GW Pharmaceuticals Reports Positive Phase 3 Pivotal Trial Results for EPIDIOLEX® (cannabidiol) Oral Solution in Patients with Seizures Associated With Tuberous Sclerosis Complex

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- Achieved primary efficacy measure with both EPIDIOLEX doses as compared to placebo -

- Represents the fifth consecutive positive Phase 3 pivotal trial for EPIDIOLEX -

- Expect to file sNDA in Q4 2019 -

CARLSBAD, Calif., May 06, 2019 (GLOBE NEWSWIRE) -- GW Pharmaceuticals plc and its U.S. subsidiary Greenwich Biosciences Inc. (NASDAQ: GWPH, GW, the Company or the Group), the world leader in the science, development, and commercialization of cannabinoid prescription medicines, today announced positive top-line results of a randomized, double-blind, placebo-controlled Phase 3 clinical trial of EPIDIOLEX® (cannabidiol or CBD) CV in the treatment of seizures associated with Tuberous Sclerosis Complex (TSC), a rare and severe form of childhood-onset epilepsy. In this trial, EPIDIOLEX met its primary endpoint, which was the reduction in seizure frequency compared to baseline of the Epidiolex 25 mg/kg/day dose group vs placebo (p=0.0009). Results for both the 25 and 50 mg/kg/day dose groups were similar, with seizure reductions of 48.6% and 47.5% from baseline respectively, vs 26.5% for placebo (50 mg/kg/day vs placebo, p=0.0018). All key secondary endpoints were supportive of the effects on the primary endpoint. The safety profile observed is consistent with findings from previous studies, with no new safety risks identified.

“The positive outcome in this trial of EPIDIOLEX in patients with Tuberous Sclerosis Complex expands both our knowledge of this newly available medicine and its potential utility beyond the current indications,” stated Elizabeth Thiele, M.D., Ph.D., Director of the Herscot Center for Tuberous Sclerosis Complex at Massachusetts General Hospital, Professor of Neurology at Harvard Medical School and the lead investigator of the trial. “Data from previous controlled clinical trials of EPIDIOLEX have shown clinically meaningful seizure reductions and consistent safety and tolerability in children and adults with Lennox-Gastaut syndrome and Dravet syndrome. Based on the positive results of this trial in TSC patients, EPIDIOLEX, if approved for this additional indication, may become an important treatment option also in this disease state with significant unmet medical need.”

“The positive results from this trial represent the fifth positive Phase 3 trial for EPIDIOLEX and follows the recent U.S. launch of EPIDIOLEX for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. These new data show EPIDIOLEX reduced TSC-associated seizures, which include both focal and generalized seizures types, expanding the body of reliable science supporting the use of EPIDIOLEX,” stated Justin Gover, GW’s CEO. “With these data, we look forward to submitting an sNDA to the FDA in the fourth quarter with the goal of expanding the product label in 2020 to help the lives of patients suffering with TSC.”

“Some of the most challenging and frustrating aspects of tuberous sclerosis complex (TSC) are seizures that cannot be effectively controlled by existing medications,” explained Kari Luther Rosbeck, President and CEO of the Tuberous Sclerosis Alliance, “A new safe and effective treatment option such as Epidiolex is desperately needed. Further, we are grateful to GW, the researchers and the members of the TSC community who participated in this clinical trial. We are truly excited about the potential approval of Epidiolex to treat seizures in TSC as it brings much needed hope to those with TSC and their families who live daily with this difficult disorder.”

Trial Overview and Results

Patients aged 1-65 years with a confirmed diagnosis of treatment-resistant TSC were eligible to participate in this Phase 3, randomized double-blind placebo-controlled trial. The trial randomized 224 patients into three arms, where EPIDIOLEX 25 mg/kg/day (n=75), EPIDIOLEX 50 mg/kg/day (n=73) or placebo (n=76) was added to current anti-epileptic drug (AED) treatment. The average age of trial participants was 14 years (range 1-57). On average, patients were taking 3 AEDs, having previously tried and discontinued 4 other AEDs. The most common concomitant AEDs in this trial were valproic acid (45 percent), vigabatrin (33 percent), levetiracetam (29 percent), and clobazam (27 percent).

TSC associated seizures, as measured in the primary endpoint of this trial, differ from previous Epidiolex clinical trials in LGS and Dravet syndrome. These seizure types comprise focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures; and generalized seizures (tonic–clonic, tonic, clonic, or atonic) that are countable. The median baseline seizure frequency of the TSC associated seizure types was 57 per month.

