SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SOLIRIS®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Eculizumab is a humanised monoclonal ($IgG_{2/4\kappa}$) antibody produced in NS0 cell line by recombinant DNA technology.

One vial of 30 ml contains 300 mg of eculizumab (10 mg/ml).

After dilution, the final concentration of the solution to be infused is 5 mg/ml.

Excipients with known effect: Sodium (5 mmol per vial), polysorbate 80 (6.6 mg per vial).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colorless, pH 7.0 solution and osmolality of approximately 290-310 mOsm/kg.

Patient safety information card

The marketing of Soliris is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Soliris is indicated for the treatment of patients with:

- Paroxysmal nocturnal haemoglobinuria (PNH).
  Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1). Eculizumab has not been studied in clinical trials in patients with PNH below 11 years of age.
- Atypical haemolytic uremic syndrome (aHUS) (see section 5.1).
- Refractory generalized myasthenia gravis (gMG) in patients aged 6 years and above who are anti-acetylcholine receptor (AChR) antibody-positive (see section 5.1).

Soliris is indicated in adults for the treatment of:

- Neuromyelitis optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease who have received prior therapy (see section 5.1).

4.2 Posology and method of administration

Soliris must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological, renal, neuromuscular or neuro-inflammatory disorders.

Posology

In Paroxysmal Nocturnal Haemoglobinuria (PNH) in adults:
The PNH dosing regimen for adult patients (≥18 years of age) consists of a 4-week initial phase followed by a maintenance phase:

- Initial phase: 600 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every week for the first 4 weeks.
- Maintenance phase: 900 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion for the fifth week, followed by 900 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every 14 ± 2 days (see section 5.1).

Atypical Haemolytic Uremic Syndrome (aHUS), refractory generalized Myasthenia Gravis (gMG) and Neuromyelitis Optica Spectrum Disorder (NMOSD) in adults:
The aHUS, refractory gMG and NMOSD dosing regimen for adult patients (≥18 years of age) consists of a 4 week initial phase followed by a maintenance phase:

- Initial phase: 900 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every week for the first 4 weeks.
- Maintenance phase: 1,200 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion for the fifth week, followed by 1,200 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every 14 ± 2 days (see section 5.1).

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

Paediatric patients in PNH, aHUS or refractory gMG:
Paediatric PNH patients, above 11 years old, aHUS or refractory gMG patients with body weight ≥ 40 kg are treated with the adult dosing recommendations.

In paediatric PNH patients, above 11 years old, aHUS and refractory gMG patients with body weight below 40 kg, the Soliris dosing regimen consists of:

For paediatric patient with aHUS		
Patient Body Weight	**Initial Phase**	**Maintenance Phase**
30 to <40 kg	600 mg weekly for the first 2 weeks	900 mg at week 3; then 900 mg every 2 weeks
20 to <30 kg	600 mg weekly for the first 2 weeks	600 mg at week 3; then 600 mg every 2 weeks
10 to <20 kg	600 mg single dose at week 1	300 mg at week 2; then 300 mg every 2 weeks
5 to <10 kg	300 mg single dose at week 1	300 mg at week 2; then 300 mg every 3 weeks

For paediatric patient with refractory gMG, above 6 years old		
Patient Body Weight	**Initial Phase**	**Maintenance Phase**
30 to <40 kg	600 mg weekly for the first 2 weeks	900 mg at week 3; then 900 mg every 2 weeks
20 to <30 kg	600 mg weekly for the first 2 weeks	600 mg at week 3; then 600 mg every 2 weeks

For paediatric patient with PNH, above 11 years old		
Patient Body Weight	**Initial Phase**	**Maintenance Phase**
30 to <40 kg	600 mg weekly for the first 2 weeks	900 mg at week 3; then 900 mg every 2 weeks

Soliris has not been studied in patients with PNH or refractory gMG who weigh less than 40 kg. The posology of Soliris to be used in paediatric patients with PNH patients weighing less than 40 kg and who are above 11 years old or refractory gMG is identical to the weight-based dose recommendation provided for paediatric patients with aHUS. Based on the pharmacokinetic (PK)/pharmacodynamic (PD) data available in patients with aHUS and PNH treated with Soliris, this body-weight based dose regimen for paediatric patients is expected to result in an efficacy and safety profile similar to that in adults. For patients with refractory gMG weighing less than 40 kg this body-weight based dose regimen is also expected to result in an efficacy and safety profile similar to that in adults.

Soliris has not been studied in paediatric patients with NMOSD.

Supplemental dosing of Soliris is required in the setting of concomitant plasmapheresis (PP) or plasma exchange (PE), or fresh frozen plasma infusion (PI) as described below:

Type of Plasma Intervention	**Most Recent Soliris Dose**	**Supplemental Soliris Dose With Each PP/PE/PI Intervention**	**Timing of Supplemental Soliris Dose**
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Abbreviations: PP/PE/PI = plasmapheresis/plasma exchange/plasma infusion

Supplemental dose of Soliris is required in the setting of concomitant intravenous immunoglobulin (IVIg) treatment as described below (see also Section 4.5):

Most Recent Soliris Dose	**Supplemental Soliris Dose**	**Timing of Supplemental Soliris Dose**
≥ 900 mg	600 mg per IVIg cycle	As soon as possible after IVIg cycle
≤ 600 mg	300 mg per IVIg cycle	

Abbreviation: IVIg = intravenous immunoglobulin

Treatment monitoring
aHUS patients should be monitored for signs and symptoms of thrombotic microangiopathy (TMA) (see section 4.4 aHUS laboratory monitoring).
Soliris treatment is recommended to continue for the patient's lifetime, unless the discontinuation of Soliris is clinically indicated (see section 4.4).

Elderly
Soliris may be administered to patients aged 65 years and over. There is no evidence to suggest that any special precautions are needed when older people are treated – although experience with Soliris in this patient population is still limited.

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.1).

Hepatic impairment
The safety and efficacy of Soliris have not been studied in patients with hepatic impairment.

Paediatric population
The safety and efficacy of Soliris in children with refractory gMG aged less than 6 years old have not been established.
The safety and efficacy of Soliris in children with NMOSD aged less than 18 years old have not been established.

Method of administration
Do not administer as an intravenous push or bolus injection. Soliris should only be administered via intravenous infusion as described below.

For instructions on dilution of the medicinal product before administration, see section 6.6. The diluted solution of Soliris should be administered by intravenous infusion over 25 – 45 minutes (35 minutes ± 10 minutes) in adults and 1-4 hours in paediatric patients under 18 years of age via gravity feed, a syringe-type pump, or an infusion pump. It is not necessary to protect the diluted solution of Soliris from light during administration to the patient.
Patients should be monitored for one hour following infusion. If an adverse event 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 may not exceed two hours in adults and four hours in paediatric patients under 18 years of age.

4.3 Contraindications

Hypersensitivity to eculizumab, murine proteins or to any of the excipients listed in section 6.1.

Soliris therapy must not be initiated in patients (see section 4.4):
- 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.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Soliris is not expected to affect the aplastic component of anaemia in patients with PNH.

Meningococcal Infection
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 at least 2 weeks prior to receiving Soliris, unless the risk of delaying Soliris therapy outweighs the risks of developing a meningococcal infection. Patients who initiate Soliris treatment less than 2 weeks after receiving a tetravalent meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against all available serogroups including A, C, Y, W 135 and B, are recommended in preventing the commonly pathogenic meningococcal serogroups.. Patients must be vaccinated and revaccinated according to current national guidelines for vaccination use.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH, aHUS, refractory gMG and NMOSD, may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH), TMA (aHUS), MG exacerbation (refractory gMG) or relapse (NMOSD). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. Cases of serious or fatal meningococcal infections have been reported in Soliris-treated patients. Sepsis is a common presentation of meningococcal infections in patients treated with Soliris (see section 4.8). All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. Patients should be informed of these signs and symptoms and steps taken to seek medical care immediately. Physicians must discuss the benefits and risks of Soliris therapy with patients and provide them with a Patient guide and a patient card.

Other Systemic Infections

Due to its mechanism of action, Soliris therapy should be administered with caution to patients with active systemic infections. Patients may have increased susceptibility to infections, especially with *Neisseria* and encapsulated bacteria. Serious infections with Neisseria species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.
Patients should be provided with information to increase their awareness of potential serious infections and the signs and symptoms of them. Physicians should advise patients about gonorrhoea prevention.

Infusion Reactions

Administration of Soliris may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis). In clinical trials, 1 (0.9%) refractory gMG patient experienced an infusion reaction which required discontinuation of Soliris. No PNH, aHUS, refractory gMG or NMOSD paediatric patients experienced an infusion reaction which required discontinuation of Soliris. Soliris administration should be interrupted in all patients experiencing severe infusion reactions and appropriate medical therapy administered.

Immunogenicity

Infrequent antibody responses have been detected in Soliris-treated patients across all clinical studies. In PNH placebo controlled studies, low antibody responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%).
In patients with aHUS treated with Soliris, antibodies to Soliris were detected in 3/100 (3%) by the ECL bridging format assay. 1/100 (1%) aHUS patients had low positive values for neutralizing antibodies.
In a refractory gMG placebo controlled study, none (0/62) of the Soliris treated patients showed antidrug antibody response during the 26 week active treatment, whereas in a refractory gMG extension study, a total of 3/117 (2.6%) overall were positive for ADAs at any post-baseline visit. Positive ADA results appeared to be transient, as positive titers were not observed at subsequent visits, and there were no clinical findings in these patients suggestive of an effect of positive ADA titers.
In a NMOSD placebo controlled study, 2/95 (2.1%) of the Soliris treated patients showed antidrug antibody response post-baseline. Both patients were negative for neutralizing antibodies. Positive ADA samples were low titer and transient. There has been no observed correlation of antibody development to clinical response or adverse events.

Immunization
Prior to initiating Soliris therapy, it is recommended that PNH, aHUS, refractory gMG and NMOSD patients initiate immunizations according to current immunization guidelines. Additionally, all patients must be vaccinated against meningococcal infections at least 2 weeks prior to receiving Soliris unless the risk of delaying Soliris therapy outweighs the risks of developing a meningococcal infection. Patients who initiate Soliris treatment less than 2 weeks after receiving a tetravalent meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against all available serogroups including A, C, Y, W 135 and B are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must be vaccinated and revaccinated according to current national guidelines for vaccination use (see Meningococcal Infection).

Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections, and strictly need to adhere to the national vaccination recommendations for each age group.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH, aHUS, refractory gMG and NMOSD may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH), TMA (aHUS), MG exacerbation (refractory gMG) or relapse (NMOSD). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

Anticoagulant therapy
Treatment with Soliris should not alter anticoagulant management.

Immunosuppressant and anticholinesterase therapies

Refractory gMG
When immunosuppressant and anticholinesterase therapies are decreased or discontinued, patients should be monitored closely for signs of disease exacerbation.

Neuromyelitis Optica Spectrum Disorder
When immunosuppressant therapy is decreased or discontinued, patients should be monitored closely for signs and symptoms of potential NMOSD relapse.

PNH Laboratory Monitoring
PNH patients should be monitored for signs and symptoms of intravascular haemolysis, including serum lactate dehydrogenase (LDH) levels. PNH patients receiving Soliris therapy should be similarly monitored for intravascular haemolysis 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).

aHUS Laboratory Monitoring
aHUS patients receiving Soliris therapy should be monitored for thrombotic microangiopathy by measuring platelet counts, serum LDH and serum creatinine, and may require dose adjustment within the recommended 14±2 day dosing schedule during the maintenance phase (up to every 12 days).

Treatment Discontinuation for PNH
If PNH patients discontinue treatment with Soliris they should be closely monitored for signs and symptoms of serious intravascular haemolysis. Serious haemolysis 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 haemoglobin level of <5 g/dL or a decrease of >4 g/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 haemolysis and other reactions.
If serious haemolysis 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. In PNH clinical studies, 16 patients discontinued the Soliris treatment regimen. Serious haemolysis was not observed.

Treatment Discontinuation for aHUS
Thrombotic microangiopathy (TMA) complications have been observed as early as 4 weeks and up to 127 weeks following discontinuation of Soliris treatment in some patients. Discontinuation of treatment should only be considered if medically justified.

In aHUS clinical studies, 61 patients (21 paediatric patients) discontinued Soliris treatment with a median follow-up period of 24 weeks. Fifteen severe thrombotic microangiopathy (TMA) complications in 12 patients were observed following treatment discontinuation, and 2 severe TMA complications occurred in an additional 2 patients that received a reduced dosing regimen of Soliris outside of the approved dosing regimen (See Section 4.2). Severe TMA complications occurred in patients regardless of whether they had an identified genetic mutation, high risk polymorphism or auto-antibody. Additional serious medical complications occurred in these patients, including severe worsening of kidney function, disease-related hospitalization and progression to end stage renal disease requiring dialysis. Despite Soliris re-initiation following discontinuation, progression to end stage renal disease occurred in one patient.

If aHUS patients discontinue treatment with Soliris, they should be monitored closely for signs and symptoms of severe thrombotic microangiopathy complications. Monitoring may be insufficient to predict or prevent severe thrombotic microangiopathy complications in patients with aHUS after discontinuation of Soliris.
Severe thrombotic microangiopathy 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.

If severe thrombotic microangiopathy complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, supportive care with PE/PI, or appropriate organ-specific supportive measures including renal support with dialysis, respiratory support with mechanical ventilation or anticoagulation.

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

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

Educational materials
All physicians who intend to prescribe Soliris must ensure they are familiar with the guide for Healthcare Professionals to prescribing. Physicians must discuss the benefits and risks of Soliris therapy with patients and provide them with a Patient guide and a Patient card.
Patients should be instructed that if they develop fever, headache accompanied with fever and/or stiff neck or sensitivity to light, they should immediately seek medical care as these signs may be indicative of meningococcal infection.

Excipients with known effect

Sodium
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicinal product contains 0.88 g sodium per 240 mL at the maximal dose, equivalent to 44.0% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Once diluted with sodium chloride 4.5 mg/mL (0.45%) solution for injection, this medicinal product contains 0.67 g sodium per 240 mL at the maximal dose, equivalent to 33.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Polysorbate 80
This medicinal product contains 6.6 mg of polysorbate 80 in each vial (30mL vial) which is equivalent to 0.66 mg/kg or less at the maximum dose for adult patients and paediatric patients with body weight more than 10 kg and is equivalent to 1.32 mg/kg or less at the maximum dose for paediatric patients with body weight 5 to <10 kg. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on the potential inhibitory effect of eculizumab on complement-dependent cytotoxicity of rituximab, eculizumab may reduce the expected pharmacodynamic effects of rituximab.

Plasma exchange (PE), plasmapheresis (PP), fresh frozen plasma infusion (PI) and intravenous immunoglobulin (IVIg) have been shown to reduce eculizumab serum levels. A supplemental dose of eculizumab is required in these settings. See Section 4.2 for guidance in case of concomitant PE, PP, PI, or IVIg treatment.

Concomitant use of eculizumab with intravenous immunoglobulin (IVIg) may reduce effectiveness of eculizumab. Closely monitor for reduced effectiveness of eculizumab.

Concomitant use of eculizumab with neonatal Fc receptor (FcRn) blockers may lower systemic exposures and reduce effectiveness of eculizumab. Closely monitor for reduced effectiveness of eculizumab.

4.6 Fertility, pregnancy and lactation

The use of adequate contraception to prevent pregnancy and for at least 5 months after the last dose of treatment with eculizumab should be considered for women of childbearing potential.

Pregnancy
There are no well-controlled studies in pregnant women treated with eculizumab. Data on a limited number of pregnancies exposed to eculizumab (less than 300 pregnancy outcomes) indicate there is no increased risk of foetal malformation or foetal-neonatal toxicity. However, due to the lack of well-controlled studies, uncertainties remain. Therefore, an individual risk benefit analysis is recommended before starting and during treatment with eculizumab in pregnant women. Should such a treatment be considered necessary during pregnancy, a close maternal and foetal monitoring according to local guidelines is recommended.

Animal reproduction studies have not been conducted with eculizumab (see section 5.3).

Human IgG are known to cross the human placental barrier, and thus eculizumab may potentially cause terminal complement inhibition in the foetal circulation. Therefore, Soliris should be given to a pregnant woman only if clearly needed.

Breast-feeding
No effects on the breastfed newborn / infant are anticipated as limited data available suggest that eculizumab is not excreted in human breast milk. However, due to the limitations of the available data,

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

Fertility
No specific study of eculizumab on fertility has been conducted.

4.7 Effects on ability to drive and use machines

Soliris has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Supportive safety data were obtained from 33 clinical studies that included 1,555 patients exposed to eculizumab in complement-mediated disease populations, including PNH, aHUS, refractory gMG and NMOSD. The most common adverse reaction was headache (occurred mostly in the initial phase of dosing), and the most serious adverse reaction was meningococcal infection.

Tabulated list of adverse reactions
Table 1 gives the adverse reactions observed from spontaneous reporting and in eculizumab completed clinical trials, including PNH, aHUS, refractory gMG and NMOSD studies. Adverse reactions reported at a very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) ,rare (≥1/10,000 to <1/1,000) or not known (cannot be estimated from the available data) frequency with eculizumab, are listed by system organ class and preferred term. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse Reactions reported in eculizumab clinical trials, including patients with PNH, aHUS, refractory gMG and NMOSD as well as from postmarketing experience

MedDRA System Organ Class	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known (cannot be estimated from the available data)**
Infection and infestations		Pneumonia, Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Urinary tract infection, Oral Herpes	Meningococcal infection[b], Sepsis, Septic shock, Peritonitis, Lower respiratory tract infection, Fungal infection, Viral infection, Abscess[a], Cellulitis, Influenza, Gastrointestinal infection, Cystitis, Infection, Sinusitis, Gingivitis	Aspergillus infection[c], Arthritis bacterial[c], Genitourinary tract gonococcal infection, *Haemophilus* infection, Impetigo,	
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Malignant melanoma, Myelodysplastic syndrome	

Blood and lymphatic system disorders		Leukopenia, Anaemia	Thrombocytopenia, Lymphopenia	Haemolysis*, Abnormal clotting factor, Red blood cell agglutination, Coagulopathy	
Immune system disorders			Anaphylactic reaction, Hypersensitivity		
Endocrine disorders				Grave's disease	
Metabolism and nutrition disorders			Decreased appetite		
Psychiatric disorders		Insomnia	Depression, Anxiety, Mood swings, Sleep disorder	Abnormal dreams	
Nervous system disorders	Headache	Dizziness	Paraesthesia, Tremor, Dysgeusia, Syncope		
Eye disorders			Vision blurred	Conjunctival irritation	
Ear and labyrinth disorders			Tinnitus, Vertigo		
Cardiac disorders			Palpitation		
Vascular disorders		Hypertension	Accelerated hypertension, Hypotension, Hot flush, Vein disorder	Haematoma	
Respiratory, thoracic and mediastinal disorders		Cough, Oropharyngeal pain	Dyspnoea, Epistaxis, Throat irritation, Nasal congestion, Rhinorrhoea		
Gastrointestinal disorders		Diarrhoea, Vomiting, Nausea, Abdominal pain	Constipation, Dyspepsia, Abdominal distension	Gastroesophageal reflux disease, Gingival pain	
Hepatobiliary disorders			Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased	Jaundice	Liver injury[d]
Skin and subcutaneous tissue disorders		Rash, Pruritus, Alopecia	Urticaria, Erythema, Petechiae, Hyperhidrosis, Dry skin, Dermatitis	Skin depigmentation	
Musculoskeletal and connective tissue disorders		Arthralgia, Myalgia, Pain in extremity	Muscle spasms, Bone pain, Back pain, Neck pain	Trismus, Joint swelling	
Renal and urinary disorders			Renal impairment, Dysuria, Haematuria		

Reproductive system and breast disorders			Spontaneous penile erection	Menstrual disorder	
General disorders and administration site conditions		Pyrexia, Fatigue, Influenza-like illness	Edema, Chest discomfort, Asthenia, Chest pain, Infusion site pain, Chills	Extravasation, Infusion site paraesthesia, Feeling hot	
Investigations			Haematocrit decreased, Haemoglobin decreased	Coombs test positive[c]	
Injury, poisoning and procedural complication		Infusion related reaction			

Included Studies: Asthma (C07-002), aHUS(C08-002, C08-003, C10-003, C10-004), Dermatomyositis (C99-006), refractory gMG (C08-001, ECU-MG-301, ECU-MG-302, ECU-MG-303), Neuromyelitis Optica Spectrum Disorder (ECU-NMO-301, ECU-NMO-302), IMG (C99-004, E99-004), PNH (C02-001, C04-001, C04-002, C06-002, C07-001, E02-001, E05-001, E07-001, M07-005, X03-001, X03-001A), Psoriasis (C99-007), RA (C01-004, C97-001, C99-001, E01-004, E99-001), STEC-HUS (C11-001), SLE (C97-002). MedDRA version 26.1.

