ラブリズマブ (遺伝子組換え)

ユルトミリス点滴静注 300mg

ユルトミリス HI 点滴静注 300mg/3mL

ユルトミリス HI 点滴静注 1100mg/11mL

アレクシオンファーマ合同会社

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.5　起原又は発見の経緯及び開発の経緯

1　起原又は発見の経緯

ラブリズマブ（遺伝子組換え）は米国 Alexion Pharmaceuticals 社が創製した補体 C5 に対する遺伝子組換えヒト化モノクローナル抗体の点滴静注製剤である。本邦ではこれまで「発作性夜間ヘモグロビン尿症」（PNH）及び「非典型溶血性尿毒症症候群」（aHUS）を効能・効果として製造販売承認を取得している。詳細を M2.5-1.1 項に記載する。

2　開発の経緯

2.1　品質に関する試験の概略

品質に関する試験は実施していない。

2.2　非臨床試験の概略

新たな非臨床試験は実施していない（M2.4 及び M2.6 参照）。

2.3　臨床試験の概略

ラブリズマブの全身型重症筋無力症（gMG）に関する開発として、Alexion Pharmaceuticals 社では国際共同第 3 相試験（ALXN1210-MG-306 試験、以下 MG-306 試験）を 2019 年 3 月から開始し、本邦からも本試験に参加した。2021 年 5 月にデータカットオフした結果、日本人を含む gMG 患者に対してラブリズマブの良好な有効性及び安全性が示されたことから、承認事項一部変更承認申請を行うこととした。

開発の経緯図を Figure 1 に示す。また、臨床での開発の経緯を M2.5-1.4 項に、臨床試験の概略を M2.5-1.5 項に、本剤の有効性を M2.5-4 項に、安全性を M2.5-5 項に、ベネフィットとリスクに関する結論を M2.5-6 項に記載する。

Figure 1:　開発の経緯図

	2019 年				2020 年				2021 年				2022 年				2023 年				2024 年				2025 年			
四半期	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
ALXN 1210-MG-306 試験	[redacted]																											

2.4　規制当局からの助言

本邦での gMG 患者を対象とするラブリズマブの開発計画に関し、独立行政法人医薬品医療機器総合機構（PMDA）と以下の相談を実施し、基本的な考え方に対する合意を得た。

- [redacted]

- [redacted]
- [redacted]

2.5　申請効能以外での開発

ラブリズマブの gMG 以外の開発として、日本では視神経脊髄炎スペクトラム障害、筋萎縮性側索硬化症、造血幹細胞移植後の血栓性微小血管症、補体介在性血栓性微小血管症、新型コロナウイルス感染症による重症肺炎、急性肺損傷または急性呼吸窮迫症候群を対象疾患とした臨床試験を実施している。海外では、皮膚筋炎、IgA 腎症、ループス腎炎、小児での PNH を対象とした臨床試験を実施しているほか、皮下製剤を開発している。

また、現在、ラブリズマブの小児 gMG 患者を対象とした開発を検討しており、国際共同第3 相試験を20[redacted]年[redacted]四半期より開始することを計画している。以下に、小児開発が必要と判断した理由及び開発計画を記載する。

2.5.1　小児開発が必要と判断した理由

本邦での MG 発症年齢は、小児期、特に 5 歳未満でひとつのピークがあり、2006 年の疫学調査では 5 歳未満の患者が 7.0%と多かった。小児 MG では、早期の診断と適切な治療により、多くは寛解する。しかし、症状の持続や増悪することもあり、また、完全寛解の数年後に再発することもある。そのため、長期の経過観察が必要である（重症筋無力症診療ガイドライン, 2014）。

小児での治療法は成人と同様であり、抗コリンエステラーゼ薬、経口ステロイド、免疫抑制薬、血液浄化療法、免疫グロブリン静注療法が用いられる（エクリズマブは推奨されていない）。しかし、小児を対象に承認を取得している治療法はなくエビデンスが不足しており、また、ステロイドによる副作用、長期にわたる治療のための頻繁な通院や治療に伴う入院といった問題がある。

このような医療状況下、ラブリズマブは、MG-306 試験で日本人を含む gMG 患者に対して良好なベネフィット・リスクプロファイルを示した。ラブリズマブは、8 週間ごと（年 7 回）の少ない投与回数で症状を長期にコントロールできることが小児にも期待されること、小児への安全性も成人と同様であることが aHUS 患者を対象とした臨床試験で明らかとなっていることから、小児 gMG 患者にも有用であると考えたため、開発を行うこととした。なお、本試験の用法・用量は aHUS を参考に設定する予定であり、試験結果より小児 gMG 患者へのラブリズマブの有用性が認められた場合、適切な用法・用量を設定する計画である。

2.5.2　開発計画

Paediatric Investigation Plan（欧州）及び Pediatric Study Plan（米国）に基づき、小児対象試験を Table 1 のように計画している。

Table 1:　計画している小児対象試験の概要

試験デザイン：
[redacted]

タイムライン：

患者の対象年齢：

対象患者：

目標患者数：

用法・用量：

治療期間：

3　参考文献

日本神経学会監修．重症筋無力症診療ガイドライン 2014．南江堂；2014.

TABLE OF CONTENTS

1.6　外国における使用状況等に関する資料

1　外国における使用状況

「ユルトミリス HI 点滴静注 300mg/3mL、同 1100mg/11mL」（ラブリズマブ 100mg/mL 製剤）及び「ユルトミリス点滴静注 300mg」（ラブリズマブ 10mg/mL 製剤）の全身型重症筋無力症（generalized myasthenia gravis：gMG）に対する適応症について、米国で 2022 年 4 月 27 日に製造販売承認を取得した。2022 年 6 月 30 日現在、欧州、カナダ、ブラジル、コロンビア、及びイスラエルで承認申請中である。

2　外国における添付文書

2.1　企業中核データシート

2.2　米国の添付文書

COMPANY CORE DATA SHEET

ULTOMIRIS® (RAVULIZUMAB)

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CCDS Version: [redacted]

Date: [redacted]

[redacted]

[redacted]

*非公表のため、2～59頁を削除

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ULTOMIRIS safely and effectively. See full prescribing information for ULTOMIRIS.

ULTOMIRIS® (ravulizumab-cwvz) injection, for intravenous use
Initial U.S. Approval: 2018

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risks of developing a meningococcal infection. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection.**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infection. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program (5.1).

RECENT MAJOR CHANGES

Indications and Usage (1.1)	06/2021
Indications and Usage (1.3)	04/2022
Dosing and Administration (2.2)	06/2021
Dosing and Administration (2.3, 2.4)	04/2022
Warnings and Precautions (5.1, 5.2, 5.5)	04/2022

INDICATIONS AND USAGE

ULTOMIRIS is a complement inhibitor indicated for:

- the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH) (1.1).
- the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) (1.2).

  Limitations of Use:
  ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive (1.3).

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for instructions on dosage, preparation, and administration (2.1, 2.2, 2.3, 2.4).
- Dilute ULTOMIRIS before use (2.4).
- Only administer as an intravenous infusion through a 0.2 or 0.22 micron filter (2.4).

DOSAGE FORMS AND STRENGTHS

Injection:
300 mg/30 mL (10 mg/mL) in a single-dose vial (3).
300 mg/3 mL (100 mg/mL) in a single-dose vial (3).
1,100 mg/11 mL (100 mg/mL) in a single-dose vial (3).

CONTRAINDICATIONS

ULTOMIRIS is contraindicated in:

- Patients with unresolved *Neisseria meningitidis* infection (4).
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection (4, 5.1).

WARNINGS AND PRECAUTIONS

- Other Infections: Use caution when administering ULTOMIRIS to patients with any other systemic infection (5.2).
- Infusion-Related Reactions: Monitor patients during infusion, interrupt for reactions, and institute appropriate supportive measures (5.5).

ADVERSE REACTIONS

Most common adverse reactions in patients with PNH (incidence ≥10%) were upper respiratory tract infection and headache (6.1).

Most common adverse reactions in patients with aHUS (incidence ≥20%) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia (6.1).

Most common adverse reactions in adult patients with gMG (incidence ≥10%) were diarrhea and upper respiratory tract infection (6.1).

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

DRUG INTERACTIONS

- Plasma Exchange, Plasmapheresis, or Intravenous Immunoglobulins: concomitant use requires supplemental dose of ULTOMIRIS (7.1).
- Neonatal Fc Receptor Blockers: Closely monitor for reduced effectiveness of ULTOMIRIS (7.2).

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2022

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early *[see Warnings and Precautions (5.1)]*.

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a meningococcal infection. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection.**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program *[see Warnings and Precautions (5.1)]*. Enrollment in the ULTOMIRIS REMS program and additional information are available by telephone: 1-888-765-4747 or at www.ultomirisrems.com.

1 INDICATIONS AND USAGE

1.1 Paroxysmal Nocturnal Hemoglobinuria

ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).

1.2 Atypical Hemolytic Uremic Syndrome

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

Limitations of Use:

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

1.3 Generalized Myasthenia Gravis

ULTOMIRIS is indicated for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Vaccination and Prophylaxis

Vaccinate patients for meningococcal disease according to current ACIP guidelines to reduce the risk of serious infection *[see Warnings and Precautions (5.1, 5.2)]*.

Provide 2 weeks of antibacterial drug prophylaxis to patients if ULTOMIRIS must be initiated immediately and vaccines are administered less than 2 weeks before starting ULTOMIRIS therapy.

Healthcare professionals who prescribe ULTOMIRIS must enroll in the ULTOMIRIS REMS *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Weight-Based Dosage Regimen – PNH, aHUS, and gMG

The recommended dosing regimen in adult and pediatric patients, one month of age or older weighing 5 kg or greater, with PNH and aHUS, or in adult patients with gMG weighing 40 kg or greater, consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The dosing is based on the patient's body weight, as shown in Table 1. Starting 2 weeks after the loading dose administration, begin maintenance doses once every 4 or 8 weeks, based on body weight.

The dosing schedule is allowed to occasionally vary within 7 days of the scheduled infusion day (except for the first maintenance dose of ULTOMIRIS); but subsequent doses should be administered according to the original schedule.

Table 1: ULTOMIRIS Weight-Based Dosing Regimen – PNH, aHUS, and gMG*

Indications	Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg) and Dosing Interval	
PNH and aHUS	5 to less than 10	600	300	Every 4 weeks
	10 to less than 20	600	600	
	20 to less than 30	900	2,100	Every 8 weeks
	30 to less than 40	1,200	2,700	
PNH, aHUS, and gMG	40 to less than 60	2,400	3,000	
	60 to less than 100	2,700	3,300	
	100 or greater	3,000	3,600	

* see Tables 3, 4, 6, and 7 for selection of the proper total volume and maximum infusion rate *[see Dosage and Administration (2.4)]*

2.3 Dosing Considerations

Switch from Eculizumab to ULTOMIRIS

For patients switching from eculizumab to ULTOMIRIS, administer the loading dose of ULTOMIRIS 2 weeks after the last eculizumab maintenance infusion (or 1 week after the last eculizumab induction infusion), and then administer ULTOMIRIS maintenance doses once every 4 weeks or every 8 weeks depending on body weight, as shown in Table 1), starting 2 weeks after loading dose administration.

Supplemental Dose of ULTOMIRIS

Plasma exchange (PE), plasmapheresis (PP), and intravenous immunoglobulin (IVIg) have been shown to reduce ULTOMIRIS serum levels. A supplemental dose of ULTOMIRIS is required in the setting of PE, PP, or IVIg (Table 2).

Table 2: Supplemental Dose of ULTOMIRIS after PE, PP, or IVIg*

Body Weight Range (kg)	Most Recent ULTOMIRIS Dose (mg)	Supplemental Dose (mg) following each PE or PP Intervention	Supplemental Dose (mg) following Completion of an IVIg Cycle
40 to less than 60	2,400	1,200	600
	3,000	1,500	
60 to less than 100	2,700	1,500	600
	3,300	1,800	
100 or greater	3,000	1,500	600
	3,600	1,800	
Timing of ULTOMIRIS Supplemental Dose		Within 4 hours following each PE or PP intervention	Within 4 hours following completion of an IVIg cycle

Abbreviations: IVIg = intravenous immunoglobulin; PE = plasma exchange; PP = plasmapheresis
* see Table 5 and Table 8 for selection of the proper total volume and maximum infusion rate *[see Dosage and Administration (2.4)]*

2.4 Preparation and Administration

Preparation of ULTOMIRIS

Dilute before use.

Each vial of ULTOMIRIS is intended for single-dose only.

Do not mix ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials) and 10 mg/mL (30 mL vial) concentrations together.

Use aseptic technique to prepare ULTOMIRIS as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose *[see Dosage and Administration (2.2)]*.
2. Prior to dilution, visually inspect the solution in the vials; the solution should be free of any particulate matter or precipitation. Do not use if there is evidence of particulate matter or precipitation.

3. Withdraw the calculated volume of ULTOMIRIS from the appropriate number of vials and dilute in an infusion bag using 0.9% Sodium Chloride Injection, USP to a final concentration of:
    - 50 mg/mL for the 3 mL and 11 mL vial sizes or
    - 5 mg/mL for the 30 mL vial size.

The product should be mixed gently. Do not shake. Protect from light. Do not freeze.

Refer to the following reference tables for preparation and minimum infusion duration:

- ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials): see Table 3 (loading doses), Table 4 (maintenance doses), and Table 5 (supplemental doses)
- ULTOMIRIS 10 mg/mL (30 mL vial): see Table 6 (loading doses),Table 7 (maintenance doses), and Table 8 (supplemental doses)

4. Administer the prepared solution immediately following preparation.
5. If the diluted ULTOMIRIS infusion solution is not used immediately, storage under refrigeration at 2°C - 8°C (36°F - 46°F) must not exceed 24 hours taking into account the expected infusion time. Once removed from refrigeration, administer the diluted ULTOMIRIS infusion solution within 6 hours if prepared with ULTOMIRIS 30 mL vials or within 4 hours if prepared with ULTOMIRIS 3 mL or 11 mL vials.

Administration of ULTOMIRIS

Only administer as an intravenous infusion through a 0.2 or 0.22 micron filter.

Dilute ULTOMIRIS to a final concentration of:

- 50 mg/mL for the 3 mL and 11 mL vial sizes or
- 5 mg/mL for the 30 mL vial size.

Prior to administration, allow the admixture to adjust to room temperature (18°C - 25°C, 64°F - 77°F). Do not heat the admixture in a microwave or with any heat source other than ambient air temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Table 3: Loading Dose Reference Table for ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials)

Body Weight Range (kg)[a]	Loading Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
5 to less than 10[c]	600	6	6	12	1.4	8
10 to less than 20[c]	600	6	6	12	0.8	16
20 to less than 30[c]	900	9	9	18	0.6	30
30 to less than 40[c]	1,200	12	12	24	0.5	46
40 to less than 60	2,400	24	24	48	0.8	64
60 to less than 100	2,700	27	27	54	0.6	92
100 or greater	3,000	30	30	60	0.4	144

[a] Body weight at time of treatment.
[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.
[c] For PNH and aHUS indications only.

Table 4: Maintenance Dose Reference Table for ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials)

Body Weight Range (kg)[a]	Maintenance Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
5 to less than 10[c]	300	3	3	6	0.8	8
10 to less than 20[c]	600	6	6	12	0.8	16
20 to less than 30[c]	2,100	21	21	42	1.3	33
30 to less than 40[c]	2,700	27	27	54	1.1	49
40 to less than 60	3,000	30	30	60	0.9	65
60 to less than 100	3,300	33	33	66	0.7	99
100 or greater	3,600	36	36	72	0.5	144

[a] Body weight at time of treatment.
[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.
[c] For PNH and aHUS indications only.

Table 5: Supplemental Dose Reference Table for ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials)

Body Weight Range (kg)[a]	Supplemental Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
40 to less than 60	600	6	6	12	0.25	48
	1,200	12	12	24	0.42	57
	1,500	15	15	30	0.5	60
60 to less than 100	600	6	6	12	0.20	60
	1,500	15	15	30	0.36	83
	1,800	18	18	36	0.42	86
100 or greater	600	6	6	12	0.17	71
	1,500	15	15	30	0.25	120
	1,800	18	18	36	0.28	129

Note: Refer to Table 2 for selection of ravulizumab supplemental dose

[a] Body weight at time of treatment.

[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.

