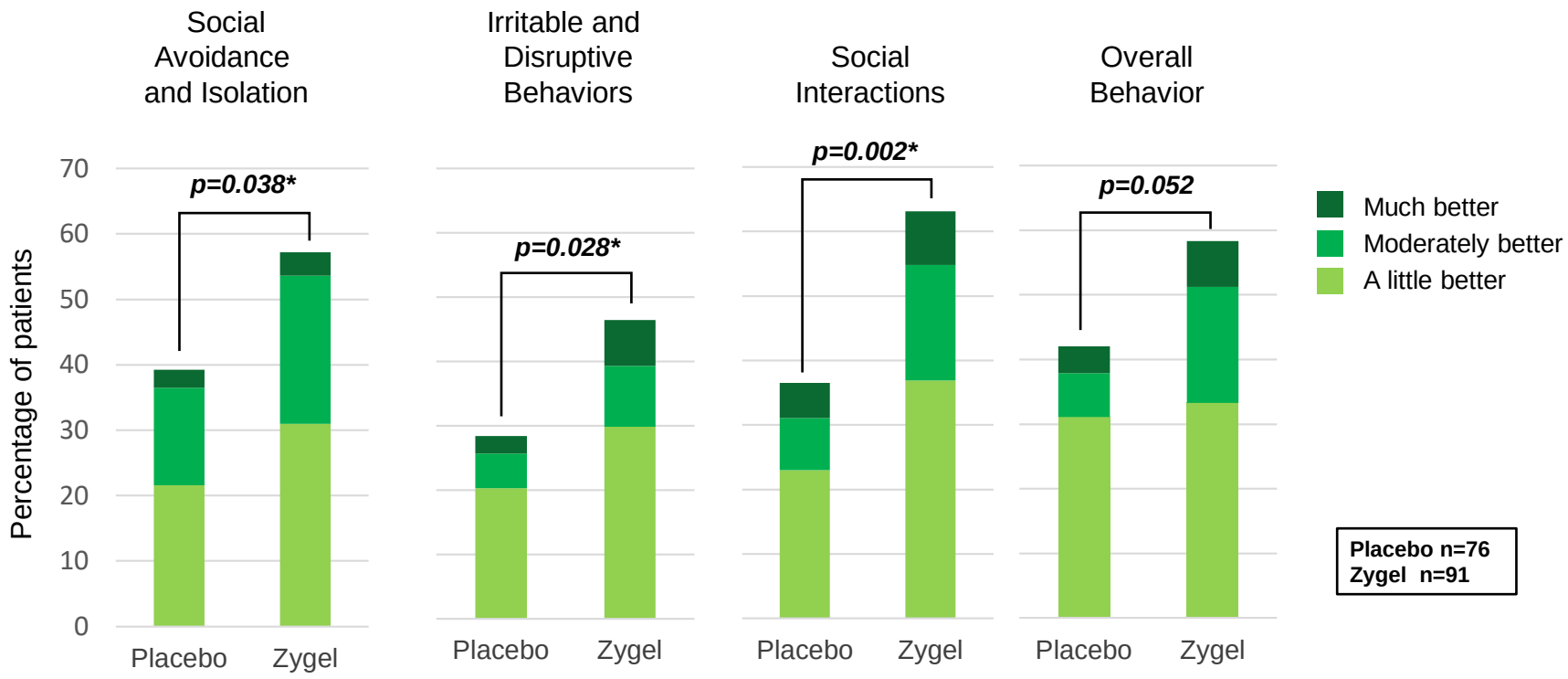
Zygel group demonstrated greater improvement versus placebo



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

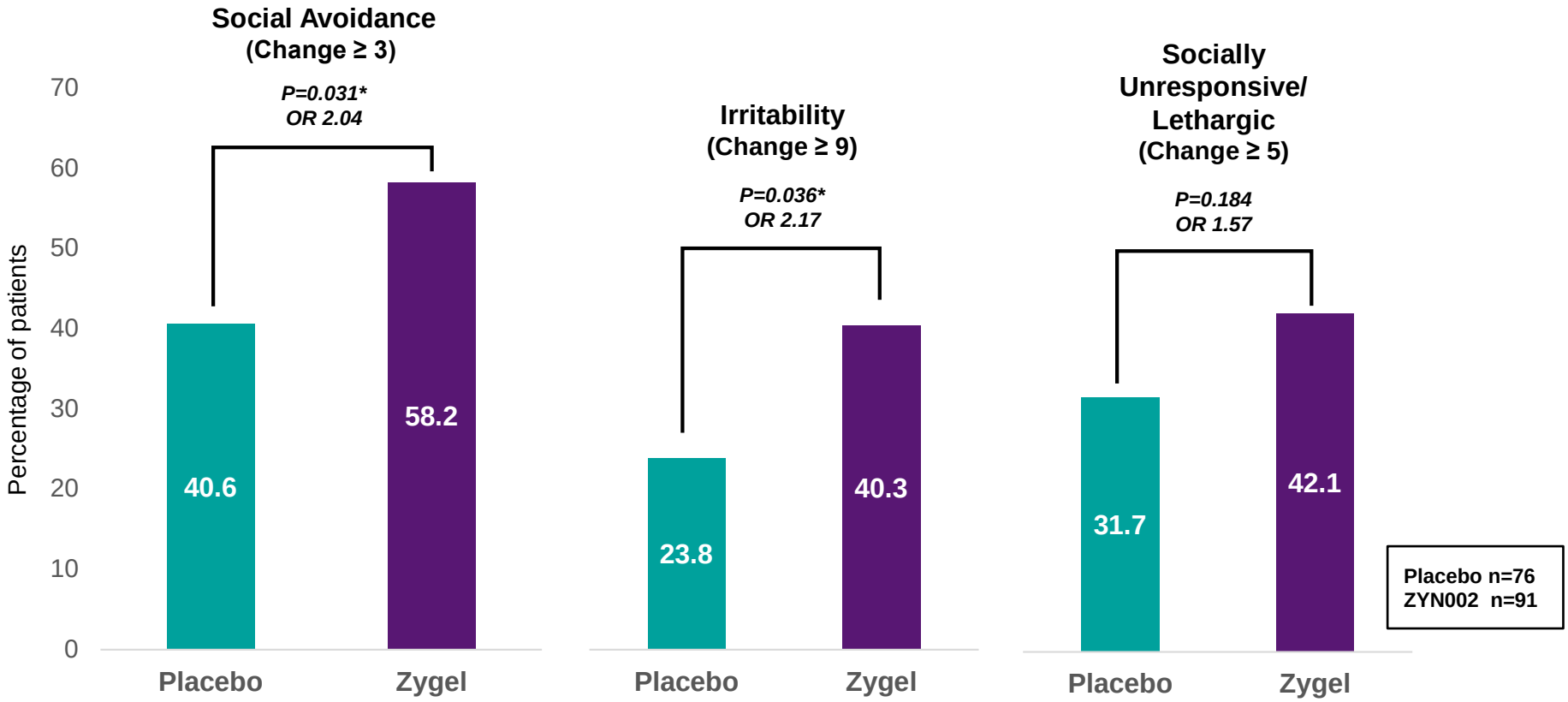
Psychometric Analyses Determined Clinically Meaningful Changes for ABC-C_{FXS}

