Alexion Announces Positive Top-Line Results from Phase 3 Study of ULTOMIRIS™ (Ravulizumab-cwvz) in Complement Inhibitor-Naïve Patients with atypical Hemolytic Uremic Syndrome (aHUS)

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-- Study met primary objective of complete thrombotic microangiopathy (TMA) response --

-- Regulatory submission in the U.S. planned for first half of 2019, followed by the European Union and Japan --

BOSTON--(BUSINESS WIRE)--Jan. 28, 2019-- Alexion Pharmaceuticals, Inc. (NASDAQ:ALXN) today announced that the Phase 3 study of ULTOMIRIS™ (ravulizumab-cwvz), the company's long-acting C5 complement inhibitor, met its primary objective in complement inhibitor-naïve patients with atypical hemolytic uremic syndrome (aHUS). In the initial 26 week treatment period, 53.6 percent of patients (95% CI [39.6%, 67.5%]) demonstrated complete thrombotic microangiopathy (TMA) response. ULTOMIRIS provided immediate and complete inhibition of the complement C5 protein that was sustained over the entire eight-week dosing interval.

The primary endpoint of complete TMA response was defined by hematologic normalization and improved kidney function. Treatment with ULTOMIRIS resulted in:

- reduced thrombocytopenia, as measured by normalization in platelet count, in 83.9 percent of patients (95% CI [73.4%, 94.4%]),
- reduced hemolysis (the destruction of red blood cells), as measured by normalization in lactate dehydrogenase (LDH) level, in 76.8 percent of patients (95% CI [64.8%, 88.7%]) and
- improved kidney function, as measured by ≥ 25 percent improvement in serum creatinine level from baseline, in 58.9 percent of patients (95% CI [45.2%, 72.7%]). For patients on dialysis at enrollment, baseline was established after they had come off dialysis.

To achieve complete TMA response, patients had to meet all three criteria at the same time at least once. In addition, each of the criteria had to be met for at least 28 consecutive days.

The safety profile was consistent with that observed in two large Phase 3 studies in patients with paroxysmal nocturnal hemoglobinuria (PNH).[1,2]

"We are very pleased with these data, which demonstrate that ULTOMIRIS can provide clinically meaningful benefits to patients with aHUS," said John Orloff, M.D., Executive Vice President and Head of Research & Development at Alexion. "The results met the high bar of complete TMA response, defined by hematologic normalization and improved kidney function, and provide confidence that ULTOMIRIS has the potential to become the new standard of care for patients with aHUS. We are preparing regulatory submissions for ULTOMIRIS in aHUS in the U.S., European Union and Japan as quickly as possible."

Atypical HUS is a severe and chronic ultra-rare disease that can cause progressive damage to vital organs, predominantly the kidneys, leading to kidney failure and premature death. The disease is characterized by TMA (inflammation and blood clotting in small blood vessels throughout the body) that is mediated by chronic, uncontrolled activation of the complement system.[3,4,5,6,7]

"If left untreated, many patients progress to end-stage renal disease or die during the first clinical manifestations of aHUS or in the first year following these manifestations despite supportive care," said Spero Cataland, M.D., hematologist at Ohio State University Wexner Medical Center and an investigator in the study. "I am very excited about these data and the potential for an effective new treatment option that can provide hematologic normalization and improved kidney function, including the potential to stop dialysis, when administered every eight weeks."

The most frequently observed adverse events in this study were headache, diarrhea and vomiting. The most frequently observed serious adverse events were pneumonia and hypertension. In these critically ill patients, there were four patient deaths, none of which were considered related to treatment with ULTOMIRIS. No case of meningococcal infection was observed. Meningococcal infections are a known risk with terminal complement inhibition. To minimize the risk for patients, specific risk-mitigation plans have been established for ULTOMIRIS, based on plans that have been in place for more than 11 years for SOLIRIS® (eculizumab).

Detailed results from this Phase 3 study will be presented at a future medical congress. A Phase 3 study of ULTOMIRIS in children and adolescents with aHUS is currently ongoing.

