Corporate Overview

January 2021

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 targeting high unmet medical needs; translating into multi-billion dollar market opportunity with Zygel™ (Cannabidiol Gel)
- Focused on completing development of Zygel in Fragile X Syndrome (FXS)
  - Pre-planned ad hoc analyses of CONNECT-FX data identified patient population who appear to benefit from Zygel
  - As a result of meeting with FDA in 4Q2020, Zynerba plans to conduct a trial in patients with a highly methylated *FMR1* gene to confirm positive results seen in CONNECT-FX responders
- Continuing to pursue three additional neuropsychiatric indications:
  - 22q11.2 deletion syndrome (22q) – Phase 2 ongoing
  - Autism spectrum disorder (ASD) – Phase 2 complete
  - Developmental and epileptic encephalopathies (DEE) – Phase 2 complete
- Experienced team with development and commercial expertise in transdermal delivery, orphan diseases, neurology, and psychiatry
- Cash runway expected to be sufficient to fund operations into 2023

Deep Clinical Pipeline & Near-term Milestones

Zygel
Cannabidiol Gel

Indication	Preclinical	Phase 1	Phase 2	Pivotal	Expected Milestones
Fragile X Syndrome (FXS)*					
	Preparing for confirmatory trial				Review trial design and protocol with FDA in 1H21; initiate confirmatory pivotal trial before the end of 2021
22q Deletion Syndrome (22q)**					
	INSPIRE: Ongoing				Completion of enrollment once COVID-19 restrictions in Australia are eased
Autism Spectrum Disorder (ASD)					
	BRIGHT: Topline data released				Discuss Phase 2 results and regulatory path forward with FDA in 1H2021
Developmental and Epileptic Encephalopathies (DEE)					
	BELIEVE: Topline data released				Finalize target syndrome selection in 2021

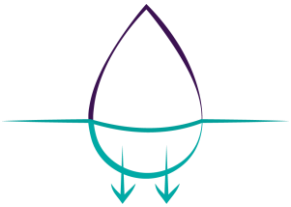
*Orphan Drug and Fast Track designation
**Orphan Drug designation

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

Fragile X Syndrome (FXS)

FXS

- Rare genetic developmental disability
- Leading known cause of both inherited intellectual disability and ASD
- No approved drugs indicated for FXS
- Symptoms linked to deficiencies in the endocannabinoid system (ECS)
- Mutation impacts *FMR1* gene and causes ECS dysregulation, causing core cognitive, social, and behavioral symptoms of FXS
  - Easily identified mutation manifests as multiple CGG repeats in *FMR1* (full mutation = >200 repeats)
- U.S. patents provide IP protection to 2038

~70K U.S. patients with full mutation FXS

Role of *FMR1* Methylation

- *FMR1* gene codes for production of FMRP* which is vital to synapse development
- Methylation of *FMR1* also plays a role in determining functionality of the gene
  - When methylation of *FMR1* silences the gene, no FMRP is produced: Systems and processes affected by FMRP become dysregulated
- These patients are generally the most severely impacted by the disorder: lower IQ, more impacted behaviors
  - ~60% of patients are believed to fall into this category

