PRODUCT MONOGRAPH

Pr**SOLIRIS®**

(eculizumab)

30 mL Parenteral Solution (10 mg/mL)

(Humanized Monoclonal Antibody)

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SOLIRIS®
(eculizumab)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous (IV) infusion	300 mg single-use vial	polysorbate 80 (vegetable origin) *For a complete listing, see Dosage Forms, Composition and Packaging Section.*

DESCRIPTION

SOLIRIS® is a formulation of eculizumab which is a recombinant humanized monoclonal IgG2/4κ 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. The bulk drug substance manufacturing process also includes specific viral inactivation and removal steps.

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.

INDICATIONS AND CLINICAL USE

SOLIRIS® (eculizumab) is indicated for the treatment of 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 **Clinical Trials**).

SOLIRIS® (eculizumab) 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).

Distribution restrictions:
Soliris should be administered under the supervision of a qualified health professional familiar with treating atypical HUS.

Geriatrics (>65 years of age): Nineteen patients 65 years of age or older (15 with PNH and 1 with atypical HUS) were treated with Soliris. 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.

Pediatrics (<18 years of age): The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients below the age of 18 years have not been established.

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). Alexion also conducted a retrospective chart review in atypical HUS patients treated with Soliris outside of the scope of a clinical trial which included 19 pediatric patients. The safety and effectiveness of Soliris for the treatment of atypical HUS appear similar in pediatric and adult patients.

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.

CONTRAINDICATIONS

Hypersensitivity to eculizumab, murine proteins or to any of the excipients listed in the DESCRIPTION section.

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 the **WARNINGS AND PRECAUTIONS, Serious Meningococcal Infections** section.

WARNINGS AND PRECAUTIONS

WARNING: SERIOUS 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 a meningococcal vaccine 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 and, as a result, patients with complement-mediated diseases, including PNH and atypical HUS, may experience increased symptoms of their underlying disease, such as hemolysis (PNH) or TMA complications (atypical HUS). 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 **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 encapsulated bacteria. 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 influenza* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenza* 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 **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.

General:

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 for PNH and atypical HUS, no patients experienced an infusion reaction which required discontinuation of Soliris. Postmarketing reports of infusion reactions have been received (see **Sensitivity/Resistance**). Interrupt Soliris infusion and institute appropriate treatment and supportive measures if signs of cardiovascular instability or respiratory compromise occur.

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 1, 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 PNH patients 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 **Warnings and Precautions**).

Thrombotic microangiopathy complications were observed after Soliris discontinuation in the atypical HUS clinical studies. If atypical HUS patients 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 (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.

Cardiovascular

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

Thrombosis Prevention and Management

In clinical studies of patients with PNH, there were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment (see **Table 18**). The effect of withdrawal of anticoagulant therapy during Soliris treatment has not been established. Therefore, treatment with Soliris should not alter anticoagulant management.

Immunization

Prior to initiating Soliris therapy, it is recommended that PNH and atypical HUS patients should receive immunizations according to current immunization guidelines. Additionally, all patients must receive a meningococcal vaccine 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 where available, 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.

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 **Toxicology**).

Dependence/Tolerance

There is no evidence to suggest that the use of Soliris is associated with drug abuse or dependence.

Ear/Nose/Throat

There were no serious ENT adverse events.

Endocrine and Metabolism

There were no serious endocrine or metabolic adverse events.

Gastrointestinal

Rare episodes of severe abdominal pain were reported.

Genitourinary

There were no serious genitourinary adverse events.

Hematologic

The safety and efficacy of Soliris has not been established in patients with underlying hematologic diseases (e.g., hemolytic anemia, sickle cell anemia, thalassemia, porphyria). In clinical trials, analysis by history of bone marrow failure showed that eculizumab was effective in reducing the burden of hemolysis (as measured by hemolysis indicator LDH AUC) and reduced transfusion requirements in subjects with both PNH and history of bone marrow failure (e.g., aplastic anemia, myelodysplasias).

Hepatic/Biliary/Pancreatic

There were no serious hepatic dysfunctions after Soliris therapy. The safety and efficacy of Soliris have not been assessed in patients with hepatic disease.

Immune

As with all proteins, there is a potential for immunogenicity with eculizumab. The immunogenicity of Soliris has been evaluated using two different immunoassays for the detection of anti-eculizumab antibodies: a direct enzyme-linked immunosorbent assay (ELISA) using the Fab fragment of eculizumab as target was used for the PNH indication; and an electro-chemiluminescence (ECL) bridging assay using the eculizumab whole molecule as target was used for the atypical HUS indication, as well as for additional patients with PNH. In the PNH population, antibodies to Soliris were detected in 3/196 (2%) patients with PNH treated with Soliris using the ELISA assay and in 5/161 (3%) patients treated with Soliris using the ECL assay. In patients with atypical HUS treated with Soliris, antibodies to Soliris were detected in 3/100 (3%) using the ECL assay. An ECL based neutralizing HAHA assay with a low sensitivity of 2 mcg/mL was performed to detect neutralizing antibodies for the 3 patients with atypical HUS and also for the 5 patients with PNH with positive samples using the ECL assay. 2/161 (1.2%) patients in the PNH group and 1/100 patients in the atypical HUS group (1%) had low positive values for neutralizing antibodies. No apparent correlation of antibody development to clinical response was observed in either indication. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Soliris in an ELISA-based assay and/or an ECL-based assay and are highly dependent on the sensitivity and specificity of the assay used. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Soliris with the incidence of antibodies to other products may be misleading.

Soliris blocks terminal complement; therefore patients may have increased susceptibility to *Neisseria meningitis* (see boxed **Warning: Serious Meningococcal Infections** section above).

Infections

Patients are at increased risk of serious infections caused by encapsulated bacteria.

Meningococcal infections are the most serious adverse reactions experienced by patients receiving Soliris.

In clinical studies, 2 out of 196 PNH patients 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.

Cases of meningococcal meningitis and septicemia have been reported post-market.

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

Neurologic

Transient severe headaches were reported.

Ophthalmologic

There were no serious ophthalmologic adverse events.

Peri-Operative Considerations

There is no data on continuing or discontinuing Soliris or adjusting dose for Peri-Operative considerations.

Psychiatric

There were no serious psychiatric adverse events.

Renal

There was no evidence of serious renal impairment after Soliris therapy. The safety and efficacy of Soliris have not been assessed in patients with renal disease (except with atypical HUS).

Respiratory

There were no serious respiratory adverse events.

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).

Sexual Function/Reproduction

The safety of Soliris during pregnancy and breastfeeding has not been established. See section on '**Pregnant Women**' below.

Skin

There were no serious skin (photosensitivity, photoallergic or phototoxic) adverse events.

Special Populations:

Formal studies have not been conducted to evaluate the pharmacokinetics of Soliris administration in special PNH patient populations based on gender, race, age (geriatric), or metabolic status (renal or hepatic impairment).

The pharmacokinetics of Soliris has been studied in atypical HUS patients with a range of renal impairment and age. There have been no observed differences in pharmacokinetic parameters noted in these subpopulations of atypical HUS patients.

Table 1: Atypical HUS Studies PK Parameter Estimates by Age Cohort using One-Compartment Model

Age Cohort	Parameter	Studies 1, 2 and 3			Study 4		
		N	Induction	Maintenance	N	Induction	Maintenance
≥1 – <23 months	C_{min} (µg/mL)	5	131. 4 (108.3 – 161.1)	95.4 (15.1 – 246.0)	5	244.4 (207.8 – 396.2)	185.6 (146.0 – 342.7)
	C_{max} (µg/mL)	5	197.9 (154.4 – 310.8)	303.4 (253.3 – 400.1)	5	372.0 (282.4 – 686.2)	513.7 (467.6 – 583.5)
≥23 month – < 5 years	C_{min} (µg/mL)	2	136.1 (120.1 – 152.2)	87.1 (35.7 – 138.4)	5	252.4 (188.9 – 337.5)	257.1 (50.2 – 338.0)
	C_{max} (µg/mL)	2	282.4 (182.6 – 382.3)	273.6 (226.7 – 320.6)	5	386.2 (290.3 – 439.0)	449.7 (267.4 – 534.3)
≥5–< 12 years	C_{min} (µg/mL)	6	158.2 (118.9 – 167.6)	220.4 (78.2 – 249.0)	8	184.2 (143.8 – 205.7)	344.4 (231.1 – 531.1)
	C_{max} (µg/mL)	6	229.9 (168.6 – 279.1)	449.8 (217.5 – 501.3)	8	240.2 (205.0 – 282.2)	580.9 (461 – 1094.4)
≥12 – 18 years	C_{min} (µg/mL)	7	103.0 (87.8 – 133.2)	199.0 (109.5 – 284.3)	4	118.3 (89.9 – 157.0)	215.2 (179.8 – 298.1)
	C_{max} (µg/mL)	7	148.3 (129.6 – 194.1)	390.9 (303.9 – 490.5)	4	173.6 (121.2 – 221.0)	437.8 (357.7 – 592.1)

Table 2: PK Parameter Estimates by Renal Impairment Category using Prospective (Study 1 and Study 2) Data in atypical HUS Patients using a One-Compartment Model

Renal Impairment Category	N	Clearance (L/hr)		Volume (L)	
		Median	Range	Median	Range
Mild (eGFR 60 to 89)	2	0.0127	0.0120, 0.0135	5.25	5.15, 5.35
Moderate (eGFR 30 to 59)	11	0.0126	0.0095, 0.0218	5.93	4.15, 9.78
Severe (eGFR 15 to 29)	12	0.0113	0.0086, 0.0230	6.01	4.44, 7.33
ESRD (eGFR <15)	12	0.0138	0.0089, 0.0527	6.16	2.94, 8.91

eGFR: estimated glomerular filtration rate (mL/min/1.73m^2)

Pregnant Women: PNH and atypical HUS are serious illnesses. Women of childbearing potential should use adequate contraception methods during treatment and up to 5 months after treatment.

Pregnant women with PNH and their fetuses have high rates of morbidity and mortality during pregnancy and the postpartum period. There are no adequate and well-controlled studies of Soliris in pregnant women. Animal reproduction studies have not been conducted with Soliris. Soliris, a recombinant IgG molecule (humanized anti-C5 antibody), is expected to cross the placenta. Based on animal data, Soliris may cause fetal harm. One infant was born premature with a meconium plug and microcolon and two infants with cardiac disorders were born to mothers exposed to Soliris. Safety data on 52 pregnancies in PNH women exposed to Soliris allows the following analysis: major maternal complications 8 (15%), major fetal complication 4 (8%), maternal death in 2 (4%), and fetal death in 2 (4%).

Soliris should not be used during pregnancy unless the potential benefit justifies the potential risk to the mother and the fetus.