Table 6: Loading Dose Reference Table for ULTOMIRIS 10 mg/mL (30 mL vial)

Body Weight Range (kg)[a]	Loading Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
5 to less than 10[c]	600	60	60	120	3.8	31
10 to less than 20[c]	600	60	60	120	1.9	63
20 to less than 30[c]	900	90	90	180	1.5	120
30 to less than 40[c]	1,200	120	120	240	1.3	184
40 to less than 60	2,400	240	240	480	1.9	252
60 to less than 100	2,700	270	270	540	1.7	317
100 or greater	3,000	300	300	600	1.8	333

[a] Body weight at time of treatment.

[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.

[c] For PNH and aHUS indications only.

Table 7: Maintenance Dose Reference Table for ULTOMIRIS 10 mg/mL (30 mL vial)

Body Weight Range (kg)[a]	Maintenance Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
5 to less than 10[c]	300	30	30	60	1.9	31
10 to less than 20[c]	600	60	60	120	1.9	63
20 to less than 30[c]	2,100	210	210	420	3.3	127
30 to less than 40[c]	2,700	270	270	540	2.8	192
40 to less than 60	3,000	300	300	600	2.3	257
60 to less than 100	3,300	330	330	660	2	330
100 or greater	3,600	360	360	720	2.2	327

[a] Body weight at time of treatment.
[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.
[c] For PNH and aHUS indications only.

Table 8: Supplemental Dose Reference Table for ULTOMIRIS 10 mg/mL (30 mL vial)

Body Weight Range (kg)[a]	Supplemental Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
40 to less than 60	600	60	60	120	0.5	240
	1,200	120	120	240	1.0	240
	1,500	150	150	300	1.2	250
60 to less than 100	600	60	60	120	0.4	300
	1,500	150	150	300	1.0	300
	1,800	180	180	360	1.1	327
100 or greater	600	60	60	120	0.4	300
	1,500	150	150	300	1.0	300
	1,800	180	180	360	1.1	327

Note: Refer to Table 2 for selection of ravulizumab supplemental dose
[a] Body weight at time of treatment.
[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.

If an adverse reaction occurs during the administration of ULTOMIRIS, the infusion may be slowed or stopped at the discretion of the physician. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion-related reaction.

3 DOSAGE FORMS AND STRENGTHS

ULTOMIRIS 100 mg/mL

Injection: 300 mg/3 mL (100 mg/mL) and 1,100 mg/11 mL (100 mg/mL) as a translucent, clear to yellowish color solution in a single-dose vial.

ULTOMIRIS 10 mg/mL

Injection: 300 mg/30 mL (10 mg/mL) as a clear to translucent, slight whitish color solution in a single-dose vial.

4 CONTRAINDICATIONS

ULTOMIRIS is contraindicated in:

- Patients with unresolved *Neisseria meningitidis* infection *[see Warnings and Precautions (5.1)]*.
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Meningococcal Infections

Risk and Prevention

Life-threatening meningococcal infections have occurred in patients treated with ULTOMIRIS. The use of ULTOMIRIS increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis). Meningococcal disease due to any serogroup may occur.

Vaccinate for meningococcal disease according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations considering the duration of ULTOMIRIS therapy.

Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of ULTOMIRIS. If urgent ULTOMIRIS therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide patients with 2 weeks of antibacterial drug prophylaxis.

In clinical studies, 59 adult patients with PNH and 2 adult patients with gMG were treated with ULTOMIRIS less than 2 weeks after meningococcal vaccination. All of these patients received antibiotics for prophylaxis of meningococcal infection until at least 2 weeks after meningococcal vaccination. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established.

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In PNH clinical studies in adult patients, 3 out of 261 PNH patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS; all 3 had been vaccinated. These 3 patients recovered while continuing treatment with ULTOMIRIS. In the PNH study in pediatric patients, no meningococcal infections occurred among the 13 patients receiving treatment with ULTOMIRIS.

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and steps to be taken to seek immediate medical care. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

REMS

Due to the risk of meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program.

Prescribers must counsel patients about the risk of meningococcal infection/sepsis, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines.

Enrollment in the ULTOMIRIS REMS and additional information are available by telephone: 1-888-765-4747 or at www.ultomirisrems.com.

5.2 Other Infections

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

If ULTOMIRIS therapy is administered to patients with active systemic infections, monitor closely for signs and symptoms of worsening infection.

5.3 Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

Treatment Discontinuation for PNH

After discontinuing treatment with ULTOMIRIS, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH along with sudden decrease in PNH clone size or hemoglobin, or reappearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues ULTOMIRIS for at least 16 weeks to detect hemolysis and other reactions. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

Treatment Discontinuation for aHUS

ULTOMIRIS treatment of aHUS should be a minimum duration of 6 months. Due to heterogeneous nature of aHUS events and patient-specific risk factors, treatment duration beyond the initial 6 months should be individualized.

There are no specific data on ULTOMIRIS discontinuation.

After discontinuing treatment with ULTOMIRIS, patients should be monitored for clinical symptoms and laboratory signs of TMA complications for at least 12 months.

TMA complications post-discontinuation can be identified if any of the following is observed:

- Clinical symptoms of TMA include changes in mental status, seizures, angina, dyspnea, thrombosis or increasing blood pressure.
- In addition, at least two of the following laboratory signs observed concurrently and results should be confirmed by a second measurement 28 days apart with no interruption
    - a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment;
    - an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment;
    - an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment.

If TMA complications occur after ULTOMIRIS discontinuation, consider reinitiation of ULTOMIRIS treatment or appropriate organ-specific supportive measures.

5.4 Thromboembolic Event Management

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

5.5 Infusion-Related Reactions

Administration of ULTOMIRIS may result in infusion-related reactions, including anaphylaxis *[see Adverse Reactions (6.3)]* and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Meningococcal Infections *[see Warnings and Precautions (5.1)]*
- Other Infections *[see Warnings and Precautions (5.2)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Adult Population with PNH

The data described below reflect exposure of 441 adult patients with PNH in Phase 3 studies who received ULTOMIRIS (n = 222) or eculizumab (n = 219) at the recommended dosing regimens with median treatment duration of 6 months for ULTOMIRIS and 6 months for eculizumab. The most frequent adverse reactions (≥10%) with ULTOMIRIS were upper respiratory tract infection and headache. Table 9 describes adverse reactions that occurred at a rate of 5% or more among patients treated with ULTOMIRIS in PNH studies.

Serious adverse reactions were reported in 15 (6.8%) patients with PNH receiving ULTOMIRIS. The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse reaction was reported in more than 1 patient treated with ULTOMIRIS.

One fatal case of sepsis was identified in a patient treated with ULTOMIRIS.

Table 9: Adverse Reactions Reported in 5% or More of ULTOMIRIS-Treated Patients in Complement Inhibitor Naïve and Eculizumab-Experienced Adult Patients with PNH

Body System Adverse Reaction	Number of Patients	
	ULTOMIRIS (N=222) n (%)	Eculizumab (N=219) n (%)
Gastrointestinal disorders		
Diarrhea	19 (9)	12 (5)
Nausea	19 (9)	19 (9)
Abdominal pain	13 (6)	16 (7)
General Disorders and Administration Site Conditions		
Pyrexia	15 (7)	18 (8)
Infections and Infestations		
Upper respiratory tract infection[a]	86 (39)	86 (39)
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	14 (6)	11 (5)
Arthralgia	11 (5)	12 (5)
Nervous System Disorders		
Headache	71 (32)	57 (26)
Dizziness	12 (5)	14 (6)

[a] Grouped term includes: nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, viral upper respiratory tract infection, rhinitis, respiratory tract infection, rhinorrhea, pharyngitis, and upper respiratory tract inflammation

Clinically relevant adverse reactions in 1% of patients include infusion-related reactions.

Pediatric Population with PNH

In pediatric patients with PNH (aged 9 to 17 years old) included in the pediatric PNH Phase 3 study, the safety profile appeared similar to that observed in adult patients with PNH and in pediatric and adult patients with aHUS. The most common adverse reactions (>20%) were upper respiratory tract infection, anemia, abdominal pain, and headache. Table 10 describes the adverse reactions that occurred at a rate of 10% or more among pediatric patients treated with ULTOMIRIS in Study ALXN1210-PNH-304.

Table 10: Adverse Reactions Reported in 10% or More of ULTOMIRIS-Treated Pediatric Patients with PNH in Study ALXN1210-PNH-304

Body System Adverse Reaction	Treatment Naïve (N=5)	Eculizumab Experienced (N=8)	Total (N=13)
	n (%)	n (%)	n (%)
Blood and lymphatic system disorders			
Anemia[a]	1 (20)	2 (25)	3 (23)
Gastrointestinal disorders			
Abdominal pain	0 (0)	3 (38)	3 (23)
Constipation	0 (0)	2 (25)	2 (15)
General disorders and administration site conditions			
Pyrexia	1 (20)	1 (13)	2 (15)
Infections and infestations			
Upper Respiratory tract infection[b]	1 (20)	6 (75)	7 (54)
Musculoskeletal and connective tissue disorders			
Pain in extremity	0 (0)	2 (25)	2 (15)
Nervous system disorders			
Headache	1 (20)	2 (25)	3 (23)

[a] Grouped term includes: anemia and iron deficiency anemia

[b] Grouped term includes: nasopharyngitis, upper respiratory tract infection, oropharyngeal pain and viral upper respiratory tract infection

Atypical Hemolytic Uremic Syndrome (aHUS)

The data described below reflect exposure of 58 adult and 16 pediatric patients with aHUS in single-arm trials who received ULTOMIRIS at the recommended dose and schedule. The most frequent adverse reactions reported in ≥20% of patients treated with ULTOMIRIS were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension, and pyrexia. Table 11, Table 12, and Table 13 describe adverse reactions that occurred at a rate of 10% or more among patients treated with ULTOMIRIS in aHUS studies. Serious adverse reactions were reported in 42 (57%) patients with aHUS receiving ULTOMIRIS. The most frequent serious adverse reactions reported in more than 2 patients (2.7%) treated with ULTOMIRIS were hypertension, pneumonia and abdominal pain. Four patients died during the ALXN1210-aHUS-311 study. The cause of death was sepsis in two patients and intracranial hemorrhage in one patient. The fourth patient, who was excluded from the trial after a diagnosis of STEC-HUS, died due to pretreatment cerebral arterial thrombosis.

Table 11: Adverse Reactions Reported in ≥10% of ULTOMIRIS-Treated Patients with aHUS in Study ALXN1210-aHUS-311

Body System Adverse Reaction	ALXN1210-aHUS-311 (N=58)	
	All Grades*** (n=53) n (%)	≥ Grade 3 (n=14) n (%)
Blood and lymphatic system disorders		
Anemia	8 (14)	0 (0)
Gastrointestinal disorders		
Diarrhea	18 (31)	2 (3)
Nausea	15 (26)	2 (3)
Vomiting	15 (26)	2 (3)
Constipation	8 (14)	1 (2)
Abdominal pain	7 (12)	1 (2)
General disorders and administration site conditions		
Pyrexia	11 (19)	1 (2)
Edema peripheral	10 (17)	0 (0)
Fatigue	8 (14)	0 (0)
Infections and infestations		
Upper respiratory tract infection*	15 (26)	0 (0)
Urinary tract infection	10 (17)	5 (9)
Gastrointestinal infection**	8 (14)	2 (3)
Metabolism and nutrition disorders		
Hypokalemia	6 (10)	1 (2)
Musculoskeletal and connective tissue disorders		
Arthralgia	13 (22)	0 (0)
Back pain	7 (12)	1 (2)
Muscle spasms	6 (10)	0 (0)
Pain in extremity	6 (10)	0 (0)
Nervous system disorders		
Headache	23 (40)	1 (2)
Psychiatric disorders		
Anxiety	8 (14)	1 (2)
Respiratory, thoracic and mediastinal disorders		
Cough	10 (17)	0 (0)
Dyspnea	10 (17)	1 (2)
Skin and subcutaneous tissue disorders		
Alopecia	6 (10)	0 (0)
Dry skin	6 (10)	0 (0)
Vascular disorders		
Hypertension	14 (24)	7 (12)

*: Grouped term includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinitis, viral upper respiratory tract infection, rhinovirus infection, viral pharyngitis, rhinorrhea, and oropharyngeal pain.

**: Grouped term includes gastroenteritis, gastrointestinal infection, enterocolitis infectious, infectious colitis, and enterocolitis.

***: Graded per CTCAE v5.0.

Clinically relevant adverse reactions include viral tonsilitis (in <10% of patients) and infusion-related reactions (in 3% of patients).

Table 12: Adverse Reactions Reported in ≥10% of ULTOMIRIS-Treated Patients with aHUS in Study ALXN1210-aHUS-312

Body System Adverse Reaction	ALXN1210-aHUS-312 (N=16)	
	All Grades** (n=16) n (%)	≥ Grade 3 (n=6) n (%)
Blood and lymphatic system disorders		
Anemia	2 (13)	1 (6)
Lymphadenopathy	2 (13)	0 (0)
Gastrointestinal disorders		
Diarrhea	6 (38)	0 (0)
Constipation	4 (25)	0 (0)
Vomiting	4 (25)	1 (6)
Abdominal pain	3 (19)	0 (0)
Nausea	2 (13)	0 (0)
General disorders and administration site conditions		
Pyrexia	8 (50)	0 (0)
Infections and infestations		
Upper respiratory tract infection*	7 (44)	1 (6)
Gastroenteritis viral	2 (13)	2 (13)
Pneumonia	2 (13)	1 (6)
Tonsillitis	2 (13)	0 (0)
Injury, poisoning and procedural complications		
Contusion	3 (19)	0 (0)
Investigations		
Vitamin D decreased	3 (19)	0 (0)
Metabolism and nutrition disorders		
Decreased appetite	2 (13)	0 (0)
Iron deficiency	2 (13)	0 (0)
Musculoskeletal and connective tissue disorders		
Myalgia	3 (19)	0 (0)
Pain in extremity	2 (13)	0 (0)
Nervous system disorders		
Headache	5 (31)	0 (0)
Respiratory, thoracic and mediastinal disorders		
Cough	3 (19)	0 (0)
Dyspnea	2 (13)	0 (0)
Skin and subcutaneous tissue disorders		
Rash	3 (19)	0 (0)
Vascular disorders		
Hypertension	4 (25)	1 (6)
Hypotension	2 (13)	0 (0)

*: Grouped term includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinitis, viral upper respiratory tract infection, rhinovirus infection, viral pharyngitis, rhinorrhea, and oropharyngeal pain.
**: Graded per CTCAE v5.0.

Clinically relevant adverse reactions in <10% of patients include viral infection.

Table 13: Adverse Reactions Reported in ≥10% of ULTOMIRIS-Treated Patients from Birth to 16 Years of Age with aHUS in Study ALXN1210-aHUS-312

Body System Adverse Reaction	ALXN1210-aHUS-312			
	Age 0 to <2 (N=2)	Age 2 to <12 (N=12)	Age 12 to 16 (N=1)	Total (N=15)
	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders				
Lymphadenopathy	0 (0)	2 (17)	0 (0)	2 (13)
Gastrointestinal disorders				
Diarrhea	1 (50)	3 (25)	1 (100)	5 (33)
Constipation	0 (0)	4 (33)	0 (0)	4 (27)
Vomiting	0 (0)	3 (25)	0 (0)	3 (20)
Abdominal pain	0 (0)	2 (17)	0 (0)	2 (13)
General disorders and administration site conditions				
Pyrexia	1 (50)	5 (42)	1 (100)	7 (47)
Infections and infestations				
Upper respiratory tract infection*	1 (50)	6 (50)	0 (0)	7 (47)
Gastroenteritis viral	0 (0)	2 (17)	0 (0)	2 (13)
Tonsillitis	1 (50)	1 (8)	0 (0)	2 (13)
Injury, poisoning and procedural complications				
Contusion	0 (0)	2 (17)	0 (0)	2 (13)
Investigations				
Vitamin D decreased	0 (0)	2 (17)	1 (100)	3 (20)
Metabolism and nutrition disorders				
Decreased appetite	1 (50)	1 (8)	0 (0)	2 (13)
Iron deficiency	0 (0)	2 (17)	0 (0)	2 (13)
Musculoskeletal and connective tissue disorders				
Myalgia	1 (50)	1 (8)	0 (0)	2 (13)
Pain in extremity	0 (0)	2 (17)	0 (0)	2 (13)
Nervous system disorders				
Headache	0 (0)	4 (33)	0 (0)	4 (27)
Respiratory, thoracic and mediastinal disorders				
Cough	0 (0)	3 (25)	0 (0)	3 (20)
Dyspnea	1 (50)	1 (8)	0 (0)	2 (13)
Skin and subcutaneous tissue disorders				
Rash	1 (50)	2 (17)	0 (0)	3 (20)
Vascular disorders				
Hypertension	1 (50)	3 (25)	0 (0)	4 (27)
Hypotension	0 (0)	2 (17)	0 (0)	2 (13)

*: Grouped term includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinitis, viral upper respiratory tract infection, rhinovirus infection, viral pharyngitis, rhinorrhea, and oropharyngeal pain

Clinically relevant adverse reactions in <10% of patients include viral infection.

