PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**SOLIRIS®**

(eculizumab for injection)

30 mL Parenteral Solution (10 mg/mL)

(Humanized Monoclonal Antibody)

Produced in a murine myeloma (NS0 cell line) expression system.

Pharmaceutical standard: Professed

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	07/2024
1 INDICATIONS, 1.1 Pediatrics	07/2024
4 Dosage and Administration, 4.2 Recommended Dose and Dose Adjustment	07/2024
4 Dosage and Administration, 4.4 Administration	07/2024
7 WARNINGS AND PRECAUTIONS	07/2024

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SOLIRIS (eculizumab for injection) is indicated for:

- Paroxysmal Nocturnal Hemoglobinuria (PNH)

  Soliris (eculizumab for injection) is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. SOLIRIS was studied in clinical trials in patients with a history of at least one transfusion during the past two years (see 14 CLINICAL TRIALS).

- Atypical Hemolytic Uremic Syndrome (atypical HUS)

  Soliris (eculizumab for injection) is indicated for the treatment of patients with atypical hemolytic uremic syndrome (atypical HUS) to reduce complement-mediated thrombotic microangiopathy.

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

- Generalized Myasthenia Gravis (gMG)

  Soliris (eculizumab for injection) is indicated in adult patients with generalized Myasthenia Gravis (gMG).

  SOLIRIS was studied in clinical trials in patients who were anti-acetylcholine receptor (AChR) antibody positive and refractory, defined as failure of treatment with two or more immunosuppressive therapies (ISTs) either in combination or as monotherapy, or failed at least one IST and required chronic plasmapheresis, plasma exchange (PE), or intravenous immunoglobulin (IVIg) to control symptoms. Patients continued to receive standard therapy throughout the pivotal clinical trial.

- Neuromyelitis Optica Spectrum Disorder (NMOSD)

  Soliris (eculizumab for injection) is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.
  SOLIRIS is not intended for acute treatment of an NMOSD relapse.

- Soliris should be administered by a qualified healthcare professional.

1.1 Pediatrics

Pediatrics (<18 years of age):

PNH

The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients below the age of 18 years have not been established. Therefore, Health Canada has not authorized an indication for pediatric use. In children and adolescent patients with PNH (aged 11 years to less than 18 years) included in the pediatric PNH Study, the safety profile appeared similar to that observed in adult patients with PNH. The most common adverse reaction reported in pediatric patients was headache.

Atypical HUS

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Soliris in 28 pediatric patients with atypical HUS has been established; therefore, Health Canada has authorized an indication for pediatric use (see 14 CLINICAL TRIALS , atypical HUS).

gMG

The safety and effectiveness of Soliris for the treatment of gMG in pediatric patients below the age of 18 years have not been established.

NMOSD

The safety and effectiveness of Soliris for the treatment of NMOSD in pediatric patients below the age of 18 years have not been established.

Administer vaccinations for the prevention of infection due to *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) according to the National Advisory Committee on Immunization (NACI) guidelines.

1.2 Geriatrics

Geriatrics (≥65 years of age):

Soliris may be administered to patients aged 65 years and over. Fifty-two patients 65 years of age or older (15 with PNH, 4 with atypical HUS, 26 with gMG and 7 with NMOSD) were treated with Soliris in clinical studies. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond similarly to younger patients.

2 CONTRAINDICATIONS

Soliris is contraindicated in patients who are hypersensitive to this drug, murine proteins, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

Do not initiate Soliris therapy in patients:

- with unresolved *Neisseria meningitidis* infection
- who are not currently vaccinated against *Neisseria meningitidis* (unless they receive prophylactic

treatment with appropriate antibiotics until 2 weeks after vaccination)

Please refer to section 7 WARNINGS AND PRECAUTIONS **, Serious Meningococcal Infections**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Meningococcal infections

Cases of serious or fatal meningococcal infections have been reported in patients treated with Soliris. Meningococcal infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Comply with the most current National Advisory Committee on Immunization (NACI) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **All patients must be vaccinated with meningococcal vaccines prior to, or at the time of, initiating Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection; revaccinate according to current medical guidelines for vaccine use.**
- **All patients must be monitored for early signs of meningococcal infections, evaluated immediately if infection is suspected, and treated with antibiotics, if necessary.**

Vaccination may not prevent all meningococcal infections.

Serious Meningococcal Infections:

Due to its mechanism of action, the use of Soliris increases the patient's susceptibility to meningococcal infection (*Neisseria meningitidis*). Meningococcal disease due to any serogroup may occur. To reduce the risk of infection, all patients must be vaccinated against meningococcal infections prior to, or at the time of, initiating Soliris. Patients who initiate Soliris treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W 135 and B where available, are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to current national vaccination guidelines for vaccination use. Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Vaccination, particularly with a vaccine against serogroup B meningococcal infection, may further activate complement. As a result, patients with complement-mediated diseases, including PNH, atypical HUS, gMG and NMOSD, may experience increased signs and symptoms of their underlying disease, such as hemolysis (PNH), TMA complications (atypical HUS), MG exacerbation (gMG) or relapse (NMOSD). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination. For patients stabilized on Soliris and receiving maintenance therapy, and for whom additional vaccination is warranted, careful consideration should be given to the timing of vaccination (or booster in patients previously vaccinated against meningococcal infections) relative to administration of Soliris. It is recommended to vaccinate only when the underlying complement mediated disease is clinically

controlled with Soliris, and when systemic eculizumab concentrations are considered to be relatively high (i.e. within one week following a Soliris infusion).

Cases of serious or fatal meningococcal infections have been reported in Soliris treated patients. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with antibiotics, if necessary. Patients should be informed of these signs and symptoms and steps to take to seek medical care immediately (see 8 ADVERSE REACTIONS). Discontinue Soliris in patients who are undergoing treatment for serious meningococcal infections.

Other Systemic Infections:

Due to its mechanism of action, Soliris therapy should be administered with caution to patients with active systemic infections. Soliris blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with *Neisseria* and encapsulated bacteria. Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported. Counsel patients about gonorrhea prevention and advise regular testing for patients at risk. Additionally, Aspergillus infections have occurred in immunocompromised and neutropenic patients. Patients should be provided with information from the Patient Information Brochure to increase their awareness of potential serious infections and their signs and symptoms.

Children treated with Soliris 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 national guidelines. For patients stabilized on eculizumab and receiving maintenance therapy, and for whom additional vaccination is warranted, careful consideration should be given to the timing of vaccination relative to administration of Soliris (see 7 WARNINGS AND PRECAUTIONS, Serious Meningococcal Infections)

Serious infections, infectious agents and subsequent treatments for these infections should be documented for all patients treated with Soliris.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Soliris should be administered by a qualified healthcare professional.
- Do not administer as an IV Push or Bolus Injection

4.2 Recommended Dose and Dosage Adjustment

Recommended Dosage Regimen - PNH

For patients 18 years of age and older, Soliris therapy consists of:

- 600 mg every 7 days for the first 4 weeks, followed by
- 900 mg for the fifth dose 1 week later, then
- 900 mg every 2 weeks thereafter.

Soliris should be administered at the recommended dosage regimen time points, or within two days of these time points (see 7 WARNINGS AND PRECAUTIONS).

Recommended Dosage Regimen – atypical HUS, gMG and NMOSD
For patients 18 years of age and older Soliris therapy consists of:

- 900 mg weekly for the first 4 weeks, followed by
- 1200 mg for the fifth dose 1 week later, then
- 1200 mg every 2 weeks thereafter

For patients with atypical HUS and less than 18 years of age, administer Soliris based upon body weight, according to the following schedule **(Table 1)**:

Table 1: Dosing recommendations in patients less than 18 years of age with atypical HUS

Patient Body Weight	**Induction**	**Maintenance**
40 kg and over	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

For adult patients with atypical HUS, gMG or NMOSD, and pediatric patients with atypical HUS, supplemental dosing of Soliris is required in the setting of concomitant support with plasmapheresis (PP) or plasma exchange (PE); or fresh frozen plasma infusion (PI) **(Table 2).** The goal of the additional dosing after plasma intervention is to restore and maintain the plasma concentration above targeted therapeutic concentration. The impact of IVIg on eculizumab levels in patients with gMG has not been studied.

Table 2 : Supplemental dose of Soliris after PP/PE/PI

Type of Intervention	**Most Recent Soliris Dose**	**Soliris Dose with Each PP/PE/PI Intervention**	**Timing of Supplemental Soliris Dose**
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	600 mg or more	600 mg per each plasmapheresis or	

		plasma exchange session	
Fresh frozen plasma infusion	300 mg or more	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Abbreviations: PP/PE/PI = plasmapheresis/plasma exchange/plasma infusion
Based on pharmacokinetic simulation and data from PNH and atypical HUS patients who received plasma intervention while on eculizumab therapy. Plasma exchange resulted in an approximately 50% decline in eculizumab concentrations following a 1-hour intervention and the half-life of eculizumab was reduced to 1.3 hours.

The recommended doses in **Table 1** and **Table 2** are based entirely on estimates from a one-compartment model which was demonstrated to adequately describe eculizumab pharmacokinetics.

Soliris should be administered at the recommended dosage regimen time points, or within two days of these time points (see 7 WARNINGS AND PRECAUTIONS).

4.3 Reconstitution

Parenteral Products:

Soliris must be diluted to a final admixture concentration of 5 mg/mL using the following steps:

- Withdraw the required amount of Soliris from the vial into a sterile syringe
- Transfer the recommended dose to an infusion bag
- Dilute Soliris to a final concentration of 5 mg/mL by adding the appropriate amount (equal volume of diluent to drug volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP to the infusion bag.
- The final admixed Soliris 5 mg/mL infusion volume is 60 mL for 300 mg doses, 120 mL for 600 mg doses, 180 mL for 900 mg doses or 240 mL for 1200 mg doses **(Table 3)**. Gently invert the infusion bag containing the diluted Soliris solution to ensure thorough mixing of the product and diluent.
- Prior to administration, the admixture should be allowed to adjust to room temperature [18°-25°C, 64°-77°F]. The admixture must not be heated in a microwave or with any heat source other than ambient air temperature. The Soliris admixture should be inspected visually for particulate matter and discolouration prior to administration.

Table 3 – Reconstitution

Dose	Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
300 mg	30 mL x 1	30 mL	60 mL	5 mg/mL
600 mg	30 mL x 2	60 mL	120 mL	5 mg/mL
900 mg	30 mL x 3	90 mL	180 mL	5 mg/mL
1200 mg	30 mL x 4	120 mL	240 mL	5 mg/mL

Discard any unused portion left in a vial, as the product contains no preservatives.

4.4 Administration

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

The Soliris admixture should be administered by intravenous infusion over 35 minutes in adults and 1-4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump. Admixed solutions of Soliris are stable for 24 hours at 2-8°C and at room temperature. However, Soliris contains no preservative so infusion of the admixture should begin as soon as possible after mixing.

If an adverse reaction occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time should not exceed two hours in adults and four hours in pediatric patients. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

Home infusion

Home infusion under the supervision of a healthcare professional may be considered for patients who are not hypersensitive/allergic to eculizumab, murine proteins, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. The decision of a patient to receive home infusions should be made after evaluation and recommendation from the prescribing and/or treating physician. Home infusions should be performed by a qualified healthcare professional.

Appropriate medical infrastructure, resources and procedures must be established and available to health care professionals administering home infusions. Personnel trained in emergency measures should be readily available during the Soliris infusion and for a specified time after infusion.

If a patient experiences an anaphylactic or another acute reaction, immediately discontinue the Soliris infusion, initiate appropriate medical treatment and seek the attention of a physician (see 7 WARNINGS AND PRECAUTIONS). If severe or serious reactions occur, subsequent infusions should only occur in a setting where resuscitation measures are available. The dose and/or infusion rate must not be changed without consulting the prescribing and/or treating physician.

4.5 Missed Dose

In case of a missed dose, resume the regular schedule as soon as possible.

5 OVERDOSAGE

Soliris is to be administered under the supervision of a healthcare professional which minimizes the potential of a significant overdose. No cases of overdose have been reported during clinical studies.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 4– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (IV) infusion	300 mg single-use vial	Polysorbate 80 (vegetable origin) Sodium chloride Sodium phosphate dibasic Sodium phosphate monobasic Water for Injection USP

Soliris is a sterile, clear, colourless, preservative-free 10 mg/mL solution for intravenous (IV) infusion and is supplied in 30-mL single-use vials. The product is formulated at pH 7.0 and each vial contains 300 mg of eculizumab, 13.8 mg sodium phosphate monobasic, 53.4 mg sodium phosphate dibasic, 263.1 mg sodium chloride, 6.6 mg polysorbate 80 (vegetable origin) and Water for Injection, USP.

Soliris is supplied as 300 mg single-use vials each containing 30 mL of 10 mg/mL sterile, preservative-free eculizumab solution. Each carton contains one vial.

7 WARNINGS AND PRECAUTIONS

Please see the 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

Hypersensitivity/Allergy/Infusion Reactions

As with all protein products, administration of Soliris may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, 1(0.9%) patient with gMG experienced an infusion reaction which required discontinuation of Soliris. No patients with PNH, atypical HUS, or NMOSD experienced an infusion reaction which required discontinuation of Soliris. Post-marketing reports of severe and serious infusion reactions, including anaphylaxis, have been received (see **Sensitivity/Resistance** section). Interrupt Soliris infusion and institute appropriate treatment and supportive measures if signs of cardiovascular instability or respiratory compromise occur. Prior to infusions, patients should be informed of these signs and symptoms and steps to take to seek medical care immediately.

Monitoring Disease Manifestations after Soliris Discontinuation/Missed Dose

Treatment Discontinuation for PNH

Since Soliris therapy increases the number of PNH cells (e.g., in the double-blind, placebo-controlled PNH Study C04-001, the proportion of PNH RBCs increased among Soliris-treated patients by a median of 28% from baseline (range from -25% to 69%), patients who discontinue treatment with Soliris may be at increased risk for serious hemolysis. Serious hemolysis is identified by serum LDH levels greater than the pre-treatment level, along with any of the following: greater than 25% absolute decrease in PNH clone size (in the absence of dilution due to transfusion) in one week or less; a hemoglobin level of <5 gm/dL or a decrease of >4 gm/dL in one week or less; angina; change in mental status; a 50% increase in serum creatinine level; or thrombosis. Monitor any patient who discontinues Soliris for at least 8 weeks to detect serious hemolysis and other reactions.

