#1 PRESCRIBED TREATMENT FOR ATYPICAL-HUS[1,2,a]

ULTOMIRIS for the management of patients with atypical-HUS, pre- and post-kidney transplant

[a]ULTOMIRIS had more than a 50% share of patients with atypical-HUS actively taking Alexion medications every month from August 2021 through August 2023.[1]

Atypical-HUS=atypical hemolytic uremic syndrome.

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

ULTOMIRIS, a complement inhibitor, increases the risk of serious infections caused by *Neisseria meningitidis* [*see Warnings and Precautions (5.1)*] Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.**
- **Patients receiving ULTOMIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.**

Because of the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS [*see Warnings and Precautions (5.2)*].

INDICATION

ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Limitation of Use:

ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

Please see additional Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Atypical Hemolytic Uremic Syndrome (atypical-HUS) is a medical emergency that may affect your patients with kidney transplant

Thrombotic microangiopathy (TMA)

A serious medical syndrome characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and signs of end organ damage, including AKI.[3,4]

Atypical-HUS

A type of TMA caused by complement dysregulation—requires urgent intervention to avoid poor clinical outcomes.[4]

PRE-TRANSPLANT[4]

Atypical-HUS can be caused **by complement-triggering conditions including:**

- Malignant hypertension or hypertensive emergency
- Solid organ or bone marrow transplantation
- Autoimmune diseases (eg, SLE, APS, scleroderma)
- Pregnancy or postpartum
- Glomerulonephritis
- Malignancy
- Infections
- Certain prescription medications or illicit drugs
- Surgery or trauma

POST-TRANSPLANT[5,6]

Atypical-HUS can be the **cause of de novo or recurrent TMA** confounded by multiple other causes including:

- Antibody mediated rejection (AMR)
- Immunosuppressive drugs (CNIs & mTORs)
- Infections (CMV, BK virus, etc)
- Ischemia reperfusion
- Antiphospholipid syndrome (APS)
- Other complement-triggering conditions

AKI=acute kidney injury; CMV=cytomegalovirus; CNI=calcineurin inhibitor; ESKD=end-stage kidney disease; mTOR=mechanistic target of rapamycin; SLE=systemic lupus erythematosus.

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Initiation in patients with unresolved serious *Neisseria meningitidis* infection.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections

ULTOMIRIS, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by meningococcal bacteria (septicemia and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.

Please see accompanying full Prescribing Information for ULTOMIRIS (ultomirishcp.com/PI), including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Patients with atypical-HUS may experience poor outcomes pre- and post-kidney transplant[7]

PRE-TRANSPLANT

Unmanaged patients with atypical-HUS may progress to kidney loss[8]

~50%

of adult patients with atypical-HUS **are at risk for ESKD at 5 years[8]**

POST-TRANSPLANT

Atypical-HUS could be the cause of recurrent TMA or de novo TMA and graft loss in your post-transplant patients[7]

~60%

of patients with aHUS have TMA recurrence[7]

~80%

of patients with untreated aHUS and TMA recurrence may experience graft loss within the first year post-kidney transplant in patients with certain genetic mutations[9]

Rapidly identify atypical-HUS as the potential cause of recurrent or de novo TMA and kidney loss


Actor portrayal

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)
Serious Meningococcal Infections (cont'd)

Revaccinate patients in accordance with ACIP recommendations considering the duration of ULTOMIRIS therapy. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent ULTOMIRIS therapy is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, provide antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including ULTOMIRIS. The benefits and risks of treatment with ULTOMIRIS, as well as those associated with antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by *Neisseria meningitidis*.

PRE-TRANSPLANT

Identify if atypical-HUS is the cause of kidney loss prior to transplant

STEP 1 Identify patients with unknown etiology of kidney loss and review medical history for TMA recurrence which may be caused by atypical-HUS[a]

- **Potential complement-triggering conditions:** Pregnancy or postpartum, malignant hypertension or hypertensive emergency, solid organ or bone marrow transplantation, autoimmune diseases (eg, SLE, APS, scleroderma), glomerulonephritis, malignancy, infections, certain prescription medications or illicit drugs, surgery, or trauma[4]

Other important factors to consider:

- **Family history, pediatric onset, and genetic predisposition**[10-13]
- **Previous kidney transplant and graft loss**[14,15]
- **History of kidney biopsy showing signs of TMA**[4]

STEP 2 Identify atypical-HUS as the cause of TMA[4,a,b]

Thrombocytopenia
Platelet count <150 x 10^9/L or >25% decrease from baseline

AND

Microangiopathic hemolysis
Schistocytes and/or elevated LDH and/or decreased haptoglobin and/or decreased hemoglobin

Plus 1 or more of the following

Common Symptoms

- **Neurological symptoms**
- **Kidney impairment**
- **Gastrointestinal symptoms**

Other Symptoms

- **Cardiovascular symptoms**
- **Pulmonary symptoms**
- **Visual symptoms**

Evaluate ADAMTS13 activity and Shiga toxin/EHEC test[c]

While ADAMTS13 results are awaited, a platelet count >30 x 10^9/L and/or SCr >1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)

