ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Uplizna 100 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of inebilizumab in 10 mL at a concentration of 10 mg/mL. The final concentration after dilution is 1.0 mg/mL.

Inebilizumab is a humanised monoclonal antibody produced in Chinese hamster ovary cell line by recombinant DNA technology.

Excipients with known effect

This medicinal product contains 16.1 mg of sodium per vial.
This medicinal product contains 1 mg of polysorbate 80 per vial which is equivalent to 0.1 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to slightly yellow solution. The solution has a pH of approximately 6.0 and an osmolality of approximately 280 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuromyelitis optica spectrum disorders (NMOSD)

Uplizna is indicated as monotherapy for the treatment of adult patients with NMOSD who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive (see section 5.1).

Immunoglobulin G4-related disease (IgG4-RD)

Uplizna is indicated for the treatment of adult patients with active IgG4-RD (see section 5.1).

Generalized myasthenia gravis (gMG)

Uplizna is indicated as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of NMOSD or IgG4-RD or gMG and with access to appropriate medical support to manage potential severe reactions such as serious infusion-related reactions.

The patient should be monitored for infusion reactions during and for at least one hour after the completion of the infusion (see section 4.4).

Assessments prior to first dose of inebilizumab

Prior to initiating treatment, testing should be performed for

- Quantitative serum immunoglobulins, B-cell count, and complete blood count (CBC), including differentials (see sections 4.3 and 4.4)
- Hepatitis B virus (HBV) screening (see sections 4.3 and 4.4)
- Hepatitis C virus (HCV) screening and treatment started prior to initiating inebilizumab treatment (see section 4.4)
- Evaluate for active tuberculosis and test for latent infection (see sections 4.3 and 4.4)

All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to initiation of inebilizumab for live or live-attenuated vaccines (see section 4.4).

If loss of efficacy is thought to be caused by immunogenicity, the physician should follow B-cell counts as a direct measure of clinical impact (see section 5.1).

Posology

Initial doses

The recommended loading dose is 300 mg (3 vials of 100 mg) intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion.

Maintenance doses

The recommended maintenance dose is 300 mg intravenous infusion every 6 months. Inebilizumab is for chronic treatment.

Based upon the chronic nature of IgG4-RD, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

Delayed or missed doses

If an infusion of inebilizumab is missed, it should be administered as soon as possible and not delayed until the next planned dose.

Premedication for infusion-related reactions

Infection assessment
Prior to every infusion of inebilizumab, it should be determined whether there is a clinically significant infection. In case of infection, infusion of inebilizumab should be delayed until the infection resolves.

Required premedication
Premedication with a corticosteroid (e.g., methylprednisolone 80-125 mg intravenous or equivalent) should be administered approximately 30 minutes prior to each inebilizumab infusion; and an antihistamine (e.g., diphenhydramine 25-50 mg orally or equivalent) and an anti-pyretic (e.g.,

paracetamol 500-650 mg orally or equivalent) approximately 30-60 minutes prior to each inebilizumab infusion (see section 4.4).

Special populations

Elderly

Inebilizumab has been administered to 72 elderly patients (≥ 65 years of age) in clinical studies. Based on the data available, no dose adjustment is considered necessary in patients over 65 years old (see section 5.2).

Renal and hepatic impairment

Inebilizumab has not been studied in patients with severe renal or hepatic impairment. However, dose adjustment based on renal or hepatic function is not warranted because immunoglobulin (Ig) G monoclonal antibodies are not primarily cleared via renal or hepatic pathways (see section 5.2).

Paediatric population

The safety and efficacy of inebilizumab in children and adolescents aged 0 to 18 years has not yet been established. No data are available.

Method of administration

For intravenous use.
Vials should not be shaken.
Vials should be stored upright.

The prepared solution should be administered intravenously via an infusion pump at an increasing rate to completion (approximately 90 minutes) through an intravenous line containing a sterile, low protein-binding 0.2 or 0.22 micron in-line filter according to the schedule in table 1.

Table 1. Recommended infusion rate for administration when diluted in a 250 mL intravenous bag

Elapsed time (minutes)	Infusion rate (mL/hour)
0-30	42
31-60	125
61-completion	333

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Severe active infection, including active chronic infection such as hepatitis B
- Active or untreated latent tuberculosis
- History of progressive multifocal leukoencephalopathy (PML)
- Severely immunocompromised state
- Active malignancies

4.4 Special warnings and precautions for use

Instructions for patients at the time of prescribing

Patients treated with Uplizna should be given a patient card which includes information that inebilizumab treatment may increase the risk of infections, including serious infections, viral reactivation, opportunistic infections, and progressive multifocal leukoencephalopathy (PML), and how to seek early medical care in case of signs and symptoms of infection and PML.