- Clinically meaningful treatment responses over 12 weeks of treatment determined to be an improvement of:
  - Three (3) points or greater for the Social Avoidance subscale
  - Nine (9) points or greater for the Irritability subscale
  - Five (5) points or greater for the Socially Unresponsive / Lethargic subscale

Data reported at the 2020 Joint 16th International Child Neurology Congress (ICNC) & 49th Annual Child Neurology Society (CNS) Meeting

FMet Patients With Clinically Meaningful Change in ABC-C_{FXS} Subscales

Zygel achieved statistically significant separation from placebo in Social Avoidance & Irritability subscales



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OR= odds ratio
*Statistically significant. LS Means

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 significantly 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)

Clinically Meaningful Improvements in ABC-C_{FXS} Subscales at Week 12

- Significantly more patients achieved a clinically meaningful change in ABC-C_{FXS} Social Avoidance (≥3 points; p=0.031*) and Irritability (≥9 points; P=0.036*) with Zygel vs. Placebo

* Statistically significant

** Not specific to Social Avoidance

CONNECT-FX: Safety

- 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

- In 4Q2020, Zynerba expects to announce the outcome of its meeting with the FDA and the regulatory path forward in FMet patients
- Additional 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

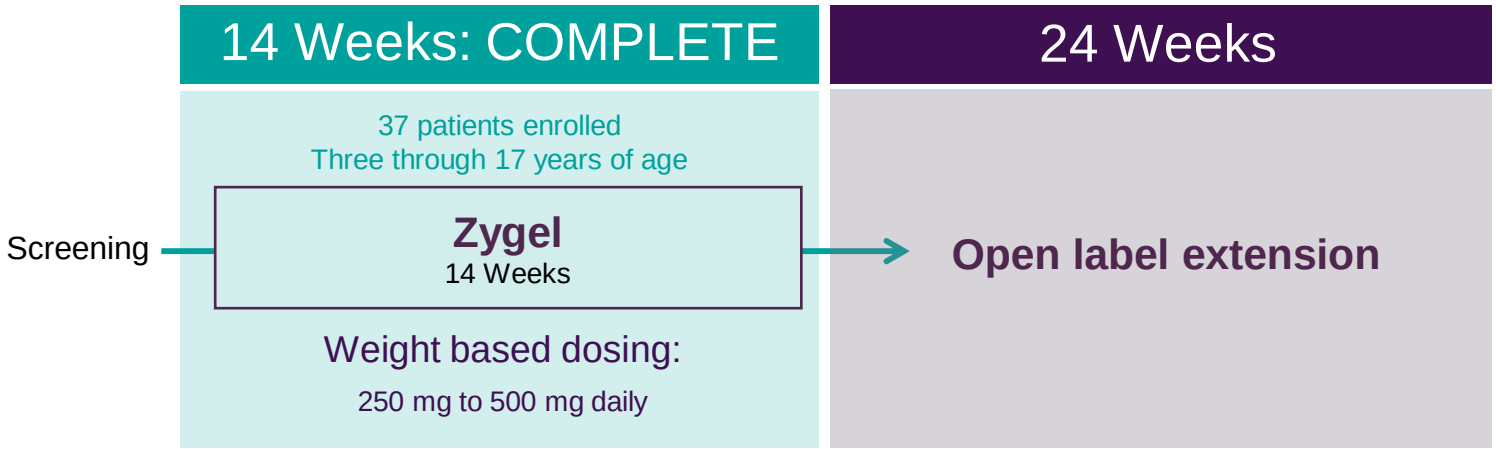
Rationale for Developing Zygel in ASD

- 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 Cannabidiol displayed an improvement in social avoidance and anxiety
  - 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

