Zynerba®
PHARMACEUTICALS

A clinical-stage specialty pharmaceutical company dedicated to the development and commercialization of innovative transdermal pharmaceutically-produced cannabinoid treatments for patients with high unmet medical needs

December 2017

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Company Highlights

- Two pivotal study-ready ZYN002 programs (FXS and OA)
  - Expected meetings with FDA in 1Q18
- New STAR 2 epilepsy data suggest clinically meaningful response with continued use of ZYN002
  - Data help clarify new trial design
  - Outline details of path forward in epilepsy: 1Q18
- Global ownership of two proprietary product candidates with potential applicability to numerous disorders
- Experienced team with proven track record in CNS, pain, and transdermal delivery
- $66.3 million in cash and cash equivalents as of September 30, 2017
  - Runway into 2019
  - Additional $3.0 million in proceeds from ATM program from 9/28-10/26/17 to be recorded in fourth quarter

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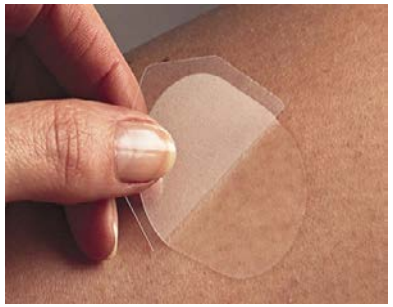
Compelling Pipeline with Multiple Anticipated Near-Term Milestones

Product Candidate	Indication	Preclinical	Phase 1	Phase 2	Next Milestones
ZYN002 – CBD Gel 	Fragile X Syndrome (US FDA Orphan Drug Designation)				1Q18 FDA meeting; initiate pivotal Ph2/3 program in 1H18
	Osteoarthritis				1Q18 FDA meeting; initiate pivotal Ph2/3 program in 2018
	Epilepsy in Adults with Focal Seizures				Outline path forward in 1Q18
ZYN001 – THC Pro-Drug Patch 	Fibromyalgia				Complete Phase 1 in 1H18 Phase 2 Initiation 2018
	Peripheral Neuropathic Pain				

- ZYN002 patent protected through 2030
- ZYN001 patent protected through 2031

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ZYN002
CBD Gel Clinical Program

Developing pharmaceutically-produced CBD formulated as a patent-protected permeation-enhanced gel

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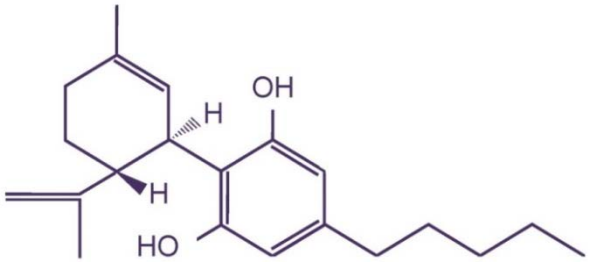
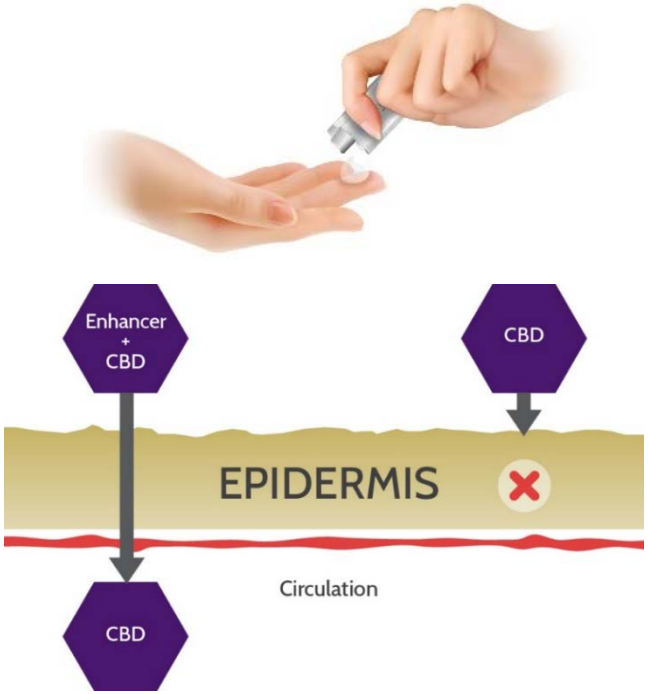
ZYN002 – CBD Gel

- **First and only patent-protected permeation-enhanced pharmaceutically-produced cannabidiol gel formulated for transdermal delivery**
  - **The permeation enhancer in ZYN002 increases the delivery of CBD through the layers of the epidermis and into the circulatory system**

CBD



Delivery



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ZYN002
CBD Gel Clinical Program