Generalized Myasthenia Gravis (gMG)

Adult Population with gMG

The safety of ULTOMIRIS has been evaluated in 175 adult patients with gMG, including 169 patients who received at least one dose of ULTOMIRIS, 142 patients who were exposed for at least 6 months, and 95 who were exposed for at least 12 months *[see Clinical Studies (14.3)].* In a randomized, double-blind, placebo-controlled trial (ALXN1210-MG-306), the most frequent adverse reactions (≥10%) with ULTOMIRIS were diarrhea and upper respiratory tract infection. Table 14 describes adverse reactions that occurred at a rate of 5% or more and at greater frequency than placebo. Serious adverse reactions were reported in 20 (23%) patients with gMG receiving ULTOMIRIS and in 14 (16%) patients receiving placebo. The most frequent serious adverse reactions were infections reported in at least 8 (9%) patients treated with ULTOMIRIS and in 4 (4%) patients treated with placebo *[see Warnings and Precautions (5.2)]*. Of these infections, one fatal case of COVID-19 pneumonia was identified in a patient treated with ULTOMIRIS and one case of infection led to discontinuation of ULTOMIRIS.

Table 14: Adverse Reactions Reported in ≥5% and at Greater Frequency than Placebo in ULTOMIRIS-Treated Adult Patients with gMG in Study ALXN1210-MG-306

Body System **Adverse Reaction**	**Number of Patients**	
	ULTOMIRIS (N=86) n (%)	**Placebo (N=89)** n (%)
Gastrointestinal Disorders		
Diarrhea	13 (15)	11 (12)
Abdominal pain	5 (6)	0
Infections and Infestations		
Upper respiratory tract infection	12 (14)	7 (8)
Urinary tract infection	5 (6)	4 (4)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	7 (8)	5 (6)
Nervous System Disorders		
Dizziness	8 (9)	3 (3)

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibodies) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ravulizumab-cwvz products may be misleading.

The immunogenicity of ravulizumab-cwvz has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding anti-ravulizumab-cwvz antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies.

In clinical studies, treatment-emergent antibodies to ravulizumab-cwvz were detected in 1 of 219 (0.5%) patients with PNH and 1 of 71 (1.4%) patients with aHUS. In these 2 patient populations, no apparent correlation of antibody development to altered pharmacokinetic profile, clinical response, or adverse events was observed.

No treatment-emergent antibodies to ravulizumab-cwvz were detected in patients with gMG treated with ULTOMIRIS.

However, the assay used to measure anti-drug antibodies (ADA) is subject to interference by serum ravulizumab-cwvz, possibly resulting in an underestimation of the incidence of antibody formation. Due to the limitation of the assay conditions, the potential clinical impact of antibodies to ravulizumab-cwvz is not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ULTOMIRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ULTOMIRIS exposure.

Serious Adverse Reaction: Anaphylaxis *[see Warnings and Precautions (5.5)]*

7 DRUG INTERACTIONS

7.1 Plasma Exchange, Plasmapheresis, and Intravenous Immunoglobulins

Concomitant use of ULTOMIRIS with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg) treatment can reduce serum ravulizumab concentrations and requires a supplemental dose of ULTOMIRIS *[see Dosage and Administration (2.3)]*.

7.2 Neonatal Fc Receptor Blockers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on ULTOMIRIS use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated PNH and aHUS in pregnancy (*see Clinical Considerations*). Animal studies using a mouse analogue of the ravulizumab-cwvz molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring at doses 0.8-2.2 times the human dose *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or fetal/neonatal risk

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages, and increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery.

In pregnancy, aHUS is associated with adverse maternal outcomes, including preeclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including intrauterine growth restriction (IUGR), fetal death and low birth weight.

Data

Animal Data

Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 1-2.2 times (loading dose) and 0.8-1.8 times (maintenance dose) the recommended human ULTOMIRIS dose, based on a body weight comparison. When animal exposure to the antibody occurred in the time period from before mating until early gestation, no decrease in fertility or reproductive performance was observed. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose; however, the exposure did not increase fetal loss or neonatal death. When maternal exposure to the antibody occurred in the time period from implantation through weaning, a higher number of male offspring became moribund or died (1/25 controls, 2/25 low dose group, 5/25 high dose group). Surviving offspring had normal development and reproductive function. Human IgG are known to cross the human placental barrier, and thus ULTOMIRIS may potentially cause terminal complement inhibition in fetal circulation.

8.2 Lactation

Risk summary

There are no data on the presence of ravulizumab-cwvz in human milk, the effect on the breastfed child, or the effect on milk production. Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in a nursing child, breastfeeding should be discontinued during treatment and for 8 months after the final dose.

8.4 Pediatric Use

The safety and effectiveness of ULTOMIRIS for the treatment of PNH have been established in pediatric patients aged one month and older. Use of ULTOMIRIS for this indication is supported by evidence from adequate and well-controlled trials in adults with additional pharmacokinetic, efficacy and safety data in pediatric patients aged 9 to 17 years *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*. The safety and efficacy for the treatment of pediatric and adult patients with PNH appear similar. Use of ULTOMIRIS in pediatric patients with PNH aged less than 9 years and body weight <30 kg is based on extrapolation of pharmacokinetic / pharmacodynamic (PK/PD), and efficacy and safety data from aHUS and PNH clinical studies *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

The safety and effectiveness of ULTOMIRIS for the treatment of aHUS have been established in pediatric patients aged one month and older. Use of ULTOMIRIS for this indication is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic, safety, and efficacy data in pediatric patients aged 10 months to <17 years. The safety and efficacy of ULTOMIRIS for the treatment of aHUS appear similar in pediatric and adult patients *[see Adverse Reactions (6.1), and Clinical Studies (14.2)]*.

Safety and effectiveness of ULTOMIRIS for the treatment of gMG in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ULTOMIRIS did not include sufficient numbers of subjects aged 65 and over (58 patients with PNH, 9 with aHUS, and 54 with gMG) to determine whether they respond differently from younger subjects.

Other reported clinical experience has not identified differences in responses between elderly and younger patients.

11 DESCRIPTION

Ravulizumab-cwvz, a complement inhibitor, is a humanized monoclonal antibody (mAb) produced in Chinese hamster ovary (CHO) cells. Ravulizumab-cwvz consists of 2 identical 448 amino acid heavy chains and 2 identical 214 amino acid light chains and has a molecular weight of approximately 148 kDa. The constant regions of ravulizumab-

cwvz include the human kappa light chain constant region, and the protein engineered "IgG2/4" heavy chain constant region.

The heavy chain CH1 domain, hinge region, and the first 5 amino acids of the CH2 domain match the human IgG2 amino acid sequence, residues 6 to 36 in the CH2 region (common to both human IgG2 and IgG4 amino acid sequences), while the remainder of the CH2 domain and the CH3 domain match the human IgG4 amino acid sequence. The heavy and light chain variable regions that form the human C5 binding site consist of human framework regions grafted to murine complementarity-determining regions.

ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials)

ULTOMIRIS (ravulizumab-cwvz) injection 100 mg/mL is a sterile, translucent, clear to yellowish color, preservative-free solution for intravenous use. Each single-dose vial contains 300 mg or 1,100 mg ravulizumab-cwvz at a concentration of 100 mg/mL with a pH of 7.4. Each mL also contains L-arginine (4.33 mg), polysorbate 80 (0.5 mg) (vegetable origin), sodium phosphate dibasic (4.42 mg), sodium phosphate monobasic (4.57 mg), sucrose (50 mg) and Water for Injection, USP.

ULTOMIRIS 10 mg/mL (30 mL vial)

ULTOMIRIS (ravulizumab-cwvz) injection 10 mg/mL is a sterile, clear to translucent, slight whitish color, preservative-free solution for intravenous use. Each single-dose vial contains 300 mg ravulizumab-cwvz at a concentration of 10 mg/mL with a pH of 7.0. Each mL also contains polysorbate 80 (0.2 mg) (vegetable origin), sodium chloride (8.77 mg), sodium phosphate dibasic (1.78 mg), sodium phosphate monobasic (0.46 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ravulizumab-cwvz is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]) thus preventing MAC formation. ULTOMIRIS inhibits terminal complement-mediated intravascular hemolysis in patients with PNH and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS.

The precise mechanism by which ravulizumab-cwvz exerts its therapeutic effect in gMG patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.

12.2 Pharmacodynamics

Complete inhibition of serum free C5 (concentration of less than 0.5 mcg/mL) was observed by the end of the first ULTOMIRIS infusion and sustained throughout the entire 26-week treatment period in both adult and pediatric patients with PNH, in the majority (93%) of adult and pediatric patients with aHUS, and all adult patients with gMG.

The extent and duration of the pharmacodynamic response in patients with PNH, aHUS, and gMG were exposure-dependent for ULTOMIRIS. Free C5 levels of <0.5 mcg/mL were correlated with maximal intravascular hemolysis control and complete terminal complement inhibition in patients with PNH.

Complete terminal complement inhibition following initiation of ULTOMIRIS treatment led to normalization of serum LDH by week 4 in complement-inhibitor naïve patients with PNH, and maintained LDH normalization in patients previously treated with eculizumab with PNH *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Ravulizumab-cwvz pharmacokinetics increase proportionally over a dose range of 200 to 5400 mg. Ravulizumab-cwvz C_{max} and C_{trough} parameters are presented in Table 15, Table 16, and Table 17.

Table 15: Mean (%CV) Pharmacokinetic Parameters of ULTOMIRIS in Patients with PNH who are Complement Inhibitor-Naïve and Patients Previously Treated with Eculizumab

		Pediatric Patients				Adult Patients			
		ALXN1210-PNH-304				ALXN1210-PNH-301		ALXN1210-PNH-302	
		N	Complement Inhibitor-Naïve	N	Previously Treated with Eculizumab	N	Complement Inhibitor-Naïve	N	Previously Treated with Eculizumab
C_{max} (mcg/mL)	LD	4	733 (14.5)	8	885 (19.3)	125	771 (21.5)	95	843 (24.1)
	MD	4	1490 (26.7)	8	1705 (9.7)	124	1,379 (20.0)	95	1,386 (19.4)
C_{trough} (mcg/mL)	LD	4	368 (14.7)	8	452 (15.1)	125	391 (35.0)	96	405 (29.9)
	MD	4	495 (21.3)	8	566 (12.2)	124	473 (33.4)	95	501 (28.6)

LD = Loading Dose; MD = Maintenance Dose

Table 16: Mean (%CV) Pharmacokinetic Parameters of ULTOMIRIS in Patients with aHUS

		Pediatric Patients (ALXN1210-aHUS-312)				Adult Patients (ALXN1210-aHUS-311)	
		N	< 20 kg MD Q4W	N	≥ 20 to < 40 kg MD Q8W	N	≥ 40 kg MD Q8W
C_{max} (mcg/mL)	LD	8	656 (38.1)	4	600 (17.3)	52	754 (35.2)
	MD	7	1,467 (37.8)	6	1,863 (15.3)	46	1,458 (17.6)
C_{trough} (mcg/mL)	LD	9	241 (52.1)	5	186 (16.5)	55	313 (33.9)
	MD	7	683 (46.1)	6	549 (34.1)	46	507 (42.5)

LD = Loading Dose; MD = Maintenance Dose; Q4W = Every 4 Weeks; Q8W = Every 8 Weeks

Table 17: Mean (%CV) Pharmacokinetic Parameters of ULTOMIRIS in Adult Patients with gMG

		N	Adult Patients (ALXN1210-MG-306)
C_{max} (mcg/mL)	LD	86	874 (21.1)
	MD	76	1548 (23.2)
C_{trough} (mcg/mL)	LD	85	418 (27.6)
	MD	70	587 (29.6)

LD = Loading Dose; MD=Maintenance Dose

Distribution

The mean (standard deviation [SD]) volume of distribution at steady state in patients with PNH, aHUS, and gMG are shown in Table 18.

Elimination

The mean (standard deviation [SD]) terminal elimination half-life and clearance of ravulizumab-cwvz are shown in Table 18.

Table 18: Distribution, Biotransformation, and Elimination parameters

	Adult patients with PNH	Adult and pediatric patients with aHUS	Adult patients with gMG
Distribution			
Volume of distribution at steady state (liters) Mean (SD)	5.35 (0.92)	5.22 (1.85)	5.74 (1.16)
Biotransformation and Elimination			
Terminal elimination half-life (days) Mean (SD)	49.7 (8.9)	51.8 (16.2)	56.6 (8.36)
Clearance (liters/day) Mean (SD)	0.08 (0.022)	0.08 (0.04)	0.08 (0.02)

Specific Populations

No clinically significant differences in the pharmacokinetics of ravulizumab-cwvz were observed based on sex, age (10 months to 83 years), race, hepatic impairment, or any degree of renal impairment, including patients with proteinuria or receiving dialysis.

Body weight was a clinically significant covariate on the pharmacokinetics of ravulizumab-cwvz.

Drug Interactions

No drug-drug interaction studies have been performed.

Intravenous immunoglobulin (IVIg) and FcRn blocker treatment may interfere with the endosomal neonatal FcRn recycling mechanism of monoclonal antibodies such as ravulizumab and thereby decrease serum ravulizumab concentrations *[see Drug Interactions (7.1, 7.2)]*.

Concomitant PE, PP, or IVIg treatment requires a supplemental dose of ULTOMIRIS *[see Dosage and Administration (2.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of ravulizumab-cwvz have not been conducted.

Genotoxicity studies have not been conducted with ravulizumab-cwvz.

Effects of ravulizumab-cwvz upon fertility have not been studied in animals. Intravenous injections of male and female mice with a murine anti-C5 antibody at up to 0.8-2.2 times the equivalent of the clinical dose of ULTOMIRIS had no adverse effects on mating or fertility.

14 CLINICAL STUDIES

14.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

The safety and efficacy of ULTOMIRIS in adult patients with PNH was assessed in two open-label, randomized, active-controlled, non-inferiority Phase 3 studies: PNH Study 301 and PNH Study 302. Study 301 enrolled patients with PNH who were complement inhibitor naïve and had active hemolysis. Study 302 enrolled patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months. The safety and efficacy of ULTOMIRIS in pediatric patients with PNH was assessed in PNH Study 304, open-label, Phase 3 study conducted in eculizumab-experienced and complement inhibitor treatment naïve pediatric patients with PNH.

In both adult studies, ULTOMIRIS was dosed intravenously in accordance with the weight-based dosing described in Section 2.2 (4 infusions of ULTOMIRIS over 26 weeks) above. Eculizumab was administered on Days 1, 8, 15, and 22, followed by maintenance treatment with 900 mg of eculizumab on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment, according to the approved dosing regimen of eculizumab which was the standard-of-care for PNH at the time of the studies.

Patients were vaccinated against meningococcal infection prior to or at the time of initiating treatment with ULTOMIRIS or eculizumab, or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. Prophylactic treatment with appropriate antibiotics beyond 2 weeks after vaccination was at the discretion of the provider.

Study in Complement-Inhibitor Naïve Adult Patients with PNH

The Complement-Inhibitor Naïve Study [ALXN1210-PNH-301; NCT02946463] was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 246 patients naïve to complement inhibitor treatment prior to study entry.

Patients with PNH with flow cytometric confirmation of at least 5% PNH cells were randomized 1:1 to either ULTOMIRIS or eculizumab. The mean total PNH granulocyte clone size was 85%, the mean total PNH monocyte clone size was 88%, and the mean

total PNH RBC clone size was 39%. Ninety-eight percent of patients had a documented PNH-associated condition diagnosed prior to enrollment on the trial: anemia (85%), hemoglobinuria (63%), history of aplastic anemia (32%), history of renal failure (12%), myelodysplastic syndrome (5%), pregnancy complications (3%), and other (16%). Major baseline characteristics were balanced between treatment groups. Table 19 provides the baseline characteristics for the patients enrolled in the complement-inhibitor naïve study.

