Ovid Therapeutics Announces Phase 1b/2a Results of OV935/TAK-935 in Adults with Rare Epilepsies

December 17, 2018

-- Met primary endpoint of safety and tolerability --

-- A dose-dependent reduction of plasma 24HC levels was observed, consistent with target engagement --

-- Exploratory analysis of clinical activity of OV935 shows a decrease in seizure frequency associated with the drop in 24HC levels --

-- OV935 is an investigational new class of medicine with a novel mechanism of action different from current anti-epileptic drugs --

-- Conference call and webcast today at 8:00 am ET --

NEW YORK, Dec. 17, 2018 (GLOBE NEWSWIRE) -- Ovid Therapeutics Inc. (NASDAQ:OVID), a biopharmaceutical company committed to developing medicines that transform the lives of people with rare neurological diseases, today announced results from a 12-week, Phase 1b/2a clinical trial of OV935/TAK-935 that enrolled 18 adults with rare developmental and epileptic encephalopathies (DEE) who were not successfully treated with available treatment regimens. The trial achieved its primary endpoint of safety and tolerability and showed OV935 was generally well tolerated. Exploratory analysis of OV935 showed reduction in seizure frequency that was correlated with decreases in plasma 24-hydroxycholesterol (24HC) levels in adults across multiple DEE. OV935 is a potent, highly-selective first-in-class inhibitor of the enzyme cholesterol 24-hydroxylase (CH24H) being investigated as a novel approach to treating epilepsy. Preclinical data suggest that inhibition of brain CH24H indirectly reduces glutamatergic signaling via NMDA receptors and modulates glial function and inflammation, which may impact disease pathology and epileptogenesis.

“There is an urgent need for new medicines to treat rare DEE,” said Jeremy Levin, DPhil, MB, BChir, chairman and chief executive officer of Ovid Therapeutics. “We believe further development of OV935 could provide an opportunity to address the needs of children and adults with these intractable epilepsies. Moreover, the anti-epileptogenic preclinical data, now coupled with the observed exploratory seizure data, suggest the potential of OV935 as an early treatment option.”

“We're encouraged by the results from this small study, especially the signals on seizure reduction as well as the dose- and time-associated changes in plasma 24HC, which could be a potentially important, new biomarker for assessing treatment outcome and disease management,” said Amit Rakhit, M.D., MBA, chief medical and portfolio management officer of Ovid Therapeutics. “We look forward to our ongoing collaboration with Takeda and continuing our development program in pediatric DEE with the ongoing ARCADE and ELEKTRA trials.”

About the Phase 1b/2a Trial
The primary objective of the Phase 1b/2a clinical trial was to characterize the safety and tolerability profile of OV935 in adult patients with a documented DEE. The secondary objective was to characterize the multiple dose pharmacokinetics (PK) profile of OV935 in adults patients with a documented DEE. The trial was designed to have two-parts. Part 1 was a randomized, double-blind, placebo-controlled (OV935 vs. placebo with a ratio of 4:1), 30-day phase that included a titration period (20 days: 100 mg, 200 mg twice daily), and treatment period (10 days). The target final dose of 300 mg twice daily could be reached after the 20-day titration period. Part 2 was a 60-day open-label phase to explore the extent to which OV935 reduces seizure frequency as well as longer-term safety, tolerability, PK, and 24HC plasma levels. Patients who rolled over to Part 2 started OV935 at 200 mg twice daily for 10 days (second titration period) and increased to 300 mg twice daily until Day 85 followed by down titration to Day 92 (end of treatment period). Patients received study drug or placebo in addition to their standard antiepileptic treatment regimens.

Patient demographics
Eighteen patients (aged 19 to 45 years; mean of 28.5 years) who had at least one motor seizure per month were enrolled. At baseline, placebo patients had fewer seizures than OV935-treated patients, median 10 and 34 seizures per month, respectively, as measured by a caregiver diary. Patients experienced multiple seizure types, including tonic, tonic-clonic, atonic, myoclonic, clonic, and hyperkinetic. The majority of patients enrolled in the study were unsuccessfully treated with at least two prior treatment regimens and approximately 45 percent of patients were taking four or more anti-epileptic drugs (AEDs). The most common AEDs taken by the patients were lorazepam, lamotrigine, clonazepam, zonisamide, clobazam, lacosamide, and perampanel. The trial did not enrich for any specific condition and patients enrolled were each diagnosed with one of multiple DEE.