About the ULTOMIRIS aHUS-311 Study
This global, multicenter, single arm, Phase 3 study evaluated the safety and efficacy of ULTOMIRIS administered by intravenous infusion in 56 adults (≥ 18 years of age) who hadn't been treated with a complement inhibitor before. The study consists of an up to seven-day screening period, a 26-week initial evaluation period and an extension period of up to two years, which is still ongoing. Patients received a weight-based loading dose (≥ 40 to < 60 kg = 2,400 mg; ≥ 60 to < 100 kg = 2,700 mg; ≥ 100 kg = 3,000 mg) on Day 1, followed by weight-based maintenance doses (≥ 40 to < 60 kg = 3,000 mg; ≥ 60 to < 100 kg = 3,300 mg; ≥ 100 kg = 3,600 mg) on Day 15 and once every eight weeks thereafter. The primary endpoint was defined as complete TMA response during the 26-week initial evaluation period, as evidenced by normalization of platelet count and lactate dehydrogenase

(LDH) level and an improvement in serum creatinine of ≥ 25 percent from baseline. For patients on dialysis at enrollment, baseline was established after they had come off dialysis. To achieve complete TMA response, patients had to meet all three criteria at the same time at least once. In addition, each of the criteria had to be met for at least 28 consecutive days. Complete C5 inhibition was defined as free C5 levels of <0.5 µg/mL.

About atypical Hemolytic Uremic Syndrome (aHUS)
Atypical hemolytic uremic syndrome (aHUS) is a chronic, progressive and debilitating ultra-rare disease that affects both children and adults and can lead to potentially irreversible damage to kidneys and other vital organs, sudden or progressive kidney failure (requiring dialysis or transplant) and premature death.[3,4,7,8] aHUS is characterized by inflammation and the formation of blood clots in small blood vessels throughout the body (thrombotic microangiopathy [TMA]) mediated by chronic, uncontrolled activation of the complement system, which is part of the body's immune system. [3,4,5,6,7] TMA consists of reduced platelet count (thrombocytopenia), hemolytic anemia (as a result of hemolysis [destruction of red blood cells]) and acute kidney injury (AKI).[5,7,9,10] If left untreated, significant proportions of adults (46 percent) and children (16 percent) can progress to end-stage renal disease (ESRD) or die during first clinical manifestations of aHUS despite supportive care, including plasma exchange or plasma infusion (PE/PI). One year following clinical manifestations, 56 percent of adults and 29 percent of children can progress to ESRD or die, if left untreated.[11] Early and careful diagnosis of aHUS is critical as many coexisting diseases and events are known or suspected to activate the complement cascade, and as patients may not necessarily present with the classic TMA triad of thrombocytopenia, hemolytic anemia and renal impairment[12] or may have less severe renal involvement.[13] Available tests can help distinguish aHUS from other hemolytic diseases with similar symptoms such as HUS caused by Shiga toxin-producing Escherichia coli (STEC-HUS) and thrombotic thrombocytopenic purpura (TTP).[7]

About ULTOMIRIS™
ULTOMIRIS (ravulizumab-cwvz, formerly known as ALXN1210) is the first and only long-acting C5 inhibitor administered every eight weeks that works by inhibiting the C5 protein in the terminal complement cascade, a part of the body's immune system. The terminal complement cascade, when activated in an uncontrolled manner, plays a role in severe ultra-rare disorders like paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and anti-acetylcholine receptor (AchR) antibody-positive myasthenia gravis (MG). ULTOMIRIS is approved in the U.S. as a treatment for adults with PNH. Regulatory authorities in the European Union (EU) and Japan have accepted and are reviewing applications for the approval of ULTOMIRIS as a treatment for adults with PNH. In Phase 3 clinical studies in complement inhibitor-naïve patients with PNH[1] and patients with PNH who had been stable on SOLIRIS® (eculizumab),[2] intravenous treatment with ULTOMIRIS every eight weeks demonstrated non-inferiority to intravenous treatment with SOLIRIS every two weeks on all 11 endpoints. ULTOMIRIS is also currently being evaluated in a Phase 3 clinical study in complement inhibitor-naïve children and adolescents with aHUS, administered intravenously every eight weeks. In addition, Alexion plans to initiate a Phase 3 clinical study of ULTOMIRIS delivered subcutaneously once per week as a potential treatment for patients with PNH and aHUS. Alexion is also planning to initiate the development of ULTOMIRIS, intravenously administered every eight weeks, as a potential treatment for patients with generalized MG (gMG) and neuromyelitis optica spectrum disorder (NMOSD).

ULTOMIRIS has received Orphan Drug Designation (ODD) for the treatment of patients with PNH in the U.S. and EU, and for the subcutaneous treatment of patients with aHUS in the U.S.