Labor and Delivery: It is not known whether Soliris has an effect on the mother and the fetus during labor and delivery.

Nursing Women: It is not known whether Soliris is secreted into human milk. IgG is excreted in human milk, so it is expected that Soliris will be present in human milk. However, published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Caution should be exercised when Soliris is administered to a nursing woman. Lactation should be discontinued during treatment and up to 5 months after treatment. The unknown risks to the infant from gastrointestinal or limited systemic exposure to Soliris should be weighed against the known benefits of breastfeeding.

Pediatrics (<18 years of age): The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients below the age of 18 years have not been established.

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 atypical HUS patients 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 **Warnings and Precautions**).

Geriatrics (>65 years of age): Nineteen patients 65 years of age or older (15 with PNH and 4 with atypical HUS) were treated with Soliris. 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.

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).[1]

Atypical HUS

Atypical HUS patients 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 **Monitoring after Discontinuation**). Patients may require dose adjustment within the recommended 14±2 day dosing schedule during the maintenance phase (up to every 12 days).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Meningococcal infections are the most important adverse reactions experienced by patients receiving Soliris.

In clinical studies, 2 out of 196 PNH patients 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 (see **Warnings and Precautions**).

PNH

Soliris for the treatment of PNH was studied in three clinical studies that included 195 eculizumab-treated patients and most of these patients have been enrolled in the PNH extension study. There was one clinical pivotal trial (PNH Study 1) comparing the eculizumab-treatment arm to a placebo-treatment arm. Meningococcal infections are the most important adverse reactions experienced by patients receiving Soliris therapy. In PNH studies, two patients experienced serious meningococcal sepsis. Both patients had previously received a meningococcal vaccine. In clinical studies among non-PNH patients, meningococcal meningitis and septicaemia occurred in one unvaccinated patient (see **Warnings and Precautions**).

The most commonly reported adverse events regardless of causality are headache, nasopharyngitis, upper respiratory infections, nausea, diarrhea and arthralgia, each occurring in at least 20 percent of patients, and pyrexia, myalgia, fatigue, and herpes simplex, each occurring in ≥5/100 patients.

Adverse events reported at a very common (>10%) or common incidence (>1 to <10%) with eculizumab in a total of 140 patients in PNH Study 1 and PNH Study 2 are listed by system organ class and preferred term in Tables 3, 4 and 5. Adverse events were mostly mild to moderate in severity. Incidence of uncommon or rare events cannot be accurately estimated due to limited patient exposure (195 PNH patients); see also: **Uncommon Clinical Trial Adverse Drug Reactions (<1%)**.

Supportive safety data were obtained in 11 clinical studies that included 716 patients exposed to eculizumab in six disease populations other than PNH. There was an un-vaccinated patient in a study for idiopathic membranous glomerulonephropathy who experienced severe meningococcal meningitis and septicaemia. In double-blind, placebo-controlled studies for patients with diseases other than PNH (N=526 patients with Soliris; N=221 patients with placebo), adverse events reported with Soliris at an incidence of 2% or greater than the incidence reported with placebo were: upper respiratory tract infection, rash, and injury.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In the double blind randomized phase III trial for PNH (PNH Study 1), 43 patients received Soliris and 44 received placebo. The duration of treatment was 6 months in both treatment groups. Drug-related adverse events occurring in more than 2 Soliris-treated patients are summarized in **Table 3**. The most frequent were headaches and fatigue. Most headaches were mild and did not persist after the initial administration phase of Soliris and resolved within 24-48 hours after Soliris infusion.

Headaches were observed in 44.2% (19/43 patients) of patients treated with Soliris and 27.3% (12/44 patients) in placebo-treated patients and were mild/moderate in all but 1 Soliris-treated and 1 placebo-treated patients. Most headaches did not persist after the initial administration

phase of Soliris. In addition, the following adverse event incidence was increased by 5% or more with Soliris as compared to placebo: nasopharyngitis (25.0%), nausea (17.1%), pyrexia (14.3%), myalgia (7.9%), fatigue (7.9%), and herpes simplex (5.7%).

Among 193 patients with PNH treated with Soliris in the single arm, clinical study (PNH Study 2) or the follow-up study, the 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%).

There was no evidence of an increased incidence of infection across PNH studies with Soliris as compared to placebo, including serious infections, severe infections or multiple infections.

Overall serious adverse event (SAE) rates were similar between patients treated with Soliris (16.4%) versus placebo (20.5%) in the combined PNH Study 1 and PNH Study 2 phase 3 PNH studies.

A total of 28 drug-related Serious Adverse events were reported by 20 (10.3%) of the 195 PNH patients enrolled in clinical trials (PNH Pilot Study, PNH Study 1, PNH Study 2 and extension). The most common drug-related SAEs were pyrexia (5), headache (3), septic shock (2), and viral infection (2). The only SAE in more than one patient considered related to Soliris was pyrexia (1.4%). SAEs that occurred in more than one patient were anemia (2.9%), pyrexia (2.1%), headache (1.4%), hemolysis (1.4%), and intervertebral disc protrusion (1.4%).

In PNH studies, 2 patients died of adverse events. The causes of death were chronic myelomonocytic leukemia, and cerebral herniation. In non-PNH trials, there were 3 deaths, 2 in eculizumab-treated patients (complications post cholecystectomy; electrocution); and one in a placebo-treated patient (pulmonary embolism). None of the deaths was considered to be treatment-related.

In PNH Study 1, there was a single adverse event that led to study discontinuation with Soliris treatment due to pregnancy. There were no other adverse events leading to discontinuation in the Soliris or placebo treatment groups in that study. In PNH Study 2, there was one patient who discontinued study participation due to a fatal cerebral herniation adverse event that was considered unrelated to study medication.

Table 3: Adverse Reactions* Reported in ≥2 patients in PNH Study 1

	PNH Study 1	
	Soliris (N=43)	**Placebo (N=44)**
GASTROINTESTINAL		
NAUSEA	2 (4.7%)	1 (2.3%)
ABDOMINAL PAIN	2 (4.7%)	1 (2.3%)
GENERAL		
FATIGUE	3 (7.0%)	0 (0.0%)
INFECTIONS AND INFESTATIONS		
UPPER RESPIRATORY TRACT INFECTION	2 (4.7%)	0 (0.0%)
ORAL HERPES	2 (4.7%)	0 (0.0%)

NERVOUS SYSTEM		
HEADACHE	15 (34.9%)	2 (4.5%)
SKIN AND SUBCUTANEOUS TISSUE		
DRY SKIN	2 (4.7%)	0 (0.0%)

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

Table 4 summarizes adverse reactions occurring in Soliris-treated patients for PNH Study 1, PNH Study 2, and all Soliris-treated patients in clinical trials (PNH Pilot Study, PNH Study 1, PNH Study 2 and extension). They were mostly mild to moderate in severity. There were minimal differences between PNH Study 1, PNH Study 2 and the total Soliris experience. The most common drug related adverse event was headache; all others were reported with a frequency of 6.7% or lower.

Table 4: Adverse Reactions Reported in ≥2 patients in Soliris Clinical Studies

	PNH Study 1 (N=43)	**PNH Study 2 (N=97)**	**Total Soliris Patients (N=195)**
GASTROINTESTINAL DISORDERS			
NAUSEA	2 (4.7%)	7 (7.2%)	12 (6.2%)
VOMITING	1 (2.3%)	4 (4.1%)	8 (4.1%)
DIARRHEA	0 (0.0%)	1 (1.0%)	6 (3.1%)
CONSTIPATION	0 (0.0%)	3 (3.1%)	5 (2.6%)
ABDOMINAL PAIN	2 (4.7%)	2 (2.1%)	4 (2.1%)
DYSPEPSIA	0 (0.0%)	1 (1.0%)	2 (1.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
PYREXIA	1 (2.3%)	6 (6.2%)	12 (6.2%)
FATIGUE	3 (7.0%)	3 (3.1%)	9 (4.6%)
CHILLS	0 (0.0%)	0 (0.0%)	3 (1.5%)
INFECTIONS AND INFESTATIONS			
UPPER RESPIRATORY TRACT INFECTION	2 (4.7%)	2 (2.1%)	4 (2.1%)
URINARY TRACT INFECTION	0 (0.0%)	3 (3.1%)	4 (2.1%)
NASOPHARYNITIS	0 (0.0%)	1 (1.0%)	3 (1.5%)
ORAL HERPES	2 (4.7%)	1 (1.0%)	3 (1.5%)
VIRAL INFECTION	0 (0.0%)	1 (1.0%)	3 (1.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
MYALGIA	0 (0.0%)	4 (4.1%)	7 (3.6%)
ARTHRALGIA	0 (0.0%)	4 (4.1%)	6 (3.1%)
PAIN IN EXTREMITY	1 (2.3%)	2 (2.1%)	6 (3.1%)
NECK PAIN	1 (2.3%)	2 (2.1%)	3 (1.5%)
NERVOUS SYSTEM DISORDERS			
HEADACHE	15 (34.9%)	42 (43.3%)	71 (36.4%)
DIZZINESS	0 (0.0%)	8 (8.2%)	13 (6.7%)
DYSGEUSIA	0 (0.0%)	1 (1.0%)	3 (1.5%)

	PNH Study 1 (N=43)	PNH Study 2 (N=97)	Total Soliris Patients (N=195)
MIGRAINE	Not listed	Not listed	5 (2.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
COUGH	1 (2.3%)	0 (0.0%)	5 (2.6%)
PHARYNGOLARYNGEAL PAIN	0 (0.0%)	1 (1.0%)	3 (1.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
PRURITIS	1 (2.3%)	3 (3.1%)	8 (4.1%)
ALOPECIA	0 (0.0%)	1 (1.0%)	3 (1.5%)

Adverse events of all causes (drug related and non-drug related) are summarized in **Table 5** for all 195 patients included in all PNH trials (PNH Pilot study, PNH Study 1, PNH Study 2 and extension).

