Cannabis and Cannabinoid Research Publishes Data Demonstrating the Degradation of Cannabidiol to Psychoactive Cannabinoids when Exposed to Simulated Gastric Fluid

April 12, 2016

Transdermal CBD Gel ZYN002 has the potential to avoid bioconversion to psychoactive THC by bypassing the gastrointestinal tract

DEVON, Pa., April 12, 2016 (GLOBE NEWSWIRE) -- Zynerba Pharmaceuticals, Inc. (NASDAQ:ZYNE), a specialty pharmaceutical company dedicated to the development of innovative transdermal synthetic cannabinoid treatments, today announced the publication of important *in vitro* data demonstrating that the acidic pH conditions provided by simulated gastric fluid (SGF) converts cannabidiol (CBD) into the psychoactive components Δ^9- tetrahydrocannabinol (THC), Δ^8-THC and other psychoactive cannabinoids. The paper, titled "Identification of Psychoactive Degradants of Cannabidiol in Simulated Gastric and Physiological Fluid," was published online in C*annabis and Cannabinoid Research* on April 9, 2016. The full publication can be accessed here.

"This study demonstrated the acid-catalyzed conversion of CBD to the psychoactive cannabinoids Δ^9-THC and Δ^8-THC, compared to no evidence of CBD conversion in neutral pH physiological buffer," said Terri Sebree, president of Zynerba. "The consistent degradation of CBD in simulated gastric fluid led to an understanding of the kinetics of THC formation in an acidic environment. The characterization of this rate enables us to estimate the conversion of CBD to THC following oral dosing of CBD-containing medications, the levels of which may exceed the threshold for a psychoactive response. We believe that alternative delivery methods such as that used by ZYN002, a transdermal formulation of CBD, will avoid the potential for formation of psychoactive cannabinoids by bypassing the acidic environment of the stomach. ZYN002 is currently being evaluated in a Phase 1 multiple rising dose study, and we look forward to reporting topline results by the end of the first half of 2016."

In recent studies, pediatric patients with epilepsy who received orally administered CBD, showed a relatively high incidence of adverse events (≤44%), with somnolence (≤21%) and fatigue (≤17%) among the most common.[1] [2] Previous research[3] suggests that when CBD is exposed to an acidic environment, it degrades to THC and other psychoactive cannabinoids.

Zynerba undertook the current study to assess the formation of psychoactive cannabinoids when CBD is exposed to SGF. The study showed that CBD was degraded to Δ^9-THC and Δ^8-THC with less significant levels of other related cannabinoids formed. The degradation followed first-order kinetics at a rate constant of -0.031 min^{-1} (R^2 = 0.9933). CBD in physiological buffer performed as a control did not degrade to THC. Confirmation of THC formation was demonstrated by comparison of mass spectral analysis, mass identification, and retention time of Δ^9-THC and Δ^8-THC in the SGF samples against authentic reference standards.

The conversion of CBD into the psychoactive components Δ^9-THC and Δ^8-THC suggests that the oral route of administration may increase the potential for psychoactive adverse effects. The results from this *in vitro* study suggests that the acidic gastric environment during normal gastrointestinal transit may expose patients treated with oral CBD to levels of THC and other psychoactive cannabinoids that exceed the threshold for a physiological response.

ZYN002 is currently being evaluated in a Phase 1 multiple rising dose trial in healthy volunteers and patients with epilepsy. Zynerba expects to report results from this Phase 1 study by the end of the first half of 2016 and to begin three Phase 2 studies of ZYN002 in each of epilepsy, osteoarthritis and Fragile X syndrome (FXS) patients in the second half of 2016.

About ZYN002 CBD Gel
Zynerba's ZYN002 CBD gel is the first and only synthetic CBD formulated as a patent-protected permeation-enhanced gel and is being studied in refractory epilepsy, Fragile X syndrome and osteoarthritis. ZYN002 is a clear, permeation-enhanced gel that is designed to provide consistent, controlled drug delivery transdermally with convenient once- or twice-daily dosing. Transdermal therapeutics are absorbed through the skin directly into the systemic circulation, avoiding first-pass liver metabolism and potentially enabling lower dosage levels of active pharmaceutical ingredients and rapid and reliable absorption with high bioavailability. In addition, transdermal delivery avoids the gastrointestinal tract and potential stomach acid degradation of CBD into THC (associated with psychoactive effects).

About Zynerba Pharmaceuticals, Inc.
Zynerba Pharmaceuticals (NASDAQ:ZYNE) is a specialty pharmaceutical company focused on developing and commercializing proprietary next-generation synthetic cannabinoid therapeutics formulated for transdermal delivery. Zynerba is developing therapeutic candidates based on proprietary transdermal technologies that, if successfully developed, may allow sustained, consistent and controlled delivery of therapeutic levels of two cannabinoids: cannabidiol (CBD), a non-psychoactive cannabinoid, and THC. Transdermal delivery has the potential to reduce adverse effects associated with oral dosing. ZYN002, the Company's CBD gel, is the first and only synthetic CBD formulated as a patent protected permeation-enhanced gel and is being studied in refractory epilepsy, FXS and osteoarthritis. Zynerba is also developing ZYN001, which utilizes a synthetically manufactured pro-drug of THC in a transdermal patch to deliver THC through the skin and into the bloodstream. ZYN001 will be studied in fibromyalgia and peripheral neuropathic pain. Learn more at www.zynerba.com and follow the Company on Twitter at @ZynerbaPharma.

Cautionary Note on Forward-Looking Statements
This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. We may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from the

Company's current expectations. For example, there can be no guarantee that the Company will obtain approval for ZYN002 or ZYN001 from the U.S. Food and Drug Administration (FDA) or foreign regulatory authorities; even if ZYN002 or ZYN001 are approved, the Company may not be able to obtain the label claims that it is seeking from the FDA. Management's expectations and, therefore, any forward-looking statements in this press release could also be affected by risks and uncertainties relating to a number of other factors, including the following: the success, cost and timing of the Company's product development activities, studies and clinical trials; the success of competing products that are or become available; the Company's ability to commercialize its product candidates; the size and growth potential of the markets for the Company's product candidates, and the Company's ability to service those markets; the Company's ability to develop sales and marketing capabilities, whether alone or with potential future collaborators; the rate and degree of market acceptance of the Company's product candidates; and the Company's expectations regarding its ability to obtain and adequately maintain sufficient intellectual property protection for its product candidates. These and other risks are described in the Company's periodic reports, including the annual report on Form 10K, quarterly reports on Form 10Q and current reports on Form 8-K, filed with or furnished to the Securities and Exchange Commission and available at www.sec.gov. Any forward-looking statements that the Company makes in this press release speak only as of the date of this press release. The Company assumes no obligation to update forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

[1] Press, C., Knupp, K., Chapman K., Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy Behav. 2015;45:49–52.

[2] Devinsky, O., Sullivan, J., Friedman, D., et al. Epidiolex (cannabidiol) in treatment- resistant epilepsy. Poster presented at 67th Annual Meeting of the American Academy of Neurology; April 18–25, 2015; Washington, DC.

[3] Watanabe, K., Itokawa, Y., Yamaori, S., et al. Conversion of cannabidiol to D9-tetrahydrocannabinol and related cannabinoids in artificial gastric juice, and their pharmacological effects in mice. Forensic Toxicol. 2007;25:16–21.

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