Zynerba Pharmaceuticals Announces Positive Top Line Results from Open-Label Phase 2 INSPIRE Trial of Zygel™ in 22q11.2 Deletion Syndrome

June 22, 2022

– The INSPIRE trial achieved statistically significant and clinically meaningful improvements from baseline in multiple efficacy assessments –

– Safety data reinforce excellent tolerability profile of Zygel –

– Company will focus resources on FXS and 22q development –

– Cash runway extended through the end of 2023 / early 2024 –

– Zynerba to host conference call and webcast tomorrow, June 22, 2022 at 9:00 a.m. ET –

DEVON, Pa., June 21, 2022 (GLOBE NEWSWIRE) -- Zynerba Pharmaceuticals, Inc. (Nasdaq: ZYNE), the leader in innovative pharmaceutically-produced transdermal cannabinoid therapies for orphan neuropsychiatric disorders, today announced positive top line results from the exploratory, open label Phase 2 INSPIRE (Assessing the **I**mpact of Zygel [Tra**ns**dermal CBD Gel] on **P**ediatr**i**c Behavio**r**al and **E**motional Symptoms of 22q11.2 Deletion Syndrome) trial. Based on the positive Phase 2 data, the Company will request a meeting with the U.S. Food and Drug Administration (FDA) to discuss the data and the regulatory path forward.

The Phase 2 trial was designed for signal detection by assessing the safety, tolerability and efficacy of Zygel (also known as ZYN002) for the treatment of behavioral symptoms of chromosome 22q11.2 deletion syndrome (22q) in children and adolescents. Zygel was administered to patients with 22q as add-on therapy to their standard of care and utilized a variety of efficacy assessments. Key findings from the trial disclosed today include:

- The total score and all five subscales of the Anxiety, Depression and Mood Scale (ADAMS) showed statistically significant improvements at 14 weeks of treatment compared to baseline;
- All five subscales of the Aberrant Behavior Checklist – Community (ABC-C) showed statistically significant improvements at 14 weeks of treatment compared to baseline;
- The Pediatric Anxiety Rating Scale (PARS – R) showed statistically significant improvements at 14 weeks of treatment compared to baseline;
- The majority of patients showed clinically meaningful improvements at week 14 as demonstrated by the Clinical Global Impression – Improvement (CGI-I). Seventy-five percent of patients were rated by the clinicians as “improved”, “much improved” or “very much improved” with nearly two-thirds (62.5%) of the patients being “much improved” or “very much improved”;
- Zygel was shown to be well tolerated, and the safety profile was consistent with previously released data from other Zygel clinical trials.

“I am encouraged with the results from the INSPIRE trial, particularly with the potential for real reductions in general anxiety, social withdrawal, and social avoidance in children and adolescents with chromosome 22q11.2 deletion syndrome,” said Tony J. Simon, Ph.D. Professor Emeritus at the University of California, Davis School of Medicine and the UC Davis MIND Institute. “I’m especially encouraged that ZYN002 is a unique, cannabidiol gel free of THC and manufactured to pharmaceutical specifications. Children and adolescents with 22q should avoid THC which may increase the likelihood of developing psychosis. I look forward to the further development of ZYN002 for this underserved population.”

“We believe the data from this Phase 2 trial are very encouraging and reinforce the potential of Zygel for the treatment of behavioral symptoms in children and adolescents with 22q, and we look forward to discussing the regulatory path forward with the FDA with these data in hand,” said Armando Anido, Chairman and Chief Executive Officer of Zynerba. “In the near term, we will focus our resources on completing the RECONNECT trial for children and adolescents with Fragile X syndrome and progressing 22q.”

INSPIRE Trial Design

The 14-week INSPIRE trial was an open-label, Phase 2 clinical trial designed to evaluate the safety, tolerability and efficacy of Zygel in children and adolescents (ages four through 15) with genetically-confirmed 22q11.2 deletion syndrome. Enrolled patients received weight-based doses of 250 mg or 500 mg daily of Zygel. Patients were allowed to increase the daily dose after six weeks of treatment to 500 mg and 750 mg if the investigator felt such increase was appropriate. One patient’s dose was increased from 250 mg to 500 mg, and no patients increased to 750 mg in the treatment period. At the completion of the trial, thirteen (13) patients entered into an extension study for up to six months.

