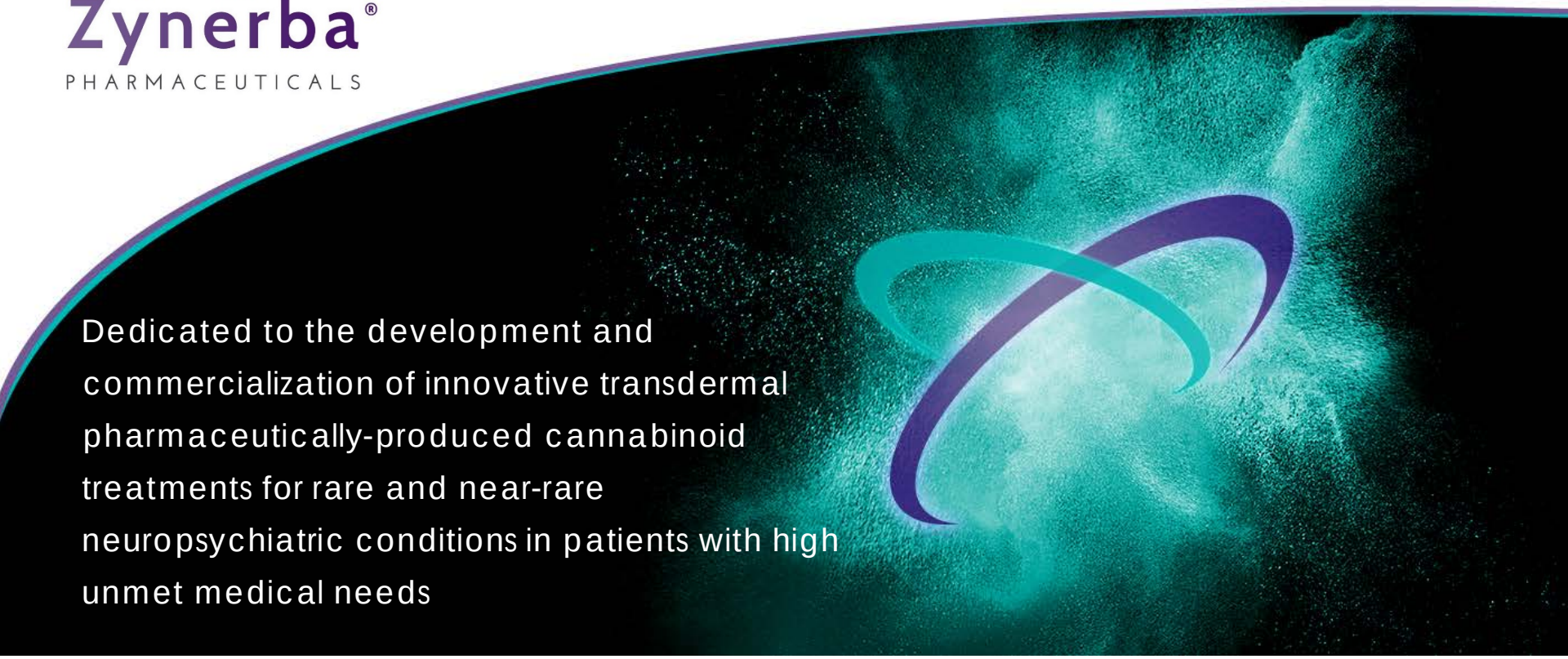
Zynerba®
PHARMACEUTICALS



Dedicated to the development and commercialization of innovative transdermal pharmaceutically-produced cannabinoid treatments for rare and near-rare neuropsychiatric conditions in patients with high unmet medical needs

March 2018

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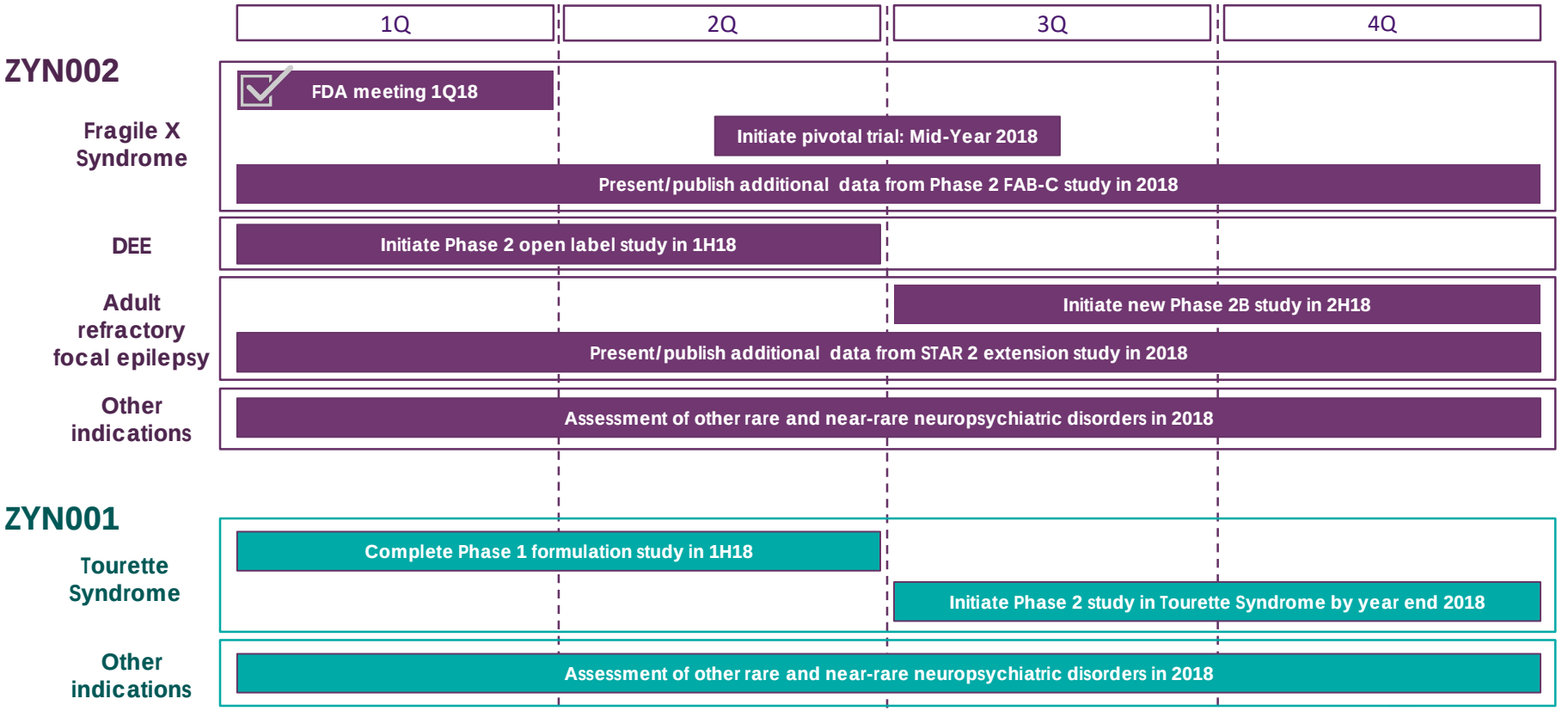
Zynerba® PHARMACEUTICALS

Zynerba Pharmaceuticals
A Rare/Near-Rare Neuropsychiatric Company

- Two patent protected compounds: ZYN002 (CBD gel) and ZYN001 (THC pro-drug patch)
- Focused on high unmet medical needs
  - Fragile X syndrome (FXS): ~71K U.S. patients; no approved products
  - Developmental and epileptic encephalopathies (DEE): ~45K U.S. patients
  - Adult refractory focal epilepsy: ~500K U.S. patients remain uncontrolled on existing AEDs
  - Tourette Syndrome (TS): ~200K U.S. patients have the most severe form of TS
- Opportunities for efficient development and commercialization strategy
  - Orphan drug designation provides opportunity for rapid development/approval
  - Other regulatory designations available; if granted, can accelerate approval of drugs meeting criteria
  - Targeted physician audience = modest commercial investment
  - Potential for consistent Orphan drug pricing across indications (>$25K per patient per year for ZYN002)
- Experienced team with proven development and commercialization track record in transdermal delivery, orphan diseases, neurology, and psychiatry
- Well capitalized with cash runway well into 2019
- Multiple expected near term milestones