Fragile X Syndrome

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Fragile X Syndrome (FXS) Overview

- **Autism spectrum disorder with no approved treatment options**
- **~71,000 US patients[1]; most common inherited intellectual disability**
- **X-linked dominant; affects both males and females[2]**
- **Intellectual disability, attention problems, anxiety, social avoidance co-occur**
  - **Autism, self injury, aggression and seizures common, particularly in males[3]**
- **Early intervention gives children best chance of developing a full range of skills[4]**
- **Significant financial burden / employment impact associated with disorder[5]**

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[1] Data per The National Fragile X Foundation
[2] The National Fragile X Foundation, Handbook of Fragile X-associated disorders, 3rd Addition
[3] Centers for Disease Control and Prevention, Fragile X Syndrome: https://www.cdc.gov/ncbddd/fxs/data.html
[4] NIH: https://www.nichd.nih.gov/health/topics/fragilex/conditioninfo/Pages/treatments.aspx
[5] J Intellect Disabil Res. 2010 Oct;54(10):918-28. doi: 10.1111/j.1365-2788.2010.01320.x. Epub 2010 Aug 26

The Endocannabinoid (EC) System
A Critical Pathway in Fragile X Syndrome

- **ECs form a system of neurotransmitters that regulates emotional responses, behavioral reactivity to context, and social interaction**
- **Due to a mutation in FMR1, patients with FXS suffer from dysregulation of the EC system resulting in the significant social, behavioral, and cognitive deficits**
- **Modulation of the EC system with CBD may have therapeutic potential in ameliorating some of those symptoms**
- **Strong scientific rationale in FXS validated by Phase 2 clinical data**

U.S. Orphan Drug designation for use of CBD as treatment of Fragile X syndrome

May provide fastest pathway to approval

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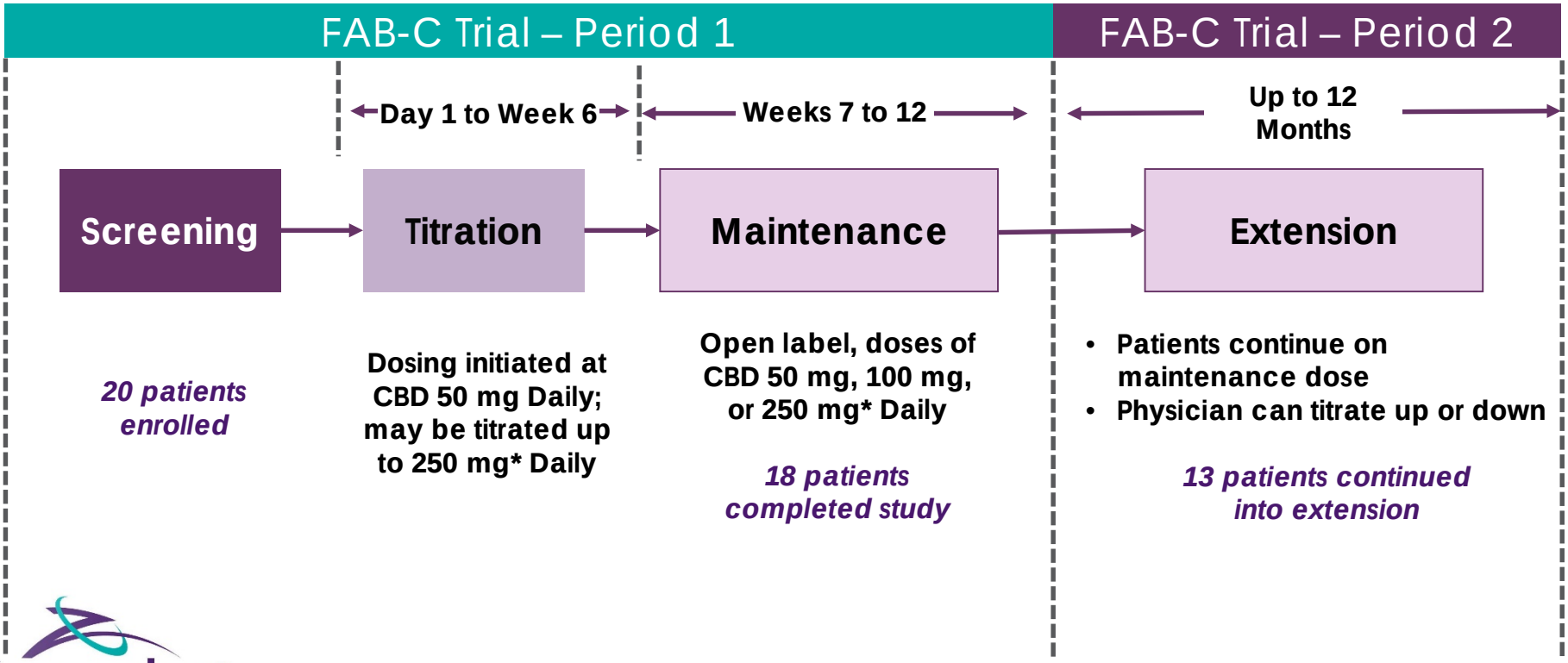
Fragile X Syndrome
Open Label Phase 2 Clinical Trial

