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Neuropsychological Effects of ZYN002 (Synthetic Cannabidiol) Transdermal Gel in Healthy Subjects and Patients With Epilepsy: Phase 1, Randomized, Double-Blind, Placebo-Controlled Studies

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1 Background

- Cannabidiol (CBD), the main non-euphoric component of cannabis, has shown initial therapeutic efficacy in a myriad of chronic medical conditions, including epilepsy[1]
- Early clinical work has indicated that CBD does not elicit euphoric or negative neuropsychological effects commonly associated with Δ9-tetrahydrocannabinol (THC)[2-4]
- ZYN002 is the first and only patent-protected permeation-enhanced synthetic CBD gel, formulated for transdermal delivery[5]
- Due to limitations of existing CBD studies (e.g., not well controlled; oral routes of administration, which can convert to THC in an acidic environment), the potential neuropsychological effects of ZYN002 are unknown

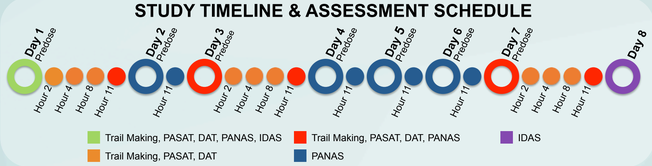
2 Objective

- To characterize the neuropsychological effects of ZYN002, a synthetic CBD transdermal gel, in healthy subjects and patients with epilepsy

3 Methods

- Phase 1, 7-day randomized, double-blind, placebo-controlled study in (1) healthy adults and (2) epilepsy patients
- Healthy Adults - Multiple-dose study with 4 treatment groups:
  - Placebo (N=5)
  - 200 mg/d, 10 g x 1% ZYN002 BID (N=6)
  - 250 mg/d, 10 g x 2.5% ZYN002 QD (N=6)
  - 500 mg/d, 10 g x 2.5% ZYN002 BID (N=6)
- Epilepsy Patients (EPI) - 2 treatment groups:
  - Placebo (N=3)
  - 500 mg/d, 10 g x 2.5% ZYN002 BID (N=9)
- Treatment was applied to clean, dry, intact skin of the upper arms and shoulders.
- Assessments:
  - Trail Making Test (visual attention and task switching)
  - Paced Auditory Serial Addition Test (information processing)
  - Divided Attention Test (multi-tasking)
  - Positive And Negative Affect Schedule
  - Inventory of Depression and Anxiety Symptoms

STUDY TIMELINE & ASSESSMENT SCHEDULE



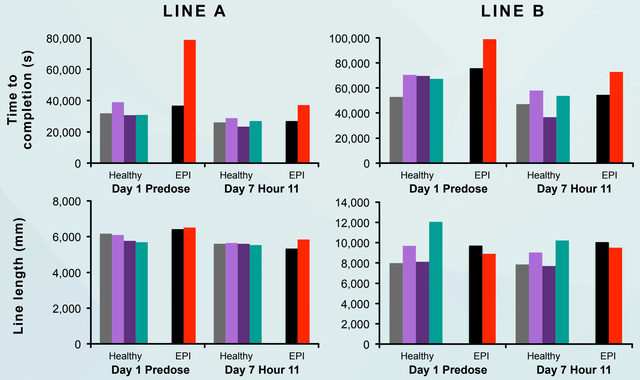
4 Results

- Repeated Measures ANOVAs were conducted for time, dose, and dose by time interactions (key measure of drug effect).

Summary of Neuropsychological Findings

Effect	Significant Effects in Healthy Subjects	Significant Effects in Epilepsy Patients
Main effect of time Difference over course of study, independent of treatment group	• **Trail Making** (Line A time to completion & line length) • **Trail Making** (Line B line length) • **PASAT** (Total correct & Mean RT Correct) • **PANAS** (Positive & Negative Affect) • **IDAS** (Well-Being)	• **Trail Making** (Line B time to completion) • **PASAT** (Total Correct) • **PANAS** (Positive Affect) • **IDAS** (General Depression, Social Anxiety, Total Symptoms)
Main effect of dose Difference between treatment groups, independent of study schedule	• **IDAS** (Lassitude, Panic, Appetite Gain)	• **IDAS** (Appetite Gain)
Dose by time interaction Difference between treatment groups that emerged over course of study	None	• **PASAT** (Total Correct) **Approached Significance (p = .052)

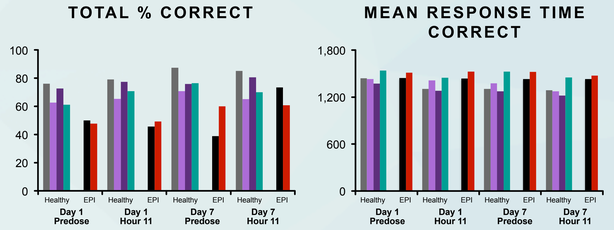
Figure 1. Trail Making Test Results



➢ Among both healthy adults and epilepsy patients, study drug did not impact participant visual attention or task switching over time.

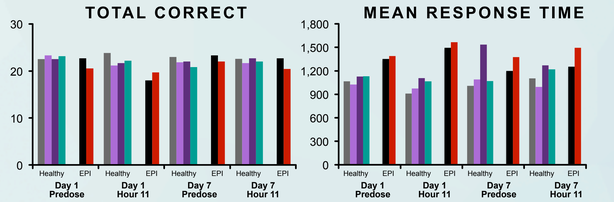
4 Results *cont.*

Figure 2. PASAT Results



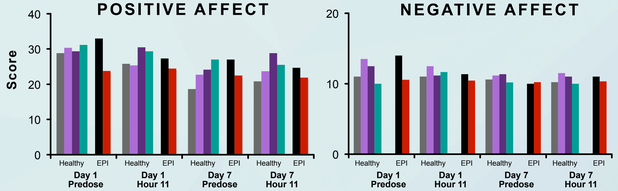
➢ Among healthy adults, study drug did not impact the speed or flexibility that participants processed information over time. However, among epilepsy patients, there was a non-significant trend toward improved performance among those who received ZYN002 over time.

Figure 3. DAT Results



➢ Among both healthy adults and epilepsy patients, study drug did not impact the ability of participants to multitask over time.

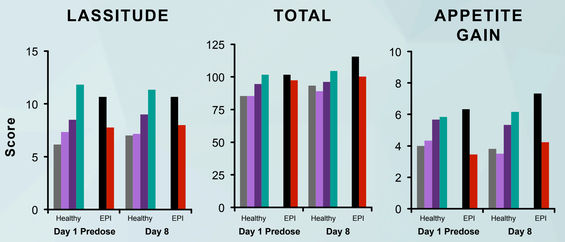
Figure 4. PANAS Results



➢ Among both healthy adults and epilepsy patients, study drug did not impact the experience of either positive or negative affect over time.

4 Results *cont.*

Figure 5. IDAS Results



➢ Neither healthy adults nor epilepsy patients experienced anxiety or depressive symptoms as a function of study drug over time.

5 Conclusions

- Results indicate that ZYN002 does not produce impairment in critical areas of cognitive functioning often impacted by CNS drugs in healthy subjects and patients with epilepsy
- Results also indicate that ZYN002 is not associated with declines in psychological health in healthy subjects and patients with epilepsy
- Unlike THC, ZYN002 may provide therapeutic benefit for chronic medical conditions while minimizing neuropsychological risk

6 References

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