Table 5: Adverse Events Regardless of Causality Reported in ≥5% of PNH Patients in all Clinical Studies

	No (%) of patients (N=195)
GASTROINTESTINAL DISORDERS	
NAUSEA	49 (25.1)
DIARRHEA	43 (22.1)
VOMITING	32 (16.4)
ABDOMINAL PAIN	25 (12.8)
CONSTIPATION	23 (11.8)
ABDOMINAL PAIN UPPER	16 (8.2)
DYSPEPSIA	10 (5.1)
GENERAL	
PYREXIA	33 (16.9)
INFLUENZA-LIKE ILLNESS	22 (11.3)
FATIGUE	19 (9.7)
PERIPHERAL EDEMA	12 (6.2)
CHEST PAIN	12 (6.2)
INFECTIONS AND INFESTATIONS	
UPPER RESPIRATORY TRACT INFECTIONS	60 (30.80)
NASOPHARYNGITIS	82 (42.1)
VIRAL INFECTIONS	22 (11.3)
URINARY TRACT INFECTION	22 (11.3)
ORAL HERPES	15 (7.7)
INFLUENZA	14 (7.2)
SINUSITIS	12 (6.2)
RESPIRATORY TRACT INFECTIONS	12 (6.2)
RHINITIS	11 (5.6)
BRONCHITIS	10 (5.1)

	No (%) of patients (N=195)
INJURY POISONING	
CONTUSION	22 (11.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
BACK PAIN	39 (20)
ARTHRALGIA	31 (15.9)
PAIN IN EXTREMITIES	28 (14.4)
MYALGIA	21 (10.8)
MUSCLE SPASM	14 (7.2)
MUSCULOSKELETAL PAIN	12 (6.2)
NECK PAIN	10 (5.1)
JOINT SWELLING	10 (5.1)
NERVOUS SYSTEM DISORDERS	
HEADACHE	100 (51.3)
DIZZINESS	30 (15.4)
PSYCHIATRIC DISORDERS	
INSOMNIA	23 (11.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
COUGH	31 (15.9)
PHARYNGOLARYNGEAL PAIN	28 (14.4)
EPISTAXIS	19 (9.7)
DYSPNEA	12 (6.2)
NASAL CONGESTION	10 (5.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
PRURITUS	15 (7.7)
RASH	13 (6.7)
VASCULAR DISORDERS	
HEMATOMA	11 (5.6)

Atypical HUS

The safety of Soliris therapy in patients with atypical HUS was evaluated in four prospective, single-arm studies, 3 in adult and adolescent patients (atypical HUS Studies 1 and 2 and 4), one in pediatric and adolescent patients (atypical HUS Study 5) and one retrospective chart review (atypical HUS Study 3). Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below were derived from 78 adult and adolescent patients with atypical HUS enrolled in atypical HUS Study 1, atypical HUS Study 2 and atypical HUS Study4. All patients received the recommended dosage of Soliris. Median exposure was 67 weeks (range: 2-145 weeks).

Table 6 summarizes all adverse drug reactions reported in at least 10% of patients in atypical HUS Studies 1, 2 and 4 combined.

Table 6: Per Patient Incidence of Adverse Drug Reactions (ADRs) in 10% or More Adult and Adolescent Patients Enrolled in atypical HUS Study 1, atypical HUS Study 2 and atypical HUS Study 4 Separately and in Total

MedDRA ver. 15.1	Number (%) of Patients			
	Study 1 (n=17)	Study 2 (n=20)	Study 4 (n=41)	Total (n=78)
Blood and Lymphatic System Disorders				
Leukopenia	2 (11.8)	2 (10.0)	0 (0.0)	4 (5.1)
Lymphopenia	0 (0.0)	2 (10.0)	0 (0.0)	2 (2.6)
Gastrointestinal Disorders				
Nausea	2 (11.8)	0 (0.0)	0 (0.0)	2 (2.6)
Vomiting	3 (17.6)	0 (0.0)	1 (2.4)	4 (5.1)
Nervous System Disorders				
Headache	1 (5.9)	3 (15.0)	0 (0.0)	4 (5.1)
Respiratory, Thoracic and Mediastinal Disorders				
Cough [a]	0 (0.0)	2 (10.0)	0 (0.0)	2 (2.6)
Vascular Disorders				
Hypertension [b]	3 (17.6)	0 (0.0)	0 (0.0)	3 (3.8)

[a] Includes preferred terms Cough and Productive Cough
[b] Includes preferred terms Hypertension and Accelerated Hypertension

In atypical HUS Studies 1, 2 and 4 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%). Five patients discontinued Soliris due to adverse events; three due to worsening renal function, one due to new diagnosis of Systemic Lupus Erythematosus, and one due to meningococcal meningitis.

The following Adverse Drug Reactions occurred in >1% to <10% of Adult and Adolescent Patients enrolled in atypical HUS Study 1, atypical HUS Study 2 and atypical HUS Study 4.

Table 7: Per Patient Incidence of Adverse Drug Reactions in >1% and <10% Adult and Adolescent Patients Enrolled in atypical HUS Study 1, atypical HUS Study 2 and atypical HUS Study 4 Separately and in Total

MedDRA ver. 15.1	Number (%) of Patients			
	Study 1 (n=17)	Study 2 (n=20)	Study 4 (n=41)	Total (n=78)
Blood and Lymphatic System Disorders				
Abnormal clotting factor	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Anemia	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Neutropenia	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Cardiac Disorders				
Cardiomyopathy	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Ear and Labyrinth Disorders				
Deafness bilateral	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Vertigo	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Eye Disorders				
Lacrimation increased	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Gastrointestinal Disorders				
Abdominal pain	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Diarrhea	1 (5.9)	0 (0.0)	1 (2.4)	2 (2.6)
Stomatitis	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
General Disorders and Administration Site Conditions				
Asthenia	1 (5.9)	0 (0.0)	2 (4.9)	3 (3.8)
Chest discomfort	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Extravasation	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Fatigue	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Pyrexia	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Infections and Infestations				
Asymptomatic bacteriuria	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Bacterial infection	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
BK virus infection	0 (0.0)	1 (5.0)	1 (2.4)	2 (2.6)
Herpes zoster	1 (5.9)	0 (0.0)	1 (2.4)	2 (2.6)
Impetigo	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Influenza	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Meningitis meningococcal	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Meningococcal sepsis	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Nasopharyngitis	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Peritonitis	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Pneumonia	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Pyelonephritis	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)

MedDRA ver. 15.1	Number (%) of Patients			
	Study 1 (n=17)	Study 2 (n=20)	Study 4 (n=41)	Total (n=78)
Q fever	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Urinary tract infection	1 (5.9)	0 (0.0)	1 (2.4)	2 (2.6)
Investigations				
Haematocrit decreased	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Haemoglobin decreased	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Metabolism and nutrition disorders				
Decreased appetite	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	0 (0.0)	0 (0.0)	2 (4.9)	2 (2.6)
Pain in extremity	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Nervous System Disorders				
Paraesthesia	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Tremor	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Renal and urinary Disorders				
Haematuria	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Reproductive system and Breast Disorders				
Menorrhagia	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoea	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Dyspnoea exertional	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Nasal congestion	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Oropharyngeal pain	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Rhinorrhoea	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Skin and subcutaneous tissue Disorders				
Alopecia	0 (0.0)	1 (5.0)	2 (4.9)	3 (3.8)
Dermatitis	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Erythema	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.3)
Photosensitivity reaction	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Pruritus	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Rash[a]	0 (0.0)	0 (0.0)	2 (4.9)	2 (2.6)
Skin discolouration	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)
Vascular Disorders				
Hypotension	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Vein disorder	0 (0.0)	1 (5.0)	0 (0.0)	1 (1.3)
Venous thrombosis	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.3)

[a] Includes rash and rash papular

Atypical HUS Study 5 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).

The following Adverse Drug Reactions were reported >10% in atypical HUS Study 5:

- 3 (16.8%) respiratory tract infection viral (includes preferred terms: respiratory tract infection viral, viral upper respiratory tract infection and respiratory syncytial virus infection) in 1 month to <12 yrs patients
- 2 (11.8%) rash in 1 month to <12 yrs patients

Table 8 summarizes Adverse Drug Reactions occurred in >1% to <10% of Paediatric Patients enrolled in atypical HUS Study 5.

Table 8: Per Patient Incidence of Adverse Drug Reactions in >1% and <10% Paediatric Patients Enrolled in atypical HUS Study 5, 1 month to <12 yrs and in Total

MedDRA ver. 15.1	**Number (%) of Patients**	
	1 month to <12 yrs (n=18)	**Total (n=22)**
Eye Disorders		
Eye discharge	1 (5.6%)	1 (4.5%)
Gastrointestinal Disorders		
Abdominal discomfort	1 (5.6%)	1 (4.5%)
Diarrhoea	1 (5.6%)	1 (4.5%)
Dyspepsia	0 (0.0)	1 (4.5%)
General Disorders and Administration Site Conditions		
Injection site rash	1 (5.6%)	1 (4.5%)
Pain	1 (5.6%)	1 (4.5%)
Infections and Infestations		
Ear infection	1 (5.6%)	1 (4.5%)
Fungal infection	1 (5.6%)	1 (4.5%)
Nasopharyngitis	1 (5.6%)	1 (4.5%)
Respiratory syncytial virus infection	1 (5.6%)	1 (4.5%)
Respiratory tract infection viral	1 (5.6%)	1 (4.5%)
Viral upper respiratory tract infection	1 (5.6%)	1 (4.5%)
Nervous System Disorders		
Headache	1 (5.6%)	1 (4.5%)
Psychiatric Disorders		
Agitation	1 (5.6%)	1 (4.5%)

Skin and subcutaneous tissue Disorders		
Alopecia	1 (5.6%)	1 (4.5%)
Dermatitis diaper	1 (5.6%)	1 (4.5%)
Eczema	1 (5.6%)	1 (4.5%)

Analysis of retrospectively collected adverse event data from pediatric and adult patients enrolled in atypical HUS Study 3 (N=30) revealed a safety profile that was similar to that which was observed in the two prospective studies. Atypical HUS Study 3 included 19 pediatric patients less than 18 years of age.

Overall, the safety of Soliris in pediatric patients with atypical HUS enrolled in Study 3 appeared similar to that observed in adult patients. The most common (≥15%) adverse drug reactions occurring in pediatric patients are presented in **Table 9**.

Table 9: Adverse Reactions Occurring in at Least 15% of Patients Less than 18 Years of Age Enrolled in atypical HUS Study 3

MedDRA ver. 11.0	**Number (%) of Patients**			
	< 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.

In Studies 1, 2 and 4 the following serious adverse drug reactions (SADRs) were reported in more than 1 patient: hypertension (including accelerated hypertension), BK virus infection, Herpes zoster and Urinary Tract Infection.

There were no deaths in Studies 1, 4 and 5. One patient died in Study 2 due to Gastrointestinal Hemorrhage. There were 2 deaths in Study 3 due to arterial dissection in one patient and complications of graft versus host disease and aspergillosis in the other patient.

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 regarding **Monitoring After Soliris Discontinuation / Missed Dose).**

The grade of AEs was not recorded in the retrospective chart review; therefore there was no SAE reporting for Study 3.

Uncommon Clinical Trial Adverse Drug Reactions (<1%)

PNH

The following Adverse Reactions were reported by 2 patients or less in the Soliris clinical trials (195 PNH patients). These reactions are presented by frequency category: common reactions are those reported in 2 patients (1%), uncommon reactions are those occurring in 1 patient (<1%).