Zynerba® PHARMACEUTICALS

Expected 2018 Milestones

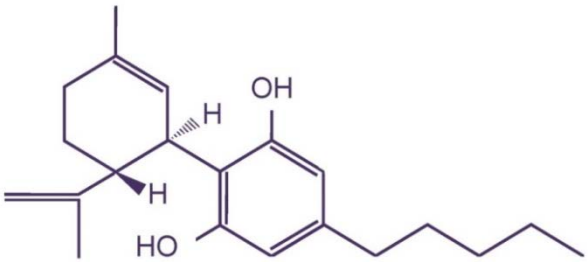


Zynerba® PHARMACEUTICALS

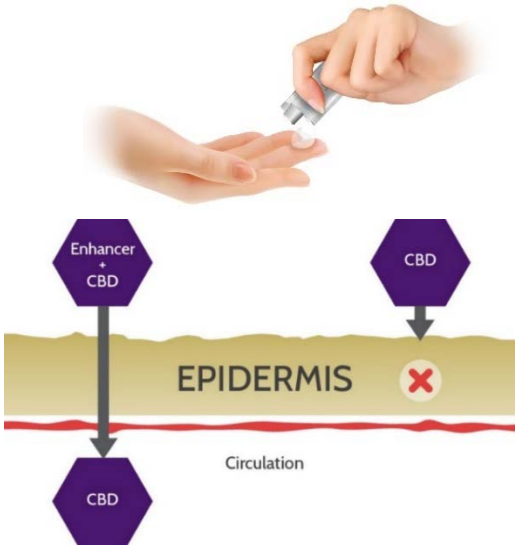
ZYN002
Cannabidiol (CBD) Gel

- **First and only patent-protected permeation-enhanced pharmaceutically-produced cannabidiol (CBD) gel formulated for transdermal delivery**
  - **CBD binds to multiple receptors and may mediate a number of pathways, including the endocannabinoid pathway**
  - **Patented formulation increases the delivery of CBD through the layers of the epidermis and into the circulatory system**

CBD



Transdermal gel delivery



Zynerba® PHARMACEUTICALS

Fragile X Syndrome (FXS)
Preparing for 2018 Pivotal Study

FXS

- Rare genetic developmental disability in ~71,000 U.S. patients
- Leading known cause of inherited intellectual disability and ASD
- Symptoms including significant behavioral, social, and cognitive deficits
- Symptoms linked to deficiencies in the endocannabinoid system caused by FMR1 mutation

- U.S. Orphan Drug Designation for use of CBD as a treatment of Fragile X (Feb. 2016)
- Positive open label Phase 2 data (Sept. 2017):
  - Achieved primary and numerous secondary endpoints with statistical significance vs. baseline
  - Extremely well tolerated
- Conducted positive meeting with FDA (Jan. 2018)
- Expect to initiate single pivotal trial in pediatric and adolescent FXS patients mid-year 2018 to support NDA
- Results expected in 2019

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Developmental & Epileptic Encephalopathies (DEE)
New Phase 2 Program in 1H2018

DEE

- Category including a number of rare and ultra-rare severe brain disorders that manifest with seizures in children
- ~45,000 U.S. children and adolescents with DEE
- Includes Doose, Dravet, Lennox-Gastaut, and West Syndromes, etc.
- All highly resistant to treatment

- Third party clinical data show impact of CBD on seizures and behavioral issues in children
- Expect to initiate Phase 2 study in 1H2018
  - 24 week multi-dose study in 48 DEE patients (3 to <18 years)
- Results expected in 2019

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Adult Refractory Focal Epilepsy
Phase 2B Anticipated in 2018

Adult Refractory Focal Seizures

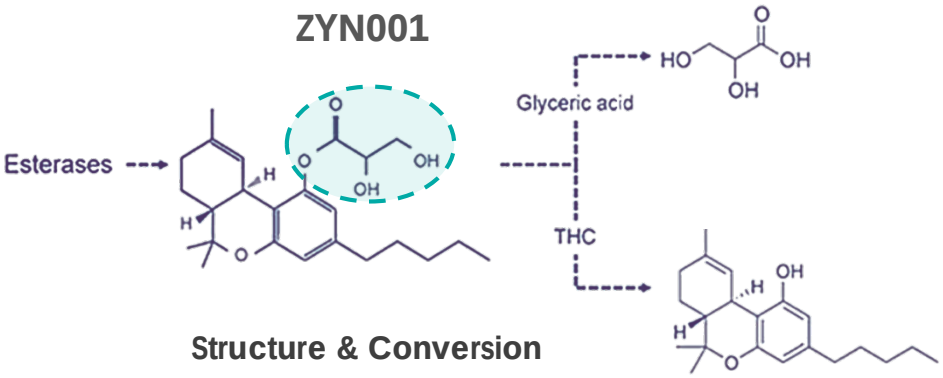
- Focal seizures are the most common epilepsy in adults
- Substantial U.S. market
  - ~500,000 refractory patients
- New treatment options with improved quality of life (safety and efficacy) needed

- STAR 2 data suggest clinically meaningful response with longer term use of ZYN002
  - Consistent improvements in median seizure rate at three, six and nine months of treatment with ZYN002
- Learnings from Phase 2 STAR 1 study and open label STAR 2 extension provide input into Phase 2b trial design
  - Planned modifications include increased baseline seizure frequency, patient count, and trial duration
- Expect to initiate ~300 patient double blind placebo controlled study in 2H2018

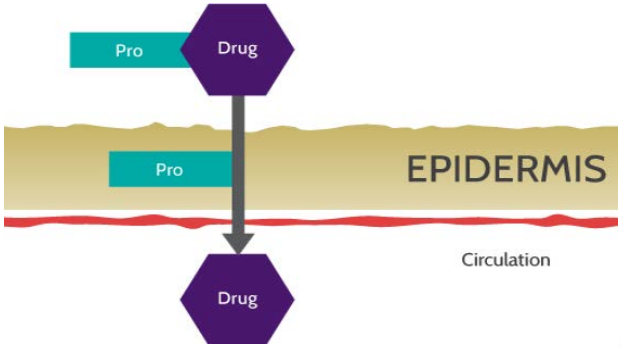
Zynerba® PHARMACEUTICALS

ZYN001
THC Pro-Drug Patch

- **Patent-protected pharmaceutically-produced D-glyceric acid ester-Δ9-tetrahydrocannabinol (THC) in a transdermal patch**
- **ZYN001 is a pro-drug**
  - **A drug administered in an inactive or less active form, designed to enable more effective delivery, and then converted into a different form through a normal metabolic process**
  - **Unlike THC, ZYN001 is able to be efficiently absorbed through the skin via transdermal delivery**
  - **After crossing the stratum corneum, ZYN001 is hydrolyzed to THC and glyceric acid under physiological conditions**
  - **THC binds multiple cannabinoid receptors and may mediate a number of pathways, including the endocannabinoid pathway**



Structure & Conversion



Delivery

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Potential for THC in Tourette Syndrome (TS)

Tourette Syndrome

- Neurodevelopmental disorder characterized by motor / vocal tics
  - Evident in early childhood
  - ~200K U.S. pts have most severe form
  - Up to 1:100 exhibit milder and less complex symptoms
- Central cannabinoid receptor system believed to play role in Tourette Syndrome pathology

- Third party double blind, placebo controlled studies show activity of THC in TS
- Phase 1 formulation work expected to be completed in 1H2018
- Phase 2 study in Tourette Syndrome expected to initiate in late 2H2018

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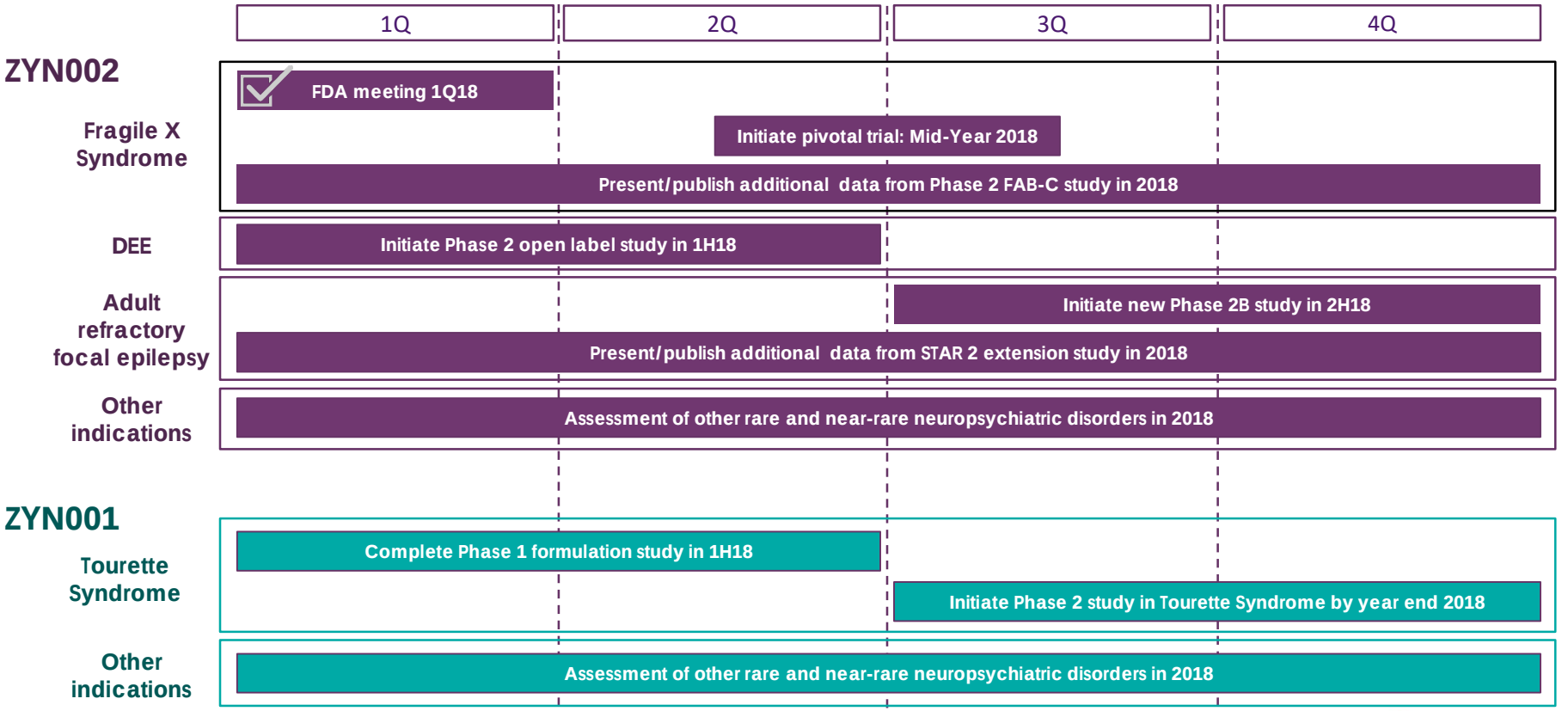
Expected 2018 Milestones