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



*In 4.2% gel

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FAB-C Endpoints

Primary Endpoint (recommended by FDA)

Changes in Anxiety, Depression and Mood vs. Baseline as Measured by the ADAMS Scale

Secondary Endpoints
Aberrant Behavior Checklist – FXS Specific (ABC-FXS)
Clinical Global Impression – Improvement (CGI-I)
Pediatric Anxiety Rating Scale (PARS-R)
Visual Analog Scale (VAS): Anxiety, hyperactivity, and tantrum/mood lability
Vineland Adaptive Behavior III (VABS-III): Communication, living skills, socialization
Quality of Sleep: Sleep onset, total sleep, sleep onset latency, nighttime awakenings
Pediatric Quality of Life (PedsQL™)

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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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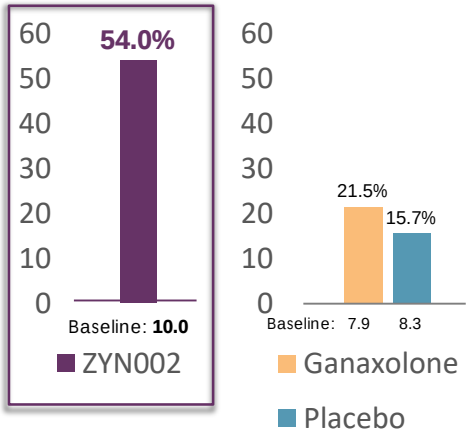
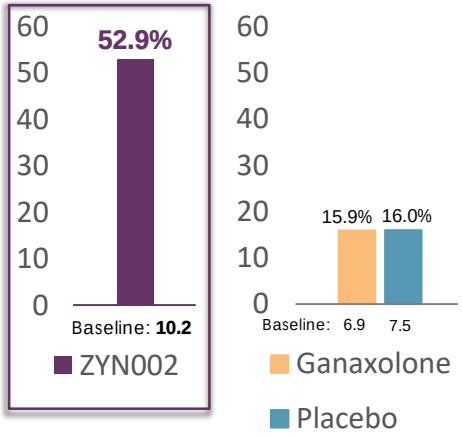
ADAMS Subscales

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

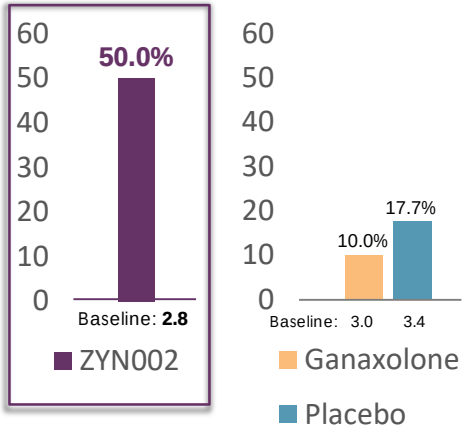
General Anxiety



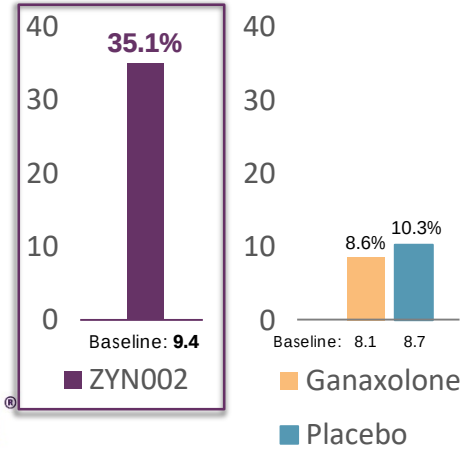
Social Avoidance



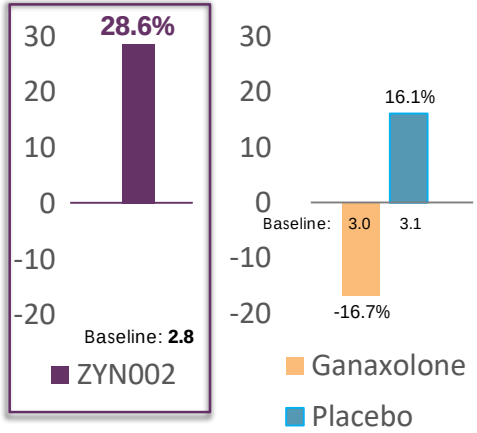
Compulsive Behavior



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.

