A Permeation-Enhanced Synthetic Cannabidiol (CBD) Transdermal Gel for the Treatment of PTSD

Marcel O. Bonn-Miller, PhD[1] and Donna L. Gutterman, PharmD[2]

1, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; 2, Zynerba Pharmaceuticals Inc., Devon, PA, USA

Background

- Posttraumatic stress disorder (PTSD) is a major public health problem, particularly among active military personnel and veterans
- The Veterans Health Administration (VHA) has observed a 60% increase in PTSD diagnosis between 2001 and 2007,[1] with approximately 229,000 of 1.64 million (14%) veterans of Operations Enduring Freedom and Iraqi Freedom meeting diagnostic criteria for PTSD[2]
- While several empirically-supported pharmacological and behavioral interventions are available for individuals with PTSD,[3,4] a majority of patients continue to experience PTSD following treatment[5]
- Cannabidiol (CBD) has been shown to modulate the endocannabinoid system,[6] which regulates physiological processes including pain sensation, mood, and memory
- In PTSD treatment models, various formulations of CBD have been shown to:[7-9]
  - Reduce or eliminate the physiological and emotional salience of fearful memories
  - Reduce anxiety, particularly among those with anxiety disorders
  - Improve sleep
- A permeation-enhanced synthetic CBD transdermal gel — ZYN002 — is being developed for treatment of patients with PTSD
- As an initial step toward the examination of ZYN002 among individuals with PTSD, a Phase I investigation of its safety, tolerability, and cognitive effects was conducted

Objectives

- The objectives of this study were to evaluate the:
  - Safety and tolerability of ZYN-002
  - Cognitive effects of ZYN-002

Methods

- Single-dose, randomized, double-blind, placebo-controlled trial in healthy volunteers
- Subjects were randomized 3:1 to receive single applications of ZYN002 transdermal gel or placebo
  - The gel was applied to clean, dry, intact skin of the shoulders and/or upper arms by a member of the research facility
  - Subjects were not permitted to wash the application site for at least 12 hours after application
- Study drug treatments were applied as follows:
  - Period 1: ZYN002 50 mg (1% × 5 g)
  - Period 2: ZYN002 100 mg (1% × 10 g)
  - Period 3: ZYN002 125 mg (2.5% × 5 g)
  - Period 4: ZYN002 250 mg (2.5% × 10 g)
  - Placebo:
    - Periods 1 and 3 (5 g)
    - Periods 2 and 4 (10 g)
- Outcome measures included:
  - Safety/Tolerability: baseline,15, 30 minutes, and 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours post-application
    - Physical exams
    - Application site irritation
    - Vital signs and pulse oximetry
    - Electrocardiograms (ECGs)
    - Safety laboratories
    - Urinalysis
    - Spontaneously reported adverse events
  - Cognitive Effects (Trail Making Test [A and B]): baseline and 2, 4, 8, and 24 hours post-application
    - Time to complete each trail
    - Total line length

Results

Table 1. Demographics (N = 32)

Parameter		Value
Age (years), n (%)	Mean	25.9
	Min, max	19.0, 52.0
Gender, n (%)	Male	21 (65.6)
	Female	11 (34.4)
Race, n (%)	White	25 (78.1)
	Asian	2 (6.3)
	Various[a]	5 (15.6)

[a]1 subject each was classified as Brazilian; White/Caribbean; White/Black; Latino; White/Asian

Safety/Tolerability

- The incidence of treatment-emergent adverse events with ZYN002 was similar to placebo (Table 2)

Table 2. Treatment-Emergent Adverse Events

Preferred Term	Period 1 n = 6	Period 2 n = 6	Period 3 n = 6	Period 4 n = 6	Placebo Pooled n = 8
Abdominal discomfort		1			
Diarrhea				1	
Nausea		1			
Vessel puncture site bruise			1		1
Headache	1	1	1	2	1
Erythema[a]			1		1

[a]P3 dressing tape and blood pressure cuff

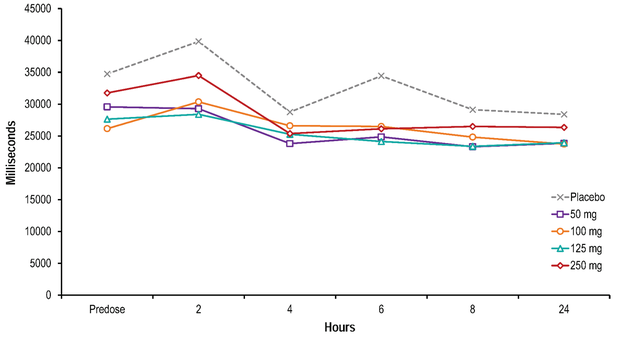
- No erythema was reported by ZYN002- or placebo-treated subjects at 24, 48, 72, and 96 hours post-application
- There were no clinically significant changes in laboratory values, ECGs, or vital signs in subjects treated with ZYN002 or placebo

Cognitive Effects

- For line length, no main effects of Drug Condition and no Drug x Time interaction were found on Trails A or B
- For time to completion, subjects receiving 50 mg ZYN002 outperformed those in the placebo group on Trail A (Figure 1)

Results *cont.*

Figure 1. Time to Completion, Trail A (msec)



- No effects of Drug Condition or Drug x Time interactions were observed

Conclusions

- ZYN002 has an acceptable tolerability profile for the treatment of PTSD
- The frequency and severity of adverse events with ZYN002 were comparable to placebo
- There was no evidence of cognitive impairment on the Trail Making task, a validated measure of psychomotor ability and executive function, indicating psychomotor functioning and executive function were not impacted by exposure to ZYN002
- Future work — a Phase 2a clinical trial of the effects of ZYN002 in patients with PTSD

References

1. Seal KH et al. *Arch Intern Med*. 2007;167(5):476–482.
2. Tanielian T et al. RAND Corporation, 2008. Available at: http://www.rand.org/pubs/research_briefs/RB9336.html.
3. Amos T et al. *Cochrane Database Syst Rev*. 2014;(7):CD006239.
4. Bisson J et al. *Cochrane Database Syst Rev*. 2013;12:CD003388.
5. Marmar CR et al. *JAMA Psychiatry*. 2015;72:875–881.
6. Mechoulam R et al. *Chem Phys Lipids*. 2002;121(1-2):35–43.
7. Bitencourt RM et al. *Eur Neuropsychopharmacol*. 2008;18(12):849–859.
8. Campos AC et al. *Psychopharmacology*. 2008;199(2):223-230.
9. Belendiuk KA et al. *Addict Behav*. 2015;50:178–181.