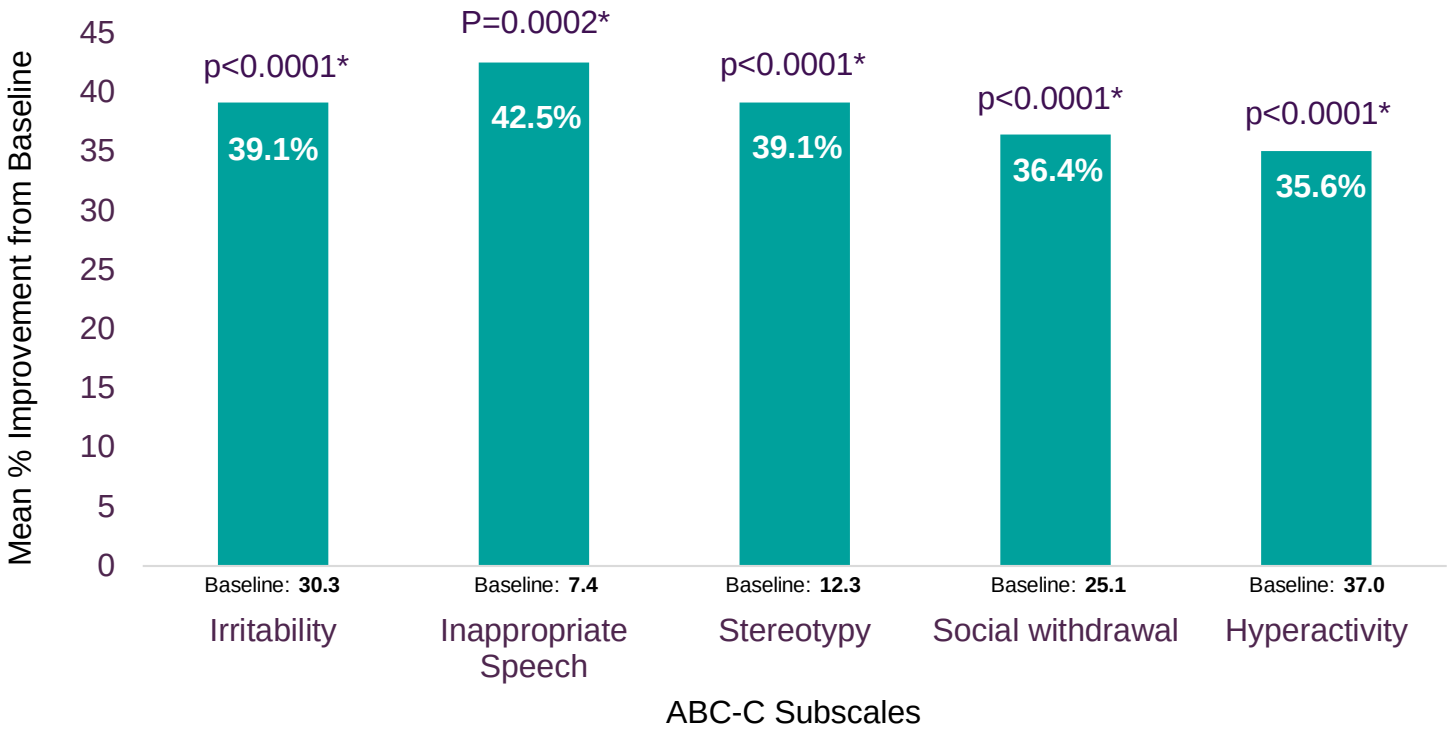
Baseline Patient Demographics	
Patients enrolled, n	37
Age, years	
Mean (range)	9.2 (3-16)
Sex, n (%)	
Male	34 (91.9%)
Female	3 (8.1%)
Race, %	
White	70.3%
Asian	8.1%
Native Hawaiian or other Pacific Island	2.7%
Other	18.9%
Time to diagnosis, years	5.4
Underlying medication, %	
Subjects entering with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