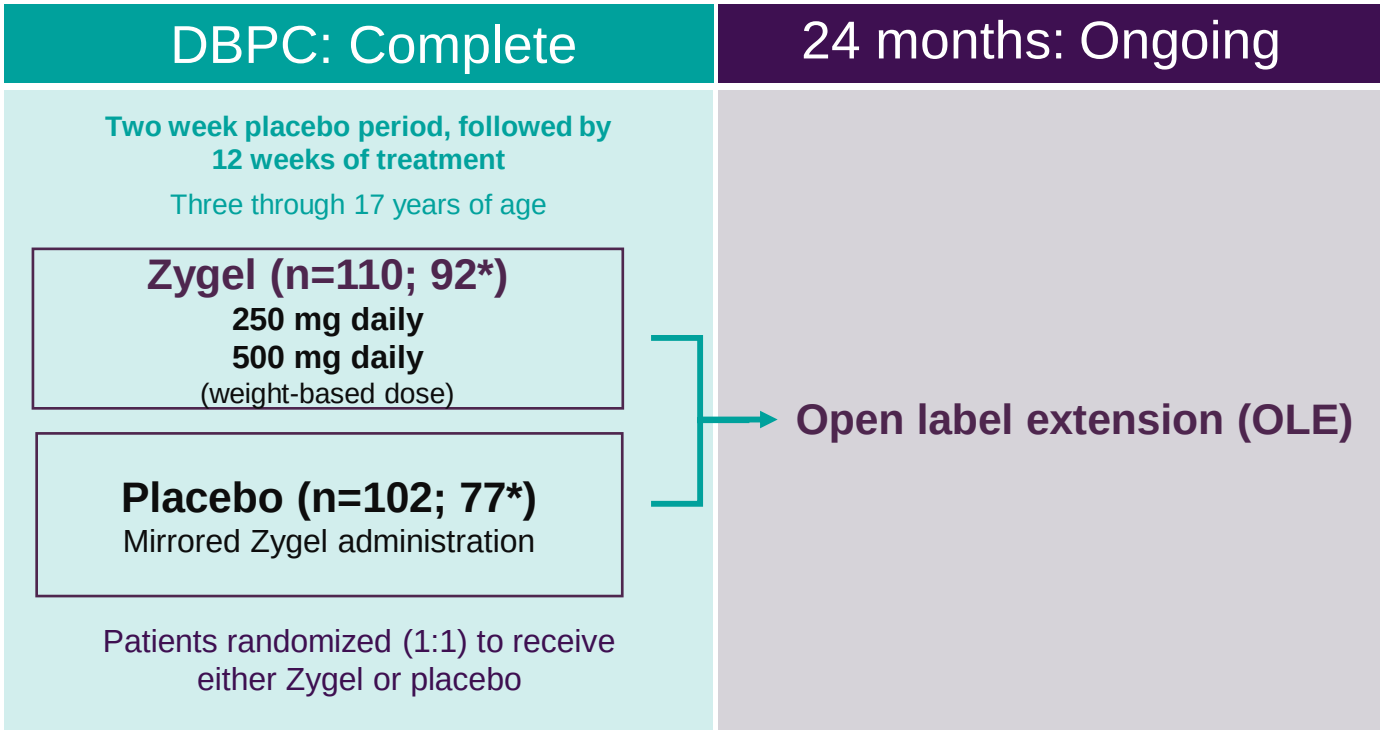
~40K U.S. patients ≥90% FMR1 methylation

FXS is routinely diagnosed by assessing (1) CGG repeats and (2) methylation status

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

CONNECT-FX Trial Design

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



*Patients with ≥90% *FMR1* methylation (167 total ~ 80% of trial population) included in pre-planned ad hoc analyses

CONNECT-FX

Endpoints and Data Collected

- 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

CONNECT-FX Results: ≥90% *FMR1* Methylation

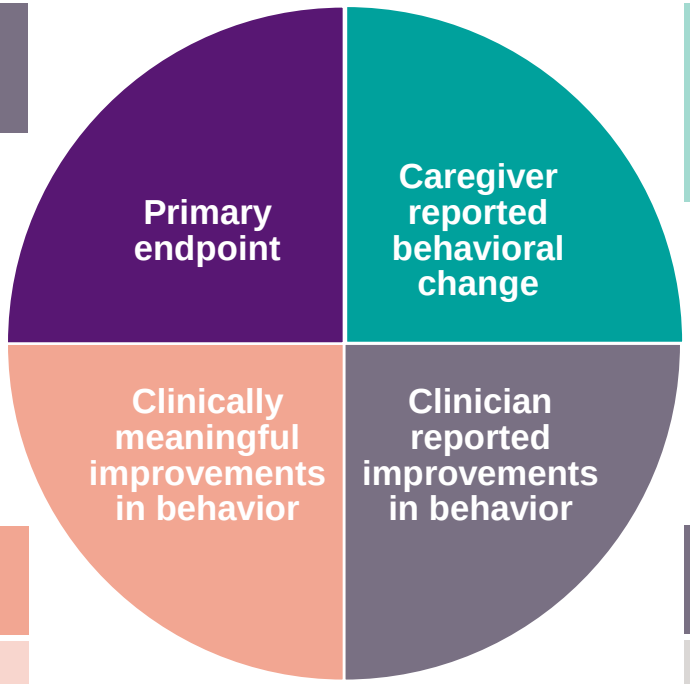
Consistent Improvements Observed with Zygel vs. Placebo

ABC-C_{FXS} Social Avoidance subscale

40% median percent improvement in socially avoidant behaviors (*p*=0.020*)

Caregiver Global Impression of Change

Social interaction (*p*=0.002*)
Irritable/Disruptive Behaviors (*p*=0.028*)
Social Avoidance/Isolation (*p*=0.038*)
Overall behavior (*p*=0.052)