*See paragraph Description of selected adverse reactions.

[a] Abscess includes the following group of PTs: Abscess limb, Colonic abscess, Renal abscess, Subcutaneous abscess, Tooth abscess, Liver abscess, Perirectal abscess, Rectal abscess.

[b] Meningococcal infection includes the following group of PTs: Meningococcal infection, Meningococcal sepsis, Meningitis meningococcal.

[c] ADRs identified in postmarketing reports.

[d] Frequency cannot be estimated from the available postmarketing data.

Description of selected adverse reactions

In all clinical studies, the most serious adverse reaction was meningococcal sepsis which is a common presentation of meningococcal infections in patients treated with Soliris (see section 4.4).
Other cases of *Neisseria species* have been reported including sepsis with *Neisseria gonorrhoeae*, *Neisseria sicca/subflava, Neisseria spp* unspecified.

Antibodies to Soliris were detected in 2% of patients with PNH using an ELISA assay, 3% of patients with aHUS and 2% of patients with NMOSD using the ECL bridging format assay. In refractory gMG placebo-controlled studies, no antidrug antibodies were observed. As with all proteins there is a potential for immunogenicity.

Cases of haemolysis have been reported in the setting of missed or delayed Soliris dose in PNH clinical trials (see also Section 4.4).

Cases of thrombotic microangiopathy complication have been reported in the setting of missed or delayed Soliris dose in aHUS clinical trials (see also Section 4.4).

Paediatric population

In children and adolescent PNH patients (aged 11 years to less than 18 years) included in the paediatric PNH Study M07-005, the safety profile appeared similar to that observed in adult PNH patients. The most common adverse reaction reported in paediatric patients was headache.

In paediatric aHUS patients (aged 2 months to less than 18 years) included in the aHUS studies C08-002, C08-003, C09-001r and C10-003, the safety profile appeared similar to that observed in adult aHUS patients. The safety profiles in the different paediatric subsets of age appear similar.

In paediatric patients with refractory gMG (aged 12 to less than 18 years) included in Study ECU-MG-303, the safety profile appeared similar to that observed in adult patients with refractory gMG.

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

Elderly population
No overall differences in safety were reported between elderly (≥ 65 years) and younger refractory gMG patients (< 65 years) (see section 5.1).

Patients with other diseases
Safety Data from Other Clinical Studies
Supportive safety data were obtained in 12 completed clinical studies that included 934 patients exposed to eculizumab in other disease populations other than PNH, aHUS, refractory gMG or NMOSD. There was an un-vaccinated patient diagnosed with idiopathic membranous glomerulonephropathy who experienced meningococcal meningitis. Adverse reactions reported in patients with disease other than PNH, aHUS, refractory gMG or NMOSD were similar to those reported in patients with PNH, aHUS, refractory gMG or NMOSD (see Table 1 above). No specific adverse reactions have emerged from these clinical studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

No case of overdose has been reported in any of the clinical studies.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Complement Inhibitors, ATC code: L04AJ01

Soliris is a recombinant humanised monoclonal $IgG_{2/4k}$ 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 148 kDa.

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.

Mechanism of action

Eculizumab, the active ingredient in Soliris, is a terminal complement inhibitor 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. Eculizumab preserves the early components of complement activation that are essential for opsonization of microorganisms and clearance of immune complexes.

In PNH patients, uncontrolled terminal complement activation and the resulting complement-mediated intravascular haemolysis are blocked with Soliris treatment.
In most PNH patients, eculizumab serum concentrations of approximately 35 microgram/mL are sufficient for essentially complete inhibition of terminal complement-mediated intravascular haemolysis.
In PNH, chronic administration of Soliris resulted in a rapid and sustained reduction in complement-mediated haemolytic activity.

In aHUS patients, uncontrolled terminal complement activation and the resulting complement-mediated thrombotic microangiopathy are blocked with Soliris treatment.
All patients treated with Soliris, when administered as recommended, demonstrated rapid and sustained reduction in terminal complement activity. In all aHUS patients, eculizumab serum concentrations of approximately 50 - 100 microgram/mL are sufficient for essentially complete inhibition of terminal complement activity.
In aHUS, chronic administration of Soliris resulted in a rapid and sustained reduction in complement-mediated thrombotic microangiopathy.

In refractory gMG patients, uncontrolled terminal complement activation causes membrane attack complex (MAC) dependent lysis and C5a-dependent inflammation at the Neuromuscular Junction (NMJ) leading to failure of neuromuscular transmission. Chronic administration of Soliris results in immediate, complete, and sustained inhibition of terminal complement activity (eculizumab serum concentrations ≥ 116 microgram/ml).

In patients with NMOSD, uncontrolled terminal complement activation caused by autoantibodies against AQP4 leads to the formation of the MAC and C5a-dependent inflammation which results in astrocyte necrosis and increased permeability of the blood brain barrier, as well as death of the surrounding oligodendrocytes and neurons. Chronic administration of Soliris results in immediate, complete, and sustained inhibition of terminal complement activity (eculizumab serum concentrations ≥ 116 microgram/ml).

Clinical efficacy and safety

Paroxysmal Nocturnal Haemoglobinuria

The safety and efficacy of Soliris in PNH patients with haemolysis were assessed in a randomized, double-blind, placebo-controlled 26 week study (C04-001). PNH patients were also treated with Soliris in a single arm 52 week study (C04-002), and in a long term extension study (E05-001). Patients received meningococcal vaccination prior to receipt of Soliris. In all studies, the dose of eculizumab was 600 mg 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 (35 minutes ± 10 minutes). An observational non-interventional Registry in patients with PNH (M07-001) was also initiated to characterize the natural history of PNH in untreated patients and the clinical outcomes during Soliris treatment.

In study C04-001 (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/microliter 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 haemoglobin concentration (the "set-point") which would define each patient's haemoglobin stabilization and transfusion outcomes. The haemoglobin 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 haemoglobin stabilization (patients who maintained a haemoglobin concentration above the haemoglobin 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. Haemolysis 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 2).

In the non-controlled study C04-002 (SHEPHERD), PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter 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 2.

Table 2: Patient Demographics and Characteristics in C04-001 and C04-002

Parameter	C04-001		C04-002
	Placebo N = 44	**Soliris** N = 43	**Soliris** N = 97
Mean Age (SD)	38.4 (13.4)	42.1 (15.5)	41.1 (14.4)
Gender - Female (%)	29 (65.9)	23 (53.5)	49 (50.5)
History of Aplastic Anaemia 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)]	17.0 (13.5, 25.0)	18.0 (12.0, 24.0)	8.0 (4.0, 24.0)
Mean Hgb level (g/dL) at setpoint (SD)	7.7 (0.75)	7.8 (0.79)	N/A
Pre-treatment LDH levels (median, U/L)	2,234.5	2,032.0	2,051.0
Free Haemoglobin at baseline (median, mg/dL)	46.2	40.5	34.9

In TRIUMPH, study patients treated with Soliris had significantly reduced ($p< 0.001$) haemolysis resulting in improvements in anaemia as indicated by increased haemoglobin stabilization and reduced need for RBC transfusions compared to placebo treated patients (see Table 3). These effects were seen among patients within each of the three pre-study RBC transfusion strata (4 - 14 units; 15 - 25 units; > 25 units). After 3 weeks of Soliris treatment, 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 study, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular haemolysis, as measured by serum LDH levels, was sustained for the treatment period and resulted in increased transfusion avoidance, a reduced need for RBC transfusion and less fatigue. See Table 3.

Table 3: Efficacy Outcomes in C04-001 and C04-002

	C04-001			C04-002*	
	Placebo N = 44	**Soliris** N = 43	**P – Value**	**Soliris** N = 97	**P – Value**
Percentage of patients with stabilized Haemoglobin levels at end of study	0	49	< 0.001	N/A	
PRBC transfused during treatment (median)	10	0	< 0.001	0	< 0.001
Transfusion Avoidance during treatment (%)	0	51	< 0.001	51	< 0.001
LDH levels at end of study (median, U/L)	2,167	239	< 0.001	269	< 0.001
LDH AUC at end of study (median, U/L x Day)	411,822	58,587	< 0.001	-632,264	< 0.001
Free Haemoglobin at end of study (median, mg/dL)	62	5	< 0.001	5	< 0.001
FACIT-Fatigue (effect size)		1.12	< 0.001	1.14	< 0.001

* Results from study C04-002 refer to pre- versus post-treatment comparisons.

From the 195 patients that originated in C04-001, C04-002 and other initial studies, Soliris-treated PNH patients were enrolled in a long term extension study (E05-001). All patients sustained a reduction in intravascular haemolysis 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. However, this finding was shown in non-controlled clinical trials.

The PNH registry (M07-001) was used to evaluate the efficacy of Soliris in PNH patients with no history of RBC transfusion. These patients had high disease activity as defined by elevated haemolysis (LDH ≥1.5x ULN) and the presence of related clinical symptom(s): fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin <100 g/L), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction.

In the PNH Registry, patients treated with Soliris were observed to have a reduction in haemolysis and associated symptoms. At 6 months, patients treated with Soliris with no history of RBC transfusion had significantly ($p<0.001$) reduced LDH levels (median LDH of 305 U/L; Table 4). Furthermore, 74% of the patients without a history of transfusion and treated with Soliris experienced clinically meaningful improvements in FACIT-Fatigue score (i.e., increase by 4 points or more) and 84% in EORTC fatigue score (i.e., decrease by 10 points or more).

Table 4: Efficacy Outcomes (LDH level and FACIT-Fatigue) in Patients with PNH with No History of Transfusion in M07-001

	M07-001
Parameter	**Soliris No transfusion**
LDH level at baseline (median , U/L)	N=43 1447
LDH level at 6 months (median, U/L)	N=36 305
FACIT-Fatigue score at baseline (median)	N=25 32
FACIT-Fatigue score at last available assessment (median)	N=31 44

FACIT-Fatigue is measured on a scale of 0-52, with higher values indicating less fatigue.

Atypical Haemolytic Uremic Syndrome

Data from 100 patients in four prospective controlled studies, three in adult and adolescent patients (C08-002A/B, C08-003A/B, C10-004), one in paediatric and adolescent patients (C10-003) and 30 patients in one retrospective study (C09-001r) were used to evaluate the efficacy of Soliris in the treatment of aHUS.