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.

Infusion-related reactions and hypersensitivity

Inebilizumab can cause infusion-related reactions and hypersensitivity reactions, which can include headache, nausea, somnolence, dyspnoea, fever, myalgia, rash, palpitations or other symptoms. Infusion-related reactions were most common with the first infusion but were also observed during subsequent infusions. Although rare, serious infusion reactions did occur in clinical trials of inebilizumab (see section 4.8).

Before the infusion

Premedication with a corticosteroid (e.g., methylprednisolone 80-125 mg intravenous or equivalent), an antihistamine (e.g., diphenhydramine 25-50 mg orally or equivalent), and an antipyretic (e.g., paracetamol 500-650 mg orally or equivalent) should be administered (see section 4.2).

During the infusion

The patient should be monitored for infusion-related reactions. Management recommendations for infusion reactions depend on the type and severity of the reaction. For life-threatening infusion reactions, treatment should be stopped immediately and permanently, and appropriate supportive treatment should be administered. For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

After the infusion

The patient should be monitored for infusion reactions for at least one hour after the completion of the infusion.

Infections

Inebilizumab causes reduction in peripheral blood lymphocyte count and Ig levels consistent with the mechanism of action of B-cell depletion. Reduction of neutrophil counts were also reported. Therefore, inebilizumab may increase the susceptibility to infections (see section 4.8).

A recent (i.e. within 6 months) complete blood cell count (CBC) including differentials and immunoglobulins should be obtained before initiation of inebilizumab. Assessments of CBC including differentials and immunoglobulins are also recommended periodically during treatment and after discontinuation of treatment until B-cell repletion. Prior to every infusion of inebilizumab, it should be determined whether there is a clinically significant infection. In case of infection, infusion of inebilizumab should be delayed until the infection resolves. Patients should be instructed to promptly report symptoms of infection to their physician. Treatment discontinuation should be considered if a patient develops a serious opportunistic infection or recurrent infections if Ig levels indicate immune compromise.

The most common infections reported by inebilizumab-treated NMOSD patients across the randomised controlled period (RCP) and the open-label period (OLP) included urinary tract infection (26.2%), nasopharyngitis (20.9%), upper respiratory tract infection (15.6%), influenza (8.9%), and bronchitis (6.7%). In the IgG4-RD RCP and OLP, the most common infections reported by inebilizumab-treated patients were upper respiratory tract infection (10.7%), nasopharyngitis (9.8%), urinary tract infection (8.9%), and influenza (6.3%). In the gMG RCP and OLP, the most common infections reported by inebilizumab-treated patients were nasopharyngitis (6.9%) and upper respiratory tract infection (6.9%).

Hepatitis B virus reactivation

Risk of HBV reactivation has been observed with other B-cell -depleting antibodies. One case of HBV reactivation was observed in a patient treated with inebilizumab during the gMG clinical trial. Patients with chronic HBV were excluded from clinical trials with inebilizumab. HBV screening should be performed in all patients before initiation of treatment with inebilizumab. Inebilizumab should not be administered to patients with active hepatitis due to HBV who are positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients who are chronic carriers of HBV [HBsAg+] should consult a liver disease expert before starting and during treatment (see section 4.3).

Hepatitis C virus

Patients positive for HCV were excluded from clinical trials with inebilizumab. Baseline screening for HCV is required to detect and start treatment prior to initiating inebilizumab treatment.

Tuberculosis

Prior to initiating inebilizumab, patients should be evaluated for active tuberculosis and tested for latent infection. For patients with active tuberculosis or positive tuberculosis screening without a history of appropriate treatment, infectious disease experts should be consulted before starting treatment with inebilizumab.

Progressive multifocal leukoencephalopathy (PML)

PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically occurs in patients who are immunocompromised, and that may lead to death or severe disability. JCV infection resulting in PML has been observed in patients treated with other B-cell-depleting antibodies.

No confirmed cases of PML were identified in inebilizumab clinical trials. In inebilizumab clinical trials, one subject (NMOSD trial) died following the development of new brain lesions for which a definitive diagnosis could not be established. However, the differential diagnosis included atypical NMOSD attack, PML, or acute disseminated encephalomyelitis.

Physicians should be vigilant for clinical symptoms or magnetic resonance imaging (MRI) findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

At the first sign or symptom suggestive of PML, treatment with inebilizumab should be suspended until PML has been excluded. Further evaluation, including consultation with a neurologist, MRI scan preferably with contrast, cerebrospinal fluid testing for JC viral DNA, and repeat neurological assessments, should be considered. If confirmed, treatment with inebilizumab should be discontinued.