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



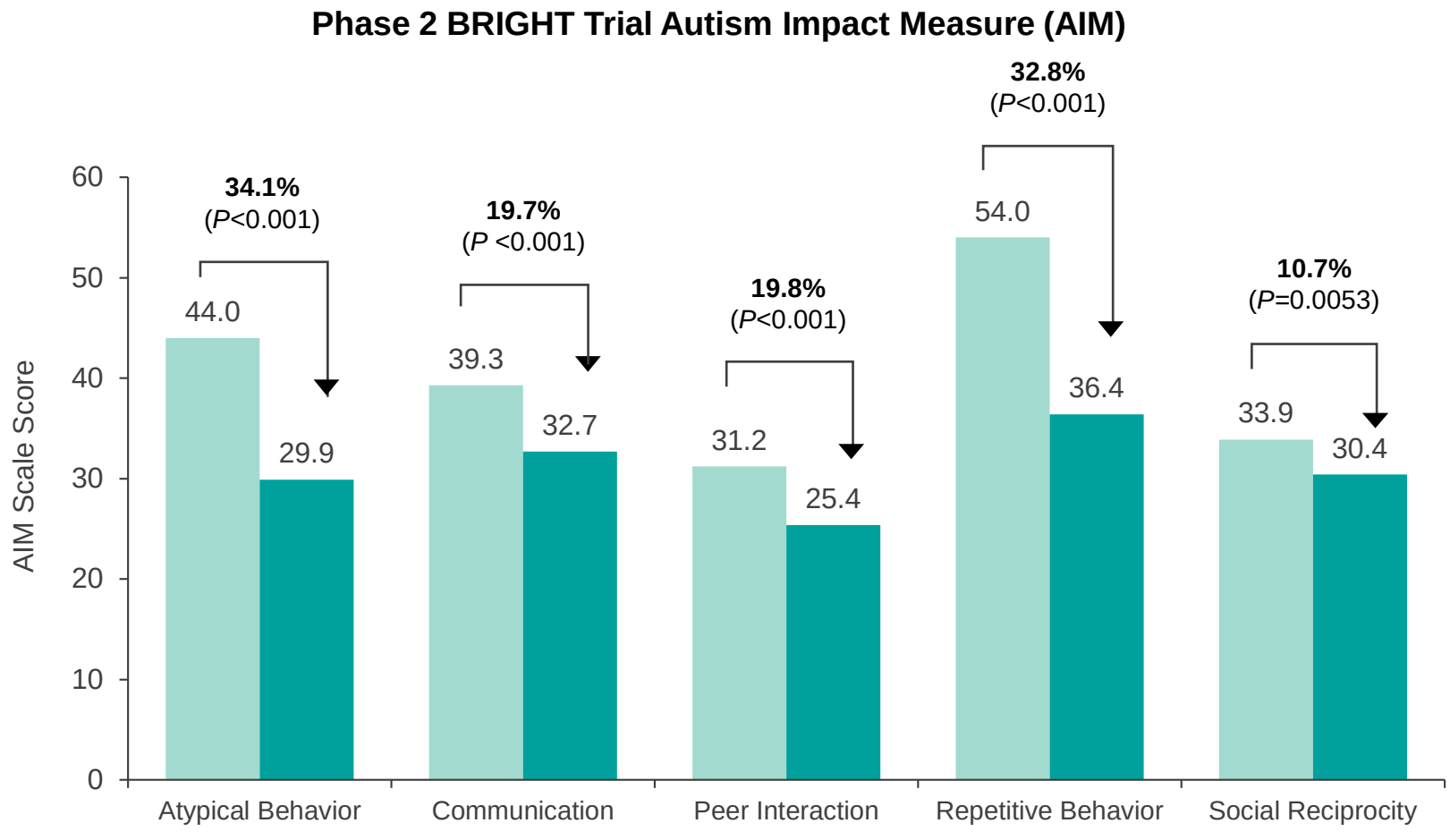
* Statistically significant

ABC-C Responses Supported by Other Efficacy Assessments

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

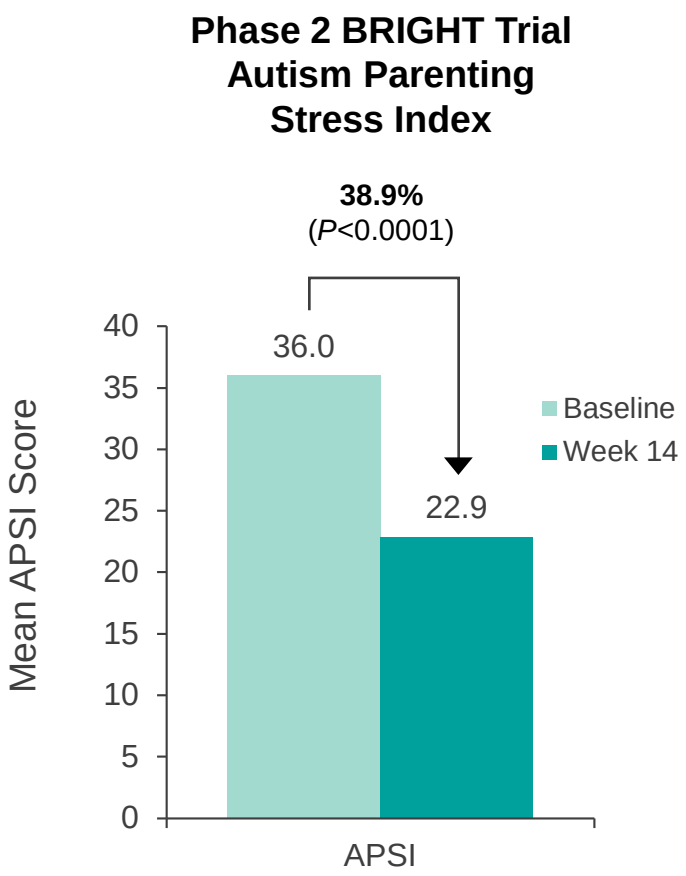
- Parent Rated Anxiety Scale - Autism Spectrum Disorder (PRAS-ASD):
  - Mean improvement of 46% at week 14 from baseline ($p<0.0001$)
- Clinical Global Impression - Improvement (CGI-I)
  - 57% of patients were rated by clinician as Very Much or Much Improved at week 14

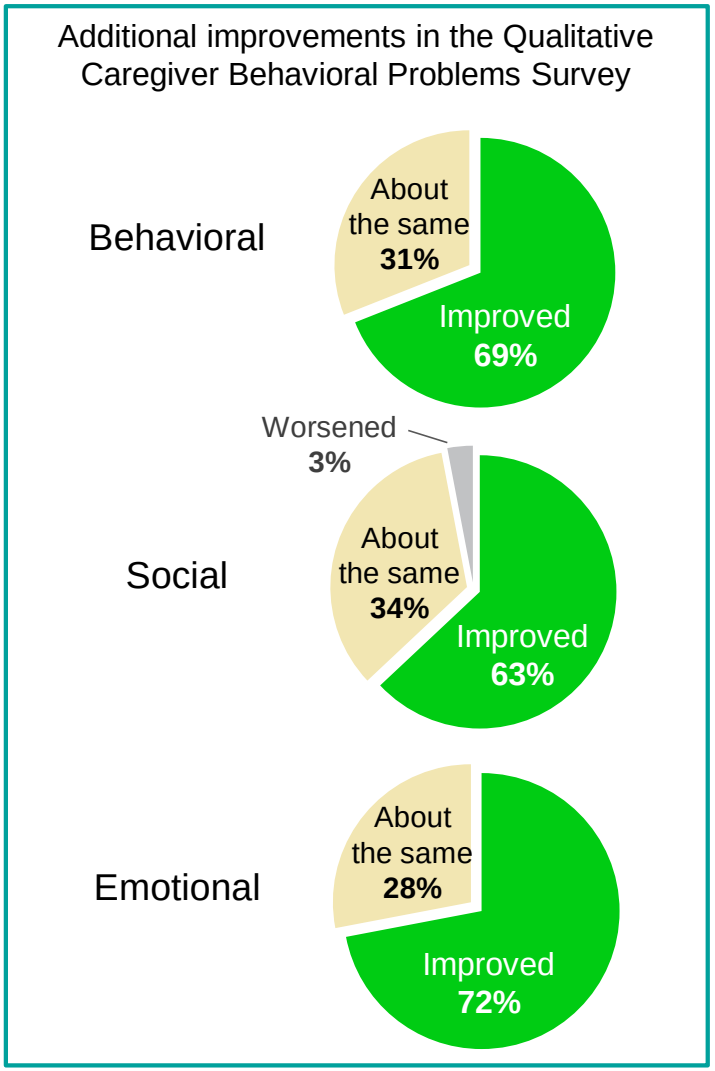
Statistically Significant Improvements in Autism Impact Measure Scores