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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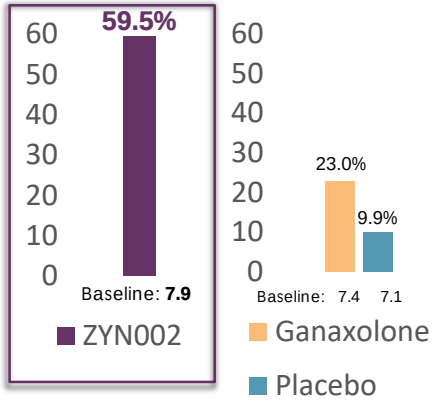
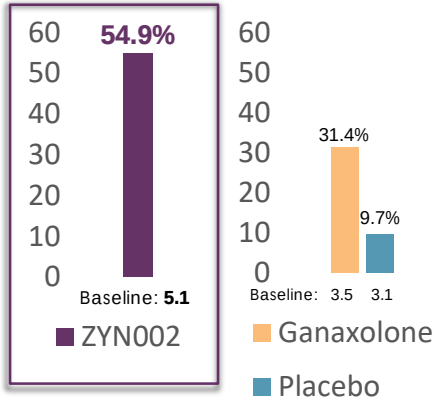
ABC-FXS Subscales

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

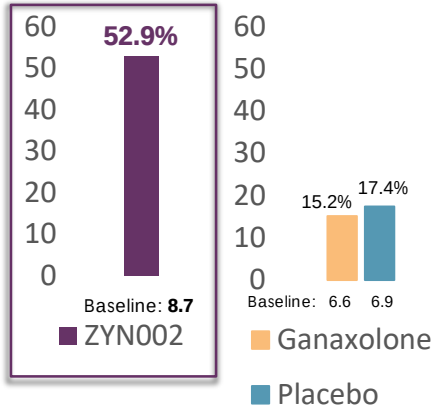
Stereotypy
Repetitive Movements



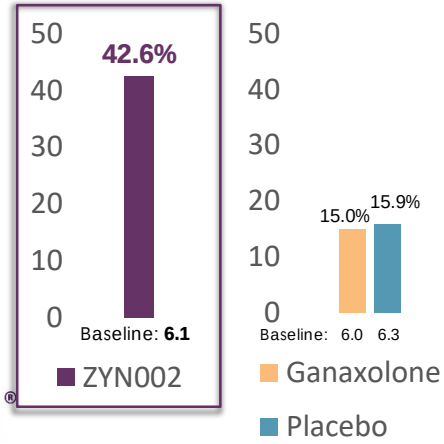
Social Avoidance
Seeks Isolation



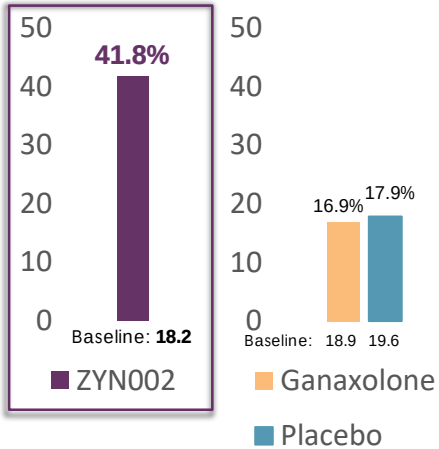
Socially Unresponsive / Lethargic
Does Not Pay attention



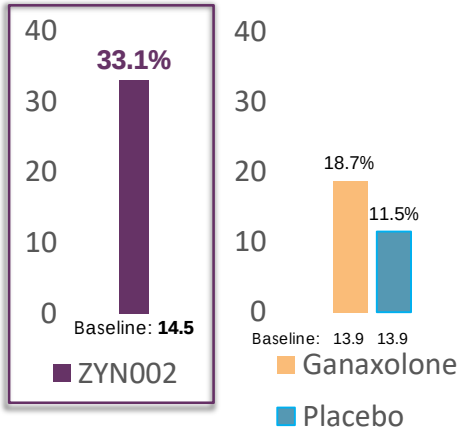
Inappropriate Speech
Repeats Words / Phrases



Irritability
Temper Tantrums



Hyperactivity
Disrupts Group Activities



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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**

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ZYN002 in Fragile X Syndrome: Next Steps

- **Expect to meet with FDA in 1Q18 to discuss data and pivotal trial design**
- **Goal to begin pivotal Phase 2/3 program in pediatric and adolescent patients with FXS in 1H18**
- **Assessing opportunity to present / publish full data set as soon as possible**
- **Evaluating opportunities for FDA fast-track, breakthrough status, and priority review**

