Corporate Overview

September 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 INCLUDING RECONNECT TRIAL 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; THE COMPANY’S PLANNED RECONNECT TRIAL MAY NOT BE DETERMINED TO BE SUFFICIENT TO SUPPORT AN NDA SUBMISSION; 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)
  - Confirmatory RECONNECT pivotal trial initiated September 2021, with topline results expected 2H 2023
- Company guidance on path forward in three additional neuropsychiatric indications by end of 2021 following evaluation and prioritization of development plans:
  - Autism spectrum disorder (ASD) – Phase 2 complete
  - 22q11.2 deletion syndrome (22q) – Phase 2 ongoing
  - 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 well into 1H 2024

Deep Clinical Pipeline & Near-term Milestones

Zygel
Cannabidiol Gel

Indication	Preclinical	Phase 1	Phase 2	Pivotal	Expected Milestones
Fragile X Syndrome (FXS)*					
	RECONNECT: Pivotal confirmatory trial initiated				**Topline results expected 2H 2023**
Autism Spectrum Disorder (ASD)					
	BRIGHT: Topline data released				**Company guidance on path forward by end of 2021**
22q Deletion Syndrome (22q)**					
	INSPIRE: Ongoing				**Screening of patients has resumed; timing for top line results TBD when enrollment complete**
Developmental and Epileptic Encephalopathies (DEE)					
	BELIEVE: Data published 9/3/21 in JAMA Network Open				**Finalize target syndrome selection in 2021**

*Orphan Drug and Fast Track designation

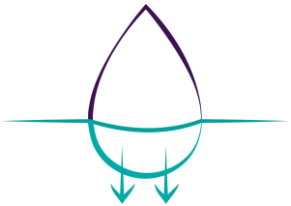
**Orphan Drug designation

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
- ~60% of patients are believed to fall into the completely methylated category

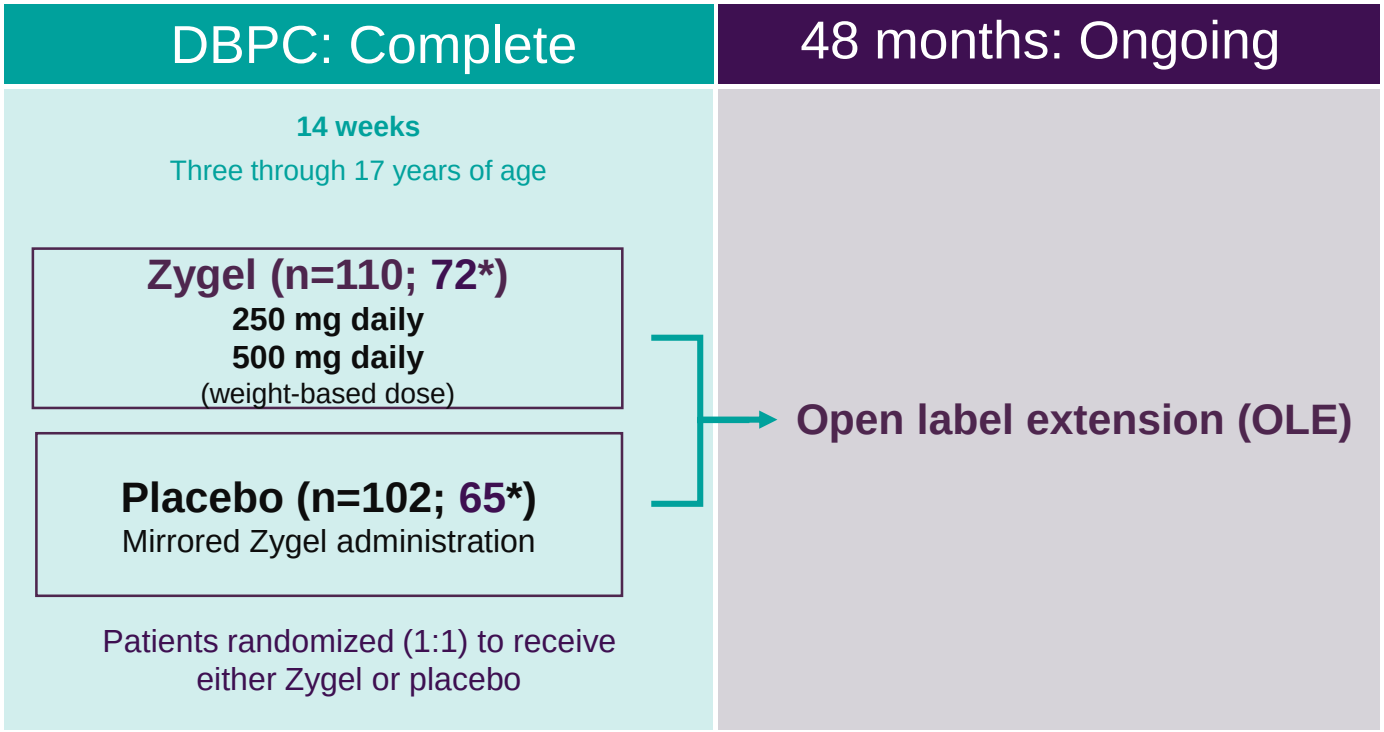
~40K U.S. patients with complete methylation

