



Alexion Announces Phase 3 Study of Weekly Subcutaneous ULTOMIRIS® (ravulizumab-cwvz) Met Primary Endpoint

June 24, 2020

- Ongoing Phase 3 study demonstrated PK non-inferiority of ULTOMIRIS SC versus ULTOMIRIS IV at Day 71 -

- Preliminary safety data consistent with the known safety profile of ULTOMIRIS -

BOSTON--(BUSINESS WIRE)--Jun. 24, 2020-- [Alexion Pharmaceuticals, Inc.](#) (NASDAQ:ALXN) today announced topline results from a Phase 3 study of weekly self-administered subcutaneous (SC) ULTOMIRIS® (ravulizumab-cwvz) in adults with paroxysmal nocturnal hemoglobinuria (PNH). The ongoing study met its primary objective of pharmacokinetic (PK)-based non-inferiority of ULTOMIRIS SC versus intravenous (IV) ULTOMIRIS at Day 71. Pending completion of the study, including collection of 12-month safety data as agreed to with the U.S. Food and Drug Administration (FDA), Alexion now expects to file for approval in the U.S. and E.U. for the ULTOMIRIS SC formulation and device combination in PNH and atypical hemolytic uremic syndrome (aHUS) in the third quarter of 2021.

“These data demonstrate that subcutaneous ULTOMIRIS may offer the same benefits of immediate, complete and sustained complement inhibition as the intravenous formulation, while also providing an additional treatment choice for those who would rather self-administer their medicine,” said John Orloff, M.D., Executive Vice President and Head of Research and Development at Alexion. “Delivered via a rapid, patient-friendly delivery device, subcutaneous ULTOMIRIS is an example of Alexion’s continued commitment to innovating for patients. It has the potential to be the first subcutaneous treatment option for both PNH and aHUS and may also offer improved quality of life for patients.”

About the Phase 3 Study

This ongoing global Phase 3, randomized, open-label, parallel-group, multicenter study is evaluating ULTOMIRIS SC compared with ULTOMIRIS IV. The study enrolled 136 adults with PNH who are clinically stable and have previously been treated with SOLIRIS® (eculizumab) for at least three months prior to study entry. The study’s primary objective is to evaluate PK noninferiority of ULTOMIRIS SC compared with ULTOMIRIS IV, as assessed by ULTOMIRIS serum trough concentration at Day 71. The study remains ongoing to assess secondary endpoints, including safety, immunogenicity and various PK/PD, quality of life, device performance and efficacy measures.

Patients were stratified by weight groups (≥ 40 to < 60 kg and ≥ 60 to < 100 kg) and then randomized 2:1 to receive either ULTOMIRIS SC or ULTOMIRIS IV. All patients received an initial IV loading dose on Day 1. On Day 15, patients in the ULTOMIRIS SC group began receiving a once-weekly self-administered fixed-dose of ULTOMIRIS SC, and patients in the ULTOMIRIS IV group received a single infusion of the approved weight-based IV dose.

The study met its primary objective, with ULTOMIRIS SC demonstrating PK-based non-inferiority versus ULTOMIRIS IV at Day 71 ($p < 0.0001$ for non-inferiority in serum ULTOMIRIS trough concentration - C_{trough}). Serum free C5 concentrations were maintained below the target threshold in all patients, and mean lactate dehydrogenase levels remained stable below the upper limit of normal. Preliminary safety data through the 71-day randomized treatment period of the study were consistent with the known safety profile of ULTOMIRIS and did not result in any unexpected safety findings. No adverse events led to withdrawal of study drug in either arm. No serious adverse device effects or meningococcal cases were reported, and no anti-drug antibodies were observed.

Of the 135 patients who completed the randomized controlled treatment portion of the study, all but one participant chose to continue in the ongoing SC-only extension period, where all patients are receiving weekly ULTOMIRIS SC for up to an additional 182 weeks. The extension period will provide 12 months of safety data required for regulatory submissions to applicable health authorities, now anticipated in the third quarter of 2021 to accommodate all regulatory requirements for this combination device filing.

About ULTOMIRIS SC Delivery

Each weekly dose of ULTOMIRIS SC is delivered via two specifically designed, patient-friendly devices that adhere to the body and can be self-administered with the push of a button. The devices can be used either concurrently or sequentially, and when administered concurrently, a full dose of ULTOMIRIS SC can be delivered hands-free in approximately 10 minutes. Previously approved by the FDA for use with another therapy, the single-use SmartDose® device contains a pre-filled cartridge and was developed in collaboration with West Pharmaceutical Services, Inc. to provide patients with a more flexible ULTOMIRIS treatment option.