Late neutropenia

Cases of late onset of neutropenia have been reported (see section 4.8). Although some cases were grade 3, the majority of cases were grade 1 or 2. Cases of late onset of neutropenia have been reported at least 4 weeks after the latest infusion of inebilizumab. In patients with signs and symptoms of infection, measurement of blood neutrophils is recommended.

Treatment of severely immunocompromised patients

Patients in a severely immunocompromised state must not be treated until the condition resolves (see section 4.3).

If combining inebilizumab with another immunosuppressive therapy, consider the potential for increased immunosuppressive effects.

Patients with a known congenital or acquired immunodeficiency, including HIV infection or splenectomy, have not been studied.

Vaccinations

All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to initiation of inebilizumab. The efficacy and safety of immunisation with live or live-attenuated vaccines following inebilizumab therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion.

Infants of mothers exposed to inebilizumab during pregnancy should not be administered live or live-attenuated vaccines before confirming recovery of B-cell counts in the infant. Depletion of B cells in these exposed infants may increase the risks from live or live-attenuated vaccines. Non-live vaccines, as indicated, may be administered prior to recovery from B-cell and Ig-level depletion, but consultation with a qualified specialist should be considered to assess whether a protective immune response was mounted.

B-cell repletion time

The time to B-cell repletion following administration of inebilizumab is not known (see section 5.1).

Pregnancy

As a precautionary measure, it is preferable to avoid the use of inebilizumab during pregnancy and in women of childbearing potential not using contraception (see section 4.6). Patients should be instructed that if they are pregnant or plan to become pregnant while taking inebilizumab, they should inform their healthcare provider. Women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) while receiving Uplizna and for 6 months after the last administration of Uplizna.

Malignancy

Immunomodulatory medicinal products may increase the risk of malignancy. Current data do not seem to suggest any increased risk of malignancy; however, the possible risk for the development of solid tumours cannot be excluded at this time (see section 4.8).

gMG patients with a Myasthenia Gravis Foundation of America (MGFA) Class V

Inebilizumab has not been studied in gMG patients with a MGFA Class V.

Excipients with known effects

Sodium content

This medicinal product contains 48.3 mg sodium per dose, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Polysorbate

This medicinal product contains 1 mg of polysorbate 80 per vial which is equivalent to 0.1 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The primary elimination pathway for therapeutic antibodies is clearance by the reticuloendothelial system. Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in the clearance of therapeutic antibodies. Therefore, the potential risk of pharmacokinetic interactions between inebilizumab and other medicinal products is low.

Vaccinations

The efficacy and safety of immunisation with live or live-attenuated vaccines following inebilizumab therapy has not been studied. The response to vaccination could be impaired when B cells are depleted. It is recommended that patients complete immunisations prior to the start of inebilizumab therapy (see section 4.4).

Immunosuppressants

In the pivotal NMOSD study, during the RCP, a 2-week course of oral corticosteroids (plus a 1-week taper) was given to all subjects following the first administration of inebilizumab. In the pivotal IgG4-RD study, during the RCP, subjects were at a uniform dose of glucocorticoids (GCs) at the time of initiation of inebilizumab and then began a prespecified taper to discontinuation at the end of 8 weeks. In the pivotal gMG study, subjects were on oral corticosteroids or stable dose of other immunosuppressants at the time of initiation of inebilizumab treatment. Subjects began a prespecified corticosteroid taper to 5 mg/day from week 4 to week 24, but were permitted to continuing receiving other immunosuppressants while receiving inebilizumab (see section 5.1).

Concomitant usage of inebilizumab with immunosuppressants, including systemic corticosteroids, may increase the risk of infection. The effects of inebilizumab on B cells and immunoglobulins may persist for 6 months or longer following its administration.

When initiating inebilizumab after other immunosuppressive therapies with prolonged immune effects or initiating other immunosuppressive therapies with prolonged immune effects after inebilizumab, the duration and mode of action of these medicinal products should be taken into account because of potential additive immunosuppressive effects (see section 5.1).

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) while receiving Uplizna and for 6 months after the last administration of Uplizna.

Pregnancy

There are limited amount of data from the use of inebilizumab in pregnant women. Inebilizumab is a humanised IgG1 monoclonal antibody and immunoglobulins are known to cross the placental barrier. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B-cell-depleting antibodies during pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity; however, they have shown a B-cell depletion in the foetal livers of progeny (see section 5.3).

