Synthetic Transdermal Cannabidiol for the Treatment of Focal Epilepsy in Adults

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INTRODUCTION

- Cannabidiol (CBD) is the primary non-psychoactive cannabinoid found in *Cannabis*[1]
- Evidence suggests that CBD can reduce seizures in patients with epilepsy[2]
- Human work has focused on orally-delivered CBD for children with refractory epilepsy[3,4]

OBJECTIVE

- Evaluate the safety and efficacy of ZYN002, a permeation-enhanced, pharmaceutically-produced synthetic CBD gel formulated for transdermal delivery, as adjunctive therapy for the treatment of focal epilepsy 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 (Figure 1)
- After an 8-week baseline period that assessed seizure frequency and type, patients were randomized to receive 195 mg CBD daily (given as 97.5 mg CBD BID), 390 mg CBD daily (given as 195 mg CBD BID) or placebo in a 1:1:1 ratio
- Following the 12-week treatment period, patients who completed STAR 1 could elect to participate in an 18-month open-label 390 mg/day CBD extension study (STAR 2); the dose could be reduced to 195 mg CBD daily as needed

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, according to the International League Against Epilepsy Classification[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; any change in anti-epileptic drug (AED) regimen in the 4 weeks before entering the study; used any of the following AEDs: clobazam, ethosuximide, felbamate, or vigabatrin

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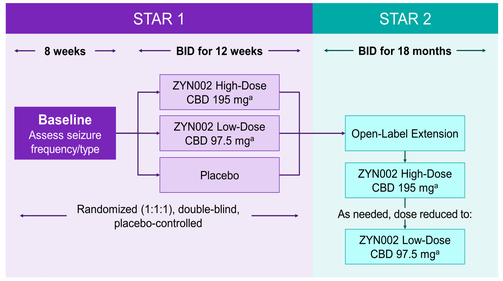
METHODS *cont.*

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



[a]In 4.2% gel

Assessments

- STAR 1 primary efficacy analysis: log-transformed seizure frequency per 28-day period (SF28) during the 12-week treatment period, controlling for the baseline period
- Post-hoc analyses: Percent reduction from STAR 1 baseline at Months 3 and 6 of STAR 2; the efficacy analysis in STAR 2 is based on data collected through mid-August 2017
- Safety assessments: Adverse events (AEs); physical and neurological examinations; 12-lead ECG; clinical laboratory assessments, pregnancy test, Columbia Suicide Severity Rating Scale (C-SSRS); and skin irritation examinations

RESULTS

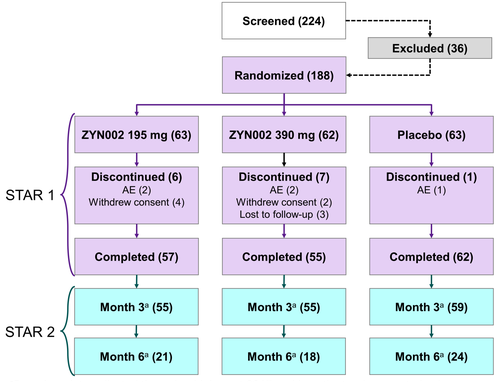
- In total, 188 patients were randomized, 186 were analyzed for efficacy, and 174 completed STAR 1 (Figure 2)
- Of the 14 patients who discontinued, 13 received ZYN002; 5 patients discontinued due to AEs (4 in the ZYN002 groups and 1 in the placebo group), and 3 patients discontinued due to lack of efficacy with ZYN002
- 171 patients (98% of STAR 1 completers) continued into STAR 2
- Partial data through 6 months of STAR 2 is presented

Demographics and Baseline Characteristics

- Most patients were female (54.8%) and white (88.3%), with a mean age of 39.2 years (Table 1)
- At baseline, median SF28 was comparable in the 390 mg CBD daily and placebo groups and higher in the 195 mg CBD daily treatment group; the overall median monthly seizure frequency was 10.6 (3-335)
- Patients were taking a wide range of antiepileptic drugs (AEDs), with an average of 2.5 AEDs and a median of 3.0 AEDs (Table 2)

RESULTS *cont.*

Figure 2. Disposition of Patients



[a]Based on data collected through mid-August 2017 and in patients who reported seizure frequency data during the respective time period.
AE, adverse event