Table 19: Baseline Characteristics in the Complement-Inhibitor Naïve Study

Parameter	Statistics	ULTOMIRIS (N=125)	Eculizumab (N=121)
Age (years) at first infusion in study	Mean (SD) Min, max	44.8 (15.2) 18, 83	46.2 (16.2) 18, 86
Sex Male	n (%)	65 (52.0)	69 (57.0)
Race Asian White Black or African American American Indian or Alaska Native Other Not reported	n (%)	 72 (57.6) 43 (34.4) 2 (1.6) 1 (0.8) 4 (3.2) 3 (2.4)	 57 (47.1) 51 (42.1) 4 (3.3) 1 (0.8) 4 (3.3) 4 (3.3)
Pre-treatment LDH levels (U/L)	Median Min, max	1513.5 (378.0, 3759.5)	1445.0 (423.5, 3139.5)
Units of pRBC/whole blood transfused within 12 months prior to first dose	Median Min, max	6.0 (1, 44)	6.0 (1, 32)
Antithrombotic agents used within 28 days prior to first dose	n (%)	22 (17.6)	22 (18.2)
Patients with a history of MAVE [a]	n (%)	17 (13.6)	25 (20.7)
Patients with a history of thrombosis	n (%)	17 (13.6)	20 (16.5)
Patients with concomitant anticoagulant treatment	n (%)	23 (18.4)	28 (23.1)

[a] MAVE = major adverse vascular event

Efficacy was established based upon transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance was defined as patients who did not receive a transfusion and did not meet the protocol specified guidelines for transfusion from baseline up to Day 183. Supportive efficacy data included the percent change from baseline in LDH levels, the proportion of patients with breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy and the proportion of patients with stabilized hemoglobin.

Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across endpoints in the complement-inhibitor naïve treatment population described in Table 20 below.

Table 20: Efficacy Results in the Complement-Inhibitor Naïve Study

	ULTOMIRIS (N=125)	Eculizumab (N=121)	Statistic for Comparison	Treatment Effect (95% CI)
Transfusion avoidance rate	73.6%	66.1%	Difference in rate	6.8 (-4.66, 18.14)
LDH normalization	53.6%	49.4%	Odds ratio	1.19 (0.80, 1.77)
LDH percent change	-76.84%	-76.02%	Difference in % change from baseline	-0.83 (-5.21, 3.56)
Breakthrough hemolysis	4.0%	10.7%	Difference in rate	-6.7 (-14.21, 0.18)
Hemoglobin stabilization	68.0%	64.5%	Difference in rate	2.9 (-8.80, 14.64)

Note: LDH = lactate dehydrogenase; CI = confidence interval

For the transfusion avoidance endpoint, treatment differences (95% CIs) are based on estimated differences in percent with 95% CI. For the lactate dehydrogenase normalization endpoint, the adjusted prevalence within each treatment is displayed.

There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. Patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment.

Study in Eculizumab-Experienced Adult Patients with PNH

The study in eculizumab-experienced patients [ALXN1210-PNH-302; NCT03056040] was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 195 patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.

Patients who demonstrated clinically stable disease after being treated with eculizumab for at least the prior 6 months were randomized 1:1 to either continue eculizumab or to switch to ULTOMIRIS. The mean total PNH granulocyte clone size was 83%, the mean total PNH monocyte clone size was 86%, and the mean total PNH RBC clone size was 60%. Ninety five percent of patients had a documented PNH-associated condition diagnosed prior to enrollment in the trial: anemia (67%), hematuria or hemoglobinuria (49%), history of aplastic anemia (37%), history of renal failure (9%), myelodysplastic syndrome (5%), pregnancy complication (7%), and other (14%). Major baseline characteristics were balanced between the two treatment groups. Table 21 provides the baseline characteristics for the patients enrolled in the eculizumab-experienced study.

Table 21: Baseline Characteristics in Eculizumab-Experienced Adult Patients with PNH

Parameter	Statistics	ULTOMIRIS (N=97)	Eculizumab (N=98)
Age (years) at first infusion in study	Mean (SD) Min, max	46.6 (14.41) 18, 79	48.8 (13.97) 23, 77
Race White Asian Black or African American Other Not reported Unknown Multiple	n (%)	 50 (51.5) 23 (23.7) 5 (5.2) 2 (2.1) 13 (13.4) 3 (3.1) 1 (1.0)	 61 (62.2) 19 (19.4) 3 (3.1) 1 (1.0) 13 (13.3) 1 (1.0) 0
Sex Male	n (%)	 50 (51.5)	 48 (49.0)
Pre-treatment LDH levels (U/L)	Median Min, max	224.0 135.0, 383.5	234.0 100.0, 365.5
Units of pRBC/whole blood transfused within 12 months prior to first dose	Median Min, max	4.0 (1, 32)	2.5 (2, 15)
Antithrombotic agents used within 28 days prior to first dose	n (%)	20 (20.6)	13 (13.3)
Patients with a history of MAVE[a]	n (%)	28 (28.9)	22 (22.4)
Patients with a history of thrombosis	n (%)	27 (27.8)	21 (21.4)
Patients with concomitant anticoagulant treatment	n (%)	22 (22.7)	16 (16.3)

[a] MAVE = major adverse vascular event

Efficacy was established based on hemolysis as measured by LDH percent change from baseline to Day 183 and supportive efficacy data was transfusion avoidance, proportion of patients with stabilized hemoglobin, and the proportion of patients with breakthrough hemolysis through Day 183.

Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across endpoints in the patients with PNH previously treated with eculizumab described in Table 22 below.

Table 22: Efficacy Results in the Eculizumab-Experienced Adult Patients with PNH Eculizumab-Experienced Study

	ULTOMIRIS N = 97	Eculizumab N = 98	Statistic for Comparison	Treatment Effect (95% CI)
LDH percent change	-0.82%	8.4%	Difference in % change from baseline	9.2 (-0.42, 18.8)
Breakthrough hemolysis	0%	5.1%	Difference in rate	5.1 (-8.9, 19.0)
Transfusion avoidance	87.6 %	82.7%	Difference in rate	5.5 (-4.3, 15.7)
Hemoglobin stabilization	76.3%	75.5%	Difference in rate	1.4 (-10.4, 13.3)

Note: CI = confidence interval

There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. Patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment.

Study in Eculizumab-Experienced and Complement-Inhibitor Naïve Pediatric Patients with PNH

The pediatric study, ALXN1210-PNH-304, was a multi-center, open-label Phase 3 study conducted in eculizumab-experienced and complement inhibitor treatment-naïve pediatric patients with PNH. A total of 13 pediatric patients with PNH completed ULTOMIRIS treatment during the Primary Evaluation Period (26 weeks). Five of the 13 patients had never been treated with complement inhibitors and 8 patients were treated with eculizumab. Eleven of the thirteen patients were between 12 and 17 years of age at first infusion, with 2 patients under 12 years old (11 and 9 years old). Table 23 presents the baseline characteristics of the pediatric patients enrolled in Study ALXN1210-PNH-304.

Table 23: Baseline Characteristics for Pediatric Patients with PNH

Variable	Complement Inhibitor Treatment-naïve Patients (N = 5)	Eculizumab-Experienced Patients (N = 8)	All Patients (N = 13)
Sex, n (%)			
Male	4 (80.0)	1 (12.5)	5 (38.5)
Female	1 (20.0)	7 (87.5)	8 (61.5)
Age at first infusion (years)			
Mean (SD)	14.4 (2.2)	14.4 (3.1)	14.4 (2.7)
Median (min, max)	15.0 (11, 17)	15.0 (9, 17)	15.0 (9, 17)
Age at first infusion (years) category, n (%)			
<12 years	1 (20.0)	1 (12.5)	2 (15.4)
≥12 years	4 (80.0)	7 (87.5)	11 (84.6)
Baseline weight (kg)			
Mean (SD)	56.3 (11.6)	56.3 (12.2)	56.3 (11.5)
Median (min, max)	55.6 (39.5, 72.0)	55.5 (36.7, 69.0)	55.6 (36.7, 72.0)
Baseline weight (kg) category, n (%)			
≥30 to <40 kg	1 (20.0)	1 (12.5)	2 (15.4)
≥40 to <60 kg	3 (60.0)	4 (50.0)	7 (53.8)
≥60 to <100 kg	1 (20.0)	3 (37.5)	4 (30.8)
Units of pRBC/whole blood transfused within 12 months prior to first dose			
Median (min, max)	7.0 (3, 11)	2.0 (2, 2)	-
Pre-treatment LDH levels (U/L)			
Median (min, max)	588.5 (444, 2269.7)	251.5 (140.5, 487)	-

Note: Percentages were based on the total number of patients in each cohort, or overall.
kg = kilogram; max = maximum; min = minimum; SD = standard deviation.

Based on body weight, patients received a loading dose of ULTOMIRIS on Day 1, followed by maintenance treatment on Day 15 and once every 8 weeks (q8w) thereafter for patients weighing ≥20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg. For patients who entered the study on eculizumab therapy, Day 1 of study treatment was planned to occur 2 weeks from the patient's last dose of eculizumab.

The weight-based dose regimen of ravulizumab-cwvz provided inhibition of terminal complement in all patients throughout the entire 26-week treatment period regardless of prior experience with eculizumab. Following initiation of ravulizumab-cwvz treatment, steady-state therapeutic serum concentrations of ravulizumab-cwvz were achieved after the first dose and maintained throughout the primary evaluation period in both cohorts. Three of 5 complement inhibitor treatment-naïve patients and 6 out of 8 eculizumab-experienced patients achieved hemoglobin stabilization by Week 26, respectively. Transfusion avoidance was reached for 11 out of 13 of patients during the 26-week Primary Evaluation Period. One patient experienced breakthrough hemolysis during the extension period. Table 24 presents secondary efficacy outcomes for the primary evaluation period.

Table 24: Efficacy Outcomes from the 26-Week Primary Evaluation Period of Pediatric Patient Study in PNH (ALXN1210-PNH-304)

End Point	Treatment Naïve (N = 5)	Eculizumab Experienced (N = 8)
LDH- Percent Change from Baseline (%)[a]	-47.9 (-113.4, 17.5)	4.7 (-36.7, 46.0)
Transfusion Avoidance (%)[b]	60.0 (14.7, 94.7)	100.0 (63.1, 100.0)
Change in FACIT-Fatigue[a]	3.4 (-4.2, 11.0)	1.3 (-3.1, 5.7)
Hemoglobin Stabilization (%)[b]	60.0 (14.7, 94.7)	75.0 (34.9, 96.8)
Breakthrough Hemolysis (%)	0	0[c]

[a] 95% CIs for the mean obtained from t-distribution were presented.

[b] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.

[c] No patients experienced breakthrough hemolysis during the primary evaluation period. One patient experienced breakthrough hemolysis at 1.8 years during the extension period; however, at the time of the BTH event the patient had adequate C5 inhibition (free C5 < 0.5 µg/mL).

LDH = lactate dehydrogenase

A clinically relevant improvement from baseline in fatigue as assessed by Pediatric FACIT-Fatigue (i.e., mean improvement of > 3 units for Pediatric FACIT Fatigue scores) was sustained throughout the primary evaluation period in the 5-complement inhibitor treatment naïve patients. A slight improvement was also observed in eculizumab-experienced patients. However, patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment.

The efficacy of ULTOMIRIS in pediatric patients with PNH is similar to that observed in adult patients with PNH enrolled in pivotal studies.

14.2 Atypical Hemolytic Uremic Syndrome (aHUS)

The efficacy of ULTOMIRIS in patients with aHUS was assessed in 2 open-label, single-arm studies. Study ALXN1210-aHUS-311 enrolled adult patients who displayed signs of TMA. In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis.

Study ALXN1210-aHUS-312 enrolled pediatric patients who displayed signs of TMA. In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine level ≥97.5% percentile at screening or required dialysis. In both studies, enrollment criteria excluded patients presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, Shiga toxin *Escherichia coli* related hemolytic uremic syndrome (STEC-HUS) and genetic defect in cobalamin C metabolism. Patients with confirmed diagnosis of STEC-HUS after enrollment were excluded from the efficacy evaluation.

Study in Adult Patients with aHUS

The adult study [ALXN1210-aHUS-311; NCT02949128] was conducted in patients who were naïve to complement inhibitor treatment prior to study entry. The study consisted of a 26-week Initial Evaluation Period and patients were allowed to enter an extension period for up to 4.5 years.

A total of 56 patients with aHUS were evaluated for efficacy. Ninety-three percent of patients had extra-renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. At baseline, 71.4% (n = 40) of patients had Stage 5 chronic kidney disease (CKD). Fourteen percent had a medical history of kidney transplant and 51.8% were on dialysis at study entry. Eight patients entered the study with evidence of TMA for > 3 days after childbirth (ie, postpartum).

Table 25 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the Full Analysis Set.

Table 25: Demographics and Baseline Characteristics in Study ALXN1210-aHUS-311

Parameter	Statistics	ULTOMIRIS (N=56)
Age at time of first infusion (years)	Mean (SD) Min, max	42.2 (14.98) 19.5, 76.6
Sex Female	 n (%)	 37 (66.1)
Race [a] White Asian Unknown Other	n (%)	 29 (51.8) 15 (26.8) 8 (14.3) 4 (7.1)
Platelets (10^9/L) blood [normal range 130 to 400 × 10^9/L]	n Median (min,max)	56 95.25 (18, 473)
Hemoglobin (g/L) blood [normal range 115 to 160 g/L (female), 130 to 175 g/L (male)]	n Median (min,max)	56 85.00 (60.5, 140)
LDH (U/L) serum [normal range 120 to 246 U/L]	n Median (min,max)	56 508.00 (229.5, 3249)
eGFR (mL/min/1.73 m^2) [normal range ≥60 mL/min/1.73 m^2]	n (%) Mean (SD) Median (min,max)	55 15.86 (14.815) 10.00 (4, 80)

Note: Percentages are based on the total number of patients.

[a] Patients can have multiple races selected.

eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum.

The efficacy evaluation was based on Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥25% improvement in serum creatinine from baseline. Patients had to meet each Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Complete TMA Response was observed in 30 of the 56 patients (54%) during the 26-week Initial Evaluation Period as shown in Table 26.

Table 26: Efficacy Results in aHUS during the 26-Week Initial Evaluation Period (ALXN1210-aHUS-311)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	56	30	0.54 (0.40, 0.67)
Components of Complete TMA Response			
Platelet count normalization	56	47	0.84 (0.72, 0.92)
LDH normalization	56	43	0.77 (0.64, 0.87)
≥25% improvement in serum creatinine from baseline	56	33	0.59 (0.45, 0.72)
Hematologic normalization	56	41	0.73 (0.60, 0.84)

[a] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.
CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

One additional patient had a Complete TMA Response that was confirmed after the 26-week Initial Evaluation Period. Complete TMA Response was achieved at a median time of 86 days (range: 7 to 169 days). The median duration of Complete TMA Response was 7.97 months (range: 2.52 to 16.69 months). All responses were maintained through all available follow-up.

Other endpoints included platelet count change from baseline, dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR).

An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 118.52 × 10^9/L at baseline to 240.34 ×10^9/L at Day 8 and remaining above 227 × 10^9/L at all subsequent visits in the Initial Evaluation Period (26 weeks).

Renal function, as measured by eGFR, was improved or maintained during ULTOMIRIS therapy. The mean eGFR (+/- SD) increased from 15.86 (14.82) at baseline to 51.83 (39.16) by 26 weeks. In patients with Complete TMA Response, renal function continued to improve after the Complete TMA Response was achieved.

Seventeen of the 29 patients (59%) who required dialysis at study entry discontinued dialysis by the end of the available follow-up and 6 of 27 (22%) patients were off dialysis at baseline were on dialysis at last available follow-up.

Study in Pediatric Patients with aHUS

The Pediatric Study [ALXN1210-aHUS-312; NCT03131219] is a 26-week ongoing, multicenter, single-arm study conducted in 16 pediatric patients.

A total of 14 eculizumab-naïve patients with documented diagnosis of aHUS were enrolled and included in this interim analysis. The median age at the time of first infusion was 5.2 years (range 0.9, 17.3 years). The overall mean weight at Baseline was 19.8 kg; half of the patients were in the baseline weight category ≥10 to <20 kg. The majority of patients (71%) had pretreatment extra-renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline.

At baseline, 35.7% (n = 5) of patients had a CKD Stage 5. Seven percent had history of prior kidney transplant and 35.7% were on dialysis at study entry.

Table 27 presents the baseline characteristics of the pediatric patients enrolled in Study ALXN1210-aHUS-312.