Study C08-002A/B was a prospective, controlled, open-label study which accrued patients in the early phase of aHUS with evidence of clinical thrombotic microangiopathy manifestations with platelet count ≤ 150 x 10^9/L despite PE/PI, and LDH and serum creatinine above upper limits of normal. Study C08-003A/B was a prospective, controlled, open-label study which accrued patients with longer term aHUS without apparent evidence of clinical thrombotic microangiopathy manifestations and receiving chronic PE/PI (≥1 PE/PI treatment every two weeks and no more than 3 PE/PI treatments/week for at least 8 weeks before the first dose). Patients in both prospective studies were treated with Soliris for 26 weeks and most patients enrolled into a long-term, open-label extension study. All patients enrolled in both prospective studies had an ADAMTS-13 level above 5%.

Patients received meningococcal vaccination prior to receipt of Soliris or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. In all studies, the dose of Soliris in adult and adolescent aHUS patients was 900 mg every 7 ± 2 days for 4 weeks, followed by 1,200 mg 7 ± 2 days later, then 1,200 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 35 minutes. The dosing regimen in paediatric patients and adolescents weighing less than 40 kg was defined based on a pharmacokinetic (PK) simulation that identified the recommended dose and schedule based on body weight (see section 4.2).

Primary endpoints included platelet count change from baseline in study C08-002A/B and thrombotic microangiopathy (TMA) event-free status in study C08-003A/B. Additional endpoints included TMA intervention rate, haematologic normalization, complete TMA response, changes in LDH, renal function and quality of life. TMA-event free status was defined as the absence for at least 12 weeks of the following: decrease in platelet count of > 25% from baseline, PE/PI, and new dialysis. TMA interventions were defined as PE/PI or new dialysis. Haematologic normalization was defined as normalization of platelet counts and LDH levels sustained for ≥2 consecutive measurements for ≥4 weeks. Complete TMA response was defined as haematologic normalization and a ≥25% reduction in serum creatinine sustained in ≥ 2 consecutive measurements for ≥ 4 weeks.
Baseline characteristics are shown in Table 5.

Table 5: Patient Demographics and Characteristics in C08-002A/B and C08-003A/B

Parameter	C08-002A/B	C08-003A/B
	Soliris N = 17	**Soliris** N = 20
Time from first diagnosis until screening in months, median (min, max)	10 (0.26, 236)	48 (0.66, 286)
Time from current clinical TMA manifestation until screening in months, median (min, max)	< 1 (<1, 4)	9 (1, 45)
Number of PE/PI sessions for current clinical TMA manifestation, median (min, max)	17 (2, 37)	62 (20, 230)
Number of PE/PI sessions in 7 days prior to first dose of eculizumab, median (min, max)	6 (0, 7)	2 (1, 3)
Baseline platelet count ($\times 10^9$/L), mean (SD)	109 (32)	228 (78)
Baseline LDH (U/L), mean (SD)	323 (138)	223 (70)
Patients without identified mutation, n (%)	4 (24)	6 (30)

Patients in aHUS Study C08-002 A/B received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients continued to receive Soliris by enrolling into an extension study. In aHUS Study C08-002A/B, the median duration of Soliris therapy was approximately 100 weeks (range: 2 weeks to 145 weeks).
A reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Table 6 summarizes the efficacy results for aHUS Study C08-002A/B. All rates of efficacy endpoints improved or were maintained through 2 years of treatment. complete TMA response was maintained by all responders. When treatment was continued for more than 26 weeks, two additional patients achieved and maintained complete TMA response due to normalization of LDH (1 patient) and a decrease in serum creatinine (2 patients).
Renal function, as measured by eGFR, was improved and maintained during Soliris therapy. Four of the five patients who required dialysis at study entry were able to discontinue dialysis for the duration of Soliris treatment, and one patient developed a new dialysis requirement. Patients reported improved health-related quality of life (QoL).

In aHUS Study C08-002A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Patients in aHUS study C08-003A/B received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients continued to receive Soliris by enrolling into an extension study. In aHUS Study C08-003A/B, the median duration of Soliris therapy was approximately 114 weeks (range: 26 to 129 weeks). Table 6 summarizes the efficacy results for aHUS Study C08-003A/B.

In aHUS Study C08-003A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins. Reduction in terminal complement activity was observed in all patients after commencement of Soliris. All rates of efficacy endpoints improved or were maintained through 2 years of treatment. Complete TMA response was maintained by all responders. When treatment was continued for more than 26 weeks, six additional patients achieved and maintained complete TMA response due to a decrease in serum creatinine. No patient required new dialysis with Soliris. Renal function, as measured by median eGFR, increased during Soliris therapy.

Table 6: Efficacy Outcomes in Prospective aHUS Studies C08-002A/B and C08-003A/B

	C08-002A/B N=17		**C08-003A/B N=20**	
	At 26 weeks	At 2 years[1]	At 26 weeks	At 2 years[1]
Normalization of platelet count All patients, n (%) (95% CI) Patients with abnormal baseline, n/n (%)	 14 (82) (57-96) 13/15 (87)	 15 (88) (64-99) 13/15 (87)	 18 (90) (68-99) 1/3 (33)	 18 (90) (68-99) 1/3 (33)
TMA event-free status, n (%) (95% CI)	15 (88) (64-99)	15 (88) (64-99)	16 (80) (56-94)	19 (95) (75-99)
TMA intervention rate Daily pre-eculizumab rate, median (min, max) Daily during-eculizumab rate, median (min, max) *P*-value	 0.88 (0.04, 1.59) 0(0, 0.31) *P*<0.0001	 0.88 (0.04, 1.59) 0(0, 0.31) *P*<0.0001	 0.23 (0.05, 1.09) 0 *P* <0.0001	 0.23 (0.05, 1.09) 0 *P*<0.0001
CKD improvement by ≥1 stage, n (%) (95% CI)	10 (59) (33-82)	12 (71) (44-90)	7 (35) (15-59)	12 (60) (36-81)
eGFR change mL/min/1.73 m^2: median (range)	20 (-1, 98)	28 (3, 82)	5 (-1, 20)	11 (-42, 30)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%) (95% CI)	8 (47) (23-72)	10 (59) (33-82)	1 (5) (0-25)	8 (40) (19-64)
Change in Hgb > 20g/L, n (%) (95% CI)	11 (65) (38-86)[2]	13 (76) (50-93)	9 (45) (23-68)[3]	13 (65) (41-85)
Haematologic normalization, n (%) (95% CI)	13 (76) (50-93)	15 (88) (64-99)	18 (90) (68-99)	18 (90) (68-99)
Complete TMA response, n (%) (95% CI)	11(65) (38-86)	13(76) (50-93)	5 (25) (9-49)	11(55) (32-77)

[1] At data cut-off (20 April 2012).

[2] Study C08-002: 3 patients received ESA which was discontinued after eculizumab initiation.

[3] Study C08-003: 8 patients received ESA which was discontinued in 3 of them during eculizumab therapy.

aHUS Study C10-004 enrolled 41 patients who displayed signs of thrombotic microangiopathy (TMA). In order to qualify for enrolment, patients were required to have a platelet count < lower limit of normal range (LLN), evidence of haemolysis 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 aHUS Study C10-004 had an ADAMTS-13 level above 5%. 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 7 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS C10-004.

Table 7: Baseline Characteristics of Patients Enrolled in aHUS Study C10-004

Parameter	aHUS Study C10-004 N = 41
Time from aHUS diagnosis to first study dose (months), median (min, max)	0.79 (0.03, 311)
Time from current clinical TMA manifestation until first study dose (months), median (min, max)	0.52 (0.03, 19)
Baseline platelet count ($\times 10^9$/L), median (min, max)	125 (16, 332)
Baseline LDH (U/L), median (min, max)	375 (131, 3318)
Baseline eGFR (mL/min/1.73 m^2), median (min, max)	10 (6, 53)

Patients in aHUS Study C10-004 received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients elected to continue on chronic dosing.

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 aHUS C10-004, mean (±SD) platelet count 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]. Renal function, as measured by eGFR, was improved during Soliris therapy. Twenty of the 24 patients who required dialysis at baseline were able to discontinue dialysis during Soliris treatment. Table 8 summarizes the efficacy results for aHUS study C10-004.

Table 8: Efficacy Outcomes in Prospective aHUS Study C10-004

Efficacy Parameter	aHUS Study C10-004 **(N = 41)** At 26-weeks
Change in platelet count through week 26 (10^9/L)	111 (-122, 362)
Hematologic Normalization, n (%) Median duration of hematologic normalization, weeks (range) [1]	36 (88) 46 (10, 74)
Complete TMA response, n (%) Median duration of complete TMA response, weeks (range) [1]	23 (56) 42 (6, 74)
TMA Event-free Status, n (%) 95% CI	37 (90) 77; 97
Daily TMA Intervention Rate, median (range) Before eculizumab On eculizumab treatment	 0.63 (0, 1.38) 0 (0, 0.58)

[1] Through data cut-off (September 4, 2012), with median duration of Soliris therapy of 50 weeks (range: 13 weeks to 86 weeks).

Longer term treatment with Soliris (median 52 weeks ranging from 15 to 126 weeks) was associated with an increased rate of clinically meaningful improvements in adult patients with aHUS. When Soliris treatment was continued for more than 26 weeks, three additional patients (63% of patients in total) achieved complete TMA response and four additional patients (98% of patients in total) achieved hematologic normalization. At the last evaluation, 25 of 41 patients (61%) achieved eGFR improvement of ≥ 15 mL/min/1.73 m^2 from baseline.

Refractory Generalized Myasthenia Gravis

Data from 139 patients in two prospective controlled studies (Studies C08-001 and ECU-MG-301), and one open-label extension trial (Study ECU-MG-302) were used to evaluate the efficacy of Soliris in the treatment of patients with refractory gMG.

Study ECU-MG-301 (REGAIN) was a 26-week double-blind, randomized, placebo-controlled, multi-center Phase 3 study of Soliris in patients who had failed previous therapies and remain symptomatic. One hundred and eighteen (118) of the 125 (94%) patients completed the 26-week treatment period and 117 (94%) patients subsequently enrolled in Study ECU-MG-302, an open-label, multi-center long-term safety and efficacy extension study in which all patients received Soliris treatment.

In Study ECU-MG-301, gMG patients with a positive serologic test for anti-AChR antibodies, MGFA (Myasthenia Gravis Foundation of America) clinical classification class II to IV and MG-ADL total score ≥6 were randomized to either Soliris (n = 62) or placebo (n = 63). All patients included in the trial were refractory gMG patients and met the following predefined criteria:

1) Failed treatment for at least one year with 2 or more immunosuppressant therapies (either in combination or as monotherapy), i.e., patients continued to have impairment in activities of daily living despite immunosuppressant therapies.

