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Medication Policy Manual

Policy No: dru385

Topic: Complement Inhibitors

- Empaveli, pegcetacoplan
- Fabhalta, iptacopan
- PiaSky, crovalimab-akkz
- eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh)
- Tavneos, avacopan
- Ultomiris, ravulizumab-cwvz
- Veopoz, pozelimab
- Voydeya, danicopan
- Zilbrysq, zilucoplan

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Complement inhibitors are medications that bind to and inhibit the complement protein, preventing proteins from destroying red blood cells. They are used to treat specific rare blood and inflammatory disorders.

PLEASE NOTE: This policy and the coverage criteria below do **not** apply to Syfovre (pegcetacoplan intravitreal) or Izervay (avacincaptad pegol intravitreal solution).

Policy/Criteria

Most contracts require pre-authorization approval of complement inhibitors prior to coverage.

I. Continuation of therapy (COT): Complement inhibitors may be considered medically necessary for COT when criteria A through D below are met.

A. One of the following (1, 2, or 3) is met:

1. For diagnoses NOT listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. **For non-preferred eculizumab products (Soliris; biosimilars Bkemv, unbranded eculizumab-aagh) only**: There is a documented intolerance or contraindication to Epysqli (eculizumab-aagh).

AND

C. **For eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) OR Ultomiris (ravulizumab-cwvz) IV only**: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

D. "Administration, Quantity Limitations, and Authorization Period" below applies, as well as "Investigational Uses" for combination therapy.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Complement inhibitors (as listed in *Table 1*) may be considered medically necessary when clinical documentation (such as chart notes) that the applicable diagnosis-based criteria below are met.

Table 1:

Diagnosis: **Atypical hemolytic uremic syndrome (aHUS)** (a form of complement-associated thrombotic microangiopathy [TMA])	
Coverable medication(s)	**AND the following are met**:
• eculizumab (Soliris IV; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) • Ultomiris IV/SC (ravulizumab-cwvz)	**1.** The diagnosis has been established by or in consultation with a specialist in hematology or nephrology. **AND** **2.** Common causes of typical hemolytic uremic syndrome have been ruled out, including both of the following (criteria a and b): **a.** Infectious causes of HUS, including Shiga toxin-related hemolytic uremic syndrome have been ruled out. **AND** **b.** Thrombotic thrombocytopenic purpura (TTP) has been ruled out [confirmed by a disintegrin and metalloprotease with thrombospondin type 1 motif, 13 (ADAMTS13) activity ≥10%]. **AND** **3. For non-preferred eculizumab products (Soliris; biosimilars, Bkemv, unbranded eculizumab-aagh) only**: Both of the following criteria (a and b) below are met: **a.** There is a documented intolerance or contraindication to Epysqli (eculizumab-aagh). **AND** **b.** Ultomiris (ravulizumab-cwvz) has been ineffective as documented by symptom relapse or not tolerated unless there is documented medical contraindication to use. **AND** **4. For eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) OR Ultomiris (ravulizumab-cwvz) IV only**: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

Diagnosis: **Active severe anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitis** (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])	
Coverable medication(s)	**AND the following are met**:
Tavneos (avacopan)	**1.** The diagnosis has been established by or in consultation with a rheumatologist**.** **AND** **2.** The patient has been screened for hepatitis B virus and severe hepatic impairment and is negative for both. **AND** **3.** The patient has an EGFR ≥15ml/min and does not require dialysis or a kidney transplant. **AND** **4.** The patient will continue to receive standard of care therapy, including but not limited to, rituximab, cyclophosphamide, glucocorticoids, azathioprine, methotrexate, or mycophenolate mofetil. **AND** **5.** The patient has previously failed induction with standard therapy (rituximab or cyclophosphamide with glucocorticoids) or has relapsed since previously achieving remission within the previous 12 months.
Diagnosis: **Complement 3 Glomerulopathy (C3G)**	
Coverable medication(s)	**AND the following are met**:
• Empaveli (pegcetacoplan) • Fabhalta (iptacopan)	**1.** A diagnosis of biopsy-confirmed complement 3 glomerulopathy (C3G) was established by a specialist in nephrology. **AND** **2.** Documentation of an estimated glomerular filtration rate (eGFR) of ≥ 30 ml/min/1.73m^2. **AND** **3.** Native kidney or post-kidney transplant with no evidence of active rejection. **AND** **4.** No tubular atrophy, interstitial fibrosis, or more than 50% global glomerulosclerosis on renal biopsy. **AND** **5.** Persistent proteinuria with a urine protein-to-creatinine ratio of (UPCR) ≥ 1.0 g/g despite the following criteria a through c below being met. **a.** Adherent use of a stable maximized dose of ACEI/ARB for previous 3 months.

	AND **b.** A previous course of corticosteroid plus mycophenolate mofetil (MMF) has been ineffective (persistent UPCR ≥ 1.0 g/g), contraindicated, or not tolerated. **AND** **c.** A previous course of at least 4 months of SGLT2 inhibitor has been ineffective (persistent UPCR ≥ 1.0 g/g), contraindicated, or not tolerated. **AND** **6. For Fabhalta (iptacopan) only**: Empaveli (pegcetacoplan) has been ineffective (no clinical response after 3 months of treatment), not tolerated, or is contraindicated.
Diagnosis: **CD55-deficient protein-losing enteropathy (CHAPLE disease)**	
Coverable medication(s)	**AND the following are met**:
• eculizumab (Soliris IV; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) • Veopoz (pozelimab)	**1.** The diagnosis has been established by a specialist (immunologist, hematologist, gastroenterologist, or medical geneticist). **AND** **2.** Documented confirmation of the CD55 loss of function genetic mutation. **AND** **3. For Veopoz (pozelimab) only**: eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) has been ineffective (as documented by no clinical response after 3 months of treatment), or not tolerated unless there is documented medical contraindication to use. **AND** **4. For non-preferred eculizumab products (Soliris; biosimilars Bkemv, unbranded eculizumab-aagh) only**: There is a documented intolerance or contraindication to Epysqli (eculizumab-aagh). **AND** **5. For eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) IV only**: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

Diagnosis: **Primary Immunoglobulin A Nephropathy (IgAN)**	
Coverable medication(s)	**AND the following are met**:
Fabhalta (iptacopan)	**1.** A diagnosis of biopsy-confirmed primary immunoglobulin A nephropathy (IgAN), established by a specialist in nephrology. **AND** **2.** Documentation of an estimated glomerular filtration rate (eGFR) of ≥ 30ml/min/1.73m^2. **AND** **3.** Fabhalta (iptacopan) will be used with ongoing ACEI or ARB. **AND** **4.** Persistent proteinuria with a urine protein to-creatinine ratio of (UPCR) ≥ 1.5 g/g despite the following criteria (a through e) below being met. **a.** Adherent use of a stable maximized dose of ACEI/ARB for previous 3 months. **AND** **b.** Documentation that the patient has been counseled on the importance of optimized supportive therapy, including blood pressure control, cardiovascular risks, sodium intake, weight control, smoking, and exercise (see *Appendix 2*). **AND** **c.** A previous course of at least 8 weeks of high-dose prednisone (at least 0.8 mg/kg/day, or equivalent; see *Appendix 3*) has been ineffective (persistent UPCR ≥ 1.5 g/g), contraindicated, or not tolerated. **AND** **d.** A previous course of at least 9 months of (Filspari) sparsentan has been ineffective (persistent UPCR ≥ 1.5 g/g), contraindicated, or not tolerated. **AND** **e.** A previous course of at least 4 months of SGLT2 inhibitor has been ineffective (persistent UPCR ≥ 1.5 g/g), contraindicated, or not tolerated.

Diagnosis: Primary Immune-Complex Membranoproliferative Glomerulonephritis (Primary IC-MPGN)	
Coverable medication	**AND the following are met**:
Empaveli (pegcetacoplan)	**1.** A diagnosis of biopsy-confirmed *primary* immune-complex membranoproliferative glomerulonephritis (IC-MPGN) was established by a specialist in nephrology. **AND** **2.** Documentation of an estimated glomerular filtration rate (eGFR) of ≥ 30 ml/min/1.73m^2. **AND** **3.** Native kidney or post-kidney transplant with no evidence of active rejection. **AND** **4.** No tubular atrophy, interstitial fibrosis, or more than 50% global glomerulosclerosis on renal biopsy. **AND** **5.** Persistent proteinuria with a urine protein-to-creatinine ratio of (UPCR) ≥ 1.0 g/g despite the following criteria a through c below being met. **a.** Adherent use of a stable maximized dose of ACEI/ARB for previous 3 months. **AND** **b.** A previous course of corticosteroids with or without mycophenolate mofetil (MMF) or cyclophosphamide has been ineffective (persistent UPCR ≥ 1.0 g/g), contraindicated, or not tolerated. **AND** **c.** A previous course of at least 4 months of SGLT2 inhibitor has been ineffective (persistent UPCR ≥ 1.0 g/g), contraindicated, or not tolerated.

Diagnosis: **Refractory myasthenia gravis (MG)**	
Coverable medication(s)	**AND the following are met**:
• eculizumab (Soliris IV; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) • Ultomiris IV (ravulizumab-cwvz) • Zilbrysq (zilucoplan)	**1.** The diagnosis has been established by or in consultation with a neurologist who is a sub-specialist in neuromuscular disorders. **AND** **2.** A positive serologic test for anti-acetylcholine receptor (anti-aChR) antibodies. **AND** **3.** Prior to starting complement inhibitor therapy, there is documentation of a myasthenia gravis activities of daily living (MG-ADL) <u>total</u> score of greater than or equal to 6. **AND** **4.** Both the following (criteria a and b) have been ineffective (lack of MG symptom control or relapse as verified by a MG scoring tool), or not tolerated unless there is documented medical contraindication to use: **a.** The patient has had a thymectomy. **AND** **b.** At least one neonatal Fc receptor (FcRn) antagonist [Imaavy (nipocalimab), Rystiggo (rozanolixizumab), Vyvgart/Vyvgart Hytrulo (efgartigimod)]. **AND** **5. For non-preferred eculizumab products (Soliris; biosimilars Bkemv, unbranded eculizumab-aagh) only**: Both of the following criteria (a and b) below are met: **a.** There is a documented intolerance or contraindication to Epysqli (eculizumab-aagh). **AND** **b.** Ultomiris (ravulizumab-cwvz) has been ineffective as documented by symptom relapse or not tolerated unless there is documented medical contraindication to use. **AND** **6. For eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) OR Ultomiris (ravulizumab-cwvz) IV only**: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

Diagnosis: **Neuromyelitis Optica Spectrum Disorder (NMOSD)**	
Coverable medication(s)	**AND the following are met**:
• eculizumab (Soliris IV; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) • Ultomiris IV (ravulizumab-cwvz)	**1.** The diagnosis has been established by or in consultation with a neurologist. **AND** **2.** Documentation of a positive serologic test for aquaporin-4 immunoglobulin (AQP4-IgG) antibodies. **AND** **3.** Rituximab has been ineffective as documented by symptom relapse after completion of induction (at least one month after the first dose of rituximab) or not tolerated unless there is documented medical contraindication to use. **AND** **4. For non-preferred eculizumab products (Soliris; biosimilars Bkemv, unbranded eculizumab-aagh) only**: Both of the following criteria (a and b) below are met: **a.** There is a documented intolerance or contraindication to Epysqli (eculizumab-aagh). **AND** **b.** The following (i through iii) have been ineffective as documented by symptom relapse or not tolerated unless there is documented medical contraindication to use. **i.** Ultomiris (ravulizumab-cwvz) **AND** **ii.** Enspryng (satralizumab) **AND** **iii.** Uplizna (inebilizumab) **AND** **5.** Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

Diagnosis: **Paroxysmal nocturnal hemoglobinuria (PNH)**	
Coverable medication(s)	**AND the following are met**:
• Empaveli (pegcetacoplan) • Fabhalta (iptacopan) • PiaSky (crovalimab-akkz) • eculizumab (Soliris IV; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) • Ultomiris IV/SC (ravulizumab-cwvz) • Voydeya (danicopan)	**1.** The diagnosis has been confirmed by high sensitivity flow cytometry and established by or in consultation with a specialist in hematology. **AND** **2.** The complement inhibitor will be used in one of the following two settings, based on prior therapy used (a or b): **a. For <u>complement-naïve</u> PNH [Empaveli, (pegcetacoplan), PiaSky (crovalimab), eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh), and Ultomiris IV/SC (ravulizumab-cwvz) only]**: Both of the following criterion (i and ii) below are met: **i.** One of the following criteria (1 or 2) below are met: **1.** Transfusion-dependence prior to initiation of complement inhibitor treatment. *PLEASE NOTE*: *Transfusion-dependence is defined as at least one transfusion in the previous 24 months due to documented hemoglobin < 9 g/dL in patients with symptoms from anemia or < 7 g/dL regardless of symptoms.* **OR** **2.** A history of a major adverse vascular event from thromboembolism, including but not limited to: deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, peripheral arterial disease (PAD), and/or Budd-Chiari syndrome. **AND** **ii. For non-preferred eculizumab products (Soliris; biosimilars Bkemv, unbranded eculizumab-aagh) and PiaSky (crovalimab) only**: Both of the following criteria (1 and 2) below are met: **1.** There is a documented intolerance or contraindication to Epysqli (eculizumab-aagh). **AND** **2.** Ultomiris (ravulizumab-cwvz) has been ineffective as documented by symptom relapse or not tolerated unless there is documented medical contraindication to use. **OR** **b. For <u>complement-experienced</u> PNH [Empaveli (pegcetacoplan), Fabhalta (iptacopan), and Voydeya (danicopan) only]**: When breakthrough symptoms despite at least 6 months of C5 inhibitor [eculizumab (Soliris; biosimilars