Blood and Lymphatic Disorders: Common: thrombocytopenia; Uncommon: coagulopathy

Cardiac Disorder: Uncommon: palpitation

Ear and Labyrinth Disorders: Uncommon: tinnitus, vertigo

Endocrine Disorders: Uncommon: Basedow's disease

Eye Disorders: Uncommon: conjunctival irritation, blurred vision

Gastrointestinal Disorders: Uncommon: abdominal distension, gastroesophageal reflux disease, gingival pain, infrequent bowel movements

General Disorders and Administration Site Conditions: *Common:* chest discomfort, infusion reaction; Uncommon: peripheral edema, chest pain, face edema, physical health deterioration, influenza-like illness

Hepatobiliary Disorders: Uncommon: Jaundice

Immune System Disorders: Uncommon: hypersensitivity

Infections and Infestations: Common: bronchitis, gastrointestinal infection, sepsis, septic shock; Uncommon: influenza, abscess, cellulitis, fungal infection, gingival infection, hemophilus infection, lower respiratory tract infection, meningococcal sepsis, *Neisseria* infection, sinusitis

Investigation: Uncommon: alanine aminotransferase increase, aspartate aminotransferase increase, gamma glutamyltransferase increase

Metabolism and Nutrition Disorders: Uncommon: anorexia, decreased appetite

Musculoskeletal and Connective Tissue Disorders: Common: back pain, musculoskeletal pain; Uncommon: bone pain, joint swelling, muscle spasms, trismus

Neoplasm benign, malignant and unspecified: Uncommon: malignant melanoma, myelodysplastic syndrome

Nervous System Disorders: Common: paresthesia; Uncommon: syncope

Psychiatric Disorders: Common: depression; Uncommon: anxiety, insomnia, mood swings, sleep disorder

Renal and Urinary Disorders: Common: dysuria; Uncommon: renal impairment

Reproductive System and Breast Disorders: Uncommon: menstrual disorder

Respiratory, Thoracic and Mediastinal Disorders: Common: nasal congestion, throat irritation; Uncommon: rhinorrhea, epistaxis

Skin and Subcutaneous Tissue Disorders: Common: dry skin, rash; Uncommon: hyperhydrosis, petechiae, skin depigmentation, urticaria

Vascular Disorders: Uncommon: hematoma, hot flush, hypotension

During PNH clinical trials, three patients became pregnant while being treated with Soliris; all discontinued treatment as per protocol. One pregnancy was continued to term and a healthy baby was delivered. Women of childbearing potential should use adequate contraception methods during treatment and up to 5 months after treatment.

Pregnancies have been reported in the post-marketing setting (see **Special Populations, Pregnant Women**). Information is missing on some embryos or fetuses.

Atypical HUS

Not applicable

Abnormal Hematologic and Clinical Chemistry Findings

PNH

CTC Grades 3 and 4 laboratory abnormalities were tabulated for PNH patients who had normal values at baseline (**Table 10**). 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 10: 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 $\geq$0.5-1.0 x 10^9/L, Grade 4 <0.5 x 10^9/L); thrombocytopenia (Grade 3 $\geq$10-50 x 10^9/L , Grade 4 <10 x 10^9/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%) PNH patients treated with Soliris and in 1/44 (2.3%) 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.

Post-Market Adverse Drug Reactions

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

There has been limited post-marketing experience with Soliris in atypical HUS.

DRUG INTERACTIONS

Overview

Drug interaction studies have not been performed with Soliris.

Drug-Drug Interactions

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

Drug-Food Interactions

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

Drug-Herb Interactions

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

Drug-Laboratory Interactions

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

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

Recommended Dose and Dosage Adjustment

Recommended Dosage Regimen - PNH

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 **Warnings and Precautions**).

Recommended Dosage Regimen – atypical HUS

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 less than 18 years of age, administer Soliris based upon body weight, according to the following schedule (Table 11):

Table 11: Dosing recommendations in patients less than 18 years of age

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

The goal of the dosing regimen is a trough concentration above 50-100 ug/mL of Soliris and on the basis of clinical experience, the length of time that this trough concentration should be maintained.

Soliris should be administered at the recommended dosage regimen time points, or within two days of these time points.

Supplemental dosing of Soliris is required in the setting of concomitant support with PE/PI (plasmapheresis or plasma exchange; or fresh frozen plasma infusion) (**Table 12**). The goal of the additional dosing after plasma intervention is to restore and maintain the plasma concentration above 50 – 100 µg/ml.

Table 12: Supplemental dose of Soliris after PE/PI

Type of Intervention	**Most Recent Soliris Dose**	**Soliris Dose With Each 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

Based on pharmacokinetic simulation and data from PNH patients who received plasma intervention while on eculizumab therapy

The recommended doses in Tables 11 and 12 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 **Warnings and Precautions**).

Dose Modifications / Discontinuations

A fixed dosage regimen was studied in clinical studies in PNH and atypical HUS. In case of a missed dose, resume the regular schedule as soon as possible. Supplemental dosing is recommended when Soliris is administered to atypical HUS patients receiving plasma infusion or exchange (see **Dosage and Administration**).

Discontinuation: please refer to ***Monitoring after Discontinuation*** section above.

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 children aged less than 12 years. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

Reconstitution:

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 13**). Gently invert the infusion bag containing the diluted Soliris solution to ensure thorough mixing of the product and diluent. Discard any unused portion left in a vial, as the product contains no preservatives.
- 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 discoloration prior to administration.

Table 13: Reconstitution of Soliris

Dose	Vial Size	Volume of Diluent	Approximate Available Volume	Nominal 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

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

A genetic mutation in PNH patients leads to the generation of populations of abnormal blood cells that are deficient in terminal complement inhibitors (known as PNH cells), rendering PNH red blood cells sensitive to persistent terminal complement-mediated destruction. The subsequent intravascular hemolysis is the primary disease manifestation in PNH patients. The destruction and loss of these PNH cells results in low blood counts (anemia), and also fatigue, difficulty in functioning, pain, dark urine, shortness of breath, and blood clots.

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. Soliris inhibits terminal complement mediated intravascular hemolysis in PNH patients.

In atypical HUS, impairment in the regulation of complement activity leads to uncontrolled terminal complement activation, resulting in platelet activation, endothelial cell damage and thrombotic microangiopathy.

Pharmacodynamics

Pharmacotherapeutic group: Immunomodulators, ATC code: L04AA25. Soliris is a recombinant humanized monoclonal IgG2/4κ antibody that binds to the human C5 complement protein and inhibits the activation of terminal complement. The Soliris antibody contains human constant regions and murine complementarity determining regions grafted onto the human framework light- and heavy-chain variable regions. Soliris is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148kDa.

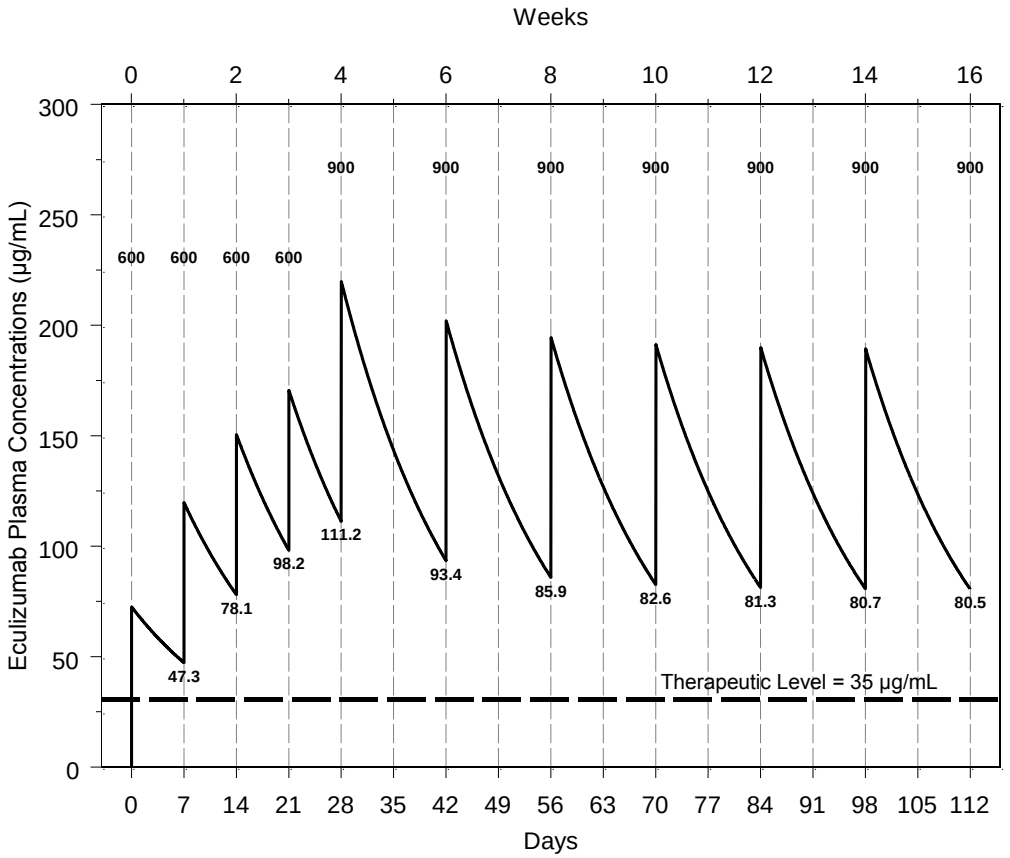
Soliris is produced in a murine myeloma (NS0 cell line) expression system and purified by affinity and ion exchange chromatography. The bulk drug substance manufacturing process also includes specific viral inactivation and removal steps.

Pharmacokinetics

PNH

In 40 patients with PNH, the pharmacokinetic parameters were estimated with a 1-compartmental model as an approximation to the complex disposition of monoclonal antibodies after multiple doses. Mean clearance was 0.28 ± 0.12 mL/hr/kg, mean volume of distribution was 110.3 ± 17.9 mL/kg, and mean elimination half-life was 11.3 ± 3.4 days. Based on these approximations, the onset of steady state is predicted to be approximately 49 – 64 days with a corresponding accumulation by a factor of about 2 fold within this time period. Pharmacodynamic activity correlates directly with eculizumab serum concentrations and maintenance of trough levels above ≥35 μg/mL results in essentially complete blockade of hemolytic activity in the majority of patients.

Figure 1: Serum Profile of IV Infusion of Soliris Estimated with a One Compartment Model (PK Parameters: Vdist = 110.3 mL/kg; Half-life=11.3 days, Body Weight = 75 ± 11.8kg)



Trough serum concentrations of Soliris progressively increase during the 5-week induction period with 600 mg of Soliris dosed every week for 4 weeks from approximately 47.3 µg/mL one week after the first dose to 111.2 µg/mL one week after the fourth 600 mg dose. The last induction dose of 900 mg of Soliris is given one week later. Trough serum concentrations of Soliris then slowly decrease to approximately 80 µg/mL during the maintenance phase of dosing (steady-state) with 900 mg of Soliris administered every 2 weeks.