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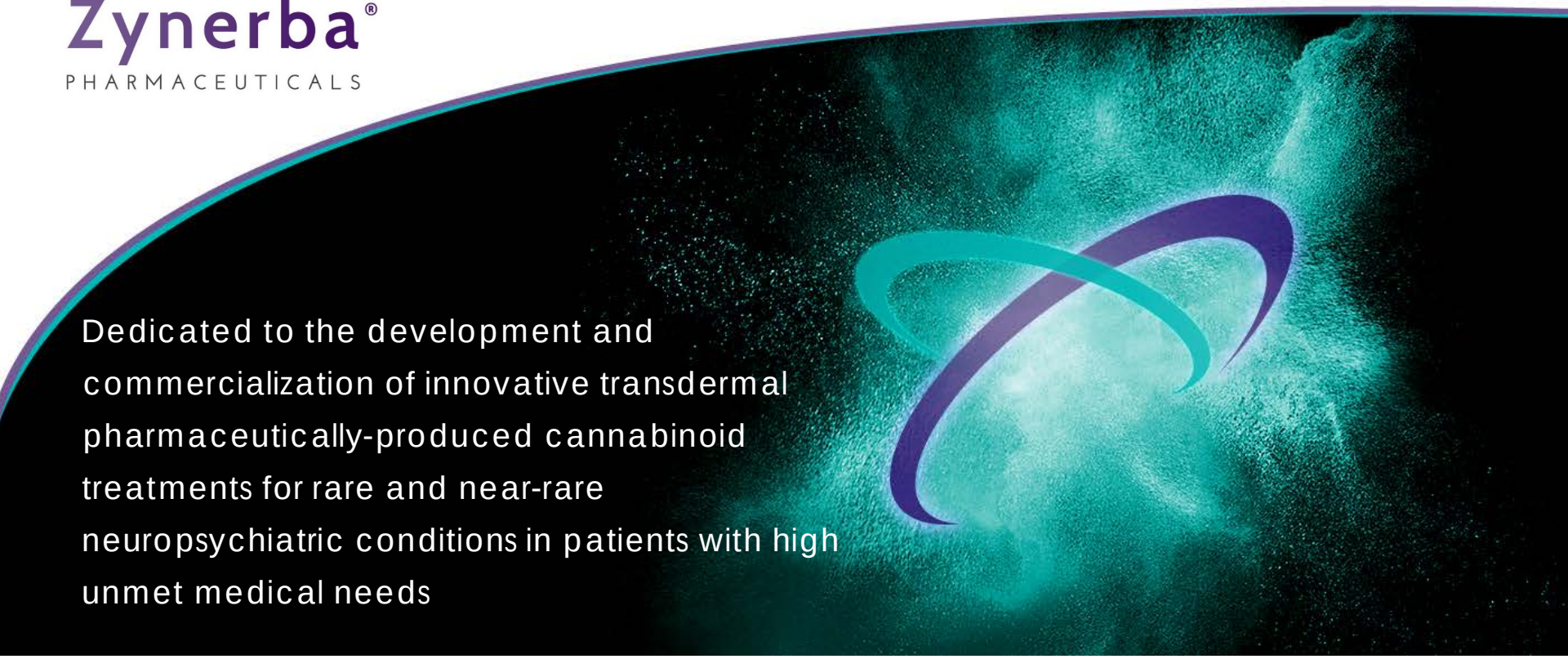

Dedicated to the development and commercialization of innovative transdermal pharmaceutically-produced cannabinoid treatments for rare and near-rare neuropsychiatric conditions in patients with high unmet medical needs

March 2018

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ZYN002
CBD Gel Clinical Program

Fragile X Syndrome

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Fragile X Syndrome (FXS)
The Endocannabinoid (EC) System is a Critical Pathway

- **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 form system of neurotransmitters regulating emotional responses, behavioral reactivity to context, social interaction**
  - **FMR1 mutation in FXS causes dysregulation of the EC system resulting in significant social, behavioral, and cognitive deficits**
  - **Modulation of EC system with CBD may have therapeutic potential in ameliorating some of those symptoms**
  - **Strong scientific rationale in FXS validated by Phase 2 FAB-C clinical data**

U.S. Orphan Drug Designation for use of CBD as a treatment of Fragile X syndrome has been granted by the FDA (Feb. 2016)

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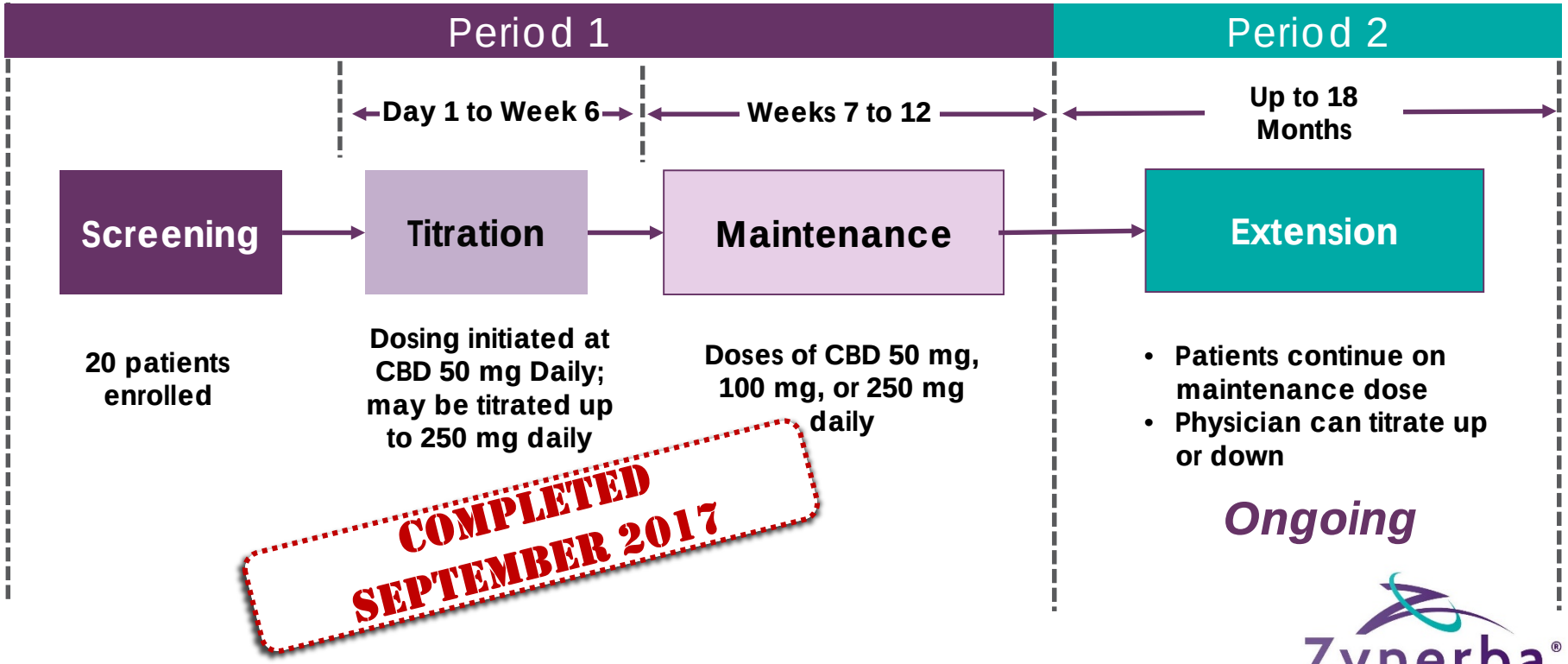
Fragile X Syndrome Open Label Phase 2
Trial Design

Treatment of Fragile X Syndrome Anxiety and Behavioral Challenges with CBD (FAB-C)



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Positive FAB-C Open Label Phase 2 Efficacy Data
Primary Endpoint: ADAMS Total Score

ADAMS total score	Improvement vs. baseline (N=20)
Changes in Anxiety, Depression and Mood	46% *(p<0.0001)*