Treatment with inebilizumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

In case of exposure during pregnancy, depletion of B cells may be expected in newborns due to the pharmacological properties of the product and findings from animal studies (see section 5.3). B-cell levels in infants following maternal exposure to inebilizumab have not been studied in clinical trials. The potential duration of B-cell depletion in infants exposed to inebilizumab *in utero*, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown (see sections 4.4 and 5.1). Consequently, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines, such as Bacillus Calmette-Guérin (BCG) vaccine, should be postponed until the infant's B-cell count has recovered (see section 4.4).

Breast-feeding

The use of inebilizumab in women during lactation has not been studied. It is unknown whether inebilizumab is excreted in human milk. In humans, excretion of IgG antibodies in milk occurs during the first few days after birth, which is decreasing to low concentrations soon afterwards. Consequently, a risk to the breast-fed child cannot be excluded during this short period. Afterwards, Uplizna could be used during breast-feeding if clinically needed. However, if the patient was treated with Uplizna up to the last few months of pregnancy, breast-feeding can be started immediately after birth.

Fertility

There are limited data on the effect of inebilizumab on human fertility; however, studies in animals have shown reduced fertility. The clinical significance of these nonclinical findings is not known (see section 5.3).

4.7 Effects on ability to drive and use machines

The pharmacological activity and adverse reactions reported to date suggest that inebilizumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions by inebilizumab-treated patients from the 3 NMOSD, IgG4-RD and gMG pivotal clinical trials were urinary tract infection (26.2%), nasopharyngitis (20.9%), upper respiratory tract infection (15.6%), arthralgia (17.3%), back pain (13.8%), lymphopenia (10.7%) and headache (10.3%) across both the randomised controlled period (RCP) and open-label period (OLP).

The most frequently reported serious adverse reactions by inebilizumab-treated patients across the RCP and OLP were infections (11.1%) (including urinary tract infections (4.0%), pneumonia (1.8%)) and NMOSD (1.8%).

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials and post-marketing experience following treatment with inebilizumab are listed in table 2 according to the following frequency categories: 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), very rare (< 1/10 000), not known (cannot be estimated from the available data).

Table 2. Adverse reactions reported in inebilizumab clinical trials, including patients with NMOSD, gMG and IgG4-RD as well as from post-marketing experience

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**
Infections and infestations	Urinary tract infection, respiratory tract infection, nasopharingitis, influenza	Pneumonia, cellulitis, herpes zoster, sinusitis	Sepsis, subcutaneous abscess, bronchiolitis
Blood and lymphatic system disorders	Lymphopenia*	Neutropenia, Late-on-set neutropenia	
Musculoskeletal and connective tissue disorders	Arthralgia, back pain	Myalgia	
General disorders and administration site conditions		Pyrexia	
Nervous system disorder	Headache		
Investigations	Immunoglobulins decreased		
Injury, poisoning and procedural complications	Infusion-related reaction		
Respiratory, thoracic and mediastinal disorders		Cough	

* Lymphopenia includes lymphocyte count decreased

Description of selected adverse reactions

Infusion-related reactions

Inebilizumab can cause infusion-related reactions, which can include headache, nausea, somnolence, dyspnoea, fever, myalgia, rash, palpitations or other symptoms. All patients were given premedication. Infusion reactions were observed in 9.2% of NMOSD patients during the first course of inebilizumab compared to 10.7% of placebo-treated patients. Infusion reactions to inebilizumab were observed in 7.4% of IgG4-RD patients compared to 14.9% of placebo-treated patients during the RCP. Infusion reactions to inebilizumab were observed in 10.1% of gMG patients compared to 5.9% of placebo-treated patients during the RCP. Infusion-related reactions were most common with the first infusion but were observed during subsequent infusions. The majority of infusion-related reactions reported in inebilizumab-treated patients were either mild or moderate in severity.

Infections

In clinical trials, an infection was reported by 74.7% of NMOSD patients, 70.5% of IgG4-RD patients and 42.9% of gMG patients treated with inebilizumab across the RCP and OLP. The most common

infections in NMOSD patients included urinary tract infection (26.2%), nasopharyngitis (20.9%), and upper respiratory tract infection (15.6%), influenza (8.9%), and bronchitis (6.7%). Serious infections reported by more than one inebilizumab-treated NMOSD patient were urinary tract infection (4.0%) and pneumonia (1.8%). The most common infections in IgG4-RD patients included upper respiratory tract infection (10.7%), nasopharyngitis (9.8%), urinary tract infection (8.9%), and influenza (6.3%). Serious infections reported by more than one inebilizumab-treated IgG4-RD patient was pneumonia (1.8%). The most common infections in gMG patients included nasopharyngitis (6.9%) and upper respiratory tract infection (6.9%). Serious infections reported by more than one inebilizumab-treated gMG patient was pneumonia (1.5%). See section 4.4 for action to be taken in case of infection.

