Corporate Overview

March 2022

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 THE COMPANY’S ONGOING OR PLANNED CLINICAL TRIALS IN FXS, ASD OR 22Q, OR IN ANY 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 A SUBMISSION FOR REGULATORY APPROVAL, INCLUDING AN NDA OR MAA; 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; 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)
- Two Phase 3 clinical development programs ongoing/planned
  - Confirmatory RECONNECT pivotal trial in Fragile X syndrome (FXS) initiated September 2021, with topline results expected 2H 2023
  - Plan to initiate pivotal Phase 3 program in autism spectrum disorder (ASD) 2H 2022
- Phase 2 study in 22q11.2 deletion syndrome (22q) fully enrolled, with topline results expected mid-year 2022
- Experienced team with development and commercial expertise in transdermal delivery, orphan diseases, neurology, and psychiatry
- Cash runway expected to be sufficient to fund operations and capital requirements into 2H 2023

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		**Initiate Phase 3 program 2H 2022**
22q Deletion Syndrome (22q)**					
			INSPIRE: Enrollment complete		**Topline results expected mid-year 2022**

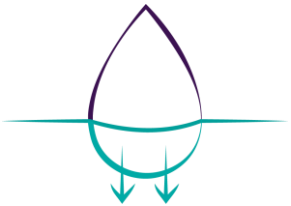
*U.S. Orphan Drug and Fast Track designations; EU Orphan Drug designation
**U.S. Orphan Drug designation

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

~78K U.S. patients and ~121K EU/UK 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

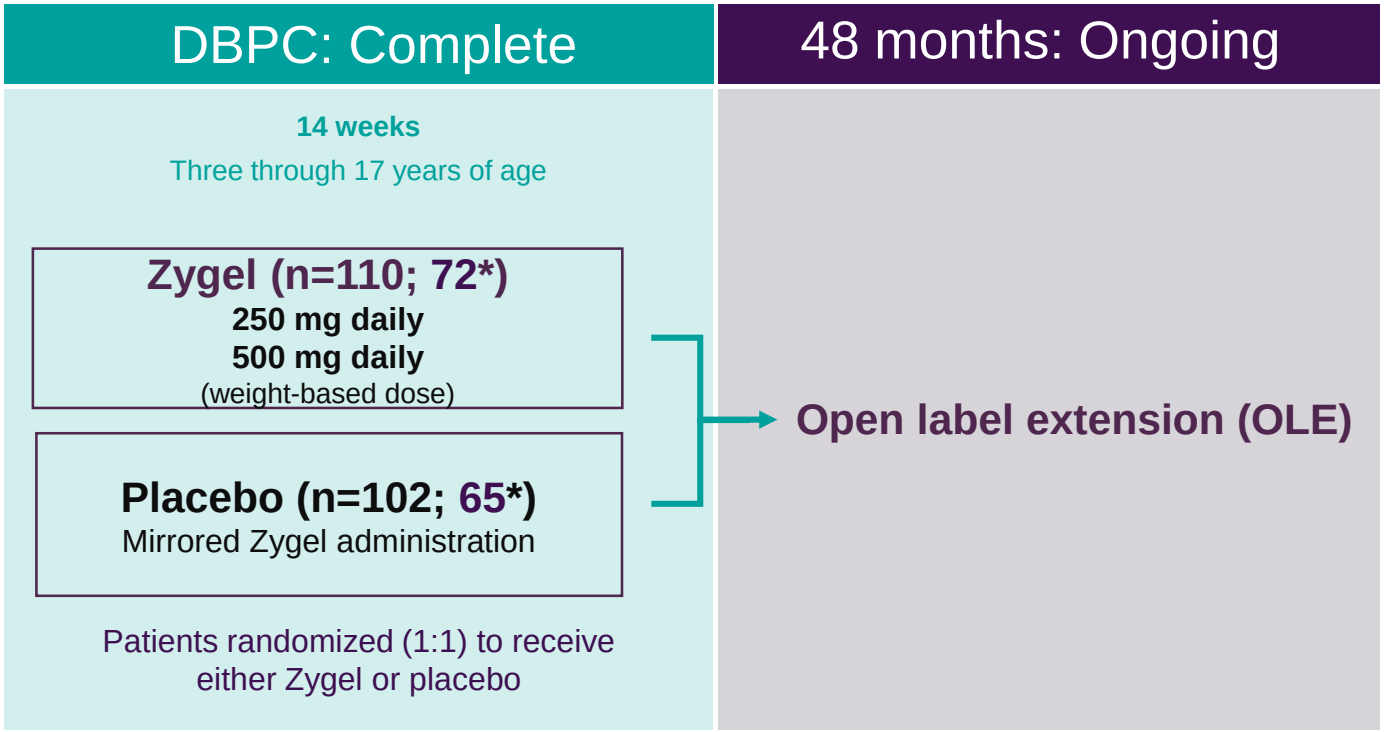
~47K U.S. patients and ~73K EU/UK patients with complete methylation