Primary Endpoint: Safety and Tolerability Results
OV935 achieved the primary endpoint of safety and tolerability as measured by incidence of adverse events (AEs). AEs in patients treated with OV935 were similar to those who received placebo in Part 1. The majority of AEs in both treatment arms were mild. Overall, the data are consistent with a favorable safety and tolerability profile and support the continued clinical development of OV935.

Adverse events that occurred more frequently in the OV935-treatment group versus the placebo group are: dysarthria, insomnia, lethargy, seizure cluster, and upper respiratory infection. Four patients discontinued due to an AE or a serious AE in the OV935 treatment arm. Of these, in Part 1, one patient discontinued due to difficulty with walking and worsening lethargy and a second discontinued due to weakness. In Part 2, one patient discontinued due to a single episode of seizure cluster and a second experienced multiple seizure clusters.

An increase in seizure frequency was seen in three patients, all of whom were on perampanel. This suggests the potential for a drug-drug interaction between medicines acting on different glutamatergic receptors. Accordingly, changes in seizure frequency data for the Phase 1b/2a trial are reported today including and excluding the three patients on perampanel.

Secondary and Exploratory Endpoint Results
PK parameters: The data reaffirm the PK profile seen in previous studies. Specifically, plasma levels of OV935 were dose-proportional and consistent

with levels observed in four prior Phase 1 studies in healthy volunteers.

24HC levels and target engagement:
In Part 1, a dose-dependent reduction of plasma 24HC levels was observed with OV935 treatment compared to placebo. A similar reduction was observed in Part 2 in both the OV935-treatment arm and patients in the placebo arm who crossed over to receive study drug. Importantly, there was an association between the reduction of 24HC and the median reduction of seizure frequency with OV935 treatment. By end of treatment period, 12 of 14 patients had interpretable 24HC data and seizure frequency counts. Individuals achieving plasma levels of <10 ng/ml (an approximate 80 percent decrease from baseline) at Day 85 (n=7) showed a median seizure reduction of 69 percent compared to 3 percent for those who did not obtain this degree of 24HC reduction (n=5). Accordingly, 24HC will be further studied as a potential biomarker in OV935 clinical trials.

Exploratory analysis of seizure data: Median percent reduction from baseline seizure frequency is being reported on patients treated with OV935 during the 60-day open-label Part 2 period for all seizure types (Table 1). Based on individual patient analysis, three patients on concomitant perampanel had increased seizure frequency during the study, consistent with a potential drug-drug interaction, as described above. A subset analysis was conducted on 11 patients, who were not taking perampanel. (Table 1).

Overall, seizure frequency reduction was observed with maximal effect in the later part of the treatment period.

Table 1:

	Median Seizure Frequency	
	Full Analysis Set (FAS) Part 2*	**FAS Part 2 excluding patients on Perampanel****
Reduction from Baseline in Seizure Frequency		
Day 92 (measured from Day 65-92)	45% (n=14)	61% (n=11)
Day 85 (measured from Day 58-85)	28% (n=14)	41% (n=11)
Day 69 (measured from Day 42-69)	24% (n=16)	37% (n=13)
Total Seizure Free Days		
Baseline	11.7 (n=16)	12.7 (n=13)
Day 92 (measured from Day 65-92)	14.0 (n=14)	16.8 (n=11)
Responder Analysis – Proportion of Patients with Seizure Reduction from Baseline		
Day 65-92: 100% reduction (seizure free)	14.3% (n=14)	18.2% (n=11)
Day 65-92: ≥50% reduction	42.9% (n=14)	54.5% (n=11)

*FAS: 18 patients randomized to receive OV935 in Part 1 (titration period). Two withdrew from Part 1 and 16 patients rolled over to Part 2 (treatment period); 14 patients completed the trial.
**FAS Part 2 without perampanel: Excludes 3 patients taking perampanel for a total of 13 patients; 11 patients completed the trial.

Detailed findings are expected to be reported at an upcoming medical conference.

Next Steps for OV935 Program
Ovid and Takeda will continue to enroll eligible patients in the ENDYMION open-label extension study.