Patient Disposition and Baseline Demographics

Twenty (20) patients were enrolled in the trial, which was conducted at two clinical sites in Australia and one clinical site in the U.S. All 20 patients are included in the safety analysis. Seventeen (17) patients completed the 14-week trial and three patients discontinued. One patient was lost to follow-up,

one patient withdrew due to adverse events not related to Zygel, and one patient withdrew consent. Efficacy analyses included 16 patients as one patient did not have valid assessments at week 14.

The mean age of patients enrolled in the trial was 9.9 years, and twelve (60%) of the patients were male. Patients weighed between 13.7 and 79.8 kilograms (mean=37.4; median=33.5).

Top-line Efficacy Results

As a signal-seeking Phase 2 trial, multiple efficacy assessments were administered, including the Anxiety, Depression and Mood Scale (ADAMS), the Aberrant Behavior Checklist – Community (ABC-C), the Pediatric Anxiety Ratings Scale (PARS – R) and Clinical Global Impression – Severity and Improvement.

Results of the ADAMS:

Subscale	Baseline	Week 14	Change from Baseline	Mean % Improvement	p Value	Median % Improvement
Total Score	36.1	17.7	-18.4	45.3%	0.0005	43.0%
General Anxiety	10.4	5.1	-5.4	43.6%	0.0005	48.8%
Depressed Mood	7.6	3.4	-4.3	50.3%	0.0033	52.8%
Social Avoidance	8.7	4.3	-4.4	41.3%	0.0084	50.0%
Obsessive/Compulsive Behavior	3.0	1.1	-1.9	64.0%	0.0037	66.7%
Manic / Hyperactive Behavior	7.6	4.4	-3.1	38.2%	0.0032	27.4%

Results of the ABC-C:

Subscale	Baseline	Week 14	Change from Baseline	Mean % Improvement	p Value	Median % Improvement
Social Withdrawal	14.4	7.9	-6.4	27.6%	0.0110	46.4%
Inappropriate Speech	4.2	2.4	-1.8	18.3%	0.0166	50.0%
Stereotypic Behavior	3.9	1.6	-2.3	52.1%	0.0155	58.3%
Irritability	18.4	10.0	-8.4	36.3%	0.0055	39.6%
Hyperactivity	18.1	10.4	-7.6	16.5%	0.0091	38.1%

Results of the PARS – R:

	Baseline	Week 14	Change from Baseline	Mean % Improvement	p Value	Median % Improvement
Total Score	14.7	8.5	-6.2	40.6%	0.0005	40.0%

Results of the CGI-I:

The investigators rated 12 of 16 patients (75%) as improved, “much improved” or “very much improved” at week 14, with 62.5% being “much improved” or “very much improved”.

Safety Data

Zygel was shown to be well tolerated, and the safety profile was consistent with previously released data from other Zygel clinical trials. Three patients reported treatment related adverse events which were all mild application site adverse events. One patient discontinued treatment due to adverse events not related to Zygel.

Prioritizing Orphan Development Programs; Cash Runway Extended to Late 2023 / Early 2024

In the near term the Company has decided to prioritize its resources on Fragile X syndrome (FXS) and 22q, both of which have been granted orphan drug designation by the FDA and both of which have no approved products. While the data from the Company’s autism spectrum disorder (ASD) clinical development program to date are compelling, given the difficult financing market, the Company will defer the start of the Phase 3 development program in ASD previously planned for the second half of 2022. As a result, the Company now believes its $69.7 million of cash and cash equivalents as of March 31, 2022 are sufficient to fund planned operations and capital requirements through the end of 2023 or early 2024, after the expected availability of top line results from its confirmatory pivotal Phase 3 RECONNECT trial of Zygel in patients with FXS.

Conference call information

Zynerba management will host a live conference call and webcast tomorrow, June 22, 2022, at 9:00 a.m. Eastern Time to discuss results of the INSPIRE trial and updates to its clinical development plans. The call can be accessed by dialing (866) 573-0180 (U.S. and Canada) or (430) 775-1345 (international) and referencing conference ID 4453857. To access the live webcast or the replay, visit the investor page of the Company’s website at http://ir.zynerba.com/. The webcast will be recorded and available on the Company’s website for 30 days.