Opportunistic and serious infections

In NMOSD study during the RCP, no opportunistic infections occurred in either treatment group, and a single grade 4 infectious adverse reaction (atypical pneumonia) occurred in a patient treated with inebilizumab. During the OLP, 2 inebilizumab-treated patients (0.9%) experienced an opportunistic infection (one of which was not confirmed) and 3 inebilizumab-treated patients (1.4%) experienced a grade 4 infectious adverse reaction. See section 4.4 for action to be taken in case of infection. In IgG4-RD study, 3 inebilizumab-treated patients (2.7%) experienced an opportunistic infection (all non-serious herpes zoster) across the RCP and OLP. In the gMG study, 1 inebilizumab-treated patient (0.8%) experienced a grade 3 serious event (herpes zoster disseminated) during the RCP.

Laboratory abnormalities

Decreased immunoglobulins

Consistent with its mechanism of action, average immunoglobulin levels decreased with inebilizumab use. In NMOSD study, at the end of the 6.5-month RCP, the proportion of patients with levels below the lower limit of normal was as follows: IgA 9.8% inebilizumab and 3.1% placebo, IgE 10.6% inebilizumab and 12.5% placebo, IgG 3.8% inebilizumab and 9.4% placebo, and IgM 29.3% inebilizumab and 15.6% placebo. A single adverse reaction of IgG decreased was reported (grade 2, during the OLP). The proportion of inebilizumab-treated patients with IgG levels below the lower limit of normal at year 1 was 7.4% and at year 2 was 9.9%. With a median exposure of 3.2 years, the frequency of moderate IgG reduction (300 to < 500 mg/dL) was 14.2% and the frequency of severe IgG reduction (< 300 mg/dL) was 3.6%. In IgG4-RD study at the end of the 12-month RCP, the total immunoglobulin level was reduced by approximately 12% from baseline for patients treated with inebilizumab as compared to an increase of 21% in patients treated with placebo. The mean decreases from baseline in immunoglobulin G (IgG) and immunoglobulin M (IgM) were approximately 9% and 32%, respectively, in patients treated with inebilizumab, whereas IgG was increased by 26% and IgM was increased by approximately 3% in placebo-treated patients. In the gMG study at the end of the 6-month RCP, the total immunoglobulin level was reduced by 13.3% from baseline for patients treated with inebilizumab as compared to an increase of 14.5% in patients treated with placebo. The mean decreases from baseline in immunoglobulin G (IgG) and immunoglobulin M (IgM) were 8.4% and 30%, respectively, in patients treated with inebilizumab, whereas IgG and IgM were increased by 17.8% and 4.9%, respectively, in placebo-treated patients.

Decreased neutrophil counts

In NMOSD study, after 6.5 months of treatment, neutrophil counts between 1.0-1.5 $\times 10^9$/L (grade 2) were observed in 7.5% of inebilizumab-treated patients versus 1.8% of placebo-treated patients. Neutrophil counts between 0.5-1.0 $\times 10^9$/L (grade 3) were observed in 1.7% of inebilizumab-treated patients versus 0% of placebo-treated patients. In IgG4-RD study during the 12-month RCP, neutrophil counts between 1.0-1.5 $\times 10^9$/L were observed in 7.5% of inebilizumab-treated patients versus 3% of placebo-treated patients. Neutrophil counts between 0.5-1.0 $\times 10^9$/L were observed in 0% of inebilizumab-treated patients versus 1.5% of placebo-treated patients. Neutropenia was generally transient and was not associated with serious infections.