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ZYN002
CBD Gel Clinical Program

Focal Seizures in Epilepsy

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New Data Presented at 2017 American Epilepsy Society (AES) meeting

Key Findings Through Six Months of STAR 2

- **Data suggest clinically meaningful response with continued use of ZYN002**
  - **Median reduction in focal seizures from baseline:**
    - **>30% after six months (3 months STAR 1 + 3 months STAR 2) of ZYN002**
    - **48% to 65% after nine months (3 months STAR 1 + 6 months STAR 2) of ZYN002**
- **Improvements in seizure reductions not due to minor changes in background AED by a small number of patients**
- **ZYN002 was very well tolerated in STAR 1 and STAR 2 with an incidence of AEs comparable to placebo**

Data help clarify new trial design

Path forward in epilepsy will be outlined in 1Q18

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New Data Presented at AES
Demographics and Baseline Characteristics

- **188 patients randomized into STAR 1**
  - **186 analyzed for efficacy**
  - **174 completed the study**
  - **171 continued into STAR 2**
- **STAR 1 baseline median monthly seizure frequency of 10.6 (3-335)**
  - **14.0 for ZYN002 195 mg treatment group**
  - **10.14 for ZYN002 390 mg treatment group**
  - **10.5 for placebo group**
- **Patients on a wide range of antiepileptic drugs (AEDs)**
  - **Median of 3.0 AEDs; mean of 2.5 AEDs**
  - **Use of clobazam excluded in STAR 1 and STAR 2 studies**

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New Data Presented at AES
Efficacy Data

- **Company believes that 12 week STAR 1 Phase 2 study failed to achieve endpoints due to bimodal distribution of placebo patient responses:**
  - **>50% reductions in focal seizures in 24% placebo patients**
    - ↗ **13 of 15 of these high responders had lower baseline seizure rate of <15 per month**
  - **No improvement or worsening of focal seizures in 76% of placebo patients**
- **Patients with more severe epilepsy at baseline (seizure frequency of ≥15 per month) taking ZYN002 had a greater percent reduction in seizures compared to patients with severe epilepsy receiving placebo**
- **Continued ZYN002 exposure in STAR 2 may result in clinically meaningful reduction in seizures**

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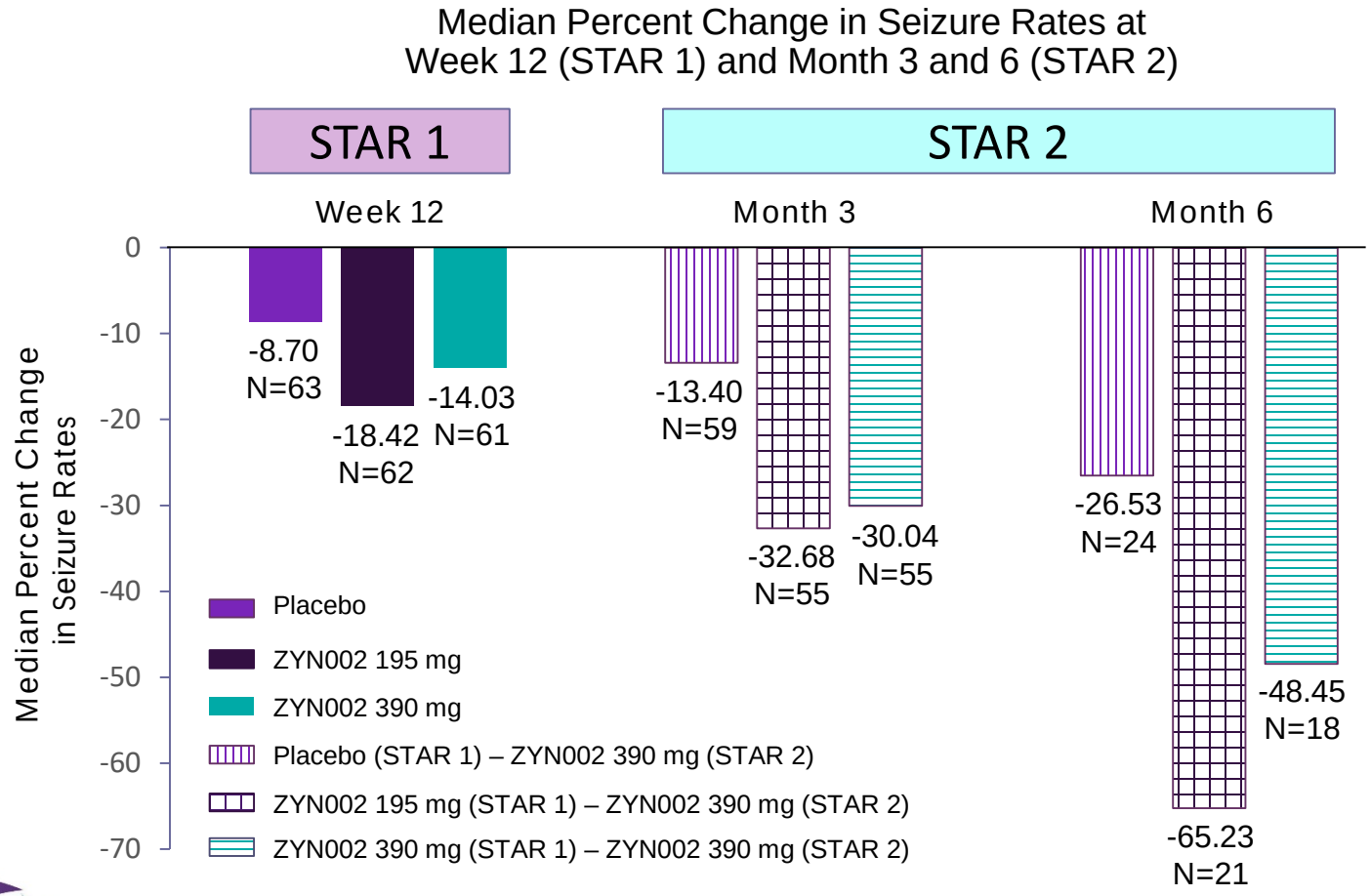
New Data Presented at AES
Efficacy Data



