Ovid Therapeutics Announces Positive Topline Data from Phase 2 STARS Trial of OV101 for the Treatment of Angelman Syndrome

-- OV101 achieved primary endpoint of safety and tolerability --

-- Robust and statistically significant improvement (p=0.0006) in the first prespecified efficacy endpoint (CGI-I) observed at 12 weeks of treatment in once-daily dose group compared to placebo --

-- STARS data support plans to advance OV101 development and discuss with regulatory authorities next steps for a registrational pathway --

-- Conference call and webcast today at 8:00 a.m. EDT --

NEW YORK, Aug. 06, 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 that the Phase 2 STARS trial of OV101 achieved its primary endpoint of safety and tolerability. The investigational medicine showed a favorable safety profile and was well tolerated in adults and adolescents with Angelman syndrome. OV101 is the only selective extrasynaptic $GABA_A$ receptor agonist in development shown to mediate tonic inhibition, a key underlying pathophysiological mechanism of Angelman syndrome. Ovid's founder, president and chief scientific officer, Matthew During, M.D., DSc, FACP, will present the data today at the 2018 Angelman Syndrome Foundation/Duplication15q Research Symposium in Chapel Hill, North Carolina.

The Phase 2 STARS international study is the first industry-sponsored, randomized, double-blind, placebo-controlled clinical trial for Angelman syndrome. The study randomized 88 patients across three groups: a once-daily or twice-daily dose of OV101, or placebo. At the prespecified efficacy analysis at 12 weeks of treatment, OV101 showed a statistically significant improvement compared to placebo in the physician-rated clinical global impressions of improvement (CGI-I) – a measure commonly used in clinical trials that allows the physician to capture a constellation of clinical symptoms. CGI-I was ranked first in the topline statistical plan.

Subsequent analyses in the hierarchy were conducted on a prespecified subset of scales across the domains of behavior, sleep and gait. While the analysis of these prespecified subsets did not show a statistically significant difference from placebo, full data analyses on these domains are ongoing and will be communicated in the future. Ovid intends to discuss these data with regulatory authorities to determine the next steps for a registrational pathway. Based on these data, the company plans to initiate in the fourth quarter of 2018 an open-label extension study (named ELARA); Angelman syndrome patients who completed any prior OV101 study may be eligible to receive the investigational medicine in this study.

Angelman syndrome is a rare, lifelong, genetic disorder that affects 1 in 15,000 people in the U.S. It is characterized by severe impairment in behavior, learning, verbal communication, motor skills, and sleep, and there are no FDA-approved medicines or an established treatment paradigm for this condition. If approved, OV101 could be the first medicine to specifically target a key underlying neurological dysfunction of Angelman syndrome -- impaired tonic inhibition, which is most commonly caused by a disruption of the UBE3A gene.

“We are excited by these data, as this is the first demonstration of positive clinical effect on overall symptomology in Angelman syndrome,” said Jeremy Levin, DPhil, MB, BChir, chairman and chief executive officer of Ovid Therapeutics. “In collaboration with the Angelman community, we designed a robust study to evaluate prespecified endpoints that may pave the way for a registrational pathway for a disorder that has no previously approved medicines. These data are a tribute to the patients and their families, and we thank them.”

“These initial data from the STARS study are encouraging, particularly the statistically significant improvement in overall symptoms that we see in the CGI-I scale in the once-daily dosing group. Angelman syndrome is a complex disorder, and the CGI-I scale captures the totality of global neurological deficits and helps to define the impact of medicines on the individual and their families,” said Ron Thibert, D.O., MsPH, chairperson, STARS clinical trial steering committee, director, Angelman syndrome clinic at MassGeneral Hospital for Children, and assistant professor Harvard Medical School. “The data reported today are the first data in Angelman syndrome to show a compound specifically targeting the syndrome having a clinical effect. Ovid is the first company to have conducted a double-blind, placebo-controlled study in Angelman syndrome, providing important clinical and scientific data. Based on these data, I believe OV101 has the potential to offer a clinically meaningful benefit specific to people living with Angelman syndrome.”

“The STARS study was designed to provide information to allow us to progress the development of OV101,” said Amit Rakhit, M.D., MBA, chief medical and portfolio management officer of Ovid Therapeutics. “With these findings, we have advanced our understanding of relevant endpoints to evaluate key symptoms of Angelman syndrome. Furthermore, we demonstrated that a once-daily dose of OV101 could be sufficient to drive clinically meaningful benefit to patients. We look forward to discussing the data with regulatory authorities to inform our future development plans.”