Table 27: Demographics and Baseline Characteristics in Study ALXN1210-aHUS-312

Parameter	Statistics	ULTOMIRIS (N = 14)
Age at time of first infusion (years) category	n (%)	
Birth to < 2 years		2 (14.3)
2 to < 6 years		7 (50.0)
6 to < 12 years		4 (28.6)
12 to < 18 years		1 (7.1)
Sex	n (%)	
Female		9 (64.3)
Race[a]	n (%)	
White		7 (50.0)
Asian		4 (28.6)
Black or African American		2 (14.3)
American Indian or Alaskan Native		1 (7.1)
Unknown		1 (7.1)
Platelets (10^9/L) blood [normal range 229 to 533 × 10^9/L]	Median (min, max)	64.00 (14, 125)
Hemoglobin (g/L) blood [normal range 107 to 131 g/L]	Median (min, max)	74.25 (32, 106)
LDH (U/L) serum [normal range 165 to 395 U/L]	Median (min, max)	2077.00 (772, 4985)
eGFR (mL/min/1.73 m^2) [normal range ≥60 mL/min/1.73 m^2]	Mean (SD) Median (min, max)	28.4 (23.11) 22.0 (10, 84)

Note: Percentages are based on the total number of patients.

[a] Patients can have multiple races selected.

eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum.

Efficacy evaluation was based upon Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥25% improvement in serum creatinine from baseline. Patients had to meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Complete TMA Response was observed in 10 of the 14 patients (71%) during the 26-week Initial Evaluation Period as shown in Table 28.

Table 28: Efficacy Results in aHUS during the 26-Week Initial Evaluation Period (ALXN1210-aHUS-312)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	14	10	0.71 (0.42, 0.92)
Components of Complete TMA Response			
Platelet count normalization	14	13	0.93 (0.66, 0.99)
LDH normalization	14	12	0.86 (0.57, 0.98)
≥25% improvement in serum creatinine from baseline	14	11	0.79 (0.49, 0.95)
Hematologic normalization	14	12	0.86 (0.57, 0.98)

Note: 1 patient withdrew from study after receiving 2 doses of ravulizumab-cwvz.

[a] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.

CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Complete TMA Response during the Initial Evaluation Period was achieved at a median time of 30 days (range:15 to 88 days). The median duration of Complete TMA Response was 5.08 months (range: 3.08 to 5.54 months). All responses were maintained through all available follow-up.

Other endpoints included platelet count change from baseline, dialysis requirement, and renal function as evaluated by eGFR.

An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 60.50×10^9/L at baseline to 296.67×10^9/L at Day 8 and remained above 296×10^9/L at all subsequent visits in the Initial Evaluation Period (26 weeks). The mean eGFR (+/- SD) increased from 28.4 (23.11) at baseline to 108.0 (63.21) by 26 weeks.

Four of the 5 patients who required dialysis at study entry were able to discontinue dialysis after the first month in study and for the duration of ULTOMIRIS treatment. No patient started dialysis during the study.

14.3 Generalized Myasthenia Gravis (gMG)

The efficacy of ULTOMIRIS for the treatment of gMG was demonstrated in a randomized, double-blind, placebo-controlled, multicenter study (ALXN1210-MG-306; NCT03920293). Patients were randomized 1:1 to either receive ULTOMIRIS (n=86) or placebo (n=89) for 26 weeks. ULTOMIRIS was administered intravenously according to the weight-based recommended dosage *[see Dosage and Administration (2.2)]*.

Patients with gMG with a positive serologic test for anti-AChR antibodies, Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV, and Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥6 were enrolled. Baseline and disease characteristics were similar between treatment groups (including age at first dose [mean of 58 years for ULTOMIRIS versus 53 years for placebo], gender [51% female for ULTOMIRIS versus 51% female for placebo], race as White, Asian, and Black or African American [78%, 17%, and 2% for ULTOMIRIS versus 69%, 18%, and 5% for placebo, respectively], and duration of MG since diagnosis [mean of 10 years, ranging from 0.5 to 39.5 years, for ULTOMIRIS versus mean of 10.0 years, ranging from 0.5 to 36.1 years, for placebo].

Over 80% of patients were receiving acetylcholinesterase inhibitors, 70% were receiving corticosteroids, and 68% were receiving non-steroidal immunosuppressants (ISTs) at study entry. Patients on concomitant medications to treat gMG were permitted to continue on therapy throughout the course of the study.

The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the MG-ADL total score at Week 26. The MG-ADL is a categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. The total score ranges from 0 to 24, with the higher scores indicating more impairment.

The secondary endpoints, also assessed from baseline to Week 26, included the change in the Quantitative MG total score (QMG). The QMG is a 13-item categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness. A total score ranges from 0 to 39, where higher scores indicate more severe impairment.

Other secondary endpoints included the proportion of patients with improvements of at least 5 and 3 points in the QMG and MG-ADL total scores, respectively.

Treatment with ULTOMIRIS demonstrated a statistically significant change in the MG-ADL and QMG total scores from baseline at Week 26 as compared to placebo (Table 29).

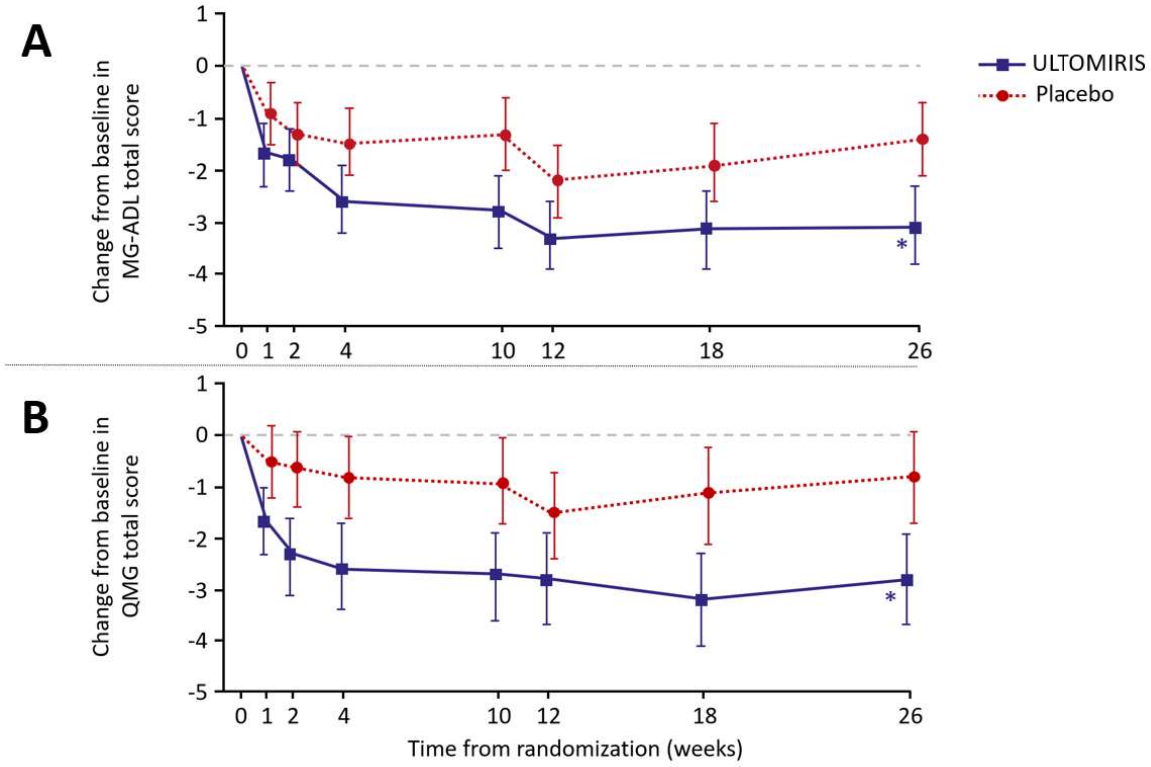
Table 29: Efficacy Results in Patients with gMG

Efficacy Endpoints: Change from Baseline At Week 26	**Placebo (n = 89) LS Mean**	**ULTOMIRIS (n = 86) LS Mean**	**Treatment Effect (95% CI)**	**p-value***
Primary Endpoint				
MG-ADL	-1.4	-3.1	-1.6 (-2.6, -0.7)	<0.001
Secondary Endpoint				
QMG	-0.8	-2.8	-2.0 (-3.2, -0.8)	<0.001

*p-value calculated using mixed effect model for repeated measures
Abbreviations: CI = confidence interval, LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; QMG = Quantitative Myasthenia Gravis score for disease severity

The proportion of QMG responders with at least a 5-point improvement at week 26 was greater for ULTOMIRIS (30.0%) compared to placebo (11.3%) p = 0.005. The proportion of MG-ADL responders with at least a 3-point improvement at week 26 was also greater for ULTOMIRIS (56.7%) compared to placebo (34.1%). The proportion of clinical responders at higher response thresholds (≥4-, 5-, 6-, 7-, or 8-point improvement on MG-ADL, and ≥6-, 7-, 8-, 9-, or 10-point improvement on QMG) was consistently greater for ULTOMIRIS compared to placebo.

Figure 1: Change from Baseline in MG-ADL Total Score (A) and QMG Total Score (B) Through Week 26 of the Randomized Controlled Period of ALXN1210-MG-306 (Mean and 95% CI)



Note: *p<0.001 versus placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

ULTOMIRIS (ravulizumab-cwvz) injection 100 mg/mL is translucent, clear to yellowish color solution supplied in single-dose vials as:

- 300 mg/3 mL (100 mg/mL) carton containing one vial: NDC 25682-025-01
- 1,100 mg/11 mL (100 mg/mL) carton containing one vial: NDC 25682-028-01

ULTOMIRIS (ravulizumab-cwvz) injection 10 mg/mL is clear to translucent, slight whitish color solution supplied in single-dose vials as:

- 300 mg/30 mL (10 mg/mL) carton containing one vial: NDC 25682-022-01

Store ULTOMIRIS vials refrigerated at 2°C - 8°C (36°F - 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

Refer to *Dosage and Administration (2)* for information on the stability and storage of diluted solutions of ULTOMIRIS.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Meningococcal Infection

Advise patients of the risk of meningococcal infection/sepsis. Inform patients that they are required to receive meningococcal vaccination at least 2 weeks prior to receiving the first dose of ULTOMIRIS, if they have not previously been vaccinated. They are required to be revaccinated according to current medical guidelines for meningococcal vaccines use while on ULTOMIRIS therapy. Inform patients that vaccination may not prevent meningococcal infection. Inform patients about the signs and symptoms of meningococcal infection/sepsis, and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms are as follows:

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Inform patients that they will be given an ULTOMIRIS Patient Safety Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

Other Infections

Counsel patients of the increased risk of infections, particularly those due to encapsulated bacteria, especially *Neisseria* species. Advise patients of the need for vaccination against meningococcal infections according to current medical guidelines. Counsel patients about gonorrhea prevention and advise regular testing for patients at risk. Advise patients to report any new signs and symptoms of infection.

Discontinuation

Inform patients with PNH or aHUS that they may develop hemolysis or TMA, respectively, when ULTOMIRIS is discontinued and that they will be monitored by their healthcare professional for at least 16 weeks for PNH or at least 12 months for aHUS following ULTOMIRIS discontinuation.

Inform patients who discontinue ULTOMIRIS to keep the ULTOMIRIS Patient Safety Card with them for eight months after the last ULTOMIRIS dose, because the increased risk of meningococcal infection persists for several months following discontinuation of ULTOMIRIS.

Infusion-Related Reactions

Advise patients that administration of ULTOMIRIS may result in infusion-related reactions.

Manufactured by:

Alexion Pharmaceuticals, Inc.
121 Seaport Boulevard
Boston, MA 02210 USA

US License Number 1743

This product, or its use, may be covered by one or more US patents, including US Patent No. 9,079,949; 9,107,861; 9,206,251; 9,371,377; 9,663,574; 9,803,007; and 10,227,400 in addition to others including patents pending.

ULTOMIRIS is a trademark of Alexion Pharmaceuticals, Inc.

TABLE OF CONTENTS

LIST OF TABLES

1.7　同種同効品一覧表

本剤は、全身型重症筋無力症患者において終末補体介在性の神経筋伝達障害を抑制する抗補体(C5)モノクローナル抗体の点滴静注製剤である。ミニマルターゲッティング技術を用いてエクリズマブの重鎖の 4 アミノ酸を置換したリサイクリング抗体である。

本邦では全身型重症筋無力症に係る効能・効果を有する医薬品として、コリンエステラーゼ阻害剤（ピリドスチグミン臭化物、アンベノニウム塩化物等)、ステロイド（プレドニゾロン、デキサメタゾン等)、カルシニューリン阻害剤（シクロスポリン、タクロリムス水和物)、静注用人免疫グロブリン製剤（ポリエチレングリコール処理人免疫グロブリン)、補体 C5 阻害剤（エクリズマブ)、及び抗 FcRn 抗体フラグメント製剤（エフガルチギモド　アルファ）が承認されている。

これら重症筋無力症又は全身型重症筋無力症の効能・効果を有する医薬品のうち、本剤の作用機序、効能・効果「全身型重症筋無力症（免疫グロブリン大量静注療法又は血液浄化療法による症状の管理が困難な場合に限る)」、及び臨床的位置づけの観点から、エクリズマブ（ソリリス点滴静注)、エフガルチギモド　アルファ（ウィフガート点滴静注)、ポリエチレングリコール処理人免疫グロブリン G（献血ヴェノグロブリン IH 静注)、タクロリムス水和物（プログラフ顆粒／カプセル)、及びシクロスポリン（ネオーラルカプセル／内用液）を同種同効品として一覧（Table 1）に示す。なお、複数の製品が承認されている品目については代表となる品目を示し、その添付文書を添付した。

Table 1:　　同種同効品一覧表

販売名	ユルトミリス点滴静注 300 ㎎ ユルトミリス HI 点滴静注 300mg/3mL、 1100mg/11mL	ソリリス点滴静注 300 mg	ウィフガート点滴静注 400mg	献血ヴェノグロブリン IH5%静注 0.5g/10mL、1g/20mL、2.5g/50mL、5g/100mL、10g/200mL 献血ヴェノグロブリン IH 10%静注 0.5g/5mL、2.5g/25mL、5g/50mL、10g/100mL、20g/200mL	プログラフカプセル 0.5mg 同 1mg プログラフ顆粒 0.2mg、1mg	ネオーラル内用液 10% ネオーラル 10mg カプセル、25mg カプセル、50mg カプセル
一般名	ラブリズマブ（遺伝子組換え）	エクリズマブ（遺伝子組換え）	エフガルチギモド　アルファ（遺伝子組換え）	ポリエチレングリコール処理人免疫グロブリン	タクロリムス水和物	シクロスポリン
会社名	アレクシオンファーマ合同会社	アレクシオンファーマ合同会社	アルジェニクスジャパン株式会社	一般社団法人日本血液製剤機構	アステラス製薬株式会社	ノバルティスファーマ株式会社
効能又は効果	• 発作性夜間ヘモグロビン尿症 • 非典型溶血性尿毒症症候群 • 全身型重症筋無力症	• 発作性夜間ヘモグロビン尿症における溶血抑制 • 非典型溶血性尿毒症症候群における血栓性微小血管障害の抑制 • 全身型重症筋無力症（免疫グロブリン大量静注療法又は血液浄化療法による症状の管理が困難な場合に限る） • 視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の再発予防	全身型重症筋無力症（ステロイド剤又はステロイド剤以外の免疫抑制剤が十分に奏効しない場合に限る）	1. 低並びに無ガンマグロブリン血症 2. 重症感染症における抗生物質との併用 3. 特発性血小板減少性紫斑病（他剤が無効で，著明な出血傾向があり，外科的処置又は出産等一時的止血管理を必要とする場合） 4. 川崎病の急性期（重症であり，冠動脈障害の発生の危険がある場合） 5. 多発性筋炎・皮膚筋炎における筋力低下の改善（ステロイド剤が効果不十分な場合に限る） 6. 慢性炎症性脱髄性多発根神経炎（多巣性運動ニューロパチーを含む）の筋力低下の改善	• 下記の臓器移植における拒絶反応の抑制 腎移植、肝移植、心移植、肺移植、膵移植、小腸移植 • 骨髄移植における拒絶反応及び移植片対宿主病の抑制 • 重症筋無力症 • 関節リウマチ（既存治療で効果不十分な場合に限る） • ループス腎炎（ステロイド剤の投与が効果不十分、又は副作用により困難な場合） • 難治性（ステロイド抵抗性、ステロイド依存性）の活動期潰瘍性大腸炎（中等症～重症に限る） • 多発性筋炎・皮膚筋炎に合併する間質性肺炎	• 下記の臓器移植における拒絶反応の抑制 腎移植、肝移植、心移植、肺移植、膵移植、小腸移植 • 骨髄移植における拒絶反応及び移植片対宿主病の抑制 • ベーチェット病（眼症状のある場合）、及びその他の非感染性ぶどう膜炎（既存治療で効果不十分であり、視力低下のおそれのある活動性の中間部又は後部の非感染性ぶどう膜炎に限る） • 尋常性乾癬（皮疹が全身の 30%以上に及ぶものあるいは難治性の場合）、膿疱性乾癬、乾癬性紅皮症、関節症性乾癬