≤5%[d] ADAMTS13 activity	>5% ADAMTS13 activity	Shiga toxin/EHEC positive
TTP	Atypical-HUS	STEC-HUS

Consider ULTOMIRIS for transplant patients experiencing TMA caused by atypical-HUS[16]
Treatment beyond the initial 6 months should be individualized[2]

Consider genetic testing including complement genes prior to transplant in patients with unknown etiology of kidney loss[17,e]

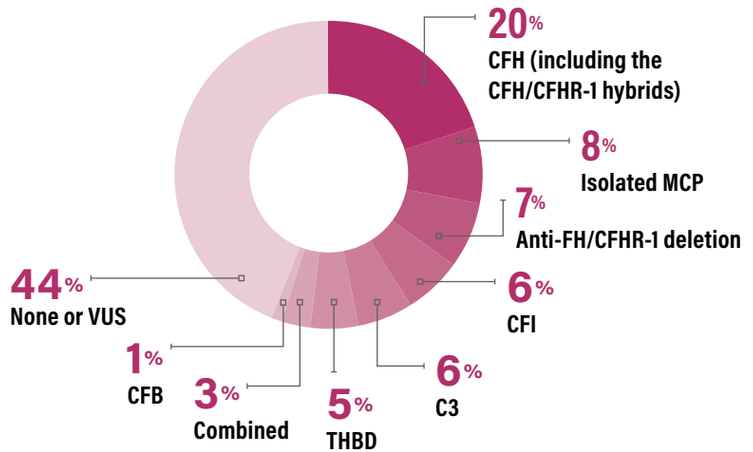
[a]The information in this presentation is intended as educational information for healthcare professionals. It does not replace a healthcare professional's judgment or clinical diagnosis.
[b]This is not an exhaustive list of all causes of TMA that would need to be ruled out.
[c]Shiga toxin/EHEC test is warranted with history/presence of GI symptoms.[4]
[d]Range found in published literature is <5%-10%.[4]
[e]Recommendation based on the Kidney Diseases: Improving Global Outcomes (KDIGO) 2021 Conference on Genetics in Chronic Kidney Disease.[17]
ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; APS=antiphospholipid syndrome; atypical-HUS=atypical hemolytic uremic syndrome; EHEC=enterohemorrhagic *Escherichia coli*; ESKD=end-stage kidney disease; LDH=lactate dehydrogenase; SCr=serum creatinine; SLE=systemic lupus erythematosus; STEC-HUS=Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

PRE-TRANSPLANT

Assess individual risk factors and genetics to identify patients with atypical-HUS at risk of TMA recurrence[18]

- **Family history, pediatric onset, and genetic predisposition** are associated with a high risk of TMA recurrence in patients with atypical-HUS[10-12,19-21]
- Approximately **60-70%** of patients with atypical-HUS have an identified genetic mutation[8,22-25]
- Individuals with certain identified mutations are associated with a **higher risk of TMA recurrence, ESKD progression, or death** within the next year or in the first episode[7,26-28]
- The risk of TMA recurrence is increased after a **kidney transplant in certain mutations**[7,26]

Percentages of genetic mutations identified in patients with atypical-HUS[24,25,29]



Adapted from Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5(10):1844-1859; Bresin E, et al. *J Am Soc Nephrol.* 2013;24(3):475-486; and Bruel A, et al. *Clin J Am Soc Nephrol.* 2017;12(8):1237-1247.

Clinical outcomes of adult and pediatric patients with atypical-HUS carrying identified genetic mutations[7,26,a]

Gene	Risk of death or ESKD within the next year or in the first episode	Risk of TMA recurrence	Risk of TMA recurrence after kidney transplant
CFH	50%-70%	50%	75%-90%
MCP	0%-6%	70%-90%	<20%
Anti-FH	30%-40%	40%-60%	Higher with increased antibody titers
CFI	50%	10%-30%	45%-80%
C3	60%	50%	40%-70%
THBD	50%	30%	1 patient
CFB	50%	3/3 without ESKD	100%

Clinical outcomes of patients with unmanaged atypical-HUS. Adapted from Abbas F, et al. *World J Transplant.* 2018;8(5):122-141 and Campistol JM, et al. *Nefrologia.* 2015;35(5):421-447.

[a]Standalone data for adults is unavailable, therefore this data is reflective of both adult and pediatric populations.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)
Serious Meningococcal Infections (cont'd)
Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection depending on the risks of interrupting treatment in the disease being treated.

Please see accompanying full Prescribing Information for ULTOMIRIS (ultomirishcp.com/PI), including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

POST-TRANSPLANT

Rapidly determine if atypical-HUS is the cause of de novo or recurrent TMA post transplant

Recognize when recurrent or de novo TMA caused by atypical-HUS can occur

Symptoms of atypical-HUS may develop in the early post-transplant period, but could present anytime in the post-transplant course[30-32]

STEP 1 Recognize TMA[4]

Thrombocytopenia
Platelet count <150 x 10^9/L or >25% decrease from baseline

AND

Microangiopathic hemolysis
Schistocytes and/or elevated LDH and/or decreased haptoglobin and/or decreased hemoglobin

Plus 1 or more of the following

- **Renal impairment**
- **Gastrointestinal symptoms**
- **Neurological symptoms**
- **Cardiovascular symptoms**
- **Visual symptoms**
- **Pulmonary symptoms**