Please see the full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

Important ULTOMIRIS Safety Information
ULTOMIRIS is a prescription medicine called a monoclonal antibody. ULTOMIRIS is used to treat adults with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). It is not known if ULTOMIRIS is safe and effective in children.

ULTOMIRIS is a medicine that affects the immune system. ULTOMIRIS can lower the ability of the immune system to fight infections. ULTOMIRIS increases the chance of getting serious and life-threatening meningococcal infections. Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.

Meningococcal vaccines must be received at least 2 weeks before the first dose of ULTOMIRIS if one has not already had this vaccine. If one's doctor decided that urgent treatment with ULTOMIRIS is needed, meningococcal vaccination should be administered as soon as possible. If one has not been vaccinated and ULTOMIRIS therapy must be initiated immediately, 2 weeks of antibiotics should also be administered with the vaccinations. If one had a meningococcal vaccine in the past, additional vaccination might be needed before starting ULTOMIRIS. Call one's doctor or get emergency medical care right away if any of these signs and symptoms of a meningococcal infection occur: headache with nausea or vomiting, headache with a stiff neck or stiff back, fever and a rash, muscle aches with flu-like symptoms, headache and fever, fever, confusion, and eyes sensitive to light.

ULTOMIRIS is only available through a program called the ULTOMIRIS REMS.

ULTOMIRIS may also increase the risk of other types of serious infections. People who take ULTOMIRIS may have an increased risk of getting infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Certain people may also have an increased risk of gonorrhea infection. To find out if one is at risk for gonorrhea infection, about gonorrhea prevention, and regular testing, talk to the healthcare provider. Call the healthcare provider right away if one has any new signs or symptoms of infection.

Before one receives ULTOMIRIS, tell the doctor about all of the medical conditions, including if one: has an infection or fever, are pregnant or plan to become pregnant, and are breastfeeding or plan to breastfeed. It is not known if ULTOMIRIS will harm an unborn baby. It is not known if ULTOMIRIS passes into the breast milk. One should not breast feed during treatment and for 8 months after one's final dose of ULTOMIRIS.

Tell the doctor about all the medicines one takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ULTOMIRIS and other medicines can affect each other causing side effects. Know the medications one takes and the vaccines one receives. Keep a list of them to show the doctor and pharmacist when one gets a new medicine.

If one stops receiving ULTOMIRIS, the doctor will need to monitor closely for at least 16 weeks after one stops ULTOMIRIS. Stopping ULTOMIRIS may cause breakdown of the red blood cells due to PNH. Symptoms or problems that can happen due to red blood cell breakdown include: drop in the number of the red blood cell count, tiredness, blood in the urine, stomach-area (abdomen) pain, blood clots, shortness of breath, trouble swallowing, and erectile dysfunction (ED) in males.

ULTOMIRIS can cause serious side effects including infusion reactions. Infusion reactions may happen during one's ULTOMIRIS infusion. Symptoms of an infusion reaction with ULTOMIRIS may include lower back pain, pain with the infusion, or feeling faint. Tell the doctor or nurse right away if these symptoms develop, or any other symptoms during the ULTOMIRIS infusion that may mean one is having a serious infusion reaction, including: chest pain, trouble breathing or shortness of breath, swelling of the face, tongue, or throat, and feel faint or pass out. One's doctor will treat the symptoms as needed. The most common side effects of ULTOMIRIS are upper respiratory infection and headache.

Please see the full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

About Alexion

Alexion is a global biopharmaceutical company focused on serving patients and families affected by rare diseases through the discovery, development and commercialization of life-changing therapies. As the global leader in complement biology and inhibition for more than 20 years, Alexion has developed and commercializes two approved complement inhibitors to treat patients with paroxysmal nocturnal hemoglobinuria (PNH), as well as the first and only approved complement inhibitor to treat atypical hemolytic uremic syndrome (aHUS) and anti-acetylcholine receptor (AchR) antibody-positive generalized myasthenia gravis (gMG), and is also developing it for patients with neuromyelitis optica spectrum disorder (NMOSD). Alexion also has two highly innovative enzyme replacement therapies for patients with life-threatening and ultra-rare metabolic disorders, hypophosphatasia (HPP) and lysosomal acid lipase deficiency (LAL-D). In addition, the company is developing several mid-to-late-stage therapies, including a second complement inhibitor, a copper-binding agent for Wilson disease and an anti-neonatal Fc receptor (FcRn) antibody for rare Immunoglobulin G (IgG)-mediated diseases. Alexion focuses its research efforts on novel molecules and targets in the complement cascade and its development efforts on the core therapeutic areas of hematology, nephrology, neurology and metabolic disorders. Alexion has been named to the *Forbes* list of the World's Most Innovative Companies seven years in a row and is headquartered in Boston, Massachusetts' Innovation District. The company also has offices around the globe and serves patients in more than 50 countries. This press release and further information about Alexion can be found at: www.alexion.com.