Decreased lymphocyte counts

In NMOSD study, during 6.5 months of treatment, a reduction in lymphocyte counts was observed more commonly in patients treated with inebilizumab than placebo: lymphocyte counts between 500-< 800/mm^3 (grade 2) were observed in 21.4% of inebilizumab-treated patients versus 12.5% of placebo-treated patients. Lymphocyte counts between 200-< 500/mm^3 (grade 3) were observed in 2.9% of inebilizumab-treated patients versus 1.8% of placebo-treated patients. In IgG4-RD study, during 12 months of treatment in RCP, a reduction in lymphocyte counts was observed more commonly in patients treated with inebilizumab than placebo: lymphocyte counts between 500-< 800/mm^3 (grade 2) were observed in 26.9% of both inebilizumab-treated and placebo-treated patients. Lymphocyte counts between 200-< 500/mm^3 (grade 3) were observed in 10.4% of inebilizumab-treated patients versus 3.0% of placebo-treated patients. In the gMG study, at the end of the 6-month RCP, a reduction in lymphocyte counts was observed in 35% of inebilizumab-treated versus 30.8% of placebo-treated patients. Lymphocyte counts between 500-< 800/mm^3 (grade 2) were observed in 21.4% of inebilizumab-treated patients versus 12.8% of placebo-treated patients. Lymphocyte counts between 200-< 500/mm^3 (grade 3) were observed in 10.3% of inebilizumab-treated patients versus 7.7% of placebo-treated patients. This finding is consistent with the mechanism of action of B-cell depletion since B cells are a subset of the lymphocyte population.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest dose of inebilizumab tested in autoimmune patients was 1 200 mg, administered as two 600 mg intravenous infusions separated by 2 weeks. The adverse reactions were similar to what was observed in the inebilizumab pivotal clinical study.

There is no specific antidote in the event of an overdose; the infusion should be interrupted immediately and the patient should be observed for infusion-related reactions (see section 4.4). The patient should be closely monitored for signs or symptoms of adverse reactions and supportive care instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, monoclonal antibodies, ATC code: L04AG10

Mechanism of action

Inebilizumab is a monoclonal antibody that specifically binds to CD19, a cell surface antigen present on pre-B and mature B-cell lymphocytes, including plasmablasts and some plasma cells. Following cell surface binding to B lymphocytes, inebilizumab supports antibody-dependent cellular cytolysis (ADCC) and antibody-dependent cellular phagocytosis (ADCP). B cells are believed to play a central role in the pathogenesis of NMOSD, IgG4-RD and gMG. The mechanism by which inebilizumab exerts its therapeutic effects in these diseases is presumed to involve B-cell depletion and may include the suppression of antibody secretion, antigen presentation, B-cell–T-cell interaction, and the production of inflammatory mediators.

Pharmacodynamic effects

Pharmacodynamics of inebilizumab were assessed with an assay for CD20+ B cells, since inebilizumab can interfere with the CD19+ B-cell assay. Treatment with inebilizumab reduces CD20+ B-cell counts in blood by 8 days after infusion. In the clinical study of 174-NMOSD patients, CD20+ B-cell counts were reduced below the lower limit of normal by 4 weeks in 100% of patients treated with inebilizumab and remained below the lower limit of normal in 94% of patients for 28 weeks after initiation of treatment. In the clinical study of 68-IgG4-RD patients, CD20+ B-cell counts were reduced below the lower limit of normal by week 2 in 100% of patients treated with inebilizumab and remained below the lower limit of normal in 82% and 79% of patients at week 26 and 52, respectively, with 6-month treatment interval. In the gMG study, CD20+ B-cell counts were reduced below the lower limit of normal by week 4 in ≥ 99% of inebilizumab-treated patients in the overall population (anti-AChR-Ab+ and anti-MuSK-Ab+). B cell counts remained below the lower limit of normal in ≥ 96% of patients in the overall population at the end of the 6-month randomised-controlled period (RCP). After 1 year of inebilizumab treatment in patients with anti-AChR-Ab+ gMG, 92% of patients had B-cell counts below the lower limit of normal. The time to B-cell repletion following administration of inebilizumab is not known.

ADA (anti-drug antibodies)-positive status appeared to have no clinically relevant impact on PK and PD (B-cell) parameters and did not impact the long-term safety profile. There was no apparent effect of ADA status on the efficacy outcome; however, the impact cannot be fully assessed given the low incidence of ADA associated with inebilizumab treatment.

Clinical efficacy and safety

Neuromyelitis optica spectrum disorders (NMOSD)

The efficacy of inebilizumab for the treatment of NMOSD was studied in a randomised (3:1), double-blind, placebo-controlled clinical trial in adults with AQP4-IgG seropositive or seronegative NMOSD. The study included patients who had experienced at least one acute NMOSD attack in the prior year or at least 2 attacks in the prior 2 years that required rescue therapy (e.g., steroids, plasma exchange, intravenous immunoglobulin), and had an Expanded Disability Severity Scale (EDSS) score ≤ 7.5 (patients with a score of 8.0 were eligible if the patient was reasonably able to participate). Patients were excluded if previously treated with immunosuppressant therapies within an interval specified for each such therapy. Background immunosuppressant therapies for the prevention of NMOSD attacks were not permitted. A 2-week course of oral corticosteroids (plus a 1-week taper) was administered at the start of inebilizumab treatment in the pivotal study.