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)



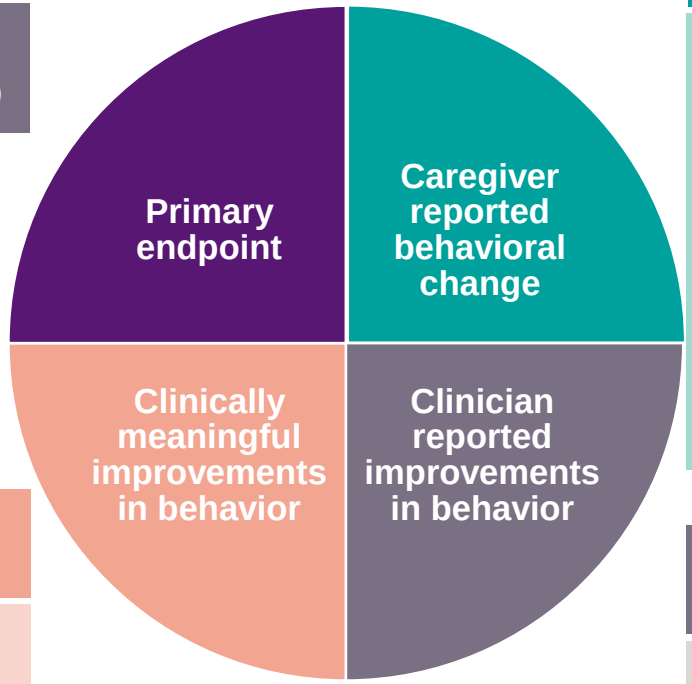
***Patients with complete methylation of their *FMR1* gene (137 total ~ 65% of trial population)**