Data reported at the 2020 Joint 16th International Child Neurology Congress (ICNC) & 49th Annual Child Neurology Society (CNS) Meeting

Statistically Significant Improvement in Autism Parenting Stress Index





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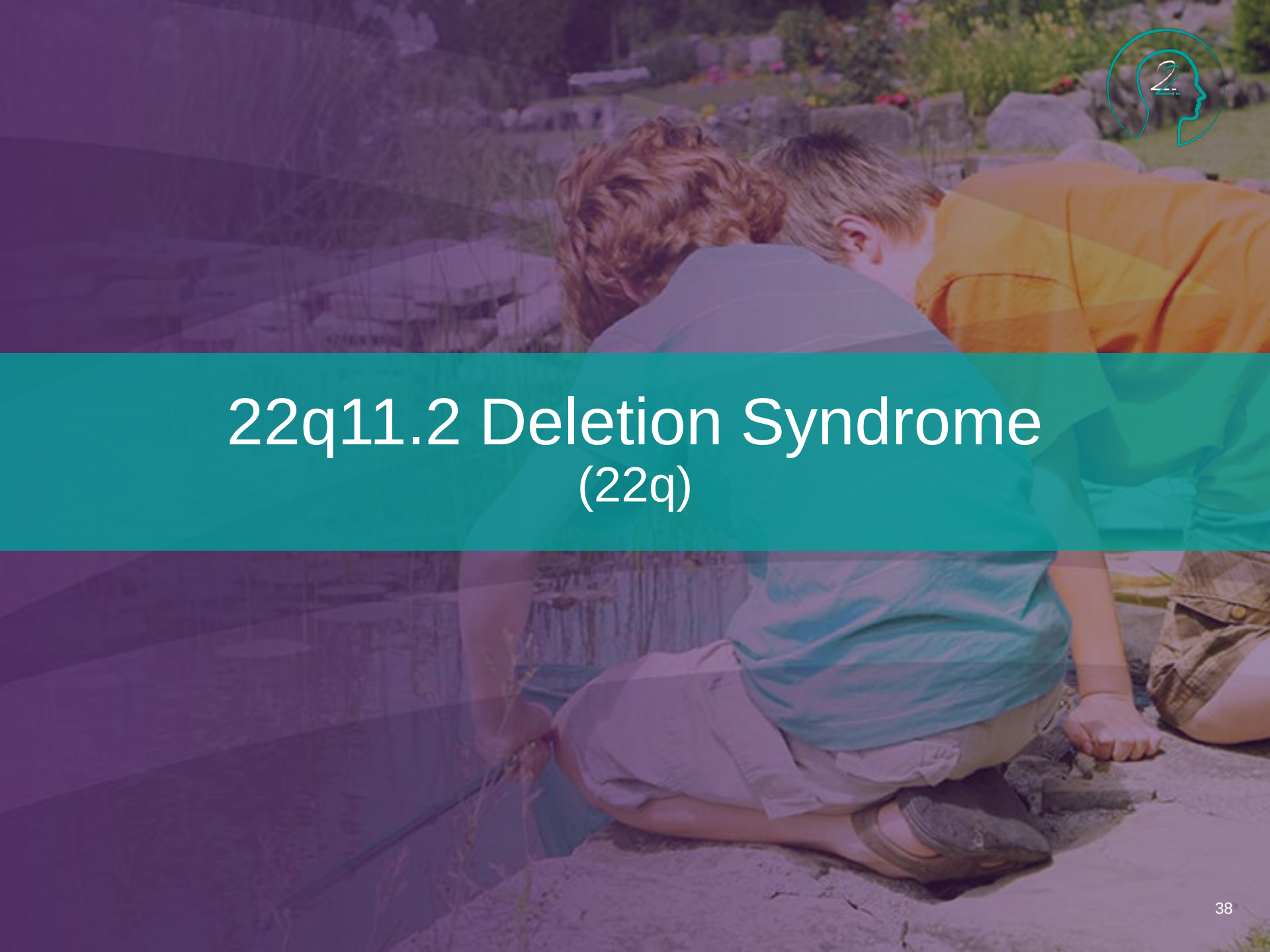
Next Steps in ASD Program

- Zynerba Intends to discuss the results of the Phase 2 BRIGHT trial and the path forward with the FDA in 1H2021
- Present additional data at future medical meetings