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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ZYN002
CBD Gel Clinical Program

Osteoarthritis

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Potential Path Forward for ZYN002 in Osteoarthritis

- Phase 2 study data help clarify efficacy, safety, dose, inclusion and exclusion criteria, primary and secondary endpoints, placebo response in OA patients
- FDA guidelines require pain and function endpoints in pivotal OA programs
- ZYN002 achieved statistical significance in responder analysis of both pain and function for 250 mg of ZYN002 daily (p=0.016)
  - Did not achieve primary endpoint of reduction from baseline in the weekly mean of the 24-hour average worst pain score at week 12
- Excellent tolerability, consistent with previously released data
- FDA meeting anticipated in 1Q18
- Initiation of pivotal Phase 2/3 program expected in 2018

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ZYN001
THC Pro-Drug Patch Clinical Program

Studying a pharmaceutically-produced pro-drug of THC in a state-of-the-art drug-adhesive matrix transdermal patch

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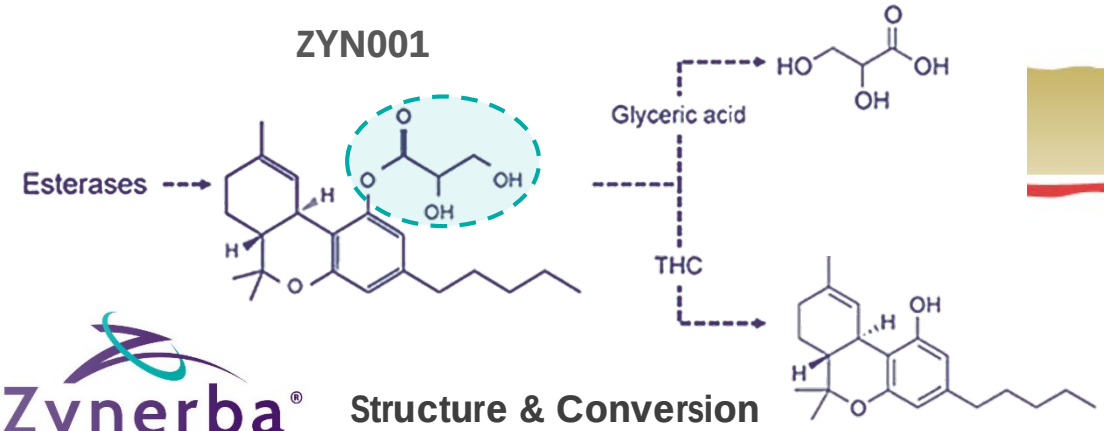
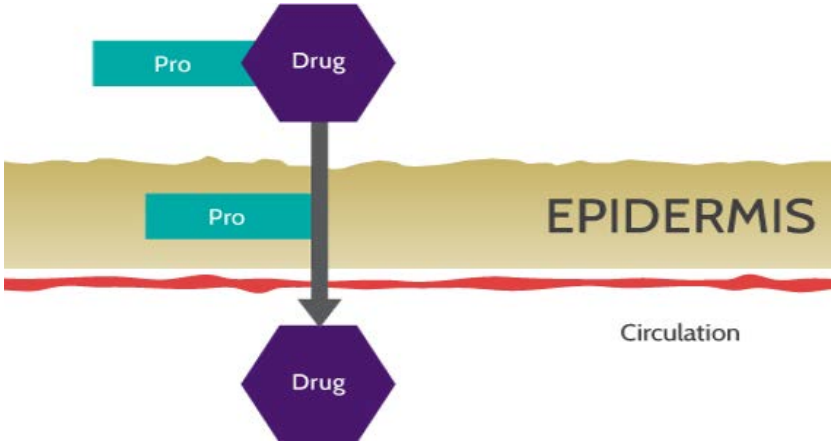
ZYN001 – THC Pro-Drug Patch

