AES Poster
2.214

Safety and Tolerability of ZYN002 (Synthetic Cannabidiol) Transdermal Permeation-Enhanced Gel in Healthy Subjects and Patients With Epilepsy: Three Phase 1, Randomized, Double-Blind, Placebo-Controlled Studies

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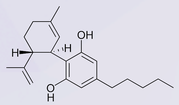
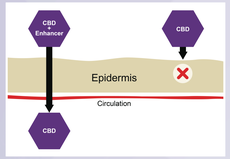
1 Background

- Cannabidiol (CBD) is the main non-euphoric and non-psychoactive component of *Cannabis*
- CBD is well characterized with a high therapeutic index and has shown promise as an anticonvulsant with novel mechanisms of action[1]
- An abundance of animal pharmacology studies support the use of cannabinoids in the treatment of seizures and epilepsy[1]





- Studies in patients with epilepsy have shown that oral formulations of CBD are safe but can be associated with side effects including somnolence, decreased appetite, fatigue, and diarrhea[2]
- ZYN002 is the first and only patent-protected permeation-enhanced synthetic CBD gel that is formulated for transdermal delivery[3]

2 Objective

- **To evaluate the safety and tolerability of ZYN002 synthetic CBD transdermal gel in healthy subjects and patients with epilepsy**

3 Methods

- Three Phase 1 studies, all randomized, double-blind, placebo-controlled:
  - Single rising dose and 7-day multiple rising dose studies in healthy adults and well-controlled patients with epilepsy
  - 14-Day repeat application in healthy adults
- Studies tested once-daily and twice daily application, dose levels ranging from 50 to 504 mg/day of CBD, three concentrations of CBD (1%, 2.5%, and 4.2%), and four volumes of gel (4.7, 5, 6, and 10 g)
- ZYN002 was applied to clean, dry, intact skin of the upper arms and shoulders or upper thighs
- Standard safety measures across three studies included physical exams, vital signs, ECGs, safety labs, Columbia Suicide Severity rating Scale (C-SSRS), adverse events and daily examination of skin for erythema at application site using a 5-point scale
- Pharmacokinetic data (urine and plasma) was collected

3 Methods *cont.*

ZYN2-CL-01 Single Rising Dose Study	ZYN2-CL-02 7-Day Multiple Rising Dose Study	ZYN2-CL-08 14-Day Multiple Rising Dose Study
32 healthy subjects and 10 patients with epilepsy	24 healthy subjects and 12 patients with epilepsy	42 healthy subjects
• 50 mg (5 g x 1%) • 100 mg (10 g x 1%) • 125 mg (5 g x 2.5%) • 250 mg (10 g x 2.5%) • Placebo	• 200 mg (10 g x 1% BID) • 250 mg (10 g x 2.5% QD) • 500 mg (10 g x 2.5% BID) • Placebo	• 395 mg (4.7 g x 4.2% BID) • 500 mg (10 g x 2.5% BID) • 504 mg (6.0 g x 4.2% BID) • Placebo

4 Results

Table 1. Baseline Demographics Across Studies

	ZYN2-CL-01		ZYN2-CL-02		ZYN02-CL-08
	Healthy subjects	Patients with epilepsy	Healthy subjects	Patients with epilepsy	Healthy subjects
N	24	10	32	12	42
Mean age, years	25.9	30.1	29.6	39.6	27.9
Sex, % female	34	100	38	58	60
Race, % white	78	90	92	83	76

- 98 healthy volunteers and 22 patients with epilepsy were treated (86 ZYN002 and 34 placebo)
- Skin erythema for ZYN002 and placebo was negligible. ZYN002 and placebo were extremely well tolerated across all three studies:
  - ZYN2-CL-01: no post-dose erythema (24, 48, 72, 96 hours)
  - ZYN2-CL-02: 7-day application with no erythema at most evaluation points. When recorded, it was scored as minimal erythema, except for one score of moderate erythema on day 2 (no erythema on day 3).
  - ZYN2-CL-08: 14-day application with no erythema at most evaluation points. When recorded, it was scored as minimal erythema, except for three subjects with a score of moderate erythema on days 6, 8, and 13, respectively. In each case, erythema resolved within 48 hours.
- There were no clinically significant changes:
  - during physical exams
  - on electrocardiograms
  - in vital signs
- In clinical labs, only one patient had a significant change. An epilepsy patient from the ZYN2-CL-02 study had decreased neutrophil count, likely associated with a pre-existing condition and treatment with carbamazepine
- There was one serious AE in study ZYN2-CL-02 – a healthy subject who was administered placebo had a catheter-related infection that was deemed unrelated to study drug