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Forward-Looking Statement

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 that involve risks and uncertainties relating to future events and the future performance of Alexion, including the following statements relating to: ULTOMIRIS can provide clinically meaningful benefits to patients with aHUS; ULTOMIRIS has the potential to become the new standard of care for patients with aHUS; plans to file regulatory submissions for ULTOMIRIS in aHUS in the U.S., EU and Japan (and the timing for submitting such filings); the benefits of ULTOMIRIS for patients, including its potential as an effective new treatment option that can provide hematologic normalization and improved kidney function, including the potential to stop dialysis; plans to issue detailed Phase 3 study results in the future; future plans to initiate additional clinical trials for ULTOMIRIS, including trials for intravenous administration every eight weeks for patients with gMG and NMOSD and trials for subcutaneous delivery as a potential treatment for patients with PNH and aHUS. Forward-looking statements are subject to factors that may cause Alexion's results and plans to differ materially from those expected by these forward looking statements, including for example: ULTOMIRIS may not obtain regulatory approval as a treatment for aHUS (due to failure to meet regulatory requirements); ULTOMIRIS may not gain market acceptance and/or may not be recognized by patients and physicians as the standard of care for patients with aHUS; the benefits (including safety and efficacy) of ULTOMIRIS evidenced in clinical trials are not witnessed in a broader patient population; any potential post-approval restrictions that the FDA may impose on ULTOMIRIS; our dependence on sales from our principal product (SOLIRIS); future competition from biosimilars and other products; decisions of regulatory authorities regarding the adequacy of our research, marketing approval or material limitations on the marketing of our products; delays or failure of product candidates to obtain regulatory approval; delays or the inability to launch product candidates due to regulatory restrictions, anticipated expense or other matters; interruptions or failures in the manufacture and supply of our products and our product candidates; failure to satisfactorily address matters raised by the FDA and other regulatory agencies with respect to product candidates; results in early stage clinical trials may not be indicative of full results or results from later stage or larger clinical trials (or broader patient populations) and do not ensure regulatory approval; the possibility that results of clinical trials are not predictive of safety and efficacy and potency of our products (or we fail to adequately operate or manage our clinical trials) which could cause us to halt trials, delay or prevent us from making regulatory approval filings or result in denial of approval of our product candidates; unexpected delays in clinical trials; future product improvements may not be realized due to expense or feasibility; the possibility that current rates of adoption of SOLIRIS in PNH, aHUS, gMG or other diseases are not sustained; the adequacy of our pharmacovigilance and drug safety reporting processes; failure to protect and enforce our data, intellectual property and proprietary rights and the risks and uncertainties relating to intellectual property claims and challenges against us (including intellectual property lawsuits relating to ULTOMIRIS brought by third parties against Alexion); the risk that third party payers (including governmental agencies) will not reimburse or continue to reimburse for the use of our products at acceptable rates or at all; failure to realize the benefits and potential of investments, collaborations, licenses and acquisitions; delay of collection or reduction in reimbursement due to adverse economic conditions or changes in government and private insurer regulations and approaches to reimbursement; uncertainties surrounding legal proceedings (including intellectual property suits initiated against Alexion and our products), company investigations and government investigations, including investigations of Alexion by the U.S. Securities and Exchange Commission (SEC) and U.S. Department of Justice; the risk that estimates regarding the number of patients with PNH, aHUS, gMG, HPP and LAL-D and other future indications we are pursuing are inaccurate; the risks of changing foreign exchange rates; risks relating to the potential effects of the Company's restructurings; and a variety of other risks set forth from time to time in Alexion's filings with the SEC, including but not limited to the risks discussed in Alexion's Quarterly Report on Form 10-Q for the period ended September 30, 2018 and in our other filings with the SEC. Alexion disclaims any obligation to update any of these forward-looking statements to reflect events or circumstances after the date hereof, except when a duty arises under law.

References

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