STEP 2 Rapidly determine the cause of TMA[4,5,33-35,a]

Antibody-Mediated Rejection	Immunosuppression[b]	Infection[b]	atypical-HUS	TTP	STEC-HUS
	• CNIs • mTORs	• Cytomegalovirus (CMV) • Epstein-Barr Virus (EBV)	ADAMTS13 activity >5%	• ADAMTS13 activity ≤5-10% • PLASMIC score ≥5	• Stool culture for *E. coli* • PCR in stool sample for Shiga toxin

Persistent TMA despite having addressed the potential cause (eg, management of antibody-mediated rejection, adjustment of immunosuppressant therapy, management of infection) may also indicate atypical-HUS[36]

Consider ULTOMIRIS for your patients with atypical-HUS[16]
Treatment beyond the initial 6 months should be individualized[2]

[a]This is not an exhaustive list of all causes of TMA that would need to be ruled out.
[b]Immunosuppressive drugs and infections can also trigger atypical-HUS.[4,5]

Please see accompanying full Prescribing Information for ULTOMIRIS (ultomirishcp.com/PI), including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Reconsider if plasmapheresis/plasma exchange (PE) is appropriate for your patient with atypical-HUS

The use of plasma therapy (PE/PI) in patients with atypical-HUS has not been shown to improve graft survival.[37]

In a **retrospective study of 40 patients with non–Shiga toxin–associated HUS** who had received at least one kidney transplant...[9]

60% of adult patients with atypical-HUS **experienced TMA recurrence**, of which **92%** **had loss of graft function**[9]

In a **retrospective study of 22 patients who were diagnosed with atypical-HUS** post transplantation, 13 were treated with plasma exchange and 92% (12/13) achieved hematologic remission[38], however...

Only 15% (2/13) achieved **total renal recovery**[38,a]

Only 15% (2/13) had a **partial renal response**[38,b]

[a]Complete renal response was defined as the recovery of renal function compared with baseline SCr or, in cases of atypical-HUS in the immediate post-transplant phase, as the normalization of graft function (eGFR >60 mL/min) estimated by the Modification of Diet in Renal Disease equation.[38]

[b]A partial renal response was defined as a >25% reduction of the peak SCr value without reaching previous baseline SCr or, in cases of early atypical-HUS, as partial recovery of graft function.[38]

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; atypical-HUS=atypical hemolytic uremic syndrome; C5=complement component 5; CNI=calcineurin inhibitor; eGFR=estimated glomerular filtration rate; LDH=lactate dehydrogenase; mTOR=mechanistic target of rapamycin; PCR=polymerase chain reaction; PE/PI=plasma exchange/plasma infusion; SCr=serum creatinine; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

SELECT IMPORTANT SAFETY INFORMATION

ULTOMIRIS and SOLIRIS REMS

Due to the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program called ULTOMIRIS and SOLIRIS REMS.

Prescribers must enroll in the REMS, counsel patients about the risk of serious meningococcal infection, provide patients with the REMS educational materials, assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y, and B) and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of ULTOMIRIS. Antibacterial drug prophylaxis must be prescribed if treatment must be started urgently, and the patient is not up to date with both meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of ULTOMIRIS. Patients must receive counseling about the need to receive meningococcal vaccines and to take antibiotics as directed, signs and symptoms of meningococcal infection, and be instructed to carry the Patient Safety Card at all times during and for 8 months following ULTOMIRIS treatment.

Further information is available at www.UltSolREMS.com or 1-888-765-4747.

Initiate ULTOMIRIS for patients with atypical-HUS to inhibit complement-mediated TMA before or after kidney transplant

COMPLETE | TMA response was achieved in the majority of adult patients taking ULTOMIRIS in Study 311[2,a]

Components of Complete TMA Response Observed in Study 311[2]

Platelet Count Normalization	LDH Normalization	≥25% Improvement in Serum Creatinine From Baseline
84% (47/56) (95% CI: 72%-92%)	**77%** (43/56) (95% CI: 64%-87%)	**59%** (33/56) (95% CI: 45%-72%)

Hematologic Normalization[2]	Complete TMA Response[2,b]
Platelet Count & LDH Normalization: **73%** (41/56) (95% CI: 60%-84%)	**54%** (30/56) (95% CI: 40%-67%)

Patients with eGFR Category 5 (Select secondary endpoint)

- 68% (23/34) of patients saw an improvement by at least 1 eGFR category[16]
- Of the patients in eGFR category 5 who improved (23/34), 52% (12/23) improved to eGFR category 1 or 2[16]
- 22% (6/27) of patients who were off dialysis at baseline were on dialysis at last available follow-up[16,c]

[a]Complete TMA response was defined as normalization of hematological parameters (platelet count and LDH) and ≥25% improvement in serum creatinine from baseline during the 26-week initial evaluation period. Patients had to meet all criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart and any measurement in between.[2]
[b]Primary endpoint.[39]
[c]Stage 5 CKD is unlikely to improve.[39]

Study design[2,16,39,40]