4 Results *cont.*

- Treatment-emergent adverse events (TEAE) type, incidence and severity were similar between single rising dose study (ZYN2-CL-01), 7-Day multiple rising dose study (ZYN2-CL-02), and the 14-Day multiple-dose study (ZYN2-CL-08)

Table 2. Subjects With TEAE Across All Studies

ZYN2-CL-01 Single Rising Dose Study	ZYN002				
	50 mg/d (N=6)	100 mg/d (N=6)	125 mg/d (N=6)	250 mg/d (N=13)	Placebo (pooled) (N=11)
Subjects with any TEAE, n (%)	1 (16.7)	2 (33.3)	3 (50.0)	6 (46.2)	6 (54.5)
ZYN2-CL-02 7-Day Multiple Rising Dose Study	**ZYN002**				
	200 mg/d 10.0 g x 1.0% BID (N=6)	250 mg/d 10.0 g x 2.5% QD (N=15)	500 mg/d 10.0 g x 2.5% BID (N=6)		Placebo (pooled) (N=9)
Subjects with any TEAE, n (%)	6 (100)	5 (83.3)	13 (86.6)		8 (88.9)
ZYN2-CL-08 14-Day Multiple-Dose Study	**ZYN002**				
	395 mg/d 4.7 g x 4.2% BID (N=8)	500 mg/d 10.0 g x 2.5% BID (N=12)	504 mg/d 6.0 g x 4.2% BID (N=8)		Placebo (pooled) (N=14)
Subjects with any TEAE, n (%)	6 (75.1)	7 (87.5)	10 (83.3)		10 (71.5)

Table 3. TEAE in 14-Day Study Rated Possibly or Probably Related to Study Treatment and Corresponding Placebo

	ZYN002			
Preferred Term	395 mg/d 4.7 g x 4.2% BID (N=8)	500 mg/d 10.0 g x 2.5% BID (N=12)	504 mg/d 6.0 g x 4.2% BID (N=8)	Placebo (pooled) (N=14)
Subjects with ≥1 TEAE (possibly or probably related)	3 (37.5)	6 (50.0)	5 (62.5)	6 (42.9)
Application site dryness	1 (12.5)	1 (8.3)	1 (12.5)	2 (14.3)
Application site pain (mild)	1 (12.5)	2 (16.7)	2 (25.0)	
Application site pruritis			1 (12.5)	3 (21.4)
Application site paresthesia		1 (8.3)		
Application site reaction/rash			2 (25.0)	1 (7.1)
Headache	2 (25.0)	1 (8.3)		1 (7.1)
Abnormal dreams			1 (12.5)	1 (7.1)
Insomnia		1 (8.3)		
Photophobia		1 (8.3)		
Nausea		1 (8.3)		
Erythema and rash generalized*			2 (25.0)	
Thirst			1 (12.5)	

*Not at application site.

4 Results *cont.*

- Most AEs were transient and mild in severity
- Application site AEs were generally mild and transient
- The overall incidence of adverse events was low with mild application site events being the most common

5 Conclusions

- ZYN002 was safe and well tolerated in healthy volunteers and epilepsy patients across all studies (single ascending dose, 7-day multiple rising dose and 14-day multiple-dose studies)
- All ZYN002 doses and concentrations were well tolerated. The higher CBD concentration (4.2%) allowed patients to apply a lesser volume of gel, making application easier for subjects
- Application site dryness was the most common application site adverse event
- In the 14-day multiple dose study, there was no somnolence, fatigue, or decreased appetite, and only one gastrointestinal adverse event reported (nausea)
- ZYN002 AEs across all three studies were generally mild, transient, and similar to placebo
- There were no clinically significant drug related changes during physical exams, on ECG, in vital signs, or in clinical labs
- ZYN002 doses from 50 mg to 504 mg administered on the upper arms and shoulders or upper thighs are safe for use in patients with epilepsy
- No THC was detected in plasma or urine across all three studies

6 References

1. Leo A, Russo E, Elia M. *Pharmacol Res*. 2016;107:85-92.
2. Devinsky O, Marsh E, Friedman D, et al. *Lancet Neurol*. 2016;15(3): 270–278.
3. Data on file. Zynerba Pharmaceuticals, Inc. Devon, PA.

American Epilepsy Society Annual Meeting, December 2-6, 2016, Houston, TX, USA

This study was funded by Zynerba Pharmaceuticals, Inc.