The primary endpoint of the study was the change in seizure frequency over the 16-week treatment period (4-week titration followed by 12-week maintenance at the target dose) compared to baseline for the 25 mg/kg/day EPIDIOLEX arm vs placebo. The results for both the 25 and 50 mg/kg/day arms were similar, with seizure reductions of 48.6% and 47.5% from baseline, respectively, vs 26.5% for placebo (25mg/kg/day vs placebo, p=0.0009 and 50 mg/kg/day vs placebo, p=0.0018). All key secondary endpoints were supportive of the effects on the primary endpoint.

Previous clinical trials have evaluated the safety and efficacy of EPIDIOLEX at 10 mg/kg/day and 20 mg/kg/day, and U.S. prescribing information recommends a maintenance dose of 10 mg/kg/day. The TSC trial data represent the first pivotal safety data at the 25 mg/kg/day and 50 mg/kg/day dose levels.

The most common adverse events in patients receiving EPIDIOLEX in this study (≥10% and greater than placebo) include somnolence; decreased appetite; diarrhea; constipation; vomiting; transaminase elevations; pyrexia; seizure; cough; and infections. The incidence of diarrhea, vomiting, transaminase elevations, somnolence, and rash were higher in the 50 mg/kg/day group as compared to the 25 mg/kg/day group.

Regarding laboratory investigations, 12 percent of patients in the 25 mg/kg/day group experienced ALT elevations >3 ULN compared to 25 percent of

patients in the 50 mg/kg/day group and none in patients on placebo. Consistent with the U.S. prescribing information, patients on concomitant valproic acid and on the higher dose experienced a higher rate of ALT elevations. There were no cases of Hy's law observed and there were no deaths in this trial.

Dr. Volker Knappertz, GW's Chief Medical Officer, said, "We are delighted to report this positive trial in patients with TSC. Both doses studied in this trial have been shown to be equally effective. There is a lower incidence of known adverse events and laboratory changes in the 25 mg/kg/day group compared with 50 mg/kg/day. As a result, we expect to focus our label expansion discussions with the FDA on the lower dose, which is close to the dose range already included in the U.S. prescribing information."

This trial was conducted at more than 40 clinical sites in more than 6 countries. Detailed findings from this clinical trial will be reported at a future medical conference and subsequently published in a medical journal.

The EPIDIOLEX clinical development program now includes five randomized, controlled Phase 3 clinical trials (N=1,454) in LGS, Dravet syndrome and TSC. The previously completed Phase 3 studies have been published in The New England Journal of Medicine[1,2], and the Lancet[3]. EPIDIOLEX represents the only development program of a plant-derived cannabinoid medication approved by the FDA.

1,2: Devinsky O, Patel AD, Cross HJ, et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. *N Engl J Med*. 2018 May; 378:1888-1897. doi: 10.1056/NEJMoa1714631; Devinsky et al. Trial of cannabidiol for drug resistant seizures in the Dravet syndrome. *N Engl J Med*. 2017 May 25;376(21):2011-2020. doi: 10.1056/NEJMoa1611618.
3: Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet*. 2018 March; 391(10125):1085-1096. doi: 10.1016/S0140-6736

About Tuberous Sclerosis Complex (TSC)

Tuberous sclerosis complex (TSC) is a rare genetic condition that causes tumors to grow in many different organs of the body. Almost all of these tumors are benign and grow most often in the brain, skin, heart, eyes, kidneys and lungs and can cause a variety of health problems. The symptoms of TSC usually appear before a child is 6 months old. The severity of the condition can vary widely — in some children the disease is very mild, while other children may have life-threatening complications. At least two children born each day will have tuberous sclerosis complex. The disorder affects as many as 40,000 to 80,000 individuals in the United States and about 1 to 2 million individuals worldwide, with an estimated prevalence of one in 6,000 newborns. Epilepsy is present in greater than 90 percent of patients with TSC and may progress to become intractable to medication. More than 60 percent of individuals with TSC and epilepsy do not achieve seizure control with standard treatments such as antiepileptic drugs, epilepsy surgery, ketogenic diet, or vagus nerve stimulation, compared to 30-40 percent of individuals with epilepsy who do not have TSC who remain drug resistant. TSC is a leading cause of genetic epilepsy, often occurring in the first year of life as either focal seizures or infantile spasms. Untreated early-onset seizures are associated with an increased risk of autism and intellectual disability.

About EPIDIOLEX® (cannabidiol) oral solution

EPIDIOLEX, the first prescription, plant-derived cannabinoid medicine in the United States and the first in a new class of anti-epileptic medications, is a pharmaceutical formulation of highly purified cannabidiol (CBD) now FDA approved for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome in patients two years of age or older. GW has submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for Epidyolex (European brand name) with an expected opinion date in the second quarter of 2019. GW has received Orphan Drug Designation from the FDA, for EPIDIOLEX for the treatment of Dravet syndrome, LGS and TSC, each of which are severe childhood-onset, drug-resistant syndromes. GW has also received Orphan Designation from the European Medicines Agency, or EMA, for Epidyolex for the treatment of seizures associated with LGS, Dravet syndrome and TSC.