販売名	ユルトミリス点滴静注 300 ㎎ ユルトミリス HI 点滴静注 300mg/3mL、 1100mg/11mL	ソリリス点滴静注 300 mg	ウィフガート点滴静注 400mg	献血ヴェノグロブリン IH5%静注 0.5g/10mL、1g/20mL、2.5g/50mL、5g/100mL、10g/200mL 献血ヴェノグロブリン IH 10%静注 0.5g/5mL、2.5g/25mL、5g/50mL、10g/100mL、20g/200mL	プログラフカプセル 0.5mg 同 1mg プログラフ顆粒 0.2mg、1mg	ネオーラル内用液 10% ネオーラル 10mg カプセル、25mg カプセル、50mg カプセル
				7. 慢性炎症性脱髄性多発根神経炎（多巣性運動ニューロパチーを含む）の運動機能低下の進行抑制（筋力低下の改善が認められた場合） 8. 全身型重症筋無力症（ステロイド剤又はステロイド剤以外の免疫抑制剤が十分に奏効しない場合に限る） 9. 天疱瘡（ステロイド剤の効果不十分な場合） 10. 血清 IgG2 値の低下を伴う，肺炎球菌又はインフルエンザ菌を起炎菌とする急性中耳炎，急性気管支炎又は肺炎の発症抑制（ワクチン接種による予防及び他の適切な治療を行っても十分な効果が得られず，発症を繰り返す場合に限る）* 11. 水疱性類天疱瘡（ステロイド剤の効果不十分な場合） 12. ギラン・バレー症候群（急性増悪期で歩行困		• 再生不良性貧血、赤芽球癆 • ネフローゼ症候群（頻回再発型あるいはステロイドに抵抗性を示す場合） • 全身型重症筋無力症（胸腺摘出後の治療において、ステロイド剤の投与が効果不十分、又は副作用により困難な場合） • アトピー性皮膚炎（既存治療で十分な効果が得られない患者） • 川崎病の急性期（重症であり、冠動脈障害の発生の危険がある場合）**

販売名	ユルトミリス点滴静注 300 ㎎ ユルトミリス HI 点滴静注 300mg/3mL、 1100mg/11mL	ソリリス点滴静注 300 mg	ウィフガート点滴静注 400mg	献血ヴェノグロブリン IH5%静注 0.5g/10mL、1g/20mL、2.5g/50mL、5g/100mL、10g/200mL 献血ヴェノグロブリン IH 10%静注 0.5g/5mL、2.5g/25mL、5g/50mL、10g/100mL、20g/200mL	プログラフカプセル 0.5mg 同 1mg プログラフ顆粒 0.2mg、1mg	ネオーラル内用液 10% ネオーラル 10mg カプセル、25mg カプセル、50mg カプセル
				難な重症例） 13.抗ドナー抗体陽性腎移植における術前脱感作		
添付文書改訂日	2021 年 10 月作成	2020 年 12 月改訂（第 2 版）	2022 年 5 月作成(第 4 版)	2021 年 1 月改訂（第 38 版）	2020 年 4 月改訂（第 2 版）	2020 年 2 月改訂（第 1 版）

*「献血ヴェノグロブリン IH5%静注 10g/200mL」を除く　　**「ネオーラル内用液 10%」のみ

＊＊2022年１月改訂（第３版）
＊2020年12月改訂（第２版）

貯　　法：凍結を避け、２～８℃で保存
有効期間：30ヵ月

日本標準商品分類番号
876399

承認番号	22200AMX00316000
販売開始	2010年６月

抗補体（C5）モノクローナル抗体製剤
エクリズマブ（遺伝子組換え）点滴静注製剤
生物由来製品、劇薬、処方箋医薬品[注)]

ソリリス®点滴静注300mg

Eculizumab (Genetical Recombination)
SOLIRIS® for Intravenous Infusion 300mg

注）注意－医師等の処方箋により使用すること

1. 警告

1.1 本剤の投与により、髄膜炎菌感染症を発症することがあり、死亡例も認められているため、以下の点に十分注意すること。[5.1、11.1.1 参照]

1.1.1 本剤の投与に際しては、髄膜炎菌感染症の初期徴候（発熱、頭痛、項部硬直等）に注意して観察を十分に行い、髄膜炎菌感染症が疑われた場合には、直ちに診察し、抗菌剤の投与等の適切な処置を行うこと。

1.1.2 緊急な治療を要する場合等を除いて、原則、本剤投与前に髄膜炎菌に対するワクチンを接種すること。必要に応じてワクチンの追加接種を考慮すること。

1.1.3 髄膜炎菌感染症は致命的な経過をたどることがあるので、緊急時に十分に措置できる医療施設及び医師のもとで、あるいは髄膜炎菌感染症の診断及び治療が可能な医療施設との連携下で投与すること。

1.1.4 髄膜炎菌感染症のリスクについて患者に説明し、当該感染症の初期徴候を確実に理解させ、髄膜炎菌感染症に関連する副作用が発現した場合には、主治医に連絡するよう患者に注意を与えること。

1.2 本剤は、発作性夜間ヘモグロビン尿症、非典型溶血性尿毒症症候群、全身型重症筋無力症あるいは視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）に十分な知識を持つ医師のもとで、治療上の有益性が危険性を上まわると判断される場合にのみ投与すること。また、本剤投与開始に先立ち、本剤は疾病を完治させる薬剤ではないことを含め、本剤の有効性及び危険性を患者又はその家族に十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

2.1 髄膜炎菌感染症に罹患している患者［症状を悪化させるおそれがある。］

2.2 本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	成分		1バイアル（ストッパー付）30mL中の分量
ソリリス点滴静注300mg	有効成分	エクリズマブ（遺伝子組換え）	300mg
	添加剤	塩化ナトリウム	263.1mg
		リン酸二水素ナトリウム一水和物	13.8mg
		リン酸一水素ナトリウム七水和物	53.4mg
		ポリソルベート80	6.6mg

本剤は、マウス骨髄腫由来細胞を用いて製造される。製造工程において、培地成分としてウシの血清由来成分（アルブミン）及びウシの胎仔由来成分（血清）を使用している。

3.2 製剤の性状

販　売　名	ソリリス点滴静注300mg
性　　状	無色澄明な液
pH	pH6.8～7.2
浸 透 圧 比（生理食塩液対比）	約１（日局生理食塩液により希釈後（5mg/mL））

4. 効能又は効果

○発作性夜間ヘモグロビン尿症における溶血抑制
○非典型溶血性尿毒症症候群における血栓性微小血管障害の抑制
○全身型重症筋無力症（免疫グロブリン大量静注療法又は血液浄化療法による症状の管理が困難な場合に限る）
○視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の再発予防

5. 効能又は効果に関連する注意

〈効能共通〉

＊5.1 本剤は補体C5の開裂を阻害し、終末補体複合体C5b-9の生成を抑制すると考えられるため、髄膜炎菌をはじめとする莢膜形成細菌による感染症を発症しやすくなる可能性があることから、本剤の有効性及び安全性を十分に理解した上で、本剤投与の是非を慎重に検討し、適切な対象患者に対し投与を開始すること。また、本剤投与に際しては、緊急な治療を要する場合等を除いて、原則、本剤投与開始の少なくとも２週間前までに髄膜炎菌に対するワクチンを接種すること。特に小児への本剤投与に際しては、肺炎球菌、インフルエンザ菌b型に対するワクチンの接種状況を確認し、未接種の場合にはそれぞれのワクチンの接種を検討すること。[1.1、9.1.1、9.1.2、11.1.1、11.1.2、17.1 参照]

〈発作性夜間ヘモグロビン尿症における溶血抑制〉

5.2 フローサイトメトリー法等により検査を行い、発作性夜間ヘモグロビン尿症と確定診断された患者に投与を開始すること。

5.3 本剤を投与開始する際には、溶血のため赤血球輸血が必要と考えられ、今後も輸血の継続が見込まれる患者を対象とすること。

5.4 本剤による血栓塞栓症の抑制効果、腎機能改善効果及び延命効果は確認されていない。

5.5 本剤の急性溶血発作に対する改善効果は確認されていない。

5.6 本剤投与によりPNH赤血球クローンが増加するため、本剤を中止した場合に重篤な血管内溶血が認められるおそれがあることから、本剤の有効性及び安全性を十分に理解した上で、本剤投与の是非を慎重に検討し、適切な対象患者に対し投与を開始すること。

〈非典型溶血性尿毒症症候群における血栓性微小血管障害の抑制〉

5.7 補体制御異常による非典型溶血性尿毒症症候群※の患者に使用すること。

※「非典型溶血性尿毒症症候群（aHUS）診療ガイド2015」（日本腎臓学会・日本小児科学会）を参考にすること。

5.8 二次性血栓性微小血管症の患者に対する本剤の有効性及び安全性は確立していない（使用経験がない）。

〈全身型重症筋無力症（免疫グロブリン大量静注療法又は血液浄化療法による症状の管理が困難な場合に限る）〉

5.9 本剤は、抗アセチルコリン受容体抗体陽性の患者に投与すること。

〈視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の再発予防〉

5.10 本剤は、抗アクアポリン４抗体陽性の患者に投与すること。

5.11 視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）※の患者に使用すること。

※「多発性硬化症・視神経脊髄炎診療ガイドライン2017」（日本神経学会）を参考にすること。

6. 用法及び用量

〈発作性夜間ヘモグロビン尿症における溶血抑制〉

通常、成人には、エクリズマブ（遺伝子組換え）として、１回600mgから投与を開始する。初回投与後、週１回の間隔で初回投与を含め合計４回点滴静注し、その１週間後（初回投与から４週間後）から１回900mgを２週に１回の間隔で点滴静注する。

〈非典型溶血性尿毒症症候群における血栓性微小血管障害の抑制〉

通常、エクリズマブ（遺伝子組換え）として、下記の用法・用量で点滴静注する。

年齢又は体重	導入期	維持期
18歳以上	１回900mgを 週１回で計４回	初回投与４週間後から １回1200mgを２週に１回
18歳未満		
40kg以上	１回900mgを 週１回で計４回	初回投与４週間後から １回1200mgを２週に１回
30kg以上 40kg未満	１回600mgを 週１回で計２回	初回投与２週間後から １回900mgを２週に１回
20kg以上 30kg未満	１回600mgを 週１回で計２回	初回投与２週間後から １回600mgを２週に１回
10kg以上 20kg未満	１回600mgを 週１回で計１回	初回投与１週間後から １回300mgを２週に１回
５kg以上 10kg未満	１回300mgを 週１回で計１回	初回投与１週間後から １回300mgを３週に１回

〈全身型重症筋無力症（免疫グロブリン大量静注療法又は血液浄化療法による症状の管理が困難な場合に限る）及び視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の再発予防〉

通常、成人には、エクリズマブ（遺伝子組換え）として、１回900mgから投与を開始する。初回投与後、週１回の間隔で初回投与を含め合計４回点滴静注し、その１週間後（初回投与から４週間後）から１回1200mgを２週に１回の間隔で点滴静注する。

7. 用法及び用量に関連する注意

〈発作性夜間ヘモグロビン尿症における溶血抑制〉

7.1 本剤の血中濃度の低下により急性の溶血発作の発現が懸念されるため、投与間隔を遵守すること。

7.2 本剤投与開始２週までに血清中乳酸脱水素酵素（LDH）活性の低下が認められない場合には、本剤の投与継続の要否を検討すること。

〈非典型溶血性尿毒症症候群における血栓性微小血管障害の抑制〉

7.3 本剤の血中濃度の低下により、血栓性微小血管障害の増悪が懸念されるため、投与間隔を遵守すること。

〈全身型重症筋無力症（免疫グロブリン大量静注療法又は血液浄化療法による症状の管理が困難な場合に限る）〉

7.4 本剤の血中濃度低下により症状悪化が懸念されるため、投与間隔を遵守すること。

7.5 本剤の全身型重症筋無力症患者を対象とした臨床試験では、ほとんどの治療反応例で投与開始後12週までに症状の改善が得られた。全身型重症筋無力症患者で他の免疫抑制剤を併用している患者においては、髄膜炎菌感染症のリスクが高い可能性があることから、リスクベネフィットを考慮し、投与開始後12週までに症状の改善が認められない患者では、本剤の投与中止を検討すること。

〈視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の再発予防〉

7.6 本剤の血中濃度低下により再発のおそれがあるため、投与間隔を遵守すること。

7.7 本剤を一定期間投与後、再発の頻度について検討し、再発の頻度の減少が認められない患者では、本剤の投与中止を検討すること。

〈非典型溶血性尿毒症症候群における血栓性微小血管障害の抑制、全身型重症筋無力症（免疫グロブリン大量静注療法又は血液浄化療法による症状の管理が困難な場合に限る）及び視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の再発予防〉

7.8 血漿交換により本剤の一部が除去されること、新鮮凍結血漿内には補体C5が含まれることから、本剤投与中に血漿交換又は新鮮凍結血漿輸注を施行する必要がある場合は、血漿交換の施行後又は新鮮凍結血漿輸注の施行前に、下表を参考に本剤の補充投与を考慮すること。なお、下表はシミュレーション結果に基づき設定されたものであることから、補充投与後は患者の状態を慎重に観察すること。

	直近の 本剤投与量	本剤の補充用量	補充投与の 時期
血漿交換	300mg	１回につき300mg	施行後 60分以内
	600mg以上	１回につき600mg	
新鮮凍結 血漿輸注	300mg以上	１回につき300mg	施行 60分前

8. 重要な基本的注意

〈発作性夜間ヘモグロビン尿症〉

8.1 本剤投与によりPNH赤血球クローンが増加するため、本剤を中止した場合に重篤な血管内溶血が認められるおそれがある。本剤の投与を中止した患者に対しては、最低８週間、血管内溶血及びそれに付随する臨床症状の変化を注意深く観察し、必要に応じて適切な処置を行うこと。

〈非典型溶血性尿毒症症候群〉

8.2 本剤投与開始後は血小板数等を定期的にモニタリングし、改善傾向が認められない場合は、本剤の投与継続の要否を検討すること。なお、本剤を中止した場合に重度の血栓性微小血管障害が発現するおそれがあるため、本剤の投与中止後、最低12週間は患者の状態を注意深く観察し、必要に応じて適切な処置を行うこと。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 髄膜炎菌感染症の既往のある患者

本剤により髄膜炎菌感染症に罹患しやすくなる可能性がある。［5.1、11.1.1 参照］

＊9.1.2 感染症の患者又は感染症が疑われる患者

特に莢膜形成細菌（髄膜炎菌、肺炎球菌、インフルエンザ菌等）による感染症に罹患しやすくなる可能性がある。[5.1、11.1.1、11.1.2 参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上まわると判断される場合にのみ投与すること。

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。

9.7 小児等

〈発作性夜間ヘモグロビン尿症における溶血抑制〉

9.7.1 小児等を対象とした有効性及び安全性を指標とした臨床試験は実施していない。

〈非典型溶血性尿毒症症候群における血栓性微小血管障害の抑制〉

9.7.2 低出生体重児、新生児又は2ヵ月未満の乳児を対象とした有効性及び安全性を指標とした臨床試験は実施していない。

〈全身型重症筋無力症（免疫グロブリン大量静注療法又は血液浄化療法による症状の管理が困難な場合に限る）〉

9.7.3 小児等を対象とした有効性及び安全性を指標とした臨床試験は実施していない。

〈視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の再発予防〉

9.7.4 小児等を対象とした有効性及び安全性を指標とした臨床試験は実施していない。

9.8 高齢者

患者の状態を観察しながら、慎重に投与すること。一般に生理機能（腎機能、肝機能、免疫機能等）が低下している。

10. 相互作用

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
人免疫グロブリン製剤（ポリエチレングリコール処理人免疫グロブリン等）	人免疫グロブリン製剤との併用投与によって本剤の血清中濃度が低下することがあるので、併用する場合には、患者の状態を十分に観察すること。	本剤のエンドソームにおけるリサイクリング機構が、人免疫グロブリン製剤との継続的な併用投与により阻害され、本剤の血清中濃度が低下する可能性がある[1)2)3)]。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