- **Patent-protected pharmaceutically-produced D-glyceric acid ester-Δ9-tetrahydrocannabinol 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 into the skin through transdermal delivery**
  - **After crossing the stratum corneum, ZYN001 is hydrolyzed to THC and glyceric acid under physiological conditions**



Structure & Conversion



Delivery

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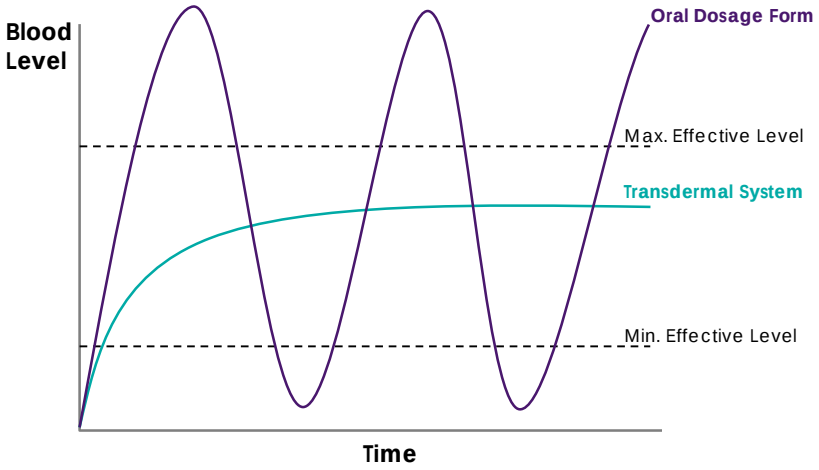
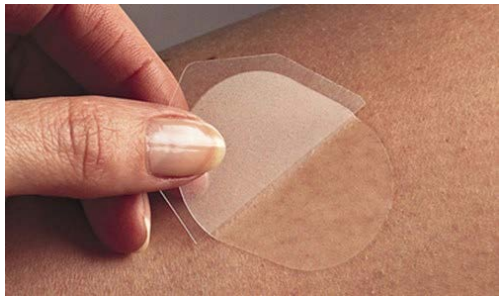
Potential Benefits of Patch Technology

Requirement	Purpose
Non-oral	• Avoids first-pass metabolism with increased bioavailability and more consistent plasma levels
Controlled	• More consistent, controlled and sustained delivery • No “peaks and valleys” as seen with oral
Safe	• Improved safety profile with lower peak plasma levels • Non-invasive

Note: Based upon FDA approved patch products. These results are not indicative of any preclinical or clinical data for ZYN001.