ADAMS subscales	Improvement vs. baseline (N=20)
General Anxiety	54% (p<*0.0001*)
Social Avoidance	53% *(p<0.0002)*
Compulsive Behavior	50% *(p=0.0262)*
Manic/Hyperactive Behavior	35% *(p=0.0003)*
Depressed Mood	29% *(p=0.1417)*

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Positive FAB-C Open Label Phase 2 Efficacy Data
Key Secondary Endpoint: ABC-FXS

ABC-FXS subscale	Improvement vs. baseline (N=20)
Stereotypy: "Repetitive Movements"	**59%** *(p=0.0006)*
Social Avoidance: "Seeks Isolation"	**55%** *(p=0.0005)*
Socially Unresponsive/Lethargic: "Does Not Pay Attention"	**53%** *(p=0.0034)*
Inappropriate Speech: "Repeats Words or Phrases"	**43%** *(p=0.0018)*
Irritability: "Has Temper Tantrums"	**42%** *(p=0.0096)*
Hyperactivity: "Disrupts Group Activities"	**33%** *(p=0.0194)*

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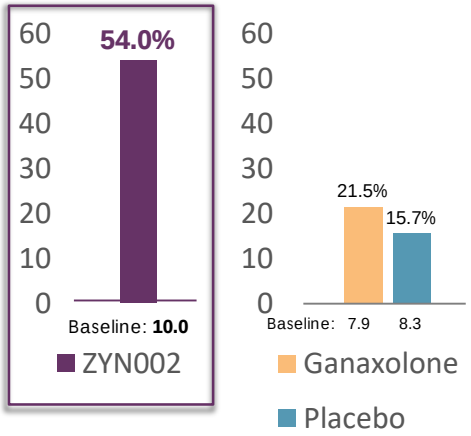
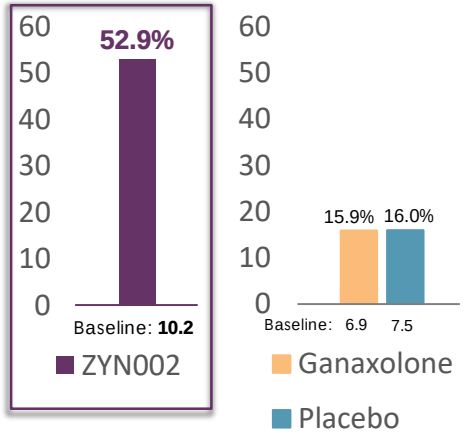
ADAMS Subscales

Week 12: Percent Improvement vs. 3rd party data*

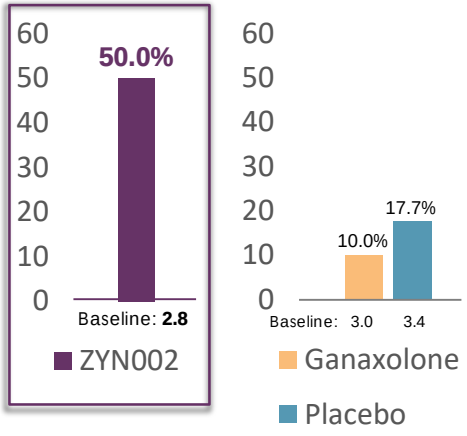
General Anxiety



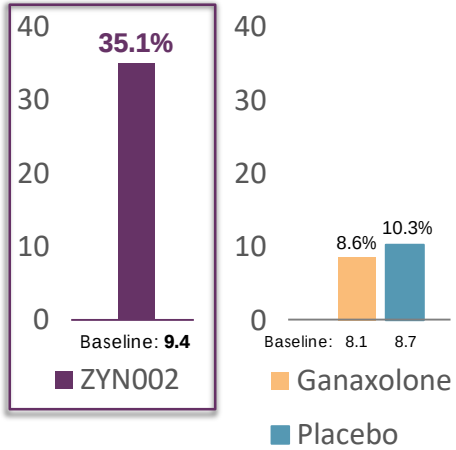
Social Avoidance



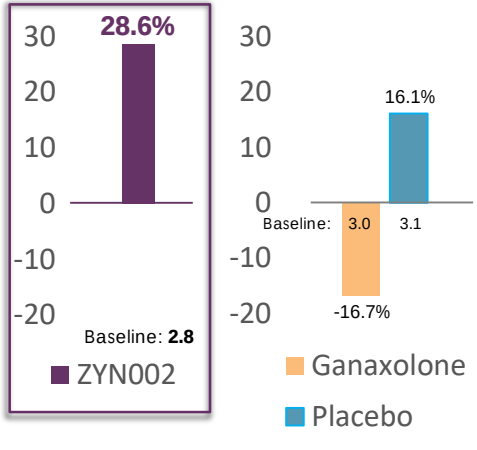
Compulsive Behavior



Manic/hyperactive Behavior



Depressed Mood



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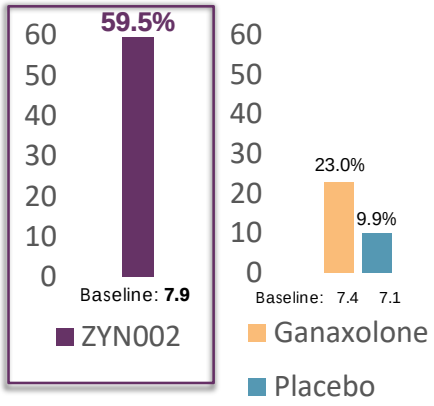
* Ligsay, A., Van Dijck, A., Nguyen, D. V., Lozano, R., Chen, Y., Bickel, E. S., et al. (2017). A randomized double-blind, placebo-controlled trial of ganaxolone in children and adolescents with fragile x syndrome. Journal of Neurodevelopmental Disorders, 9:26.

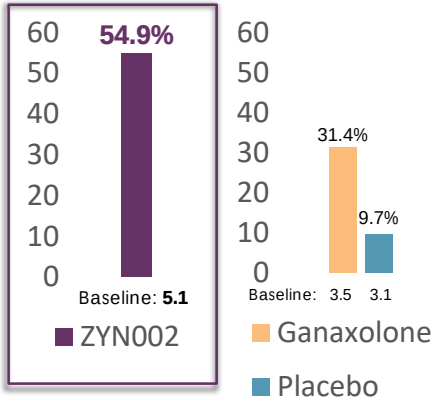
ABC-FXS Subscales

Week 12: Percent Improvement vs. 3rd Party Data*

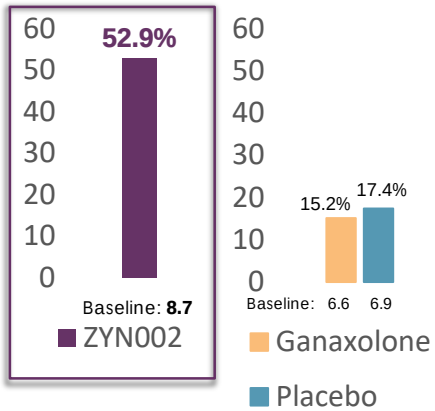
Stereotypy
Repetitive Movements



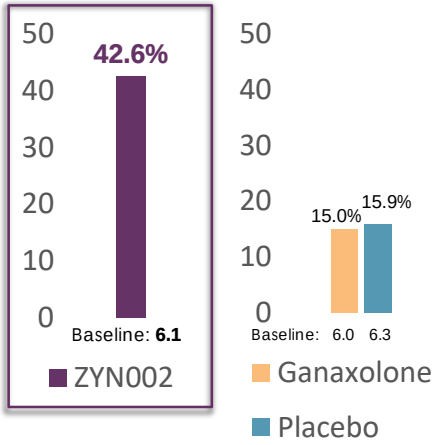
Social Avoidance
Seeks Isolation



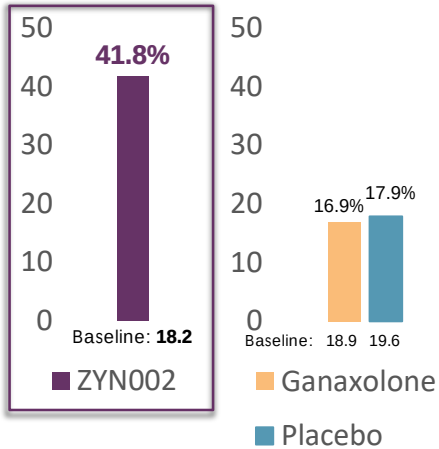
Socially Unresponsive / Lethargic
Does Not Pay attention



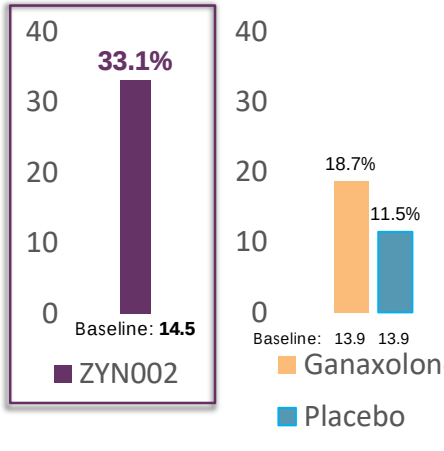
Inappropriate Speech
Repeats Words / Phrases



Irritability
Temper Tantrums



Hyperactivity
Disrupts Group Activities



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* Ligsay, A., Van Dijck, A., Nguyen, D. V., Lozano, R., Chen, Y., Bickel, E. S., et al. (2017). A randomized double-blind, placebo-controlled trial of ganaxolone in children and adolescents with fragile x syndrome. Journal of Neurodevelopmental Disorders, 9:26.