CONNECT-FX 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

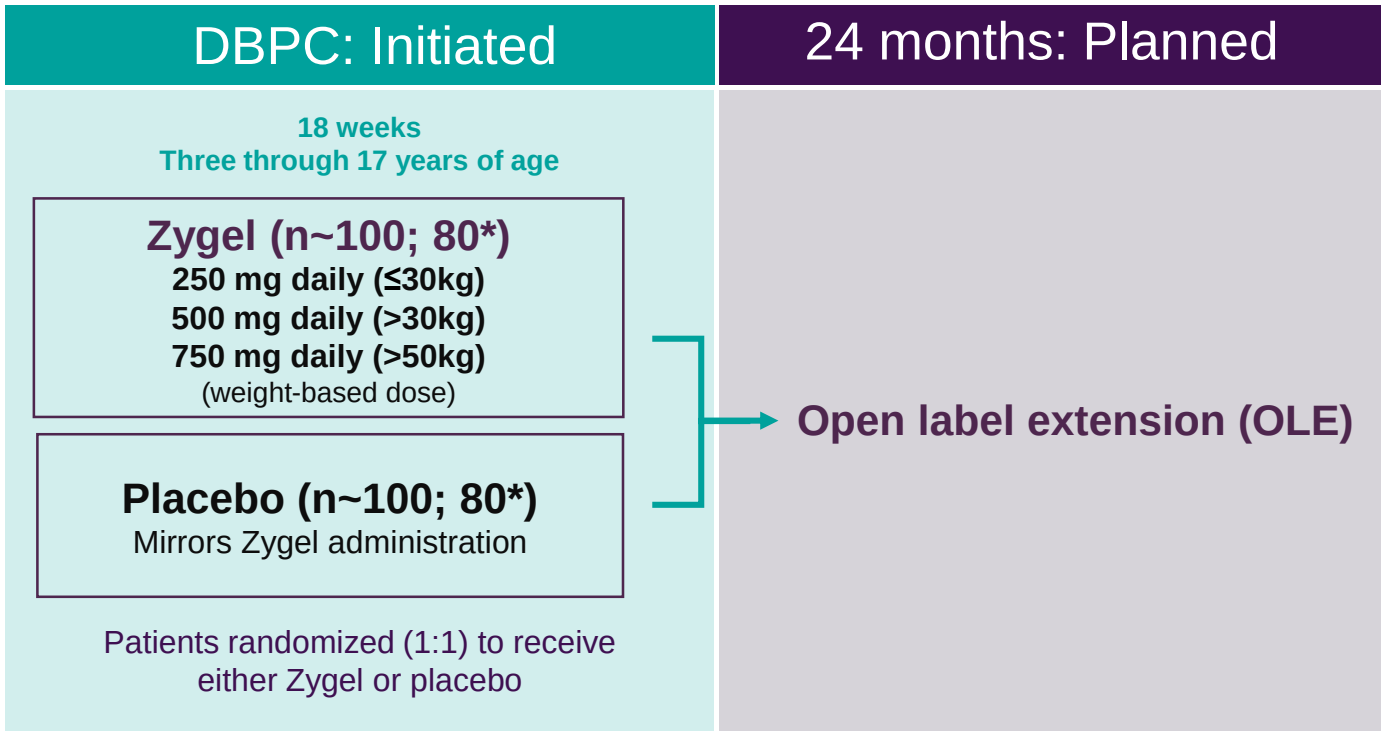
Ad hoc analysis of 136 patients with complete methylation in efficacy population

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 Confirmatory Pivotal Phase 3 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
- Successful completion of current development program for Zygel in FXS expected to satisfy requirements of submitting a New Drug Application in the U.S. and a marketing authorization application in European Union

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 with known tolerability challenges

~1.4M U.S. children and adolescents with ASD

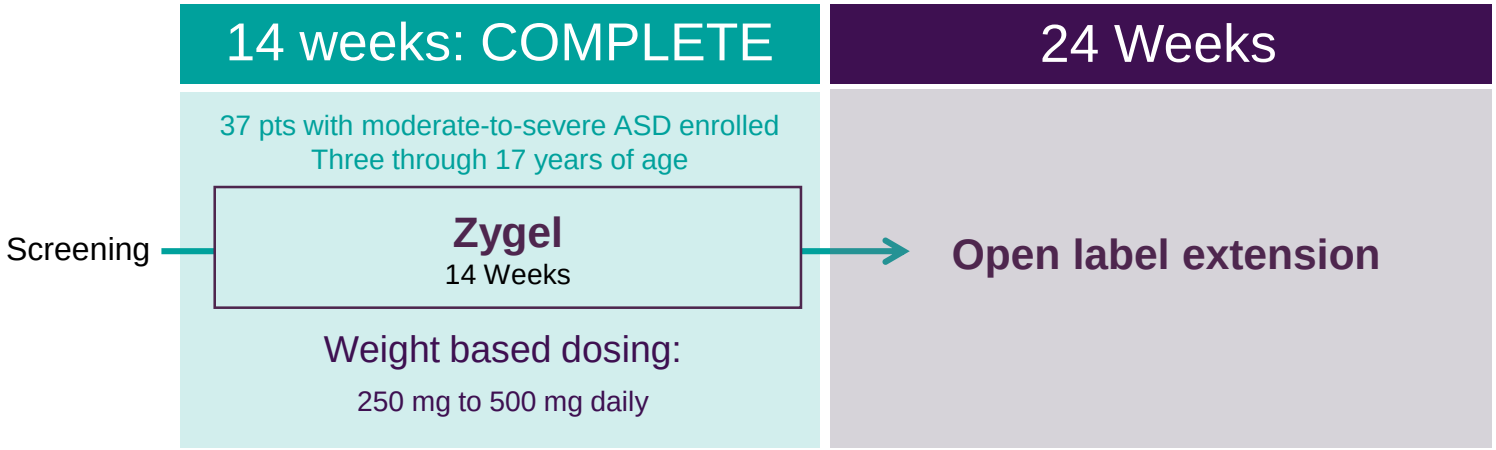
Rationale for Developing Zygel in ASD

- 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 irritability, social avoidance and anxiety, with good tolerability