	Bkemv, Epysqli, unbranded eculizumab-aagh) or Ultomiris (ravulizumab-cwvz)], defined as either criterion (i or ii) below are met: **i.** Transfusion-dependence. *PLEASE NOTE*: *Transfusion-dependence is defined as at least one transfusion in the previous 6 months due to documented hemoglobin < 9 g/dL in patients with symptoms from anemia or < 7 g/dL regardless of symptoms.* **OR** **ii.** A major adverse vascular event from thromboembolism, including but not limited to: deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, peripheral arterial disease (PAD), and/or Budd-Chiari syndrome. **AND** **3. For eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) OR Ultomiris (ravulizumab-cwvz) IV only**: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Empaveli SC (pegcetacoplan), Fabhalta oral (iptacopan), Tavneos oral (avacopan), Ultomiris SC (ravulizumab-cwvz), Voydeya oral (danicopan), and Zilbrysq SC (zilucoplan) coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers eculizumab (Soliris IV; biosimilars Bkemv, Epysqli; unbranded eculizumab-aagh), Ultomiris IV (ravulizumab-cwvz), PiaSky IV/SC (crovalimab) or Veopoz IV/SC (pozelimab) coverable only under the medical benefit (as provider-administered medications).

C. When pre-authorization is approved, complement inhibitors will be covered in quantities as follows:

1. Initial Authorization: Up to the dose and duration, as listed below in *Table 2*:

Table 2. Initial Authorization

Indication	Authorization Limits
PNH	**Empaveli (pegcetacoplan)**: Up to forty-eight (1080 mg) vials in a 24-week period, based on SC twice weekly dosing.
	Fabhalta (iptacopan): Up to sixty (200 mg) capsules every 30 days in a 6-month period, based on twice daily oral dosing.
	PiaSky (crovalimab): (≥40 kg) Up to ten doses in a 24-week period, based on a single one-time IV loading dose infusion on day 1 followed by SC injections (on days 2, 8, 15, and 22) and maintenance dose on day 29 every 4 weeks.
	eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh): Up to fifteen IV infusions in a 24-week period, based on weekly dosing for five weeks, followed by maintenance dosing every 2 weeks thereafter.
	Ultomiris (ravulizumab-cwvz) • IV: - Pediatrics (<20 kg); Up to eight IV infusions in a 24-week period, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 4 weeks thereafter. - Adults and Pediatrics (≥20 kg); Up to five IV infusions in a 24-week period, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 8 weeks thereafter. • SC: Adults (≥40 kg); Up to twenty-four doses in a 24-week period (not to exceed 490 mg/dose), based on dose of 490 mg SC once weekly.
	Voydeya (danicopan): up to **180 tablets** (50 mg or 100 mg) every 30 days for a **6-month period,** based on three times daily oral dosing.
aHUS	**eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh)** • Pediatrics (<10 kg): Up to ten IV infusions in a 24-week period, based on induction dosing weekly for two weeks, followed by maintenance dosing every 3 weeks thereafter. • Pediatrics (10 kg to <20 kg): Up to fourteen IV infusions in a 24-week period, based on induction dosing weekly for two weeks, followed by maintenance dosing every 2 weeks thereafter. • Pediatrics (20 kg to <40 kg): Up to sixteen IV infusions in a 24-week period, based on induction dosing weekly for three weeks, followed by maintenance dosing every 2 weeks thereafter. • Adults and Pediatrics (≥40 kg): Up to fifteen IV infusions in a 24-week period, based on induction dosing weekly for five weeks, followed by maintenance dosing every 2 weeks thereafter.
	Ultomiris (ravulizumab-cwvz) • IV: - Pediatrics (<20 kg); Up to eight IV infusions in a 24- week period, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 4 weeks thereafter. - Adults and Pediatrics (≥20 kg); Up to five IV infusions in a 24-week period, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 8 weeks thereafter. • SC: Adults (≥40 kg); Up to twenty-four doses in a 24-week period (not to exceed 490 mg/dose), based on dose of 490 mg SC once weekly.

Indication	Authorization Limits
MG	**eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh)**: Up to fifteen IV infusions in a 24-week period, based on induction dosing weekly for five weeks, followed by maintenance dosing every 2 weeks thereafter.
	Ultomiris (ravulizumab-cwvz) IV: Up to five IV infusions in a 24- week period, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 8 weeks thereafter.
	Zilbrysq (zilucoplan): Up to **one syringe per day for 24 weeks**, based on a weight-based dose <56kg=16.6mg; 56kg to <77kg=23 mg; or ≥77kg=32.4mg SC daily.
NMOSD	**eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh)**: Up to fifteen IV infusions in a 24-week period, based on induction dosing weekly for five weeks, followed by maintenance dosing every 2 weeks thereafter.
	Ultomiris (ravulizumab-cwvz) IV: Adults (≥40 kg); Up to five IV infusions in a 24-week period, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 8 weeks thereafter.
CHAPLE	**eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh)** • Pediatrics (<10 kg): Up to nine IV infusions in a 24-week period, based on induction dosing weekly for two weeks, followed by maintenance dosing every 3 weeks thereafter. • Pediatrics (10 kg to <40 kg): Up to thirteen IV infusions in a 24-week period, based on induction dosing weekly for up to 3 weeks, followed by maintenance dosing every 2 weeks thereafter. • Adults and Pediatrics (≥40 kg): Up to fourteen IV infusions in a 24-week period, based on induction dosing weekly for five weeks, followed by maintenance dosing every 2 weeks thereafter.
	Veopoz (pozelimab): Up to twenty-four doses in a 24-week period, based on single one-time IV loading dose infusion on day 1 followed by weekly SC injections every week thereafter
ANCA-AV	**Tavneos (avacopan)**: Up to 180 tablets every 30 days (not to exceed 60mg per day) for a 6-month period, based on dosing of 3 oral tablets twice daily.
Primary IgAN or C3G	**Fabhalta (iptacopan)**: Up to sixty (200 mg) capsules every 30 days for a 6-month period, based on twice daily oral dosing.
C3G or IC-MPGN	**Empaveli (pegcetacoplan)**: Up to forty-eight doses (1,080mg/20mL single dose vial per dose) in a 24-week period.

2. Continued Authorization: Up the dose and duration listed below in *Table 3*:

Table 3. Continued Authorization

Indication	Authorization Limits
PNH	**Empaveli (pegcetacoplan)**: • PNH stable: Up to 104 (1080 mg) vials in a 52-week period, based on SC twice weekly dosing. • PNH with breakthrough hemolysis [LDH > 2x ULN, on twice weekly Empaveli: Up to ten (1080 mg) vials per 30 days over a 24-week period.
	Fabhalta (iptacopan): Up to sixty (200 mg) capsules every 30 days for a 12-month period, based on twice daily oral dosing.
	PiaSky (crovalimab): (≥40 kg) Up to thirteen SC injections in a 52-week period based on every 4-week SC dosing.
	eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh) • PNH stable: Up to twenty-six IV infusions in a 52-week period, based on maintenance dosing every 2 weeks. • PNH with breakthrough hemolysis on every 2-week eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh): Up to thirty-one IV infusions in a 52-week period, based on a max dose of 900 mg every 12 days
	Ultomiris (ravulizumab-cwvz) • IV: - Pediatric patients (<20 kg): Up to thirteen IV infusions in a 52-week period, based on maintenance dosing every 4 weeks. - Adults and Pediatrics (≥20 kg): Up to seven infusions in a 52-week period, based on maintenance dosing every 8 weeks. • SC: Up to 104 doses in a 52-week period (not to exceed 490 mg/dose), based on dose of 490 mg SC once weekly.
	Voydeya (danicopan): up to 180 tablets (50 mg or 100 mg) every 30 days for a 12-month period, based on three times daily oral dosing.
aHUS	**eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh)**: • Pediatric Patients (<10 kg): Up to eighteen IV infusions in a 52-week period, based on maintenance dosing every 3 weeks. • Adults and Pediatrics (≥10 kg): Up to twenty-six IV infusions in a 52-week period, based on maintenance dosing every 2 weeks.
	Ultomiris (ravulizumab-cwvz) • IV: - Pediatric Patients (<20 kg): Up to thirteen IV infusions in a 52-week period, based on maintenance dosing every 4 weeks. - Adults and Pediatrics (≥20 kg): Up to seven IV infusions in a 52-week period, based on maintenance every 8 weeks. • SC: Up to 104 doses in a 52-week period (not to exceed 490 mg/dose), based on dose of 490 mg SC once weekly.
MG	**eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh)**: Up to twenty-six IV infusions in a 52-week period, based on maintenance dosing every 2 weeks.
	Ultomiris (ravulizumab-cwvz) IV: Up to seven IV infusions in a 52-week period, based on maintenance dosing every 8 weeks.
	Zilbrysq (zilucoplan): Up to one syringe per day for 52 weeks, based on a weight-based dose of <56kg=16.6mg; 56kg to <77kg=23 mg; or ≥77kg=32.4mg SC daily.

Indication	Authorization Limits
NMOSD	**eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh)**: Up to twenty-six IV infusions in a 52-week period, based on maintenance dosing every 2 weeks.
	Ultomiris (ravulizumab-cwvz) IV: Up to seven IV infusions in a 52-week period, based on maintenance every 8 weeks.
CHAPLE	**eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh)** • Pediatric Patients (<10 kg): Up to eighteen IV infusions in a 52-week period, based on maintenance dosing every 3 weeks. • Adults and Pediatrics (≥10 kg): Up to twenty-six IV infusions in a 52-week period, based on maintenance dosing every 2 weeks.
	Veopoz (pozelimab): Up to fifty-two SC injections in a 52- week period based on weekly SC dosing
ANCA-AV	**Tavneos (avacopan)**: Up to 180 tablets every 30 days (not to exceed 60mg per day) for a 12-month period, based on dosing of 3 oral tablets twice daily.
Primary IgAN or C3G	**Fabhalta (iptacopan)**: Up to sixty (200 mg) capsules every 30 days for a 12-month period, based on twice daily oral dosing.
C3G or IC-MPGN	**Empaveli (pegcetacoplan)**: Up to 104 (1080 mg) vials in a 52-week period, based on SC twice weekly dosing.

3. **Supplemental dosing**: May be given according to label, as follows:

a. **eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh)**: after plasma exchange/plasmapheresis (PLEX) or fresh frozen plasma (FFP) infusion.

b. **Ultomiris (ravulizumab)**: after plasma exchange/plasmapheresis (PLEX) or intravenous immunoglobulin (IVIG).

4. Use of doses in excess of those listed above (in *Tables 2* and *3*) are considered not medically necessary.

D. **Reauthorization**: Authorization **shall** be reviewed as follows (per the authorization time frames, as specified in *Table 3*) to confirm that current medical necessity criteria are met and that the medication is effective when criteria (1 and 2) are met:

1. For all indications: Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met and that the medication is providing clinical benefit, including disease stability or improvement must be provided, relative to baseline symptoms.

2. In addition, the following diagnostic-specific clinical documentation must be provided:

a. **For MG**: A standard disease scoring tool must be included, such as the total myasthenia gravis activities of daily living (MG-ADL)

score, total quantitative myasthenia gravis (QMG) score, and/or myasthenia gravis composite (MGC) scale.

b. **For NMOSD**: There must be a reduction of clinical relapse OR provider attestation has been received that patient is continuing to have clinical benefit (stability or improvement) and continued therapy is medically necessary.

c. **For CHAPLE**: There must be a reduction in baseline symptoms such as visceral and peripheral edema, diarrhea and abdominal pain, AND/OR a reduction in the need for supportive care including infusions of albumin and/or immunoglobulin, corticosteroid use, and hospitalizations.

d. **For Primary IgAN**: There must be a reduction in proteinuria or in urine protein creatinine ratio (UPCR) from baseline AND documentation of continued ACEI/ARB therapy will be required.

e. **For C3G and IC-MPGN**: There must be a reduction of symptoms; reduction in proteinuria or in urine protein creatinine ratio (UPCR) from baseline; improvement or stabilization of renal function (estimated glomerular filtration rate [eGFR]); or improvement of histology on renal biopsy.