OR

2) Failed at least one immunosuppressant therapy and required chronic plasma exchange or IVIg to control symptoms, i.e., patients require PE or IVIg on a regular basis for the management of muscle weakness at least every 3 months over previous 12 months.

Patients received meningococcal vaccination prior to initiating treatment with Soliris or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. In Studies ECU-MG-301 and ECU-MG-302, the dose of Soliris in adult refractory gMG patients was 900 mg every 7 ± 2 days for 4 weeks, followed by 1,200 mg at week 5± 2 days, then 1,200 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 35 minutes.

Table 9 presents the baseline characteristics of the refractory gMG patients enrolled in Study ECU-MG-301.

Table 9: Patient Demographic and Characteristics in Study ECU-MG-301

	Soliris (n=62)	Placebo (n=63)
Age at MG Diagnosis (years), Mean (min, max)	38.0 (5.9, 70.8)	38.1 (7.7, 78.0)
Female, n (%)	41 (66.1)	41 (65.1)
Duration of MG (years), Mean (min, max)	9.9 (1.3, 29.7)	9.2 (1.0, 33.8)
Baseline MG-ADL Score		
Mean (SD)	10.5 (3.06)	9.9 (2.58)
Median	10.0	9.0
Baseline QMG Score		
Mean (SD)	17.3 (5.10)	16.9 (5.56)
Median	17.0	16.0
≥3 Prior Immunosuppressive Therapies* since diagnosis, n (%)	31 (50.0)	34 (54.0)
Number of patients with prior exacerbations since diagnosis, n (%)	46 (74.2)	52 (82.5)
Number of patients with prior MG crisis since diagnosis, n (%)	13 (21.0)	10 (15.9)
Any prior ventilator support since diagnosis, n (%)	15 (24.2)	14 (22.2)
Any prior intubation since diagnosis (MGFA class V), n (%)	11 (17.7)	9 (14.3)

* Immunosuppressant's included, but are not limited to, corticosteroids, azathioprine, mycophenolate, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide.

The primary endpoint for Study ECU-MG-301 was the change from baseline in the MG Activities of Daily Living Profile (MG-ADL – a patient reported outcome measure validated in gMG) total score at Week 26. The primary analysis of the MG-ADL was a Worst-Rank ANCOVA with a mean rank of 56.6 for Soliris and 68.3 for placebo, based on 125 study patients (p=0.0698).

The key secondary endpoint was the change from baseline in the Quantitative MG Scoring System (QMG – a physician reported outcome measure validated in gMG) total score at week 26. The primary analysis of the QMG was a Worst-Rank ANCOVA with a mean rank of 54.7 for Soliris and 70.7 for placebo, based on 125 study patients (p=0.0129).

Efficacy outcomes for the pre-specified repeated measures analyses of the primary and secondary endpoints are provided in Table 10.

Table 10: ECU-MG-301 Efficacy Outcomes Change from Baseline to Week 26

Efficacy Endpoints: Total score change from baseline at week 26	Soliris (n=62) (SEM)	Placebo (n=63) (SEM)	Soliris change relative to placebo – LS Mean Difference (95% CI)	p-value (using repeated measures analysis)
MG-ADL	-4.2 (0.49)	-2.3 (0.48)	-1.9 (-3.3, -0.6)	0.0058
QMG	-4.6 (0.60)	-1.6 (0.59)	-3.0 (-4.6, -1.3)	0.0006
MGC	-8.1 (0.96)	-4.8 (0.94)	-3.4 (-6.0, -0.7)	0.0134
MG-QoL-15	-12.6 (1.52)	-5.4 (1.49)	-7.2 (-11.5, -3.0)	0.0010

SEM= Standard Error of the Mean, CI= Confidence Interval, MGC= Myasthenia Gravis Composite, MG-QoL15= Myasthenia Gravis Quality of Life 15

In Study ECU-MG-301, a clinical responder in the MG-ADL total score was defined as having at least a 3-point improvement. The proportion of clinical responders at week 26 with no rescue therapy was 59.7% on Soliris compared with 39.7% on placebo (p=0.0229).
In Study ECU-MG-301, a clinical responder in the QMG total score was defined as having at least a 5-point improvement. The proportion of clinical responders at week 26 with no rescue therapy was 45.2% on Soliris compared with 19% on placebo (p=0.0018).

Table 11 presents an overview of the patients reporting clinical deterioration and patients requiring rescue therapy over the 26 weeks.

Table 11: Clinical deterioration and rescue therapy in ECU-MG-301

Variable	Statistic	Placebo (N=63)	Soliris (N=62)
Total number of patients reporting clinical deterioration	n (%)	15 (23.8)	6 (9.7)
Total number of patients requiring rescue therapy	n (%)	12 (19.0)	6 (9.7)

Of the 125 patients enrolled in ECU-MG-301, 117 patients subsequently enrolled in a long-term extension study (Study ECU-MG-302), in which all received Soliris. Patients that were previously treated with Soliris in Study ECU-MG-301 continued to demonstrate a sustained effect of Soliris on all measures (MG-ADL, QMG, MGC and MG-QoL15) over an additional 130 weeks of treatment with eculizumab in Study ECU-MG-302. For patients who received placebo in Study ECU-MG-301 (placebo/eculizumab arm of Study ECU-MG-302), improvement occurred after initiating treatment with eculizumab and was maintained for more than 130 weeks in Study ECU-MG-302. Figure 1 presents the change from baseline in both MG-ADL (A) and QMG (B) after 26 weeks of treatment in Study ECU-MG-301 and after 130 weeks of treatment (n = 80 patients) in Study ECU-MG-302.

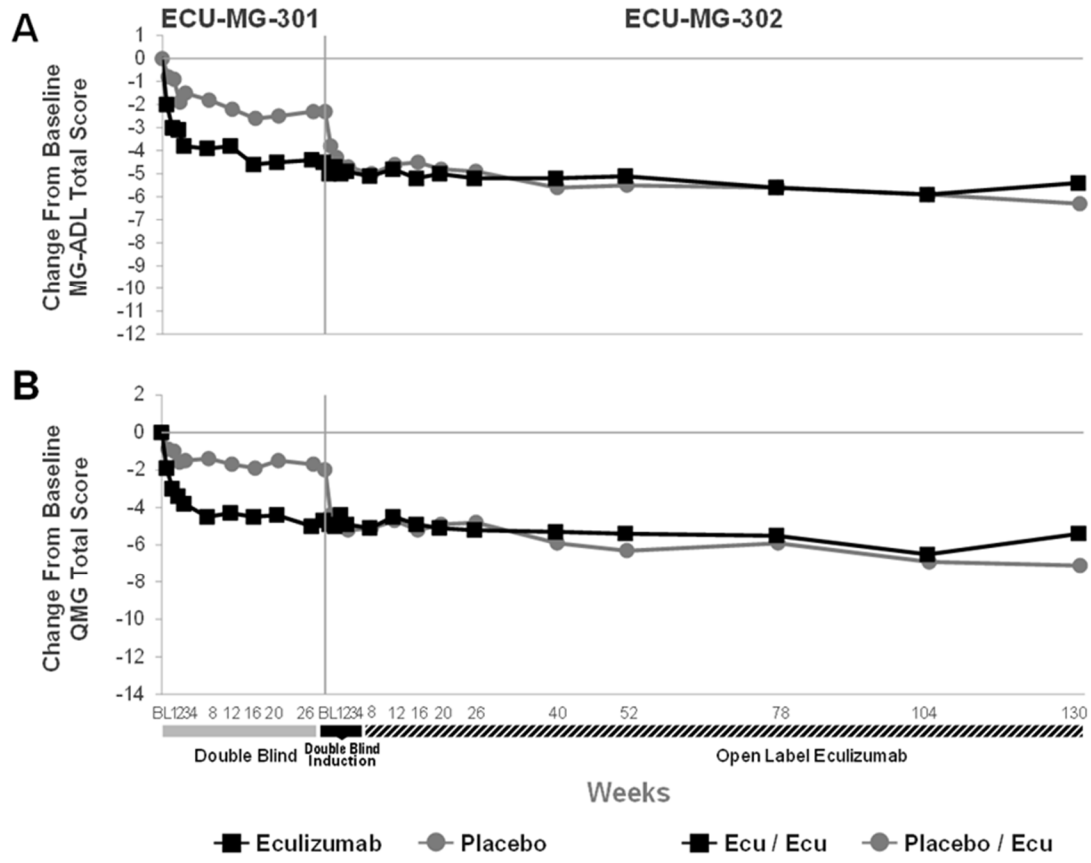

Figure 1: Mean changes from baseline in MG-ADL (1A) and QMG (1B) over Studies ECU-MG-301 and ECU-MG-302

In Study ECU-MG-302, physicians had the option to adjust background immunosuppressant therapies. In this setting, 65.0% of patients decreased their daily dose of at least 1 immunosuppressive therapy (IST); 43.6% of patients stopped an existing IST. The most common reason for change in IST therapy was improvement in MG symptoms.

Twenty-two (22) (17.6%) elderly refractory gMG patients (> 65 years of age) were treated with Soliris in the clinical trials. No substantial differences were seen in safety and efficacy related to age.

Neuromyelitis Optica Spectrum Disorder

Data from 143 patients in one controlled study (Study ECU-NMO-301) and from 119 patients who continued in one open-label extension trial (Study ECU-NMO-302) were used to evaluate the efficacy and safety of Soliris in the treatment of patients with NMOSD.

Study ECU-NMO-301 was a double-blind, randomized, placebo-controlled, multi-center, Phase 3 study of Soliris in patients with NMOSD.

In Study ECU-NMO-301, patients with NMOSD with a positive serologic test for anti-AQP4 antibodies, a history of at least 2 relapses in last 12 months or 3 relapses in the last 24 months with at least 1 relapse in the 12 months prior to screening and an Expanded Disability Status Scale (EDSS) score ≤ 7, were randomized 2:1 to either Soliris (n = 96) or placebo (n = 47). Patients were permitted to receive background immunosuppressant therapies at stable dose during the study, with the exclusion of rituximab and mitoxantrone.

Patients either received meningococcal vaccination at least 2 weeks prior to initiating treatment with Soliris or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. In the eculizumab NMOSD clinical development program, the dose of Soliris in adult patients with

NMOSD was 900 mg every 7 ± 2 days for 4 weeks, followed by 1,200 mg at week 5 ± 2 days, then 1,200 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 35 minutes.