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

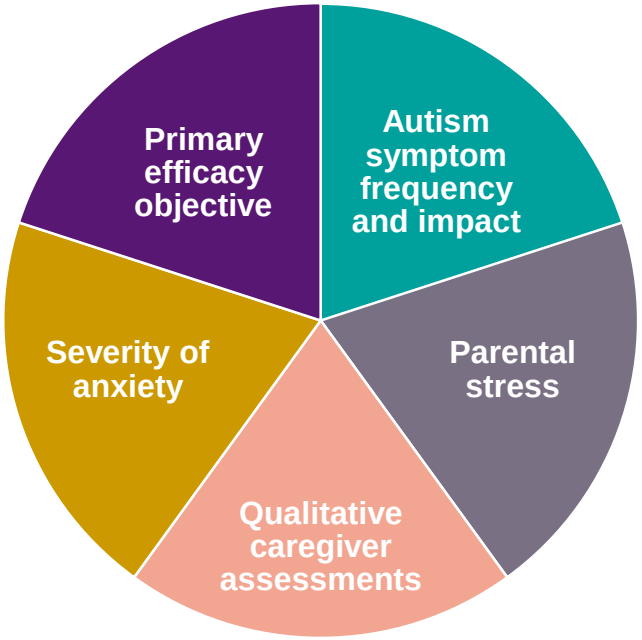
Statistically Significant Results at Week 14 Compared to Baseline

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

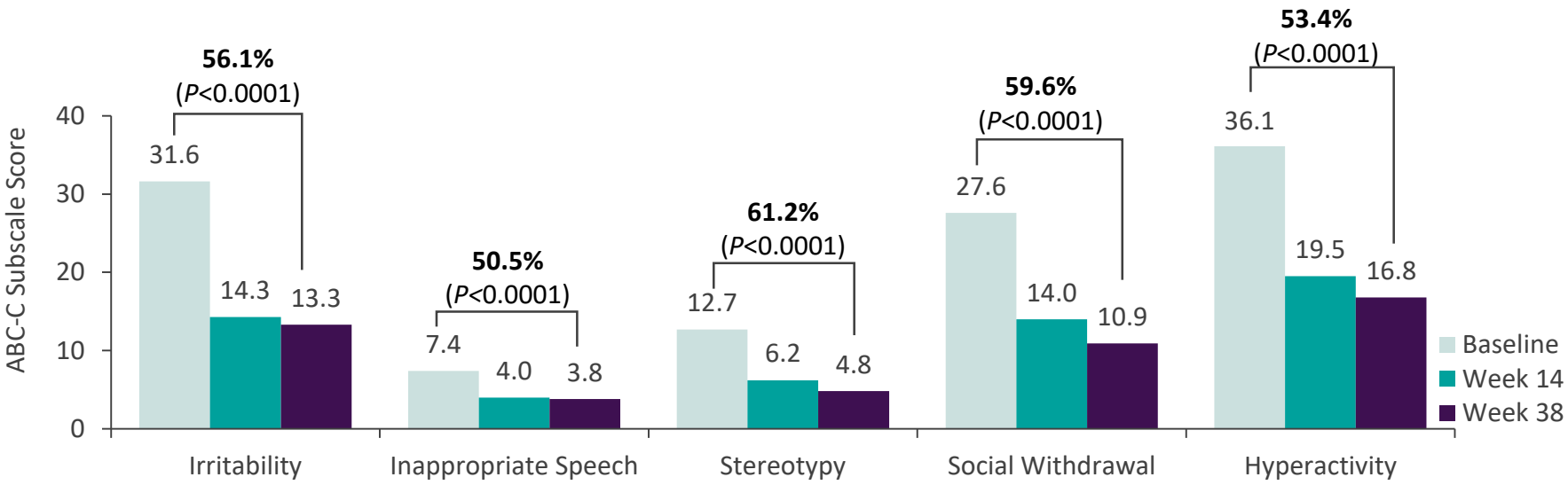
* Statistically significant

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 frequent urination at week 38
- No severe or serious AEs reported during the 38-week trial