STARS Phase 2 Topline Data Summary and Design

STARS was a 12-week, double-blind, placebo-controlled Phase 2 study. Eighty-eight patients

(adults, n=66; adolescents, n=22) aged 13 to 49 years of age diagnosed with Angelman syndrome were randomized at 13 clinical trial sites in the U.S. and Israel. The study randomized patients to one of three arms: once-daily (QD) dose of OV101 at night (15mg), twice-daily (BID) dose of OV101 (10mg in the morning and 15mg at night), and placebo.

The intent to treat (ITT) population was 88 patients. A modified intent to treat (mITT) analysis of 87 patients (mean age=22.6), which includes any patient who enrolled in the study and received at least one dose of study drug, was performed to evaluate the efficacy endpoints.

The primary endpoint of the trial was to assess the safety and tolerability of OV101 compared to placebo. The STARS trial explored the clinical utility of OV101 on improvements in clinical global impressions, maladaptive behavior, sleep, and gross and fine motor skills.

Primary Endpoint: Safety and Tolerability Data

The study met its primary endpoint of safety and tolerability given that the adverse events (AEs) with OV101 treatment were similar to placebo treatment, with the majority of AEs being mild. OV101 showed a favorable risk profile and was well tolerated through 12 weeks of treatment. Overall, the data are consistent with the favorable risk profile observed in previous insomnia trials with this investigational medicine.

The most common AEs reported in the trial were vomiting, somnolence, irritability, aggression, and pyrexia.

Table 1: Most Frequent Adverse Events*

Incidence	Placebo (n=29)	OV101 QD (n=29)	OV101 BID (n=29)
Vomiting	9 (31.0%)	5 (17.2%)	5 (17.2%)
Somnolence	5 (17.2%)	5 (17.2%)	3 (10.3%)
Irritability	4 (13.8%)	3 (10.3%)	5 (17.2%)
Aggression	5 (17.2%)	4 (13.8%)	1 (3.4%)
Pyrexia	2 (6.9%)	7 (24.1%)	1 (3.4%)

**Descriptive data*

Events occurring in greater than 5 percent (two or more patients) compared to placebo in either treatment arm included pyrexia, rash, seizure, enuresis and myoclonic epilepsy.

Table 2: Adverse Events Occurring More Frequently in OV101 Arms vs. Placebo*

Incidence	Placebo (n=29)	OV101 QD (n=29)	OV101 BID (n=29)
Pyrexia	2 (6.9%)	7 (24.1%)	1 (3.4%)
Rash	1 (3.4%)	3 (10.3%)	2 (6.9%)
Seizure	0	2 (6.9%)	3 (10.3%)
Enuresis	0	2 (6.9%)	1 (3.4%)
Myoclonic epilepsy	0	1 (3.4%)	2 (6.9%)

**Descriptive data*

Serious adverse events (SAEs) of seizure were reported in two patients: one patient in the QD dose experienced a seizure and that was deemed unrelated to study drug; one patient experienced a seizure in the BID dose group and that was assessed as possibly related to study drug by the investigator.

Treatment discontinuations due to adverse events were low. One patient in the placebo arm discontinued compared to no patients and three patients in the once-daily dose group and twice-daily dose group, respectively.

- Placebo arm: one patient with irritability
- Twice-daily arm: one patient with myoclonus; one patient with seizure, and one patient with irritability/anxiety/sleep disorder

Efficacy Endpoint Data

At 12 weeks of treatment, the first prespecified efficacy endpoint (CGI-I) demonstrated a robust and statistically significant difference (p=0.0206; Fisher's Exact test) between the combined OV101 treatment arms and placebo. This reflects an improvement in two-thirds of the combined treatment groups versus one-third in placebo.

Table 3: Response Based on CGI-I at Week 12; Comparison to Placebo

Scale**	Pooled treatment groups (10mg/15mg BID) and (15mg QD) (n=57)	Placebo (n=28)
Absolute number of patients who improved	38 (66.7%)	11 (39.3%)
p-value	0.0206	

***Clinical Global Impression Scale – Improvement (CGI-I): a clinician-rated single-item 7-point scale that measures change in a patient's condition following start of treatment. 1-3 rating represents improvement, 4 represents no change, 5-7 represents worsening of symptoms.*

In the prespecified analysis using the rigorous Mixed Model Repeated Measures (MMRM), which evaluated each OV101 treatment arm independently against placebo, the difference in CGI-I mean score at 12 weeks was statistically significant (p=0.0006) in the once-daily OV101 group versus placebo and also in the combined OV101 treatment group versus placebo (p=0.0103).

