Respiratory Evaluation of Subcutaneously Administered ZYN001 in Male Sprague-Dawley Rats

David Gauvin, PhD[1], Carol O'Neill,[2] D. Reid Patterson, DVM, PhD[3]

1. MPI Research, Mattawan, MI, USA; 2. Zynerba Pharmaceuticals Inc., Devon, PA, USA; 3. Reid Patterson Consulting, Bonita Springs, FL, USA

Poster # 48

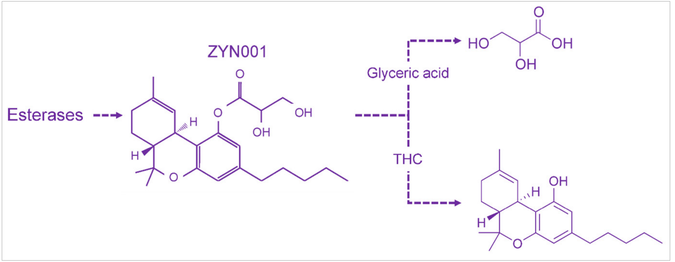
Background

- ZYN001 is a synthetic pro-drug of Δ9-tetrahydrocannabinol (THC), a cannabinoid and the primary psychoactive component in Cannabis sativa,[1] formulated for delivery via a transdermal patch that contains ZYN001 and is intended for application to the upper arm, back, or thigh
- The drug substance is produced synthetically and is not derived or extracted from botanicals
- The excipients in the patch have been classified as Generally Recognized As Safe and have been used in transdermal products previously approved by the FDA
- The pro-drug formulation is an enabling technology designed to facilitate the transport of THC, which is naturally hydrophobic, across the stratum corneum and into the systemic circulation
- The transdermal patch is a non-invasive, non-oral dosage form that may be able to achieve sustained, consistent THC plasma levels with an improved adverse effect profile
- Chemically, ZYN001 is the D-(-)-glyceric acid ester of THC, but unlike THC, ZYN001 can be absorbed into the skin transdermally
- After crossing the stratum corneum, ZYN001 is hydrolyzed back to THC and glyceric acid under physiological conditions[2] (Figure 1)
- As the rat is the usual rodent model used for evaluating the toxicity of various classes of chemicals, and there were no gender differences expected in pulmonary function, only male rats were used
- In this study, rats were injected subcutaneously rather than treated dermally to assure maximal transport into the subcutis for optimal absorption into circulation

Objective

The objective of this study was to evaluate the potential effects of ZYN001 on respiratory function.

Figure 1. Hydrolysis of ZYN001 into glyceric acid and THC



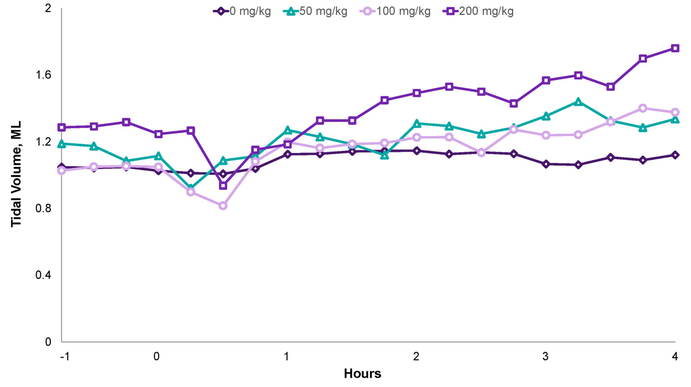
Methods

- A total of 32 male experimentally naïve Sprague-Dawley rats (weight, 205–241 g) were included in this study
- During an 11 to 18-day acclimation period, animals were observed daily with respect to general health and any signs of disease
- Rats were individually housed in whole body plethysmograph respiratory monitoring chambers ≥1.5 hours predose, temporarily removed for dosing, and returned immediately postdose so pulmonary monitoring could continue for ≥4 hours
- Rats within ±20% of the mean weight were randomly assigned to receive a single subcutaneous bolus injection of vehicle (sesame oil filtered through a 0.2 µm nylon syringe filter) or ZYN001 at doses of 50 mg/kg, 100 mg/kg, or 200 mg/kg
- The vehicle dosing formulation was prepared twice, up to three days before dosing, and was stored refrigerated (2–8°C) until acquired for dosing
- A 25 g needle was used to inject study drugs into the scapular region on the back of each animal
- Assessments of respiratory effects and general toxicity were based on respiratory function, clinical observations, body weight, and mortality
- Respiratory function was a composite value that included respiratory rate, tidal volume, minute volume, inspiration time, expiration time, peak inspiratory flow, peak expiratory flow, end inspiratory pause, and end expiratory pause

Results

- All animals survived to study termination
- Predose, one-hour postdose, and at the end of monitoring, clinical observations were all "normal"
- No clinical signs of toxicity were noted
- Body weights were consistent with expectations for the age and gender of the rats in this study
- Rats demonstrated a normal pattern of acclimation to the whole-body plethysmograph chamber, and there was no physiologically relevant respiratory depression at ZYN001 doses up to 200 mg/kg
- The group-averaged tidal volumes for ZYN001 showed a time-dependent elevation over the four-hour monitoring period, with the 200 mg/kg dose significantly increasing group mean tidal volumes by the end of the 4-hour monitoring period, as shown in Figure 2 (1.121 mL vs 1.761 mL, $P<0.01$); these effects were within the upper range of normal documented in historical control data and were not considered to be adverse

Figure 2. Mean tidal volume after subcutaneous administration of ZYN001



- There were no physiologically meaningful changes in group mean minute volumes before or after dose administrations of up to 200 mg/kg ZYN001
- No consistent alterations in air exchange were observed during the monitoring periods, but ZYN001 changed the topography of breathing by causing a substantial increase in mean end expiratory pause
- The mean end expiratory effect was most likely a compensatory response to known central nervous system and peripheral cannabinoid-related interactions and does not represent an adverse pharmacological effect on pulmonary function

Conclusions

- **ZYN001 produced no significant changes in the three core measures of respiratory dynamics (respiratory rates, tidal volumes, or minute volumes), all of which were within normative values for the strain, age, gender, and bodyweights of the rats assessed in the present study**
- **At the highest tested dose of 200 mg/kg, ZYN001 changed the topography of breathing by eliciting an increase in end expiratory pause**
- **Published literature suggests that this effect is a compensatory response to known central nervous system and peripheral cannabinoid-related interactions that does not represent an adverse pharmacological effect on pulmonary function**
- **This end expiratory finding marks an important distinction from opioids, with which respiratory depression is a common, potentially dangerous side effect**

References

1. Gaoni YM, Mechoulam R. *J Am Chem Soc*. 1964;86:1646–1647.
2. Williams FM. *Clin Pharmcokinet*. 1985;10:392–403.

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