Clinically meaningful improvement on drug

Significantly more pts achieved a clinically meaningful change in Social Avoidance (*p*=0.031*) and Irritability (*p*=0.036*) with Zygel

Clinical Global Impression of Improvement (anchored)**

Trend toward statistical significance (*p*=0.056)

* Statistically significant

** Not specific to Social Avoidance

Full data available in June 30, 2020; July 22, 2020; and October 15, 2020 press releases

CONNECT-FX: Safety

- Zygel was very well tolerated
- No serious or severe adverse events reported during the trial
- 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

The Path Forward For Zygel in FXS

Regulatory Update

- Zynerba plans to conduct a single double blind, placebo controlled pivotal trial in patients with a highly methylated *FMR1* gene to confirm results seen in CONNECT-FX responders
  - If results are positive, we believe this trial will be sufficient to support an NDA submission
  - Primary endpoint will be the Social Avoidance subscale of the ABC-C_{FXS}

Next Steps

- Trial design and protocol development ongoing for planned confirmatory trial in CONNECT-FX responder population
  - Type C meeting with FDA expected in 1H21 to review trial design and protocol
  - Initiation of confirmatory trial is expected before the end of 2021 and timing will be clarified after Type C meeting

Autism Spectrum Disorder (ASD)

ASD

- Near-rare disorder
- 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
  - Neither address the key symptoms of social impairment and anxiety

~1M U.S. children and adolescents with ASD

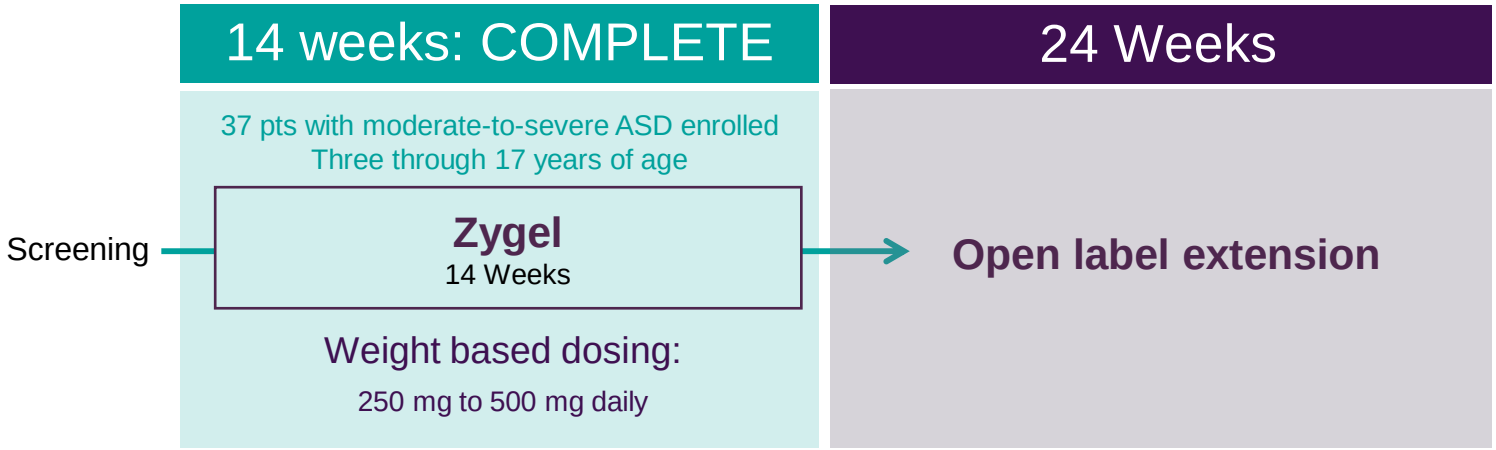
Rationale for Developing Zygel in ASD

- Results from clinical trials of Zygel suggest spectrum of activity against core behaviors
- Newer studies suggest ASD is linked to disruption of the ECS
  - Altered anandamide signaling may contribute to ASD-related social and communication impairments
  - ECS system modulates many cellular functions and molecular pathways altered in ASD
    - Cannabidiol may modulate the EC system and improve certain autism-related behaviors
- Evidence suggests that cannabidiol may improve social avoidance and anxiety