The majority (90.9%) of patients were female. Approximately half were white (49.0%). The median age at first dose of study drug was 45 years.

Table 12: Patient Disease History and Baseline Characteristics in Study ECU-NMO-301

Variable	Statistic	Placebo (N = 47)	Eculizumab (N = 96)	Total (N = 143)
NMOSD History				
Age at NMOSD Initial Clinical Presentation (years)	Mean (SD)	38.5 (14.98)	35.8 (14.03)	36.6 (14.35)
	Median	38.0	35.5	36.0
	Min, Max	12, 73	5, 66	5, 73
Time from NMOSD initial clinical presentation to first dose of study drug (years)	Mean (SD)	6.601 (6.5863)	8.156 (8.5792)	7.645 (7.9894)
	Median	3.760	5.030	4.800
	Min, Max	0.51, 29.10	0.41, 44.85	0.41, 44.85
Historical Annualized Relapse Rate within 24 months prior to Screening	Mean (SD)	2.07 (1.037)	1.94 (0.896)	1.99 (0.943)
	Median	1.92	1.85	1.92
	Min, Max	1.0, 6.4	1.0, 5.7	1.0, 6.4
Baseline characteristics				
Baseline EDSS score	Mean (SD)	4.26 (1.510)	4.15 (1.646)	4.18 (1.598)
	Median	4.00	4.00	4.00
	Min, Max	1.0, 6.5	1.0, 7.0	1.0, 7.0
No IST usage at baseline	n (%)	13 (27.7)	21 (21.9)	34 (23.8)

Abbreviations: ARR = adjudicated relapse rate; EDSS = Expanded Disability Status Scale; IST = immunosupressant therapy; Max = maximum; Min = minimum; NMOSD = neuromyelitis optica spectrum disorder; SD = standard deviation.

The primary endpoint for Study ECU-NMO-301 was the time to first on-trial relapse as adjudicated by an independent committee who were blinded to treatment. A significant effect on the time to first adjudicated On-trial Relapse was observed for eculizumab compared with placebo (relative risk reduction 94%; hazard ratio 0.058; p<0.0001) (Figure 2). Soliris-treated patients experienced similar improvement in time to first adjudicated on-trial relapse with or without concomitant IST treatment.

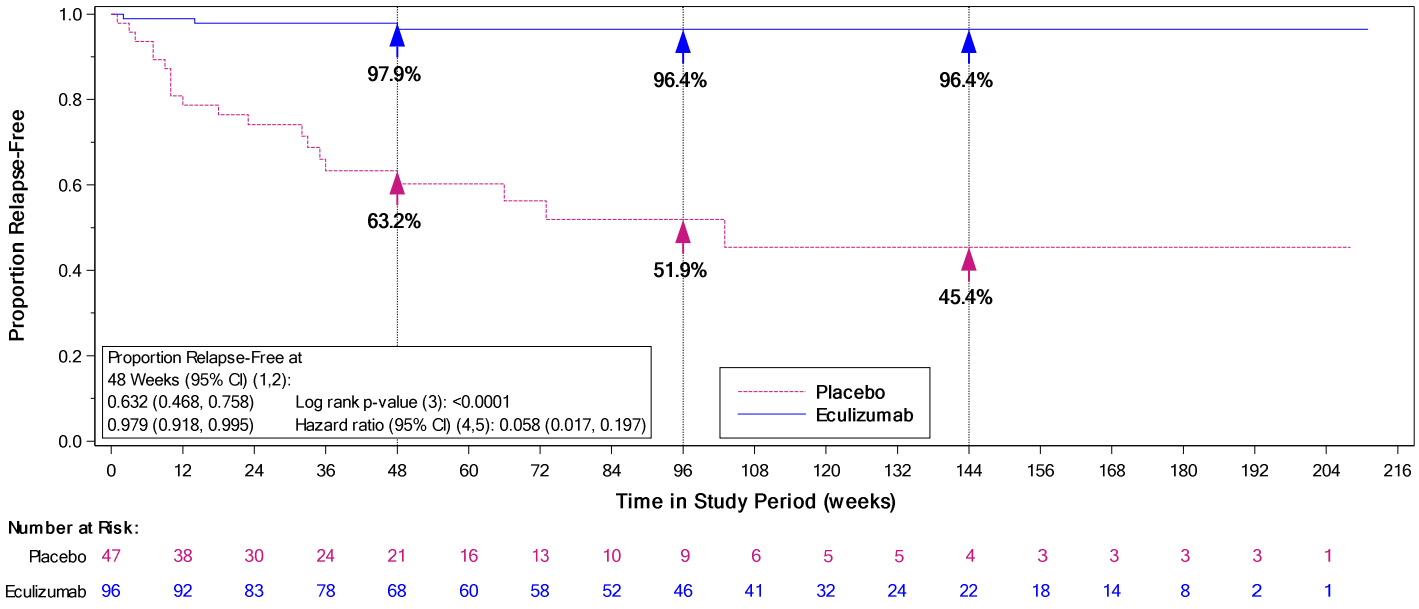

Figure 2: Kaplan-Meier Survival Estimates for Time to First Adjudicated On-Trial Relapse in Study ECU-NMO-301 – Full Analysis Set

Note: Patients who did not experience an adjudicated On-trial Relapse were censored at the end of the Study Period. Stratified analyses are based on 4 randomization strata:
(i) low EDSS at randomization (≤ 2.0), (ii) high EDSS (≥ 2.5 to ≤ 7) and treatment naive at randomization, (iii) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomization, (iv) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomization.
1 Based on the Kaplan-Meier product limit method.
2 Based on the complementary log-log transformation.
3 Based on a stratified log-rank test.
4 Based on a stratified Cox proportional hazards model.
5 Wald confidence interval.
Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; IST = immunosuppressive therapy.

The adjudicated on-trial annualized relapse rate (ARR) ratio (95% CI) for eculizumab compared with placebo was 0.045 (0.013, 0.151), representing a 95.5% relative reduction in adjudicated On-trial ARR for patients treated with eculizumab compared with placebo (p<0.0001) (Table 13).

Table 13: Adjudicated On-trial Annualized Relapse Rate in Study ECU-NMO-301 – Full Analysis Set

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

[a] Based on a Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to screening.
Abbreviations: ARR = annualized relapse rate; CI = confidence interval.

Compared to placebo-treated patients, Soliris-treated patients had reduced annualized rates of hospitalizations (0.04 for Soliris versus 0.31 for placebo), of intravenous corticosteroid administrations to treat acute relapses (0.07 for Soliris versus 0.42 for placebo), and of plasma exchange treatments (0.02 for Soliris versus 0.19 for placebo).

The distribution of changes from Baseline to End of Study on other secondary endpoints favoured eculizumab treatment over placebo across all neurologic disability (EDSS score [p=0.0597] and mRS [nominal p=0.0154]), functional disability (HAI [nominal p=0.0002]) and quality of life (EQ-5D VAS [nominal p=0.0309] and EQ-5D Index [nominal p= 0.0077]) measures.

The final analysis of Study ECU-NMO-302 demonstrates a significant and clinically meaningful reduction in On-trial ARR (as determined by the treating physician) on eculizumab treatment, based on the median (min, max) change (-1.825 [-6.38, 1.02], p<0.0001) from historical ARR (24 months prior to screening in Study ECU-NMO-301).

In Study ECU-NMO-302, physicians had the option to adjust background immunosuppressant therapies. In this setting, the most common change in immunosuppressant therapy was decreased immunosuppressant therapy dose, which occurred in 21.0% of patients. Further, 15.1% of patients stopped an existing IST.

Soliris (eculizumab) has not been studied for the treatment of acute relapses in NMOSD patients.

Paediatric population

Paroxysmal Nocturnal Haemoglobinuria

A total of 7 PNH paediatric patients, with a median weight of 57.2 kg (range of 48.6 to 69.8 kg) and aged from 11 to 17 years (median age: 15.6 years), received Soliris in study M07-005.

Treatment with eculizumab at the proposed dosing regimen in the paediatric population was associated with a reduction of intravascular haemolysis as measured by serum LDH level. It also resulted in a marked decrease or elimination of blood transfusions, and a trend towards an overall improvement in general function. The efficacy of eculizumab treatment in paediatric PNH patients appears to be consistent with that observed in adult PNH patients enrolled in PNH pivotal Studies (C04-001 and C04-002) (Table 3 and 14).

Table 14: Efficacy Outcomes in Paediatric PNH Study M07-005

		P – Value	
	Mean (SD)	Wilcoxon Signed Rank	Paired t-test
Change from baseline at 12 weeks of LDH value (U/L)	-771 (914)	0.0156	0.0336
LDH AUC (U/L x Day)	-60,634 (72,916)	0.0156	0.0350
Change from baseline at 12 weeks in Plasma Free Haemoglobin (mg/dL)	-10.3 (21.13)	0.2188	0.1232
Change from baseline Type III RBC clone size (Percent of aberrant cells)	1.80 (358.1)		
Change from baseline at 12 weeks of PedsQL™4.0 Generic Core scale (patients)	10.5 (6.66)	0.1250	0.0256
Change from baseline at 12 weeks of PedsQL™4.0 Generic Core scale (parents)	11.3 (8.5)	0.2500	0.0737
Change from baseline at 12 weeks of PedsQL™ Multidimensional Fatigue (patients)	0.8 (21.39)	0.6250	0.4687
Change from baseline at 12 weeks of PedsQL™ Multidimensional Fatigue (parents)	5.5 (0.71)	0.5000	0.0289

Atypical Haemolytic Uremic Syndrome

A total of 15 paediatric patients (aged 2 months to 12 years) received Soliris in aHUS Study C09-001r. Forty seven percent of patients had an identified complement regulatory factor mutation or auto-antibody. The median time from aHUS diagnosis to first dose of Soliris was 14 months (range <1, 110 months). The median time from current thrombotic microangiopathy manifestation to first dose of Soliris was 1 month (range <1 to 16 months). The median duration of Soliris therapy was 16 weeks (range 4 to 70 weeks) for children < 2 years of age (n=5) and 31 weeks (range 19 to 63 weeks) for children 2 to <12 years of age (n=10).

Overall, the efficacy results for these paediatric patients appeared consistent with what was observed in patients enrolled in aHUS pivotal Studies C08-002 and C08-003 (Table 6). No paediatric patient required new dialysis during treatment with Soliris.