If serious hemolysis occurs after Soliris discontinuation, consider the following procedures/ treatments: blood transfusion (packed RBCs), or exchange transfusion if the PNH RBCs are >50% of the total RBCs by flow cytometry, anticoagulation, corticosteroids, or reinstitution of Soliris, but this was not tested in clinical trials.

In clinical studies, 16 of 196 patients with PNH discontinued treatment with Soliris. Patients were followed for evidence of worsening hemolysis and no serious hemolysis was observed.

Monitor patients after discontinuing Soliris for at least 8 weeks to detect hemolysis.

Treatment Discontinuation for atypical HUS

Soliris treatment is recommended to continue for the patient's lifetime, unless the discontinuation of Soliris is clinically indicated (see 7 WARNINGS AND PRECAUTIONS).

Thrombotic microangiopathy complications were observed after Soliris discontinuation in the atypical HUS clinical studies. If patients with atypical HUS discontinue treatment with Soliris they should be monitored closely for signs and symptoms of thrombotic microangiopathy complications. Monitoring may be insufficient to predict or prevent severe thrombotic microangiopathy complications in patients with atypical HUS after discontinuation of Soliris.

Thrombotic microangiopathy (TMA) complications post discontinuation can be identified by (i) Any two, or repeated measurement of any one, of the following: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during Soliris treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during Soliris treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during Soliris treatment; or by (ii) any one of the following: a change in mental status or seizures; angina or dyspnoea; or thrombosis.

Monitor any patient who discontinues Soliris for at least 12 weeks to detect thrombotic microangiopathy complications.

If thrombotic microangiopathy complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, plasma therapy [plasmapheresis, plasma exchange, or fresh frozen plasma (PE/PI)], or appropriate organ-specific supportive measures including renal support with dialysis, respiratory support with mechanical ventilation or anticoagulation. In atypical HUS clinical studies, 18 patients (5 in the prospective studies) discontinued Soliris treatment. Seven (7) thrombotic microangiopathy complications were observed following the missed dose in 5 patients and Soliris was re-initiated in 4 of these 5 patients.

Treatment Discontinuation for gMG

Use of Soliris in gMG treatment has only been studied in the setting of chronic administration. Patients that discontinue Soliris treatment should be carefully monitored for signs and symptoms of disease exacerbation.

Treatment Discontinuation for NMOSD

Use of Soliris in NMOSD treatment has been studied only in the setting of chronic administration and the effect of Soliris discontinuation has not been characterized. Patients who discontinue Soliris treatment should be carefully monitored for signs and symptoms of potential NMOSD relapse.

Immunization

Prior to initiating Soliris therapy, it is recommended that patients with PNH, atypical HUS, gMG, or NMOSD receive immunizations according to current immunization guidelines. Additionally, all patients must receive meningococcal vaccines prior to, or at the time of receiving Soliris. Patients less than 2 years of age and those who are treated with Soliris less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serotypes A, C, Y, W135, and B, are recommended in preventing the commonly pathogenic meningococcal serotypes.

Children treated with Soliris 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 NACI guidelines. Additionally, Aspergillus infections have occurred in immunocompromised and neutropenic patients. Use caution when administering Soliris to patients with any systemic infection.

Immunosuppressant and Anticholinesterase Therapies

gMG

Patients in gMG clinical trials continued treatment with immunosuppressant and anticholinesterase therapies while on Soliris treatment. Withdrawal of immunosuppressant and anticholinesterase therapies during Soliris treatment for gMG was not assessed in the placebo-controlled studies.

If background immunosuppressant or anticholinesterase therapies are decreased or discontinued, patients should be monitored closely for signs of disease exacerbation.

NMOSD

Patients who entered NMOSD clinical trials while receiving background immunosuppressant therapy continued treatment with immunosuppressant therapy while on Soliris treatment. Withdrawal of immunosuppressant therapy during Soliris treatment for NMOSD was not assessed in the placebo-controlled study. If background immunosuppressant therapy is decreased or discontinued, patients should be monitored closely for signs and symptoms of potential NMOSD relapse.

Carcinogenesis and Mutagenesis

Carcinogenesis and mutagenesis studies have not been performed. There is no evidence to suggest that the use of Soliris is associated with carcinogenesis (see 16 NON-CLINICAL TOXICOLOGY).

Cardiovascular

In atypical HUS clinical trials, serious cardiovascular events such as hypertension, venous thrombosis and tachycardia were observed.

Gastrointestinal

Rare episodes of severe abdominal pain have been reported with Soliris treatment.

Genitourinary

Serious urinary tract infections and disseminated gonococcal infections have been reported. Counsel patients about gonorrhea prevention and advise regular testing for patients at-risk.

Immune

Infrequent antibody responses have been detected in Soliris-treated patients across all clinical studies. In PNH placebo-controlled studies, low antibody responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%).

In patients with atypical HUS treated with Soliris, antibodies to Soliris were detected in 3/100 (3%) by ECL bridging format assay. 1/100 (1%) of atypical HUS patients had low positive values for neutralizing antibodies.

In a gMG placebo-controlled study, none (0/62) of the Soliris treated patients showed antidrug antibody response during the 26 week active treatment.

In an NMOSD placebo-controlled study, 2/95 (2.1%) of the Soliris treated patients showed an antidrug antibody (ADA) response. Positive ADA samples were low titer and transient. Both patients were negative for neutralizing antibodies.

There has been no observed correlation of antibody development to clinical response or adverse events.

Soliris blocks terminal complement; therefore, patients may have increased susceptibility to *Neisseria meningitis* (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

Infections

Patients are at increased risk of serious infections caused by *Neisseria* and encapsulated bacteria. Meningococcal sepsis is the most serious adverse reaction experienced by patients receiving Soliris.

In clinical studies, 2 out of 196 patients with PNH developed serious meningococcal infections while receiving treatment with Soliris; both had been vaccinated. In clinical studies among non-PNH patients, meningococcal meningitis occurred in one unvaccinated patient. In addition, 3 out of 130 previously vaccinated patients with atypical HUS developed meningococcal infections while receiving treatment with Soliris.

No meningococcal infections were reported in completed gMG and NMOSD clinical studies.

Use caution when administering Soliris to patients with any systemic infection.

Monitoring and Laboratory Tests

PNH

PNH patients receiving Soliris therapy should be monitored for intravascular hemolysis by measuring LDH levels and may require dose adjustment within the recommended 14 ± 2 day dosing schedule during the maintenance phase (up to every 12 days).

Atypical HUS

Patients with atypical HUS receiving Soliris therapy should be monitored for early signs of thrombotic

microangiopathy (TMA) including a decrease in platelet count and increases in serum LDH and creatinine levels. Follow patients for signs of TMA by monitoring serial platelet counts, serum LDH, and creatinine during Soliris therapy and for a minimum of 12 weeks after discontinuation of Soliris (see **General**, Monitoring Disease Manifestations after Soliris Discontinuation/Missed Dose). Patients may require dose adjustment within the recommended 14 ± 2-day dosing schedule during the maintenance phase (up to every 12 days).

Neurologic

Transient, severe headaches have been reported with Soliris. Headache (occurred mostly in the initial phase of dosing) is most common adverse reaction in patients treated with Soliris.

Reproductive Health: Female and Male Potential

- **Fertility**

  No specific study on fertility has been conducted (see **7.1.1 Pregnant Women**).

Sensitivity/Resistance

As with all infusions with biologic agents, there is a risk of infusion reactions and anaphylaxis. (For information regarding allergic/infusion reactions, see **General: Allergy/Infusion Reactions** above).

Thrombosis Prevention and Management

The effect of withdrawal of anticoagulant therapy during Soliris treatment has not been established.

7.1 Special Populations

7.1.1 Pregnant Women

Data in pregnant women treated with eculizumab from clinical trials and in a postmarketing setting, including PNH and atypical HUS registries, indicate that eculizumab is unlikely to increase the risk of malformative or feto-neonatal toxicity in the PNH and atypical HUS patient population. There is insufficient data to adequately characterize the safety of eculizumab in pregnant women with gMG or NMOSD.

The use of Soliris may be considered during pregnancy, if clinically needed.

In the general population, the estimated risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 10-20%, respectively.

Limited data are available from reports of pregnancy-related outcomes from the safety database. Analysis of available data show no difference in the risk of overall major birth defects for eculizumab (0.94 per 100 live births) compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) or 2-3% in the U.K. reference population. The rate of fetal death (miscarriage and stillbirth) observed in the safety database is estimated to be 16.2%. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%.

The background risk of birth defects for the indicated population of PNH or atypical HUS is not thought to be different than that in the general population. Rates of miscarriage and still birth are reported to be

as high as 26% and 10% respectively in PNH. Methodological limitations of this data analysis include the use of MACDP and published literature on PNH and atypical HUS as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Animal reproduction studies have not been conducted with Soliris due to lack of pharmacologic activity in non-human species. Reproductive toxicology studies were conducted in mice using the murine surrogate molecule BB5.1, which assessed effect of C5 blockade on the reproductive system. No clear test-article related reproductive and developmental toxicities were identified in these studies (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). Animal studies are not always predictive of human response; therefore, it is unknown whether Soliris can cause fetal harm when administered to a pregnant woman. Human IgG are known to cross the human placental barrier, and thus eculizumab may potentially cause terminal complement inhibition in the fetal circulation.

7.1.2 Breast-feeding

Limited data available suggest that eculizumab is not excreted in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for eculizumab and any potential adverse effects on the breastfed child from eculizumab or from the underlying maternal condition.

Nonclinical reproductive toxicology studies conducted in mice with the murine surrogate molecule BB5.1 identified no adverse effect to pups resulting from consuming milk from treated dams; however, animal studies are not always predictive of human response (see 16 NON-CLINICAL TOXICOLOGY**,** Reproductive and Developmental Toxicology).

7.1.3 Pediatrics

Pediatrics (< 18 years of age):

In children and adolescent patients with PNH (aged 11 years to less than 18 years) included in the pediatric PNH Study, the safety profile appeared similar to that observed in adult patients with PNH. The most common adverse reaction reported in pediatric patients was headache.

Four clinical studies assessing the safety and effectiveness of Soliris for the treatment of atypical HUS included a total of 28 pediatric patients (ages 2 months to 17 years). The safety and effectiveness of Soliris for the treatment of atypical HUS appear similar in pediatric and adult patients. Alexion also conducted a retrospective chart review in patients with atypical HUS treated with Soliris outside of the scope of a clinical trial which included 19 pediatric patients.

Administer vaccinations for the prevention of infection due to *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) according to NACI guidelines (see 7 WARNINGS AND PRECAUTIONS).

Soliris has not been studied in pediatric patients with gMG or NMOSD.

7.1.4 Geriatrics

52 patients 65 years of age or older (15 with PNH, 4 with atypical HUS, 26 with gMG and 7 with NMOSD) were treated with Soliris in clinical studies. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reaction was headache, (occurred mostly in the initial phase), and, of all meningococcal infections the most frequently reported serious adverse reaction was meningococcal sepsis.

Patients with PNH who discontinue treatment with Soliris may be at increased risk for serious hemolysis. Thrombotic microangiopathy complications were observed after Soliris discontinuation in the atypical HUS clinical studies. Patients who discontinue Soliris should be closely monitored.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

In a Phase III (Study C01-004) multi-center, double blind, placebo-controlled trial, 87 transfusion-dependent patients (≥ 18 years of age) with PNH were randomized to receive either Soliris (43) or placebo (44). The duration of treatment was 6 months for both treatment groups.

Drug related adverse events occurring in 2 or more Soliris-treated patients are summarized in **Table 5.** The most frequent adverse events were headache and fatigue. Most headaches were mild and did not persist after the initial administration phase of Soliris and resolved within 24-48 hours of Soliris infusion.

Table 5: Treatment Emergent Adverse Reactions* Reported in ≥2 patients in PNH Study C04-001

	C04-001	
	Soliris (N=43)	**Placebo (N=44)**
Gastrointestinal disorders		
Nausea	2 (5%)	1 (2%)
Abdominal Pain	2 (5%)	1 (2%)
General disorders and administration site conditions		
Fatigue	3 (7%)	0 (0%)

Infections And Infestations		
Upper Respiratory Tract Infection	2 (5%)	0 (0%)
Oral Herpes	2 (5%)	0 (0%)
Nervous System disorders		
Headache	15 (35%)	2 (5%)
Skin And Subcutaneous Tissue disorders		
Dry Skin	2 (5%)	0 (0%)

*Drug-related Adverse Events occurring at a higher frequency (1 or more patients) in the Soliris-treated patients relative to placebo.

Eculizumab dose: 600 mg of eculizumab once a week for 4 weeks, followed by 900 mg of eculizumab 1 week later for 1 dose, then 900mg eculizumab every 2 weeks for 21 weeks for a total of 26 weeks treatment. Duration of treatment: 26 weeks

Among 193 patients with PNH treated with Soliris in the single arm, clinical study or the follow-up study (C04-002), adverse reactions were similar to those reported in the placebo-controlled clinical study. Serious adverse reactions occurred among 16% of the patients in these studies. The most common serious adverse reactions were: viral infection (2%), headache (2%), anemia (2%), and pyrexia (2%).

Atypical HUS

The safety of Soliris therapy in patients with atypical HUS was evaluated in four prospective, single-arm studies, three in adult and adolescent patients (Studies C08-002, C08-003, and C10-004), one in pediatric and adolescent patients (Study C10-003), and one retrospective study (Study C09-001r).

The data described below **(Table 6)** were derived from 78 adult and adolescent patients with atypical HUS enrolled in studies C08-002, C08-003, and C10-004. All patients received the recommended dosage of Soliris, and the median exposure was 67 weeks (range: 2-145 weeks). The most commonly reported serious adverse events (SAE) were infections (24%), hypertension (5%), chronic renal failure (5%), and renal impairment (5%).

Table 6 summarizes all treatment emergent adverse drug reactions reported in at least 10% of patients in atypical HUS Studies C08-002, C08-003, and C10-004 combined.