- **26-week, open-label, single-arm study of complement inhibitor-naïve adult patients (N=56)**
- **Select inclusion criteria:** platelet count ≤150 × 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis
- **Select exclusion criteria:** patients with TMA due to ADAMTS13 deficiency, STEC-HUS, and genetic defect in cobalamin C metabolism; patients receiving prior PE/plasma infusion for ≥28 days; patients on chronic dialysis
- **Primary endpoint:** complete TMA response, which comprised: platelet count normalization (≥150 × 10^9/L), serum LDH normalization (≤246 U/L), and ≥25% improvement in serum creatinine from baseline
- **Select secondary endpoints:** time to complete TMA response and complete TMA response status over time, dialysis requirement, CKD stage change, hemoglobin response, and change from baseline in quality of life

Study 311: Select demographics and baseline characteristics

- 95% (53/56) had a hospitalization and/or emergency room visit prior to screening; of those patients, 51% (27/53) were critically ill, defined as receiving ICU-level care
- Mean platelet count was 118.52 x 10^9/L, mean LDH in serum was 702.38 U/L, mean eGFR was 15.86 mL/min/1.73 m^2
- 71.4% (40/56) had Stage 5 CKD as assessed by eGFR
- 14% (8/56) had a history of prior kidney transplant
- 14% (8/56) had evidence of TMA >3 days after childbirth
- 93% (52/56) had extrarenal signs or symptoms of atypical-HUS at baseline
- 8 patients were immediately postpartum, and 48 had received pretreatment PE/PI

Adult extension study

- Adult patients with atypical-HUS in the 26-week initial evaluation period could enter an ongoing 4.5-year extension period. Long-term extension data are from an interim analysis at Week 52

SELECT IMPORTANT SAFETY INFORMATION

Other Infections

Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.

ULTOMIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae, Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. Children treated with ULTOMIRIS may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP recommendations. Patients receiving ULTOMIRIS are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

Please see accompanying full Prescribing Information for ULTOMIRIS (ultomirishcp.com/PI), including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Consider ULTOMIRIS and its established safety profile for your adult patients with atypical-HUS

Study 311: Adverse reactions reported in ≥10% of ULTOMIRIS-treated adult patients with atypical-HUS at 26 weeks[2]

Body System Adverse Reaction	Adult patients (N=58) All Grades[a] (n=53) n (%)	Adult patients (N=58) ≥Grade 3 (n=14) n (%)
Blood and lymphatic system disorders		
Anemia	8 (14)	0 (0)
Gastrointestinal disorders		
Diarrhea	18 (31)	2 (3)
Nausea	15 (26)	2 (3)
Vomiting	15 (26)	2 (3)
Constipation	8 (14)	1 (2)
Abdominal pain	7 (12)	1 (2)
General disorders and administration site conditions		
Pyrexia	11 (19)	1 (2)
Edema peripheral	10 (17)	0 (0)
Fatigue	8 (14)	0 (0)
Infections and infestations		
Upper respiratory tract infection[b]	15 (26)	0 (0)
Urinary tract infection	10 (17)	5 (9)
Gastrointestinal infection[c]	8 (14)	2 (3)
Metabolism and nutrition disorders		
Hypokalemia	6 (10)	1 (2)
Musculoskeletal and connective tissue disorders		
Arthralgia	13 (22)	0 (0)
Back pain	7 (12)	1 (2)
Muscle spasms	6 (10)	0 (0)
Pain in extremity	6 (10)	0 (0)
Nervous system disorders		
Headache	23 (40)	1 (2)
Psychiatric disorders		
Anxiety	8 (14)	1 (2)
Respiratory, thoracic, and mediastinal disorders		
Cough	10 (17)	0 (0)
Dyspnea	10 (17)	1 (2)
Skin and subcutaneous tissue disorders		
Alopecia	6 (10)	0 (0)
Dry skin	6 (10)	0 (0)
Vascular disorders		
Hypertension	14 (24)	7 (12)

Long-term extension: safety in adult patients at 52 weeks (N=58)[40,d]

Event Type	Day 1-183 n (%)	Day 1-183 Events	Day 1 until last available follow-up n (%)	Day 1 until last available follow-up Events
Any AE	58 (100.0)	696	58 (100.0)	986
Treatment related	19 (32.8)	50	20 (34.5)	66
Not treatment related	58 (100.0)	646	58 (100.0)	920
Any SAE	28 (48.3)	60	33 (56.9)	84
Fatal TEAEs	3 (5.2)	3	3 (5.2)	3
Study discontinuation owing to				
TEAEs	3 (5.2)	3	3 (5.2)	3
TESAEs	3 (5.2)	3	3 (5.2)	3
Drug discontinuation owing to				
TEAEs	3 (5.2)	3	3 (5.2)	3
TESAEs	3 (5.2)	3	3 (5.2)	3
SAEs during study drug infusion	0 (0)	0	0 (0)	0
Meningococcal infections	0 (0)	0	0 (0)	0

- The most frequent adverse reactions reported in ≥20% of adult patients treated with ULTOMIRIS were diarrhea, nausea, vomiting, upper respiratory tract infection, arthralgia, headache, pyrexia, and hypertension[2]

[a]Graded per CTCAE v5.0.[2]