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 complete methylation of their *FMR1* gene (137 total ~ 65% of trial population)**

CONNECT-FX

Endpoints and Data Collected

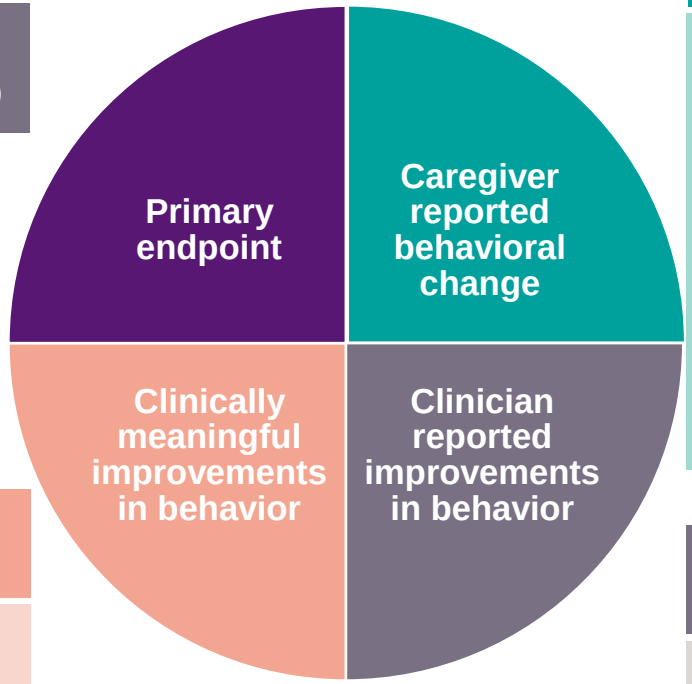
- Primary endpoint:
  - Change from baseline to end of treatment in ABC-C_{FXS} Social Avoidance subscale
- Key secondary endpoints:
  - Change from baseline to end of the treatment in
    - ABC-C_{FXS} Irritability subscale score
    - ABC-C_{FXS} Socially Unresponsive/Lethargic subscale score
  - Improvement 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: Complete *FMR1* Methylation

Consistent Improvements Observed with Zygel vs. Placebo

ABC-C_{FXS} Social Avoidance subscale

40% median percent improvement in socially avoidant behaviors (*p*=0.027*)



Caregiver Global Impression of Change

Any Improvement
Zygel vs placebo

Social interaction
63% vs 37% (*p*=0.005*)

Irritable/Disruptive Behaviors
54% vs 33% (*p*=0.027*)

Social Avoidance/Isolation
58% vs 46% (*p*=0.195)

Overall behavior
61% vs 46% (*p*=0.100)

Clinically meaningful improvement on drug

Significantly more pts achieved a clinically meaningful change
Zygel vs placebo
Social Avoidance (≥ 3 points)
56% vs 37% (*p*=0.030*)
Irritability (≥ 9 points)
37% vs 26% (*p*=0.232)

Clinical Global Impression of Improvement (anchored)**

Any Improvement
Zygel vs placebo
50% vs 36%
(*p*=0.128)