Table 6: Per Patient Incidence of Treatment Emergent Adverse Drug Reactions (ADRs) in 10% or More Adult and Adolescent Patients Enrolled in Atypical HUS Study C08-002, Atypical HUS Study C08-003, and Atypical HUS Study C10-004 Separately and in Total

MedDRA ver. 15.1	**Number (%) of Patients**			
	Study C08-002 **(N=17)**	Study C08-003, **(N=20)**	Study C10-004 **(N=41)**	**Total (N=78)**
Blood and Lymphatic System Disorders				
Leukopenia	2 (12)	2 (10)	0 (0)	4 (5)
Lymphopenia	0 (0)	2 (10)	0 (0)	2 (3)
Gastrointestinal Disorders				
Nausea	2 (12)	0 (0)	0 (0)	2 (3)
Vomiting	3 (18)	0 (0)	1 (2)	4 (5)
Nervous System Disorders				
Headache	1 (6)	3 (15)	0 (0)	4 (5)
Respiratory, Thoracic and Mediastinal Disorders				
Cough [a]	0 (0)	2 (10)	0 (0)	2 (3)
Vascular Disorders				
Hypertension [b]	3 (18)	0 (0)	0 (0)	3 (4)

[a] Includes preferred terms Cough and Productive Cough

[b] Includes preferred terms Hypertension and Accelerated Hypertension

Study C08-002: Duration of treatment in weeks: median (min, max): 100 (2, 186) weeks, Eculizumab dose: 900 mg of eculizumab once a week for 4 weeks, followed by 1200 mg of eculizumab 1 week later for 1 dose, then 1200mg eculizumab every 2 weeks thereafter.

Study C08-003: Duration of treatment in weeks: median (min, max): 156 (26, 182) weeks, Eculizumab dose: 900 mg of eculizumab once a week for 4 weeks, followed by 1200 mg of eculizumab 1 week later for 1 dose, then 1200mg eculizumab every 2 weeks thereafter

Study C10-004: Duration of treatment in months: median (min, max): 12 (3, 29) months, Eculizumab dose: 900 mg of eculizumab once a week for 4 weeks, followed by 1200 mg of eculizumab 1 week later for 1 dose, then 1200mg eculizumab every 2 weeks thereafter

In Studies C08-002A/B, C08-003A/B, and C10-004 combined, 60% (47/78) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were infections (24%), hypertension (5%), chronic renal failure (5%), and renal impairment (5%).

Generalized Myasthenia Gravis (gMG)

In a 26-week placebo-controlled trial evaluating the effect of Soliris for the treatment of gMG (gMG

Study ECU-MG-301), 62 patients received Soliris at the recommended dosage regimen and 63 patients received placebo. Patients were 19 to 79 years of age, and 66% were female. **Table 7** displays the most common adverse reactions from gMG Study ECU-MG-301 that occurred in ≥5% of Soliris-treated patients and at a greater frequency than placebo.

Table 7: Treatment Emergent Adverse Reactions Reported in 5% or More of Soliris-Treated Patients in ECU-MG-301 Study and at a Greater Frequency than in Placebo-Treated Patients

	Soliris (N=62) n (%)	**Placebo (N=63) n (%)**
Gastrointestinal Disorders		
Abdominal Pain	5 (8)	3 (5)
General Disorders and Administration Site Conditions		
Peripheral edema	5 (8)	3 (5)
Pyrexia	4 (7)	2 (3)
Infections and Infestations		
Herpes simplex virus infections	5 (8)	1 (2)
Injury, Poisoning, and Procedural Complications		
Contusion	5 (8)	2 (3)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	9 (15)	5 (8)

Duration of treatment: 26 weeks
Eculizumab dose: 900 mg of eculizumab once a week for 4 weeks, followed by 1200 mg of eculizumab 1 week later for 1 dose, then 1200mg eculizumab every 2 weeks thereafter

The most common adverse reactions (≥10%) that occurred in Soliris-treated patients in the long-term extension to gMG Study ECU-MG-301, Study ECU-MG-302, that are not included in **Table 7** were headache (26%), nasopharyngitis (24%), diarrhea (15%), arthralgia (12%), upper respiratory tract infection (11%), and nausea (10%).

Neuromyelitis Optica Spectrum Disorder (NMOSD)

In Study ECU-NMO-301, 96 patients received Soliris at the recommended dosage regimen and 47 patients received placebo. Patients were 19 to 75 years of age, and 91% were female.

Table 8 displays the most common adverse reactions from Study ECU-NMO-301 that occurred in ≥ 5% of Soliris-treated patients and at a greater frequency than placebo.

Table 8: Treatment Emergent Adverse Reactions Reported in 5% or More of Soliris-Treated Patients in Study ECU-NMO-301 and at a Greater Frequency than in Placebo-Treated Patients

	Soliris (N=96) n (%)	**Placebo (N=47) n (%)**
Events/Patients	1295/88	617/45
Blood and lymphatic system disorders		
Leukopenia	5 (5)	1 (2)
Lymphopenia	5 (5)	0 (0)
Eye disorders		
Cataract	6 (6)	2 (4)
Gastrointestinal disorders		
Diarrhoea	15 (16)	7 (15)
Constipation	9 (9)	3 (6)
General disorders and administration site conditions		
Asthenia	5 (5)	1 (2)
I**nfections and infestations**		
Upper respiratory tract infection	28 (29)	6 (13)
Nasopharyngitis	20 (21)	9 (19)
Influenza	11 (11)	2 (4)
Pharyngitis	10 (10)	3 (6)
Bronchitis	9 (9)	3 (6)
Conjunctivitis	9 (9)	4 (9)
Cystitis	8 (8)	1 (2)
Hordeolum	7 (7)	0 (0)
Sinusitis	6 (6)	0 (0)
Cellulitis	5 (5)	1 (2)
Injury, poisoning and procedural complications		
Contusion	10 (10)	2 (4)
Metabolism and nutrition disorders		
Decreased appetite	5 (5)	1 (2)

Musculoskeletal and connective tissue disorders		
Back pain	14 (15)	6 (13)
Arthralgia	11 (11)	5 (11)
Musculoskeletal pain	6 (6)	0 (0)
Muscle spasms	5 (5)	2 (4)
Nervous system disorders		
Dizziness	14 (15)	6 (13)
Paraesthesia	8 (8)	3 (6)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	7 (7)	2 (4)
Skin and subcutaneous tissue disorders		
Alopecia	5 (5)	2 (4)

Duration of treatment in weeks: eculizumab: median (min, max): 89 (3, 211) weeks, placebo: median (min, max): 41 (6, 208) weeks.
Eculizumab dose: 900 mg of eculizumab once a week for 4 weeks, followed by 1200 mg of eculizumab 1 week later for 1 dose, then 1200mg eculizumab every 2 weeks thereafter

Cumulative studies

Supportive safety data were obtained from 18 completed and two ongoing clinical studies that included 610 patients exposed to Soliris in, PNH, aHUS, gMG and NMOSD disease populations.

Table 9 lists the adverse reactions observed in Soliris completed and ongoing clinical trials, including PNH, atypical HUS, gMG, and NMOSD studies. Adverse reactions reported at a very common (≥1/10), common (≥1/100 to <1/10), or uncommon (≥1/1,000 to <1/100) frequency with eculizumab, are listed by system organ class and preferred term. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 9: Adverse Reactions reported in 610 patients included in overall Soliris clinical trials, including patients with PNH, atypical HUS, gMG and NMOSD

MedDRA System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infection and infestations	Nasopharyngitis, Upper respiratory tract infection, Urinary tract infection, Influenza	Bronchitis, Sinusitis, Viral infection, Oral herpes,	[a]Meningococcal infection, Gingivitis, Septic shock, Abscess,

		Pneumonia, Cystitis, Lower respiratory tract infection, Cellulitis, Infection, Fungal infection, Gastrointestinal infection, Tooth infection, Sepsis	Haemophilus infection, Peritonitis, Genitourinary tract gonococcal infection, Impetigo
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Malignant melanoma, Myelodysplastic syndrome
Blood and lymphatic system disorders	Anaemia	Leukopenia, Haemolysis, Thrombocytopenia, Lymphopenia	Coagulopathy, Abnormal clotting factor, Red blood cell agglutination
Immune system disorders		Hypersensitivity	
Endocrine disorders			Basedow's disease
Metabolism and nutrition disorders		Decreased appetite	
Psychiatric disorders		Insomnia, Depression, Anxiety	Sleep disorder, Abnormal dreams, Mood swings
Nervous system disorders	Headache, Dizziness	Paraesthesia, Syncope	Tremor, Dysgeusia
Eye disorders		Vision blurred	Conjunctival irritation

Ear and labyrinth disorders		Vertigo, Tinnitus	
Cardiac disorders		Palpitations	
Vascular disorders		Hypertension, Haematoma, Hypotension, Hot flush	Accelerated hypertension, Vein disorder
Respiratory, thoracic and mediastinal disorders	Cough Oropharyngeal pain	Epistaxis Dyspnoea Rhinorrhoea Nasal congestion	Throat irritation
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Abdominal pain, Constipation	Dyspepsia, Abdominal distension, Gastrooesophageal reflux disease	Gingival pain
Hepatobiliary disorders			Jaundice
Skin and subcutaneous tissue disorders		Rash, Pruritus, Alopecia, Dry skin, Erythema, Urticaria, Dermatitis, Hyperhidrosis, Petechiae	Skin depigmentation
Musculoskeletal and connective tissue disorders	Back pain, Arthralgia, Pain in extremity,	Muscle spasms, Neck pain, Joint swelling,	Trismus

	Myalgia	Bone pain	
Renal and urinary disorders		Renal impairment, Dysuria, Haematuria	
Reproductive system and breast disorders			Menstrual disorder, Spontaneous penile erection
General disorders and administration site conditions	Pyrexia, Fatigue	Influenza like illness, Chest pain, Asthenia, Chills, Chest discomfort, Oedema	Feeling hot, Infusion site pain, Extravasation, Injection site paraesthesia
Investigations		Alanine aminotransferase increased, Aspartate aminotransferase increased, Haemoglobin decreased	Gamma-glutamyltransfer-ase increased, Haematocrit decreased
Injury, poisoning and procedural complication		Infusion related reaction	

Studies include C07-002 (asthma); C08-002, C08-003, C10-003, C10-004 (aHUS); C99-006 (dermatomyositis); C08-001, ECU-MG-301, ECU-MG-302, ECU-MG-303 interim data-cutoff date 06 Jan 2022 (gMG); ECU-NMO-301, ECU-NMO-302 (NMOSD); C99-004, E99-004 (IMG); C02-001, C04-001, C04-002, C06-002, C07-001, E02-001, E05-001, E07-001, M07-005, X03-001, X03-001A (PNH); C99-007 (psoriasis); C01-004, C97-001, C99-001, E01-004, E99-001 (RA); C11-001 (STEC-HUS); C97-002 (SLE). Adverse reactions were coded using MedDRA version 24.1.

[a]Meningococcal infection includes the following group of PTs: Meningococcal sepsis, Meningococcal meningitis, Neisseria infection

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

PNH

In children and adolescent PNH patients (aged 11 years to less than 18 years) included in the pediatric PNH Study, the safety profile appeared similar to that observed in adult PNH patients. The most common adverse reaction reported in pediatric patients was headache.

Atypical HUS

Atypical HUS Study C10-003 included 22 pediatric and adolescent patients, of which 18 pediatric patients were less than 12 years of age. All patients received the recommended dosage of Soliris. Median exposure was 44 weeks (range: 1 dose-87 weeks). **Table 10** summarizes all adverse events reported in at least 10% of patients enrolled in Study C10-003.

Table 10: Per Patient Incidence of Treatment Emergent Adverse Events in 10% or More Patients Enrolled in Study C10-003

	1 month to <12 yrs (n=18)	**Total (n=22)**
Eye Disorders	3 (17)	3 (14)
Gastrointestinal Disorders		
Abdominal pain	6 (33)	7 (32)
Diarrhea	5 (28)	7 (32)
Vomiting	4 (22)	6 (27)
Dyspepsia	0	3 (14)
General Disorders and Administration Site Conditions		
Pyrexia	9 (50)	11 (50)
Infections and Infestations		
Upper respiratory tract infection	5 (28)	7 (32)
Nasopharyngitis	3 (17)	6 (27)
Rhinitis	4 (22)	4 (18)
Urinary Tract infection	3 (17)	4 (18)
Catheter site infection	3 (17)	3 (14)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	2 (11)	3 (14)
Nervous System Disorders		
Headache	3 (17)	4 (18)
Renal and Urinary Disorders	3 (17)	4 (18)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	7 (39)	8 (36)
Oropharyngeal pain	1 (6)	3 (14)
Skin and Subcutaneous Tissue Disorders		
Rash	4 (22)	4 (18)
Vascular Disorders		
Hypertension	4 (22)	4 (18)

Interim Clinical Study Report: C10-003: Cutoff date 18 July 2013

In Study C10-003, 59% (13/22) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were hypertension (9%), viral gastroenteritis (9%), pyrexia (9%), and upper respiratory infection (9%). One patient discontinued Soliris due to an adverse event (severe agitation).

Analysis of retrospectively collected adverse event data from pediatric and adult patients enrolled in atypical HUS Study C09-001r (N=30) revealed a safety profile that was similar to that which was observed in the two prospective studies. Atypical HUS Study C09-001r included 19 pediatric patients less than 18 years of age.

Overall, the safety of Soliris in pediatric patients with atypical HUS enrolled in Study C09-001r appeared similar to that observed in adult patients. The most common (≥15%) adverse drug reactions occurring in pediatric patients are presented in **Table 11.**

Table 11: Adverse Reactions Occurring in at Least 15% of Patients Less than 18 Years of Age Enrolled in atypical HUS Study C09-001r

	Number (%) of Patients			
MedDRA ver. 11.0	**< 2 yrs. (n=5)**	**2 to < 12 yrs. (n=10)**	**12 to <18 yrs. (n=4)**	**Total (n=19)**
General Disorders and Administration Site Conditions				
Pyrexia	4 (80)	4 (40)	1 (25)	9 (47)
Gastrointestinal Disorders				
Diarrhea	1 (20)	4 (40)	1 (25)	6 (32)
Vomiting	2 (40)	1 (10)	1 (25)	4 (21)
Infections and Infestations				
Upper respiratory tract infection[a]	2 (40)	3 (30)	1 (25)	6 (32)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3 (60)	2 (20)	0 (0)	5 (26)
Nasal congestion	2 (40)	2 (20)	0 (0)	4 (21)
Cardiac Disorders				
Tachycardia	2 (40)	2 (20)	0 (0)	4 (21)

[a]includes the preferred terms upper respiratory tract infection and nasopharyngitis
Analysis of retrospectively collected adverse event data from an observational and non-interventional trial to assess ecluzimab treatment effects in patients with aHUS. Patients who had been diagnosed with aHUS and had received at least one dose of ecluzimab between 2007 and Dec 2009

One patient discontinued treatment due to serious adverse events of persistent worsening renal function, fever, increased creatinine and pancytopenia considered unrelated to Soliris administration. One patient discontinued treatment with Soliris whose systemic lupus had been misdiagnosed as atypical HUS (see section 7 WARNINGS AND PRECAUTIONS, Monitoring After Soliris Discontinuation / Missed Dose).

gMG
Soliris has not been studied in pediatric patients with gMG.