Recent U.S. patents provide IP protection to 2038

BRIGHT Phase 2 Trial in ASD

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

Results of BRIGHT Phase 2 Trial

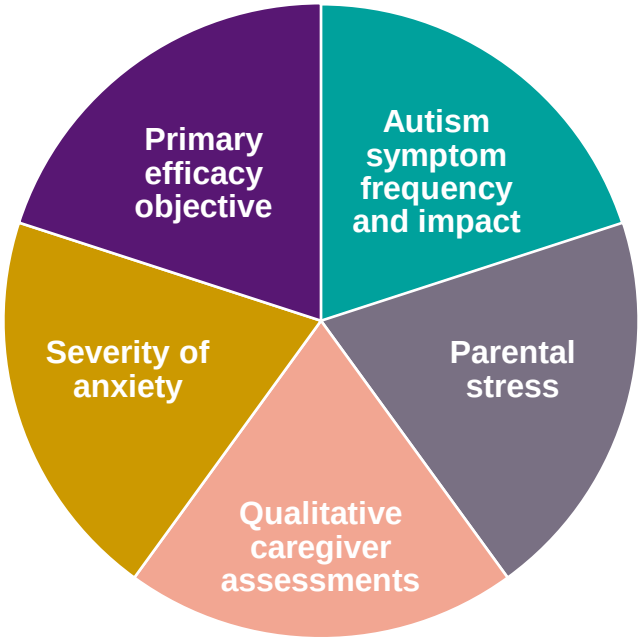
Statistically Significant Results at Week 14 Compared to Baseline

ABC-C subscales
% improvement

Irritability: 39.1% (*p*<0.0001*)
Inappropriate Speech: 42.5% (*p*=0.0002*)
Stereotypy: 39.1% (*p*<0.0001*)
Social Withdrawal: 36.4% (*p*<0.0001*)
Hyperactivity: 35.6% (*p*<0.0001*)

Parent Rated Anxiety Scale for ASD (PRAS-ASD)

Mean improvement of 46%
(*p*<0.0001*)



Autism Impact Measure (AIM)
% improvement

Atypical behavior: 34.1% (*p*<0.001*)
Communication: 19.7% (*p*<0.001*)
Peer interaction: 19.8% (*p*<0.001*)
Repetitive behavior: 32.1% (*p*<0.0001*)
Social reciprocity: 10.7% (*p*=0.0053*)

Autism Parenting Stress Index

Mean improvement of 38.9%
(*p<0.0001**)

Qualitative Caregiver Behavioral Problems Survey
% Improvements

Behavioral: 69% improved
Social: 63% improved
Emotional: 72% improved

* Statistically significant

Full data available in May 26, 2020 and October 15, 2020 press releases

Well Tolerated Safety 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 trial

Next Steps in ASD Program

- In 1H2021, Zynerba intends to discuss data supporting the potential efficacy of Zygel in ASD, including the results of the Phase 2 BRIGHT trial, with the FDA to determine the regulatory path forward
- Present additional data at future medical meetings

22q11.2 Deletion Syndrome (22q)

22q

- Rare disorder; most common contiguous gene deletion syndrome
- Midline condition with abnormalities affecting palate, face, heart and other organs; surgically corrected in infancy
- Neuropsychiatric illnesses (anxiety disorders, ASD) and learning disabilities common
  - 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
- No drugs currently approved to treat 22q