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

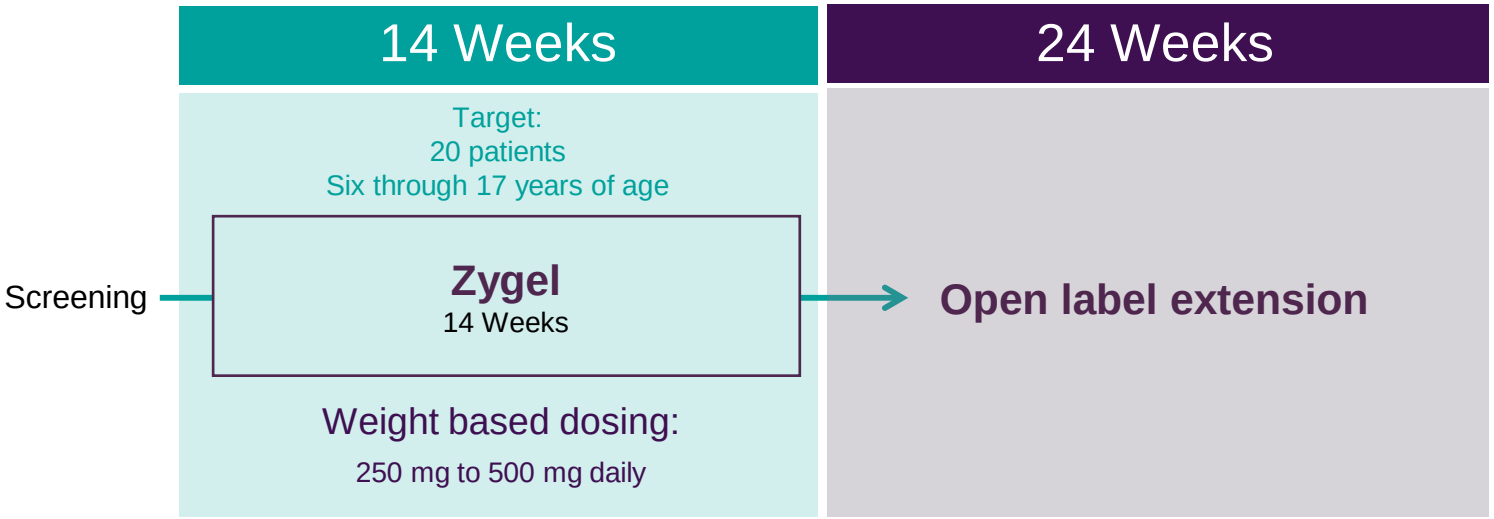
Rationale for Developing Zygel in 22q

- Cannabidiol 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
- Orphan Drug designation received for Cannabidiol for treatment of 22q

INSPIRE Phase 2 Trial in 22q

Enrollment Ongoing

Assessing the Impact of Zygel (Transdermal Cannabidiol 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

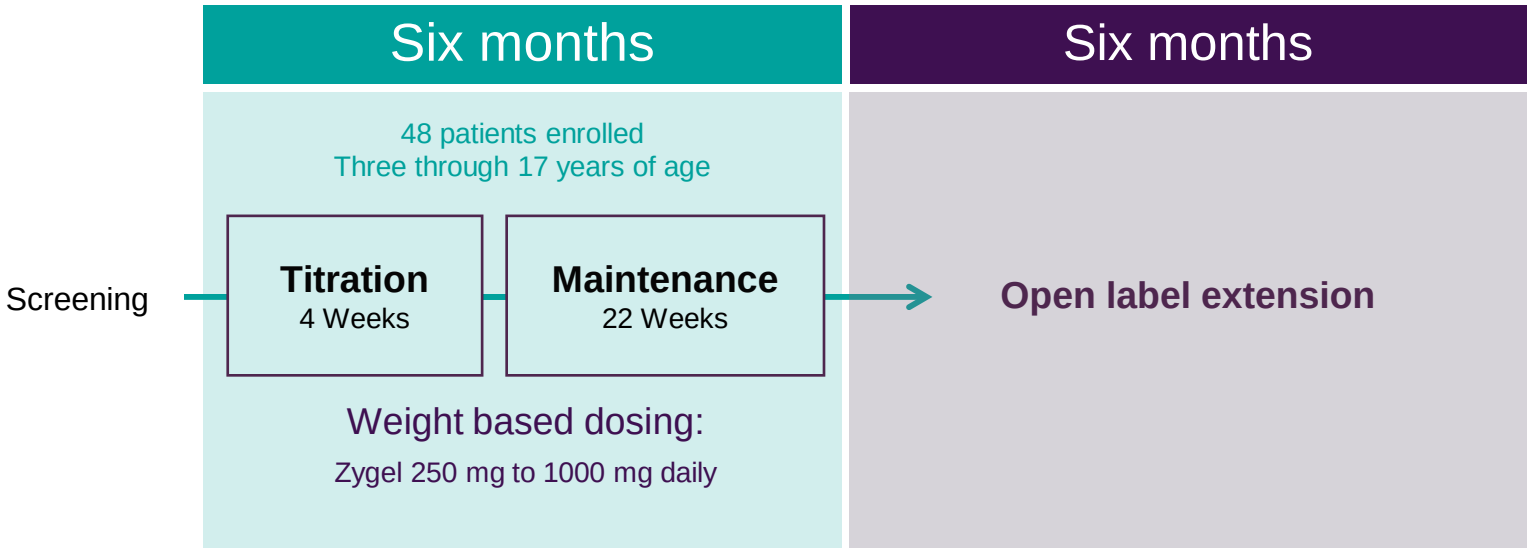
DEE Patients are Medically Fragile

- 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)