NMOSD
Soliris has not been studied in pediatric patients with NMOSD.

Table 9 lists uncommon (≥1/1,000 to <1/100) frequency adverse reactions with eculizumab.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

PNH

CTC Grades 3 and 4 laboratory abnormalities were tabulated for PNH patients who had normal values at baseline (**Table 12**). Laboratory abnormalities were seen in 0% (creatinine) to 15.6% (direct bilirubin) of Soliris-treated patients and they occurred at similar or slightly lower frequency in placebo-treated patients.

Table 12: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of Soliris in PNH Patients

	Percent of patients*	
	Soliris (N=195)	**Placebo (N=44)**
Neutropenia	14.8	3.8
Thrombocytopenia	0.8	6.4
Elevated ALT	1.1	2.5
Elevated AST	11.1	N/A**
Elevated Direct Bilirubin	15.6	8.3
Elevated total Bilirubin	3.6	0
Elevated BUN	5.5	0
Elevated Creatinine	0	0

*Worst on-study values in patients with normal baseline

CTC grades: neutropenia (Grade 3 ≥0.5-1.0 x 10^9/L, Grade 4 <0.5 x 10^9/L); thrombocytopenia (Grade 3 ≥10-50 x 10^9/L , Grade 4 <10 x 10^9/L, Grade 4<10 x10^9/L); Elevated AST and ALT(Grade 3 >3-10 x ULN, Grade 4 >10 x ULN); Elevated Bilirubin (Grade 3 >3 -10 x ULN, Grade 4 >10 x ULN); Elevated BUN; Elevated Creatinine (Grade 3>3-6 x ULN, Grade 4>6 x ULN)

** All placebo treated patients had elevated AST at baseline

Low titer human anti-human antibodies were detected in 3/140 (2.1%) of PNH patients treated with Soliris and in 1/44 (2.3%) of placebo-treated PNH patients. These low titer antibodies occurred transiently and with no apparent correlation between antibody development and either clinical response (i.e., reduction in hemolysis) or adverse events to Soliris; these responses in the placebo group were therefore considered as false positive.

In the rheumatoid arthritis clinical trial of Soliris, one patient exhibited an increase in anti-DNA antibody titer from 1:40 to 1:80 that was deemed an adverse drug reaction. Nine Soliris- and one placebo-treated patient had anti-DNA antibody titers of >1:80 at the end of 26 weeks of treatment. The clinical significance of these observations is unknown.

Atypical HUS

Overall, laboratory events were uncommon and no clinically meaningful changes in laboratory values were reported.

gMG

Overall, there were no clinically meaningful differences between the placebo arm and the eculizumab arm in the change from Baseline in any hematology or chemistry parameters.

No difference between treatment arms was observed in ECG parameters.

NMOSD

Overall, there were no clinically meaningful differences between the placebo arm and the eculizumab arm in the change from Baseline in any hematology or chemistry parameters. No difference between treatment arms was observed in ECG parameters.

8.5 Post-Market Adverse Reactions

Overall, safety data from post-marketing reports for patients with PNH or atypical HUS are consistent with the known safety profile observed in clinical studies. Cases of serious or fatal meningococcal infections have been reported.

Post-marketing experience in patients with gMG and NMOSD is limited; however, clinical trial data demonstrated no difference of Soliris safety profile across indication.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drug interaction studies have not been performed with Soliris.

9.3 Drug-Behavioural Interactions

There are no drug-behavioural interactions known at this time.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

PP, PE, PI have been shown to reduce Soliris serum levels. A supplemental dose of Soliris is required in these settings. See Section 4.2 Recommended Dose and Dosage Adjustment for guidance in case of concomitant PP, PE or PI treatment.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action
Eculizumab, the active ingredient in Soliris, is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9 and free C5a.

Soliris inhibits terminal complement-mediated intravascular hemolysis in patients with PNH and complement-mediated thrombotic microangiopathy (TMA) in patients with atypical HUS.

In patients with gMG, the mechanism of action of Soliris is unknown. It is presumed to inhibit the terminal complement mediated C5b-9 complex deposition at the Neuromuscular Junction (NMJ).

In patients with NMOSD, the exact mechanism by which eculizumab exerts its therapeutic effect is unknown but is presumed to involve inhibition of aquaporin-4 (AQP4) antibody induced terminal complement C5b-9 deposition and C5a-dependent inflammation.

10.2 Pharmacodynamics
Pharmacodynamic activity measured by free C5 concentrations of <0.5 g/mL, is correlated with essentially complete blockade of terminal complement activity in patients with PNH, atypical HUS, gMG and NMOSD.

10.3 Pharmacokinetics
Following intravenous maintenance doses of 900 mg once every 2 weeks in patients with PNH, the week 26 observed mean ± SD serum eculizumab maximum concentration (C_{max}) was 194 ± 76 µg/mL and the trough concentration (C_{trough}) was 97 ± 60 µg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with aHUS, the week 26 observed mean ± SD C_{trough} was 242 ± 101 µg/mL.

Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with gMG, the week 26 observed mean ± SD C_{max} was 783 ± 288 µg/mL and the C_{trough} was 341 ± 172 µg/mL.

Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with NMOSD at week 24, the observed mean±SD C_{max} was 877±331 and the C_{trough} was 429±188 mcg/mL.

Steady state was achieved 4 weeks after starting eculizumab treatment, with accumulation ratio of approximately 2-fold in all studied indications. Population pharmacokinetic analyses showed that eculizumab pharmacokinetics were dose-linear and time-independent over the 600 mg to 1200 mg dose range, with inter-individual variability of 21% to 38%.

Absorption

Soliris is administered intravenously; therefore, eculizumab bioavailability is assumed to be 100% with immediate absorption into the vascular space.

Distribution:

Soliris is a humanized antibody and is expected to have distribution similar to native human antibodies, primarily limited to the vascular space. The eculizumab volume of distribution for a typical 70 kg patient was 5 L to 8 L.

Metabolism:

Eculizumab contains only naturally- occurring amino acids and has no known active metabolites. Human antibodies are predominately catabolized by lysosomal enzymes to small peptides and amino acids.

Elimination

The half-life of eculizumab is 11.3 days to 17.3 days.

Special Populations and Conditions

- **Renal Insufficiency** The pharmacokinetics of Soliris have been studied in patients with atypical HUS with a range of renal impairment and age. There have been no observed differences in pharmacokinetic parameters noted in these subpopulations of patients with atypical HUS.
- **Drug Interactions** Intravenous human immunoglobulin (IVIg) treatment may interfere with the endosomal neonatal Fc receptor (FcRn) recycling mechanism of monoclonal antibodies such as eculizumab and thereby decrease serum eculizumab concentrations. Drug interaction studies have not been conducted with eculizumab in patients treated with IVIg.

11 STORAGE, STABILITY AND DISPOSAL

Soliris vials must be stored in the original carton until time of use under refrigerated conditions at 2 to 8ºC and protected from light. Soliris vials may be held in the original carton at room temperature (not more than 25ºC) for a single period of up to 3 days. Do not use beyond the expiration date stamped on the carton. Refer to 4 DOSAGE AND ADMINISTRATION, **4.3 Reconstitution** for information on the stability and storage of diluted solutions of Soliris.

12 SPECIAL HANDLING INSTRUCTIONS

Do not Freeze. Do Not Shake.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

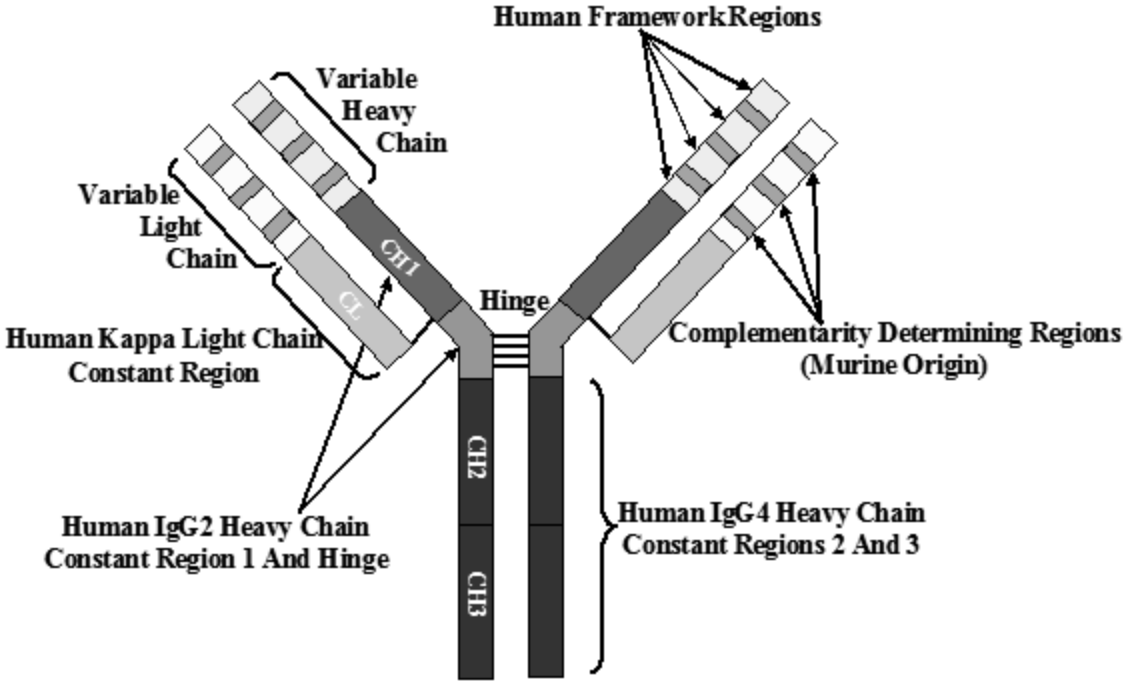
Drug Substance

Proper name: eculizumab

Chemical name: immunoglobulin, anti-(human complement C5 α-chain) (human-mouse monoclonal 5G1.1 heavy chain), disulfide with human-mouse monoclonal 5G1.1 light chain, dimer

Molecular formula and molecular mass: Approximately 148 kDa

Structural formula:



Physicochemical properties:

Product Characteristics:

Soliris is a formulation of eculizumab, which is a recombinant humanized monoclonal $IgG_{2/4K}$ antibody that binds to the human C5 complement protein and inhibits the activation of terminal complement. Eculizumab contains human constant regions and murine complementarity-determining regions grafted onto the human framework light-and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

Eculizumab is produced in a murine myeloma (NS0 cell line) expression system and purified by affinity and ion exchange chromatography.

Pharmaceutical standard: Professed

Viral Inactivation

The bulk drug substance manufacturing process includes specific viral inactivation and removal steps.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Trial Design and Study Demographics

The safety and efficacy of Soliris in patients with PNH with hemolysis were assessed in a randomized, double blind, placebo-controlled 26-week study (C04-001) and a single arm 52-week study (C04-002). Patients received meningococcal vaccination prior to receipt of Soliris.

Table 13: Summary of patient demographics for clinical trials in PNH

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex N (%)
C04-001	Randomized, double blind, placebo-controlled, multicentre	Dosage: 600mg every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days, then 900 mg every 14 ± 2 days for study duration Route of administration: intravenous infusion for 25-45 minutes Duration: 26 weeks	Placebo 44 Soliris 43	Placebo 38.4 (18.0,78.0) Soliris 42.1 (20.0, 85.0)	Placebo Female 29 (65.9) Soliris Female 23 (53.5)
C04-002	Single arm, non-controlled, multicentre	Dosage: 600mg every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days, then 900 mg every 14 ± 2 days for study duration Route of administration: intravenous infusion for 25 to 45 minutes Duration: 52 weeks	Soliris 97	41.1 (18.0, 78.0)	Female 49 (50.5)

In study C04-001, patients with PNH with at least 4 transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/µL were randomized to either Soliris (n = 43) or placebo (n = 44). Prior to randomization, all patients underwent an initial

observation period to confirm the need for RBC transfusion and to identify the hemoglobin concentration (the "set-point") which would define each patient's hemoglobin stabilization and transfusion outcomes. The hemoglobin set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Primary efficacy endpoints were hemoglobin stabilization (patients who maintained a hemoglobin concentration above the hemoglobin set-point and avoid any RBC transfusion for the entire 26-week period) and blood transfusion requirement. Fatigue and health-related quality of life were relevant secondary endpoints. Hemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH RBCs was monitored by flow cytometry. Patients receiving anticoagulants and systemic corticosteroids at baseline continued these medications. Major baseline characteristics were balanced (see **Table 14**).

In the non-controlled Study C04-002, patients with PNH with at least one transfusion in the prior 24 months and at least 30,000 platelets/µL received Soliris over a 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the patients and systemic corticosteroids in 40% of the patients. Baseline characteristics are shown in **Table 14**.