In clinical trials, patients in the lowest weight quartile had the highest median serum trough levels of Soliris. Although analysis of safety data by weight quartile demonstrates that patients in the lowest weight quartile do not appear to be at an increased safety risk, the results must be interpreted with caution. As with all patients treated with Soliris, low weight patients should be closely monitored.

The recommended dosage regimen for Soliris was designed to maintain threshold concentrations of Soliris in plasma greater than approximately 35 µg/mL to inhibit terminal complement activation in treated patients.

A second population PK analysis with a standard 1 compartmental model was conducted on the multiple dose PK data from 57 atypical HUS patients receiving the recommended Soliris regimen in studies 1, 2 and 3. In this model, the clearance of Soliris for an adult patient with

atypical HUS patient weighing 70 kg was 14.6 mL/hr and the volume of distribution was 6.14 L. The elimination half-life was 291 h (approximately 12.1 days).

The clearance and half-life of eculizumab were also evaluated during plasma exchange interventions. Plasma exchange increased the clearance of eculizumab to 3660 mL/hr and reduced the half-life to 1.26 hours. Supplemental dosing is recommended when Soliris is administered to atypical HUS patients receiving plasma infusion or exchange [see **Recommended Dosage Regimen**].

All atypical HUS patients treated with Soliris when administered as recommended demonstrated rapid and sustained reduction in terminal complement activity. In atypical HUS patients, pharmacodynamic activity correlates directly with eculizumab serum concentrations and maintenance of trough levels of approximately 50-100 microgram/ml result in essentially complete blockade of terminal complement activity in all atypical HUS patients.
Dedicated studies have not been conducted to evaluate the PK of Soliris in special patient populations identified by gender, race, age (geriatric), or the presence of renal or hepatic impairment. Pediatric and adolescent patients (less than 18 years of age) and patients with renal impairment were included in the atypical HUS clinical studies [see **Clinical Studies**]. Population PK analysis showed age, gender, race, and renal function do not influence the PK of eculizumab. However, this one-compartment pharmacokinetic model has not been assessed for its sensitivity to detect the influence of all of these factors.

Absorption, Distribution, Metabolism, and Excretion: No specific human studies have been performed with Soliris to evaluate ADME in humans.

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.

Metabolism: Human antibodies undergo endocytotic digestion in the cells of the reticuloendothelial system. 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.

Excretion: No specific studies have been performed to evaluate the hepatic, renal, lung, or gastrointestinal routes of excretion/elimination for Soliris. In normal kidneys, antibodies are not excreted and are excluded from filtration by their size.

STORAGE AND STABILITY

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

DO NOT FREEZE. DO NOT SHAKE.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Soliris is a sterile, clear, colorless, 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.

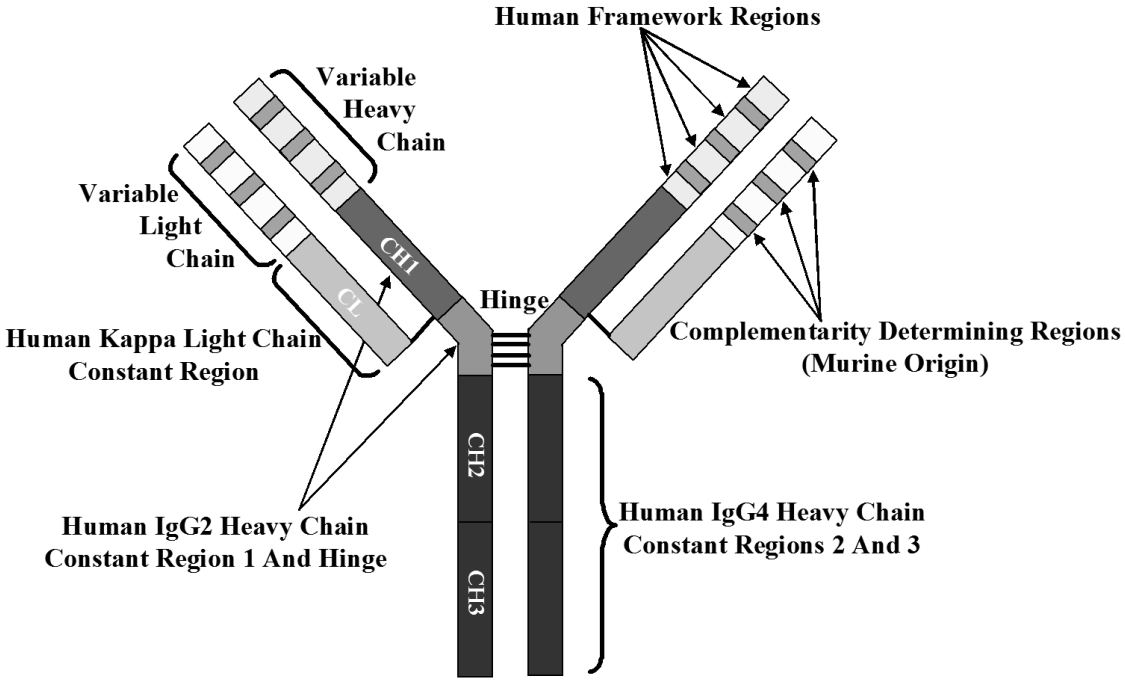
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: **eculizumab**

Structural formula:



Product Characteristics

Soliris is a formulation of eculizumab which is a recombinant humanized monoclonal IgG2/4κ 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.

Viral Inactivation

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

CLINICAL TRIALS

PNH

The safety and efficacy of Soliris in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26 week study (PNH Study 1); PNH patients were also treated with Soliris in a single arm 52 week study (PNH Study 2); and in a long term extension study (PNH extension study). Patients received meningococcal vaccination prior to receipt of Soliris. In all studies, the dose of Soliris was 600 mg study drug every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 25 – 45 minutes.

In study PNH Study 1 (TRIUMPH), PNH patients 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 PNH Study 2 (SHEPHERD), PNH patients 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 PNH Study 1 and PNH Study 2

	PNH Study 1		**PNH Study 2**
Parameter	**Placebo N=44**	**Soliris N=43**	**Soliris N=97**
Mean Age (SD) Range	38.4 (13.4) (18.0, 78.0)	42.1 (15.5) (20.0, 85.0)	41.1 (14.4) (18.0, 78.0)
Gender – Female (%)	29 (65.9)	23 (53.5)	49 (50.5)
History of Aplastic Anemia or MDS* (%)	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 setpoint (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)

* myelodysplastic syndromes

In TRIUMPH (PNH Study 1), 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 SHEPHERD (PNH Study 2), 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 1

	PNH Study 1		
	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, 886544)	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: ForPNH Study 1, LDH AUC was calculated using trapezoid rule for the actual LDH values
(d) FACIT effect size: ForPNH Study 1, 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 1 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]
	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 2

	PNH Study 2[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 2 refer to pre- versus post-treatment comparisons.
(b) P value calculated with Wilcoxon signed rank test
(c) LDH AUC: ForPNH Study 2, LDH AUC was calculated using trapezoid rule for change of LDH from baseline.
(d) FACIT effect size: ForPNH Study 2, 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 1, PNH Study 2 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 **Warnings and Precautions**).

Table 18: Thromboembolic Events in Patients during the 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 non-parametric signed rank test

Atypical HUS

Four single-arm prospective studies (atypical HUS Studies 1, 2, 4 and 5) 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. In all studies, the dose of Soliris in adult and adolescent patients was 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.

Atypical HUS Study 3 was a retrospective chart review. The dosage regimen for pediatric patients weighing less than 40 kg enrolled in atypical HUS Study 5 was based on body weight [see **Dosage and Administration**].

- Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints, including 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 new dialyses required per patient per day).*

Atypical HUS Resistant to PE/PI (atypical HUS Study 1)

Atypical HUS Study 1 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 atypical HUS Study 1 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 19** summarizes the key baseline clinical and disease-related characteristics of patients enrolled in atypical HUS Study 1.

Table 19: Baseline Characteristics of Patients Enrolled in atypical HUS Study 1

Parameter	**atypical HUS Study 1** 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 atypical HUS Study 1 received Soliris for a minimum of 26 weeks. In atypical HUS Study 1, the median duration of Soliris therapy was approximately 100 weeks (range: 2 weeks to 145 weeks). The primary endpoint was change in platelet count from baseline through Week 26.

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

atypical HUS Study 1, 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 20 summarizes the efficacy results for atypical HUS Study 1.

Table 20: Efficacy Results for atypical HUS Study 1

Efficacy Parameter	Atypical HUS Study 1 at 26 wks[1] N=17	Atypical HUS Study 1 at 2 yrs[2] N=17
Platelet Count Normalization[3]	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)

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

Atypical HUS Sensitive to PE/PI (atypical HUS Study 2)

Atypical HUS Study 2 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 atypical HUS Study 2. The median patient age was 28 years (range: 13 to 63 years). Patients enrolled in atypical HUS Study 2 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 atypical HUS Study 2.

Table 21: Baseline Characteristics of Patients Enrolled in atypical HUS Study 2

Parameter	atypical HUS Study 2 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 ($\times 10^9$/L), median (range)	218 (105, 421)
Baseline LDH (U/L), median (range)	200 (151, 391)

Patients in atypical HUS Study 2 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 atypical HUS Study 2, the median duration of Soliris therapy was approximately 114 weeks (range: 26 to 129 weeks).

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 22 summarizes the efficacy results for atypical HUS Study 2.

Table 22: Efficacy Results of Patients Enrolled in atypical HUS Study 2

Efficacy Parameter	Atypical HUS Study 2 at 26 wks[1] N=20	Atypical HUS Study 2 at 2 yrs[2] 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)
TMA Event-free status n (%)	16 (80)	19 (95)

Efficacy Parameter	Atypical HUS Study 2 at 26 wks[1] N=20	Atypical HUS Study 2 at 2 yrs[2] N=20
Daily TMA intervention rate, median (range)		
Before eculizumab	0.23 (0.05, 1.09)	0.23 (0.05, 1.09)
On eculizumab treatment	0	0
Hematologic normalization[4], n (%)	18 (90)	18 (90)
Median duration of hematologic normalization, weeks (range)[3]	38 (22, 52)	114 (33, 125)

1. At data cut-off (September 8, 2010).
2. At data cut-off (April 20, 2012).
3. Calculated at each post-dose day of measurement (excluding Days 1 to 4) using a repeated measurement ANOVA model.
4. In atypical HUS Study 2, 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.

In Studies 1, 2 and 4, 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 5, 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 is small. Efficacy outcomes were independent whether patient had in an identified genetic mutation.