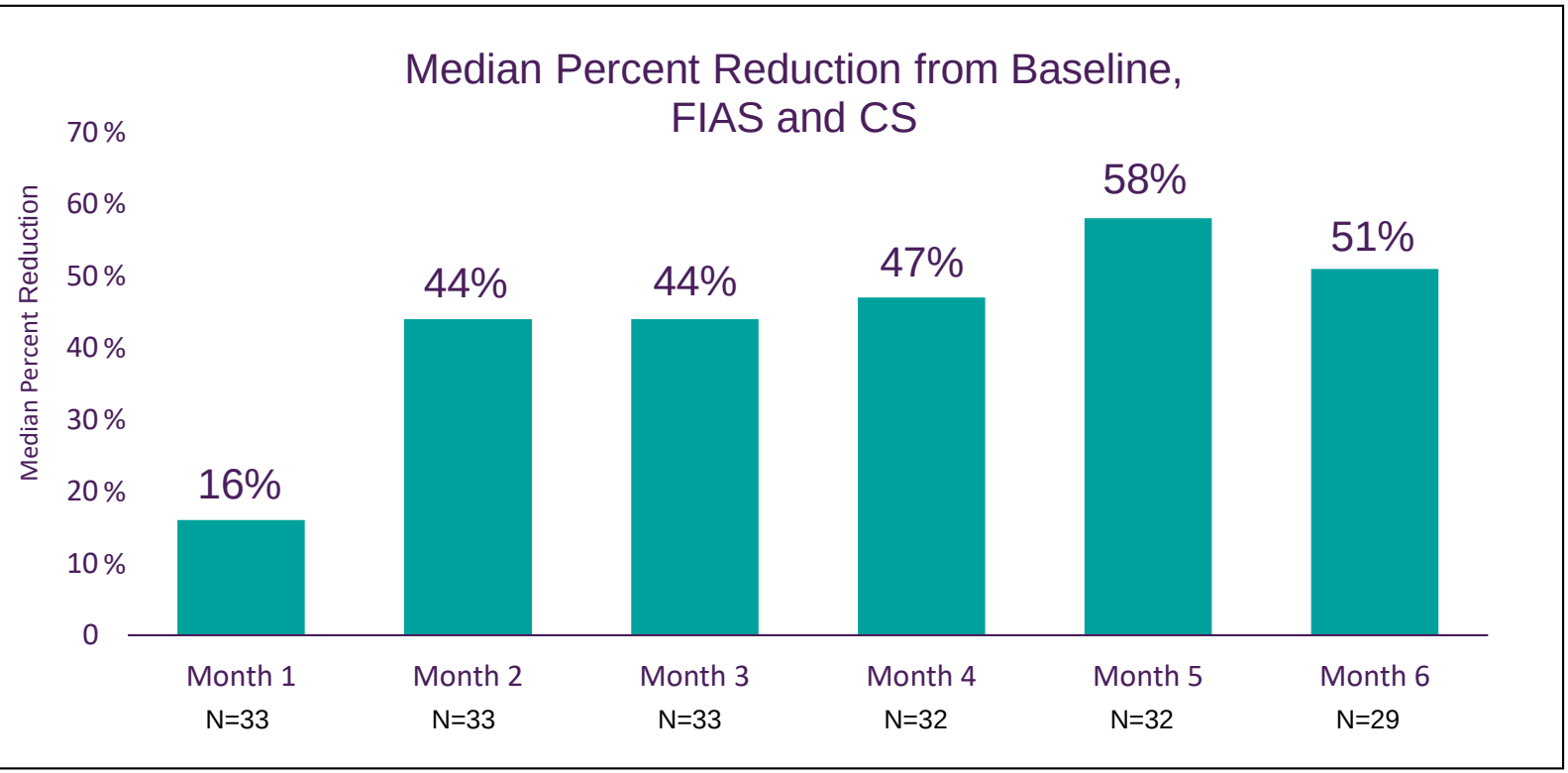
BELIEVE Phase 2 Trial in DEE

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

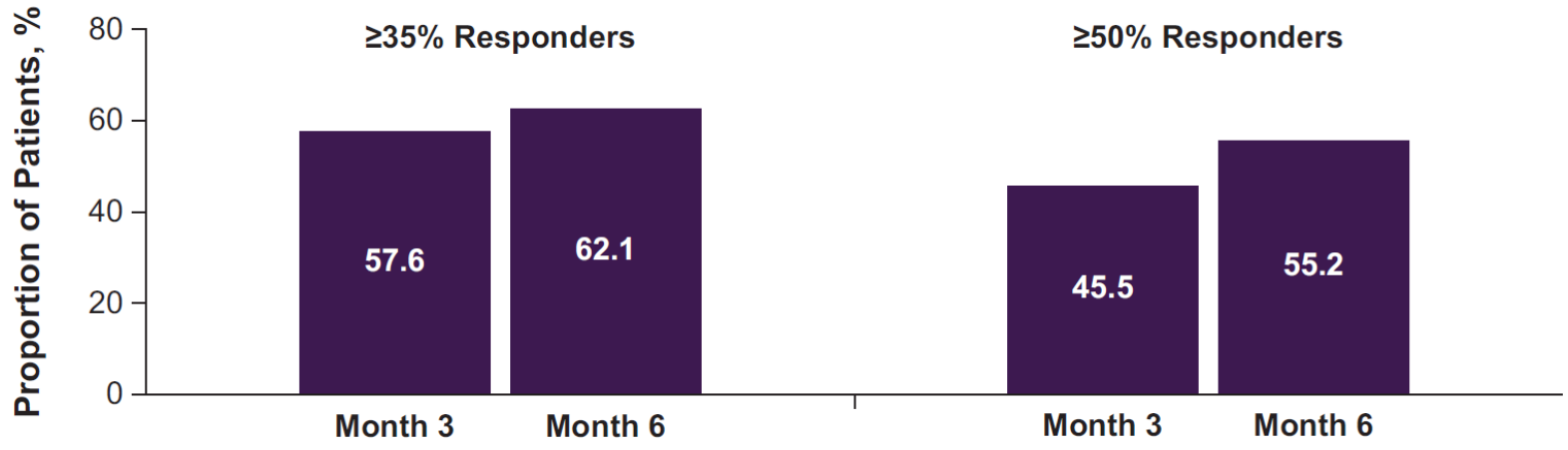


BELIEVE: Clinically Meaningful Seizure Reductions from Baseline and Sustained through Six Months in DEE



BELIEVE: Percentage of Patients with ≥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