Positive FAB-C Open Label Phase 2 Safety Data

- **Very well tolerated, consistent with previously reported clinical data**
- **Two sibling patients discontinued due to worsening of pre-existing eczema**
- **Four other patients experienced an AE; no SAEs**
- **No drug-related GI events**
- **No THC was detected in the plasma**
- **13 patients continued into open label extension; 12 remain as of 3/5/18**
  - **Twelve patients have exceeded 6 months on ZYN002**
  - **Six patients have exceeded 9 months on ZYN002**

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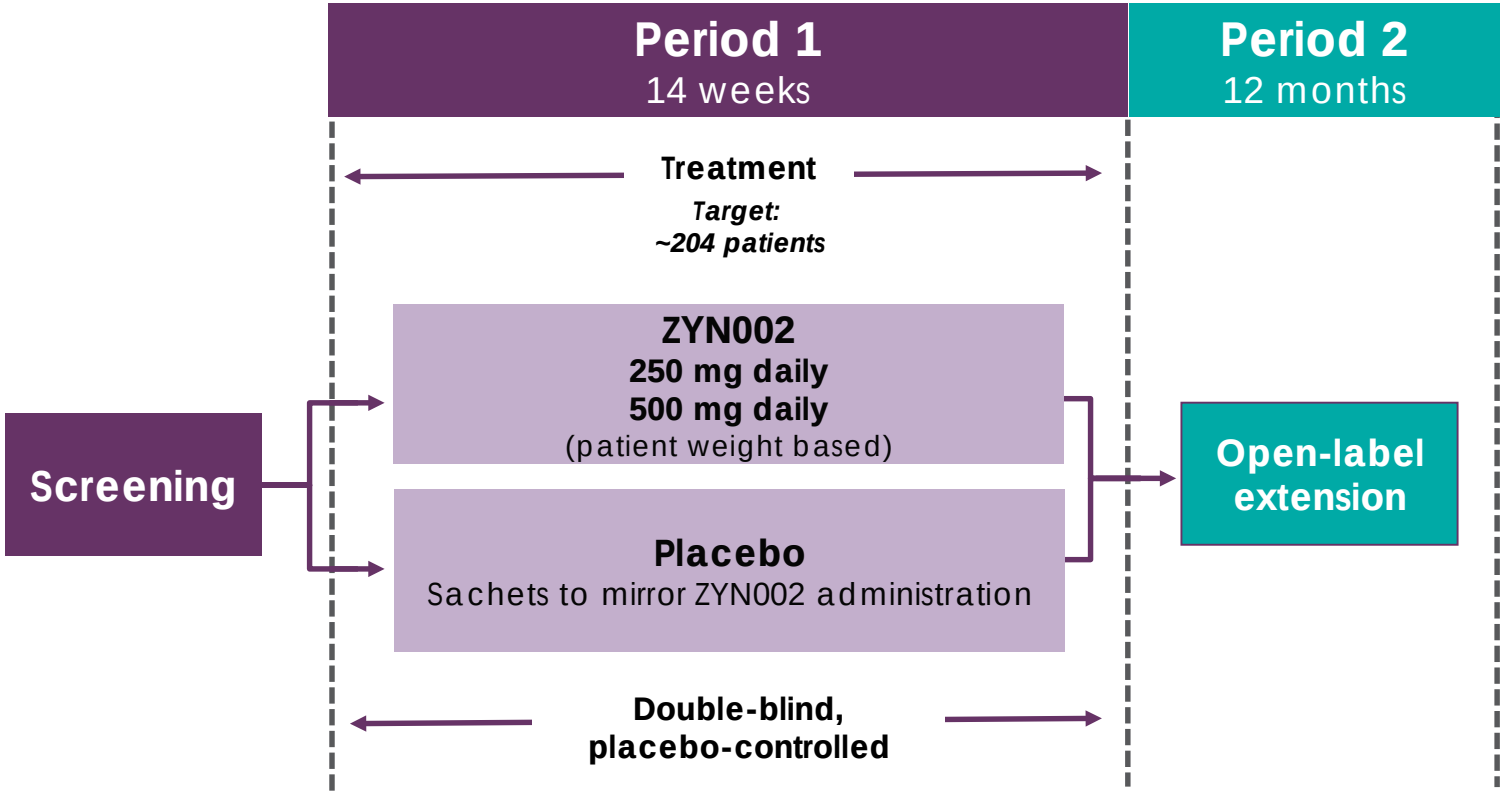
Fragile X Syndrome Pivotal Study
Proposed Trial Design*



Patients will be randomized (1:1) to receive either ZYN002 or placebo

*Note: Subject to change due to further regulatory, clinical and other considerations.

ZYN002 in Fragile X Syndrome
Next Steps

- **Expect to begin pivotal trial in pediatric and adolescent patients with FXS mid-year 2018**
  - **204 patients from U.S., Australia and New Zealand**
  - **Key endpoints will assess observable behaviors: ABC-FXS**
  - **Top line data expected in 2019**
- **Assessing opportunities to present / publish full FAB-C data set as soon as possible in 2018**
  - **Targeting three FXS meetings June-August 2018**
- **Evaluating opportunities for FDA fast-track, breakthrough status, and/or priority review**

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ZYN002
CBD Gel Clinical Program

Developmental Epileptic Encephalopathies (DEE)

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Developmental and Epileptic Encephalopathies

DEE category includes:
Doose Syndrome
Dravet Syndrome
Early Myoclonic Encephalopathy
Epilepsy of Infancy With Migrating Focal Seizures
Epilepsy with Generalized Tonic-Clonic Seizures alone (EGTCS)
Juvenile Myoclonic Epilepsy (JME)
Landau-Kleffner Syndrome
Lennox-Gastaut Syndrome
Ohtahara Syndrome (Early Infantile Epileptic Encephalopathy)
West Syndrome / Infantile Spasms

- Category of rare and ultra-rare severe brain disorders that manifest with seizures or EEG abnormalities that can directly worsen cognition or behavior
- Often progressive; highly resistant to treatment
- Treatment of seizures or EEG abnormalities expected to improve the cognitive or behavioral deficits and reduce the seizures
- Third party clinical data show impact of CBD on seizures and behavioral issues

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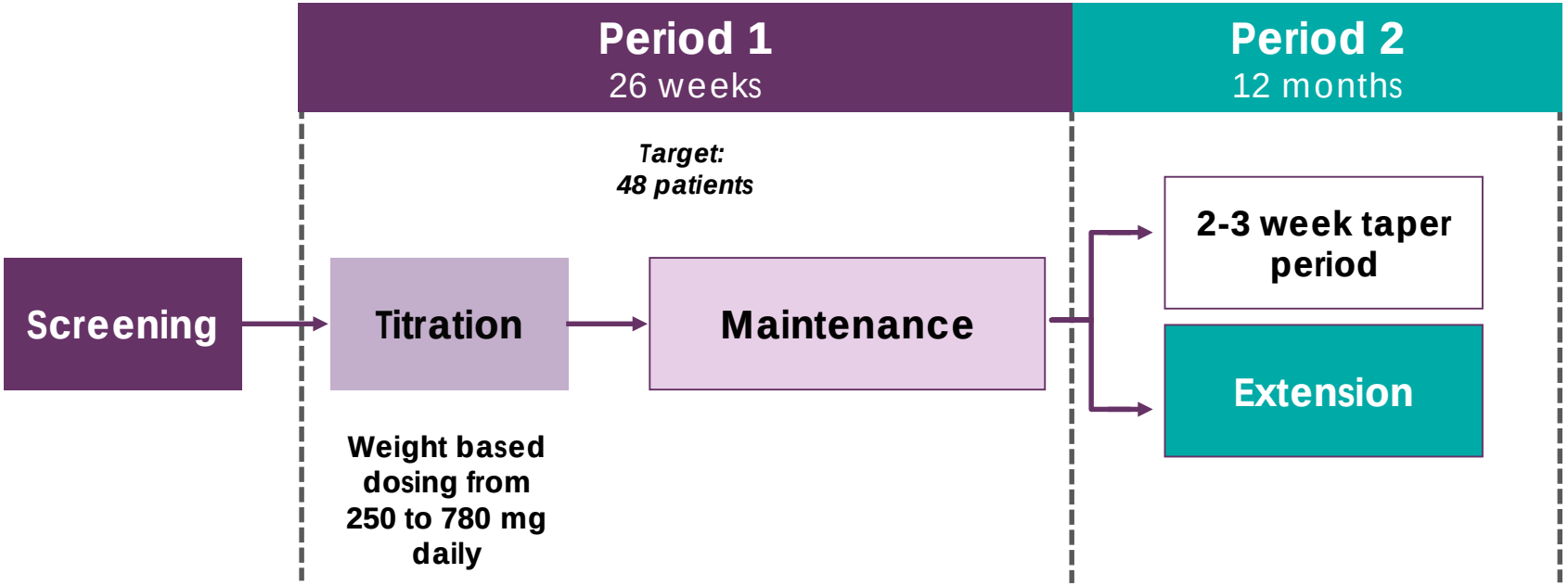
DEE Open Label Phase 2 Study

Proposed Trial Design*



- Initiation planned for 1H2018
- Primary endpoints: reduction in seizures at 12 and 24 weeks
- Results expected in 2019

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*Note: Subject to change due to further regulatory, clinical and other considerations.