Table 1. Demographics and Baseline Characteristics

	Placebo (%)	ZYN002 195 mg (%)	ZYN002 390 mg (%)
	n=63	n=63	n=62
Median Seizure Frequency/Month	10.5	14.0	10.14
Age, years			
Mean	40.3	37.0	40.4
Min, Max	18, 71	18, 64	19, 68
Sex			
Male	27 (43)	32 (51)	26 (42)
Female	36 (57)	31 (49)	36 (58)
Race			
White	56 (89)	56 (89)	54 (87)
Asian	3 (5)	4 (6)	5 (8)
Other	4 (6)	3 (5)	3 (5)

Table 2. Anti-Epileptic Drug Use at Baseline

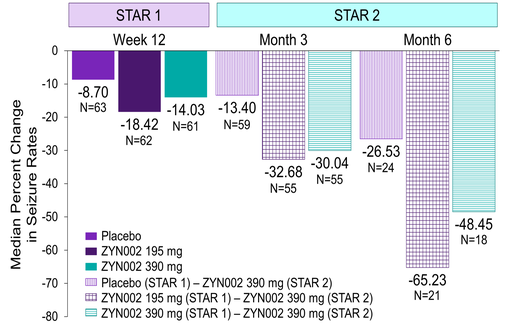
Agent	n (%)	Agent	n (%)
Levetiracetam	85 (45)	Clonazepam	26 (14)
Carbamazepine	77 (41)	Zonisamide	24 (13)
Lamotrigine	61 (33)	Perampanel	21 (11)
Lacosamide	53 (28)	Phenytoin	20 (11)
Valproate	41 (22)	Oxcarbazepine	13 (7)
Topiramate	30 (16)	Phenobarbitone	3 (1.6)

RESULTS *cont.*

Efficacy

- Patients treated for 12 weeks with 195 mg CBD daily or 390 mg CBD daily did not experience statistically significant reductions in focal seizures versus placebo (p=0.89 and p=0.32, respectively)
- The failure of ZYN002 to separate from placebo was likely due in part to 15 placebo-treated patients (24%) who achieved at least a 50% reduction in focal seizures (73% were female); 13 of these 15 patients (87%) had a relatively low baseline seizure rate (SF28 <15)
- Patients with severe epilepsy (defined as baseline SF28 ≥15) taking 195 mg or 390 mg CBD daily had a greater median percent reduction in seizures than patients with severe epilepsy receiving placebo

Figure 3. Median Percent Change in Seizure Rates at Week 12 (STAR 1) and Months 3 and 6 (STAR 2)



- Patients taking 195 mg or 390 mg CBD daily for 6 months (3 months in STAR 1 and 3 months in STAR 2) had greater seizure reductions compared with patients who took 195 mg or 390 mg CBD daily for 3 months (placebo in STAR 1 and 3 months in STAR 2, Figure 3)
- At Month 6 of STAR 2, seizure rates continued to improve

Safety

- ZYN002 was very well tolerated with an incidence of AEs comparable to placebo and no significant differences between the active treatment groups (Table 3)
- The safety profile of ZYN002 was consistent with previously released data from the Phase 1 trials[6]

RESULTS *cont.*

Table 3. STAR 1 Treatment-Emergent Adverse Events[a]

	Placebo n (%)	ZYN002 195 mg n (%)	ZYN002 390 mg n (%)
	n=63	n=63	n=62
Patients with ≥1 AE	26 (41.3)	31 (49.2)	32 (51.6)
Nausea	2 (3)	2 (3)	4 (7)
Fatigue	1 (2)	4 (6)	3 (5)
Application Site Dryness	0	1 (2)	4 (7)
Application Site Pruritus	0	0	3 (5)
Nasopharyngitis	2 (3)	1 (2)	3 (5)
Urinary Tract Infection	1 (2)	3 (5)	1 (2)
Thermal Burn	0	3[b] (5)	0
Headache	2 (3)	4 (6)	3 (5)

AE, adverse event
[a]Occurring in at least 5% of patients and greater than placebo
[b]Seizure-related for 1 patient, 1 patient had an unrelated boiling water spill and 1 patient had a trauma related thermal burn

CONCLUSIONS

- After 12 weeks of blinded treatment, the change in seizure frequency did not statistically differ between placebo and both doses of ZYN002
- A 50% response among 24% of placebo-treated patients contributed to the lack of separation
- ZYN002 was well tolerated, and there were no clinically significant changes in ECGs or laboratory results
- The unblinded use of ZYN002 for an additional 3 and 6 months appeared to result in clinically meaningful seizure reductions and was not due to an increase or addition of other AEDs
- These data indicate further study with longer-term blinded evaluation is warranted

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