IV. Complement inhibitors (as listed in *Table 1*) are considered investigational when used for all other conditions, including but not limited to:

A. Amyotrophic lateral sclerosis (ALS).

B. Delayed hemolytic transfusion reaction in sickle cell disease.

C. Use of Tavneos (avacopan) for deposit disease/C3 glomerulonephritis.

D. Hemolytic cold agglutinin disease.

E. Ocular myasthenia gravis.

F. Myasthenia gravis with MUSK antibodies or antibodies other than anti-ACh-R.

G. Non-exudative (dry) macular degeneration.

H. Preeclampsia with hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome.

I. Prevention of delayed graft rejection.

J. Shiga toxin E. coli-related hemolytic uremic syndrome (STEC-HUS) Systemic lupus erythematosus.

K. Thrombotic thrombocytopenic purpura (TTP).

L. For NMOSD: Use of multiple targeted therapies for NMOSD, including but not limited to complement inhibitors such as Ultomiris (ravulizumab-cwvz), eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh), anti-CD20 therapy (rituximab product), anti-CD19 therapy [Uplizna (inebilizumab)], or anti-IL6 therapy [Actemra (tocilizumab), Enspryng (satralizumab)].

M. For PNH: Combination use of the following complement inhibitors: Empaveli (pegcetacoplan), Fabhalta (iptacopan), eculizumab (Soliris; biosimilars Bkemv, Epysqli, unbranded eculizumab-aagh), Ultomiris (ravulizumab-cwvz).

N. For IgAN: Combination use of Fabhalta (iptacopan) with an endothelin receptor antagonist for kidney disease, including but not limited to Filspari (sparsentan) or Vanrafia (atrasentan).

O. Use of Fabhalta (iptacopan) in C5-inhibitor naïve PNH.

P. For gMG: Use in combination with other targeted therapies for MG, such as FcRn antagonists: Imaavy (nipocalimab), Vyvgart (efgartigimod) or Rystiggo (rozanolixizumab) or IVIG maintenance therapy.

Q. Eosinophilic granulomatosis with polyangiitis (EPGA, formerly known as Churg-Strauss Syndrome).

R. Hidradenitis Suppurativa.

S. Use of Tavneos (avacopan) for aHUS.

T. Use of Tavneos (avacopan) for non-severe ANCA- associated vasculitis.

U. Use of Veopoz (pozelimab) for aHUS, MG, NMOSD, or PNH.

V. Secondary IC-MPGN: where IC-MPGN is caused by another condition including, but not limited to, infection, malignancy, monoclonal gammopathy, a systemic autoimmune disease, or a medication.

Position Statement

- Complement inhibitors (as listed in *Table 1*) are monoclonal antibodies that bind to complement proteins and inhibit activation of the complement pathway.
    - Empaveli (pegcetacoplan), Fabhalta (iptacopan), and Voydeya (danicopan) are proximal complement inhibitors.
    - Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), Veopoz (pozelimab), and Zilbrysq (zilucoplan), and PiaSky (crovalimab) are terminal complement inhibitors, also referred to as complement 5 inhibitors ("C5 inhibitors").
    - Tavneos (avacopan) is an orally administered complement 5a (C5a) receptor antagonist that inhibits the C5a-mediated neutrophil activation and migration pathway.
- The intent of the policy is to allow for coverage of complement inhibitors for the specific diagnoses for which they have been studied (as outlined in the coverage criteria), when managed by a specialist, limit to more severe disease and encourage the use of lower cost therapies (when appropriate), and limit coverage to doses studied and shown to be safe and effective in clinical trials. For diagnoses with multiple targeted treatment options for refractory disease, including compliment inhibitors, higher cost targeted treatment options are coverable only when lower cost targeted treatments are not an option.
    - Where there is lack of proven additional benefit and/or lack of demonstrated health outcomes relative to alternative therapies, use of complement inhibitors alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").

    * It is important to note that a medication being FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.

- Ultomiris (ravulizumab-cwvz) is a complement inhibitor that is a derivative of Soliris (eculizumab) with a more convenient, extended dosing regimen. It is coverable only for the indications for which it has been studied and the dose is known, as detailed in the coverage criteria.
- Tavneos (avacopan) is FDA approved for adjunctive use in severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, including granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in combination with standard therapy. However, the health plan considers use in newly diagnosed patients to be non-coverable as this regimen has not adequately been demonstrated to provide any superior benefit versus the lower-cost standard of care treatment options.
- Veopoz (pozelimab) approved only for use in CD55-deficient protein-losing enteropathy, also known as CHAPLE disease is only coverable when the lower cost alternative Soliris (eculizumab) has been ineffective or not tolerated.

Paroxysmal nocturnal hemoglobinuria (PNH) summary

- PNH is a rare and life-threatening blood disorder, characterized by a reduced (type II) or deficient (type III) glycosylphosphatidylinositol (GPI)-linked proteins from the surface of red blood cells. Red blood cells are susceptible to complement-mediated lysis leading to anemia, hemoglobinuria, and other complications. [1 2]
- C5 inhibitors [Ultomiris (ravulizumab), Soliris (eculizumab), and PiaSky (crovalimab)] have become the standard of care for PNH, as clinical experience has shown their utility in reducing symptoms and thrombosis.
- Some patients continue to have breakthrough symptoms despite treatment with standard doses of C5 inhibitors. Proximal inhibitors [Empaveli (pegcetacoplan), Fabhalta (iptacopan), or Voydeya (danicopan)] may be coverable when standard of care C5 inhibitors are ineffective or not a treatment option for complement-experienced PNH.
- There is no scientific basis to prefer one FDA-approved C5 inhibitor over another (by mechanism of action); given similar efficacy and safety, most contracts consider more costly products not medically necessary. Specifically, at this time, Ultomiris (ravulizumab) is the lower cost C5 inhibitor for PNH. Therefore, higher cost C5 inhibitors, Soliris (eculizumab) and PiaSky (crovalimab), is coverable only when the overall lower cost option, Ultomiris (ravulizumab), is not a treatment option.
- Treatment with complement inhibitors (C5 inhibitors and proximal inhibitors) may be considered effective if there is a decrease in the number of transfusions or disabling symptoms, stabilization of hemoglobin levels, a reduction in thrombotic events, and/or an improvement in quality of life.
- Complement Inhibitors (*as listed in Table 1*) may be covered for PNH at the doses proven to be safe and effective in clinical trials.
- *Higher dosing for refractory PNH*: For breakthrough hemolysis with PNH, Soliris (eculizumab) can be dosed more frequently (at 900 mg every 12 days). However, higher dosing of Soliris (eculizumab) (1200 mg every 14 days) is considered 'not medically

necessary," as is more costly but not proven to be safer or more effective than more frequent dosing for breakthrough PNH. In addition, there are several complement inhibitor options now available for breakthrough PNH, including Empaveli (pegcetacoplan), Fabhalta (iptacopan), and Voydeya (danicopan). For breakthrough hemolysis with PNH when LDH exceeds two times the upper limit of normal (ULN), Empaveli (pegcetacoplan) can be dosed at 1080 mg every three days.

Atypical hemolytic uremic syndrome (aHUS) summary

- Hemolytic uremic syndrome (HUS) is a condition caused by the premature destruction of red blood cells and is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (>95% of patients). [3]
- Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) are FDA-approved for complement-mediated HUS (aHUS).
- Evidence of efficacy of certain complement inhibitors primarily comes from positive open-label, single arm trials, retrospective reviews, and case studies.
- Despite a lack of high-quality evidence, complement inhibitors are an important treatment option for patients with aHUS. [4] However, there are still many unknowns about complement inhibitors including evidence of efficacy for meaningful clinical outcomes, such as mortality, comparative efficacy with plasmapheresis, long term safety, and validated strategies for starting and stopping therapy.
- Treatment with certain complement inhibitors may be considered effective if treatment results in a decrease in the signs of thrombotic microangiopathy (TMA), indicated by normalization of platelet counts and lactate dehydrogenase (LDH) levels.
- There is no evidence that Soliris (eculizumab) is more effective than other compliment inhibitors (targeted aHUS product), Ultomiris (ravulizumab). Among the FDA-approved agents for refractory aHUS, Ultomiris (ravulizumab) is a lower cost option with lower administration burden. There is no scientific basis to prefer one FDA-approved targeted aHUS product over another; given similar efficacy and safety, most contracts consider more costly products not medically necessary.
- Currently there is insufficient evidence to establish the safety and efficacy of Tavneos (avacopan), an oral complement antagonist, for aHUS.
- There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of TTP.

Refractory myasthenia gravis (MG) summary

- Myasthenia gravis (MG) is a rare autoimmune disease arising from T cell-dependent immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction, resulting in striated muscle weakness.
- Complement inhibitors, Soliris (eculizumab), Ultomiris (ravulizumab-cwvz) and Zilbrysq (zilucoplan), provide newer treatment options for refractory gMG. While the clinical data is promising, there are several limitations in the body of evidence. Use should be limited to patients who have failed other options, as detailed in the coverage criteria.
- Standard therapies recommended by treatment guidelines for management of MG include acetylcholinesterase (ACh) inhibitors (pyridostigmine), corticosteroids, various DMARDs for immunosuppressant therapy (IST), intravenous immunoglobulin (IVIG),

plasmapheresis/plasma exchange (PLEX), and thymectomy. [5-10]

- There is no evidence that complement inhibitors are more effective than other targeted MG products such as neonatal Fc receptor (FcRn) antagonists Imaavy (nipocalimab), Vyvgart (efgartigimod) or Rystiggo (rozanolixizumab). Among the FDA-approved agents for deeply refractory gMG, FcRn antagonists are lower cost options. Among the complement inhibitors, Ultomiris (ravulizumab) and Zilbrysq (zilucoplan) may represent lower cost options with lower administration burden versus Soliris (eculizumab). There is no scientific basis to prefer one FDA-approved targeted MG product over another; given similar efficacy and safety, most contracts consider more costly products not medically necessary.
- Complement inhibitors have not been studied and shown to be safe or effective in patients with other antibodies, including MuSK antibodies, antibodies to the agrin receptor low-density lipoprotein receptor–related protein 4 (LRP4), or any other antibodies. In addition, they have not been studied in patients with ocular MG (without generalized MG symptoms) or those in myasthenic crisis (MGFA Class V).
- Complement inhibitors have not been studied when used in combination with one another, with chronic maintenance IVIG, or with FcRn antagonists. In clinical trials, patients were transitioned off chronic maintenance IVIG prior to initiating complement inhibitors.
- Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Zilbrysq (zilucoplan) may be covered for refractory MG at the doses proven to be safe and effective in clinical trials, as detailed in the coverage criteria.

Neuromyelitis optica spectrum disorder (NMOSD) summary [11-14]

- NMOSD, also known as Devic disease or neuromyelitis optica (NMO), is a chronic demyelinating disease of the central nervous system dominated by inflammation of the optic nerve and spinal cord and may often be misdiagnosed as multiple sclerosis (MS).
- Patients with NMOSD are treated for acute episodes/ relapse with steroids. Plasma exchange (PLEX) is used acutely for incomplete response to steroids.
- Immunosuppressive therapy (IST; corticosteroids, azathioprine, mycophenolate mofetil, or rituximab) is therapy to reduce the frequency of relapse (maintenance therapy).
- Not all patients with NMOSD test positive for AQP4-IgG. However, all patients in clinical trials of Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) for NMOSD were AQP4-IgG positive. Therefore, the safety and efficacy of Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) in AQP4-IgG negative patients is unknown.
- Neither Soliris (eculizumab) nor Ultomiris (ravulizumab-cwvz) have not been directly compared to any other IST for NMOSD. However, use of rituximab for NMOSD is supported by clinical evidence for reducing relapse rate [including a single randomized controlled trial (RCT)] [15] is recommended by guidelines, and has years of experience in clinical practice. [11 14 16-21] Therefore Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) for NMOSD is coverable only when rituximab is ineffective or not a treatment option.
- There is no evidence that Soliris (eculizumab) is more effective than other targeted treatments for refractory NMOSD, Ultomiris (ravulizumab-cwvz), Enspryng

(satralizumab) and Uplizna (inebilizumab). Among the FDA-approved targeted agents for refractory NMOSD, Ultomiris (ravulizumab-cwvz), Enspryng (satralizumab) and Uplizna (inebilizumab) are lower cost options with lower administration burden. There is no scientific basis to prefer one FDA-approved targeted NMOSD product over another; given similar efficacy and safety, most contracts consider more costly products not medically necessary.

