Synthetic Transdermal Cannabidiol for the Treatment of Focal Epilepsy in Adults

Poster #2.253

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INTRODUCTION

- Cannabidiol (CBD) is the primary non-euphoric cannabinoid in cannabis[1]
- ZYN002 is the first and only permeation-enhanced pharmaceutically produced transdermal CBD gel
- Evidence suggests that CBD can reduce seizures in patients with epilepsy[2]
- Most recent clinical work has focused on orally-delivered CBD for children with refractory epilepsy[3,4]

OBJECTIVES

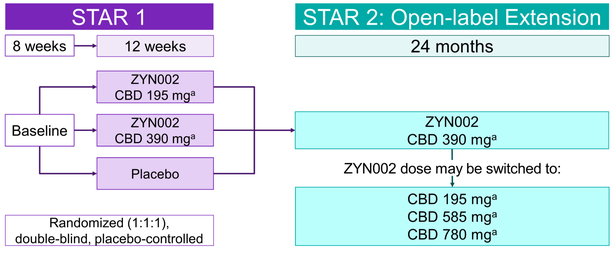
- Evaluate the long-term safety and efficacy of ZYN002 (transdermal CBD gel) as adjunctive therapy for the treatment of focal seizures in adults

METHODS

STUDY CONDUCT

- Synthetic Transdermal CAnnabidiol for the TReatment of Epilepsy (STAR 1) was a Phase 2A, randomized, double-blind, placebo-controlled study of the efficacy and safety of ZYN002 in adults with focal seizures
- STAR 2 is the open-label extension study for completers of the 12-week STAR 1 study (Figure 1)
- All patients from Star 1 who exited double-blind and continued in Star 2 were converted from their blinded dose (placebo, 195 mg, or 390 mg) to open-label 390 mg transdermal CBD daily; at Month 5 they were permitted to titrate to 585 mg and 780 mg daily or to 195 mg daily

Figure 1. Design of the STAR 1 and STAR 2 Studies



[a]In 4.2% gel, dosing BID

PATIENTS

- Inclusion Criteria: Aged 18 to 70 years and in generally good health at screening and at least a 2-year history of epilepsy with partial onset (focal) seizures with or without secondary generalization[5]
- All patients had their seizure history and diagnosis reviewed and confirmed by the Epilepsy Study Consortium prior to randomization
- Exclusion Criteria: Use of cannabis-, CBD-, or THC-containing products within 4 weeks of screening or anytime during the study; use of any of the following AEDs: clobazam, ethosuximide, felbamate, or vigabatrin

METHODS *cont*

ASSESSMENTS

- STAR 2 primary efficacy analysis: Percent reduction from STAR 1 baseline at Months 3, 6, 9, 12, 15, and 18 of STAR 2 (as of 31 July 2018)
- Safety assessments: Clinical labs, physical examination, and adverse events (AEs) as of July 31,2018
- The cohort group is defined as patients included in the Month 18 analysis

RESULTS

- Of the 174 patients who completed STAR 1, 171 patients rolled over into STAR 2 (Tables 1 and 2)
- By the end of STAR 1, patients who received ZYN002 did not have a statistically significant reduction in focal seizures versus placebo
- As of July 31, 2018, 76 patients (44%) remained in the STAR 2 study

Table 1. Patient Disposition in STAR 2

	N (%)
Enrolled	171 (100.0)
Discontinued study	95 (55.6)
Due to AE	5 (2.9)
Withdrew consent	60 (35.1)
Investigator decision	24 (14.0)
Ongoing in the study (as of 31 July 2018)	76 (44.4)
Cohort in Month 18 analysis	63 (36.8)

Table 2. Demographics and Baseline Characteristics in STAR 2

	Discontinued N=95	Ongoing N=76	Total N=171
Age, years			
Mean	39.8	39.0	39.5
Min, Max	18, 71	18, 67	18, 71
Male, n (%)	47 (49.5)	34 (44.7)	81 (47.4)
Female, n (%)	48 (50.5)	42 (55.3)	90 (52.6)
Baseline SF28 seizure rate	10.5	11.05	

- Patients were taking a wide range of antiepileptic drugs (AEDs), and the most commonly used AEDs were levetiracetam, carbamazepine, lamotrigine, lacosamide, and valproate

RESULTS *cont.*

EFFICACY

- Among all treated patients, there was an apparent increase in efficacy of ZYN002 over 18 months (Figure 2); as the cohort group had a substantial reduction at Month 3 that was maintained to Month 18 (Figure 3), this suggests that early drop outs could account for the improved efficacy seen in Figure 2
- Half the patients stayed on 390 mg, and of the half that titrated to higher doses, most went to 780 mg
- As shown in Figure 4, the 390 mg group had the best and most consistent seizure reduction out to Month 18, and the 585/780 mg groups only provided some benefit