* Statistically significant

** Not specific to Social Avoidance

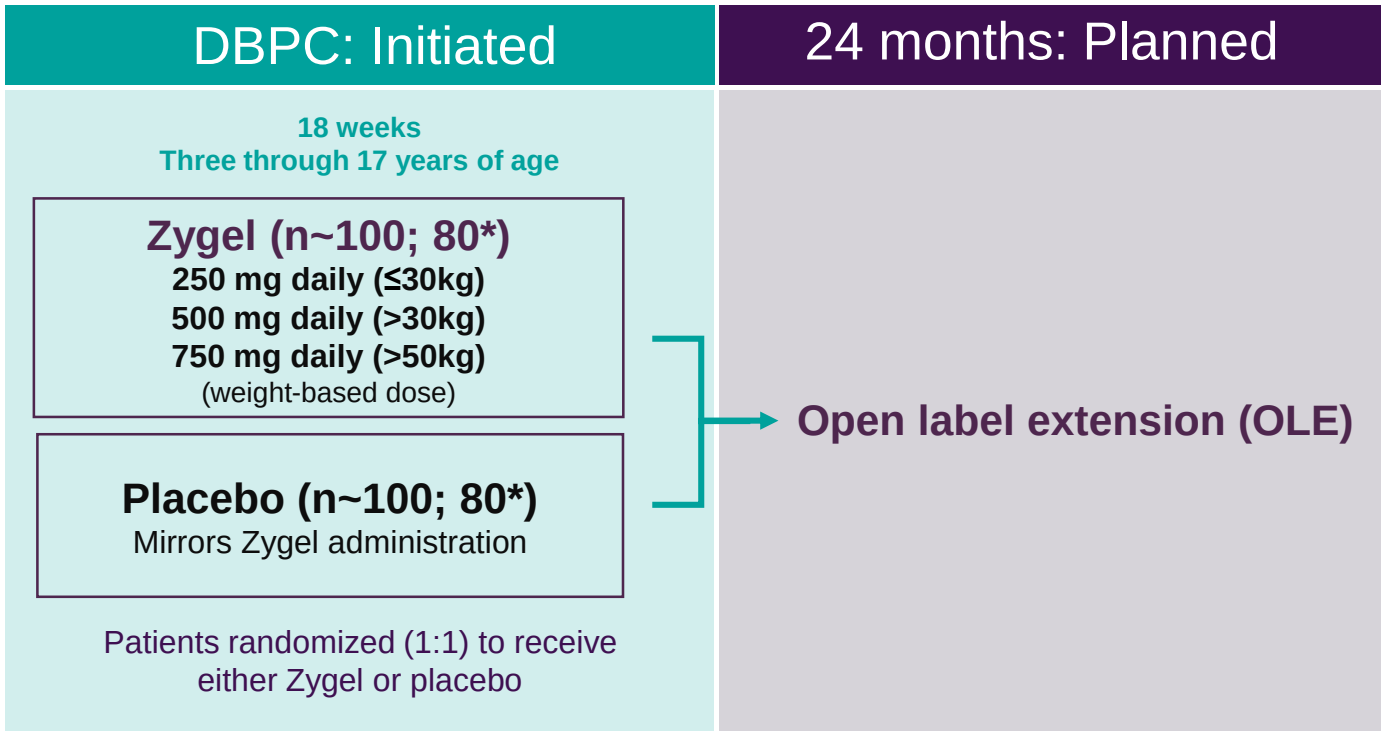
N=136 patients with complete methylation

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

RECONNECT Trial Design

Randomized, Double-Blind, Placebo-Controlled, Multiple-Center, Efficacy and Safety Study of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with Fragile X Syndrome



***Patients with complete methylation of *FMR1* gene**

RECONNECT Trial Design

Primary endpoint

- Change from baseline to end of treatment in ABC-C_{FXS} Social Avoidance subscale in patients who have complete (100%) methylation of the *FMR1* gene

Secondary endpoints

- Change from baseline to end of treatment in:
  - ABC-C_{FXS} Irritability subscale in patients who have complete methylation
  - ABC-C_{FXS} Social Avoidance subscale among all randomized patients (complete and partial methylation)
- Percent of patients:
  - Any improvement on the Caregiver Global Impression of Change (CaGI-C) for Social Interactions among patients with complete methylation
  - Rated as improved on the Clinical Global Impression- Improvement (CGI-I) scale among patients with complete methylation

RECONNECT Trial Design

Key study design elements

- 18 week trial design will allow us to evaluate improvement in behavioral symptoms over time

- Added a third dosing group of 750 mg for individuals >50 kg to maintain appropriate dosing levels for patients