~81K U.S. patients with 22q

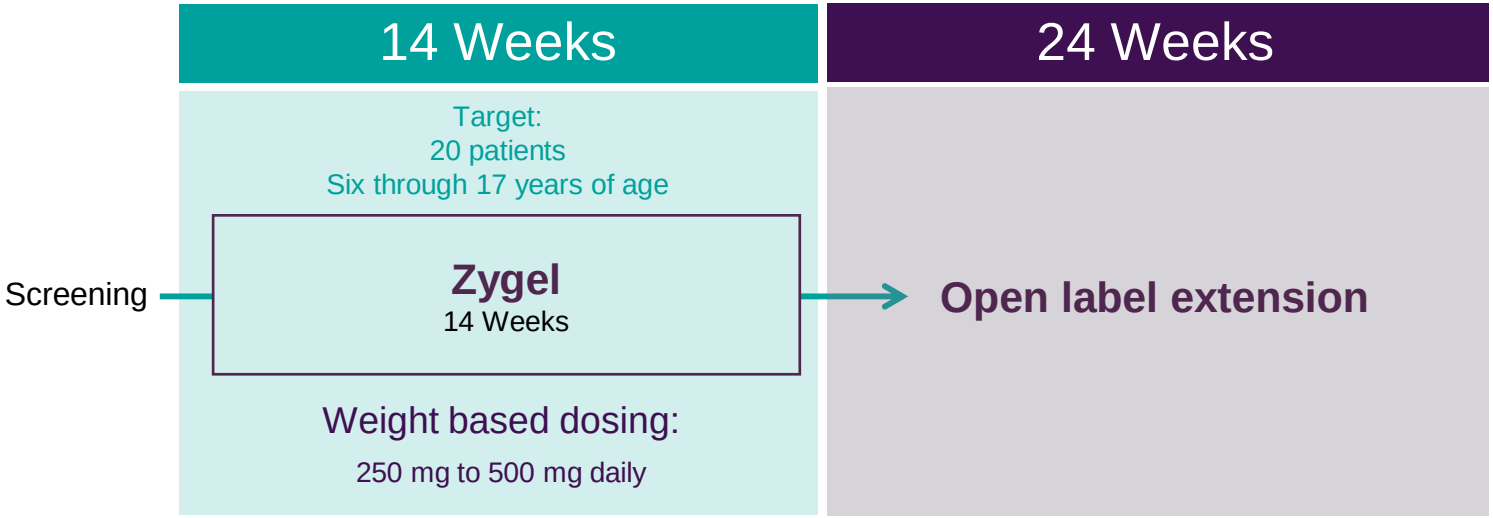
Rationale for Developing Zygel in 22q

- Overlapping target symptoms in FXS and ASD have been shown to respond to Zygel in trials to date
- Cannabidiol may treat neuropsychiatric symptoms due to activity as:
  - Modulator of endocannabinoid system
  - Agonist at serotonin$_{1A}$ receptors
  - Antagonist at GPR55 receptors
- Phase 2 trial underway in pediatric and adolescent patients with 22q
  - Enrollment delayed due to COVID-19 restrictions in Australia; topline results timeline to be announced following lifting of restrictions

Orphan Drug designation for treatment of 22q

INSPIRE Phase 2 Trial in 22q

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

Developmental and Epileptic Encephalopathies (DEE)

DEE

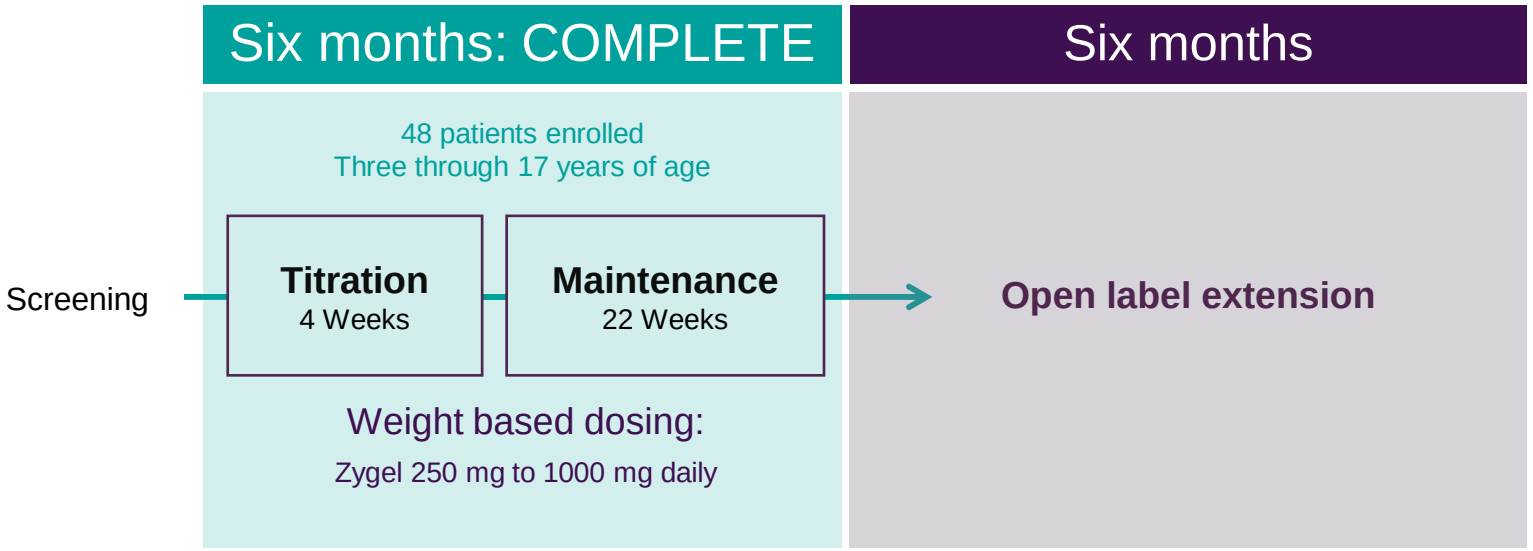
- Group of rare / ultra rare childhood-onset epilepsies with impaired or regressed developmental progress
- Cognitive impairment, psychiatric problems, and behavioral disturbances are phenotypic
- Medically fragile population
  - Comorbidities include cerebral palsy, chronic respiratory infections, gait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