About 22q11.2 Deletion Syndrome (22q)

As the second most common chromosomal disorder after Down syndrome, 22q is caused by a small missing piece of the 22nd chromosome. The deletion occurs near the middle of the chromosome at a location designated q11.2. It is considered a mid-line condition, with physical symptoms including characteristic palate abnormalities, heart defects, immune dysfunction, and esophageal / GI issues, as well as debilitating neuropsychiatric and behavioral challenges. Anxiety is among the most common neuropsychiatric symptoms of 22q and researchers have found that for children with 22q, anxiety is linked to poorer adaptive behaviors such as self-care and communication skills that affect daily life. Children with 22q also experience withdrawn behavior, ADHD, cognitive impairment, and autism spectrum disorder that affect communication and social interaction. Later in life, they are at an increased risk of developing mental illnesses such as schizophrenia. It is estimated that 22q occurs in between one in 3,000 and one in 6,000 live births, suggesting that there are approximately 83,000 people living with 22q in the U.S.

About Zygel

Zygel is the first and only pharmaceutically-manufactured cannabidiol formulated as a patent-protected permeation-enhanced clear gel, designed to provide controlled drug delivery into the bloodstream transdermally (i.e. through the skin). Recent studies suggest that cannabidiol may modulate the endocannabinoid system and improve certain behavioral symptoms associated with neuropsychiatric conditions. Zygel is an investigational drug product in development for the potential treatment of behavioral symptoms associated with Fragile X syndrome (FXS), 22q11.2 deletion syndrome (22q) and autism spectrum disorder (ASD). The Company has received orphan drug designation for cannabidiol, the active ingredient in Zygel, from the FDA and the European Commission for the treatment of FXS and by the FDA for the treatment of 22q. Additionally, Zygel has been designated a Fast Track development program for treatment of behavioral symptoms of FXS.

About Fragile X Syndrome (FXS)

FXS is a rare genetic developmental disability that is the leading known cause of both inherited intellectual disability and autism spectrum disorder, affecting 1 in 3,600 to 4,000 males and 1 in 4,000 to 6,000 females. It is the most common inherited intellectual disability in males and a significant cause of intellectual disability in females, and the leading genetic cause of autism spectrum disorder (ASD). The disorder negatively affects synaptic function, plasticity and neuronal connections, and results in a spectrum of intellectual disabilities and behavioral symptoms, such as social avoidance and irritability. In the U.S., there are approximately 78,000 people suffering with FXS, and approximately 121,000 in the EU and UK. We believe that approximately 60% of all patients with FXS have complete methylation of their *FMR1* gene.

About Zynerba Pharmaceuticals, Inc.

Zynerba Pharmaceuticals is the leader in innovative pharmaceutically-produced transdermal cannabinoid therapies for rare and near-rare neuropsychiatric disorders. We are committed to improving the lives of patients and their families living with severe, chronic health conditions including Fragile X syndrome, 22q11.2 deletion syndrome and autism spectrum disorder. Learn more at www.zynerba.com and follow us 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. 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 Company’s cash and cash equivalents may not be sufficient to support its operating plan for as long as anticipated; the Company’s expectations, projections and estimates regarding expenses, future revenue, capital requirements, incentive and other tax credit eligibility, collectability and timing, and availability of and the need for additional financing; the Company’s ability to obtain additional funding to support its clinical development programs; the results, cost and timing of the Company’s clinical development programs, including any delays to such clinical trials relating to enrollment or site initiation; clinical results for the Company’s product candidates may not be replicated or continue to occur in additional trials and may not otherwise support further development in a specified indication or at all; actions or advice of the U.S. Food and Drug Administration, the European Medicines Agency and other foreign regulatory agencies may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional clinical trials; the Company’s ability to obtain and maintain regulatory approval for its product candidates, and the labeling under any such approval; the Company’s reliance on third parties to assist in conducting pre-clinical and clinical trials for its product candidates; delays, interruptions or failures in the manufacture and supply of the Company’s product candidates 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; the Company’s expectations regarding its ability to obtain and adequately maintain sufficient intellectual property protection for its product candidates; the extent to which health epidemics and other outbreaks of communicable diseases, including COVID-19, could disrupt our operations or adversely affect our business and financial conditions; and the extent to which inflation or global instability, including political instability, may disrupt our business operations or our financial condition. This list is not exhaustive and these and other risks are described in the Company’s periodic reports, including the annual report on Form 10-K, quarterly reports on Form 10-Q 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.

Zynerba Contacts

Peter Vozzo
ICR Westwicke
Office: 443.213.0505
Cell: 443.377.4767
Peter.Vozzo@Westwicke.com