- Made trial more patient and family friendly than CONNECT–FX trial – virtual visits, fewer assessments administered, reduced frequency of lab and ECG tests, provided each family an electronic tablet for recording of assessments and skin diaries

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

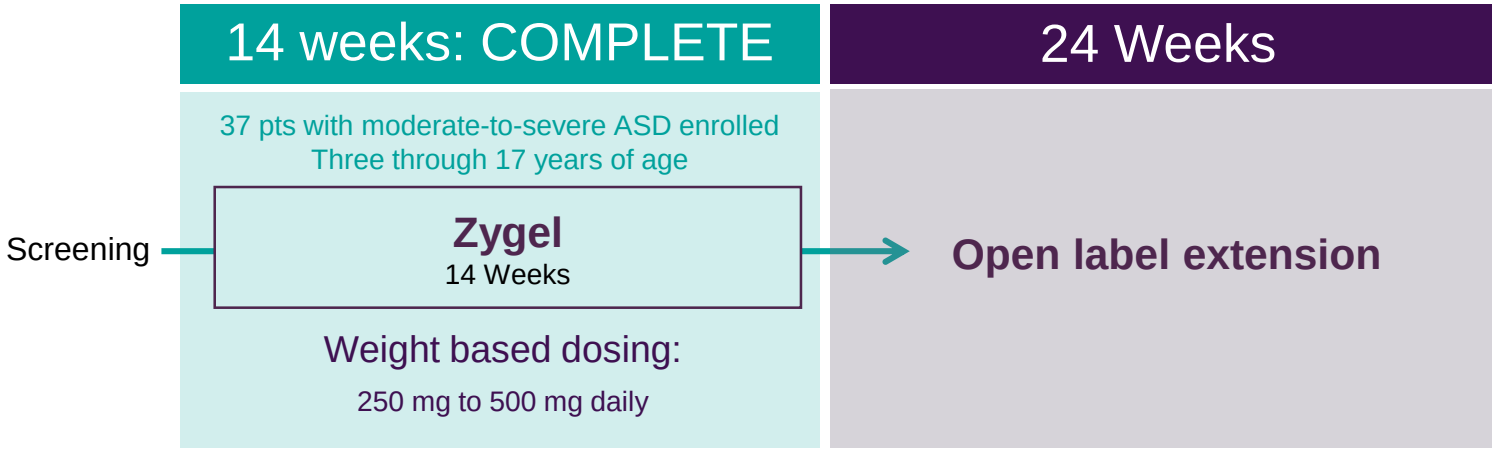
Rationale for Developing Zygel in ASD

- 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

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

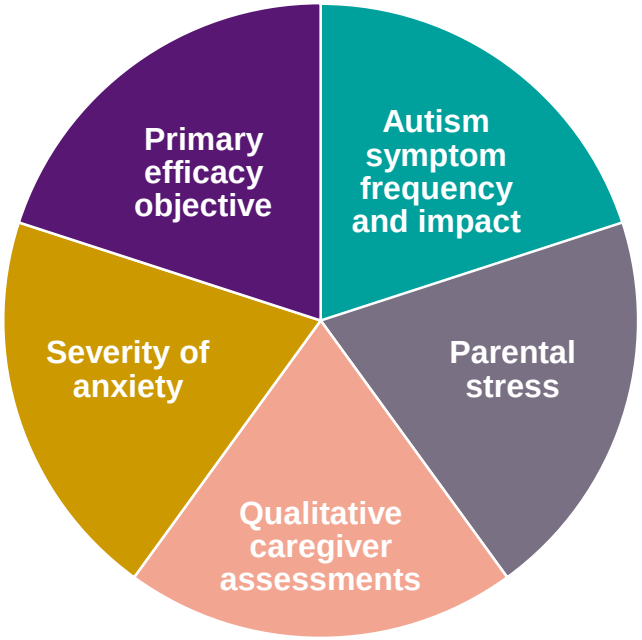
Statistically Significant Results at Week 14 Compared to Baseline