[b]Grouped term includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinitis, viral upper respiratory tract infection, rhinovirus infection, viral pharyngitis, rhinorrhea, and oropharyngeal pain.[2]

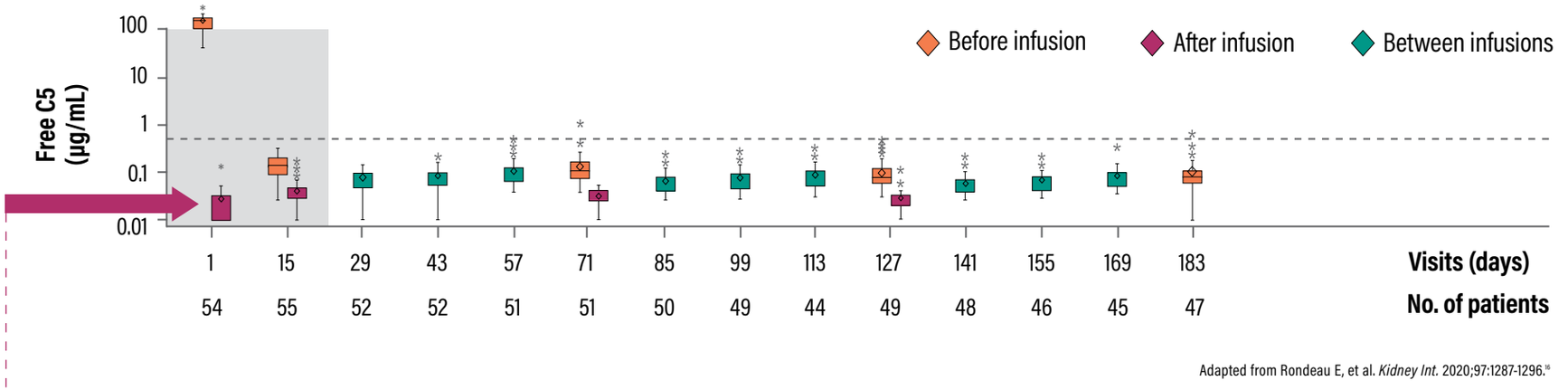
[c]Grouped term includes gastroenteritis, gastrointestinal infection, enterocolitis infection, infectious colitis, and enterocolitis.[2]

[d]Safety outcomes at the last available follow-up with ULTOMIRIS.[2]

AE=adverse event; atypical-HUS=atypical hemolytic uremic syndrome; CKD=chronic kidney disease; CTCAE=Common Terminology Criteria for Adverse Events; eGFR=estimated glomerular filtration rate; ICU=intensive care unit; LDH=lactate dehydrogenase; PE/PI=plasma exchange/plasma infusion; SAE=serious adverse event; TEAE=treatment-emergent adverse event; STEC-HUS=Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome; TMA=thrombotic microangiopathy; TESAE=treatment-emergent serious adverse event.

Four patients died during the adult atypical-HUS study. Patient deaths were determined by study investigators as unrelated to study drug; the cause of death was sepsis in 2 patients and intracranial hemorrhage in one patient. The 4th patient, who was discontinued per protocol from the trial after a diagnosis of STEC-HUS, died due to pretreatment cerebral arterial thrombosis.[2,16,39]

Pharmacodynamic findings showed that free C5 was immediately and completely[a] inhibited in adult patients taking ULTOMIRIS[2,16]



Adapted from Rondeau E, et al. *Kidney Int.* 2020;97:1287-1296.[16]

Box plot of free C5 vs time (semi-log scale). Pharmacodynamics of free C5 in serum concentrations from Rondeau et al, 2020. Dashed line: free C5 concentration of 0.5 µg/mL (denotes complete terminal complement inhibition). Box and whisker plot: the horizontal line in the middle of each box indicates the median, a diamond indicates the mean, and the upper and lower borders of the boxes denote the 75th and 25th percentiles, respectively. The whiskers depict the highest and lowest values within 1.5-fold the interquartile range from the lower and upper quartiles. Outliers are represented by asterisks beyond the whiskers.

The data from Study 311 showed that ULTOMIRIS inhibited C5 immediately and completely by the end of the first infusion. Complete inhibition of serum free C5 (concentration of less than 0.5 µg/mL) was observed by the end of the first ULTOMIRIS infusion and sustained throughout the entire 26-week treatment period in the majority (93%) of adult and pediatric patients with atypical-HUS.[2,16,b]

- **>99.5%** of all free C5 serum samples in adult patients showed complete inhibition of C5 throughout the 6-month study period with ULTOMIRIS[16,a]

[a]Defined as a free serum C5 concentration <0.5 µg/mL.[2,b]
[b]Data for pediatric patients were consistent with those for adults.[41]

SELECT IMPORTANT SAFETY INFORMATION

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

ULTOMIRIS treatment of aHUS should be a minimum duration of 6 months. Due to heterogeneous nature of aHUS events and patient-specific risk factors, treatment duration beyond the initial 6 months should be individualized. There are no specific data on ULTOMIRIS discontinuation. After discontinuing treatment with ULTOMIRIS, patients should be monitored for clinical symptoms and laboratory signs of TMA complications for at least 12 months. TMA complications post-discontinuation can be identified if any of the following is observed: Clinical symptoms of TMA include changes in mental status, seizures, angina, dyspnea, thrombosis or increasing blood pressure.