Important Safety Information

CONTRAINDICATION: HYPERSENSITIVITY

EPIDIOLEX (cannabidiol) oral solution is contraindicated in patients with a history of hypersensitivity to cannabidiol or any ingredients in the product.

WARNINGS & PRECAUTIONS

Hepatocellular Injury:

EPIDIOLEX can cause dose-related transaminase elevations. Concomitant use of valproate and elevated transaminase levels at baseline increase this risk. Transaminase and bilirubin levels should be obtained prior to starting treatment, at one, three, and six months after initiation of treatment, and periodically thereafter, or as clinically indicated. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX, reduction of EPIDIOLEX and/or concomitant valproate, or without dose reduction. For patients with elevated transaminase levels, consider dose reduction or discontinuation of EPIDIOLEX or concomitant medications known to affect the liver (e.g., valproate or clobazam). Dose adjustment and slower dose titration is recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury.

Somnolence and Sedation:

EPIDIOLEX can cause somnolence and sedation that generally occurs early in treatment and may diminish over time; these effects occur more commonly in patients using clobazam and may be potentiated by other CNS depressants.

Suicidal Behavior and Ideation:

Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior. Inform patients, caregivers, and families of the risk and advise to monitor and report any signs of depression, suicidal thoughts or behavior, or unusual changes in mood or behavior. If these symptoms occur, consider if they are related to the AED or the underlying illness.

Withdrawal of Antiepileptic Drugs:

As with most AEDs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

Adverse Reactions:

The most common adverse reactions in patients receiving EPIDIOLEX (≥10% and greater than placebo) include somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder and poor-quality sleep; and infections. Hematologic abnormalities were also observed.

Pregnancy:

EPIDIOLEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

Drug Interactions:

Moderate or strong inhibitors or inducers of CYP3A4 and CYP2C19 may affect EPIDIOLEX exposure. EPIDIOLEX may affect exposure to CYP2C19 substrates (e.g., clobazam, diazepam) or others. Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations. Dosage adjustment of EPIDIOLEX or other concomitant medications may be necessary.

Drug Abuse:

EPIDIOLEX is a Schedule V controlled substance and has a low potential for abuse.

Indications:

EPIDIOLEX (cannabidiol) oral solution is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.

Please refer to the EPIDIOLEX full Prescribing Information for additional important information.

About GW Pharmaceuticals plc and Greenwich Biosciences, Inc.
Founded in 1998, GW is a biopharmaceutical company focused on discovering, developing and commercializing novel therapeutics from its proprietary cannabinoid product platform in a broad range of disease areas. GW, along with its U.S. subsidiary Greenwich Biosciences, has received U.S. FDA approval for EPIDIOLEX (cannabidiol) oral solution for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome in patients two years of age or older and which is now available by prescription in the U.S. The Company has submitted a regulatory application in Europe for the adjunctive treatment of seizures associated with LGS and Dravet syndrome. The company continues to evaluate EPIDIOLEX in additional rare epilepsy conditions including Tuberous Sclerosis Complex (TSC) andRett syndrome. GW commercialized the world's first plant-derived cannabinoid prescription drug, Sativex® (nabiximols), which is approved for the treatment of spasticity due to multiple sclerosis in numerous countries outside the United States and for which the company is now planning a U.S. Phase 3 trial. The Company has a deep pipeline of additional cannabinoid product candidates which includes compounds in Phase 1 and 2 trials for epilepsy, glioblastoma, and schizophrenia. For further information, please visit www.gwpharm.com.

Forward-looking statements
This news release contains forward-looking statements that reflect GW's current expectations regarding future events, including statements regarding financial performance, the timing of clinical trials, the timing and outcomes of regulatory or intellectual property decisions, the relevance of GW products commercially available and in development, the clinical benefits of EPIDIOLEX (cannabidiol) oral solution and the safety profile and commercial potential of EPIDIOLEX. Forward-looking statements involve risks and uncertainties. Actual events could differ materially from those projected herein and depend on a number of factors, including (inter alia), the success of GW's research strategies, the applicability of the discoveries made therein, the successful and timely completion and uncertainties related to the regulatory process, and the acceptance of Sativex, EPIDIOLEX and other products by consumer and medical professionals. A further list and description of risks and uncertainties associated with an investment in GW can be found in GW's filings with the U.S. Securities and Exchange Commission, including the most recent Form 10-KT filed on February 26, 2018. Existing and prospective investors are cautioned not to place undue reliance on forward-looking statements, which speak only as of the date hereof. GW undertakes no obligation to update or revise the information contained in this press release, whether as a result of new information, future events or circumstances or otherwise.

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