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

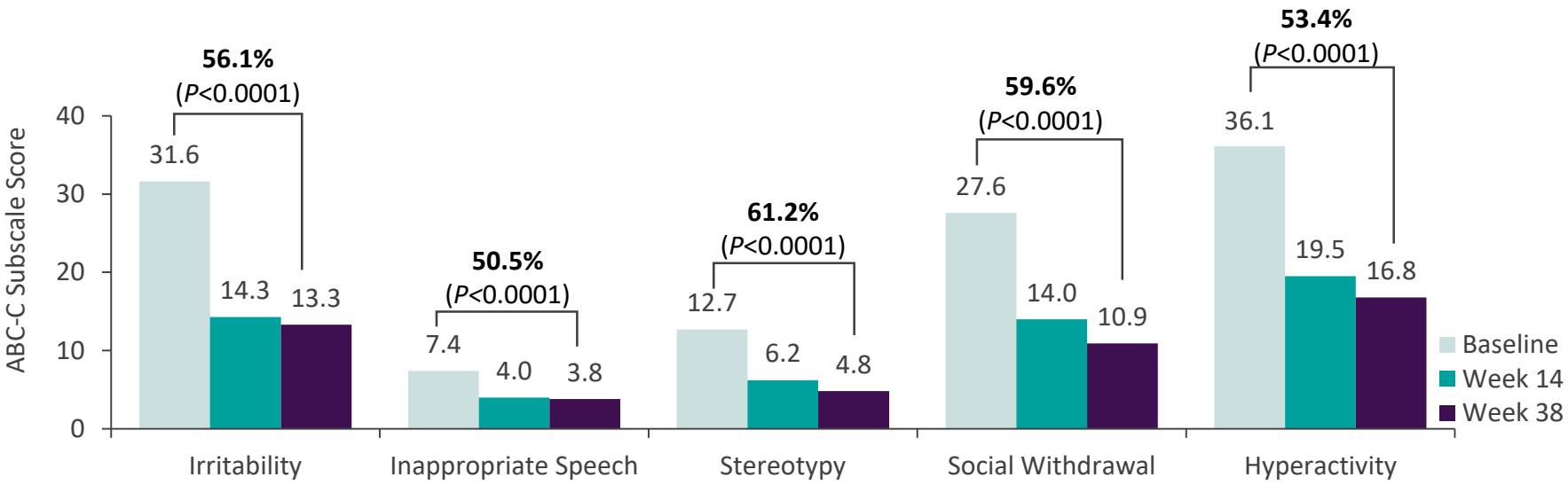
* Statistically significant

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

BRIGHT Phase 2 Trial in ASD

Statistically Significant Improvements from Baseline In All ABC-C Subscale Scores Sustained Through Week 38[1]

Mean Scores and Percent Improvement Through Week 38*



n=18

*Lower values reflect improvement in each ABC-C subscale.

[1]18 of 27 patients that completed week 14 demonstrated ≥35% improvement in the ABC-C at week 14 and were allowed to continue treatment for additional 24 weeks.

Well Tolerated Safety Profile in BRIGHT Trial in ASD

- Well tolerated and consistent with previously released data at week 14 and week 38, compared to baseline
- Approximately half the patients experienced a treatment-emergent adverse event (TEAE; any event, whether unrelated or related to study drug): 49% through week 14 and 54% at week 38
  - Most were mild and transient
- Only 14% and 19% of patients experienced a treatment-related AE at week 14 and week 38, respectively
  - All application site-related at week 14
  - Most application site-related and 1 each of sleep disorder, increased appetite and pollakiuria at week 38
- No severe or serious AEs reported during the 38-week trial

Next Steps in ASD Program

- In 1H 2021, Zynerba discussed 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
- Positive guidance from FDA included agreement on utilizing the irritability subscale of the Aberrant Behavior Checklist – Community (ABC-C) as the primary endpoint to support an indication for the treatment of irritability in ASD
- Company guidance on path forward by end of 2021
- 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