Developing Zygel in DEE

- Strong positive data observed in open label BELIEVE trial
- Due to the heterogeneity of DEE patients, FDA suggests pursuing individual syndromes rather than considering DEE as a single condition
- Evaluation of potential target indication(s) is ongoing
- Expect to finalize target syndrome selection in 2021 in one or more DEE syndromes

BELIEVE Phase 2 Trial in DEE

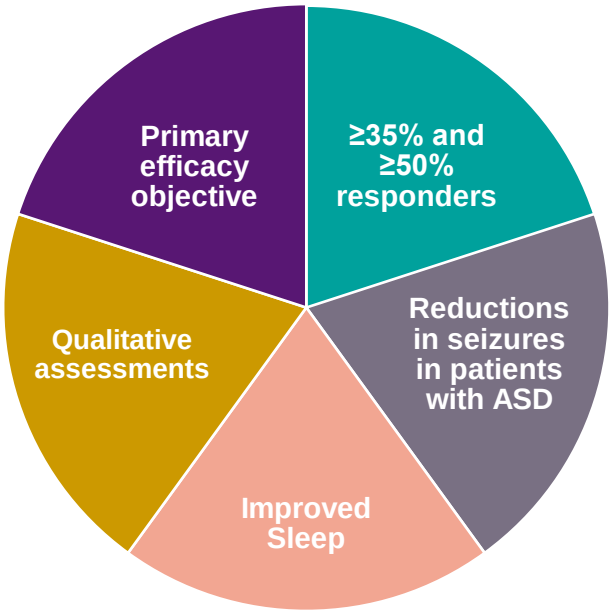
Open LaBel Study to Assess the Safety and Efficacy of ZYN002 Administered as a TransdermaL Gel to ChIldren and AdolEscents with DeVelopmental and Epileptic Encephalopathy



Results of BELIEVE Phase 2 Trial

Clinically Meaningful Improvements in FIAS / TCS and QoL vs. Baseline

Mean % Reductions in Seizures
Month 3 (n=33): 44%
Month 6 (n=29): 51%
Month 9 (n=18): 60%
Month 12 (n=18): 73%



% of patients with ≥35% and ≥50% Reductions in FIAS and TCS	
≥35% reductions	**≥50% reductions**
Month 3: 58%	Month 3: 46%
Month 6: 62%	Month 6: 55%
Month 12: 89%	Month 12: 83%

ELDQOL	Caregiver Feedback
Statistically significant reductions in subscale scores for seizure severity, behavior, and mood (p<0.01)	Verbatim feedback included improved vitality, concentration and cognition, and school improvement

Mean % Reductions in Seizures: Comorbid ASD
Month 3 (n=33): 45%
Month 6 (n=29): 59%
Month 9 (n=18): 67%
Month 12 (n=18): 74%

Sleep Disturbance Scale for Children (SDSC) % Improvement
Statistically significant improvements observed in
Total Score: 36%; p=0.012
Disorders of initiating/maintaining sleep: 22%; p=0.006
Disorders of arousal/nightmares: 100%; p=0.031
Sleep wake transition disorder: 31%; p=0.030

Full data available in September 18, 2019 and December 4, 2020 press releases

BELIEVE Safety

Zygel Well Tolerated over 12 months: No Safety Signal Identified

- Tolerability profile consistent with the safety database for Zygel
- Most treatment-emergent adverse events (TEAEs) (any event, whether unrelated or related to study drug) were mild or moderate
- Two SAEs deemed possibly drug-related (LRTI and status epilepticus)
- No drug-related clinically significant changes in vital signs, ECGs, or laboratory findings

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 into 2023

Deep Clinical Pipeline & Near-term Milestones

Zygel
Cannabidiol Gel

Indication	Preclinical	Phase 1	Phase 2	Pivotal	Expected Milestones
Fragile X Syndrome (FXS)*					
	Preparing for confirmatory trial				Review trial design and protocol with FDA in 1H21; initiate confirmatory pivotal trial before the end of 2021
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**Orphan Drug designation

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