- The evidence for Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) in NMOSD is limited to a single phase 3 trials. Although these drugs reduced the frequency of NMOSD relapse, their effect on quality life (QoL) and disability are unknown.

  The safety and efficacy combination targeted therapies for NMOSD, such as rituximab, Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), Enspryng (satralizumab) and Uplizna (inebilizumab), have not been studied and have not been established.

CD55-defiecent protein-losing enteropathy (CHAPLE disease) summary[22]

- CHAPLE disease is a recently discovered, ultra-rare, recessive disorder, caused by mutations in the CD55 gene, leading to an overactivation of the complement system, resulting in intestinal protein loss (albumin and immunoglobulins) due to damage in blood and lymph vessels along the digestive tract.
- Diagnosis of CHAPLE disease is based on clinical signs and symptoms, with confirmation via positive genetic test for CD55 loss of function mutation.
- Published data on CHAPLE disease treatment is limited due to its rarity and newness. Currently there are no consensus guidelines for CHAPLE treatment, as the only guidance has been limited to case reports and small natural history studies.
- Soliris (eculizumab) has shown efficacy in CHAPLE disease in a small observational trial for which all patients reported normalization of serum albumin and improvement in symptoms. Treatment with off label Soliris (eculizumab) has since become the standard of care for patients with CHAPLE disease.
- Veopoz (pozelimab) recently received FDA approval-based efficacy results from a small single arm trial in patients with confirmed CHAPLE disease.
- Currently, there is insufficient evidence to establish therapy with Veopoz (pozelimab) is more effective or safer than the lower-cost alternative Soliris (eculizumab), which has a much more robust real world safety profile in patients with confirmed CHAPLE disease. Therefore, the use of Veopoz (pozelimab) for patients with confirmed CHAPLE disease is coverable only in patients who have had an insufficient response or intolerance to Soliris (eculizumab).
- The safety and efficacy of combining targeted therapies for CHAPLE disease, such as Soliris (eculizumab) and Veopoz (pozelimab), has not been studied; therefore, use in combination is considered investigational.

Antineutrophil cytoplasmic antibody-associated vasculitis (ANCA-AV) (MPA or GPA) summary [23-27]

- ANCA-AV is a rare multisystem autoimmune disease caused by inflammation and necrosis of the small and medium arteries. ANCA-AV includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (EPGA, formerly known as Churg-Strauss syndrome). However, EPGA is clinically and pathologically

different from GPA and MPA, and patients with EGPA were excluded from clinical trials. Therefore, the safety and efficacy of Tavneos (avacopan) in EGPA is unknown and its use for EGPA is considered investigational.

- Tavneos (avacopan) received FDA approval based on a single trial as adjunctive therapy for severe ANCA-AV (MPA or GPA), in combination with standard therapy, including corticosteroids.
- Currently there is insufficient evidence to establish add-on therapy with Tavneos (avacopan) is more effective than the lower cost standard of care immunosuppressant treatment options for patients with severe active ANCA-associated vasculitis. Therefore, the use of Tavneos (avacopan) for patients diagnosed with severe ANCA-associated vasculitis will only be covered as add on therapy to the standard of care in patients who have previous failed induction therapy with standard of care options (rituximab or cyclophosphamide with glucocorticoids) or who have relapsed since previously achieving remission in the past 12 months
- The 2021 American College of Rheumatology (ACR) ANCA-AV guidelines recommend:
    * In non-severe active disease, treatment with methotrexate or azathioprine in combination with glucocorticoids is recommended. Mycophenolate mofetil in combination with glucocorticoids is a second-line option.
    * In severe active disease, first-line treatment is rituximab in combination with low dose glucocorticoids. Cyclophosphamide (IV or oral) in combination with low dose glucocorticoids is another option for induction if previous treatment with rituximab has failed.
- Tavneos (avacopan) is not included in the guidelines, which were released prior to FDA approval of Tavneos (avacopan).

Primary immunoglobulin A nephropathy (IgAN) summary[28] [11-14]

- Primary IgAN (also known as Berger's disease) is an autoimmune kidney disease in which an overproduction of immunoglobulin A (IgA) accumulates and attacks the glomeruli, impairing the kidney's ability to filter. This results in blood and protein leaking into the urine, eventually leading to end stage renal disease (ESRD) in up to 40% of patients that live with IgAN ≥ 10 years.
- In clinical trials, sparsentan was shown to decrease proteinuria compared to placebo at 9 months.[29]SGLT2i have been shown to decrease proteinuria within 4-12 months of treatment.[30]
- The KDIGO guideline was last updated in 2021 and is currently under revision. Draft guidelines list ACEi/ARB, SGLT2i, sparsentan, and corticosteroids as standard of care for the management of IgAN but do not address Fabhalta (iptacopan).

Complement 3 glomerulopathy (C3G) and immune-complex membranoproliferative glomerulonephritis (IC-MPGN) summary[31-35]

- C3G and IC-MPGN are ultra-rare, progressive glomerular kidney diseases resulting from the dysregulation of the complement pathway (alternative and classical complement pathways, respectively), leading to the deposition of complement protein products in the glomeruli. When the glomeruli become obstructed and damaged, they lose their ability to filter blood effectively, causing toxin accumulation subsequent

kidney damage and eventual kidney failure.

- C3G encompasses two main subtypes: dense deposit disease (DDD) and C3 glomerulonephritis (C3GN).
- Both C3G and IC-MPGN are MPGN-associated conditions, characterized by an MPGN lesion on kidney biopsy. They share some overlapping pathological features but can be distinguished by immunofluorescence microscopy from a biopsy of the MPGN lesion, which identifies unique complement protein products associated with each respective condition.
- C3G is predominantly a primary type of glomerulopathy, where IC-MPGN can be primary or, more commonly, secondary. The cause of *primary* C3G or primary IC-MPGN are typically mutations in complement regulating proteins that cause excessive complement activation. Secondary IC-MPGN typically results from infection or an autoimmune disease and usually resolves with treatment of the underlying disease. In the clinical trials for Fabhalta (iptacopan) and Empaveli (pegcetacoplan), patients had *primary* types of C3G and IC-MPGN; patients with either recent infections or secondary causes (chronic infections, autoimmune disease, malignancies) were excluded.
- Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type-1 receptor blockers (ARBs) are first-line drugs to slow the progression of chronic glomerular disease through aggressive blood pressure control and reduction of proteinuria. Other conservative measures include dietary sodium and animal protein restriction, and cholesterol management.
- To target the inflammatory component of both conditions. corticosteroids and mycophenolate mofetil (MMF) for C3G, or corticosteroids alone or combined with immunosuppressants (MMF or cyclophosphamide) for IC-MPGN, may be used if conservative and supportive measures are insufficient. Several studies with corticosteroids (alone or with immunosuppressants) have demonstrated higher rates of proteinuria remission and an improved estimated glomerular filtration rate (eGFR), both of which are surrogate markers of kidney function. The effect of these guideline-recommended treatment options on true clinical outcomes such as the delay of end stage kidney disease (ESKD) progression or mortality is unknown.
- In pivotal trials, Fabhalta (iptacopan) demonstrated improvements in proteinuria, while Empaveli (pegcetacoplan) demonstrated improvements in both proteinuria and eGFR. The effect of these newer treatments on ESKD progression and mortality has not been established.
- Although sodium-glucose transporter-2 inhibitors (SGLT2i) have not specifically been studied in C3G, they have demonstrated significant benefits in large CKD trials which included patients with proteinuric CKD. They have been shown to reduce chronic kidney disease (CKD) progression, proteinuria, and cardiovascular events. SGLT2i have been shown to decrease proteinuria within 4-12 months of treatment.
- Soliris (eculizumab) is occasionally used off-label for rapidly progressive cases, but data for its use is sparse and of poor quality.
- Both graft rejection and C3G can occur together in kidney transplant recipients and are identified by distinct but sometimes overlapping histopathological features on allograft biopsy. Rejection is characterized by cellular or antibody-mediated injury with C4d and

donor specific antibodies (DSA), while C3G is defined by dominant C3 deposition (dominant C3 staining with minimal or absent immunoglobulin deposition) and complement pathway dysregulation.

- At 6 months, in the pivotal C3G trial for Fabhalta (iptacopan), patients treated with iptacopan demonstrated a 30% decrease in proteinuria, compared to an 8% increase in placebo-treated patients, resulting in a 35% treatment difference between iptacopan and placebo in the reduction of proteinuria. However, there was not a statistically significant difference in the change in eGFR from baseline between treatments.
- At 6 months, in the pivotal C3G and IC-MPGN trial for Empaveli (pegcetacoplan), patients treated with pegcetacoplan demonstrated a 67% reduction in proteinuria, compared to a 3% increase in placebo-treated patients, resulting in a 68% treatment difference between pegcetacoplan and placebo in the reduction of proteinuria. A stabilization of eGFR (surrogate measure of kidney function) from baseline favoring treatment with pegcetacoplan was also demonstrated.

In the absence of direct comparison evidence between Fabhalta (iptacopan) and Empaveli (pegcetacoplan), their relative safety and efficacy are unknown; therefore, the best treatment value is Empaveli (pegcetacoplan) for C3G.

Paroxysmal nocturnal hemoglobinuria (PNH)

Background

- PNH is a rare and life-threatening blood disorder, characterized by a reduced (type II) or deficient (type III) glycosylphosphatidylinositol (GPI)-linked proteins from the surface of red blood cells. The GPI-linked protein CD59 blocks the formation of the terminal complement complex, preventing cell lysis. In the absence of CD59, red blood cells are susceptible to complement-mediated lysis leading to anemia, hemoglobinuria, and other complications.
- There are few treatment options for patients with PNH.
    * Active monitoring of the patient is appropriate for those with mild disease; however, most will require palliative therapy. Treatment is not standard, as the approach to treatment is specific to the manifestations of each patient's disease. Blood transfusions, anticoagulation, and supplementation with folic acid or iron may be required. [36]
    * Allogeneic hematopoietic cell transplantation (HCT) is the only curative therapy for PNH and is typically reserved for only the most severe patients due to barriers such as high rates of morbidity and mortality, and lack of suitable donors. [37]
    * FDA-approved therapies for PNH include terminal complement inhibitors [C5 inhibitors Soliris (eculizumab), Ultomiris (ravulizumab-cwvz, and PiaSky (crovalimab)], and proximal inhibitors [Empaveli (pegcetacoplan), Fabhalta (iptacopan), Voydeya (danicopan)]. These treatments are not curative, so patients are treated indefinitely. [36]
- According to the American Society of Hematology (ASH) guidelines, complement inhibitor therapy should be considered in patients with significant symptoms from hemolysis that are not adequately managed with transfusion. Additionally, most patients included in clinical trials received transfusions prior to enrollment. [38]

- Thrombosis is a common manifestation of PNH and the leading cause of mortality in this population. Due to the severity of the condition, lack of treatment options, and long-term data that suggests efficacy in preventing thrombotic events, complement inhibitor therapy is appropriate for secondary prevention in patients who have experienced a cardiovascular event due to thrombosis, regardless of transfusion history. For patients with underlying bone marrow failure from aplastic anemia, therapy should target the underlying bone marrow failure, as these patients are less likely to experience benefit from complement inhibitor therapy. [36]

Clinical Efficacy

- The evidence for C5 inhibitors in PNH is based on phase 3 trials showing complement inhibitors stabilize hemoglobin and reduces the need for transfusions for patients with PNH compared to placebo or standard of care. [2] Overall survival has not been evaluated in controlled, clinical trials for complement inhibitors. However, thrombosis, the main cause of permanent disability and death in PNH, is largely mitigated by existing C5 inhibitor therapies based on clinical experience.
- *Soliris (eculizumab):*
    * The TRIUMPH study is a 26 week, double-blind, randomized, placebo-controlled, multicenter trial that evaluates the efficacy and safety of Soliris (eculizumab) in PNH in 87 patients who had at least 4 transfusions during the previous 12 months.
        - At the end of the treatment period, 49% of patients treated with Soliris (eculizumab) had stabilized hemoglobin in the absence of transfusions, which was not accomplished by any patients receiving placebo ($p<0.001$).
        - Transfusion independence was achieved in 51% of patients in the Soliris (eculizumab) group and was not achieved by any patients receiving placebo ($p<0.001$).
    * In a long-term study, up to three years, patients in the analysis experienced a sustained reduction in hemolysis, measured by lactate dehydrogenase levels, and a reduction in thromboembolic events. [39]
    * Expert consensus indicates that Soliris (eculizumab) decreases hemolysis, the resultant symptoms, thrombosis, and transfusion requirements. Soliris (eculizumab) should be considered in patients with significant symptoms from hemolysis that are not adequately managed with transfusion (Grade 1A recommendation). [38]
- *Ultomiris (ravulizumab-cwvz):* The evidence for Ultomiris (ravulizumab-cwvz) is based on two trials that compared it to Soliris (eculizumab). The trials demonstrated that Ultomiris (ravulizumab-cwvz) is not worse than Soliris (eculizumab) for the treatment of PNH. [3 40-42]
    * Both trials demonstrated Ultomiris (ravulizumab-cwvz) was noninferior to Soliris (eculizumab) for measurements of hemolysis and transfusion avoidance.
    * Ultomiris (ravulizumab-cwvz) carries the same safety concerns as Soliris (eculizumab) including a REMS program and safety warning about meningitis.