Patients were treated with intravenous infusions of inebilizumab 300 mg on day 1 and on day 15, or matching placebo, and then followed for a period of up to 197 days or an adjudicated attack, termed the randomised-controlled period (RCP). All potential attacks were evaluated by a blinded, independent, Adjudication Committee (AC), who determined whether the attack met protocol-defined criteria. The attack criteria recognised attacks in all domains affected by NMOSD (optic neuritis, myelitis, brain, and brainstem) and included criteria based exclusively on substantial clinical manifestations, as well as criteria that augmented more modest clinical findings with the use of MRI (see table 3).

Table 3. Overview of the protocol-defined criteria for an NMOSD attack

Domain	Representative symptoms	Clinical-only findings	Clinical PLUS radiological findings
Optic nerve	Blurred vision Loss of vision Eye pain	8 criteria based on changes in visual acuity or relative afferent pupillary defect (RAPD)	3 criteria based on changes in visual acuity or RAPD plus presence of corresponding optic nerve MRI findings

Domain	Representative symptoms	Clinical-only findings	Clinical PLUS radiological findings
Spinal cord	Deep or radicular pain Extremity paraesthesia Weakness Sphincter dysfunction Lhermitte's sign (not in isolation)	2 criteria based on changes in pyramidal, bladder/bowel, or sensory functional scores	2 criteria based on changes in pyramidal, bladder/bowel, or sensory functional scores PLUS corresponding spinal cord MRI findings
Brainstem	Nausea Intractable vomiting Intractable hiccups Other neurological signs (e.g., double vision, dysarthria, dysphagia, vertigo, oculomotor palsy, weakness, nystagmus, other cranial nerve abnormality)	None	2 criteria based on symptoms or changes in brainstem/cerebellar functional scores PLUS corresponding brainstem MRI findings
Brain	Encephalopathy Hypothalamic dysfunction	None	1 criterion based on changes in cerebral/sensory/pyramidal functional scores PLUS corresponding brain MRI findings

Patients who experienced an AC-determined attack in the RCP, or who completed the day 197 visit without an attack, exited the RCP and had the option to enrol into an OLP and initiate or continue treatment with inebilizumab.

A total of 230 patients were enrolled: 213 patients were AQP4-IgG seropositive patients and 17 were seronegative patients were enrolled; 174 patients were treated with inebilizumab and 56 patients were treated with placebo in the RCP of the study. Of the 213 AQP4-IgG seropositive patients, 161 were treated with inebilizumab and 52 were treated with placebo in the RCP of the study. Baseline and efficacy results are presented for the AQP4-IgG seropositive patients.

Baseline demographics and disease characteristics were balanced across the 2 treatment groups (see table 4).

Table 4. Demographics and baseline characteristics of the AQP4-IgG seropositive NMOSD patients

Characteristic	Placebo N = 52	Inebilizumab N = 161	Overall N = 213
Age (years): mean (standard deviation [SD])	42.4 (14.3)	43.2 (11.6)	43.0 (12.3)
Age ≥ 65 years, n (%)	4 (7.7)	6 (3.7)	10 (4.7)
Sex: Male, n (%)	3 (5.8)	10 (6.2)	13 (6.1)
Sex: Female, n (%)	49 (94.2)	151 (93.8)	200 (93.9)
Expanded disability status scale (EDSS): mean (SD)	4.35 (1.63)	3.81 (1.77)	3.94 (1.75)
Disease duration (years): mean (SD)	2.92 (3.54)	2.49 (3.39)	2.59 (3.42)
Number of prior relapses: ≥ 2, n (%)	39 (75.0)	137 (85.1)	176 (82.6)
Annualised relapse rate: mean (SD)	1.456 (1.360)	1.682 (1.490)	1.627 (1.459)

Rescue therapy was initiated as needed for NMOSD attacks. All patients were pre-medicated prior to investigational product administration to reduce the risk of infusion-related reactions.

The primary efficacy endpoint was time (days) from day 1 to onset of an AC-determined NMOSD attack on or before day 197. Additional key secondary endpoint measures included worsening from baseline in EDSS at last visit during the RCP, change from baseline in low-contrast visual acuity binocular score measured by low-contrast Landolt C Broken Rings Chart at last visit during the RCP, cumulative total active MRI lesions (new gadolinium-enhancing or new/enlarging T2 lesions) during the RCP, and the number of NMOSD-related in-patient hospitalisations. A patient was considered to have a worsening in EDSS score if one of the following criteria was met: (1) worsening of 2 or more points in EDSS score for patients with baseline score of 0; (2) worsening of 1 or more points in EDSS score for patients with baseline score of 1 to 5; (3) worsening of 0.5 points or more in EDSS score for patients with baseline score of 5.5 or more. Although no comparator was available during the OLP, the annualised attack rate across both randomised and open-label treatment was determined.