Retrospective Chart Review of Patients with atypical HUS (atypical HUS Study 3)

Exploratory analyses were conducted in the retrospective chart review (atypical HUS Study 3) 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 atypical HUS Study 3. 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 23: Efficacy Results in Pediatric Patients Enrolled in atypical HUS Study 3

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 (%)[2]	2 (40)	6 (60)	1 (25)	9 (47)
Platelet count normalization, n (%)[1]	4 (80)	10 (100)	3 (75)	17 (89)
Daily TMA intervention rate, median (range)				
Before eculizumab	1 (0, 2)	<1 (0.07, 1.46)	<1 (0, 1)	0.31 (0.00, 2.38)
On eculizumab treatment	<1 (0, <1)	0 (0, <1)	0 (0, <1)	0.00 (0.00 , 0.08)

[1.] 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.
[2.] 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.

Adult Patients with atypical HUS (atypical HUS Study 4)

Atypical HUS Study 4 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. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in atypical HUS Study 4 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 24** summarizes the key baseline clinical and disease-related characteristics of patients enrolled in atypical HUS Study 4.

Table 24: Baseline Characteristics of Patients Enrolled in atypical HUS Study 4

Parameter	Atypical HUS Study 4 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 atypical HUS Study 4 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 atypical HUS Study 4, the median duration of Soliris therapy was approximately 50 weeks (range: 13 weeks to 86 weeks).

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 Submission 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 atypical HUS Study 4, 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 25 summarizes the efficacy results for atypical HUS Study 4.

Table 25: Efficacy Results for atypical HUS Study 4

Efficacy Parameter	aHUS Study 4 (N = 41)
Platelet Count Normalization[1]	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)

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

Pediatric and Adolescent Patients with atypical HUS (atypical HUS Study 5)

Atypical HUS Study 5 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. The median patient age was 6.5 (range: 5 months to 17 years). Patients enrolled in atypical HUS Study 5 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 26 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in atypical HUS Study 5.

Table 26: Baseline Characteristics of Patients Enrolled in atypical HUS Study 5

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 (x 10^9/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 5 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 5, the median duration of Soliris therapy was approximately 44 weeks (range: 1 dose to 88 weeks).

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 Study 5, 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 5.

Table 27: Efficacy Results for atypical HUS Study 5

Efficacy Parameter	Patients 1 month to <12 years (N = 18)	All Patients (N = 22)
Platelet Count Normalization[1]		21 (96%)
Complete TMA response, n (%) 95% CI Median Duration of complete TMA response, weeks (range)[2]	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)

[1]Normal platelet count is defined as $\geq 150 \times 10^9$/L.
[2] Through data cutoff (October 12, 2012)

DETAILED CLINICAL PHARMACOLOGY

Endogenous human antibodies are typically distributed within the vascular and extracellular spaces by mechanisms dominated by convection, fluid-phase endocytosis, receptor-mediated endocytosis and their interaction with FcRn receptors.[2] Since Soliris is a humanized monoclonal antibody; it can be hypothesized that its distribution is likely to be similar to that observed for other endogenous human antibodies. Population PK analyses have shown that Soliris volume of distribution approximates that of plasma volume. The amount of Soliris associated with non-C5 plasma proteins and the effects of plasma protein binding on eculizumab distribution have not been determined nor can they be predicted with the current Population PK model.

Soliris 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. The extent of catabolism is inversely proportional to FcRn receptor affinity.[3]

No specific clinical studies have been conducted to evaluate specific pathways of eculizumab excretion. Due to its molecular size, eculizumab (148 kD), like other immunoglobulins, is not expected to be eliminated by renal filtration.

No clinical studies have been specifically conducted to discern the effects of age, race, gender, or metabolic status (renal or hepatic impairment) on the PK of Soliris. The statistical algorithms applied to the consolidated PK/PD model suggested no statistical correlation between the PK

parameters for disposition of eculizumab with age, race or gender. The statistical algorithms applied to the consolidated PK/PD model suggested no statistical correlation between the PK parameters (clearance and volume of distribution) for disposition of eculizumab with age, race or gender.

Pediatric and adolescent patients (less than 18 years of age) and patients with renal impairment were included in the atypical HUS clinical studies [see **Clinical Studies**]. Population PK analysis showed age, gender, race, and renal function do not influence the PK of eculizumab. However, this one-compartment pharmacokinetic model has not been assessed for its sensitivity to detect the influence of all of these factors.

Similar to endogenous immunoglobulins, Soliris consists of naturally occurring L-amino-acids and is not subject to metabolic transformation by CYP enzymes. Therefore, no differences in Soliris PK are expected due to tobacco use, concomitant medications, genetic polymorphism, or food intake.

No apparent interactions of Soliris with other medicinal products have been observed in 6 studied indications, in which patients received numerous concomitant medications. Soliris given concomitantly with other medications resulted in no significant changes in its PK profile.

Table 28: Concomitant Use and Individual Random Effect on Clearance and Volume of Distribution (Prospective atypical HUS Studies 1 and 2 Data in atypical HUS Patients)

Individual Random Effect on Clearance									
Agent	**NO**				**YES**				
	n	**Median**	**L95**	**U95**	**n**	**Median**	**L95**	**U95**	**p-value***
Antihyper-tensive	22	0.0195	-0.0793	0.1183	15	0.0174	-0.1156	0.1503	0.4478
ESA	15	0.0174	-0.0286	0.0633	22	0.0195	-0.0963	0.1352	0.7842
Immuno-suppressive	22	0.0176	-0.0668	0.1020	15	0.0267	-0.1045	0.1579	0.7340
Individual Random Effect on Volume of Distribution									
Agent	**NO**				**YES**				
	n	**Median**	**L95**	**U95**	**n**	**Median**	**L95**	**U95**	**p-value***
Antihyper-tensive	22	-0.0671	-0.1423	0.0080	15	0.0981	-0.0239	0.2201	0.5995
ESA	15	0.0568	-0.0342	0.1478	22	-0.0165	-0.1238	0.0908	0.4482
Immuno-suppressive	22	0.0591	-0.0344	0.1526	15	-0.0478	-0.1658	0.0702	0.7899

ESA: erythrocyte stimulating agent; n: count of patients; L95/U95: approximate 95% confidence limits for the median; *: Welch Modified Two-Sample t-Test

DETAILED PHARMACOLOGY

Pharmacodynamics

The pharmacodynamic profile of eculizumab was assessed using an *in vitro* serum complement hemolysis assay that measures the extent of terminal complement inhibition in the serum of patients receiving Soliris. Administration of Soliris results in a rapid and sustained reduction in terminal complement activity. Eculizumab serum concentrations of approximately 35 µg/mL are sufficient for essentially complete inhibition of terminal complement-mediated intravascular hemolysis in PNH patients.

Administration of Soliris in an initial phase/maintenance regimen of 600 mg/week for the first 4 weeks and 900 mg in the fifth week of the initial phase, followed by a 900 mg maintenance dose every other week resulted in a rapid and sustained reduction in complement-mediated hemolytic activity. Soliris when administered as recommended provides a blood concentration sufficient to completely block hemolysis within 60 minutes and red blood cell destruction, as indicated by lactate dehydrogenase levels, is significantly reduced by one week.[4] In the Phase 3 study in PNH patients, PNH Study 1, the dosing regimen was sufficient to maintain plasma Soliris levels to essentially completely block terminal complement activation in 39/40 patients measured for the entire 26 week study period demonstrating that the proposed dosing regimen is adequate.

A Weibull function model was utilized to study the PK/PD relationship in the PNH extension study analysis of 15 densely sampled patients at steady state, and in all PNH PK/PD data combined. As shown in **Table 29**, this included data from 141 unique PNH patients (40 Soliris treated patients from PNH Study 1, 97 patients from PNH Study 2 and 4 patients from the PNH extension study who had been previously treated with placebo in PNH Study 1). The sigmoid relationship between total eculizumab concentrations in serum and complement hemolytic activity in serum is very steep, almost approaching a pure bi-modal on-off effect. The effective concentration to provide 1/e (36.8%) of the effect (C_{deff}) relative to baseline values (E0) is 30.6 µg/mL. In combination with a mean deflection (sf) of 2.61, this suggests that low concentrations of Soliris are required to provide close-to-full inhibition of complement C5. A more physiological estimate of the serum concentrations of Soliris resulting in 36.8% inhibition of hemolysis (C_{deff}) must be based on the free concentration of the drug. The resulting C_{deff} is assumed to be overestimated and should be regarded as an upper boundary for the true C_{deff} value, which is expected to be substantially lower according to the free fraction of the drug.

Table 29: PD Modeling Results

Dataset Analyzed	Model	Results		
PNH Extension Study, N = 141 (All PNH data combined)	Cumulative Weibull function	**Parameter**	**Arithmetic Mean (CV%)**	**Median (Min– Max)**
		E0 (%)	93.8 (9.35%)	95.5 (28.1 – 114.6)
		E_{diff} (%)	91.0 (9.56%)	92.8 (26.2 – 111.6)
		C_{deff} (µg/mL)	30.6 (27.2%)	30.5 (1.83 – 62.9)
		sf	2.61 (43.5%)	2.61 (0.313 – 6.01)
aHUS Study 4	Cumulative Weibull function	**Parameter**	**Typical Value**	**Between Subject Variability (%)**
		E0 (%)	100 Fixed	-
		E_{diff} (%)	98.2	0.967
		C_{deff} (µg/mL)	30.5	-
		sf	2.61 Fixed	-
Error Model				
Additive Error (Hemolysis, %)		2.40		-

Note: Due to sparseness of data, the Emax was fixed to 100% and the slope factor (Sf) was fixed to the value previously estimated for PNH.

There are no known secondary pharmacological effects of Soliris because of the highly specific interaction of Soliris with its target as indicated by the lack of Soliris binding to C5 from other species. Thus, all effects are assumed to be the result of the interaction of Soliris with its intended target.

Pharmacokinetics

Soliris exhibits a PK profile that has been adequately described using both one and two-compartmental models. Soliris has a mean elimination half-life of approximately 271 hours, and its distribution appears to be primarily limited to the vascular space due to its small volume of distribution. Based on the fixed dosing regimen utilized in the PNH development program, and using the T½ calculated with the one-compartmental model (i.e. 271 hrs), systemic clearance (CL) was estimated as 0.311 mL/hr/kg.

A standard 1 compartmental model was utilized to study the PK of Soliris in the PNH extension study analysis of 15 densely sampled patients at steady state, and in all PNH PK/PD data combined. As shown in **Table 30**, this included data from 141 unique PNH patients (40 Soliris treated patients from PNH Study 1, 97 patients from PNH Study 2, and 4 patients from the PNH extension study who had been previously treated with placebo in PNH Study 1). Based on these PK parameters, the onset of steady state in PNH patients is predicted to be approximately 57 days with an accumulation ratio of approximately 1.075. This is consistent with the long terminal elimination half-life of the drug, and indicative of minimal accumulation over time.