Please see accompanying full Prescribing Information for ULTOMIRIS (ultomirishcp.com/PI), including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Consider ULTOMIRIS—preferred by patients

In a survey of adult US patients (N=50) with confirmed atypical-HUS who had previously received short-acting therapy with eculizumab and ≥3 doses of ULTOMIRIS[42,a,b]:

Adult patient-reported survey: proportion of patients (%) who preferred ULTOMIRIS over eculizumab regarding specific parameters[42,c]					Proportion of patients (%) when asked how switching to ULTOMIRIS impacted them[42,d,e]
Frequency of infusions	Travel/ vacation	Benefit to your quality of life	Planning social activities	Length of time to receive infusion	The frequency of my infusions did not disrupt my life
100%	**98%**	**86%**	**86%**	**74%**	**96%**
n/N=50/50	n/N=48/49	n/N=43/50	n/N=42/49	n/N=37/50	n/N=48/50

For patients who responded "not applicable," responses were excluded from the percentage calculation for each question. Mean durations of eculizumab and ULTOMIRIS treatment were 46.9 and 12.9 months, respectively.[42]

[a]A web-based survey of US adults (N=50) with confirmed diagnosis of atypical-HUS who had previously received eculizumab and ≥3 doses of ravulizumab.[42]

[b]Eculizumab is infused every 2 weeks after 5 weeks of initial loading dose for adults. ULTOMIRIS is infused every 4 or 8 weeks after 2 weeks of initial loading dose, per weight-based dosing.[2,43]

[c]Percentages represent the percent of patients who preferred ULTOMIRIS vs preferring eculizumab/having no preference.[42]

[d]Percentages represent the percent of patients who agreed "quite a bit/somewhat/very much" with the survey question or agreed "not at all/a little bit" to the inverse of the question presented here.[42]

[e]Adult patients were asked about how ULTOMIRIS impacted them, based on their experience during their treatment with eculizumab and after switching to ULTOMIRIS.[42]

Fewer visits[44]	Less patient burden[44]
Fewer infusions[40]	Less risk of infection[40]
Reduced infusion time[44,g]	Less time spent at the hospital[44]

Lower frequency of infusions (about 6-7/year)[f,g] reduces patient exposure to infusion-associated risks and trauma associated with repeated venous access[2,40,45,46]

These outcomes are not specific to ULTOMIRIS alone.

[f]Eculizumab is infused every 2 weeks after 5 weeks of initial loading dose for adults. ULTOMIRIS is infused every 4 or 8 weeks after 2 weeks of initial loading dose, per weight-based dosing.[2,43]

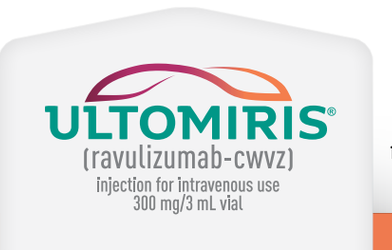
[g]Dosing schedules and infusion times vary depending on body weight and concentration administered. 6-7 ULTOMIRIS maintenance doses per year is based on patients ≥20 kg.[2]

Atypical-HUS=atypical hemolytic uremic syndrome; C5=complement component 5.

SELECT IMPORTANT SAFETY INFORMATION

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation (cont'd)

In addition, at least two of the following laboratory signs observed concurrently and results should be confirmed by a second measurement 28 days apart with no interruption: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment. If TMA complications occur after discontinuation, consider reinitiation of ULTOMIRIS treatment or appropriate organ-specific supportive measures.



Case Study: Management of patients with atypical-HUS before kidney transplant

Overview: 40-year-old female presented to clinic with ESKD due to unknown etiology on hypertensive drugs while awaiting a second kidney transplant

Family History

- Maternal side of family has a history of hypertension
- Paternal family medical history is unknown
- No known history of CKD or ESKD

Pre-transplant history:

- Pregnant with triplets at age 21; developed pre-eclampsia at 33 weeks
- Required emergency C-section
- AKI persisted post-partum and developed into Stage 4 CKD along with hypertension
- Progressed to Stage 5 CKD
- Received living donor kidney transplant at age 28; lost within 6 months due to rejection
- Developed strep throat one year ago; resulted in AKI
- Received dialysis treatment while awaiting second kidney transplant

Pre-transplant patient management:

- Tests ordered for ADAMTS13 and PRA
- CT scan of the abdomen revealed atrophic native kidneys, prior kidney transplant in left lower quadrant, and no signs of cirrhosis
- Renal genetic panel performed due to concern for complement mediated kidney failure (pre-eclampsia, failed prior transplant) which revealed a pathogenic variant of CFH mutation
- Transplant committee reviewed prior medical history in conjunction with current lab tests and genetic testing
- ADAMTS13 >5% and CFH mutation was identified. Atypical-HUS diagnosis was assumed
- Meningococcal vaccine administered per ACIP guidelines
- Started ULTOMIRIS 2 weeks later

Hypothetical patient case.