Based on the insights gained from the Phase 1b/2a trial, Ovid and Takeda will continue with the dose and titration schedule used in the Phase 2 ELEKTRA and ARCADE trials of OV935 in patients ages 2 to 17 years. In addition, Ovid will amend the protocols for these trials to exclude patients being treated with perampanel and, in light of the mode of action of OV935, the duration of treatment will be extended with the potential to observe the extent of the effects of OV935 on seizure reduction over time.

About ENDYMION Extension Study
ENDYMION is a multi-center open-label extension study of OV935 in patients with DEE who have participated in a previous OV935 clinical study. The primary objective is to assess the long-term safety and tolerability of OV935 over two years of treatment in patients with rare epilepsies. A secondary endpoint will evaluate the effect of OV935 on seizure frequency over two years. Additional details on ENDYMION can be found at www.clinicaltrials.gov

About the ELEKTRA Trial
ELEKTRA is an international Phase 2, multi-center, randomized, double-blind, placebo-controlled study that will evaluate the treatment of OV935 in pediatric patients, aged 2 to 17 years, with epileptic seizures associated with Dravet syndrome or Lennox-Gastaut syndrome (LGS). The study consists of a four to six week screening period to establish baseline seizure frequency followed by a 14-week treatment period that includes a 2-week dose titration period and a 12-week maintenance period. The primary endpoint is the change from baseline in seizure frequency in patients treated with OV935 compared to placebo by disorder (Dravet, LGS). The secondary endpoints include safety, tolerability, and pharmacokinetic (PK) assessments as well as the percentage of patients considered treatment responders, changes in Clinician's Clinical Global Impressions of Severity and Change (CGI-S/C), and correlation of OV935 concentration with plasma 24HC levels.

ELEKTRA is expected to enroll 126 pediatric patients at approximately 45 clinical trial sites in North America, Israel, Australia, and China. At the end of the study, eligible patients, including those in the placebo arm, have the option to roll over into the ENDYMION study, an open-label extension trial for patients with DEE who have previously participated in an OV935 clinical trial. Additional details on the ELEKTRA clinical trial can be found at www.clinicaltrials.gov.

About the ARCADE Trial
ARCADE is a Phase 2, multi-center, open-label, pilot study that will evaluate the treatment of OV935 in pediatric patients, aged 2 to 17 years old, with epileptic seizures associated with CDKL5 Deficiency Disorder (CDD) or Duplication 15q (Dup15q) syndrome. The primary endpoint is the change in motor seizure frequency in patients treated with OV935 by disorder (CDD and Dup15q). The key secondary endpoints include safety and tolerability,

including percentage of participants considered treatment responders, change in CGI-S/C, and correlation of OV935 concentration and plasma 24HC levels.

ARCADE is expected to enroll approximately 15 children with each condition at clinical trial sites in the United States. This study consists of a four to six week screening period to establish baseline seizure frequency followed by a 12-week treatment period (2-week dose titration and 10-week maintenance period). At the end of treatment, eligible patients can roll over into the ENDYMION study. Additional details on the ARCADE clinical trial can be found at www.clinicaltrials.gov and at www.arcadestudy.com.

Conference Call and Webcast Information
Ovid Therapeutics will host a live conference call and webcast today, December 17, 2018, at 8:00 a.m. Eastern Time. The live webcast can be accessed by visiting the Investors section of the company's website at investors.ovidrx.com. Please connect at least 15 minutes prior to the live webcast to ensure adequate time for any software download that may be needed to access the webcast. Alternatively, please call 866-830-1640 (U.S.) to listen to the live conference call. The conference ID number for the live call is 5979167. A replay of the webcast will be available on the company's website for two weeks following the live conference call.

About Developmental and Epileptic Encephalopathies
The term epileptic encephalopathy includes a group of epilepsy syndromes associated with severe cognitive and behavioral disturbances. The International League Against Epilepsy (ILAE) defines an *epileptic encephalopathy* as a condition in which "the epileptiform EEG abnormalities themselves are believed to contribute to a progressive disturbance in cerebral function."