＊11.1.1 髄膜炎菌感染症（頻度不明）

髄膜炎又は敗血症を発症し、急激に重症化することがあるので、本剤の投与に際しては、当該感染症の初期徴候（発熱、頭痛、項部硬直、羞明、精神状態の変化、痙攣、悪心・嘔吐、紫斑、点状出血等）等の観察を十分に行うこと。髄膜炎菌感染症が疑われた場合には、直ちに診察し、抗菌剤の投与等の適切な処置を行うこと。髄膜炎菌に対するワクチンを接種しても発症した例や、死亡に至った例が認められている。[1.1、5.1、9.1.1、9.1.2 参照]

＊11.1.2 重篤な感染症（頻度不明）

播種性淋菌感染症、肺炎球菌感染、インフルエンザ菌感染等の重篤な感染症があらわれることがある。[5.1、9.1.2 参照]

11.1.3 infusion reaction（頻度不明）

ショック、アナフィラキシー等があらわれることがある。

11.2 その他の副作用

	10%以上	5%～10%未満	5%未満	頻度不明
血液	-	白血球減少症	大球性貧血、好中球減少症、リンパ球減少症、鉄欠乏性貧血	貧血、凝固因子異常
耳及び迷路障害	-	耳鳴	-	回転性めまい、耳痛
眼	-	-	結膜出血、白内障、強膜出血、眼痛、結膜炎、緑内障	-
胃腸	悪心	嘔吐	上腹部痛、腸炎、下痢、腹痛、腹部膨満、胃食道逆流性疾患、舌炎	便秘、消化不良、腹部不快感、歯痛、アフタ性口内炎、嚥下障害、直腸出血、胃の不快感
全身障害及び投与局所	-	発熱	胸部不快感、疲労、腋窩痛、悪寒、注射部位硬結、倦怠感、末梢性浮腫	インフルエンザ様疾患、無力症、胸痛、注射部位疼痛、溢出、疼痛、冷感、腫脹
肝胆道	-	-	高ビリルビン血症、肝機能異常	黄疸
感染症	鼻咽頭炎	インフルエンザ、咽頭炎	単純ヘルペス、麦粒腫、口腔ヘルペス、医療機器関連感染、肺炎、上気道感染、気管支炎、蜂巣炎、膀胱炎、ウイルス性胃腸炎、扁桃炎、帯状疱疹、敗血症、腎膿瘍、アデノウイルス結膜炎、股部白癬、尿道炎、口腔カンジダ症、耳下腺炎、歯周炎	尿路感染、真菌感染、ウイルス感染、膿瘍、消化管感染、感染、副鼻腔炎、歯感染、下気道感染、膿痂疹、気道感染、鼻炎、胃腸炎、限局性感染、耳部感染、腹膜炎、BKウイルス感染、ナイセリア感染（淋菌等）
臨床検査	-	-	ALP上昇、ビリルビン上昇、C-反応性蛋白増加、白血球数増加、肝酵素増加、尿中白血球陽性、尿中血陽性、好酸球百分率増加、好中球百分率増加	ヘモグロビン減少、ハプトグロビン減少
代謝	-	-	食欲減退、糖尿病、高アルブミン血症、高血糖	低カリウム血症、ヘモクロマトーシス
筋骨格	-	-	筋肉痛、関節痛、四肢痛、背部痛	筋痙縮、頸部痛、関節腫脹、筋骨格痛、側腹部痛、筋骨格系胸痛
神経系	頭痛	-	浮動性めまい、頭部不快感、感覚鈍麻、眼振	味覚異常、振戦、失神、嗜眠、片頭痛、知覚障害
生殖系	-	-	陰嚢障害、希発月経	腟出血
呼吸器	-	-	上気道炎、咳嗽、鼻閉、鼻漏、口腔咽頭不快感	呼吸困難、鼻出血、咽喉頭疼痛、湿性咳嗽、咽喉乾燥

	10%以上	5％～10%未満	5％未満	頻度不明
皮膚	-	湿疹	発疹、皮膚乾燥、紅斑、多形紅斑、脱毛症、多毛症、接触性皮膚炎	そう痒症、蕁麻疹、点状出血、発汗、皮膚炎
免疫系	-	-	-	季節性アレルギー
精神系	-	-	うつ病、不安	不眠症、憂鬱感
血管・心臓	-	-	高血圧、動悸、起立性低血圧	進行性高血圧、ほてり、血腫、静脈硬化症
腎及び尿路障害	-	-	出血性膀胱炎、腎結石症、尿失禁、尿蛋白	排尿困難、血尿、腎疝痛
傷害	-	-	骨折	挫傷、擦過傷、転倒・転落、関節捻挫、四肢損傷
その他	-	-	皮膚乳頭腫	-

注）発現頻度は発作性夜間ヘモグロビン尿症を対象とした国内臨床試験 C07-001、非典型溶血性尿毒症症候群を対象とした国内レトロスペクティブ調査研究試験 C11-004J及び国内臨床試験 C11-005J、全身型重症筋無力症を対象とした国際共同試験 ECU-MG-301及びECU-MG-302における日本人患者の結果、視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）を対象とした国際共同試験 ECU-NMO-301及びECU-NMO-302における日本人患者の結果から集計した。

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 滅菌シリンジでバイアルから全量を抜き取り、必要量を点滴バッグ等に注入する。

14.1.2 日局生理食塩液、日局ブドウ糖注射液（５％）又は日局リンゲル液を点滴バッグ等に添加し、本剤を５mg/mLに希釈する。（希釈した液の容量は本剤300mgの場合60mL、600mgの場合120mL、900mgの場合180mL、1200mgの場合240mLである。）

14.1.3 希釈した液を含有する点滴バッグ等を静かに倒立させるなど、緩やかに溶解し、混和する。（抗体タンパクが凝集するおそれがあるため、決して激しく振らないこと。）

14.1.4 調製後、微粒子及び変色がないか、目視検査を行うこと。（変色、異物、その他異常を認めたものは使用しないこと。）

14.1.5 調製後、希釈した液は速やかに使用すること。なお、やむを得ず保存する場合は、希釈した液は２～25℃で保存し、24時間以内に使用すること。

14.1.6 希釈した液を投与前に室温になるまで放置すること。（加熱しないこと。）

14.2 薬剤投与時の注意

14.2.1 本剤は点滴静注用としてのみ用い、急速静脈内投与、皮下投与、筋肉内投与をしないこと。

14.2.2 本剤は独立したラインより投与するものとし、他の注射剤、輸液等と混合しないこと。

14.2.3 希釈した液を18歳以上では25～45分、18歳未満では１～４時間かけて点滴静注するが、患者の年齢、体重に応じて適宜調整すること。

14.2.4 本剤の投与中に副作用が発現した場合は、医師の判断で投与速度を遅くする又は投与を中止し、投与終了後、患者の症状が安定するまで慎重に観察すること。

15. その他の注意

15.1 臨床使用に基づく情報

臨床試験において抗体反応が検出された患者が認められたが、抗体発現と臨床効果又は有害事象との相関は認められなかった。

15.2 非臨床試験に基づく情報

マウスの胚・胎児発生試験（60mg/kgを器官形成期に静脈内投与）において、網膜形成異常が認められた[4]。

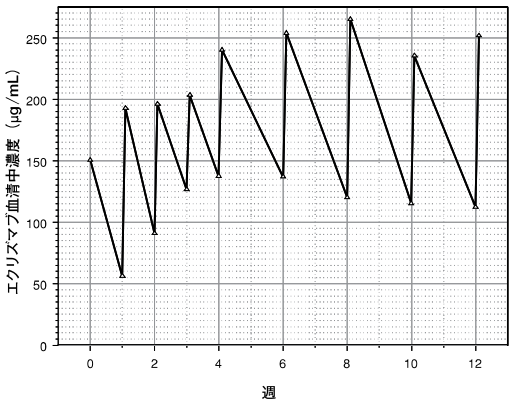
16. 薬物動態

16.1 血中濃度

〈発作性夜間ヘモグロビン尿症〉

16.1.1 国内第Ⅱ相試験 C07-001（AEGIS study）

発作性夜間ヘモグロビン尿症患者に本剤600mgを週１回で計４回、その１週間後から本剤900mgを２週に１回の頻度で計５回静脈内投与した時の血清中濃度は、下図のように推移した。また、投与12週後における血清中トラフ濃度は116.5±10.93μg/mLであった[5]。



図：国内臨床試験におけるエクリズマブの血清中濃度推移
血清中濃度の被験者数は10週のみ28例、他は29例であった。

16.1.2 海外第Ⅲ相試験 C04-001（TRIUMPH study）

発作性夜間ヘモグロビン尿症患者（43例）に本剤600mgを週１回で計４回、その１週間後から本剤900mgを２週に１回の頻度で計11回静脈内投与した時の血清中トラフ濃度は、投与１週時45.1±3.81μg/mL、投与４週時113.5±8.70μg/mL、投与６週時104.3±8.65μg/mL、投与12週時96.5±9.38μg/mL、投与26週時101.8±10.84μg/mLであった（n=40～42）。

16.1.3 海外第Ⅲ相試験 C04-002（SHEPHERD study）

発作性夜間ヘモグロビン尿症患者（97例）に本剤600mgを週１回で計４回、その１週間後から本剤900mgを２週に１回の頻度で計24回静脈内投与した時の血清中トラフ濃度は、投与１週時45.8±3.00μg/mL、投与４週時104.5±5.08μg/mL、投与６週時100.6±5.77μg/mL、投与12週時92.6±5.36μg/mL、投与26週時98.4±6.63μg/mL、投与52週時110.3±8.92μg/mLであった（n=92～96）。

〈非典型溶血性尿毒症症候群〉

16.1.4 国内第Ⅱ相試験 C11-005J

本剤投与中の非典型溶血性尿毒症症候群患者３例に本剤１回600mg又は1200mgを２週に１回の頻度で静脈内投与した時の投与12週時の血清中濃度を測定した。

年齢	体重	１回投与量	投与12週時の血清中濃度（μg/mL）	
			ピーク濃度	トラフ濃度
８歳	27.3kg	600mg	553.6	352.1
６歳	18.9kg	600mg[a)]	524.1	384.8
31歳	53.9kg	1200mg	517.1	377.1

a）10kg以上20kg未満の患者に対する１回あたりの承認用量は300mgである。

16.1.5 海外第Ⅱ相試験 C08-002A/B

非典型溶血性尿毒症症候群患者（17例）に本剤900mgを週１回で計４回、その１週間後から本剤1200mgを２週に１回の頻度で静脈内投与した時の投与１日目の血清中ピーク濃度は188.3±47.1μg/mLであり、血清中トラフ濃度は投与４週時152.6±61.8μg/mL、投与26週時194.8±83.1μg/mLであった（n=13～16）。

16.1.6 海外第Ⅱ相試験 C08-003A/B

非典型溶血性尿毒症症候群患者（20例）に本剤900mgを週1回で計4回、その1週間後から本剤1200mgを2週に1回の頻度で静脈内投与した時の投与1日目の血清中ピーク濃度は222.7±48.9μg/mLであり、血清中トラフ濃度は投与4週時222.4±53.3μg/mL、投与26週時276.8±101.0μg/mLであった（n=18～20）。

〈全身型重症筋無力症〉

16.1.7 第Ⅲ相国際共同試験 ECU-MG-301

全身型重症筋無力症患者（62例（日本人患者3例を含む））に本剤900mgを週1回で計4回、その1週間後から本剤1200mgを2週に1回の頻度で静脈内投与した時の投与1日目の血清中ピーク濃度は336±112μg/mLであり、血清中トラフ濃度は投与4週時373±135μg/mL、投与26週時341±172μg/mLであった（n=57～61）。日本人患者（3例）の血清中ピーク濃度及び血清中トラフ濃度は、外国人患者の5～95パーセンタイルの範囲内であった。

〈視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の再発予防〉

16.1.8 第Ⅲ相国際共同試験 ECU-NMO-301

視神経脊髄炎スペクトラム障害患者（95例（日本人患者9例を含む））に本剤900mgを週1回で計4回、その1週間後から本剤1200mgを2週に1回の頻度で静脈内投与した時の投与1日目の血清中ピーク濃度は359±103μg/mLであり、血清中トラフ濃度は投与4週時432±169μg/mL、投与48週時420±218μg/mLであった（n=65～94）。日本人患者（9例）の血清中ピーク濃度及び血清中トラフ濃度は、外国人患者の5～95パーセンタイルの範囲内にほぼ含まれていた[6]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈発作性夜間ヘモグロビン尿症〉

発作性夜間ヘモグロビン尿症患者を対象とした臨床試験は、すべて髄膜炎菌ワクチン接種下で実施された。［5.1 参照］

17.1.1 国内第Ⅱ相試験 C07-001（AEGIS study）

過去2年以内に赤血球輸血が必要と判断され、赤血球中のGPI欠損赤血球クローン（PNHタイプⅢ）の存在比が10%以上の発作性夜間ヘモグロビン尿症患者29例を対象とし、本剤600mgを週1回で計4回、その1週間後から本剤900mgを2週に1回の頻度で計5回静脈内投与した。ベースラインのLDH（中央値［最小値、最大値］）は1,814.0U/L［627.8U/L、3,642.5U/L］、投与12週目のLDHは244.0U/L［187.0U/L、2,715.0U/L］であり、LDHの低下が認められた（p<0.0001、Wilcoxonの符号付順位検定）[5]。副作用発現頻度は、本剤投与群で93.1%（27/29例）であった。主な副作用は、頭痛（51.7%）、鼻咽頭炎（37.9%）、悪心（20.7%）であった。

17.1.2 海外第Ⅲ相試験 C04-001（TRIUMPH study）

過去1年間に少なくとも4回赤血球輸血を受けており、赤血球中のGPI欠損赤血球クローン（PNHタイプⅢ）の存在比が10%以上の発作性夜間ヘモグロビン尿症患者87例を対象とし、本剤600mg又はプラセボを週1回で計4回、その1週間後から本剤900mgを2週に1回の頻度で計11回静脈内投与した。Hb安定化※はプラセボ群で0.0%（0/44例）及び本剤群で48.8%（21/43例）の患者で達成された（p<0.001、Fisherの正確検定）。また、濃厚赤血球輸血単位数（中央値［最小値、最大値］）は、プラセボ群で10単位［2単位、21単位］、本剤群で0単位［0単位、16単位］であった（p<0.001、Wilcoxonの順位和検定）[7]。副作用発現頻度は、本剤投与群で55.8%（24/43例）であった。主な副作用は、頭痛（32.6%）、腹痛、皮膚乾燥、単純ヘルペス、悪心、上気道感染（各4.7%）であった。

※ 各患者において、観察期間中（定義）における輸血時のHb値を輸血設定値とし、投与期間中にHb値が輸血設定値を上回り、かつ輸血を受けなかった場合にHb安定化が達成されたと定義

〈非典型溶血性尿毒症症候群〉

非典型溶血性尿毒症症候群患者を対象とした臨床試験はすべて髄膜炎菌ワクチン接種下で実施された。また、髄膜炎菌ワクチン接種前又は接種後14日以内に本剤が投与される場合には抗菌剤が予防的に投与された。なお、国内臨床試験（C11-005J）の小児患者では肺炎球菌ワクチン及びインフルエンザ菌b型ワクチンの接種下で実施された。［5.1 参照］

17.1.3 国内第Ⅱ相試験 C11-005J

本剤投与中の非典型溶血性尿毒症症候群患者3例を対象とした非盲検非対照試験において、本剤1回600mg又は1200mgを2週に1回の頻度で静脈内投与した時の血小板数の推移は下表のとおりであり、投与期間中3例とも施設基準下限値以上で推移した。また、投与期間中に血漿療法及び新規の透析を実施した患者は認められず、ベースラインから透析を実施していた1例では透析を離脱した。

年齢	体重	1回投与量	血小板数（×10⁴/μL）		
			施設基準値	ベースライン	投与期間中
8歳	27.3kg	600mg	12.0～41.0	23.7	19.1～31.1
6歳	18.9kg	600mg[a)]	13.0～35.0	36.2	24.1～41.2
31歳	53.9kg	1200mg	13.1～36.2	25.9	23.6～27.8

a）10kg以上20kg未満の患者に対する1回あたりの承認用量は300mgである。

副作用は認められなかった。

17.1.4 海外第Ⅱ相試験 C08-002A/B

18歳以上、又は12歳以上18歳未満かつ体重40kg以上で血漿療法抵抗性の非典型溶血性尿毒症症候群患者17例を対象とした非盲検非対照試験において、本剤900mgを週1回で計4回、その1週間後から本剤1200mgを2週に1回の頻度で静脈内投与した。その結果、血小板数（平均値±標準偏差）は、ベースライン時10.9±3.2×10⁴/μLから投与26週時21.0±6.8×10⁴/μLに増加し、ベースラインから投与26週時の変化量の最小二乗平均値［95%信頼区間］は7.3×10⁴/μL［4.0×10⁴/μL, 10.5×10⁴/μL］であった。