Table 14: Patient Demographics and Characteristics in C04-001 and C04-002

	C04-001		C04-002
Parameter	**Placebo N=44**	**Soliris N=43**	**Soliris N=97**
History of Aplastic Anemia or MDS[a] (%)	12 (27.3)	8 (18.7)	29 (29.9)
Concomitant Anticoagulants (%)	20 (45.5)	24 (55.8)	59 (61)
Concomitant Steroids / Immunosuppressant Treatments (%)	16 (36.4)	14 (32.6)	46 (47.4)
Discontinued treatment	10	2	1
PRBC in previous 12 months, median (Q1,Q3) Range	17.0 (13.5, 25.0) (7.0, 44.0)	18.0 (12.0, 24.0) (7.0, 36.0)	8.0 (4.0, 24.0) (0.0, 66.0)
Mean Hgb level (g/dL) at set point (SD) Range	7.7 (0.75) (6.2, 9.0)	7.8 (0.79) (6.1, 8.8)	N/A
Pre-treatment LDH levels (median, U/L) Range	2,234.5 (636.0, 5530.0)	2,032.0 (499.0, 5962.0)	2,051.0 (537.0,5245.0)
Free Hemoglobin at baseline (median, mg/dL) Range	46.2 (11.2, 502.0)	40.5 (7.5, 764.0)	34.9 (2.0, 317.5)

[a]MDS=myeloplastic syndrome

Study Results

Efficacy Results for Study C04-001 and C04-002

In Study C04-001, patients treated with Soliris had significantly reduced ($p<0.001$) hemolysis resulting in improvements in anemia as indicated by increased percentage of patients with hemoglobin stabilization and reduced median RBC transfusions compared to placebo treated patients (see **Table 15**). These effects were seen among patients within each of the three pre-study RBC transfusion strata (4 - 14 units; 15 - 25 units; >25 units), with the exception of no statistically significant hemoglobin stabilization in

patients who previously required >25 units; however, this must be interpreted with caution since the numbers in each stratum are limited (see **Table 16**). Patients reported less fatigue and improved health-related quality of life. Because of the study sample size and duration, the effects of Soliris on thrombotic events could not be determined.

In Study C04-002, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular hemolysis, as measured by median serum LDH levels, was achieved for the treatment (see **Table 17)**.

Table 15: Efficacy Outcomes in PNH Study C04-001

	PNH Study C04-001		
	Placebo N=44	**Soliris N=43**	**P-Value**
Percentage of patients with stabilized Hemoglobin levels at end of study	0	49	< 0.001[a]
Median PRBC transfused during treatment (range)	10 (2.0, 21.0)	0 (0.0, 16.0)	< 0.001[b]
Transfusion Avoidance during treatment (%)	0	51	< 0.001[a]
Median LDH levels at end of study (U/L) (Range)	2,167 (1183, 5643)	239 (142, 2984)	< 0.001[b]
Median LDH AUC at end of study (U/L x Day) (Range) [c]	411,822 (161414, 86544)	58,587 (32,417,792,006)	< 0.001[b]
Median Free Hemoglobin at end of study (mg/dL) (Range)	62 (0.7, 386)	5 (2.9, 194)	< 0.001[b]
FACIT-Fatigue (effect size) [d]		1.13	< 0.001 [e]

[a]P value calculated using Fisher's exact test
[b]P value calculated with Wilcoxon rank sum test
[c] LDH AUC: For PNH Study C04-001, LDH AUC was calculated using trapezoid rule for the actual LDH values
[d]FACIT effect size: For PNH Study C04-001, effect size was based on the difference between eculizumab and placebo group
[e]P value calculated using the 2 sided t-test

Table 16: Efficacy Outcomes in PNH Study C04-001 by Transfusion Strata

Outcome Measure	**Transfusion Strata[a]**	**Placebo (N)**	**Soliris (N)**	**P-Value**
Percentage of patients with stabilized Hemoglobin levels at end of study (%) (N)	Overall	0 (44)	49 (43)	< 0.001[b]
	4 – 14 Units	0 (15)	80 (15)	< 0.001[b]
	15 – 25 Units	0 (18)	29 (17)	0.02
	>25 Units	0 (11)	36 (11)	ns
Median PRBC transfused during treatment (N) (Range)	Overall	10 (44) (2.0, 21.0)	0 (43) (0.0, 16.0)	< 0.001[c]
	4 – 14 Units	6 (15) (2.0, 2.00)	0 (15) (0.0, 4.0)	< 0.001[c]

Outcome Measure	Transfusion Strata[a]	Placebo (N)	Soliris (N)	P-Value
	15 – 25 Units	10 (18) (2.0, 21.0)	2 (17) (0.0, 15.0)	< 0.001[c]
	>25 Units	18 (11) (10.0, 20.0)	3 (11) (0.0, 16.0)	< 0.001[c]
Transfusion Avoidance during treatment (%) (N)	Overall	0 (44)	51 (43)	< 0.001[b]
	4 – 14 Units	0 (15)	80 (15)	< 0.001[b]
	15 – 25 Units	0 (18)	35 (17)	0.008
	>25 Units	0 (11)	36 (11)	ns
Median LDH AUC at end of study (U/L x Day) (N) (Range)	Overall	411,822 (44) (161414, 886544)	58,587 (43) (32417, 792006)	< 0.001[c]
	4 – 14 Units	398,573 (15) (230352, 697638)	53,610 (15) (38341, 792006)	< 0.001[c]
	15 – 25 Units	420,338 (18) (161414, 886544)	56,127 (17) (32417, 90115)	< 0.001[c]
	>25 Units	441880 (11) (234605, 711934)	67,181 (11) (33231, 242072)	< 0.001[c]

[a]Transfusion strata based on transfusion data 12 months prior to study screening
[b]P value calculated with Fisher's exact test; ns = not significant (P>0.05)
[c]P value calculated with Wilcoxon rank sum test

Table 17: Efficacy Outcomes in PNH Study C04-002

	PNH Study C04-002[a]	
	Soliris N=97	**P- Value**
Median LDH levels at end of study (U/L) (Range)	269 (106, 2117)	< 0.001[b]
Median LDH AUC at end of study (U/L x Day) (Range)[c]	-632,264 (-1788824, -74498)	< 0.001[b]
Median Free Hemoglobin at end of study (mg/dL) (Range)	5 (1.1, 85)	< 0.001[b]
FACIT-Fatigue (effect size)[d]	1.01	< 0.001 [e]

[a]Results from Study PNH Study C04-002 refer to pre- versus post-treatment comparisons.
[b]P value calculated with Wilcoxon signed rank test
[c]LDH AUC: For PNH Study C04-002, LDH AUC was calculated using trapezoid rule for change of LDH from baseline.
[d]FACIT effect size: For PNH Study C04-002, effect size was based on change from baseline.
[e]P value calculated using the 2 sided t-test

From the 195 patients that originated in PNH Study C04-001, PNH Study C04-002 and other initial studies, Soliris-treated PNH patients were enrolled in a long-term extension study (PNH Extension Study). All patients sustained a reduction in intravascular hemolysis over a total Soliris exposure time ranging from 10 to 54 months. There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment (see **Table 18**). However, the majority of patients received

concomitant anticoagulants; the effect of anticoagulant withdrawal during eculizumab therapy was not studied (see 7 WARNINGS AND PRECAUTIONS).

Table 18: Thromboembolic Events in Patients during Soliris Treatment Period Compared to Thromboembolic Events during the Same Period of Time Pre-Soliris Treatment

	PNH Extension Study (All studies combined)
Pre-Treatment	
Patients (n)	195
Thrombolic Events (n)	39
Patient Years (n)	272.1
Thromboembolic Event Rate (n per 100 patient-years)	14.33
Soliris Treatment	
Patients (n)	195
Thromboembolic Events (n)	3
Patient Years (n)	281.0
Thromboembolic Event Rate (n per 100 patient-years)	1.07 (P<0.001)[a]

[a] p value calculated with a non-parametric signed rank test

Atypical Hemolytic Uremic Syndrome (atypical HUS)

Trial Design and Study Demographics

Four single-arm prospective studies (atypical HUS Studies C08-002, C08-003, C10-004, and C10-003) and one single-arm retrospective study (C09-001r) evaluated the safety and efficacy of Soliris for the treatment of atypical HUS. Patients with atypical HUS received meningococcal vaccination prior to receipt of Soliris or received prophylactic treatment with antibiotics until 2 weeks after vaccination. Study C09-001r was a retrospective chart review.

Table 19: Summary of patient demographics for clinical trials in atypical HUS

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex N (%)
C08-002 (Atypical HUS resistant to PE/PI*)	Phase II open-label, single arm, multi- centre	Dosage: 900 mg every 7± 2 days for 4 weeks, followed by 1200 mg 7±2 days later, then 1200 mg every 14 ± 2 days thereafter Route of administration: intravenous infusion Duration: Minimum 26 weeks, Median 100 weeks, Range 2-145 weeks	17	28 years (17-68 years)	Female 12 (71)
C08-003 (Atypical HUS sensitive to PE/PI*)	Phase II open-label, single arm, multi-centre	Dosage: 900 mg every 7± 2 days for 4 weeks, followed by 1200 mg 7±2 days later, then 1200 mg every 14 ± 2 days thereafter Route of administration: Intravenous infusion Duration: Minimum 26 weeks, Median 114 weeks, Range 26-129 weeks	20	28 years (13 to 63 years	Female 12 (60)
C10-004 (Adult patients with atypical HUS)	Open-label, single-arm, multi-centre	Dosage: 900 mg every 7± 2 days for 4 weeks, followed by 1200 mg 7±2 days later, then 1200 mg every 14 ± 2 days thereafter Route of administration: Intravenous infusion Duration: Minimum 26 weeks, Median 50 weeks, Range 13-86 weeks	41	35 years (18 to 80 years)	Female 28 (68)

<table>
<tr><th>Study #</th><th>Trial design</th><th>Dosage, route of administration and duration</th><th>Study subjects (n)</th><th>Median age (Range)</th><th>Sex N (%)</th></tr>
<tr>
<td>C10-003 (Pediatric & Adolescent patients with atypical HUS)</td>
<td>Open-label, single arm, multi-centre</td>
<td>Dosage
<table>
<tr><th>Weight (kg)</th><th>Induction mg/wk</th><th>Maint. Dose mg</th></tr>
<tr><td>≥40</td><td>900 for 4 weeks</td><td>1200 at Wk5;
Then:
1200 Q2W</td></tr>
<tr><td>30-<40</td><td>600 for 2 weeks</td><td>900 at Wk3;
Then:
900 Q2W</td></tr>
<tr><td>20-<30</td><td>600 for 2 weeks</td><td>600 at Wk3;
Then:
600 Q2W</td></tr>
<tr><td>10-<20</td><td>600 for 1 week</td><td>300 at Wk2;
Then:
300 Q2W</td></tr>
<tr><td>5-<10</td><td>300 for 1 week</td><td>300at Wk2;
Then:
300 Q3W</td></tr>
</table>
Route of administration:
Intravenous infusion

Duration :
Minimum : 26 weeks,
Median: 44 weeks,
Range: 1 dose to 88 weeks</td>
<td>22</td>
<td>6.5 years
(5 months to 17 years)</td>
<td>Female
10 (46)</td>
</tr>
</table>

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex N (%)
C09-001r	Retro-spective chart review	Dosage: Dose levels used were 300, 600, 900, and 1200mg. Actual dose administered to patients may have been different from recommendations since treatment was outside of controlled clinical trial setting. Route of Administration: Intravenous infusion Duration: Median 27.5 weeks, Range 1-94 weeks	30	12 years (2 months to 51 years) #pts per age range Infant to <2: 5 ≥ 2 to <12: 10 ≥12 to <18: 4 ≥ 18: 11	Female 16 (53

*PE/PI: Plasma Exchange/Plasma Infusion

Atypical HUS Resistant to PE/PI (Study C08-002)

Study C08-002 enrolled patients who displayed signs of thrombotic microangiopathy (TMA) despite receiving at least four PE/PI treatments the week prior to screening. One patient had no PE/PI the week prior to screening because of PE/PI intolerance. 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, without the need for chronic dialysis. The median patient age was 28 (range: 17 to 68 years). Patients enrolled in Study C08-002 were required to have ADAMTS-13 activity level above 5%; observed range of values in the trial were 70%-121%. Seventy-six percent (76%) of patients had an identified complement regulatory factor mutation or auto-antibody. **Table 20** summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C08-002.

Table 20: Baseline Characteristics of Patients Enrolled in Study C08-002

Parameter	Study C08-002 N = 17
Time from atypical HUS diagnosis until screening in months, median (min, max)	10 (0.26, 236)
Time from current clinical TMA manifestation until screening in months, median (min, max)	<1 (<1, 4)
Baseline platelet count (× 10^9/L), median (range)	118 (62, 161)
Baseline LDH (U/L), median (range)	269 (134, 634)

Patients in Study C08-002 received Soliris for a minimum of 26 weeks. Study C08-002. The median duration of Soliris therapy was approximately 100 weeks (range: 2 weeks to 145 weeks), and the primary endpoint was change in platelet count from baseline through Week 26.

Atypical HUS Sensitive to PE/PI (Study C08-003)

Study C08-003 enrolled patients undergoing chronic PE/PI who generally did not display hematologic signs of ongoing thrombotic microangiopathy (TMA). All patients had received PT at least once every two weeks, but no more than three times per week, for a minimum of eight weeks prior to the first Soliris dose. Patients on chronic dialysis were permitted to enroll in Study C08-003. Patients enrolled in Study C08-003 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 37%-118%. Seventy percent of patients had an identified complement regulatory factor mutation or auto-antibody. **Table 21** summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C08-003.

Table 21: Baseline Characteristics of Patients Enrolled in Study C08-003

Parameter	**Study C08-003** N=20
Time from atypical HUS diagnosis until screening in months, median (min, max)	48 (0.66, 286)
Time from current clinical TMA manifestation until screening in months, median (min, max)	9 (1, 45)
Baseline platelet count ($x10^9$/L), median (range)	218 (105, 421)
Baseline LDH (U/L), median (range)	200 (151, 391)

Patients in Study C08-003 received Soliris for a minimum of 26 weeks. The primary endpoint was TMA Event-Free status defined as no decrease in platelet count >25% AND no PT AND no new dialysis for 12 consecutive weeks during the study period. In Study C08-003, the median duration of Soliris therapy was approximately 114 weeks (range: 26 to 129 weeks).

Adult Patients with atypical HUS (Study C10-004)

Study C10-004 enrolled patients who displayed signs of thrombotic microangiopathy (TMA). In order to qualify for enrollment, patients were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. All patients enrolled in Study C10-004 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 28-116%. Fifty-one percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 35 patients received PE/PI prior to eculizumab. **Table 22** summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-004.

Table 22: Baseline Characteristics of Patients Enrolled in Study C10-004

Parameter	Study C10-004 N = 41
Time from atypical HUS diagnosis until screening in months, median (range)	0.79 (0.03 – 311)
Time from current clinical TMA manifestation until first study dose in months, median (range)	0.52 (0.03-19)
Baseline platelet count (× 10^9/L), median (range)	125 (16 – 332)
Baseline LDH (U/L), median (range)	375 (131 – 3318)

Patients in Study C10-004 received Soliris for a minimum of 26 weeks. The submission primary endpoint was the responder rate defined by the proportion of patients with complete TMA response as evidenced by normalization of hematological parameters [platelet count and lactate dehydrogenase (LDH)] and ≥ 25% decrease in serum creatinine from baseline during treatment with eculizumab. Complete TMA response is defined as two consecutive measurements obtained at least 4 weeks apart. In Study C10-004, the median duration of Soliris therapy was approximately 50 weeks (range: 13 weeks to 86 weeks).