Table 30: PNH Studies PK Parameter Estimates using One-Compartment Model

PK Parameter Estimates				
PNH Study 1 N = 40	**CL (mL/hr/kg)**	**Vd (mL/kg)**	**Kel (1/h)**	**T1/2 (h)**
Average	0.311183	110.3	0.002776	271.7
SD	0.125097	17.9	0.000817	81.6
%SD	40.20	16.2	29.45	30.0
Min	0.150944	79.1	0.001376	134.1
Max	0.745052	144.1	0.005169	503.8
Median	0.289969	108.3	0.002793	248.2
PNH Study 2 N = 97	**CL (mL/hr/kg)**	**Vd (mL/kg)**	**Kel (1/h)**	**T1/2 (h)**
Average	0.3349	113.93	0.003077	261.07
SD	0.13401	28.719	0.0013682	90.795
%CV	40.0	25.2	44.5	34.8
Min	0.153	47.2	0.00124	88.1
Max	0.843	184.4	0.00787	566.9
Median	0.309	109.0	0.00260	266.3
PNH Extension Study N = 15	**CL (mL/hr/kg)**	**Vd (mL/kg)**	**Kel (1/h)**	**T1/2 (h)**
Average	0.2773	106.34	0.002867	276.6
SD	0.05306	30.868	0.0011532	99.85
%CV	19.1	29.0	40.2	36.1
Min	0.189	57.2	0.00148	137
Max	0.366	159.3	0.00507	469
Median	0.265	106.8	0.00250	277
PNH Extension Study N = 141	**CL (mL/hr/kg)**	**Vd (mL/kg)**	**Kel (1/h)**	**T1/2 (h)**
Average	0.3288	112.97	0.00302	262.71
SD	0.12809	26.787	0.001249	89.90
%CV	39.0	23.7	41.4	34.2
Min	0.153	47.4	0.00126	88.4
Max	0.838	182.6	0.00784	548.6
Median	0.309	111.5	0.00270	257.1

A second population PK analysis with a standard 1 compartmental model was conducted on the multiple dose PK data from 57 atypical HUS patients receiving the recommended Soliris regimen in studies 1, 2 and 3. In this model, the clearance of Soliris for an adult patient with atypical HUS patient weighing 70 kg was 14.6 mL/hr and the volume of distribution was 6.14 L. The elimination half-life was 291 h (approximately 12.1 days).

The clearance and half-life of eculizumab were also evaluated during plasma exchange interventions. Plasma exchange increased the clearance of eculizumab to 3660 mL/hr and reduced the half-life to 1.26 hours. Supplemental dosing is recommended when Soliris is administered to atypical HUS patients receiving plasma infusion or exchange [see **Dosage and Administration**].

The population PK modeling of prospective studies (atypical HUS Studies 1 and 2) and retrospective study (atypical HUS Study 3) in atypical HUS patients is provided in **Table 31**.

Table 31: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters by Body Weight Group

Population	Protocol	Induction Period			Maintenance Period		
		Parameter[a]	Mean (CV%)	Median (Range)	Parameter	Mean (CV%)	Median (Range)
5 - <10 kg	**Study 3 (N=4)**	AUC	32699.20 (17.7)	32247.53 (26297.80 – 40003.95)	AUC	94818.72 (46.1)	80026.87 (61442.67 – 157778.48)
		C_{max}	263.91 (34.7)	249.56 (171.48 - 385.04)	C_{max}	360.28 (14.1)	361.03 (312.60 - 406.49)
		C_{min}	141.77 (3.7)	142.66 (134.60 - 147.17)	C_{min}	96.48 (100.8)	66.87 (17.05 - 235.15)
10 - <20 kg	**Study 3 (N=4)**	AUC	45453.47 (13.1)	45890.77 (38797.06 – 51235.28)	AUC	63246.51 (44.0)	58939.40 (34429.33 – 100677.90)
		C_{max}	353.08 (15.6)	370.30 (275.39 - 396.35)	C_{max}	292.79 (24.7)	273.32 (228.36 - 396.16)
		C_{min}	204.90 (22.8)	202.97 (150.83 - 262.84)	C_{min}	116.42 (68.3)	105.56 (34.35 - 220.20)
20 - <30 kg	**Study 3 (N=5)**	AUC	32068.74 (9.7)	32072.88 (27572.56 – 36298.63)	AUC	104967.00 (25.0)	101663.90 (74024.72 – 145050.16)
		C_{max}	230.73 (11.7)	225.55 (205.51 - 274.10)	C_{max}	442.50 (16.7)	436.03 (338.65 - 546.04)
		C_{min}	156.60 (10.0)	160.50 (129.07 - 167.32)	C_{min}	212.04 (36.7)	199.57 (133.35 - 334.53)

Table 31: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters by Body Weight Group (Continued)

Population	Protocol	Induction Period			Maintenance Period		
		Parameter	**Mean (CV%)**	**Median (Range)**	**Parameter**	**Mean (CV%)**	**Median (Range)**
30 - <40 kg	**Study 3 (N=1)**	AUC	23723.37 (NC)	23723.37 (23723.37-23723.37)	AUC	11891.07 (NC)	11891.07 (11891.07 - 11891.07)
		C_{max}	167.98 (NC)	167.98 (167.98 - 167.98)	C_{max}	494.64 (NC)	494.64 (494.64 - 494.64)
		C_{min}	117.80 (NC)	117.80 (117.80 - 117.80)	C_{min}	242.98 (NC)	242.98 (242.98 - 242.98)
≥40 kg	**Study 1 (N=17)**	AUC	196987.76 (20.0)	20159.02 (12222.98 – 27096.27)	AUC	78718.49 (34.0)	71899.34 (26404.96 – 137647.83)
		C_{max}	145.16 (18.3)	142.96 (100.52 - 195.39)	C_{max}	345.14 (26.0)	334.63 (176.75 - 528.05)
		C_{min}	93.66 (23.6)	93.50 (43.41 - 131.79)	C_{min}	151.80 (44.9)	141.17 (25.90 - 310.43)
	Study 2 (N=20)	AUC	22717.36 (15.6)	22379.16 (16890.79 – 29401.12)	AUC	103160.24 (19.3)	105003.73 (62906.27– 132313.05)
		C_{max}	161.47 (16.9)	157.67 (117.03 - 218.64)	C_{max}	427.48 (15.8)	425.11 (287.37 - 529.33)
		C_{min}	112.43 (15.1)	111.45 (81.96 – 138.00)	C_{min}	212.45 (25.3)	213.08 (108.84 - 291.60)
	Study 3 (N=6)	AUC	23328.02 (31.6)	21881.33 (13874.40 – 36051.85)	AUC	73766.59 (32.8)	73451.90 (41881.89 - 107816.71)
		C_{max}	181.87 (32.1)	172.72 (109.06 - 284.33)	C_{max}	363.04 (31.2)	343.56 (211.07 - 546.63)
		C_{min}	103.68 (31.7)	97.40 (60.95 - 157.73)	C_{min}	120.77 (37.9)	129.92 (65.79 - 167.87)

Population	Protocol	Induction Period			Maintenance Period		
		Parameter	**Mean (CV%)**	**Median (Range)**	**Parameter**	**Mean (CV%)**	**Median (Range)**
	Pooled (N=43)	AUC	21604.82 (21.0)	21358.24 (12222.98 – 36051.85)	AUC	89395.78 (29.4)	89179.55 (264004.96 - 137647.83)
		C_{max}	157.87 (21.6)	156.69 (100.52 - 284.33)	C_{max}	385.94 (23.5)	392.49 (176.75 - 546.63)
		C_{min}	103.79 (22.0)	103.75 (43.41 - 157.73)	C_{min}	175.68 (38.7)	170.20 (25.90 - 310.43)
Overall	**Pooled (N=57)**	AUC	25012.02 (32.8)	22971.02 (12222.98 - 51235.28)	AUC	89825.89 (31.5)	90110.39 (26404.96 - 157778.48)
		C_{max}	185.58 (37.2)	163.43 (100.52 - 396.35)	C_{max}	384.47 (23.5)	396.16 (176.75 - 546.63)
		Cmin	118.43 (31.5)	111.73 (43.41 - 262.84)	Cmin	170.33 (44.0)	167.87 (17.05 - 334.53)

[a] AUC= Area under the concentration-time curve from day zero to week one for the induction period and area under the concentration-time curve under steady-state (µg×h/mL), C_{max}= Maximum concentration (µg/mL); C_{min}= Minimum concentration (µg/mL); CV(%)= Coefficient of variation; NC= Not calculated
Note: The calculation of PK parameters during the induction period was based on the simulated concentration-time profiles during the first week following the first dose. For the maintenance period, the calculation of PK parameters was based on simulated concentration-time profiles under steady-state conditions.
The dosing regimens used for the simulations were the Alexion Dosing Strategy for pediatric and adolescent patients with atypical HUS.

Dedicated studies have not been conducted to evaluate the PK of Soliris in special patient populations identified by gender, race, age (geriatric), or the presence of renal or hepatic impairment. Pediatric and adolescent patients (less than 18 years of age) and patients with renal impairment were included in the atypical HUS clinical studies [see **Clinical Trials**.] Population PK analysis showed age, gender, race, and renal function do not appear to influence the PK of eculizumab. However, this one-compartment pharmacokinetic model has not been assessed for its sensitivity to detect the influence of all of these factors.

TOXICOLOGY

The specificity of eculizumab for C5 in human serum was evaluated in two *in vitro* studies. The species specificity of Soliris was assessed by determining its ability to inhibit hemolytic activity in non-human sera (4 primate and 4 non-primate species) using a complement-mediated hemolytic assay. The results of this study demonstrate that eculizumab does not inhibit C5 activity in sera from the species tested.

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.

Nonclinical Toxicology with BB5.1

The toxicology program was limited to toxicity and reproduction toxicology studies (**Tables 32** and **33**) using the surrogate murine anti-mouse C5 antibody (BB5.1) due to eculizumab's specificity to human C5 and the consequent absence of a pharmacologically responsive species to eculizumab. The onset, severity, and duration of the toxic effects of complement inhibition, their correlation to dosing frequency and degree of reversibility were assessed using a surrogate murine anti mouse C5 antibody in a 4-week and 26-week toxicity study in mice. The four-week study showed that 30 mg/kg given twice a week for a total dose of 60 mg/kg per week was sufficient to achieve inhibition of hemolysis. The twenty-six week study evaluated the toxicity at 30 mg/kg bw administered once or twice weekly for a total dose of 30 or 60 mg/kg per week for 26 weeks, followed by a four week recovery period. There were no observed treatment-related clinical signs. The no observed effect level (NOEL) was 30 mg/kg twice a week for a total dose of 60 mg/kg per week.