About Paroxysmal Nocturnal Hemoglobinuria (PNH)

Paroxysmal nocturnal hemoglobinuria (PNH) is a serious ultra-rare blood disorder with devastating consequences. It is characterized by the destruction of red blood cells, which is also referred to as hemolysis. PNH occurs when the complement system—a part of the body’s immune system—over-responds, leading the body to attack its own red blood cells. PNH often goes unrecognized, with delays in diagnosis from one to more than five years. Patients with PNH may experience a range of symptoms, such as fatigue, difficulty swallowing, shortness of breath, abdominal pain, erectile dysfunction, dark-colored urine and anemia. The most devastating consequence of chronic hemolysis is the formation of blood clots, which can occur in blood vessels throughout the body, damage vital organs, and potentially lead to premature death. PNH can strike men and women of all races, backgrounds and ages without warning, with an average age of onset in the early 30s.

About Atypical Hemolytic Uremic Syndrome (aHUS)

Atypical hemolytic uremic syndrome (aHUS) is an ultra-rare disease that can cause progressive injury to vital organs, primarily the kidneys, via damage to the walls of blood vessels and blood clots. Atypical HUS occurs when the complement system—a part of the body's immune system—over-responds, leading the body to attack its own healthy cells. Atypical HUS can cause sudden organ failure or a slow loss of function over time—potentially resulting in the need for a transplant, and in some cases, death. Atypical HUS affects both adults and children, and many patients present in critical condition, often requiring supportive care, including dialysis, in an intensive care unit. The prognosis of aHUS can be poor in many cases, so a timely and accurate diagnosis—in addition to treatment—is critical to improving patient outcomes. Available tests can help distinguish aHUS from other hemolytic diseases with similar symptoms.

About ULTOMIRIS® (ravulizumab-cwvz)

ULTOMIRIS® (ravulizumab-cwvz) is the first and only long-acting C5 complement inhibitor. The medication works by inhibiting the C5 protein in the terminal complement cascade, a part of the body's immune system. When activated in an uncontrolled manner, the complement cascade over-responds, leading the body to attack its own healthy cells. ULTOMIRIS is administered intravenously every eight weeks or every four weeks for pediatric patients less than 20 kg, following a loading dose. ULTOMIRIS is approved in the United States (U.S.), European Union (EU) and Japan as a treatment for adults with paroxysmal nocturnal hemoglobinuria (PNH) and in the U.S. for atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) in adult and pediatric (one month of age and older) patients.

U.S. INDICATIONS & IMPORTANT SAFETY INFORMATION FOR ULTOMIRIS (ravulizumab-cwvz) 300 mg / 30 mL injection for intravenous use

U.S. INDICATIONS

ULTOMIRIS is a prescription medicine called a monoclonal antibody. ULTOMIRIS is used to treat adults with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). ULTOMIRIS is used to treat adults and children 1 month of age and older with a disease called atypical Hemolytic Uremic Syndrome (aHUS). ULTOMIRIS is not used in treating people with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS). It is not known if ULTOMIRIS is safe and effective in children with PNH. It is not known if ULTOMIRIS is safe and effective in children younger than 1 month of age.

U.S. IMPORTANT SAFETY INFORMATION

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. One's doctor will decide if additional meningococcal vaccination is needed. Meningococcal vaccines reduce the risk of meningococcal infection but do not prevent all meningococcal infections. 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 and fever, headache with a stiff neck or stiff back, fever, fever and a rash, confusion, muscle aches with flu-like symptoms, and eyes sensitive to light. One's doctor will give a Patient Safety Card about the risk of meningococcal infection. Carry the card at all times during treatment and for 8 months after your ULTOMIRIS dose.

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 doctor. Call the doctor right away if one has any new signs or symptoms of infection.

Do not receive ULTOMIRIS if one has a meningococcal infection, or has not been vaccinated against meningococcal infection unless the doctor decides that urgent treatment with ULTOMIRIS is needed.

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 breastfeed 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 medicines 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 has PNH and 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 red blood cell count, tiredness, blood in the urine, stomach-area (abdomen) pain, shortness of breath, blood clots, trouble swallowing, and erectile dysfunction (ED) in males. If one has aHUS, the doctor will need to monitor closely for at least 12 months after stopping treatment for signs of worsening aHUS symptoms or problems related to a type of abnormal clotting and breakdown of the red blood cells called thrombotic microangiopathy (TMA). Symptoms or problems that can happen with TMA may include: confusion or loss of consciousness, seizures, chest pain (angina), difficulty breathing, and blood clots or stroke. If one misses an ULTOMIRIS infusion, call the doctor right away.