Pediatric and Adolescent Patients with atypical HUS (atypical HUS Study C10-003)

Atypical HUS Study C10-003 enrolled patients who were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥97 percentile for age without the need for chronic dialysis. Patients enrolled in Study C10-003 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 38%-121%. Fifty percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 10 patients received PE/PI prior to eculizumab. **Table 23** summarizes the key baseline clinical and disease-related characteristics of patients enrolled in atypical HUS Study C10-003.

Table 23: Baseline Characteristics of Patients Enrolled in atypical HUS C10-003

Parameter	Patients 1 month to <12 years (N = 18)	All Patients (N = 22)
Time from atypical HUS diagnosis until screening in months, median (range)	0.51 (0.03 – 58)	0.56 (0.03-191)
Time from current clinical TMA manifestation until first study dose in months, median (range)	0.23 (0.03-4)	0.2 (0.03-4)
Baseline platelet count (x10^9/L), median (range)	110 (19-146)	91 (19-146)
Baseline LDH (U/L) median (range)	1510 (282-7164)	1244 (282-7164)

Patients in atypical HUS Study C10-003 received Soliris for a minimum of 26 weeks. The primary endpoint was responder rate defined by the proportion of patients with Complete TMA response as evidenced by normalization of hematological parameters [platelet count and lactate dehydrogenase (LDH)] and ≥ 25% improvement in serum creatinine from baseline during treatment with eculizumab. Complete TMA response is defined as two consecutive measurements obtained at least four weeks apart. In atypical HUS Study C10-003, the median duration of Soliris therapy was approximately 44 weeks (range: 1 dose to 88 weeks).

Study Results

Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints including the following:

- platelet count change from baseline
- Hematologic normalization *(maintenance of normal platelet counts and LDH levels for at least four weeks)*
- Complete TMA response *(hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of four weeks)*
- TMA-event free status *(absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, plasma exchange or plasma infusion, and new dialysis requirement)*
- Daily TMA intervention rate *(defined as the number of plasma exchange or plasma infusion interventions and the number of dialyses required per patient per day)*

Atypical HUS Resistant to PE/PI (Study C08-002)

Renal function, as measured by eGFR, was improved and maintained during Soliris therapy. The mean eGFR (±SD) increased from 23 ± 15 mL/min/1.73m^2 at baseline to 56 ± 40 mL/min/1.73m^2 by 26 weeks; this effect was maintained through 2 years (56 ± 30 mL/min/1.73m^2). Four of the five patients who required dialysis at baseline were able to discontinue dialysis.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In Study C08-002, mean platelet count (± SD) increased from 109 ± 32 x10^9/L at baseline to 169 ± 72 x10^9/L by one week; this effect was maintained through 26 weeks (210 ± 68 x 10^9/L, and 2 years (205 ± 46 x 10^9/L). When treatment was continued for more than 26 weeks, two additional patients achieved Hematologic Normalization as well as Complete TMA response. Hematologic Normalization and Complete TMA response were maintained by all responders. **Table 24** summarizes the efficacy results for Study C08-002.

Table 24: Efficacy Results for Study C08-002

Efficacy Parameter	Study C08-002 at 26 wks[a] N=17	Study C08-002 at 2 yrs[b] N=17
Platelet Count Normalization[c]	14 (82)	15 (88)
Complete TMA response, n (%) Median Duration of complete TMA response, weeks (range)	11 (65) 38 (25, 56)	13 (77) 99 (25, 139)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%) Median duration of eGFR improvement, days (range)	9 (53) 251 (70, 392)	10 (59) ND
Hematologic normalization, n (%) Median Duration of hematologic normalization, weeks (range)	13 (76) 37 (25, 62)	15 (88) 99 (25, 145)
TMA event-free status, n (%)	15 (88)	15 (88)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 0.88 (0.04, 1.59) 0 (0, 0.31)	 0.88 (0.04, 1.59) 0 (0, 0.31)

[a]At data cut-off (September 8, 2010).
[b]At data cut-off (April 20, 2012).
[c]Normal platelet count is defined as ≥150 × 10^9/L.

Atypical HUS Sensitive to PE/PI (Study C08-003)

The primary endpoint of Study C08-003 was TMA Event-Free status defined as no decrease in platelet count >25% AND no PT AND no new dialysis for 12 consecutive weeks during the study period.

Renal function, as measured by eGFR, was maintained during Soliris therapy. The mean eGFR (± SD) was 31 ± 19 mL/min/1.73m^2 at baseline and was maintained through 26 weeks (37 ± 21 mL/min/1.73m^2) and 2 years (40 ± 18 mL/min/1.73m^2). No patient required new dialysis with Soliris.

Reduction in terminal complement activity was observed in all patients after the commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count (± SD) was 228 ± 78 x 10^9/L at baseline, 233 ± 69 x 10^9/L at week 26, and 224 ± 52 x 10^9/L at 2 years. When treatment was continued for more than 26 weeks, six additional patients achieved Complete TMA response. Complete TMA Response and Hematologic Normalization were maintained by all responders. **Table 25** summarizes the efficacy results for Study C08-003.

Table 25: Efficacy Results of Patients Enrolled in Study C08-003

Efficacy Parameter	Study C08-003 at 26 wks[a] N=20	Study C08-003 at 2 yrs[b] N=20
Complete TMA response, n (%) Median duration of complete TMA response, weeks (range)	5 (25) 32 (12, 38)	11 (55) 68 (38, 109)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	1 (5)	8 (40)

Efficacy Parameter	Study C08-003 at 26 wks[a] N=20	Study C08-003 at 2 yrs[b] N=20
TMA Event-free status n (%)	16 (80)	19 (95)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 0.23 (0.05, 1.09) 0	 0.23 (0.05, 1.09) 0
Hematologic normalization[d], n (%) Median duration of hematologic normalization, weeks (range)[c]	18 (90) 38 (22, 52)	18 (90) 114 (33, 125)

[a]At data cut-off (September 8, 2010).
[b]At data cut-off (April 20, 2012).
[c]Calculated at each post-dose day of measurement (excluding Days 1 to 4) using a repeated measurement ANOVA model.
[d]In atypical HUS Study C08-003, 85% of patients had normal platelet counts and 80% of patients had normal serum LDH levels at baseline, so hematologic normalization in this population reflects maintenance of normal parameters in the absence of PE/PI.

Adult Patients with atypical HUS (Study C10-004)

The primary endpoint was responder rate defined by the proportion of patients with complete TMA response as evidenced by normalization of hematological parameters [platelet count and lactate dehydrogenase (LDH)] and ≥ 25% decrease in serum creatinine from baseline during treatment with eculizumab. Complete TMA response is defined as two consecutive measurements obtained at least 4 weeks apart.

Complete TMA Response was achieved by 23 patients (56%; 95% CI: 40, 72) through Week 26 and by 26 patients (63%; 95% CI 47, 78) through data cut-off. All patients who achieved a response through Week 26 remained in response through data cut-off. The median duration of Complete TMA Response through data cut-off was nine months (range 1-17 months).

Thirty-six patients (88%; 95% CI: 74, 96) achieved a Hematologic Normalization through Week 26 and 40 patients (98%; 95% CI: 87, 99) through data cut-off. Hematologic Normalization was maintained in all 40 responders. The median duration of Hematologic Normalization through data cut-off was 10 months (range 2-17 months).

Renal function, as measured by eGFR, was improved during Soliris therapy. The mean eGFR (± SD) increased from 17 ± 12 mL/min/1.73m^2 at baseline to 47 ± 24 mL/min/1.73m^2 by 26 weeks. Of the 24 patients who required dialysis at study baseline, 5 patients discontinued dialysis prior to the first dose of Soliris and 15 were able to discontinue dialysis during Soliris treatment.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In Study C10-004, mean platelet count (± SD) increased from 119 ± 66 x10^9/L at baseline to 200 ± 84 x10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (±SD) at week 26: 252 ± 70 x10^9/L). **Table**

26 summarizes the efficacy results for Study C10-004.

Table 26: Results of Atypical HUS study C10-004

Efficacy Parameter	**Study C10-004 (N = 41)**
Platelet Count Normalization[a]	40 (98%)
Complete TMA response, n (%), 95% CI Median duration of submission complete TMA response, weeks (range)	23 (56), 40,72 42 (6, 75)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m^2, n (%)	22 (54)
Hematologic Normalization, n (%) Median duration of hematologic normalization, weeks (range)	36 (88) 46 (10, 75)
TMA Event-free Status, n (%)	37 (90)
Daily TMA Intervention Rate, median (range) Before eculizumab On eculizumab treatment	 0.63 (0, 1.38) 0 (0, 0.58)

[a]Normal platelet count is defined as ≥150 × 10^9/L.

In atypical HUS studies C08-002, C08-003, and C10-004, a total of 43% of patients with no known mutation in the gene encoding for complement regulatory protein achieved Complete TMA response compared to 54% of patients with a known mutation. In pediatric and adolescents Study C10-003, complete TMA response was achieved in 55% of patients with no known mutation compared to 73% in patients with a known mutation. The number of patients in each group was small. Efficacy outcomes were independent whether patient had in an identified genetic mutation.

Pediatric and Adolescent Patients with atypical HUS (atypical HUS Study C10-003)

The primary endpoint of Study C10-003 was responder rate defined as the proportion of patients with Complete TMA response as evidenced by normalization of hematological parameters [platelet count and lactate dehydrogenase (LDH)] and ≥ 25% improvement in serum creatinine from baseline during treatment with eculizumab. Complete TMA response is defined as two consecutive measurements obtained at least four weeks apart.

Complete TMA response was achieved in 14 of the 22 patients (64%; 95% CI: 41, 83) through Week 26 and in 15 patients (68%; 95% CI: 45, 86) through data cut-off. All 15 patients maintained their response through data cut-off, with a median duration of eight months (range 3 - 18 months).

For the 18 pediatric patients <12 years old, Complete TMA Response rates were similar through Week 26 (11 patients [61%; 95% CI: 36, 83]) and through data cut-off (12 patients [67%; 95% CI: 41, 87]).

Hematologic Normalization was observed in 18 of 22 patients (82%; 95% CI: 60, 95) through Week 26 and increased to 20 patients (91%; 95% CI: 71, 99) through data cut-off. Hematologic Normalization was maintained in all 20 responders through data cut-off with a median duration of 8 months (range 3 – 18 months).

For the 18 pediatric patients <12 years old, Hematologic Normalization was achieved in 14 patients (78; 95% CI: 52, 94) through Week 26 and 16 patients (89%; 95% CI: 65, 99) through data cut-off.

Renal function, as measured by median eGFR, was improved during Soliris therapy. The mean eGFR (± SD) increased from 33 ± 30 mL/min/1.73m^2 at baseline to 98 ± 44 mL/min/1.73m^2 by 26 weeks. Among the 20 patients with a CKD stage ≥2 at baseline, 17 (85%) achieved a CKD improvement of ≥1 stage. Among the 16 patients ages 1 month to <12 years with a CKD stage ≥2 at baseline, 14 (88%) achieved a CKD improvement by ≥1 stage. Nine of the 11 patients who required dialysis at study baseline were able to discontinue dialysis for the duration of Soliris treatment. Responses were similar across all ages from 5 months to 17 years of age.

Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. The mean platelet count (± SD) increased from 88 ± 42 x10^9/L at baseline to 281 ± 123 x10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (±SD) at week 26: 293 ± 106 x10^9/L). In atypical HUS C10-003, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H. **Table 27** summarizes the efficacy results for atypical HUS Study C10-003.

Table 27: Efficacy Results for atypical HUS Study C10-003

Efficacy Parameter	Patients 1 month to <12 years (N = 18)	All Patients (N = 22)
Platelet Count Normalization[a]		21 (96%)
Complete TMA response, n (%) 95% CI Median Duration of complete TMA response, weeks (range)[b]	11 (61) 36, 83 40 (14, 77)	14 (64) 41, 83 37 (14, 77)
eGFR improvement ≥15 mL/min/ 1.73•m^2•n (%)	16 (89)	19 (86)
Complete Hematologic Normalization, n (%) Median Duration of complete hematologic normalization, weeks (range)	14 (78) 38 (14, 77)	18 (82) 38 (14, 77)
TMA Event-Free Status, n (%)	17 (94)	21 (95)
Daily TMA Intervention rate, median (range) Before eculizumab treatment On eculizumab treatment	 0.2 (0, 1.7) 0 (0, 0.01)	 0.4 (0, 1.7) 0 (0, 0.01)

[a]Normal platelet count is defined as ≥150 × 10^9/L.
[b]Through data cutoff (October 12, 2012)

Retrospective Chart Review of Patients with atypical HUS (Study C09-001r)

Exploratory analyses were conducted in the retrospective chart review (Study C09-001r) and results

were generally consistent with results of the two prospective studies. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline. Mean platelet count (± SD) increased from 171 ± 83 x10^9/L at baseline to 233 ±109 x10^9/L after one week of therapy; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 254 ± 79 x10^9/L).

A total of 19 pediatric patients (ages 2 months to 17 years) received Soliris in Study C09-001r. The median duration of Soliris therapy was 16 weeks (range 4 to 70 weeks) for children < 2 years of age (n=5), 31 weeks (range 19 to 63 weeks) for children 2 to <12 years of age (n=10), and 38 weeks (range 1 to 69 weeks) for patients 12 to 18 years of age (n=4). Fifty three percent of pediatric patients had an identified complement regulatory factor mutation or auto-antibody. Eighty nine percent (17/19, 89%) of these pediatric patients achieved a platelet count normalization and 42% (8/19) had hematologic normalization and complete TMA responses. The daily TMA intervention rate decreased from a median of 0.31 prior to eculizumab to 0 after eculizumab. No pediatric patient required new dialysis.

