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

**Background**

- ZYN001 is a synthetic pro-drug of Δ9-tetrahydrocannabinol (THC), a cannabinoid and the primary psychoactive component in Cannabis sativa. It is 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.
- Generally Recognized As Safe (GRAS) substances are utilized in the formulation instead of the primary psychoactive component.
- 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.

**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 21.5 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 at 4°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.

**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 normal historical 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 and 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**


**Disclosure:** GRP is a paid consultant and CO is employed by Zynerba Pharmaceuticals Inc., developer of ZYN001, which supported this study.

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**Figure 1. Hydrolysis of ZYN001 into glyceric acid and THC**

**Figure 2. Mean tidal volume after subcutaneous administration of ZYN001**

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**Objective**

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