* There are ongoing clinical trials for Ultomiris (ravulizumab-cwvz) in conditions that have evidence for efficacy for Soliris (eculizumab).

- *Empaveli (pegcetacoplan):* The evidence for pegcetacoplan in PNH is primarily based on one randomized control trial (PEGASUS) in patients who were established on eculizumab and one interim phase 3 trial (PRINCE) in patients who were not on complement inhibitors at baseline.
    * The PEGASUS [43] study was a phase 3, randomized, open-label, 16-week active-control trial in 80 adults with PNH whose hemoglobin levels remained low despite treatment with eculizumab; at baseline, patients had over 6 transfusions in the 12 months prior to the study.
        - Patients in the pegcetacoplan arm demonstrated a superiority in change in hemoglobin level versus eculizumab from baseline to week 16 and noninferiority for transfusion avoidance. The benefits were sustained during the 32-week open label period. Two out of 41 patients in the pegcetacoplan group required dose escalation to 1,080 mg every 3 days.
    * The PRINCE study was a randomized, open-label, 26-week, controlled phase 3 trial in 53 adults with PNH who were not on complement inhibitors at baseline. The trial that compared pegcetacoplan with standard of care (excluding complement inhibitors).
        - Pegcetacoplan demonstrated superiority in the co-primary endpoints of hemoglobin stabilization and LDH reduction compared to standard of care. Hemoglobin stabilization was defined as less than 1g/dL decrease in hemoglobin levels in the absence of blood transfusions.
        - In addition, more patients on pegcetacoplan were transfusion-free compared to standard of care. 91% of patients on pegcetacoplan were transfusion free compared to 6% on standard of care.
- *Fabhalta (iptacopan)* was studied in two 24- week, open- label, phase III trials. APPLY-PNH compared Fabhalta (iptacopan) to C5 inhibitors in patients with residual anemia despite C5 inhibitor treatment. At baseline, a majority of patients had at least one transfusion in the 6 months prior to the trial. APPOINT-PNH was a single-arm trial that enrolled complement inhibitor-naïve patients; however, applicability is limited as a majority of patients were enrolled in China.[44 45]
    * Treatment with Fabhalta (iptacopan) resulted in statistically significant and clinically meaningful improvements in the hemoglobin level from baseline as well as greater avoidance of transfusions.
- *Voydeya (danicopan)* was studied in the ALPA trial as add-on to C5 inhibitors (eculizumab or ravulizumab) and was compared to placebo plus C5 inhibitors in patients with persistent anemia despite C5 inhibitor therapy.[46 47]
    * Treatment with add-on Voydeya (danicopan) resulted in statistically significant and clinically meaningful improvements in hemoglobin levels from baseline as well as greater avoidance of transfusions at 24 weeks versus placebo.

    * Known safety profile appears to be generally consistent with other complement inhibitors but long-term data is lacking in the setting of potential additive toxicity due to inhibition of both complement and proximal pathways.

- *PiaSky (crovalimab)* was evaluated in a randomized, open-label trial compared to Soliris (eculizumab) in patients naïve to complement inhibitors. [48]
    * PiaSky (crovalimab) demonstrated non-inferiority to Soliris (eculizumab) based on a similar percentage of patients achieving the primary co-endpoints of hemolysis control and avoidance of transfusion.
    * The known safety profile is similar to other complement inhibitors for PNH. PiaSky (crovalimab) has a Boxed Warning for the risk of serious and life-threatening infections caused by *Neisseria meningitidis* and requires a Risk Evaluation and Mitigation Strategy (REMS) program.

Atypical hemolytic uremic syndrome (aHUS)

Background

- Hemolytic uremic syndrome (HUS) is a condition caused by the premature destruction of red blood cells and is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (>95% of patients). [3] Acute presentation may also include neurological findings (including seizures), gastrointestinal symptoms, and cardiovascular involvement (including hypertensive emergency and acute coronary events. Chronic kidney disease (CKD) is the most common long-term sequelae, including the need for dialysis. [49]
    * The most common cause of HUS is infection, with most cases in the United States being associated with Shiga toxin-producing E. coli. There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of infectious-HUS.
    * Non-infectious HUS, known as atypical hemolytic uremic syndrome (aHUS), typically results from complement abnormalities. However, aHUS is a diagnosis of EXCLUSION, meaning the diagnosis of aHUS is made by excluding other primary thrombotic microangiopathy (TMA) syndromes, such as TTP or infectious HUS.
    * As a complement-related TMA, aHUS is also referred to as complement-related HUS. [3 37 50]
- Thrombotic thrombocytopenic purpura (TTP) is a group of syndromes in which patients usually present with thrombocytopenia and microangiopathic hemolytic anemia. Despite similarities in clinical features, the underlying mechanisms of aHUS and TTP differ, altering the manner in which patients respond to different therapies.
- TTP results from mutations in the gene encoding a disintegrin and metalloprotease with thrombospondin type 1 motif, 13 (ADAMTS13). Patients who are severely ADAMTS13 deficient, defined as ADAMTS13 activity <10%, have a confirmed diagnosis of TTP and may not respond to complement-inhibitor therapy.
    * There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of TTP. [50 51]

- Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) are FDA-approved for complement-mediated HUS (aHUS). There are no objective biomarkers to confirm a diagnosis of aHUS; however, TTP-HUS can be ruled out if severe ADAMTS13 deficiency is not present (ADAMTS13 activity ≥ 10%). As complement inhibitors, Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) target the underlying mechanism behind aHUS, binding to the complement protein C5 and prevent the formation of proinflammatory molecules. [52] However, complement testing is not universally used, as normal complement levels do not exclude a diagnosis of aHUS. [50]
- Prior to the availability of complement inhibitors, the treatment of choice for aHUS was plasma exchange/plasmapheresis (PLEX) or transfusion plus supportive care. Patients undergoing plasma exchanges are prone to complications including fluid-imbalance, catheter-related complications, and anaphylactic reactions. While most patients respond to plasmapheresis, patients remain at risk for chronic kidney injury. [52 53]

Clinical Efficacy

- The best available evidence for Soliris (eculizumab) in aHUS is limited to four phase 2, open-label, non-randomized, prospective, single-arm studies in populations. Two of the studies are not published at this time.
    * One study (n=17) in adolescent and adult patients who were resistant to plasma therapy and had impaired kidney function found a mean increase in platelet counts from baseline after treatment with Soliris (eculizumab) for a median length of 64 weeks. [4 54]
    * One study (n=20) in adolescent and adult patients with chronic renal impairment and no evidence of thrombotic microangiopathy found that 80% of patients treated with Soliris (eculizumab) achieved a thrombotic microangiopathy activity event-free status (defined as ≤ 25% decrease in platelet count and no plasma therapy, or new dialysis for ≥ 12 consecutive weeks). [4 54]
    * Two unpublished studies measured thrombotic microangiopathic (TMA) response in pediatrics (n=22) and adults (n=41), defined as hematological normalization and ≥ 25% improvement in serum creatinine from baseline. After a minimum of 26 weeks of treatment with Soliris (eculizumab), 64% of pediatric patients and 56% of adult patients achieved the primary endpoint. [4]
    * Reduction in mortality and other clinically meaningful endpoints have not yet been studied in a controlled clinical trial.
- The evidence for Ultomiris (ravulizumab-cwvz) for aHUS limited to two open-label, non-randomized, prospective, single-arm trials (one in adults, n=56; one in pediatric patients, n=16). [3]
    * Both trials assessed Complete TMA Response during the 26-week trial, defined as normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline.
    * After a minimum of 26 weeks of treatment with Ultomiris (ravulizumab-cwvz), 71% of pediatric patients and 54% of adult patients achieved the primary endpoint.

* The efficacy results are overall similar to trials of Soliris (eculizumab) for aHUS.

- Additional published studies that support the use of Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) in aHUS are limited to case studies and retrospective reviews.
- All studies of complement inhibitors in aHUS have significant limitations including an absence of control groups, open-label treatment, ambiguous recruitment techniques, and use of surrogate markers as primary endpoints. As such, the true benefit of Soliris (eculizumab) in aHUS is unclear and results should be interpreted with caution.
- There is interest in the use of higher doses of Ultomiris (ravulizumab-cwvz) for patients with incomplete control of symptoms. However, there is no data to support the safety and efficacy of dosing Ultomiris (ravulizumab-cwvz) more frequently than every 8 weeks in patients greater than 20 kg. There is insufficient evidence to establish the safety or efficacy for the use of Soliris (eculizumab) and/or Ultomiris (ravulizumab-cwvz) after kidney transplantation for patients with recurrent aHUS or other micro thrombotic condition-associated renal failure.
- There are no nationally published guidelines for the treatment of aHUS. National Health Service England has commissioned Soliris (eculizumab) for patients newly diagnosed with aHUS and for existing patients who are on dialysis and are suitable for a kidney transplant until a guideline is developed. [4]

Refractory myasthenia gravis (MG)

Background

- Myasthenia gravis (MG) is a rare autoimmune disease arising from T cell-dependent immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction, resulting in striated muscle weakness.
- MG presents with painless, fluctuating, fatigable weakness of specific muscle groups. Initially, patients most frequently present with ocular MG of the eyelids and extraocular muscles, presenting with asymmetric ptosis and diplopia. As weakness extends beyond ocular muscles, the disease progresses into generalized MG (gMG).
- Approximately 10-15% of all MG cases consist of refractory gMG that presents with severe debilitating muscle weakness despite substantial use of long-term corticosteroids or multiple steroid-sparing immunosuppressive agents, resulting in substantial negative effects on activities of daily living and quality of life.
- Complement inhibitors, Soliris (eculizumab), Ultomiris (ravulizumab-cwvz) and Zilbrysq (zilucoplan), provide newer treatment options for refractory gMG. While the clinical data is promising, there are several limitations in the body of evidence. Use should be limited to patients who have failed other options, as detailed in the coverage criteria.
- Standard therapies recommended by treatment guidelines for management of MG include acetylcholinesterase (ACh) inhibitors (pyridostigmine), corticosteroids, various DMARDs for immunosuppressant therapy (IST), intravenous immunoglobulin (IVIG), plasmapheresis/plasma exchange (PLEX), and thymectomy. [5-10]
    * Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms, by slowing the breakdown of acetylcholine at the neuromuscular junction. However, their use is limited as an adjunct therapy to immunotherapy

in those with residual or refractory MG or for treatment of ocular and mild gMG in those who cannot receive immune suppression. [7]

* Corticosteroids are the most widely used immune modulator for MG. Corticosteroids are effective in ocular MG and in patients with gMG with unsatisfactory responses to acetylcholinesterase inhibitors; however, they are associated with significant dose-dependent adverse events and should not be used for extended durations. [8]
* Azathioprine, cyclosporine, and mycophenolate mofetil are standard on-steroid immunosuppressant therapy (IST) and act as steroid-sparing agents. Other options include cyclophosphamide, methotrexate, and tacrolimus. [5 6 9]
    - Onset of effect is slow (up to 9-12 months). Once goals are met, steroids may be slowly tapered; however, many patients require long-term low-dose steroids for symptom control.
    - Guidelines recommend dose adjustments no more frequently than every 3 to 6 months.
    - Once treatment effective is achieved and doses are maintained for six months to two years of therapy, IST doses should be tapered to the lowest effect dose.
* Plasma exchange/plasmapheresis (PLEX) and IVIG provides short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing anti-idiopathic antibodies. However, IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid IST. [10]
* Patients with thymoma should undergo thymectomy. In non-thymomatous patients, thymectomy is a treatment option to minimize need for immunotherapy (either avoid, dose minimize or use for refractory MG symptoms). However, thymectomy may not be medically possible in unstable MG patients. [5 6]

Clinical Efficacy

- The evidence for complement inhibitors in MG is limited. In the pivotal phase 3 trials of Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Zilbrysq (zilucoplan), the active treatment arm improved functional scores in patients with refractory generalized MG compared to placebo [REGAIN [55] for Soliris (eculizumab), CHAMPION-MG [56] for Ultomiris (ravulizumab-cwvz), and RAISE [57] for Zilbrysq (zilucoplan)], a surrogate for MG symptoms.
    * Patients in who were included in the efficacy analyses of pivotal trials had a MG severity classification of MGFA Class II to IV, MG-ADL score 6 or higher, and positive serologic test for anti-AChR antibodies.
    * In addition, patients in REGAIN failed ≥2 ISTs or ≥1 IST and required chronic plasma exchange or IVIG for over 1 year. 98% of patients were on ≥2 ISTs and 52% of patients were on ≥3 ISTs for an average length of 2.5 to 7.3 years prior to enrollment. Patients in CHAMPION-MG and RAISE were not required to have prior therapies.