Illustrative Controlled Delivery





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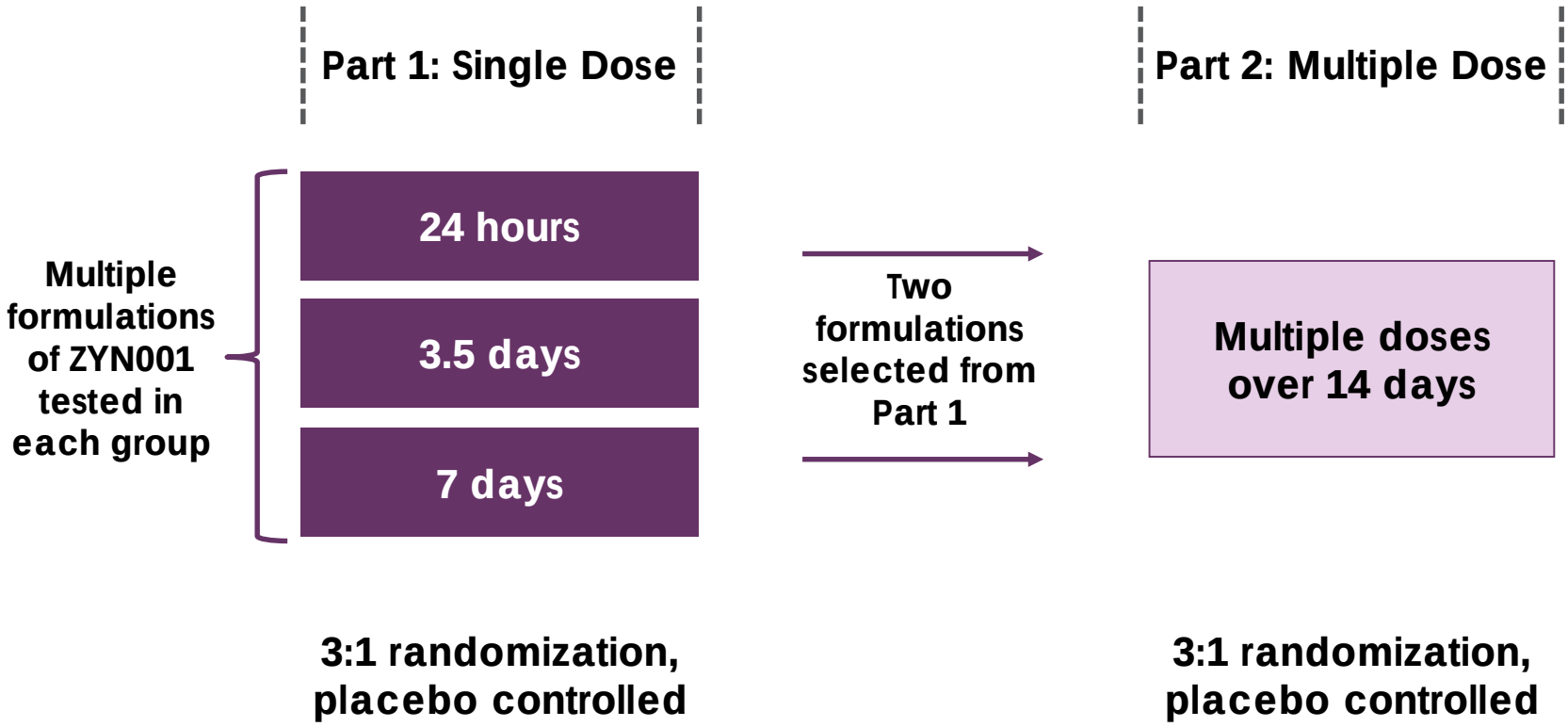
ZYN001 Phase 1 Clinical Trial Underway



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

Potential for THC in Large Indications
Role as a CB1 Agonist Modulates Activity

Fibromyalgia	Peripheral Neuropathic Pain
• Has an analgesic effect in chronic pain models • Acts at many sites along pain transmission pathways • Third-party clinical data on Nabilone (THC analogue) in patients with fibromyalgia supportive of rationale • Approximately 6 million US patients*	• Modulates nociceptive thresholds by regulating neuronal activity • Third-party clinical data of THC and vaporized/smoked/inhaled cannabis in neuropathic pain supportive of rationale • Approximately 15 million US patients*

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*Data per Decision Resources

Zynerba Remains Well Positioned in the High-Growth Cannabinoid Space

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- Experienced team with proven track record in CNS, pain, and transdermal delivery
- $66.3 million in cash and cash equivalents as of September 30, 2017
  - Runway into 2019
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Scientific Advisory Board

Randi J. Hagerman, MD	Medical Director, UC Davis MIND Institute, Distinguished Professor, Endowed Chair in Fragile X Research, Department of Pediatrics, UC Davis School of Medicine
Steven J. Siegel, MD, PhD	Chair, Department of Psychiatry and Behavioral Sciences, Keck School of Medicine, University of Southern California
Nicole Tartaglia, MD	Associate Professor, Pediatrics-Developmental Pediatrics, University of Colorado Denver School of Medicine / Children's Hospital of Colorado
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John Messenheimer, MD	Consultant, Neurologist/Epileptologist, John Messenheimer PLLC
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Rodney Radtke, MD	Professor of Neurology, Duke University Medical Center
Steven P. Cohen, MD	Professor Anesthesiology & Critical Care Medicine, Johns Hopkins School of Medicine
Mark Wallace, MD	Chair, Division of Pain Medicine, University of California San Diego
Donald Abrams, MD	Professor, University of California San Francisco School of Medicine, Chief of Hematology-Oncology at SF General Hospital

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Fragile X Syndrome | Osteoarthritis and Fibromyalgia | Epilepsy | Pain

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Cantor Fitzgerald: Elemer Piros, PhD

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A clinical-stage specialty pharmaceutical company dedicated to the development and commercialization of innovative transdermal pharmaceutically-produced cannabinoid treatments for patients with high unmet medical needs

December 2017