Table 28 : Efficacy Results in Pediatric Patients Enrolled in Study C09-001r

Efficacy Parameter	<2 yrs. (n=5)	2 to <12 yrs. (n=10)	12 to <18 yrs. (n=4)	Total (n=19)
Patients with Hematologic Normalization and Complete TMA Response	2/5 (40)	5/9 (56)	1/3 (33)	8 (47)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m^2, n (%)[b]	2 (40)	6 (60)	1 (25)	9 (47)
Platelet count normalization, n (%[a]	4 (80)	10 (100)	3 (75)	17 (89)
Daily TMA intervention rate, median (range)				0.31 (0.00, 2.38)
Before eculizumab	1 (0, 2)	<1 (0.07, 1.46)	<1 (0, 1)	0.00
On eculizumab treatment	<1 (0, <1)	0 (0, <1)	0 (0, <1)	(0.00, 0.08)

[a] Platelet count normalization was defined as a platelet count of at least 150,000 X 10^9/L on at least two consecutive measurements spanning a period of at least 4 weeks.
[b] Of the 9 patients who experienced an eGFR improvement of at least 15 mL/min/1.73 m^2, one received dialysis throughout the study period and another received Soliris as prophylaxis following renal allograft transplantation.

Generalized Myasthenia Gravis (gMG)

Trial Design and Study Demographics

Soliris was studied in clinical trials in patients who were anti-acetylcholine receptor (AchR) antibody positive and refractory, defined as failure of treatment with two or more immunosuppressive therapies (ISTs) either in combination or as monotherapy, or failed at least one IST and required chronic plasmapheresis, plasma exchange (PE), or intravenous immunoglobulin (IVIg) to control symptoms. Patients continued to receive standard therapy throughout the pivotal clinical trial.

Table 29: Summary of Patient Demographics for Clinical Trials in gMG

Study	Trial Design	Dosage, Route of Administration, and	Number of Study	Mean Age (years)	Sex

		Duration	Subjects		
ECU-MG-301	Randomized, double-blind, placebo-controlled, multicentre, Phase III	Dosage: 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg every 14 ± 2 days Route of Administration: IV over 35 minutes Duration: 26 Weeks	125	47	Female 66%
ECU-MG-302	Open-label, multicentre, extension of Study ECU-MG-301	Dosage: 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg every 14 ± 2 days Route of Administration: IV over 35 minutes Duration: Up to 4 years	117	47	

Data from 125 patients in a prospective controlled study (Study ECU-MG-301) was used to evaluate the efficacy of Soliris in the treatment of patients with gMG.

In Study ECU-MG-301, patients with gMG with a positive serologic test for anti-AchR antibodies, MGFA (Myasthenia Gravis Foundation of America) clinical classification class II to IV and MG-ADL total score ≥6 were randomized to either Soliris (n=62) or placebo (n=63). Randomization was stratified based on the assessment of clinical classification by the MGFA. Baseline characteristics were similar between treatment groups, including mean age at diagnosis (38 years in each group), gender [66% female (Soliris) versus 65% female (placebo)], and mean duration of gMG [9.9 (Soliris) versus 9.2 (placebo) years]. Also similar between the two treatment groups were the percentages of patients who were previously treated with at least 3 ISTs [50% (Soliris) versus 54 (placebo)], who had experienced an MG crisis [21% (Soliris) versus 15.9% (placebo)], who had any prior ventilation support [24.2% (Soliris) versus 22.2% (placebo)], and who had required intubation [17.7% (Soliris) versus 14.3% (placebo)].

All patients with gMG enrolled in the trial were refractory as defined by the following pre-specified criteria:

- Failed treatment for at least one year with 2 or more immunosuppressant therapies (either in combination or as monotherapy), i.e., patients continued to have impairment in activities of daily living despite immunosuppressant therapies;
  or
- Failed at least one immunosuppressant therapy and required chronic plasma exchange (PE) or intravenous immunoglobulins (IVIg) to control symptoms, i.e., patients require PE or IVIg on a regular basis for the management of muscle weakness at least every 3 months over previous 12 months.

Immunosuppressants included, but were not limited to, corticosteroids, azathioprine, mycophenolate, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide.

Patients received meningococcal vaccination prior to initiating treatment with Soliris or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. In Study ECU-MG-301, the dose of Soliris in adult patients with gMG was 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg at Week 5 ± 2 days, then 1,200 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 35 minutes. Patients continued to receive stable doses of standard therapy during the trial. One hundred and eighteen (118) of the 125 (94%) patients completed the 26-week treatment period.

Study Results

Efficacy Results for Study ECU-MG-301

The primary endpoint for Study ECU-MG-301 was the change from baseline in the MG Activities of Daily Living Profile (MG-ADL – a patient reported outcome measure validated in gMG) 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 (total score 0-24).

The key secondary endpoint was the change from baseline in the Quantitative MG Scoring System (QMG – a physician reported outcome measure validated in gMG) total score at Week 26. 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 (total score 0-39).

Efficacy results for the pre-specified repeated measures analyses of the primary and key secondary endpoint are provided in **Table 30**. These results are based on analyses that ignored the use of rescue medication and other efficacy-related protocol deviations.

Table 30: Results of Study ECU-MG-301 in gMG - Efficacy Outcomes Change from Baseline to Week 26

Efficacy Endpoints: Total score change from baseline at Week 26	Soliris (n=62) (SEM)	Placebo (n=63) (SEM)	Soliris change relative to placebo-LS Mean Difference (95% CI)	p-value (using repeated measures analysis)
MG-ADL*	-4.2 (0.49)	-2.3(0.48)	-1.9 (-3.3, -0.6)	0.0058
QMG*	-4.6 (0.60)	-1.6 (0.59)	-3.0 (-4.6, -1.3)	0.0006

SEM = Standard Error of the Mean CI= Confidence Interval LS-Mean = Least Squares Mean

* The change from baseline to week 26 in MG-ADL and QMG score was analyzed using a repeated measures analysis of variance with treatment, visit, and a treatment by visit interaction as fixed factors, and a randomization stratification variable, baseline score and immunosuppressive therapy treatment status as covariates. These analyses ignore the use of rescue medication and the occurrence of other efficacy-related protocol deviations. There were 6 subjects in the Soliris arm and 12 subjects in the placebo arm that required rescue medication.

In Study ECU-MG-301, a clinical responder in the MG-ADL total score was defined as having at least a 3-

point improvement. The proportion of clinical responders at Week 26 with no rescue therapy was 59.7% on Soliris compared with 39.7% on placebo.

In Study ECU-MG-301, a clinical responder in the QMG total score was defined as having at least a 5-point improvement. The proportion of clinical responders at Week 26 with no rescue therapy was 45.2% on Soliris compared with 19% on placebo.

Also evaluated was the Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15), a validated disease specific questionnaire, in which a 7- to 8-point improvement is indicative of treatment impact. At Week 26, using a repeated measures analysis, the change from baseline for Soliris patients showed an improvement of 12.6 points compared with 5.4 points for placebo patients, representing a treatment effect difference of 7.2 points favoring Soliris.

Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment. Discontinuation of the therapy should be considered in a patient who shows no evidence of therapeutic benefit by 12 weeks.

Based on an interim analysis of an ongoing, open-label extension to Study ECU-MG-301, the remaining subjects who were initially randomized to Soliris continue to demonstrate a sustained effect beyond 26 weeks.

Neuromyelitis optica spectrum disorder (NMOSD)

Trial Design and Study Demographics

Soliris was studied in a clinical trial in patients with NMOSD who were anti-aquaporin-4 (AQP4) antibody-positive.

Table 31: Summary of Patient Demographics for Clinical Trial in NMOSD

Study	Trial Design	Dosage and Route of Administration	Number of Study Subjects	Mean Age (years)	Sex
ECU-NMO-301	Randomized, double-blind, placebo-controlled, multicentre, Phase III	Dosage: 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg every 14 ± 2 days Route of Administration: IV over 35 minutes	143 Soliris: 96 Placebo: 47	44 Range: 19-75	Female 90.9%

The efficacy of Soliris for the treatment of NMOSD was established in Study ECU-NMO-301, a randomized, double-blind, placebo-controlled event driven trial that enrolled 143 patients with NMOSD who were anti-AQP4 antibody positive and met the following criteria at screening:

1. History of at least 2 relapses in last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to screening.
2. Expanded Disability Status Scale (EDSS) score ≤ 7 (consistent with the presence of at least

limited ambulation with aid).
3. If on immunosuppressive therapy (IST), on a stable dose regimen.
4. The use of concurrent corticosteroids was limited to 20 mg per day or less.
5. Patients were excluded if they had been treated with rituximab or mitoxantrone within 3 months or with IVIg within 3 weeks prior to screening.

Patients received meningococcal vaccination 2 weeks prior to initiating treatment with Soliris or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. All patients who were vaccinated and met all eligibility requirements were randomized in a 2:1 ratio to the Soliris group or the placebo group. A total of 96 patients were randomized to receive Soliris treatment and 47 were randomized to receive placebo. Randomization was stratified using two variables: 1) EDSS score at randomization (Day 1) (≤ 2.0 versus ≥ 2.5 to ≤ 7); and 2) patients' prior supportive (i.e., for relapse prevention) IST and IST status at randomization (Day 1) (treatment naïve patients versus patients continuing on the same IST(s) since last relapse versus patients with changes in IST(s) since last relapse). Patients could continue to receive a stable dose of the ISTs they were taking at the time of screening (with the exception of protocol-specified disallowed medications), but no new ISTs and no change in IST dosage were permitted during the study except for a known toxicity or adverse event associated with the given IST.

Baseline characteristics were similar between treatment groups, including mean age at first dose (43.9 in the Soliris group, and 45.0 in the placebo group), and gender [91.7% female (Soliris) versus 89.4% female (placebo)].

Table 32 presents the baseline characteristics of patients with NMOSD enrolled in Study ECU-NMO-301.

Table 32: Patient Disease History and Baseline Characteristics in Study ECU-NMO-301

Variable	Statistic	Placebo (N = 47)	Soliris (N = 96)	Total (N = 143)
NMOSD History				
Age at NMOSD Initial Clinical Presentation (years)	Median	38.0	35.5	36.0
	Min, Max	12, 73	5, 66	5, 73
Time from NMOSD initial clinical presentation to first dose of study drug (years)	Median	3.760	5.030	4.800
	Min, Max	0.51, 29.10	0.41, 44.85	0.41, 44.85
Historical ARR within 24 months prior to Screening	Median	1.92	1.85	1.92
	Min, Max	1.0, 6.4	1.0, 5.7	1.0, 6.4
Baseline Characteristics				
Baseline EDSS Score	Median	4.00	4.00	4.00
	Min, Max	1.0, 6.5	1.0, 7.0	1.0, 7.0
No IST usage at baseline	n (%)	13 (27.7)	21 (21.9)	34 (23.8)

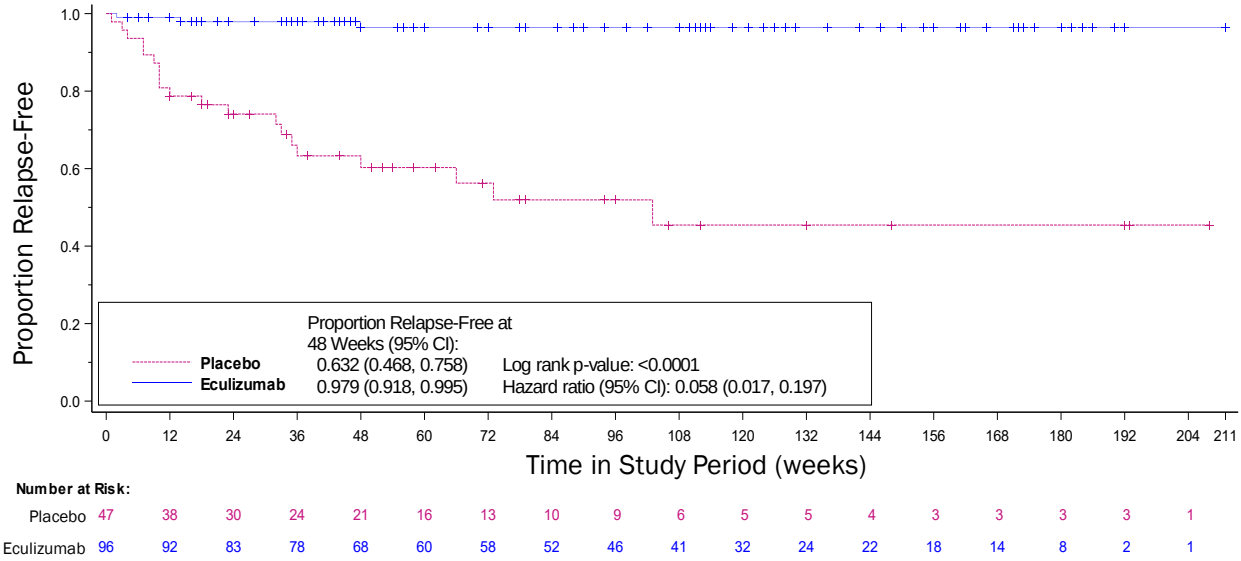
Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IST = immunosuppressant therapy; Max = maximum; Min = minimum; NMOSD = neuromyelitis optica spectrum disorder.

The primary endpoint for Study ECU-NMO-301 was the time-to-first on-trial relapse as adjudicated by an independent committee who were blinded to treatment. On-trial relapse was defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (i.e., clinical sign) on neurologic examination that persisted for more than 24 hours as confirmed by the treating physician who was blinded to treatment. An adjudicated on-trial relapse was defined as an on-trial relapse that was positively adjudicated by the Relapse Adjudication Committee. A key secondary endpoint was the Adjudicated on-trial Annualized Relapse Rate (ARR), which was computed for each patient as the number of relapses divided by the time in years.

Study Results

The time-to-first adjudicated on-trial relapse was significantly longer for patients treated with Soliris compared with placebo (p<0.0001) (**Figure 1**). The hazard ratio (95% confidence interval [CI]) for Soliris compared with placebo was 0.058 (0.017, 0.197), representing a 94.2% reduction in the risk of relapse.

Figure 1: Kaplan Meier Survival Estimates for Time to First Adjudicated On trial Relapse – Full Analysis Set



Note: Patients who did not experience an adjudicated on trial relapse were censored at the end of the Study Period.

The treatment effect on the time-to first-adjudicated on-trial relapse was observed in patients across all IST subgroups, including the subgroup with no ISTs at Baseline. During the treatment phase of the trial, 76% percent of patients received concomitant IST, including chronic corticosteroids; 24% of patients did not receive concomitant IST or chronic corticosteroids during the treatment phase of the trial.