    * In REGAIN, the primary endpoint was the mean difference of scores from baseline to week 26 of MG-ADL measured by worst-rank ANCOVA, which showed Soliris (eculizumab) was not significantly better than placebo (p=0.0698). MG-ADL is a scoring tool used in clinical practice, along with MG composite score, for monitoring progression of MG and response to therapies.
    * FDA-approval was based on non-primary sensitivity analysis outcomes with statistical significance but the magnitude of mean total score differences were insufficient to represent clinically meaningful improvement. However, it should be noted that several subjects left the trial for reasons unrelated to their MG, which affected the statistical analysis of the worst-rank ANCOVA.
    * The primary endpoint of change from baseline in MG-ADL score to week 26 was met in CHAMPION-MG. Ultomiris (ravulizumab-cwvz) also demonstrated improvements in MG-ADL muscle strength, and quality life, sustained through 60 weeks in an open-label extension.
    * The primary endpoint of change from baseline in MG-ADL score to week 12 was met in RAISE; the results represented both clinically meaningful and statistically significant improvements from baseline. Zilbrysq (zilucoplan) also demonstrated improvements in QMG score.
    * Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Zilbrysq (zilucoplan) have not been studied in patients with less severe MG, including patients with MFGA Class I or those responding to IST therapy. In addition, there is no evidence for the use in patients in myasthenic crisis (Class V).

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Background [11-14]

- NMOSD, also known as Devic disease or neuromyelitis optica (NMO), is a chronic demyelinating disease of the central nervous system dominated by inflammation of the optic nerve and spinal cord and may often be misdiagnosed as multiple sclerosis (MS).
- Stepwise deterioration due to disease relapse/attack causes an accumulation of disability. Hallmark features of NMOSD include acute nerve inflammation that led to severe visual loss, limb weakness, sensory loss, pain, paralysis, bladder dysfunction, and intractable nausea/vomiting and hiccups.
- Patients with NMOSD are treated for acute episodes/ relapse with steroids. Plasma exchange (PLEX) is used acutely for incomplete response to steroids.
- Immunosuppressive therapy (IST; corticosteroids, azathioprine, mycophenolate mofetil, or rituximab) is therapy to reduce the frequency of relapse (maintenance therapy).

Clinical Efficacy

- The evidence for Soliris (eculizumab) in NMOSD is limited. One phase 3, time-to-event trial showed that Soliris (eculizumab) reduced the frequency of first adjudicated relapse compared to placebo (PREVENT).[12]
    * Patients enrolled in the trial had “highly active” disease defined as two relapses in the past year or three relapses in the past two years, with one of those in the last year; baseline annualized relapse rate was 2, median Expanded Disability

Status Scale (EDSS) 4; 76% of patients were on immunosuppressive therapy at baseline and 32% had previous rituximab treatment.

* In PREVENT, the primary endpoint of first adjudicated relapse occurred in 3% of the Soliris (eculizumab) arm versus 43% in the placebo arm, HR 0.06 [95% CI 0.02 to 0.20]. At 144 weeks, 96.5% of patients in the Soliris (eculizumab) group and 45.4% in the placebo group remained relapse- free.
* Key secondary endpoints included change from baseline in functionality and patient-reported health outcomes as measured by EDSS as well as the modified Rankin Scale, Hauser Ambulation Index, and EQ-5D-3L. The first measure, EDSS, did not reach statistical significance. However, the remaining measures trended in favor of the treatment group.

- The evidence for Ultomiris (ravulizumab-cwvz) in NMOSD is limited to one phase 3, open-label, external control trial (N=58), CHAMPION-NMOSD[58], that demonstrated Ultomiris (ravulizumab-cwvz) reduced the frequency of first adjudicated relapse compared to historical control (placebo arm of the PREVENT trial).
  * No patients taking ravulizumab (n = 58) had an adjudicated relapse (during 84.0 patient-years of treatment) versus 20 patients with adjudicated relapses in the placebo group of PREVENT (during 46.9 patient-years; relapse risk reduction = 98.6%, 95% confidence interval = 89.7%–100.0%, p < 0.0001).
- Guidelines recommend treatment of acute episodes/ relapse and use of maintenance immunosuppressive therapy (IST), to reduce the frequency of relapse). [11 14 17 18 59]
  * Treatment of Relapse: Patients are usually treated with 1 g of intravenous (IV) methylprednisolone (IVMP) for 3–5 days. Relapses that do not respond to IV steroids may benefit from five to seven plasma exchange (PLEX) procedures over a 2-week period. Oral prednisone (1 mg/kg) for 1–6 months can be initiated after IVMP or PLEX to ensure a prolonged effect on inflammation until steroid-sparing immunosuppressants take effect.
  * Maintenance Therapy: A variety of immunosuppressive therapy (IST) are regarded by many clinicians as first-line therapy based on primarily observational or single-arm data. The most widely prescribed treatments include corticosteroids, azathioprine, mycophenolate mofetil, and rituximab. The use of azathioprine and mycophenolate mofetil has fallen out of favor due to lack of efficacy. However, if given, they are often prescribed with low doses of corticosteroids. Rituximab has evidence for reduction of relapse rates and disability in NMO, based on one RCT (n=68) and dozens of case series, including in patients who fail oral immunosuppressive treatments. [16 18-21] Paradoxical relapses may occur shortly after initiation of rituximab therapy so it is important to allow enough time for the rituximab to become effective. Complete suppression of CD19+B lymphocytes takes one month. [21]

CD55-defiecent protein-losing enteropathy (CHAPLE disease)

Background [22]

- CHAPLE disease is a recently discovered, ultra-rare, recessive disorder, caused by mutations in the CD55 gene, leading to an overactivation of the complement system, resulting in intestinal protein loss (albumin and immunoglobulins) due to damage in blood and lymph vessels along the digestive tract.
- The spectrum of severity for CHAPLE disease is not fully characterized, however it typically presents early in childhood, causing high rates of morbidity that manifest as peripheral and visceral edema (due to severe hypoalbuminemia), diarrhea, abdominal pain, hypogammaglobulinemia, malabsorption, malnutrition, infections, and impaired growth, with severe and fatal vascular occlusions being the leading cause of mortality.
- Diagnosis of CHAPLE disease is based on clinical signs and symptoms, with confirmation via positive genetic test for CD55 loss of function mutation.
- Currently there are no consensus guidelines for CHAPLE treatment, as the only guidance has been limited to case reports and small natural history studies.
- Most treatment focuses on addressing patients' symptoms with supportive care including corticosteroids, IV albumin and immunoglobulin (IVIG/SCIG), nutrition supplementation, and anticoagulation to prevent thrombosis

Clinical Efficacy

- The evidence for use of Soliris (eculizumab) in CHAPLE disease is limited to one small observational study of 16 patients with a confirmed CD55 loss of function mutation and severe CHAPLE disease manifestations requiring frequent hospitalizations, albumin, and immunoglobulin transfusions.[60]
    * Patients received Soliris (eculizumab) off label, with treatment effects observed over an average of 20 months.
    * All patient achieved normalization of their serum albumin within 2-4 weeks and remained normal for 6 months or longer.
    * The majority patients (12 of 16) no longer required any hospitalizations or transfusions, and most previous treatment interventions became unnecessary.
    * Although the evidence is of lower quality (non-controlled), Soliris (eculizumab) is the standard of care treatment option for patients with severe CHAPLE disease manifestations requiring frequent hospitalizations, albumin, and immunoglobulin transfusions.
- The evidence for Veopoz (pozelimab) obtaining FDA approval is limited to the ongoing 1878 trial (n=10), a small, phase 2/3, international, multicenter, open-label, single arm trial , of patients with confirmed, active CHAPLE disease.[22 61]
    * The trial included only patients with genetically confirmed (CD55 loss of function mutation) and symptomatic CHAPLE disease with a serum albumin of <3.2 g/dl (baseline average was 2.18 g/dl).
    * A control was generated using the patient's pretreatment medical histories to compare to post-treatment with Veopoz (pozelimab).

* Patients received a 30 mg/kg loading dose of Veopoz (pozelimab) on day 1, followed by 10 mg/kg weekly thereafter for up to 144 weeks.
* All patients (10/10) achieved the primary efficacy endpoint of normalized serum albumin (≥3.5 g /dl) by week 12 and maintained it through week 72 at the most recent analysis.
* Secondary endpoints supporting efficacy were the decrease in hospitalization days post treatment (268 days prior to treatment vs only 7 after treatment) and total number of albumin transfusions pre and post treatment (60 vs 1).

- Although both Soliris (eculizumab) and Veopoz (pozelimab) have shown some efficacy in CHAPLE disease, the available evidence for efficacy is of low quality for both. However, there is significantly more safety experience with Soliris (eculizumab) with years of real-world use and is significantly less costly than Veopoz (pozelimab). Therefore, the use of Veopoz (pozelimab) for patients with confirmed CHAPLE disease is coverable only in patients who have had an insufficient response or intolerance to Soliris (eculizumab).

Antineutrophil cytoplasmic antibody-associated vasculitis (ANCA-AV) (MPA or GPA) [23 25 27]

Background *[23-27]*

- ANCA-AV is a rare multisystem autoimmune disease caused by inflammation and necrosis of the small and medium arteries. ANCA-AV includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (EPGA, formerly known as Churg-Strauss syndrome). However, EPGA is clinically and pathologically different from GPA and MPA.
- ANCA-AV patients usually present with nonspecific symptoms (fever, malaise, myalgias, and arthralgias) and are commonly misdiagnosed, so testing for ANCA antibody is key and tissue biopsy is confirmatory.
- The 2021 American College of Rheumatology (ACR) ANCA-AV guidelines recommend treatment based on severity of disease and organ involvement, with the goals of inducing remission and maintaining remission, as follows:
  * Non-severe active disease (without organ involvement or non-life-threatening):
    - First-line options for induction of remission as well as maintenance of remission include methotrexate or azathioprine in combination with glucocorticoids. Mycophenolate mofetil in combination with glucocorticoids is a second-line option if methotrexate or azathioprine is contraindicated or not tolerated.
  * Severe active disease (with organ involvement or life-threatening manifestations):
    - First-line treatment for induction of remission is rituximab in combination with low dose glucocorticoids. Cyclophosphamide (IV or oral) in combo with low dose glucocorticoids is another option for induction if previous treatment with rituximab has failed.
    - Once remission has been induced, rituximab is used as first-line treatment for the maintenance of remission. Use of oral

immunosuppressants such as methotrexate, azathioprine, and mycophenolate mofetil are used as maintenance options if rituximab is not tolerated or contraindicated.

* Tavneos (avacopan) is not included in the guidelines, which were released prior to FDA approval of Tavneos (avacopan).

Clinical Efficacy

- The evidence for Tavneos (avacopan) obtaining FDA approval was based on one phase 3 trial. The trial was a double-blind active-controlled RCT (ADVOCATE) concluding that Tavneos (avacopan) was non-inferior to standard of care for induction and maintenance of remission in patients with ANCA-AV (MPA or GPA) (n=331). Given the lack of superior benefit versus the standard of care, and availability of effective lower-cost treatment options, the use of Tavneos (avacopan) is coverable only in patients with severe active ANCA-AV (GPA or MPA) who have previously failed standard induction therapy or relapsed since achieving remission in the past 12 months.
    * Patients enrolled in the trial had either newly diagnosed active severe ANCA-AV (69%) or relapsed active severe ANCA-AV (31%). Active severe ANCA-AV is defined by ACR guidelines as new, persistent, or worsening clinical signs or symptoms attributed to GPA or MPA that has organ or life-threatening manifestations.
    * In the trial these patients had to have one major Birmingham Vasculitis Activity Score (BVAS) item, 3 non-major items, or two renal items of hematuria and protein urea. BVAS is the clinical trial standard measure for ANCA-AV remission scoring with score of 0 being complete remission. The average BVAS score in both arms was 16.3, which indicates active severe disease.
    * The breakdown of patients with GPA vs MPA in the trial was 55% to 45%, respectively. Patients that had EGPA were excluded from this trial as EPGA is clinically and pathologically different and is therefore excluded from trials involving ANCA-AV.
    * Patients were randomized to Tavneos (avacopan) or 20-week steroid taper in addition to investigator-choice standard of care induction therapy with rituximab or cyclophosphamide. Patients in both arms were still allowed to receive additional non-study supplied steroids. In addition, the patients who received oral or IV cyclophosphamide received standard of care maintenance therapy with azathioprine beginning at week 15 till week 52, while the rituximab patients received no standard of care maintenance treatment.
        - 36% of patients in each arm received cyclophosphamide.
        - 65% of patients in each arm received rituximab.
    * Primary endpoints were remission at week 26 (BVAS of 0) and sustained remission at week 52 (BVAS of 0).
    * Results of the ADVOCATE trial showed that the Tavneos (avacopan) arm of the trial was non-inferior to standard of care at inducing remission and sustaining remission at week 52. Tavneos (avacopan) only showed superiority when compared to placebo (not standard of care) at week 52. The trial failed to prove

superiority and only showed non-inferiority when compared to current standard of care. As a result, the FDA approved labeled indication for Tavneos (avacopan) is for add-on therapy only.