ZYN002
CBD Gel Clinical Program

Adult Refractory Focal Epilepsy

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Adult Refractory Focal Epilepsy
Phase 2B Anticipated in 2018

Adult Refractory Focal Seizures

- Focal seizures are the most common epilepsy in adults
- Substantial US market
  - ~500,000 refractory patients
- New treatment options with improved quality of life (safety and efficacy) needed

- STAR 2 data suggest clinically meaningful response with longer term use of ZYN002
  - Consistent and improving median seizure rate at three, six and nine months of treatment with ZYN002
- Learnings from Phase 2 STAR 1 study and open label STAR 2 extension provide input into Phase 2B trial design
- Expect to initiate ~300 patient double blind placebo controlled Phase 2b study in 2H2018

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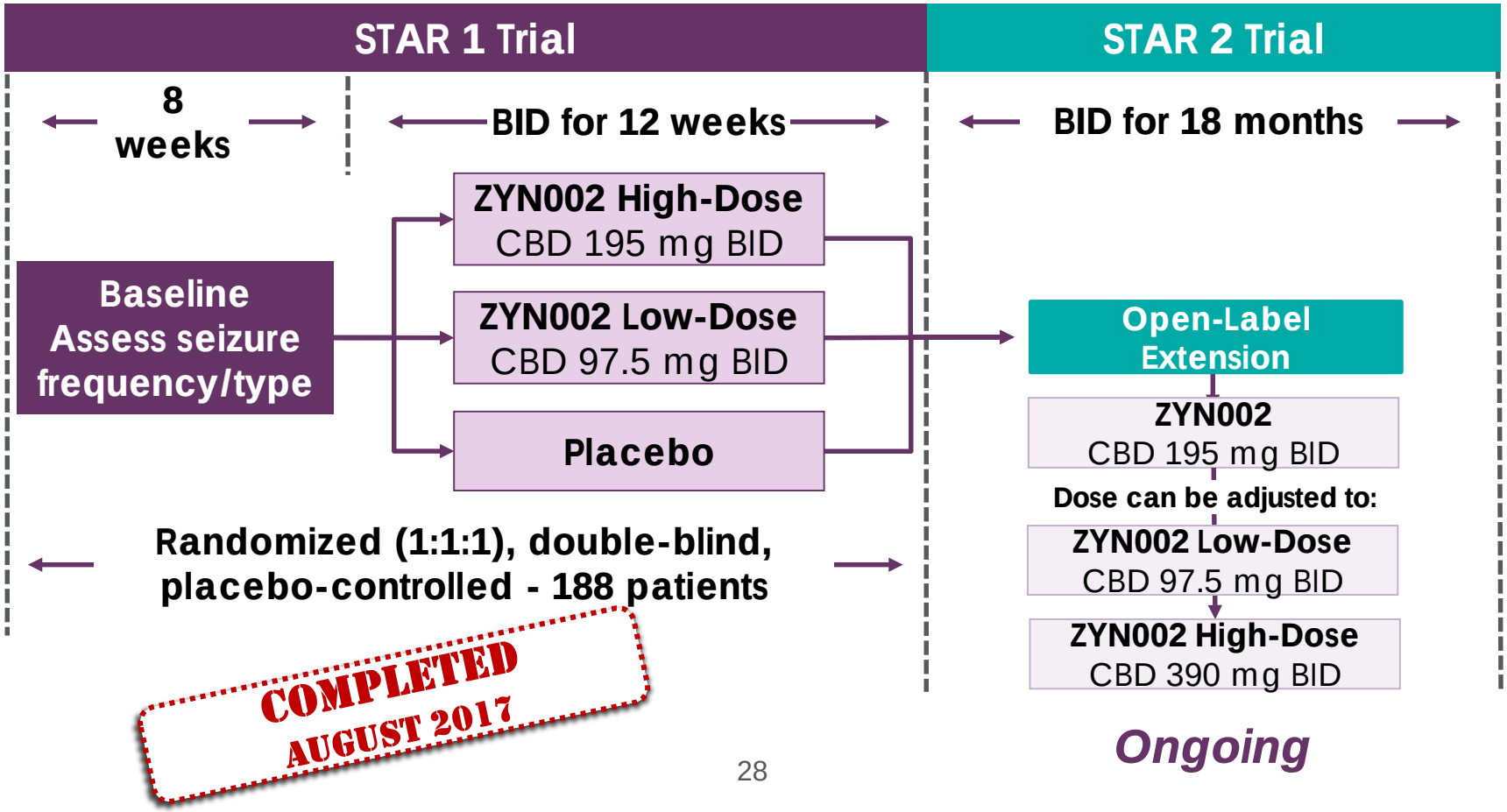
Epilepsy Phase 2 Clinical Study
Trial Design

Synthetic Transdermal CAnnabidiol for the TReatment of Epilepsy



Epilepsy Phase 2 Clinical Study
Demographics and Baseline Characteristics

STAR 1 patients	Placebo	195 mg ZYN002	390 mg ZYN002	Total
Pts Randomized	63	63	62	188
Sex	43% male 57% female	51% male 49% female	42% male 58% female	45% male 55% female
Pts Analyzed for efficacy	63	62	61	186
Pts completing study	62	57	55	174
Patients continuing into STAR 2				171
Baseline median seizure rate	10.5	14.0	10.1	10.6 (3-335)
AEDs				Median: 3.0 Mean: 2.5
Primary endpoint: Percent reduction in baseline seizures	8.7%	18.4%	14.0%	

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Epilepsy Phase 2 Clinical Study
STAR 1 and STAR 2 Results

STAR 1

- **Company believes study missed primary endpoint due to bimodal distribution of placebo patient responses :**
  - **>50% reductions in focal seizures in ~¼ of placebo patients**
  - **13 of these 15 patients were female**
- **Strong separation from placebo seen at >15 baseline seizures**
- **Excellent tolerability**

STAR 2

- **Low dropout rate: 87 patients remain in study* vs 126 as of August 8, 2017**
- **89 patients have reached 9 mo. of drug exposure; 52 have reached 12 months***
- **Excellent tolerability**
- **Data suggest clinically meaningful response with longer term use**

First cut of STAR 1 and STAR 2 data presented at the 2017 AES Meeting
Additional data cuts to be presented in 2018

Learnings provide input into revised Phase 2B clinical trial design

*As of March 5, 2018

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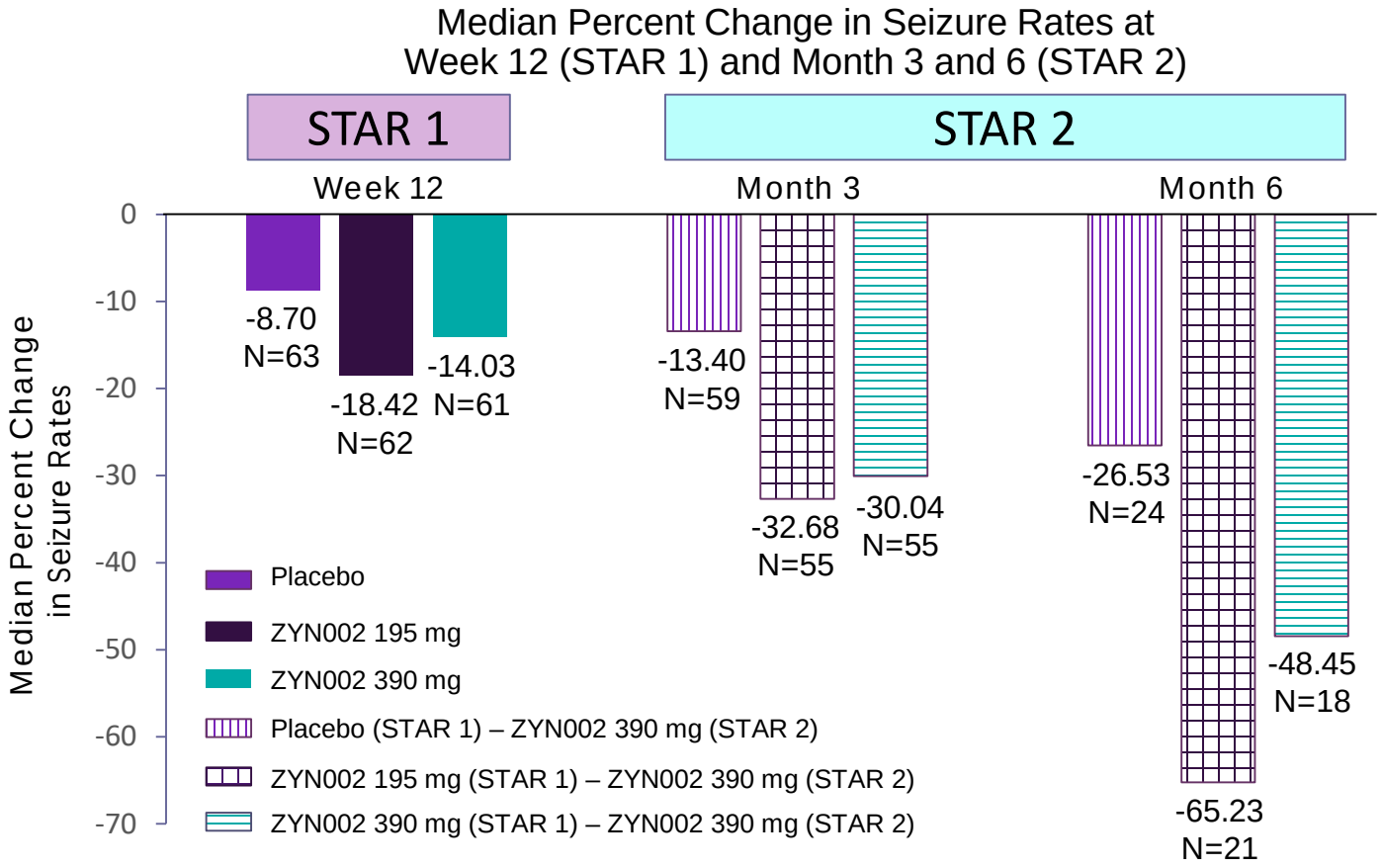
Data Presented at 2017 AES