Table 15: Efficacy Results in Paediatric Patients Enrolled in aHUS C09-001r

Efficacy Parameter	<2 years (n=5)	2 to <12 years (n=10)	<12 years (n=15)
Patients with platelet count normalization, n (%)	4 (80)	10 (100)	14 (93)
Complete TMA response, n (%)	2 (40)	5 (50)	7 (50)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 1 (0, 2) <1 (0, <1)	 <1 (0.07, 1.46) 0 (0, <1)	 <1 (0, 2) 0 (0, <1)
Patients with eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	2 (40)	6 (60)	8 (53)

In paediatric patients with shorter duration of current severe clinical thrombotic microangiopathy (TMA) manifestation prior to eculizumab, there was TMA control and improvement of renal function with eculizumab treatment (Table 15).
In paediatric patients with longer duration of current severe clinical TMA manifestation prior to eculizumab, there was TMA control with eculizumab treatment. However, renal function was not changed due to prior irreversible kidney damage (Table 16).

Table 16: Efficacy Outcomes in Paediatric Patients in Study C09-001r according to duration of current severe clinical thrombotic microangiopathy (TMA) manifestation

	Duration of current severe clinical TMA manifestation	
	< 2 months N=10 (%)	**>2 months N=5 (%)**
Platelet count normalization	9 (90)	5 (100)
TMA event-free status	8 (80)	3 (60)
Complete TMA response	7 (70)	0
eGFR improvement ≥ 15 mL/min/1.73 m^2	7 (70)	0*

*One patient achieved eGFR improvement after renal transplant.

A total of 22 paediatric and adolescents patients (aged 5 months to 17 years) received Soliris in aHUS Study C10-003.

In Study C10-003, patients who enrolled in the study were required to have a platelet count < lower limit of normal range (LLN), evidence of haemolysis such as an elevation in serum LDH above the upper limits of normal and serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median patient age was 6.5 years (range: 5 months to 17 years). Patients enrolled in aHUS C10-003 had an ADAMTS-13 level above 5%. 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 17 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study C10-003.

Table 17: Baseline Characteristics of Paediatric and Adolescents Patients Enrolled in aHUS Study C10-003

Parameter	1 month to <12 years (N = 18)	All Patients (N = 22)
Time from aHUS diagnosis until first study dose (months) median (min, max)	0.51 (0.03, 58)	0.56 (0.03, 191)
Time from current clinical TMA manifestation until first study dose (months), median (min, max)	0.23 (0.03, 4)	0.20 (0.03, 4)
Baseline platelet count (x 10^9/L), median (min, max)	110 (19, 146)	91 (19, 146)
Baseline LDH (U/L) median (min, max)	1510 (282, 7164)	1244 (282, 7164)
Baseline eGFR (mL/min/1.73 m^2), median (min, max)	22 (10, 105)	22 (10, 105)

Patients in aHUS C10-003 received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients elected to continue on chronic dosing.
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 (±SD) platelet count 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). Renal function, as measured by eGFR, was improved during Soliris therapy. Nine of the 11 patients who required dialysis at baseline no longer required dialysis after Study Day 15 of eculizumab treatment. Responses were similar across all ages from 5 months to 17 years of age. In aHUS C10-003, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 18 summarizes the efficacy results for aHUS C10-003.

Table 18: Efficacy Outcomes in Prospective aHUS Study C10-003

Efficacy Parameter	1 month to <12 years (N = 18) at 26-weeks	All Patients (N = 22) at 26-weeks
Complete Hematologic Normalization, n (%)	14 (78)	18 (82)
Median Duration of complete hematologic normalization, weeks (range)[1]	35 (13, 78)	35 (13, 78)
Complete TMA response, n (%)	11 (61)	14 (64)
Median Duration of complete TMA response, weeks (range)[1]	40 (13, 78)	37 (13, 78)
TMA Event-Free Status, n (%)	17 (94)	21 (96)
95% CI	NA	77; 99
Daily TMA Intervention rate, median (range)		0.4 (0, 1.7)
Before eculizumab treatment, median	NA	
On eculizumab treatment, median	NA	0 (0, 1.01)

Efficacy Parameter	1 month to <12 years (N = 18) at 26-weeks	All Patients (N = 22) at 26-weeks
eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	16 (89)	19 (86)
Change in eGFR (≥15 mL/min/1.73 m^2) at 26 weeks, median (range)	64 (0,146)	58 (0, 146)
CKD improvement by ≥1 stage, n (%)	14/16 (88)	17/20 (85)
PE/PI Event-Free Status, n (%)	16 (89)	20 (91)
New Dialysis Event-Free Status, n (%)	18 (100)	22 (100)
95% CI	NA	85;100

[1] Through data cut-off (October 12, 2012), with median duration of Soliris therapy of 44 weeks (range: 1 dose to 88 weeks).

Longer term treatment with Soliris (median 55 weeks ranging from 1 day to 107 weeks) was associated with an increased rate of clinically meaningful improvements in paediatric and adolescent patients with aHUS. When Soliris treatment was continued for more than 26 weeks, one additional patient (68% of patients in total) achieved Complete TMA Response and two additional patients (91% of patients in total) achieved hematologic normalization. At the last evaluation, 19 of 22 patients (86%) achieved eGFR improvement of ≥ 15 mL/min/1.73 m^2 from baseline. No patient required new dialysis with Soliris.

Refractory Generalized Myasthenia Gravis

A total of 11 paediatric patients with refractory gMG received Soliris in study ECU-MG-303. The median (range) body weight of the treated patients was 59.7 kg (37.2 to 91.2 kg) at baseline, and the median (range) age of 15 years (12 to 17 years) at screening. All patients included in the study were patients with refractory gMG who had one or more of the following:

1. Failed treatment ≥ 1 year with at least 1 IST, defined as: (i) Persistent weakness with impairment of activities of daily living, or (ii) Myasthenia gravis exacerbation and/or crisis while on treatment, or (iii) Intolerance to ISTs due to side effect or comorbid condition(s).
2. Require maintenance PE or IVIg to control symptoms (ie, patients who require PE or IVIg on a regular basis for the management of muscle weakness at least every 3 months over the last 12 months prior to screening).

The baseline characteristics of the paediatric patients with refractory gMG enrolled in study ECU-MG-303 are outlined in Table 19.

Table 19: Patient Demographic and Characteristics in Study ECU-MG-303

	Eculizumab (n = 11)	
Female	n (%)	9 (81.8%)
Duration of MG (time from MG diagnosis to first study drug date [years])	Mean (SD) Median (min, max)	3.99 (2.909) 2.90 (0.1, 8.8)
Baseline MG-ADL total score	Mean (SD) Median (min, max)	5.0 (5.25) 4.0 (0, 19)
Baseline QMG total score	Mean (SD) Median (min, max)	16.7 (5.64) 15.0 (10, 28)

Table 19: Patient Demographic and Characteristics in Study ECU-MG-303

	Eculizumab (n = 11)	
MGFA classification at Screening IIa IIb IIIa IIIb IVa IVb	n (%)	 2 (18.2) 3 (27.3) 3 (27.3) 0 3 (27.3) 0
Patients with prior MG exacerbation including MG crisis since diagnosis No Yes Exacerbation MG crisis	n (%)	 4 (36.4) 7 (63.6) 6 (54.5) 3 (27.3)
Chronic IVIg therapy at study entry Yes No	n (%)	 6 (54.5) 5 (45.5)
Number of immunosuppressant therapies at Baseline 0 1 2	n (%)	 2 (18.2) 4 (36.4) 5 (45.5)
Patients with any immunosuppressant therapies[a] at Baseline n (%) Corticosteroids Azathioprine Mycophenolate mofetil Tacrolimus	n (%)	 8 (72.7) 1 (9.1) 2 (18.2) 3 (27.3)

[a]Immunosuppressant therapies included corticosteroids, azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus. No patient received cyclosporine, cyclophosphamide, or methotrexate at Baseline.

Abbreviations: IVIg = intravenous immunoglobulin; max = maximum; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGFA = Myasthenia Gravis Foundation of America; min = minimum; QMG = Quantitative Myasthenia Gravis score for disease severity; SD = standard deviation

The primary endpoint of study ECU-MG-303 was the change from baseline in the QMG total score over time regardless of rescue therapy. Paediatric patients treated with Soliris demonstrated a statistically significant improvement from baseline in QMG total score throughout the Primary Evaluation Treatment Period of 26 weeks. The results for the primary and main secondary endpoint in study ECU-MG-303 are included in Table 20.

The efficacy of Soliris treatment in paediatric patients with refractory gMG was consistent with that observed in adult patients with refractory gMG enrolled in the pivotal study ECU-MG-301 (Table 10).

Table 20: Efficacy Outcomes in Study ECU-MG-303

Efficacy Endpoints: Total Score Change from Baseline at Week 26	**LS Mean (SEM) 95% CI**
QMG	-5.8 (1.2) (-8.40, -3.13) n[a] = 10
MG-ADL total score	-2.3 (0.6) (-3.63, -1.03) n[a] = 10
MGC total score	-8.8 (1.9) (-12.92, -4.70) n[a] = 10

[a]n is the number of patients at Week 26

Abbreviations: CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis Composite; QMG = Quantitative Myasthenia Gravis score for disease severity; SEM = standard error of mean; VAS = visual analog scale

In study ECU-MG-303, a clinical responder in the QMG and MG-ADL total scores was defined as having at least a 5-point improvement and 3-point improvement from baseline, respectively. The proportion of clinical responders in the QMG and MG-ADL total scores at Week 26 regardless of rescue therapy was 70% and 50%, respectively. The 10 patients who completed their visit at Week 26 achieved improved status of MGFA Post-Interventional Status (MGFA-PIS) at Week 26. Seven (70%) patients achieved minimal manifestation of refractory gMG at Week 26.

An event of clinical deterioration (MG crisis) was observed in 1 patient (9.1%) during the Primary Evaluation Treatment Period requiring rescue therapy (PE) which was administered between the Week 22 and Week 24 study visits. As a result and due to physician decision, this patient did not have QMG, MG-ADL or other efficacy assessments after Week 20 and did not enter the extension period. Another 2 patients experienced clinical deteriorations (MG crisis) during the Extension Period requiring rescue therapy (PE and IVIg for clinical deterioration in one case and IVIg and 2 supplemental treatments of eculizumab in the second case).

During the entire study period in paediatric patients with refractory gMG (study ECU-MG-303), 4 out of 11 patients (36.4%) decreased their daily dose of IST or anticholinesterase therapy due to improved MG symptoms. An additional patient (9.1%) decreased and subsequently increased their daily dose during the Extension Period due to improved and worsened MG symptoms respectively and 1 patient started a new corticosteroid treatment due to worsened MG symptoms.