* Factors which may impact the accuracy, applicability, and generalizability of the results for this trial include but are not limited to the following:
    - During the study, 86% of the Tavneos (avacopan) arm and 90% of the steroid arm received non-study supplied steroids.
    - The patients who received azathioprine for standard of care maintenance of remission treatment showed no difference between Tavneos (avacopan) and placebo at week 52.
    - Patients' response to Tavneos (avacopan) based on investigator BVAS scale scoring supported only non-inferiority when compared to placebo at week 52.
    - Secondary endpoints of this study included a novel glucocorticoid toxicity index scoring tool (GTI), that was determined by FDA to be not fit for its purpose and of no relevance to the benefit of avacopan in this trial. Other secondary endpoints included change in EGFR, quality of life measures (EQ-5D-5L and SF-36), and improvement of urinary albumin to creatinine ratio, all of which provide no clinical meaningful treatment benefit of Tavneos (avacopan) and were not adjusted for multiplicity.
* Sub-group analysis in patients treated with Tavneos (avacopan) who were newly diagnosed (69%) compared to the patients who had relapsed (31%), showed significant difference in the response to Tavneos (avacopan). The newly diagnosed patient's response rate of Tavneos (avacopan) compared to the prednisone arm was 66.1% vs 66.7% at week 26 and 60.9% vs 57.9% with neither being significant. Whereas the relapsed patients showed a much higher response rate to Tavneos (avacopan) compared to prednisone of 86.3% vs 78% at week 26 and 76.5% vs 48% at week 52.

- Given the lack of evidence to establish Tavneos (avacopan) is superior to placebo as add-on to current standard of care, and the availability of effective lower-cost treatment options, the use of Tavneos (avacopan) for severe active ANCA-associated vasculitis will only be coverable in patients who have previously failed standard induction therapy or have relapsed since achieving remission in the past 12 months.

<u>Primary immunoglobulin A nephropathy (IgAN)</u>[29 30 44 62-65]

Background

- Primary IgAN (also known as Berger's disease) is an autoimmune kidney disease in which an overproduction of immunoglobulin A (IgA) accumulates and attacks the glomeruli, impairing the kidney's ability to filter. This results in blood and protein leaking into the urine, eventually leading to end stage renal disease (ESRD) in up to 40% of patients that live with IgAN ≥ 10 years.
- IgAN can occur at any age, but most commonly patients are diagnosed between their 20s and 30s with symptoms presenting as: hematuria, proteinuria, flank pain, high blood pressure, and swelling.

- Kidney biopsy is the only confirmatory test to diagnosis primary IgAN.2021 Kidney Disease Improving Global Outcomes (KDIGO) glomerular diseases guideline recommends treating primary IgAN by first optimizing supportive care (including diet, exercise, and risk modification; see Appendix 2) as well as starting the patient on max tolerated dose of ACEi/ARB with goal of reducing proteinuria < 1g/day.
- The KDIGO guideline was last updated in 2021 and is currently under revision. Draft guidelines list ACEi/ARB, SGLT2i, sparsentan, and corticosteroids as standard of care for the management of IgAN but do not address Fabhalta (iptacopan).

Evidence for Fabhalta (iptacopan) for IgAN

- Fabhalta (iptacopan) received an accelerated approval for the reduction of proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g, according to the labeled indication.
- Accelerated approval was based on reduction of proteinuria; slowing of kidney function decline has not been established.
    * The evidence for Fabhalta (iptacopan) in IgAN is based on the pre-specified interim analysis results of the phase 3 APPLAUSE-IgAN trial. This trial enrolled adults with biopsy-proven primary IgAN who continued to experience proteinuria despite being on a maximally tolerated renin-angiotensin-aldosterone system inhibitor (RAASi) for at least 3 months, with or without a SGLT2i. Patients continued on concomitant maximally tolerated RAASi during the study if tolerated.
    * Patients were required to have a UPCR >1g/g for trial entry but had a median of 1.84 g/g.
    * At the interim analysis of 9 months, proteinuria was reduced by 44% in the Fabhalta (iptacopan) group compared with 9% with placebo. Although proteinuria is an important surrogate marker for kidney disease, it is not directly correlated to outcomes such as mortality or morbidity, and continued FDA approval is contingent on the demonstration of benefit in slowing kidney function decline.

Evidence for other treatment options for IgAN:[66]

- Two other medications approved for IgAN, Filspari (sparsentan) and Tarpeyo (budesonide), received full FDA approval for IgAN after demonstrating reductions in kidney function decline. However, none of the medications approved specifically for IgAN have been compared to each other in a randomized clinical trial. Therefore, the relative efficacy is unknown. As such, the use of these therapies is coverable only when the less costly alternative is ineffective, not tolerated, or use if contraindicated.
    * Results from the TESTING trial, which looked at the effect of methylprednisone on decline in kidney function in patients at risk of progressive kidney function loss with IgAN, showed methylprednisone significantly met the primary composite endpoint of reducing risk of kidney function decline (40% decline in EGFR), kidney failure (dialysis or transplant), or death when compared to placebo over a mean of 4.2 years, with 74 patients (28.8%) having primary composite endpoint occur in the methylprednisone arm compared to 106 (43.1%) in the placebo arm.

    * Studies suggest that SGLT2i may have beneficial effects on kidney outcomes in patients with IgAN, including reducing proteinuria and slowing kidney function decline. In addition, the DAPA-CKD trial demonstrated that dapagliflozin, an SGLT2i, reduced the risk of major adverse kidney events in patients with IgAN.

- Although Fabhalta (iptacopan) demonstrated improvement in an important surrogate disease marker over placebo, the available evidence for efficacy is of low quality and no clinical outcomes data are available at this time. Due to the availability of effective lower-cost treatment options with more robust efficacy data, the use of Fabhalta (Iptacopan) for primary IgAN will only be coverable in patients who have exhausted other options as listed in the coverage criteria.

Complement 3 Glomerulopathy (C3G) and Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN) [35 67]

Background

- C3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) are rare, complement-mediated glomerular diseases.
- While C3G and IC-MPGN are clinically distinct, they share overlapping pathogenic mechanisms (dysregulation of complement pathways) and presentations.
- Both C3G and IC-MPGN are membranoproliferative glomerulonephritis (MPGN) type disorders. MPGN, defined by the presence of an MPGN lesion from a kidney biopsy, is classified based upon the underlying pathogenic process, including immune complex-, monoclonal immunoglobulin- or complement dysregulation-mediated disease. C3G and IC-MPGN can be distinguished by the presence or absence of various complement fragment deposits such as C3 fragments or immune complexes (deposits of antigens, antibodies and complement protein fragments) using immunofluorescence microscopy.
- Clinical features of MPGN type conditions include hematuria, proteinuria, decreased estimated glomerular filtration rate (eGFR), hypertension, edema, and swelling. Left untreated, MPGN leads to progressive inflammation, declining kidney function, and eventual kidney failure in more than 50% of patients within 10 years of diagnosis.

Evidence for Fabhalta (iptacopan) in C3G

- The evidence for the use of Fabhalta (iptacopan) in C3G was demonstrated in the APPEAR-C3G trial in adult patients with biopsy-confirmed native kidney C3G. There is no evidence for safety and efficacy for the use of Fabhalta (iptacopan) in patients with active organ rejection. [68-71]* Patients in the trial had a urine protein-to-creatinine ratio (UPCR) ≥ 1 g/g, eGFR ≥ 30 mL/min/1.73 m^2, and reduced serum C3 levels (<77 mg/dl) despite being on maximally tolerated ACE inhibitor/ ARB for at least 90 days. Patients with rapidly progressive crescentic GN renal biopsy with interstitial fibrosis/tubular atrophy >50% were excluded from the trial.
    * At baseline, 45% of patients were on corticosteroids and/or mycophenolate mofetil/sodium (MMF/MPS) and 99% of patients were on an ACE inhibitor/ARB. All background therapies were required to be at stable doses for at least 90 days.

* During the 6-month randomized, double-blind period, patients received Fabhalta (iptacopan) or placebo in addition to supportive care, followed by a 6-month open-label period with all patients on Fabhalta (iptacopan).
* At 6 months, patients taking Fabhalta (iptacopan) showed a 30% decrease in proteinuria compared to an 8% increase in the placebo group, resulting in a statistically significant 35% difference between treatments; this reduction was sustained during the open-label phase. There was no statistically significant difference between iptacopan and placebo in stabilizing the estimated glomerular filtration rate (eGFR).

Evidence for Empaveli (pegcetacoplan) in C3G and IC-MPGN

- The evidence for Empaveli (pegcetacoplan) in C3G and IC-MPGN was demonstrated in one clinical trial in patients with either C3G or primary IC-MPGN. About 76% of patients had C3G, and 24% had IC-MPGN.[72]
  * Patients in the trial had a UPCR of ≥ 1 g/g per day, eGFR ≥ 30 mL/min/1.73 m^2, and were on a stable regimen of an ACE inhibitor/ARB, or an SGLT2 inhibitor.
  * Patients with glomerulopathy due to secondary causes (such as infection, autoimmune diseases) were excluded from the trial.
  * At baseline, 40% of patients were on corticosteroids, 72% on immunosuppressants, and 92% were on an ACE inhibitor/ARB, all of which were continued throughout the trial at stable doses.
  * For 26 weeks patients received either pegcetacoplan or placebo in addition to supportive care.
  * At 26 weeks, patients taking pegcetacoplan showed a 67% reduction in proteinuria (UPCR) compared to a 3% increase in placebo-treated patients, resulting in a statistically significant 68% treatment difference. The difference between treatment groups in the change in the estimated glomerular filtration rate (eGFR) was 6.3 mL/min/1.73m^2, favoring treatment with pegcetacoplan.

Investigational Uses

- Soliris (eculizumab) has been studied in a variety of other conditions. Due to lack of published data, lack of high-quality data, or lack of positive data these conditions are considered investigational. [73-80]
- There is interest in the use of Ultomiris (ravulizumab-cwvz) for patients with recurrent IgAN. However, there is insufficient evidence to establish the safety or efficacy of Ultomiris for IgAN. Trials are ongoing.[80]
- One Phase 2/3 trial (PROTECT) evaluated Soliris (eculizumab) versus placebo in kidney transplant patients at high risk of delayed graft function (DGF). The trial failed to show a statistically significant difference in the incidence of DGF, death, graft loss, or discontinuation at seven days following a transplant (35.9% in Soliris (eculizumab) vs. 41.7% in placebo, p = 0.398). [80]

- Ultomiris (ravulizumab-cwvz), another complement inhibitor, is not coverable for other indications, except as listed in the coverage criteria. Despite being a derivative of Soliris (eculizumab), there is insufficient evidence at this time to establish the safety or efficacy of Ultomiris (ravulizumab-cwvz) for other indications, including MG. In addition, the dose of Ultomiris (ravulizumab-cwvz) for other indications is unknown.
- An intravitreal formulation of pegcetacoplan (Syfovre) is now available for geographic atrophy secondary to age-related macular degeneration (AMD). There is no evidence for use of IV pegcetacoplan (Empaveli) for AMD.
- Tavneos (avacopan) has been studied in a variety of other conditions including aHUS and C3 glomerulonephritis. Due to lack of published and positive data, these conditions are considered investigational. [81 82]
- Veopoz (pozelimab) is being studied in a variety of other conditions including PNH and MG. Due to lack of published and positive data, use of Veopoz (pozelimab) in these conditions is considered investigational.[22]
- Although Fabhalta (danicopan) was studied in C5-inhibitor naïve PNH, the study was of poor quality (N=40, single-arm) with limited applicability to patients in the United States (half were from China, which has different standards of care).[44]
- There is no evidence for the use of endothelin receptor antagonists for kidney disease (such as Filspari [sparsentan] or Vanrafia [atrasentan]) with Fabhalta (iptacopan) for primary IgAN.