These epilepsies cause significant morbidities for patients beyond what might be expected from the known underlying pathology alone and can worsen over time. Developmental and epileptic encephalopathies typically present early in life and are often associated with severe cognitive and developmental impairment in addition to frequent treatment-resistant seizures throughout the person's lifetime. These disorders vary in age of onset, developmental outcomes, etiologies, neuropsychological deficits, electroencephalographic (EEG) patterns, seizure types, and prognosis.

Despite the availability of medicines for epilepsy, few treatment options are available for epileptic encephalopathies, and novel therapies are needed.

About Investigational OV935/TAK-935
OV935/TAK-935 is a potent, highly-selective, first-in-class inhibitor of the enzyme cholesterol 24-hydroxylase (CH24H) being investigated as an anti-epileptic drug (AED). CH24H is predominantly expressed in the brain, where it plays a central role in cholesterol homeostasis. CH24H converts cholesterol to 24-hydroxycholesterol (24HC), which then exits the brain into the peripheral circulation. Glutamate is one of the main neurotransmitters in the brain and has been shown to play a role in the initiation and spread of seizure activity. Recent literature indicates CH24H is involved in over-activation of the glutamatergic pathway through modulation of the NMDA channel, implying its potential role in central nervous system diseases such as epilepsy. In addition, preclinical data suggest OV935 has an anti-inflammatory and glial modulatory function with resultant anti-epileptogenic not simply a direct seizure suppressive activity. Ovid and Takeda believe that the novel mechanism of action of OV935 may potentially treat rare epilepsies by modifying disease pathology over time, and might ultimately be considered an early treatment option in view of this mechanism. To Ovid and Takeda's knowledge, OV935 is the only molecule with this mechanism of action in clinical development. OV935 is an investigational drug, not approved for commercial use.

The United States Food and Drug Administration (FDA) has granted orphan drug designation to OV935 for the treatment of both Dravet syndrome and LGS.

About the Takeda/Ovid Collaboration
Ovid and Takeda entered into a global development and commercialization collaboration in January 2017 to evaluate OV935/TAK-935 across a range of rare epilepsy syndromes. Under the terms of the agreement, the companies share in the development and commercialization costs on a 50/50 basis and, if successful, the companies will share in the profits on a 50/50 basis. Takeda will lead commercialization in Japan and has the option to lead in Asia and other selected geographies. Ovid leads clinical development activities and commercialization in the United States, Europe, Canada and Israel.

About Ovid Therapeutics
Ovid Therapeutics (NASDAQ: OVID) is a New York-based biopharmaceutical company using its BoldMedicine™ approach to develop medicines that transform the lives of patients with rare neurological disorders. Ovid has a broad pipeline of potential first-in-class medicines. The company's lead investigational medicine, OV101, is currently in development for the treatment of Angelman syndrome and Fragile X syndrome. Ovid is also developing OV935/TAK-935 in collaboration with Takeda Pharmaceutical Company Limited for the treatment of rare developmental and epileptic encephalopathies (DEE).

For more information on Ovid, please visit www.ovidrx.com.

Forward-Looking Statements
This press release includes certain disclosures that contain "forward-looking statements," including, without limitation, statements regarding the potential clinical benefit of OV935 to treat patients with rare epilepsies, the role of 24HC as a plasma biomarker of treatment effect, the continued clinical development of OV935, number of patients enrolled, the initiation, progress, timing, scope and results of clinical trials, the achievement of primary and/or secondary endpoints, the effects of OV935 on efficacy, safety and tolerability, and the presentation of data at upcoming medical conferences. You can identify forward-looking statements because they contain words such as "will," "believes" and "expects." Forward-looking statements are based on Ovid's current expectations and assumptions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that may differ materially from those contemplated by the forward-looking statements, which are neither statements of historical fact nor guarantees or assurances of future performance. Important factors that could cause actual results to differ materially from those in the forward-looking statements are set forth in Ovid's filings with the Securities and Exchange Commission under the caption "Risk Factors". Ovid assumes no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

Contacts
Investors:
Lora Pike
Ovid Therapeutics Inc.

lpike@ovidrx.com

Alex Gray
Burns McClellan, Inc
agray@burnsmc.com
(212) 213-0006

Media:
Jerica Pitts
W2Opure
jpitts@purecommunications.com
(312) 858-3469

Ovid Therapeutics Inc.