The adjudicated on-trial annualized relapse rate (ARR) ratio (95% CI) for Soliris compared with placebo was 0.045 (0.013, 0.151; p<0.0001), representing a 95.5% relative reduction in adjudicated ARR for patients treated with Soliris compared with placebo (**Table 33**)

Table 33: Adjudicated On-trial Annualized Relapse Rate in Study ECU-NMO-301 – Full Analysis Set

Variable	Statistic	Placebo (N = 47)	Soliris (N = 96)
Total number of relapses	Sum	21	3
Total number of patient-years in study period	n	52.41	171.32
Adjusted adjudicated ARR[a]	Rate	0.350	0.016
	95% CI	0.199, 0.616	0.005, 0.050
Treatment effect[a]	Rate ratio (eculizumab/ placebo)	…	0.045
	95% CI	…	0.013, 0.151
	p-value	…	<0.0001

[a] Based on a Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to Screening.

Abbreviations: ARR = annualized relapse rate; CI = confidence interval.

The annualized rate of on-trial relapse associated hospitalization was 0.04 for Soliris versus 0.31 for placebo. The annualized rate of on-trial relapse associated acute relapse treatment was 0.07 for Soliris versus 0.42 for placebo (IV methylprednisolone) and 0.02 for Soliris versus 0.19 for placebo (plasma exchange).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: The specificity of eculizumab for C5 in human serum was evaluated in two *in vitro* studies.

The tissue cross-reactivity of eculizumab was evaluated by assessing binding to a panel of 38 human tissues. C5 expression in the human tissue panel examined in this study is consistent with published reports of C5 expression, as C5 has been reported in smooth muscle, striated muscle, and renal proximal tubular epithelium. No unexpected tissue cross-reactivity was observed.

A 26-week, repeat-dose, toxicity study in mice with a surrogate antibody BB5.1, directed against murine C5, was performed. The treatment did not affect any of the toxicity parameters examined. C5-induced hemolytic activity in an ex vivo assay was effectively blocked throughout the course of the study in both female and male mice.

Carcinogenicity: No studies have been performed to evaluate the carcinogenic potential of eculizumab.

Genotoxicity: No studies have been performed to evaluate the genotoxic potential of eculizumab.

Reproductive and Developmental Toxicology: Animal reproductive and developmental toxicology studies have not been conducted with eculizumab, due to a lack of pharmacologic activity in non-human species but were conducted in mice with a murine surrogate complement inhibitory antibody, BB5.1. No clear treatment-related effects or adverse effects were observed in the murine surrogate reproductive and developmental toxicology studies in mice. 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, these findings were not clearly test-article related.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

SOLIRIS®
Eculizumab for injection

Read this carefully before you start taking **Soliris®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Soliris®**.

Serious Warnings and Precautions

Infections

Soliris increases the risk of serious infections including meningococcal infections. There have been reports of serious meningococcal infections including death, in patients treated with Soliris. Meningococcal infections can quickly cause death, deafness, brain damage and/or loss of limbs, especially if not recognized and treated early.

- **You must be vaccinated with meningococcal vaccines prior to, or at the time of, initiating Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection; you may be revaccinated according to current medical guidelines for vaccine use.**
- **You must be monitored for early signs of meningococcal infections, evaluated immediately if infection is suspected, and treated with antibiotics, if necessary.**
- **Vaccination may not prevent all meningococcal infections.**

BEFORE you start Soliris, talk to your doctor or pharmacist if you have Meningococcal infection (severe infection of the linings of the brain and sepsis) and other *Neisseria* infections including disseminated gonorrhea. If you receive Soliris when you have a serious infection, contact your doctor immediately if there is any worsening of symptoms of the infection. You should also check that you have received all recommended vaccinations before starting Soliris.

Meningitis vaccination does not prevent all types of meningitis infections.

If you are at risk of gonorrhea, ask your doctor or pharmacist for advice before using this medicine.

Meningococcal infection symptoms
Because of the importance of rapidly identifying and treating certain types of infection in patients who receive Soliris, you will be provided a card to carry with you, listing specific trigger symptoms. This card is named: “Patient Safety Card”. You should carry this card with you at all times during treatment and for 3 months after your last dose of Soliris. Show it to any health care professional you see during this

time. Immediately inform your doctor if you identify any symptoms.

If you experience any of the following symptoms, you should immediately inform your doctor:

- 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

What is Soliris used for?

Soliris is used to treat patients with:

- Paroxysmal Nocturnal Hemoglobinuria (PNH) to reduce hemolysis (destruction of red blood cells);
- Chronic atypical Hemolytic Uremic Syndrome (atypical HUS), a very rare disease that affects the blood system, kidney and sometimes other body organs;
- Generalized Myasthenia Gravis (gMG), a disease affecting the muscles
- Neuromyelitis optica spectrum disorder (NMOSD), a disease of the central nervous system that mainly affects the eye nerves and the spinal cord

How does Soliris work?

The active substance in Soliris, eculizumab, is a monoclonal antibody that blocks part of your immune system called the C5 complement protein.

In patients with PNH and atypical HUS, the complement proteins are over-active and damage the patients' own blood cells. Soliris works by preventing complement proteins from damaging blood cells.

In patients with gMG, over-active complement proteins damage the junction between the nerves and muscles (neuromuscular junction). Soliris is presumed to block the body's inflammatory response and its ability to attack and destroy its own muscles.

In patients with NMOSD, the eye nerves and spinal cord are attacked and damaged by the immune system. Soliris is presumed to block the body's inflammatory response, and its ability to attack and destroy its own eye nerves and spinal cord.

Soliris also lowers the ability of your immune system to fight infection.

What are the ingredients in Soliris?

Medicinal ingredients: eculizumab
Non-medicinal ingredients: polysorbate 80 (vegetable origin), sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, Water for Injection (USP)

Soliris comes in the following dosage forms:

Soliris is supplied as 300 mg single-use vials each containing 30 mL of 10 mg/mL sterile, preservative-free eculizumab solution.

Do not use Soliris if:

- You have any allergies to this drug or its ingredients
- Your doctor confirms a serious infection, such as an active *Neisseria meningitidis* infection (in the brain, spinal cord or blood)
- You have not received a meningococcal vaccine prior to or at the time of initiating

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Soliris. Talk about any health conditions or problems you may have, including if you:

- Have a disease that alters your immune system (such as HIV/AIDS) or take medication that alters your immune system (such as prednisone).

Other warnings you should know about:

Fungal infections caused by *Aspergillus* have occurred in immunocompromised patients with abnormally low white blood cells. Inform your doctor before you take Soliris if you have any infections.

Allergic Reactions:
Serious allergic reactions can happen during your Soliris infusion. Tell your doctor or nurse immediately if you get any of these symptoms during your Soliris infusion:

Chest pain
Trouble breathing or shortness of breath
Swelling of your face, tongue or throat
Feel faint or pass out

Pregnancy and Nursing:
Data in pregnant women treated with Soliris from clinical trials and postmarketing setting, including PNH and atypical HUS registries, indicate SOLIRIS is unlikely to increase the risk of harm to the fetus. There is no clinical data available on the use of SOLIRIS in pregnant gMG patients Soliris may be considered during pregnancy, if clinically needed. Tell your doctor if you are pregnant or nursing.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Soliris:

- Soliris is given through a vein [“I.V.” or “intravenously”], usually over 35 minutes, and must be administered by a health care professional.

Usual dose:
The usual dose of Soliris for adult patients with PNH is:

- 600 mg of Soliris every 7 days for the first 4 weeks, followed by
- 900 mg of Soliris for the fifth dose 1 week later, then

- 900 mg of Soliris every 2 weeks thereafter

The usual dose of Soliris for adult patients with atypical HUS, gMG or NMOSD is:

- 900 mg of Soliris weekly for the first 4 weeks, followed by
- 1200 mg of Soliris for the fifth dose 1 week later, then
- 1200 mg of Soliris every 2 weeks thereafter

If you are less than 18 years of age, the usual dose of Soliris for atypical HUS will be based on your body weight according to the following schedule:

Patient Body Weight	**Induction**	**Maintenance**
40 kg and over	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

Soliris should be administered at the recommended dates or within 48 hours of the recommended date. Your doctor should know by blood tests if Soliris is working.

Overdose:

Soliris should be given by a healthcare professional. This minimizes the chance of an overdose. No cases of overdose were seen in clinical studies.

If you think you, or a person you are caring for, have taken too much SOLIRIS, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Tell your doctor right away if you have missed a dose or if you are considering stopping treatment. Stopping treatment with Soliris may cause side effects.

If you have PNH and miss a dose of Soliris you may experience the following symptoms or problems from red blood cell destruction:

- A sudden or severe drop in your red blood cell count causing anemia
- Confusion or drowsiness
- Chest pain/angina
- Kidney problems including kidney failure

- Blood clots

If you have atypical HUS and miss a dose of SOLIRIS, your blood clotting may be abnormal, causing symptoms including:

- Stroke
- Confusion
- Seizure
- Chest pain
- Trouble breathing
- Kidney problems
- Swelling in arms or legs
- A drop in your platelet count which may cause easy bleeding and easy bruising

If you have PNH and stop treatment of Soliris, your doctor will need to monitor you closely for at least 8 weeks after stopping treatment.

If you have atypical HUS, your doctor will need to monitor you closely during treatment and for at least 12 weeks after stopping Soliris for signs of worsening atypical HUS symptoms or problems related to abnormal clotting.

If you have gMG and stop treatment with Soliris, your doctor will need to monitor you closely for at least 12 weeks after stopping treatment for signs of worsening of gMG symptoms.

If you have NMOSD and stop treatment with Soliris your doctor will need to monitor you closely for signs and symptoms of potential NMOSD relapse.

What are possible side effects from using SOLIRIS?
In all clinical studies, including PNH and atypical HUS clinical trials, the most serious side effect was meningococcal sepsis, which is a common presentation of meningococcal infections in patients treated with Soliris.

- **You must be vaccinated with meningococcal vaccines prior to, or at the time of, initiating SOLIRIS, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection; you may be revaccinated according to current medical guidelines for vaccine use.**
- **You must be monitored for early signs of meningococcal infections, evaluated immediately if infection is suspected, and treated with antibiotics, if necessary.**
- **Vaccination may not prevent all meningococcal infections.**
- **You must carry your Safety Card at all time. If you experience any symptoms listed in your safety card immediately seek for medical care.**

These are not all the possible side affects you may feel when taking Soliris. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects in people with PNH treated with Soliris include headache, stuffy nose, sore throat, nausea, fever, joint aches and pains, fatigue, and cold sores.

The most common side effects in people with atypical HUS treated with Soliris include high blood pressure, diarrhea, headache, nausea, vomiting, low white blood cell count, bladder infection, hair loss, cold sore, low lymphocyte count), cough, joint pain, weakness, and viral infection.

The most common side effects in children with atypical HUS treated with Soliris include common viral cold, and rash.

The most common side effects in people with gMG treated with Soliris include headache, upper respiratory infection, nasopharyngitis, myasthenia gravis, nausea, and diarrhea.

The most common side effects in people with NMOSD treated with Soliris include upper respiratory infection, headache, diarrhea, back pain, influenza, pharyngitis, pain or swelling of your nose or throat (nasopharyngitis), dizziness, arthralgia, and contusion.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON Headache	**X**		
Flu-like illness	**X**		
COMMON High Blood Pressure		**X**	
Low white blood cell count		**X**	
Infection of the lung (pneumonia)			**X**
Respiratory Tract infection		**X**	
Infection of the urinary system (urinary tract infection)		**X**	
Rash	**X**		
Abdominal discomfort or pain	**X**		
Rash	**X**		
Abdominal discomfort or pain	**X**		
Agitation	**X**		
Anemia		**X**	
Chills	**X**		
Deafness	**X**		
Diarrhea	**X**		
Fever		**X**	
Light headedness(dizziness)	**X**		
Low blood pressure		**X**	
Infection		**X**	
UNCOMMON Meningococcal infection including Meningococcal sepsis		**X**	**X**
Fungal infection		**X**	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction)			**X**
Hypersensitivity			**X**
Breathing difficulty			**X**
Inflammation of the peritoneum (the tissue that lines most of the organs of the abdomen)		**X**	
Increase of liver enzymes		**X**	
Relatively few platelets in blood (thrombocytopenia)		**X**	
Kidney disorder		**X**	
Muscle Aches	**X**		
Neck pain		**X**	
Pain in extremity		**X**	
Swelling (Face or Leg)			**X**
RARE Jaundice		**X**	
Disease with thyroid overactivity (Basedow's disease)		**X**	
Menstrual disorder	**X**		
Infusion related reaction		**X**	
Blood in urine		**X**	
Blood clot in vein			**X**
Bone marrow disorder		**X**	
Bacterial sexual transmitted disease		**X**	
Skin tumor (melanoma)			**X**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Prior to infusions, your healthcare professional will inform you about any signs and symptoms of infusion related reactions and steps to take to seek medical care immediately.

If you have an infusion reaction you may be given additional medicines to treat or help prevent future reactions. If the infusion reaction is severe, your doctor may stop the infusion of Soliris and start giving appropriate medical treatment.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store in original carton in a refrigerator (2°C - 8°C).
Protect from light.
Vial in original carton can stay at room temperature (not more than 25°C) for only one single period up to 3 days.
Do not use past the expiry date stamped on the carton.
DO NOT FREEZE. DO NOT SHAKE.

Keep out of reach and sight of children.

If you want more information about SOLIRIS:

- Talk to your healthcare professional
  - Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.alexion.com, or by calling 1-888-765-4747.

Alexion Pharmaceuticals, Inc. has established Registries for PNH and atypical HUS in order to continue to monitor and evaluate the safety and effectiveness of SOLIRIS. You are encouraged to participate and advised that participation may involve long-term follow-up. Information regarding the PNH Registry can be found at http://www.pnhregistry.com or by contacting the PNH Registry hotline at: 1-800-913-4893; or email: pnhregistry@iconplc.com or by calling 1-888-SOLIRIS (1-888-765-4747). For information regarding the atypical HUS Registry, please email: aHUS-Registry@increasearch.com or call 1-888-SOLIRIS (1-888-765-4747). You can only participate in the Registry through your doctor.

This document plus the full Product Monograph, prepared for health professionals, are available by contacting the sponsor, Alexion Pharma GmbH, at 1-888-765-4747.

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