Safety [3 61 75 83]

- Complement inhibitors (as listed in *Table 1*) all carry a boxed warning for life-threatening and fatal meningococcal infections. Patients should be immunized with a meningococcal vaccine at least 2 weeks prior to the first dose of complement inhibitors (as listed in *Table 1*) unless the risks of delaying complement inhibitor therapy outweigh the risks of developing a meningococcal infection.
- There is a Risk Evaluation and Mitigation Strategy (REMS) program in place for Empaveli (pegcetacoplan), Fabhalta (iptacopan), Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), Voydeya (danicopan), and Zilbrysq (zilucoplan). The purpose of the REMS program is to mitigate the occurrence and morbidity associated with meningococcal infections. Providers must be certified by the REMS program to prescribe complement inhibitors.
- There was one death related to Soliris (eculizumab) in clinical trials. The patient was part of the PREVENT trial for NMOSD and died due to pulmonary empyema.
- In trials, there was a higher incidence of hepatoxicity, hypersensitivity, and hepatitis B virus (HBV) reactivation with use of Tavneos (avacopan) compared to standard of care. Patients should be screened prior to initiation of treatment as well as monitored throughout treatment.

Administration and Dosing [3 75 84]

- Supplemental dosing: Some interventions such as plasma exchange/plasmapheresis (PLEX), fresh frozen plasma (FFP), and intravenous immunoglobulin (IVIg), have been shown to reduce eculizumab or ravulizumab serum levels.
    * In patients with aHUS or MG receiving concomitant PLEX or FFP, supplemental dosing, and frequency of Soliris (eculizumab) varies.
    * Supplemental dosing for Ultomiris (ravulizumab-cwvz) in the setting of PLEX and IVIG also varies, based on the most recent dose of Ultomiris (ravulizumab-cwvz) and the intervention.
    * Of note: use of ongoing maintenance IVIG therapy, in combination with maintenance complement inhibitor therapy is considered investigational, beyond a transition period.
- Soliris (eculizumab): For breakthrough hemolysis in PNH:
    * Soliris (eculizumab) dosing may be adjusted to 900 mg every 12 days instead of every 14 days. In the pivotal trial for the FDA labeled dose, 900 mg every 14 days, plus or minus 2 days, was used, such that 900 mg every 12 days is considered coverable per label, when there is breakthrough hemolysis.
    * There is also limited data that doses of 1200 mg every 14 days have been used for breakthrough; however, since it is more costly without proven benefit over 900 mg every 12 day dosing, it is considered 'not medically necessary.' [85 86]
    * No additional benefit is observed above the recommended dose.
- Empaveli (pegcetacoplan):
    * For lactate dehydrogenase (LDH) levels greater than 2 × the upper limit of normal (ULN), Empaveli (pegcetacoplan) dose may need to be adjusted to 1,080 mg every three days based on limited data. [84]

Cross References
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Uplizna, inebilizumab, Medication Policy Manual, Policy No. dru657
Neonatal Fc Receptor (FcRn) Antagonists, Medication Policy Manual, Policy No. dru696
Tarpeyo, budesonide delayed-release capsules, Medication Policy Manual, Policy No. dru712
Endothelin Receptor Antagonists for Kidney Disease, Medication Policy Manual, Policy No. dru752
Complement Inhibitors for the Eye, Medication Policy Manual, Policy No. dru762

Codes	Number	Description
HCPCS	Q5152	Injection, eculizumab-aeeb (Bkemv), 2 mg
HCPCS	Q5151	Injection, eculizumab-aagh (Epysqli), 2 mg
HCPCS	J1307	Injection, crovalimab-akkz (Piasky), 10 mg
HCPCS	J1299	Injection, eculizumab (Soliris), 10 mg
HCPCS	J1303	Injection, ravulizumab-cwvz (Ultomiris), 10 mg
HCPCS	J9376	Injection, pozelimab-bbfg (Veopoz), 1 mg

Appendix 1: Medications that may unmask or worsen myasthenia gravis *[73]
Aminoglycosides
Amantadine
Anti-arrhythmics (procainamide, propafenone, quinidine)
Antiepileptics (various, carbamazepine, gabapentin, phenytoin, etc.)
Cancer immunotherapies, including but not limited to: Anti-programmed death receptor-1 monoclonal antibodies (PD1s, PDL-1s; Opdivo [nivolumab], Keytruda [pembrolizumab], etc.) Yervoy (ipilimumab) Provenge (sipuleucel-T)
Antihistamines (diphenhydramine)
Beta-blockers
Calcium channel blockers (felodipine, verapamil)
Colchicine
Erythromycins (azithromycin, clarithromycin, clindamycin)
Plaquenil (hydroxychloroquine)
Interferons (various)
Lithium
Magnesium
Neuromuscular blockers (succinylcholine, etc.)
Opioids
Phenothiazines (haloperidol)
Proton pump inhibitors (lansoprazole, omeprazole)
Quinine
Quinolones (ciprofloxacin, levofloxacin, etc.)
Statins (pravastatin, etc.)

*Including but not limited to this list. Medication lists will be reviewed in full versus compendium (such as DrugDex).

Appendix 2: KDIGO 2021 Guidelines for Optimizing Supportive Therapy in Primary IgAN[28]
Target systolic blood pressure in most adult patients to <120 mm Hg
Assess cardiovascular risk and address appropriately
Restrict Dietary Sodium intake to <2 g daily
Target ideal body weight
Smoking cessation
Exercise regularly

Appendix 3: Adequate glucocorticoid dosing regimens used for patients at risk of progressive kidney function loss with IgAN in the most recent clinical trials[28 64 87]		
Medication	**Initial dose**	**Duration of initial dose for response**
Methylprednisone	0.4 to 0.8 mg/kg/d rounded to nearest 4 mg. Max dose 48 mg/day	2 months
Prednisone	0.8 to 1 mg/kg/day	2 months
Tarpeyo (budesonide, delayed release)	16 mg daily	9 months

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Revision History

Revision Date	Revision Summary
1/22/2026	• Updated quantity limit and table references with no change to intent. • Added new indication for Empaveli (pegcetacoplan) for the treatment of C3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN). • Removed requirement for documentation of reduced serum C3 (<77mg/dL) for complement 3 glomerulopathy (C3G). • Added step therapy for Fabhalta (iptacopan) with Empaveli (pegcetacoplan) in C3G. • Added secondary IC-MPGN to investigational uses.
10/02/2025	• Added the new FcRn antagonist, Imaavy (nipocalimab), as another step therapy option for generalized myasthenia gravis. • Clarified that the MG-ADL score refers to the *total* score (no change in intent).
7/10/2025	• Added Fabhalta (iptacopan) for complement 3 glomerulopathy (C3G). • Added criteria for primary immunoglobulin A nephropathy (IgAN) that Fabhalta (iptacopan) must be used in conjunction with an ACEi/ARB and continued for reauthorization. • Added investigational use of Fabhalta (iptacopan) with an endothelin receptor antagonist (ERA) for primary immunoglobulin A nephropathy (IgAN). • Added unbranded Epysqli, eculizumab-aagh, to policy at parity with Soliris. • Changed Epysqli (eculizumab-aagh) to a preferred eculizumab product. Soliris (eculizumab) and biosimilars Bkemv (eculizumab-aeeb) and unbranded eculizumab-aagh require step through Epysqli (eculizumab-aagh). • Updated Soliris HCPCS from J1300 to J1299.
4/3/2025	Updated quantity limit with no change to intent.
12/12/2024	• Added Fabhalta (iptacopan) for primary immunoglobulin A nephropathy (IgAN). • Added PiaSky (crovalimab) for paroxysmal nocturnal hemoglobinuria (PNH). • Added Soliris biosimilars, Bkemv and Epysqli, to policy.
6/20/2024	• Added Fabhalta (iptacopan) and Voydeya (danicopan) for treatment-experienced PNH. • Fabhalta (iptacopan) for treatment-naïve PNH is investigational due to poor quality of evidence. • High-dose Soliris (eculizumab) modified to not medically necessary (NMN), as several options are now available for breakthrough PNH. • Removed Empaveli (pegcetacoplan) ST through Ultomiris (ravulizumab) in treatment naïve PNH to align with standard of care.

Revision Date	Revision Summary
3/21/2024	Readded weight specification to *Table 2* Initial Authorization dosing for NMOSD.
12/7/2023	• Added newly FDA-approved Veopoz (pozelimab) to policy. Limits coverage to patients diagnosed with genetically confirmed CHAPLE disease by a specialist, when previous treatment with Soliris (eculizumab) has been ineffective or not tolerated. • Added Zilbrysq (zilucoplan) to policy for generalized myasthenia gravis (gMG). • Simplified coverage criteria for gMG. The baseline MG-ADL score was updated to "6 or more" to match trial criteria and the prior therapy requirement was simplified to at least ONE neonatal Fc receptor (FcRn) antagonist and thymectomy. • Authorization duration extended to 6 months for initial and 12 months for reauthorization for all medications in this policy,
9/13/2023	• Coverage criteria updated to allow for subcutaneous (SC) injection of Ultomiris (ravulizumab) for PNH and aHUS. • Coverage added for: - Ultomiris (ravulizumab) IV for NMOSD. Soliris (eculizumab) will now require step therapy (ST) with Ultomiris (ravulizumab), Enspryng (satralizumab) AND Uplizna (inebilizumab). - Supplemental dosing of Ultomiris (ravulizumab) or Soliris (eculizumab) after plasma exchange or IVIG. • Use of Empaveli (pegcetacoplan) in macular degeneration remains investigational, as an intravitreal formulation, Syfovre (pegcetacoplan intravitreal) is available.
9/23/2022	Coverage criteria updated to add additional step therapy (ST) for Soliris (eculizumab) as follows: • aHUS: Ultomiris (ravulizumab) • gMG: Vyvgart (efgartigimod) AND Ultomiris (ravulizumab) • PNH: Empaveli (pegcetacoplan AND Ultomiris (ravulizumab) • NMOSD: Enspryng (satralizumab) AND Uplizna (inebilizumab)
6/17/2022	Added coverage criteria for Ultomiris (ravulizumab-cwvz) for use in generalized myasthenia gravis (gMG).
3/18/2022	• Added the newly FDA-approved Tavneos (avacopan) to policy. Limits coverage to patients with severe active ANCA-AV as adjunctive therapy with standard of care including glucocorticoids, when managed by a specialist and previous standard of care therapies (rituximab, cyclophosphamide, glucocorticoids, MTX, AZA, and MMF) were ineffective at inducing or maintaining remission. • Updated MG-ADL score to greater than or equal to 5, to match Vyvgart (efgartigimod) policy. • Added combination use with Vyvgart (efgartigimod) to investigational uses.

Revision Date	Revision Summary
10/15/2021	Added the newly FDA-approved Empaveli (pegcetacoplan) to policy. Coverage for paroxysmal nocturnal hemoglobinuria (PNH) will align with current coverage criteria for Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz).
7/16/2021	• Continuation of therapy (COT) language updated to align with Enspryng (satralizumab) and Uplizna (inebilizumab). • Added quantity limit (QL) for Soliris (eculizumab) when used for PNH with breakthrough hemolysis. • Clarified use of combination therapy for NMOSD as "Investigational" (removed from medical necessity criteria). No changes to intent of coverage criteria with this annual update.
1/20/2021	• Updated COT language to new format. • Reformatted quantity limits for operational ease. No change to intent.
10/28/2020	• Added additional step with either Enspryng (satralizumab) or Uplizna (inebilizumab) for Soliris (eculizumab) in NMOSD. • Updated Soliris (eculizumab) NMOSD criteria to limit concomitant use with rituximab, Enspryng (satralizumab) or Uplizna (inebilizumab).
6/15/2020	Continuation of therapy (COT) language added. Removed references to brand Rituxan to account for preferred/non-preferred changes in biosimilars policy (dru620).
10/23/2019	Effective 11/15/2019: • Added coverage criteria for neuromyelitis optica spectrum disorder (NMOSD) for Soliris (eculizumab). • Added coverage criteria for aHUS for Ultomiris (ravulizumab-cwvz). • Updated associated investigational uses for Ultomiris (ravulizumab-cwvz).
4/24/2019	• Renamed policy "Complement Inhibitors" • Criteria added for newly-approved Ultomiris (ravulizumab-cwvz) for PNH. • Updated previous Soliris (eculizumab) criteria for HUS to add nephrology specialty and clarify coverage criteria.
3/19/2018	Effective 4/1/2018: • Added coverage criteria for myasthenia gravis. • Updated associated investigational uses. Effective 7/1/2018: Align re-authorization to biannual (every 24-weeks) for all indications.
1/13/2017	Updated quantity limit. Added additional investigational uses.
11/11/2016	Removed site of care language from the individual drug policy; however, requirements still apply. Reference to *Site of Care Review*, dru408 is provided as part of criterion I.A.
1/08/2016	Annual update, no changes to criteria.

Revision Date	Revision Summary
1/19/2015	New policy.

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