STAR 1 and STAR 2 Efficacy Data



STAR 2 results based on data collected through mid-August 2017 and in patients who reported seizure frequency data during the respective time period.

Not all patients had reached 3 and 6 months in STAR 2

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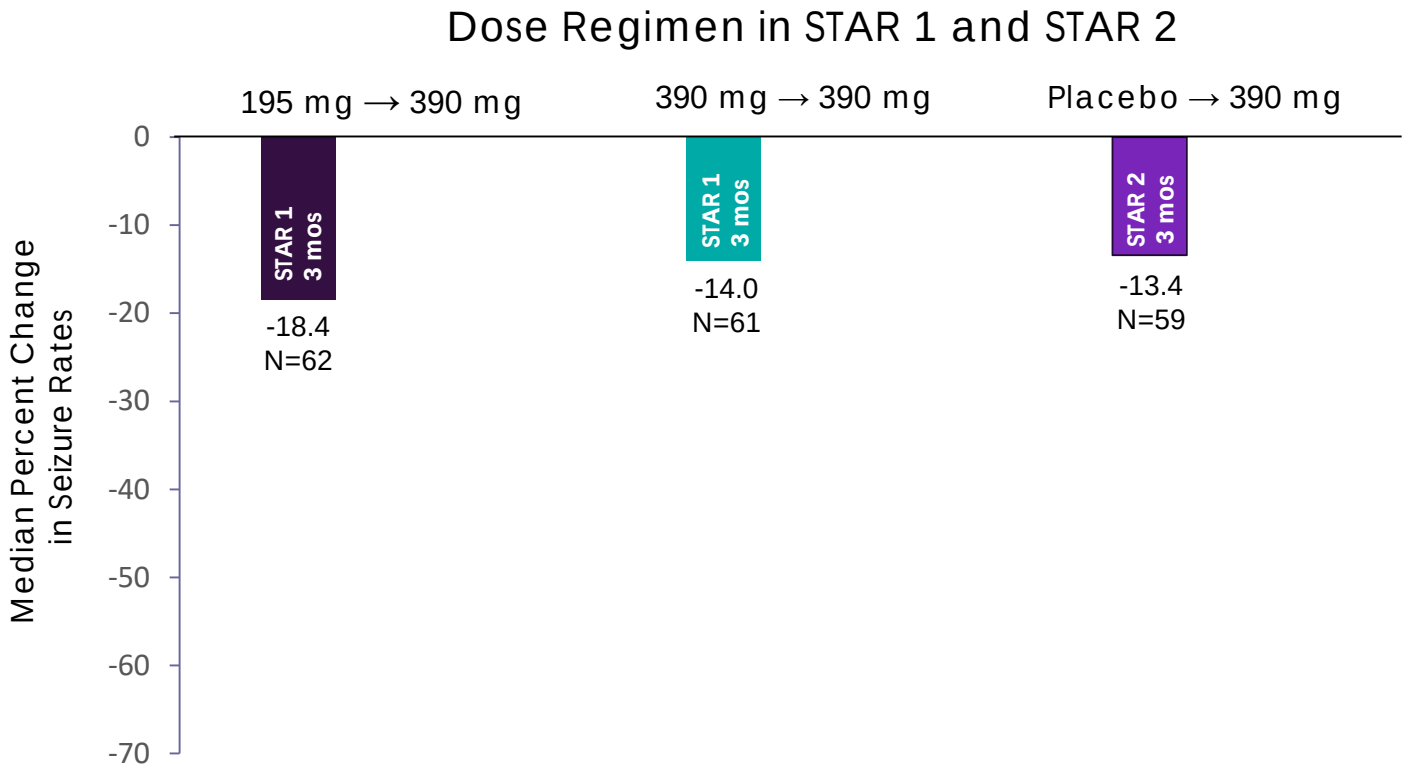
Consistent Results at Various Timeframes

Three Months on ZYN002



STAR 2 results based on data collected through mid-August 2017 and in patients who reported seizure frequency data during the respective time period.

Not all patients had reached 3 and 6 months in STAR 2 as of mid-August 2017

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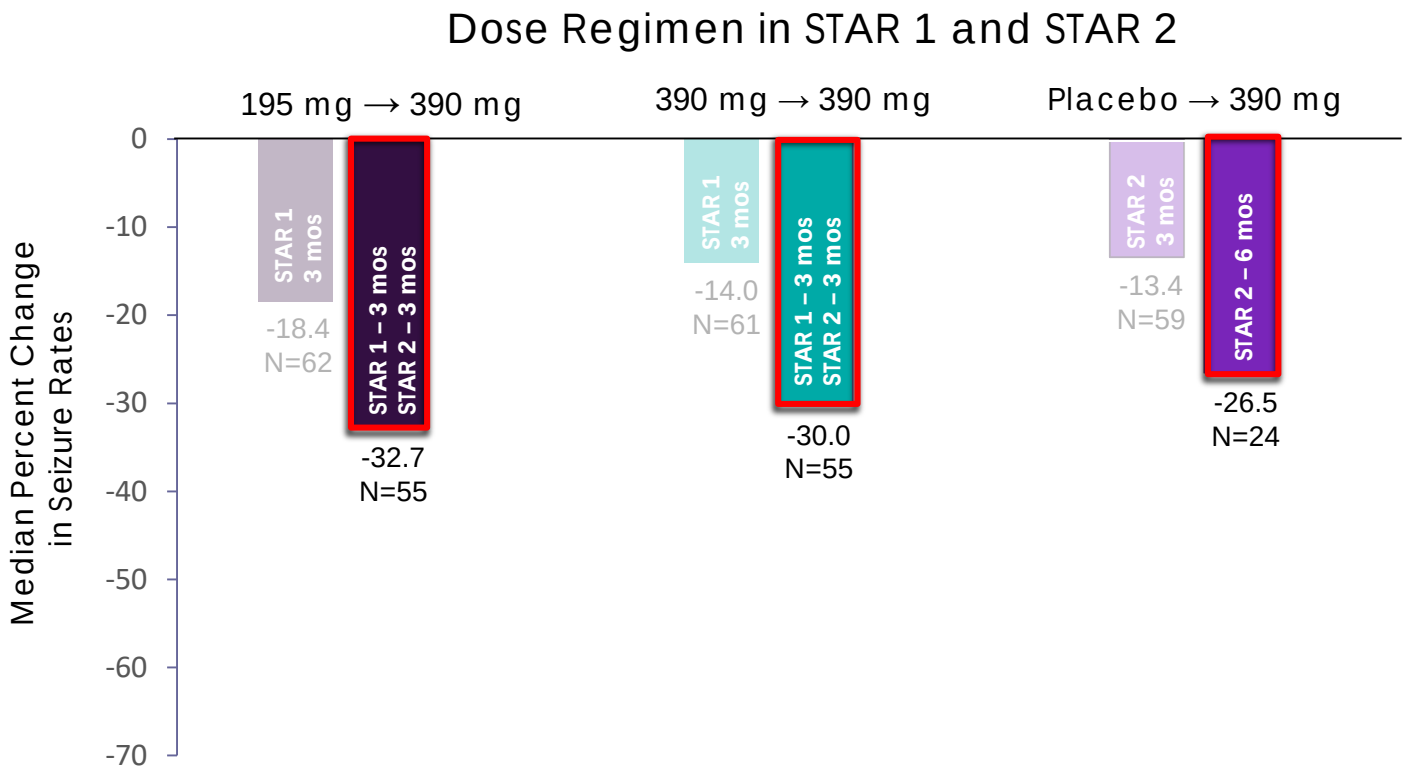
Consistent Results at Various Timeframes
Six Months on ZYN002



STAR 2 results based on data collected through mid-August 2017 and in patients who reported seizure frequency data during the respective time period.