Figure 2. Median Change (%) in Seizure Rates Months 3-18 in STAR 2 – All Patients

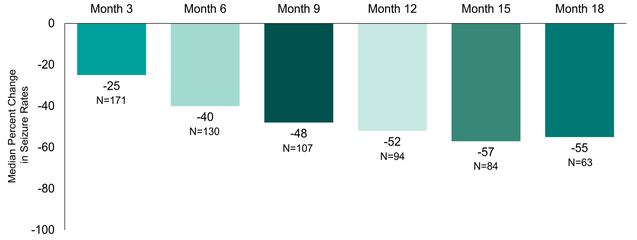


Figure 3. Median Change (%) in Seizure Rates in STAR 2 – Cohort Group (n=63)

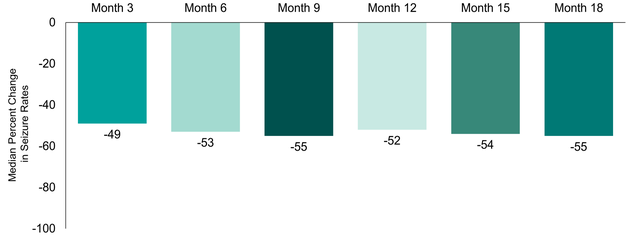
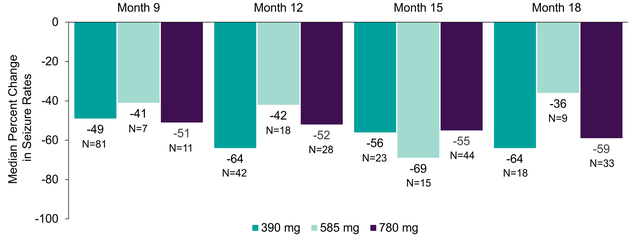


Figure 4. Median Percent Change in Each 3-Month Interval Using Actual Dose in STAR 2 – All Patients



RESULTS *cont.*

SAFETY

- ZYN002 was well tolerated, with good skin tolerability in STAR 2 (Table 3)
- Three serious adverse events were considered possibly related to ZYN002 in STAR 2: seizures (n=2) and increased anxiety (n=1)
- One patient died following the Month 15 visit; the causality is suspected SUDEP
- No abnormal liver adverse events — defined as alanine aminotransferase/aspartate aminotransferase levels > 3 times the upper limit of normal — were observed

Table 3. Treatment-Emergent Adverse Events Occurring in >2% of Patients

Event	ZYN002 n (%)	Event	ZYN002 n (%)
Patients with at least 1 AE	112 (65.5)	Insomnia	6 (3.5)
Headache	20 (11.7)	Lower respiratory tract infection	5 (2.9)
Upper respiratory tract infection	19 (11.1)	Soft tissue injury	5 (2.9)
Viral upper respiratory tract infection	16 (9.4)	Thermal burn	5 (2.9)
Laceration	15 (8.8)	Myalgia	5 (2.9)
Fatigue	10 (5.8)	Application site pain	5 (2.9)
Seizure	9 (5.3)	Application site pruritus	5 (2.9)
Contusion	8 (4.7)	Influenza	5 (2.9)
Nausea	8 (4.7)	Application site reaction	4 (2.3)
Application site dryness	7 (4.1)	Vomiting	4 (2.3)
Gastroenteritis	7 (4.1)	Somnolence	4 (2.3)
Urinary tract infection	7 (4.1)	Anxiety	4 (2.3)
Dizziness	7 (4.1)	Diarrhea	4 (2.3)
Migraine	7 (4.1)		

CONCLUSIONS – ALL PATIENTS

- **ZYN002 is safe and well tolerated at doses of 390 mg to 780 mg over 18 months of treatment**
- **ZYN002 390 mg dose demonstrates consistent apparent efficacy across STAR 2**
- **Higher doses of 585 mg and 780 mg only provided limited additional benefit**
- **No abnormal liver AEs were observed (ie, alanine aminotransferase/aspartate aminotransferase > 3x upper limit of normal)**

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Presented at the AES Annual Meeting 2018, November 30-December 4, 2018, New Orleans, LA

TOB, SFB, and JF have received honoraria and research support from Zynerba; JM was a paid consultant of Zynerba; DG and TS are employees of Zynerba Pharmaceuticals