Long-term efficacy

All patients who completed the Primary Treatment Period (N=10) entered the Extension Period of up to 208 weeks of treatment. Only two patients completed the Extension Period. Eight participants discontinued the study during the Extension Period including 4 participants transitioned to either commercially available Soliris or Ultomiris or transferred to another ongoing Ultomiris paediatric study.

Patients consistently maintained the response through the study, which was of similar magnitude to that reported to during the initial treatment period.

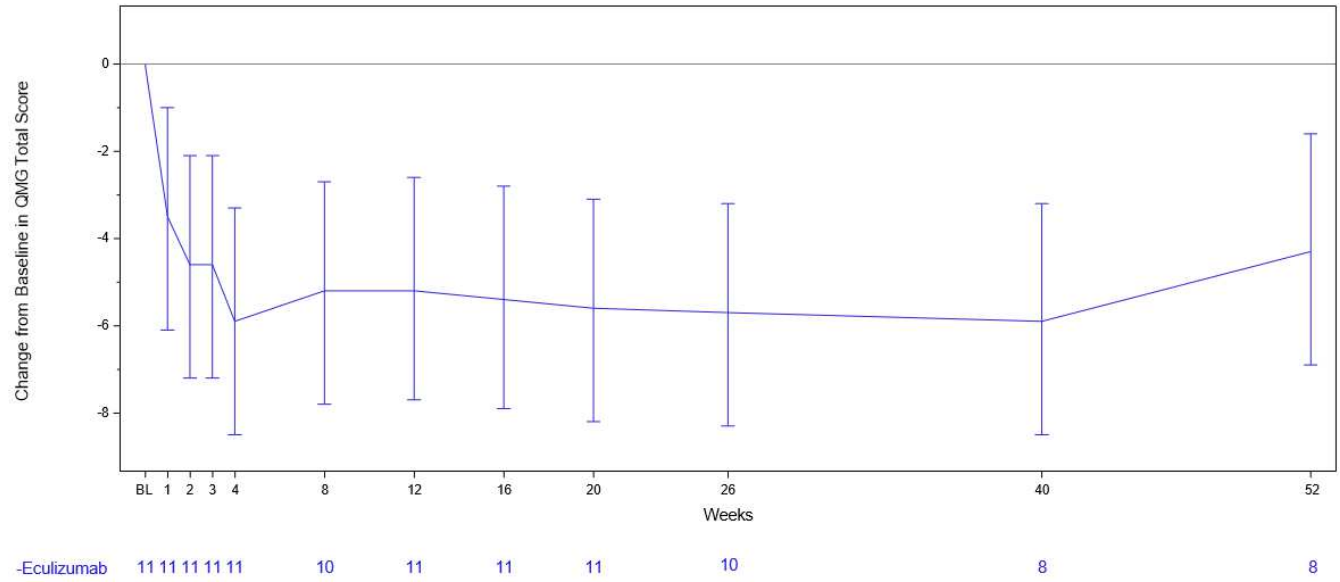

Figure 3: Change from Baseline in QMG Total Score (LS Mean and 95% CI) regardless of Rescue Therapy) during Week 1 to Week 52 Using a Repeated Measures Model

Abbreviations:; LS=Least square; CI=Confidence Interval.
Note: Baseline is defined as the last available assessment value prior to first study drug infusion.
Note: Estimates are based on MMRM that included terms of visit and baseline value.
Mean equal to 0. A compound symmetry covariance structure was used.

Neuromyelitis Optica Spectrum Disorder
Soliris has not been evaluated in paediatric patients with NMOSD.

5.2 Pharmacokinetic properties

Pharmacokinetics and Drug Metabolism

Biotransformation
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.

Elimination
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.

Pharmacokinetic/pharmacodynamic relationship(s)
In 40 patients with PNH, a 1-compartmental model was used to estimate pharmacokinetic parameters after multiple doses. Mean clearance was 0.31 ± 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. The steady state is achieved by 4 weeks using the PNH adult dosing regimen.

In PNH patients, pharmacodynamic activity correlates directly with eculizumab serum concentrations and maintenance of trough levels above ≥ 35 microgram/mL results in essentially complete blockade of haemolytic activity in the majority of PNH patients.

A second population PK analysis with a standard 1 compartmental model was conducted on the multiple dose PK data from 37 aHUS patients receiving the recommended Soliris regimen in studies

C08-002A/B and C08-003A/B. In this model, the clearance of Soliris for a typical aHUS patient weighing 70 kg was 0.0139 L/hr and the volume of distribution was 5.6 L. The elimination half-life was 297 h (approximately 12.4 days).

The second population PK model was applied to the multiple dose PK data from 22 paediatric aHUS patients receiving the recommended Soliris regimen in aHUS C10-003. The clearance and volume of distribution of Soliris are weight dependent, which forms the basis for a weight categorical based dose regimen in paediatric patients (see section 4.2). Clearance values of Soliris in paediatric aHUS patients were 10.4, 5.3, and 2.2 mL/hr with body weight of 70, 30, and 10 kg, respectively; and the corresponding volume of distribution values were 5.23, 2.76, and 1.21 L, respectively. The corresponding elimination half-life remained almost unchanged within a range of 349 to 378 h (approximately 14.5 to 15.8 days).

The clearance and half-life of eculizumab were also evaluated during plasma exchange interventions. Plasma exchange resulted in an approximately 50% decline in eculizumab concentrations following a 1 hour intervention and the elimination half-life of eculizumab was reduced to 52.4 hours. Supplemental dosing is recommended when Soliris is administered to aHUS patients receiving plasma infusion or exchange (see section 4.2).

All aHUS patients treated with Soliris when administered as recommended demonstrated rapid and sustained reduction in terminal complement activity. In aHUS patients, pharmacodynamic activity correlates directly with eculizumab serum concentrations and maintenance of trough levels of approximately 50-100 microgram/ml results in essentially complete blockade of terminal complement activity in all aHUS patients.

PK parameters are consistent across PNH, aHUS, refractory gMG and NMOSD patient populations. Pharmacodynamic activity measured by free C5 concentrations of <0.5 microgram/mL, is correlated with essentially complete blockade of terminal complement activity in PNH, aHUS, refractory gMG and NMOSD patients.

Special Populations

Dedicated studies have not been conducted to evaluate the pharmacokinetics of Soliris in special patient populations identified by gender, race, age (geriatric), or the presence of renal or hepatic impairment. Population PK (PopPK) analysis on data collected across studies in PNH, aHUS, gMG and NMOSD patients showed that gender, race, age (geriatric), or the presence of renal or hepatic impairment function do not influence the PK of eculizumab.

Paediatric population

The pharmacokinetics of eculizumab was evaluated in Study M07-005 in PNH paediatric patients (aged from 11 to less than 18 years) and in Studies C08-002, C08-003, C09-001r and C10-003 in aHUS pediatric patients (aged 2 months to less than 18 years) and in Study ECU-MG-303 paediatric patients with refractory gMG (aged from 12 years to less than 18 years) PopPK analysis showed that for PNH, aHUS, refractory gMG, and NMOSD, body weight was a significant covariate requiring body weight-based dosing for pediatric patients.

5.3 Preclinical safety data

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

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

Animal reproduction studies have not been conducted with eculizumab due to lack of pharmacologic activity in non-human species.

In a 26 week toxicity study performed in mice with a surrogate antibody directed against murine C5, treatment did not affect any of the toxicity parameters examined. Haemolytic activity during the course of the study was effectively blocked in both female and male mice.

No clear treatment-related effects or adverse effects were observed in reproductive toxicology studies in mice with a surrogate terminal complement inhibitory antibody, which was utilized to assess the reproductive safety of C5 blockade. These studies included assessment of fertility and early embryonic development, developmental toxicity, and pre and post-natal development.

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 (approximately 4 times the maximum recommended human Soliris dose, based on a body weight comparison); however, the exposure did not increase foetal loss or neonatal death.

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of eculizumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium phosphate, dibasic
Sodium phosphate, monobasic
Polysorbate 80
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After dilution, the medicinal product should be used immediately. However, chemical and physical stability has been demonstrated for 24 hours at 2°C – 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8ºC).
Do not freeze.
Store in the original package in order to protect from light.
Soliris vials in the original package may be removed from refrigerated storage **for only one single period of up to 3 days**. At the end of this period the product can be put back in the refrigerator.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

30 ml of concentrate in a vial (Type I glass) with a stopper (butyl, siliconised), and a seal (aluminium) with flip-off cap (polypropylene).

Pack size of one vial.

6.6 Special precautions for disposal and other handling

Soliris should be prepared for administration by a qualified healthcare professional using aseptic technique.

Prior to administration, the Soliris solution should be visually inspected for particulate matter and discolouration. Do not use if there is evidence of particulate matter or discolouration.

Instructions:
Reconstitution and dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

Withdraw the total amount of Soliris from the vial(s) using a sterile syringe.

Transfer the recommended dose to an infusion bag.

Dilute Soliris to a final concentration of 5 mg/ml (initial concentration divided by 2) by addition to the infusion bag using sodium chloride 9 mg/ml (0.9%) solution for injection, sodium chloride 4.5 mg/ml (0.45%) solution for injection, or 5% dextrose in water, as the diluent. For 300 mg doses, use 30 ml of Soliris (10 mg/ml) and add 30 ml of diluent. For 600 mg doses, use 60 ml of Soliris and add 60 ml of diluent. For 900 mg doses, use 90 ml of Soliris and add 90 ml of diluent. For 1,200 mg doses, use 120 ml of Soliris and add 120 ml of diluent.
The final volume of a 5 mg/ml diluted solution is 60 ml for 300 mg doses, 120 ml for 600 mg doses, 180 ml for 900 mg doses and 240 ml for 1,200 mg doses. The solution should be clear and colourless.

Gently agitate the infusion bag containing the diluted solution to ensure thorough mixing of the product and diluent.

The diluted solution should be allowed to warm to room temperature [18°C – 25°C] prior to administration by exposure to ambient air.

The diluted solution must not be heated in a microwave or with any heat source other than the prevailing room temperature.

Discard any unused portion left in a vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REGISTRATION NUMBER
144-09-32985

8. MANUFACTURER
Alexion Pharma International Operations Limited, College Business and Technology Park, Blanchardstown, Dublin 15, Ireland.

9. REGISTRATION HOLDER
Alexion Pharma Israel Ltd, P.O. Box 7063, Petach Tikva 49170, Israel.

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