Animal reproductive studies using a surrogate mouse antibody (murine anti-C5 antibody) which inhibits murine complement but is unrelated to the eculizumab molecule were conducted at the dose level of 30 mg/kg bw, administered either once or twice weekly for a total dose of 30 or 60 mg/kg per week. Hemolytic assays were used only to show exposure to a complement inhibiting drug. However, maximal inhibition of hemolysis was not attained in the majority of treated animals. This observation could not be explained. One out of three of these studies showed an increased rate of developmental abnormalities and in one out of three studies an increased rate of dead and moribund offspring at doses 2-8 times the human dose. Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 2-4 times (30 mg/kg bw for a total dose of 30 mg/kg per week) and 4-8 times (30 mg/kg bw/twice weekly for a total dose of 60 mg/kg per week) the recommended human Soliris dose, based on a body weight comparison. When animal exposure to the antibody occurred in the time period from before mating until early gestation, no decrease in fertility or reproductive performance was observed. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose; however, the exposure did not increase fetal loss or neonatal death. When maternal exposure to the antibody occurred in the time period from implantation through weaning, a higher number of male offspring became moribund or died (1/25 controls, 2/25 30 mg/kg bw/w for a total dose of 30 mg/kg per week, 5/25 30 mg/kg bw/twice weekly for a total dose of 60 mg/kg per week). Surviving offspring had normal development and reproductive performance.

Animal studies have not been conducted to evaluate the carcinogenic and genotoxic potential of eculizumab. However, a 26-week repeat dose toxicity study with a murine anti-C5 antibody did not show cytotoxic or proliferative activities suggestive of carcinogenic risk when administered at the dose level of 30 mg/kg bw, up to twice weekly for a total dose of 60 mg/kg per week.

Table 32: Summary of Animal Toxicology Studies with BB5.1

Type of Study	Species and Strain	Route	Duration of Dosing	Dose mg/kg bw	Dose frequency[a]	Results
Single Dose Toxicity	No studies were performed					
Repeat-Dose Toxicity						
Four Week Intravenous Injection Range-Finding Study in Mice with BB5.1	CD-1 Mice	i.v.	4 Weeks	0, 30	Once, twice or three times per week	No treatment-related signs of toxicity
26-Week Intravenous Injection Toxicity Study of BB5.1 in Mice with a 4-Week Recovery	CD-1 Mice	i.v.	26 Week	0, 30	Once or twice weekly	No treatment-related signs of toxicity NOAEL is 30 mg/kg bw/twice weekly
Genotoxicity	No studies were performed					
Carcinogenicity	No studies were performed					

(a) the single dose of 30 mg/kg bw was used for all toxicity studies, with variable dosing frequencies, i.e., once, twice or thrice weekly administrations.

Table 33: Summary of Reproductive Toxicity Studies with BB5.1

Type of Study	Species and Strain	Route	Duration of Dosing	Dose mg/kg bw	Dose frequency[a]	Results
Reproductive and Developmental Toxicity						
Study of Fertility and Early Embryonic Development to Implantation in Mice with BB5.1[b]	CD-1 Mice	i.v.	Males: 28 days prior to mating through to necropsy Females: 2 weeks prior to mating through to gestation day 7.	0, 30	Once, twice or three times per week	No changes in fertility parameters were observed
Mouse Developmental Toxicity Study with BB5.1[c]	CD-1 Mice	i.v.	Pregnant females: gestation days 6 through to 15	0, 30	Once or twice weekly	Maternal: No treatment-related signs of toxicity Fetal: 2 cases of retinal dysplasia,

						one case of umbilical hernia at 30 mg/kg bw/twice weekly. No other findings.
Study for Effects on Pre- and Postnatal Development, Including Maternal Function, in the Mice with BB5.1[d]	CD-1 Mice	i.v.	Pregnant mice, gestation day 6 through to lactation day 18	0, 30	Once or twice weekly	F_0: No treatment-related signs of toxicity. F_1: Increased incidence of pups "killed[e]" and of dilated renal pelves, males only, both treatment groups. No effects on pregnancy, delivery or pup development.
Carcinogenicity / Genotoxicity	No studies were performed					
Immunotoxicity / Immunogenicity	No studies were performed					
Local Tolerance	No studies were performed					

(a) the single dose of 30 mg/kg bw was used for all toxicity studies, with variable dosing frequencies, i.e., once twice or thrice weekly administrations.
(b) the % hemolysis values were high, i.e., ≥ 50%, in 40% and 60% of the sampled mice in the 30 mg/kg bw/week and 30 mg/kg bw/twice a week groups, respectively. The reason for the high hemolysis values is unknown.
(c) the % hemolysis values were high, i.e., ≥ 50%, in 60% and 60% of the sampled mice in the 30 mg/kg bw/week and 30 mg/kg bw/twice a week groups, respectively. The reason for the high hemolysis values is unknown.
(d) the % hemolysis values were high, i.e., ≥ 50%, in 80% and 100% of the sampled mice in the 30 mg/kg bw/week and 30 mg/kg bw/twice a week groups, respectively. The reason for the high hemolysis values is unknown.
(e) pups "killed" refers to pups euthanized as an unscheduled death or accidental death.

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PART III: CONSUMER INFORMATION

Soliris®
(Eculizumab)

pronounced, "soh LEER iss

This leaflet is part III of a three-part "Product Monograph" published when Soliris was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Soliris. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

SOLIRIS® (eculizumab), has been authorized for Paroxysmal Nocturnal Hemoglobinuria (PNH) and atypical Hemolytic Uremic Syndrome (atypical HUS).

What the medication is used for:
Soliris is used to treat patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) to reduce hemolysis (destruction of red blood cells) or to treat patients with chronic atypical Hemolytic Uremic Syndrome (atypical HUS), a very rare disease that affects the blood system, kidney and sometimes other body organs.

What it does:
Soliris is a monoclonal antibody that blocks part of your immune system called terminal complement. Soliris works by decreasing the destruction of your own red blood cells and platelets, but it also lowers the ability of your immune system to fight infection.

When it should not be used:
You should not start Soliris if your doctor confirms a serious infection, such as an active *Neisseria meningitidis* infection (in the brain, spinal cord or blood) or if you have not received a meningococcal vaccine prior to, or at the time of, initiating Soliris. If you subsequently receive Soliris when you have a serious infection, you should immediately contact your physician if there is any worsening of the symptoms of the infection. You must not be treated with Soliris until you are vaccinated.

Tell your doctor if you have a disease that alters your immune system (such as HIV/AIDS) or take a medication that alters your immune system (such as prednisone).

What the medicinal ingredient is:
eculizumab

What the important nonmedicinal ingredients are:
polysorbate 80 (vegetable origin)
sodium chloride
sodium phosphate dibasic
sodium phosphate monobasic
Water for Injection, USP

What dosage forms it comes in:
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.

WARNINGS AND PRECAUTIONS

WARNING: SERIOUS MENINGOCOCCAL 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 a meningococcal vaccine 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 Meningitis (infection of the linings of the brain) or an active general infection. If you subsequently receive Soliris when you have a serious infection, you should immediately contact your physician if there is any worsening of the 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.

Meningitis 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

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.

Talk to your doctor if you have any allergies to this drug or its ingredients.

Your doctor should know by blood tests if Soliris is working.

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:
There are no clinical trials on the effects of Soliris on pregnant or breastfeeding women and their babies. Based on animal data, Soliris may cause harm to the fetus. Soliris should not be used during pregnancy unless the potential benefit justifies the risks to you and your baby. Tell your doctor if you are pregnant or nursing. If you could become pregnant, discuss using birth control methods with your doctor. Birth control methods should be continued for at least five months after discontinuing Soliris.

INTERACTIONS WITH THIS MEDICATION

There are no known interactions between Soliris and other medications, but always tell your doctor about all the medications you are taking, including herbal medicines and vitamins. No increases in side-effects were observed in patients taking Soliris and other common medications in clinical trials.

PROPER USE OF THIS MEDICATION

Your "Soliris Patient Safety Card" has early warning signs of infection and other important information about treatment with Soliris and you should carry it with you at all times.

Usual dose:
Soliris is given through a vein ['I.V.' or 'intravenously'], usually over 35 minutes.

The usual dose of Soliris for PNH patients 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 atypical HUS patients 18 years of age or older 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 upon 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. In clinical studies with Soliris, no cases of overdose were seen.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Missed Dose or Stopping Treatment:
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.

Symptoms or problems from red blood cell destruction in PNH patients include:

- A sudden or severe decrease 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 your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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 (herpes complex).

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 (leukopenia), urinary tract (bladder) infection, hair loss (alopecia), cold sore (herpes simplex), low lymphocyte count (lymphopenia), cough, joint pain (arthralgia), weakness (asthenia), and viral infection.

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

You should contact your doctor if you feel **ANY** side effects after receiving Soliris.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist	
	Only if severe	In all cases*
Very Common (more than 10% of patients)		
Headache	x	
Hypertension (High Blood Pressure)		x
Low white blood cell count (leukopenia or lymphopenia)		x
Respiratory tract infection		x
Rash	x	
Common (≥1% and ≤10%)		
Abdominal discomfort or pain	x	
Agitation	x	
Anemia (low red blood count)		x
Blood in urine		x
Blood clot in vein (Venous thrombosis)		x
Breathing difficulty	x	
Chills	x	
Deafness	x	
Diarrhoea	x	
Flu-like Illness	x	
Fever		x
Light headedness (dizziness, vertigo)	x	
Low blood pressure		x
Infection (bacterial or viral, common cold, eye, nose, throat, lung, and urinary tract, and cold sore)		x
Joint Pain	x	
Meningococcal infection		x
Muscle Aches	x	
Neck Pain		x
Pain in extremity		x
Throat Pain		x
Uncommon (<1%)		
Jaundice		x
Swelling (Face or Leg)		x

** If you experience any of these symptoms, you should immediately contact your doctor. Soliris treatment may lower the ability of your immune system to fight infections, especially meningococcal infection, which requires **immediate** medical attention. This is not a complete list of side effects. For any unexpected effects while taking Soliris, contact your doctor or pharmacist.*

HOW TO STORE IT

Soliris vials must be stored in the original carton until time of use under refrigerated conditions at 2-8ºC and protected from light. Soliris vials may be held in the original carton at room temperature (not more than 25°C) for a single period of up to 3 days. Do not use beyond the expiration date stamped on the carton.

Diluted solutions of Soliris may be stored at 2-8°C and at room temperature for up to 24 hours prior to administration.

DO NOT FREEZE. DO NOT SHAKE.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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@incresearch.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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