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, feeling faint or discomfort in the arms or legs. 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 in people treated for PNH are upper respiratory infection and headache. The most common side effects

of ULTOMIRIS in people with aHUS are upper respiratory infections, diarrhea, nausea, vomiting, headache, high blood pressure, and fever.

Please see the accompanying 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 and devastating diseases through the discovery, development and commercialization of life-changing medicines. 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) and atypical hemolytic uremic syndrome (aHUS), as well as the first and only approved complement inhibitor to treat anti-acetylcholine receptor (AChR) antibody-positive generalized myasthenia gravis (gMG) and 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 copper-binding agent for Wilson disease, an anti-neonatal Fc receptor (FcRn) antibody for rare Immunoglobulin G (IgG)-mediated diseases and an oral Factor D inhibitor as well as several early-stage therapies, including one for light chain (AL) amyloidosis, a second oral Factor D inhibitor and a third complement inhibitor. 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, metabolic disorders and cardiology. Headquartered in Boston, Massachusetts, Alexion 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 that involve risks and uncertainties relating to future events and the future performance of Alexion, including statements related to: the efficacy and safety of ULTOMIRIS SC and device combination for PNH and aHUS patients; the anticipated timing for the filing of ULTOMIRIS SC formulation and device combination for regulatory approval for the treatment of PNH and aHUS in the U.S. and the E.U.; the successful completion of the Phase 3 study of ULTOMIRIS SC; that ULTOMIRIS SC may offer the same benefits of immediate, complete and sustained complement inhibition as the intravenous formulation, while also providing an additional treatment choice for those who would rather self-administer their medicine at home and that ULTOMIRIS SC and device combination has the potential to be the first subcutaneous treatment option for both PNH and aHUS patients and may also offer improved quality of life for patients and statements related to SC ULTOMIRIS delivery. 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 SC and device combination may not be approved in the U.S. or the E.U. or regulatory authorities may be delayed in providing their approval; the anticipated safety profile and the benefits of ULTOMIRIS SC for PNH and aHUS patients may not be realized (and the results of the clinical trials may not be indicative of the results once approved); results of clinical trials may not be sufficient to satisfy regulatory authorities in order to approve ULTOMIRIS SC and device combination as a treatment for PNH or aHUS (or they may request additional trials or additional information); results in clinical trials may not be indicative of results from later stage or larger clinical trials (or in broader patient populations once the product is approved for use by regulatory agencies); the device used to administer ULTOMIRIS SC may not be available or may not be approved by regulators; 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 discontinue sales of the product (or halt trials, delay or prevent us from making regulatory approval filings or result in denial of approval of our product candidates); the severity of the impact of the COVID-19 pandemic on Alexion's business, including on commercial and clinical development programs; unexpected delays in clinical trials; unexpected concerns regarding products and product candidates that may arise from additional data or analysis obtained during clinical trials or obtained once used by patients following product approval; future product improvements may not be realized due to expense or feasibility or other factors; delays (expected or unexpected) in the time it takes regulatory agencies to review and make determinations on applications for the marketing approval of our products; inability to timely submit (or failure to submit) future applications for regulatory approval for our products and product candidates; inability to timely initiate (or failure to initiate) and complete future clinical trials due to safety issues, IRB decisions, CMC-related issues, expense or unfavorable results from earlier trials (among other reasons); our dependence on sales from our principal product (SOLIRIS); future competition from biosimilars and novel 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 regulatory agencies regarding our products and product candidates; uncertainty of long-term success in developing, licensing or acquiring other product candidates or additional indications for existing products; inability to complete acquisitions or grow the product pipeline through acquisitions (including due to failure to obtain antitrust approvals); the possibility that current rates of adoption of our products 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, lawsuits and challenges against us (including intellectual property lawsuits relating to ULTOMIRIS brought by third parties); the risk that third party payors (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; the possibility that expected tax benefits will not be realized; potential declines in sovereign credit ratings or sovereign defaults in countries where we sell our products; delay of collection or reduction in reimbursement due to adverse economic conditions or changes in government and private insurer regulations and approaches to reimbursement; adverse impacts on our supply chain, clinical trials, manufacturing operations, financial results, liquidity, hospitals, pharmacies and health care systems from natural disasters and global pandemics, including COVID-19; uncertainties surrounding legal proceedings, company investigations and government investigations, including investigations of Alexion by the U.S. Securities and Exchange Commission; the risk that estimates regarding the number of patients with PNH, aHUS, gMG, NMOSD, HPP and LAL-D and other indications we are pursuing are inaccurate; the risks of changing foreign exchange rates; risks relating to the potential effects of the Company's restructuring; risks related to the pending acquisition of Portola Pharmaceuticals, the acquisition of Achillion and other companies and co-development efforts; 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 March 31, 2020 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.

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