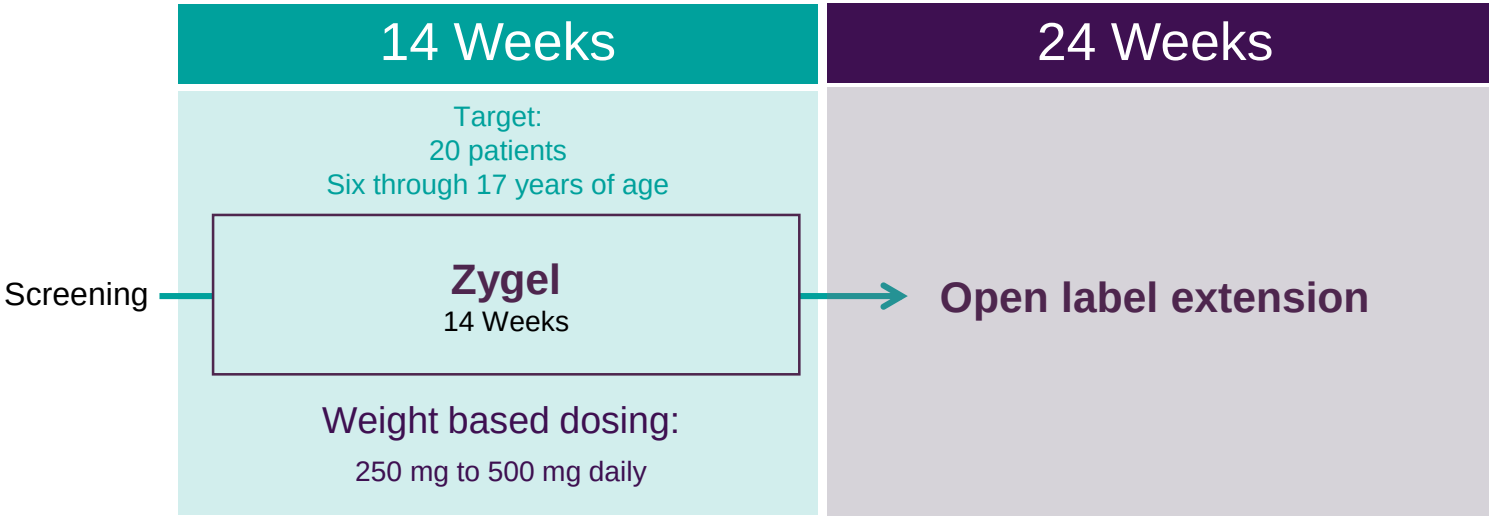
Rationale for Developing Zygel in 22q

- 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; screening has resumed in March 2021; topline results timeline to be announced following completion of enrollment

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

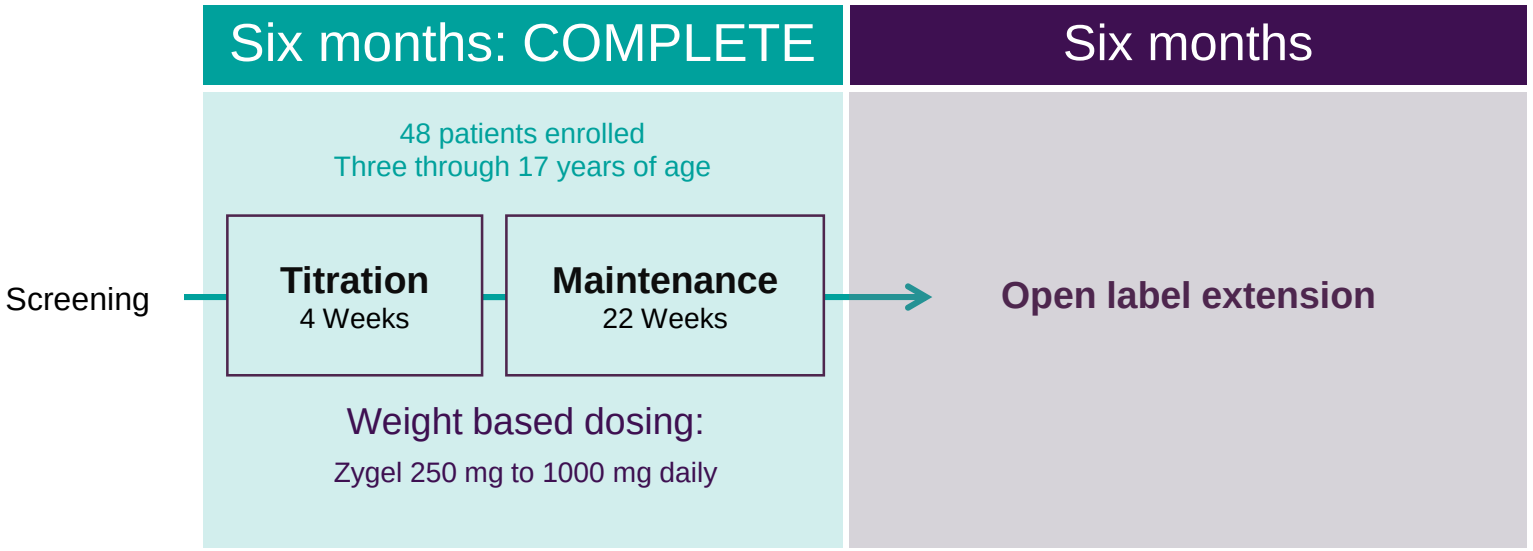
- Group of rare / ultra rare childhood-onset epilepsies with impaired or regressed developmental progress
- Cognitive impairment, psychiatric problems, and behavioral disturbances are phenotypic
- Medically fragile population
  - Comorbidities include cerebral palsy, chronic respiratory infections, gait 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
- Company guidance on path forward by end of 2021