Next Steps in ASD Program

- Discussions with 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
  - Same primary endpoint utilized in pivotal trials for existing FDA approved ASD treatments
- Submit Investigational New Drug application specific to ASD
- Finalize clinical protocol and recruit investigators to participate
- Initiate pivotal Phase 3 program – first trial expected to start 2H 2022

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

~83K U.S. patients with 22q

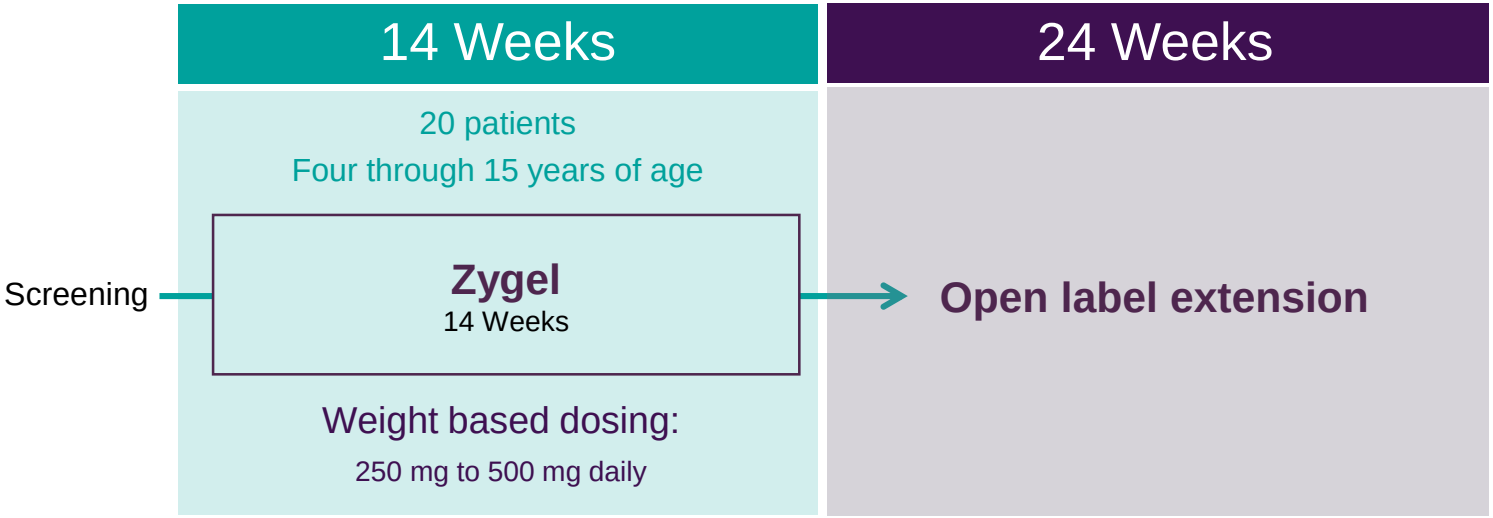
Rationale for Developing Zygel in 22q

- 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
- Enrollment complete in Phase 2 INSPIRE trial in pediatric and adolescent patients with 22q
  - Two sites in Australia and one site in U.S. participating

U.S. 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

Next Steps in 22q Program

- Topline results from INSPIRE Phase 2 trial in children and adolescents with genetically confirmed 22q expected mid-year 2022

- The Company plans to move forward in 22q as an orphan indication pending results from the ongoing INSPIRE trial and subsequent discussion with the FDA on the regulatory path forward

Financial Strength

- Clean balance sheet
  - No debt, 42.4M shares outstanding (as of February 22, 2022)
- Cash and cash equivalents of $67.8M as of December 31, 2021
- Cash runway expected to be sufficient to fund operations and capital requirements into the second half of 2023

Deep Clinical Pipeline & Near-term Milestones

Zygel
Cannabidiol Gel

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