Table 4: Mean CGI-I Symptoms Overall Score – by Dose Group at Week 12; Comparison to Placebo

Scale**	QD dose (15mg) (n=27)	BID dose (10mg/15mg) (n=28)	Pooled treatment groups (10mg/15mg BID) and (15mg QD) (n=55)	Placebo (n=27)

Mean change in CGI-I score (week 6)	3.35	3.54	3.45	3.60
Mean change in CGI-I score (week 12)	3.00	3.58	3.29	3.79
p-value*** at week 12	0.0006	0.3446	0.0103	

**** MMRM analysis was performed including fixed effects for visit, treatment, age (adult vs. adolescent) and visit by treatment interaction.*

In a post-hoc analysis of patients who were "much" or "minimally" improved having a CGI-I score of ≤3, the data suggest that younger patients who received a once-daily dose had the greatest response to OV101 compared to older age groups.

Table 5: Patients Who were 'Much' or 'Minimally' Improved in CGI-I Score (≤3) (Post-hoc Analysis)

Age	Placebo n (%)	OV101 QD n (%)
13-17	2/7 (29%)	5/6 (83%)
18-24	7/12 (58%)	10/12 (83%)
25-49	2/9 (22%)	7/10 (70%)

Ovid Therapeutics plans to present the full clinical data from the STARS study at an upcoming medical meeting.

ELARA 1-year Extension Study

In the fourth quarter of 2018, Ovid expects to initiate ELARA, an open-label extension study that will enable individuals with Angelman syndrome who completed any prior OV101 study to be eligible to receive the investigational medicine. The study will use once-daily dosing and will assess long term safety and tolerability in addition to efficacy measures.

Ovid Therapeutics has created a website specifically to provide disease education on Angelman syndrome. Learn more at angelmansyndrome.com.

Conference Call and Webcast Information

Ovid Therapeutics will host a live conference call and webcast today, August 6, 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.) or 210-874-7820 (International) to listen to the live conference call. The conference ID number for the live call is 8994338. A replay of the webcast will be available on the company's website for two weeks following the live conference call.

About Angelman Syndrome

Angelman syndrome is a genetic disorder that is characterized by a variety of signs and symptoms. Characteristic features of this disorder include delayed development, intellectual

disability, severe speech impairment, problems with movement and balance, seizures, sleep disorders and anxiety. The most common cause of Angelman syndrome is the loss of function of the gene that codes for ubiquitin protein ligase E3A (UBE3A), which plays a critical role in nerve cell communication, resulting in impaired tonic inhibition. Individuals with Angelman syndrome are highly social with a typical lifespan; however, they require constant support from a network of specialists and caregivers. Angelman syndrome affects approximately 1 in 15,000 people in the U.S. There are currently no U.S. Food and Drug Administration (FDA)-approved therapies for the treatment of Angelman syndrome.

Angelman syndrome is associated with a reduction in tonic inhibition, a function of the delta (δ)-selective $GABA_A$ receptor that allows a human brain to decipher excitatory and inhibitory neurological signals correctly without being overloaded. If tonic inhibition is reduced, the brain becomes inundated with signals and loses the ability to separate background noise from critical information.

About OV101

OV101 (gaboxadol) is believed to be the only delta (δ)-selective $GABA_A$ receptor agonist in development and the first investigational drug to specifically target the disruption of tonic inhibition, a central physiological process of the brain that is thought to be the underlying cause of certain neurodevelopmental disorders. OV101 has been demonstrated in laboratory studies and animal models to selectively activate the δ-subunit of $GABA_A$ receptors, which are found in the extrasynaptic space (outside of the synapse), and thereby impact neuronal activity through tonic inhibition.

Ovid is developing OV101 for the treatment of Angelman syndrome and Fragile X syndrome to potentially restore tonic inhibition and relieve several of the symptoms of these disorders. In preclinical studies, it was observed that OV101 improved symptoms of Angelman syndrome and Fragile X syndrome. This compound has also previously been tested in over 4,000 patients (over 1,000 patient-years of exposure) and was observed to have favorable safety and bioavailability profiles.

The FDA has granted Orphan Drug and Fast Track designations for OV101 for both the treatment of Angelman syndrome and Fragile X syndrome. The U.S. Patent and Trademark Office has granted Ovid patents directed to methods of treating Angelman syndrome and Fragile X syndrome using OV101. The issued patents expire in 2035.

About Ovid Therapeutics

Ovid Therapeutics (NASDAQ: OVID) is a New York-based biopharmaceutical company using its BoldMedicine™ approach to develop therapies that transform the lives of patients with rare neurological disorders. Ovid has a broad pipeline of 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 http://www.ovidrx.com/.

Forward-Looking Statements

This press release includes certain disclosures that contain "forward-looking statements," including, without limitation, statements regarding (i) timing and scope of any future clinical trials for OV101, (ii) the potential clinical benefit of OV101 to treat patients with Angelman syndrome, and (iii) the timing and results of any discussions with regulatory authorities regarding the registrational path for OV101. 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. Ovid assumes no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

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