Not all patients had reached 3 and 6 months in STAR 2 as of mid-August 2017

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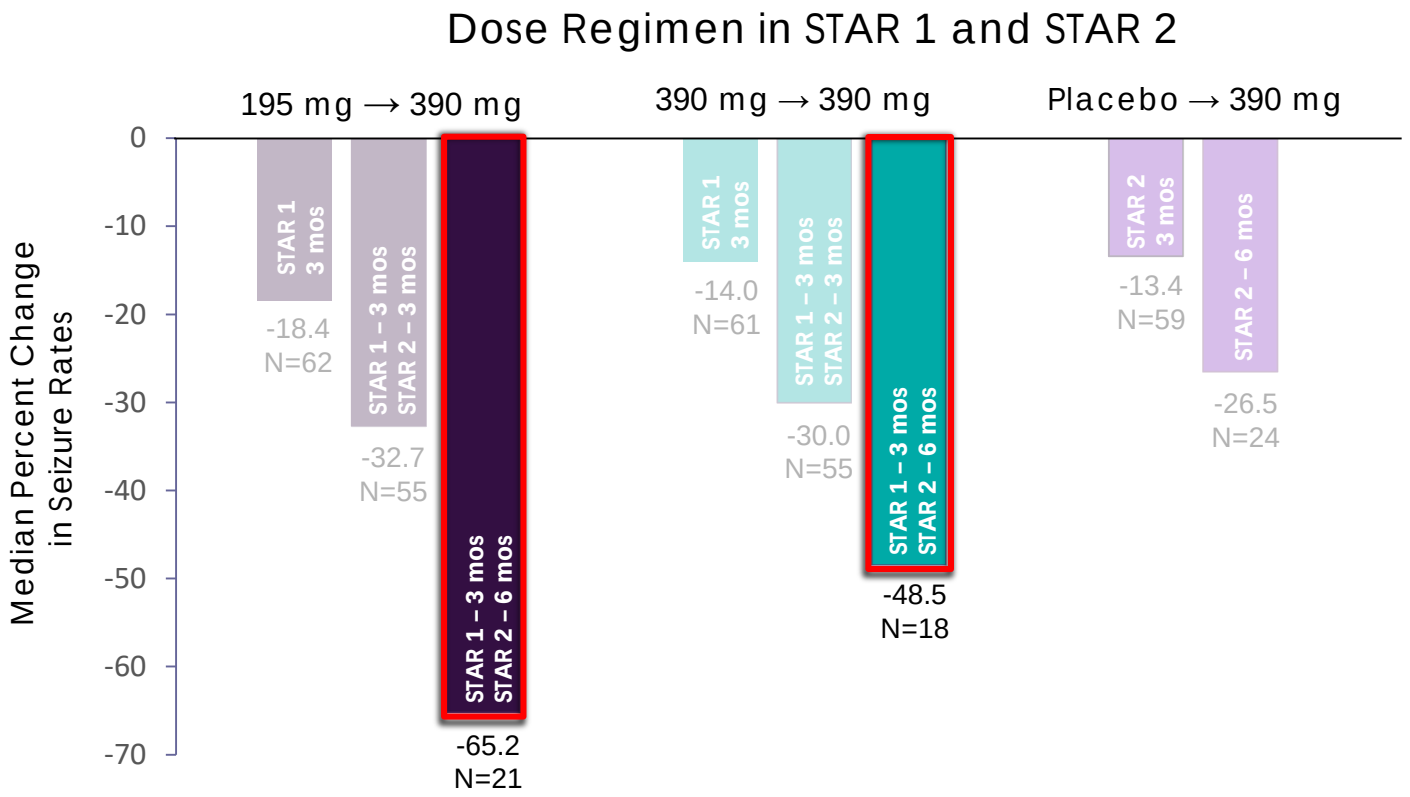
Consistent Results at Various Timeframes
Nine Months on ZYN002



STAR 2 results based on data collected through mid-August 2017 and in patients who reported seizure frequency data during the respective time period.

Not all patients had reached 3 and 6 months in STAR 2 as of mid-August 2017

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Proposed Phase 2b Study
Adult Refractory Focal Epilepsy

Trial design*

- ~300 patient double-blind placebo controlled study
- To be conducted in U.S., Australia and New Zealand
- Primary endpoint: reduction from baseline in focal seizures
- 1:1:1 ratio (195 mg: 780 mg: placebo)

Planned modifications

Learnings from STAR 1 and STAR 2 experience include:

- Stratified randomization by baseline seizure rate and gender
- Increase in patient count
- Increase trial duration
- Increase in baseline seizure frequency
  - Median seizure target: >15/month vs 10.6 in STAR 1

Expected to initiate in 2H18

Open label extension to follow

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*Note: Subject to change due to further regulatory, clinical and other considerations.

Financial Strength
As of December 31, 2017

- **Cash and cash equivalent position of $62.5 million**
  - **Includes $3.0 million in net proceeds from shares sold in September and October 2017 under our ATM program**
- **Well capitalized, expect cash to fund operations well into 2019**

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Fragile X Syndrome Epilepsy

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NASDAQ: ZYNE

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HC Wainwright: Oren Livnat

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Cantor Fitzgerald: Elemer Piros, PhD

Canaccord Genuity: Arlinda Lee, PhD

Seaport Global: Corey Davis

Oppenheimer: Derek Archila

Jefferies: Biren Amin, PhD

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Zynerba Investor Contact

Will Roberts, VP, Investor Relations and Corporate Communications 484.581.7489

484.581.7505

investorrelations@zynerba.com

www.zynerba.com

@ZynerbaPharma

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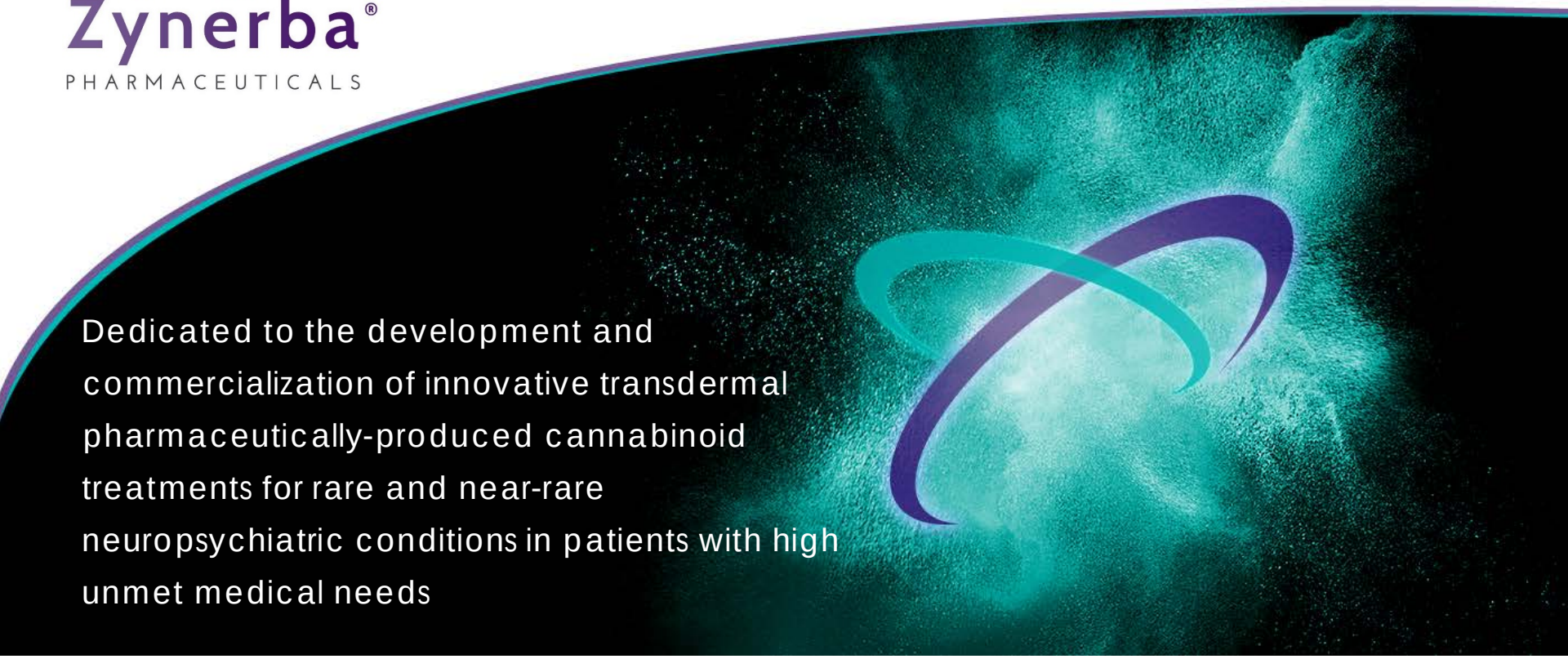

Dedicated to the development and commercialization of innovative transdermal pharmaceutically-produced cannabinoid treatments for rare and near-rare neuropsychiatric conditions in patients with high unmet medical needs

March 2018

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