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

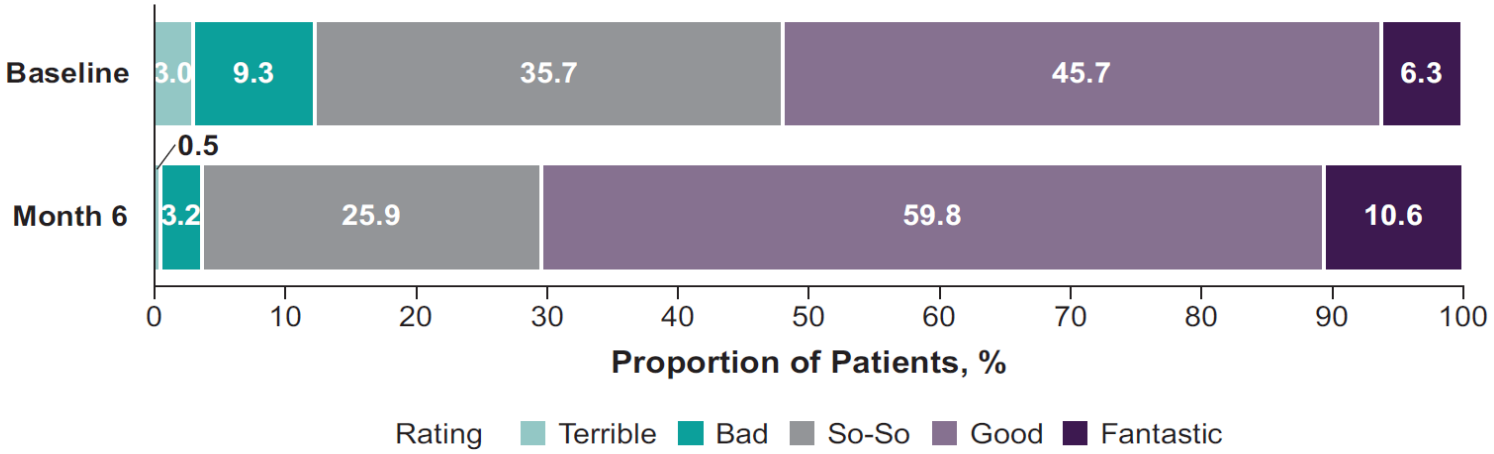
BELIEVE: Qualitative Assessments of Behavioral and Cognitive Improvements

- 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

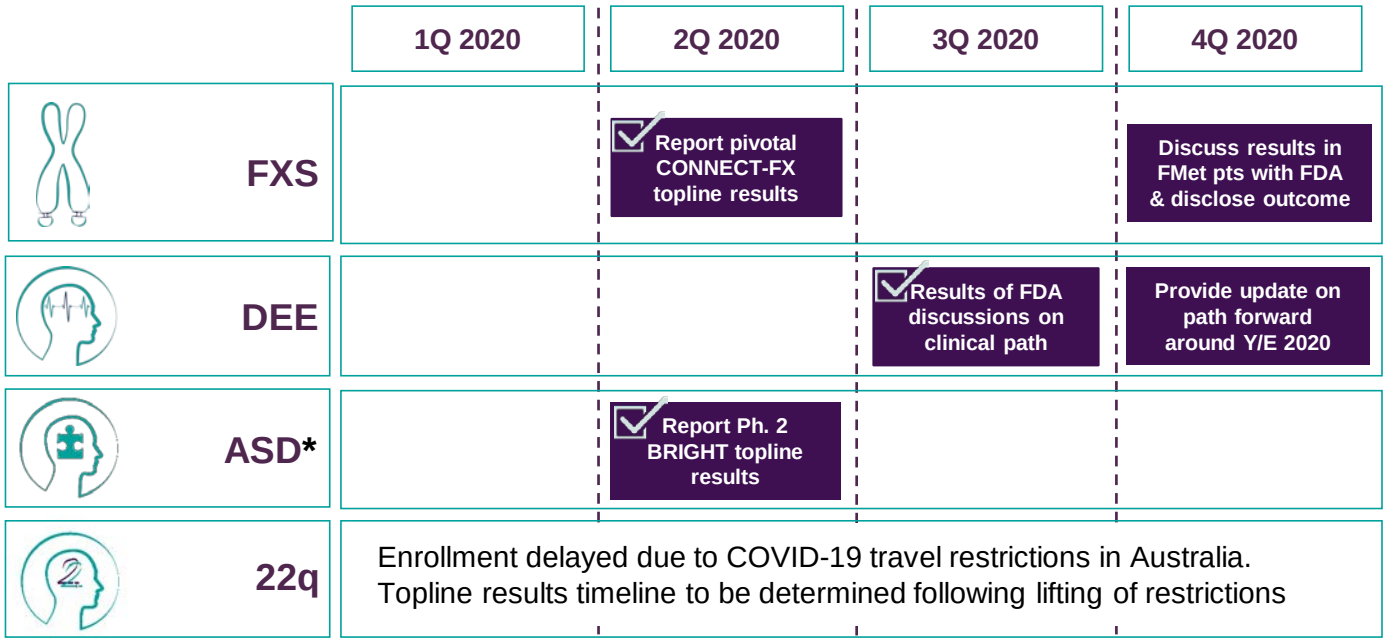
Compelling Results Suggest a Potential Pathway to Pivotal Trials

- 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
- The FDA supports a development program which would treat focal-impaired awareness and convulsive seizures
- Due to the heterogeneity of DEE patients, FDA suggests pursuing individual syndromes rather than considering DEE as a single condition
- The Company is evaluating specific DEE syndromes as possible clinical targets; expect to provide update around year-end 2020

Financial Strength

- Clean balance sheet
  - No debt, 29.4 M shares outstanding (as of November 5, 2020)
- Cash and cash equivalent position of $64.3M as of September 30, 2020
- Cash runway expected to be sufficient to fund operations and capital requirements until late in the fourth quarter of 2021

Expected Clinical Milestones in 2020



***Note: Zynerba Intends to discuss the results of the Phase 2 BRIGHT trial and the path forward with the FDA in 1H2021**

Corporate Overview

November 2020