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

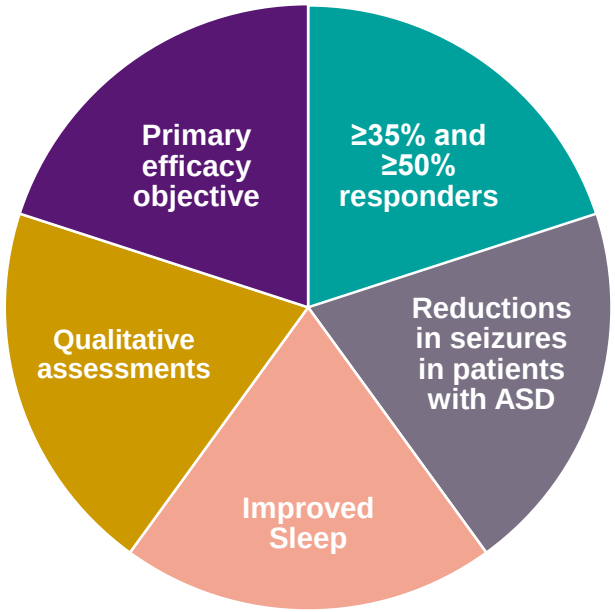


Results of BELIEVE Phase 2 Trial

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

Median % 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

Statistically significant reductions in subscale scores for seizure severity, behavior, and mood ($p<0.01$)

Caregiver Feedback

Verbatim feedback included improved vitality, concentration and cognition, and school improvement

Median % Reductions in Seizures: Comorbid ASD

Month 3 (n=10): 45%
Month 6 (n=10): 59%
Month 9 (n=8): 67%
Month 12 (n=8): 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

BELIEVE Phase 2 Trial in DEE

Results Published in *JAMA Network Open*, September 3, 2021

"Safety and tolerability of transdermal cannabidiol gel in children with developmental and epileptic encephalopathies: A nonrandomized controlled trial"[1]

JAMA Network Open™

- The authors concluded that Zygel was safe, well tolerated, and was associated with reductions in focal impaired awareness seizures (FIAS) and tonic-clonic seizure (TCS) frequency and disease burden
- The authors further noted:
  - Incidence of adverse events likely due to high baseline rate of complex morbidities & seizure severity, and to the relatively long trial duration
  - Low rate of GI AEs potential benefit of transdermal delivery
  - Study findings highlight important benefits beyond seizure reduction that improve overall quality of life for patients and families

[1] *https://protect-us.mimecast.com/s/0nw7CQWN6DsJj1nMIxLa2a?domain=jamanetwork.com*

Financial Strength

- Clean balance sheet
  - No debt, 41.3M shares outstanding (as of August 5, 2021)
- Cash and cash equivalent position of $85.8M as of June 30, 2021
- Cash runway expected to be sufficient to fund operations and capital requirements well into the first half of 2024

Deep Clinical Pipeline & Near-term Milestones

Zygel
Cannabidiol Gel

Indication	Preclinical	Phase 1	Phase 2	Pivotal	Expected Milestones
Fragile X Syndrome (FXS)*					
			RECONNECT: Pivotal confirmatory trial initiated		**Topline results expected 2H 2023**
Autism Spectrum Disorder (ASD)					
			BRIGHT: Topline data released		**Company guidance on path forward by end of 2021**
22q Deletion Syndrome (22q)**					
			INSPIRE: Ongoing		**Screening of patients has resumed; timing for top line results TBD when enrollment complete**
Developmental and Epileptic Encephalopathies (DEE)					
			BELIEVE: Data published 9/3/21 in JAMA Network Open		**Finalize target syndrome selection in 2021**

*Orphan Drug and Fast Track designation

**Orphan Drug designation

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September 2021