SELECT IMPORTANT SAFETY INFORMATION

Thromboembolic Event Management

The effect of withdrawal of anticoagulant therapy during treatment with ULTOMIRIS has not been established. Treatment should not alter anticoagulant management.

Infusion-Related Reactions

Administration of ULTOMIRIS may result in systemic infusion-related reactions, including anaphylaxis and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1 to 7% of patients, including lower back pain, abdominal pain, muscle spasms, drop or elevation in blood pressure, rigors, limb discomfort, drug hypersensitivity (allergic reaction), and dysgeusia (bad taste). These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS and institute appropriate supportive measures.

ADVERSE REACTIONS

Most common adverse reactions in patients with aHUS (incidence ≥20%) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Serious adverse reactions were reported in 42 (57%) patients with aHUS receiving ULTOMIRIS. The most frequent serious adverse reactions reported in more than 2 patients (2.7%) treated with ULTOMIRIS were hypertension, pneumonia and abdominal pain.

Adverse reactions reported in ≥20% of pediatric patients treated with ULTOMIRIS were diarrhea, constipation, vomiting, pyrexia, upper respiratory tract infection, decreased vitamin D, headache, cough, rash, and hypertension.

Please see accompanying full Prescribing Information for ULTOMIRIS (ultomirishcp.com/PI), including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Amanda received a second kidney transplant (deceased donor) about 1 year after starting ULTOMIRIS treatment

- Post-transplant follow-up indicated no issues with current transplant

Lab values			
		At presentation	Reference values[47-51]
Complete Blood Count	White blood cell count (x 10^3 cells/mcL)	6.0	4.5-11
	Hemoglobin (g/dL)	9.1	12-16
	Haptoglobin (mg/dL)	15	30-200
	Platelet count (x 10^3/mcL)	110	150-350
	LDH (U/L)	325	60-160
	Reticulocytes (%)	2	0.5-1.5
Peripheral Smear	Schistocytes present	Present	Absent
Coagulation Panel	PT/aPTT/INR (seconds)	12/26/1.1	11-13/25-35/1.0
	D-dimers (ng/mL)	300	≤500
Other Tests	ADAMTS13 (%)	60	≥70
	PRA (%)	98	
	eGFR (mL/min/1.73 m^2)	5	≥90

ACIP=Advisory Committee on Immunization Practices; ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; AKI=acute kidney injury; aPTT=activated partial thromboplastin time; atypical-HUS=atypical hemolytic uremic syndrome; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; INR=international normalized ratio; LDH=lactate dehydrogenase; PRA=panel-reactive antibody; PT=prothrombin time.

SELECT IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

Plasma Exchange, Plasmapheresis, and Intravenous Immunoglobulins

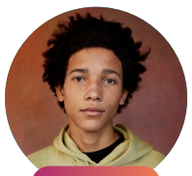
Concomitant use of ULTOMIRIS with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg) treatment can reduce serum ravulizumab concentrations and requires a supplemental dose of ULTOMIRIS.

Neonatal Fc Receptor Blockers

Concomitant use of ULTOMIRIS with neonatal Fc receptor (FcRn) blockers (e.g., efgartigimod) may lower systemic exposures and reduce effectiveness of ULTOMIRIS. Closely monitor for reduced effectiveness of ULTOMIRIS.

Case Study: Management of patients with atypical-HUS post kidney transplant

Overview: 14-year-old male reported to clinic with focal segmental glomerulosclerosis (FSGS) and ESKD



Medical History

- 2 incidents of spontaneous bacterial peritonitis
- Hyperlipidemia
- Hypertension
- Bilateral nephrectomies 6 months prior to transplant
- Had been given ibuprofen as prescribed

Family History

- Mother (53): hypertension
- Father (56): hypertension, diabetes, and hyperlipidemia

Hypothetical patient case.

- **Michael was on hemodialysis for 2 years prior to receiving a kidney transplant**
- **On post-operative Day 3 (POD 3) following the transplant, Michael was oliguric and required hemodialysis**

By POD 5, he developed significant hypertension (BP 160/100 mmHg) despite being 1.5 L negative since transplant and bleeding from the HD catheter site.

- Laboratory data were notable for anemia and thrombocytopenia Hb 6.5 g/dL, platelets 122 10^3/mcL
- PT and PTT were normal
- Initial diagnosis was thrombocytopenia secondary to thymoglobulin and anemia secondary to persistent intra-abdominal oozing from the extensive adhesion removal
- CT of abdomen did not show any evidence of a hematoma
- Transplant renal ultrasound was normal other than increased resistive indices

On POD 7, additional laboratory evaluation was initiated and revealed a low haptoglobin and a high lactate dehydrogenase.

- Peripheral smear noted presence of schistocytes
- These results raised a concern for post-transplant TMA/atypical-HUS, so tacrolimus was held
- Donor-specific antibodies, cytomegalovirus PCR, and Epstein Barr virus PCR were all negative
- Despite holding tacrolimus, platelets continued to be low and Michael remained on dialysis
- ADAMTS13 activity was >5% so atypical-HUS diagnosis was assumed

Final diagnosis was atypical-HUS

ACIP=Advisory Committee on Immunization Practices; ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; atypical-HUS=atypical hemolytic uremic syndrome; Cr=creatinine; CT=computed tomography; ESKD=end-stage kidney disease; Hb=hemoglobin; HD=hemodialysis; LDH=lactate dehydrogenase; PCR=polymerase chain reaction; Plts=platelets; PRBC=packed red blood cell; PT=prothrombin time; PTT=partial thromboplastin time; SCr=serum creatinine; TMA=thrombotic microangiopathy.