副作用発現頻度は、58.8%（10/17例）であった。主な副作用は、進行性高血圧、白血球減少症、悪心、嘔吐（各11.8%）であった。

17.1.5 海外第Ⅱ相試験 C08-003A/B

18歳以上、又は12歳以上18歳未満かつ体重40kg以上で血漿療法を8週間以上施行されている非典型溶血性尿毒症症候群患者20例を対象とした非盲検非対照試験において、本剤900mgを週1回で計4回、その1週間後から本剤1200mgを2週に1回の頻度で静脈内投与した。その結果、血栓性微小血管障害イベントフリー※1を達成した患者割合は80%（16/20例）であった。

副作用発現頻度は、30.0%（6/20例）であった。主な副作用は、頭痛、白血球減少症、リンパ球減少症（各10.0%）であった。

17.1.6 海外レトロスペクティブ調査 C09-001r

本剤の投与歴を有する非典型溶血性尿毒症症候群患者30例（生後2ヵ月以上12歳未満15例、12歳以上15例）を対象としたレトロスペクティブ調査が実施された結果、血小板数の正常化※2を達成した患者割合は、12歳未満93.3%（14/15例）、12歳以上73.3%（11/15例）であった。また、血栓性微小血管障害イベントフリー※1を達成した患者割合は、12歳未満73%（11/15例）、12歳以上60%（9/15例）であった。

有害事象発現頻度は、73.3%（22/30例）であった。主な有害事象は、発熱（30%）、下痢（27%）、嘔吐、咳嗽（各23%）、上気道感染（20%）であった。

※1 ベースライン値からの25%を超える血小板数の減少、血漿療法施行、新規透析施行のいずれも認められなかった状態が12週間以上持続した場合と定義

※2 2回以上の連続した測定で血小板数が15.0×10⁴/μL以上が4週間以上持続した場合と定義

〈全身型重症筋無力症〉

全身型重症筋無力症患者を対象とした臨床試験は、すべて髄膜炎菌ワクチン接種下で実施された。［5.1 参照］

17.1.7 第Ⅲ相国際共同試験 ECU-MG-301

全身型重症筋無力症患者125例（日本人患者11例を含む）を対象に、プラセボ又は本剤900mgを週１回で計４回、その１週間後からプラセボ又は本剤1200mgを２週に１回の頻度で静脈内投与するプラセボ対照無作為化二重盲検並行群間比較試験を実施した。その結果、主要評価項目であるベースラインに対する投与26週のMG-ADL総スコアの変化量は下表のとおりであり、プラセボ群と本剤群の間に統計学的に有意な差が認められた。

	MG-ADL総スコア[a]			臨床的イベント[b]	Worst-Rank解析[c]	
	ベースライン	投与26週	変化量	レスキュー治療	順位[d]	群間比較[e]
プラセボ群	9.9±2.64(51) 9.0(5, 18)	7.0±3.36(51) 6.0(2, 16)	-2.8±3.07(51) -2.0(-8, 7)	62.2±55.40(12) 43.5(7, 178)	70.8±4.38(63)	-16.6 [-28.90, -4.23] p=0.0089
本剤群	10.3±3.06(56) 10.0(5, 18)	5.6±4.11(56) 5.5(0, 15)	-4.7±4.20(56) -4.5(-15, 4)	95.7±71.50(6) 99.5(1, 174)	54.2±4.42(62)	

a）上段：平均値±標準偏差（評価例数）、下段：中央値（最小値，最大値）、レスキュー治療を必要としなかった患者が評価対象
b）イベントまでの期間（日）、上段：平均値±標準偏差（該当例数）、下段：中央値（最小値，最大値）
c）①レスキュー治療を受けた患者集団（レスキュー治療実施日までの日数が短い順）、②レスキュー治療を必要としなかった患者（投与26週のMG-ADL総スコアのベースラインからの変化量（LOCF）に基づく改善が小さい順）の順番で患者に対して最悪順位から順位付けを行い、その順位を応答変数とした投与群及びMGFA分類（クラス2a又は3a／4a／2b又は3b／4b）を因子、MG-ADL総スコアのベースライン値を共変量とした共分散分析モデルに基づく解析
d）順位の調整平均値±標準誤差（共分散分析モデルに基づく）（評価例数）
e）上段：群間差、中段：群間差の95%信頼区間、下段：群間比較のp値

また、重症筋無力症患者の病態及びレスキュー治療を受けずに症状悪化により早期中止した患者の影響を考慮して、事後的に順位付け方法を変更したWorst-Rank解析においても、ベースラインに対する投与26週のMG-ADL総スコアの変化量についてプラセボ群と本剤群の間に統計学的に有意な差が認められた[8]。

	MG-ADL総スコア[a]			臨床的イベント[b]		Worst-Rank解析[c]	
	ベースライン	投与26週	変化量	MGクリーゼ	レスキュー治療及び中止[d]	順位[e]	群間比較[f]
プラセボ群	9.9±2.64(51) 9.0(5, 18)	7.0±3.36(51) 6.0(2, 16)	-2.8±3.07(51) -2.0(-8, 7)	0	62.2±55.40(12) 43.5(7, 178)	70.2±4.41(63)	-15.4 [-27.80, -2.92] p=0.0160
本剤群	10.2±2.98(55) 10.0(5, 18)	5.6±4.02(55) 5.0(0, 15)	-4.7±4.23(55) -4.5(-15, 4)	127.0(1) 127(127, 127)	80.7±76.64(6) 58.0(1, 174)	54.8±4.46(62)	

a）上段：平均値±標準偏差（評価例数）、下段：中央値（最小値，最大値）、MGクリーゼを発現せず、レスキュー治療を必要とせず26週間の治験薬投与を完了した患者、及び中止例のうちレスキュー治療の実施基準に該当しなかった患者が評価対象
b）イベントまでの期間（日）、上段：平均値±標準偏差（該当例数）、下段：中央値（最小値，最大値）
c）①投与26週までに死亡した患者集団（死亡した日までの日数が短い順）、②MGクリーゼを発現した患者集団（MGクリーゼ発現までの日数が短い順）、③レスキュー治療を受けた患者、又は試験を中止した患者のうちレスキュー治療の実施基準に該当する患者集団（レスキュー治療実施日又は中止日（両方のイベントがある場合には早く発現した方）までの日数が短い順）、④レスキュー治療を受けなかった患者、又は試験を中止した患者のうちレスキュー治療の実施基準に該当しなかった患者集団（投与26週のMG-ADL総スコアのベースラインからの変化量（LOCF）に基づく改善が小さい順）の順番で患者に対して最悪順位から順位付けを行い、その順位を応答変数として投与群及びMGFA分類を因子、MG-ADL総スコアのベースライン値を共変量とした共分散分析モデル
d）試験を中止した患者のうちレスキュー治療の実施基準に該当する患者集団
e）順位の調整平均値±標準誤差（共分散分析モデルに基づく）（評価例数）
f）上段：群間差、中段：群間差の95%信頼区間、下段：群間比較のp値

副作用発現頻度は、本剤投与群で66.1%（41/62例）であった。主な副作用は、悪心、上気道感染（各12.9%）、下痢（11.3%）であった。

17.1.8 第Ⅲ相国際共同試験（長期投与試験）ECU-MG-302

全身型重症筋無力症患者を対象に実施したプラセボ対照無作為化二重盲検並行群間比較試験を完了した患者を対象に実施した長期投与試験において、有効性の評価尺度であるMG-ADL総スコアの推移は下表のとおりであった[9]。

	プラセボ-本剤集団			本剤-本剤集団		
	評価例数	総スコア	変化量	評価例数	総スコア	変化量
ベースライン（ECU-MG-301試験）	60	9.9±2.60		56	10.3±3.03	
1週	60	6.0±3.85	-3.9±3.75	55	5.3±3.94	-5.0±4.07
4週	60	5.1±3.74	-4.8±3.73	55	5.5±3.81	-4.9±4.05
12週	60	5.2±3.25	-4.7±3.39	53	5.3±3.50	-4.8±3.38
26週	55	4.7±3.20	-4.9±3.20	49	5.1±3.77	-5.2±3.77
40週	31	3.8±2.76	-5.7±3.55	29	5.2±4.22	-5.1±4.65
52週	20	4.3±3.06	-5.3±3.24	20	5.8±3.75	-4.4±3.53
最終評価時（LOCF）	60	5.2±3.97	-4.7±4.24	56	6.1±4.36	-4.3±4.11

平均値±標準偏差

副作用発現頻度は、55.6%（65/117例）であり、主な副作用は、頭痛（12.0%）、下痢（8.5%）、上気道感染（7.7%）、鼻咽頭炎（6.8%）であった。

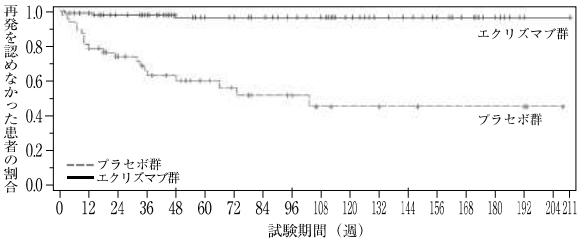
〈視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の再発予防〉

視神経脊髄炎スペクトラム障害患者を対象とした臨床試験は、すべて髄膜炎菌ワクチン接種下で実施された。［5.1 参照］

17.1.9 第Ⅲ相国際共同試験 ECU-NMO-301

視神経脊髄炎スペクトラム障害患者※143例（日本人患者14例を含む）を対象に、プラセボ又は本剤900mgを週１回投与で計４回静脈内投与し、その１週間後からプラセボ又は本剤1200mgを２週に１回静脈内投与するプラセボ対照無作為化二重盲検並行群間比較試験を実施した。その結果、主要評価項目である独立評価委員会により判定された初回再発までの期間は次図のとおりであり、プラセボ群と本剤群との間に有意な差が認められた（p<0.0001）[a]。ハザード比［95%信頼区間］[b) c)]は0.058［0.017, 0.197］であった。

a）層別ログランク検定に基づく、b）層別Cox比例ハザードモデルに基づく、c）Wald信頼区間



各時点の患者数:

プラセボ群	47	38	30	24	21	16	13	10	9	6	5	5	4	3	3	3	3	1
エクリズマブ群	96	92	83	78	68	60	58	52	46	41	32	24	22	18	14	8	2	1

副作用発現頻度は、本剤投与群で63.5%（61/96例）であった。主な副作用は、上気道感染11.5%（11例）、悪心10.4%（10例）、頭痛8.3%（８例）、浮動性めまい7.3%（７例）であった[6]。

17.1.10 第Ⅲ相国際共同試験（長期投与試験）ECU-NMO-302

視神経脊髄炎スペクトラム障害患者※を対象に実施したプラセボ対照無作為化二重盲検並行群間比較試験を完了した患者を対象に実施した長期投与試験において、年間あたりの再発回数の推移は下表のとおりであった。

	評価例数	過去の年間あたりの再発回数[a]	試験中の年間あたりの再発回数	過去の年間あたりの再発回数からの変化量
プラセボ-本剤集団	25	2.405±1.2526 1.923（1.442, 2.885）	0.237±0.6067 0.000（0.000, 0.000）	-2.168±1.4830 -1.923（-2.446, -1.442）
本剤-本剤集団	14	2.029±0.9563 1.923（1.442, 2.404）	0.198±0.4206 0.000（0.000, 0.296）	-1.831±0.7522 -1.923（-2.404, -1.442）
全体集団	39	2.270±1.1564 1.923（1.442, 2.885）	0.223±0.5416 0.000（0.000, 0.000）	-2.047±1.2686 -1.923（-2.446, -1.442）

上段：平均値±標準偏差、下段：中央値（第１四分位点、第３四分位点）
a）ECU-NMO-301試験の治験薬投与前24カ月の年間再発回数

副作用発現頻度は69.2%（27/39例）であり、主な副作用は鼻咽頭炎、尿路感染症の各12.8%（各５例）であった[10]。

※ 2006年の診断基準[11]に基づき視神経脊髄炎又は2007年の基準[12]に基づき視神経脊髄炎スペクトラム障害と診断された患者。

18. 薬効薬理

18.1 作用機序

エクリズマブは、補体タンパクC5に特異的に結合し、C5のC5a及びC5bへの開裂を阻害することで、終末補体複合体C5b-9の生成を抑制する。

18.2 その他

18.2.1 本剤は抗ニワトリ赤血球抗体で感作させたニワトリ赤血球のヒト血清による溶血を抑制した[13]。

18.2.2 本剤のヒトC5に対する解離定数（平均値±標準偏差）は46±1.6pmol/L（25℃）、120±5.5pmol/L（37℃）であった[14]。

19. 有効成分に関する理化学的知見

一般的名称：エクリズマブ（遺伝子組換え）
Eculizumab（Genetical Recombination）（JAN）

本　　質：エクリズマブは、遺伝子組換えヒト化モノクローナル抗体であり、マウス抗ヒト補体C5α鎖抗体の相補性決定部及びヒトフレームワーク部からなる改変部、並びにヒトIgG由来定常部からなる。L鎖の定常部はκ鎖に由来する。また、H鎖定常部のCH1部、ヒンジ部及びCH2部の一部はIgG2（γ2鎖）からなり、CH2部の残りとCH3部はIgG4（γ4鎖）からなる。エクリズマブは、マウス骨髄腫（NS0）細胞により産生される。エクリズマブは、448個のアミノ酸残基からなるH鎖2分子及び214個のアミノ酸残基からなるL鎖2分子で構成される糖タンパク質（分子量：約145,235）である。

20. 取扱い上の注意

外箱開封後は遮光して保存すること。

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

〈発作性夜間ヘモグロビン尿症における溶血抑制〉

21.2 国内の臨床試験成績は限られていることから、製造販売後一定期間は本剤を投与された全症例を対象に使用成績調査を実施し、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを収集し、本剤の適正使用に必要な措置を講じること。

21.3 本剤の投与が、発作性夜間ヘモグロビン尿症の診断、治療に精通し、本剤のリスク等についても十分に管理できる医師・医療機関のもとで、髄膜炎菌感染症の診断、治療に精通した医師との連携を取った上でのみ行われるよう、製造販売にあたって必要な措置を講じること。

〈非典型溶血性尿毒症症候群における血栓性微小血管障害の抑制〉

21.4 国内の臨床試験成績は限られていることから、製造販売後一定期間は本剤を投与された全症例を対象に使用成績調査を実施し、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを収集し、本剤の適正使用に必要な措置を講じること。

21.5 本剤の投与が、非典型溶血性尿毒症症候群の診断、治療に精通し、本剤のリスク等についても十分に管理できる医師・医療機関のもとで、髄膜炎菌感染症の診断、治療に精通した医師との連携を取った上でのみ行われるよう、製造販売にあたって必要な措置を講じること。

〈全身型重症筋無力症（免疫グロブリン大量静注療法又は血液浄化療法による症状の管理が困難な場合に限る）〉

21.6 国内の臨床試験成績は限られていることから、製造販売後一定期間は本剤を投与された全症例を対象に使用成績調査を実施し、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを収集し、本剤の適正使用に必要な措置を講じること。

21.7 本剤の投与が、全身型重症筋無力症の診断、治療に精通し、本剤のリスク等についても十分に管理できる医師・医療機関のもとで、髄膜炎菌感染症の診断、治療に精通した医師との連携を取った上でのみ行われるよう、製造販売にあたって必要な措置を講じること。

〈視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の再発予防〉

21.8 国内の臨床試験成績は限られていることから、製造販売後一定期間は本剤を投与された全症例を対象に特定使用成績調査を実施し、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを収集し、本剤の適正使用に必要な措置を講じること。

21.9 本剤の投与が、視神経脊髄炎スペクトラム障害（視神経脊髄炎を含む）の診断、治療に精通し、本剤のリスク等についても十分に管理できる医師・医療機関のもとで、髄膜炎菌感染症の診断、治療に精通した医師との連携を取った上でのみ行われるよう、製造販売にあたって必要な措置を講じること。

22. 包装

ソリリス点滴静注300mg　30mL［1バイアル］

23. 主要文献

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