SELECT IMPORTANT SAFETY INFORMATION

USE IN SPECIFIC POPULATIONS

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ULTOMIRIS during pregnancy. Healthcare providers and patients may call 1-833-793-0563 or go to www.UltomirisPregnancyStudy.com to enroll in or to obtain information about the registry.

Please see accompanying full Prescribing Information for ULTOMIRIS (ultomirishcp.com/PI), including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

On POD 12, the decision was made to start eculizumab with prophylactic antibiotic use and meningococcal vaccination in accordance with eculizumab PI and ACIP guidelines.

- Over the next 48 hours, Michael began to show signs of clinical recovery with normalization of hematologic parameters (haptoglobin and improvement in lactate dehydrogenase)

On POD 14, platelets and serum creatinine started to improve and he was off dialysis by POD 16.

- Tacrolimus was restarted

On POD 20, Michael was discharged from the hospital and was switched to ULTOMIRIS, with outpatient infusions scheduled.

Lab values through 1 year

POD	Hb (g/dL)	Plts (10^3/mcL)	SCr (mg/dL)	Tacrolimus (ng/mL)	LDH (units/L)	Haptoglobin (mg/dL)	ADAMTS13
3	11.2	175	5.9	<1			
5	6.5	122	6.7	2.6			
7	5.8	104		4.3	746	<10	55%
10	7.6[a]	86	7.6	3.6			
12	6.9	55	8.1	1.5			
14	7.5	80	5.6	<1	350	84	
20	8.3	188	2.3	6.8			
90	12.8	196	1.3	8.9	240	92	
180	14.6	205	1.3	6.7	246	98	
365	14.3	220	1.3	4.6	243	110	
Reference Values[47,50,52]	**14-17 g/dL**	**150-350 10^3/mcL**	**0.7-1.2 mg/dL**	**5.0-15.0 ng/mL**	**60-160 units/L**	**30-200 mg/dL**	**≥70%**

[a]PRBC transfusion received.

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Alexion: a long-standing history of commitment to supporting healthcare professionals and their patients

For Patients

ONESOURCE®
Personalized Patient Support from Alexion

We created OneSource™ to support your patients every step of the way

OneSource is a complimentary, personalized patient support program available for patients, families, and caregivers facing complement-mediated diseases to help them start and stay on the treatment as prescribed.

$0 out-of-pocket costs for eligible patients[a]

Copay assistance

- OneSource will provide financial assistance by covering eligible patients' out-of-pocket medication and infusion costs associated with ULTOMIRIS
- Valid only for patients with commercial insurance who have a valid prescription for a US FDA–approved indication of ULTOMIRIS. Not valid for patients eligible to be reimbursed by government insurance programs[b] or other federal or state programs (including any state prescription drug assistance programs)
- Additional requirements may apply. Contact Alexion OneSource at **1-888-765-4747** or **OneSource@Alexion.com** for more information on patient eligibility

[a]Based on typical commercial patient out-of-pocket deductible limits. Additional terms and conditions apply. Please contact OneSource with additional questions.
[b]Includes Medicaid, Medicare (including Medicare Part D), Medicare Advantage Plans, Medigap, Veterans Affairs, Department of Defense, or TRICARE. Patients residing in Massachusetts or Rhode Island are eligible for assistance with medication costs but are not eligible for assistance with infusion costs.
Atypical-HUS=atypical hemolytic uremic syndrome; FDA=Food and Drug Administration.

For HCPs

ALEXION ACCESS NAVIGATOR

Alexion Access Navigator

A dedicated resource where US healthcare professionals and their offices can find downloadable access and reimbursement materials, including indication-specific coding and billing guides, sample letters of medical necessity, and a link to the REMS program.
AlexionAccessNavigator.com/Ultomiris

Utilize atypical-HUS ICD-10 codes to avoid coverage challenges

D59.32 Hereditary hemolytic uremic syndrome
Atypical hemolytic uremic syndrome with an identified genetic cause
Code also, if applicable

- **Defects in the complement system (D84.1)**
- **Methylmalonic acidemia (E71.120)**

D59.39 Other hemolytic uremic syndrome
Atypical (nongenetic) hemolytic uremic syndrome
Secondary hemolytic uremic syndrome
Code first, if applicable, any associated:

- **COVID-19 (U07.1)**
- **Complications of liver transplant (T86.4-)**
- **Complications of kidney transplant (T86.1-)**
- **Complications of heart transplant (T86.2-)**

Code also, if applicable, any associated condition, such as:

- **Hypertensive emergency (I16.1)**
- **Systemic lupus erythematosus (M32.-)**
- **Malignant neoplasm (C00-C96)**

Use Additional code, if applicable, for adverse effect to identify drug
(T36-T50 with fifth or sixth character 5)

Please see additional Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

ALEXION®
AstraZeneca Rare Disease