Results in AQP4-IgG seropositive patients are presented in table 5 and figure 1. In this study, treatment with inebilizumab statistically significantly reduced the risk of an AC-determined NMOSD attack as compared to treatment with placebo (hazard ratio: 0.227, $p < 0.0001$; 77.3% reduction in risk of AC-determined NMOSD attack) in AQP4-IgG seropositive patients. There was no treatment benefit observed in AQP4-IgG seronegative patients.

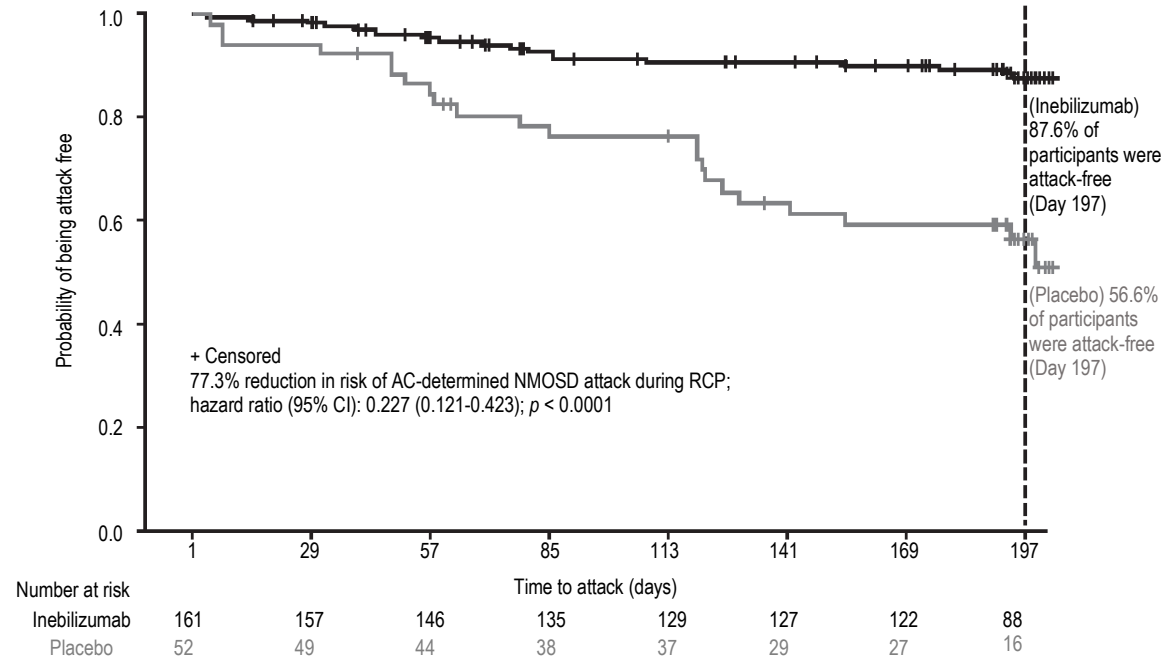
In the inebilizumab group EDDS worsening was significantly less than placebo group (14.9% versus 34.6% of the subjects). There were no differences in the low-contrast visual acuity binocular score between the study arms. The mean cumulative number of total active MRI lesions (1.7 versus 2.3) and mean cumulative number of NMOSD related hospitalisations (1.0 versus 1.4) were reduced in the inebilizumab study group.

Table 5. Efficacy results in pivotal trial in AQP4-IgG seropositive NMOSD

	Treatment group	
	Placebo N = 52	**Inebilizumab N = 161**
Time to adjudication committee-determined attack (primary efficacy endpoint)		
Number (%) of patients with attack	22 (42.3%)	18 (11.2%)
Hazard ratio (95% CI)[a]	0.227 (0.1214, 0.4232)	
p-value[a]	< 0.0001	

[a] Cox regression method, with Placebo as the reference group.

Figure 1. Kaplan-Meier plot of time to first AC-determined NMOSD attack during the RCP in AQP4-IgG seropositive patients



AC = adjudication committee; AQP4-IgG = anti-aquaporin-4 immunoglobulin G; CI = confidence interval; NMOSD = neuromyelitis optica spectrum disorders; RCP = randomised control period.

Across the RCP and OLP, the annualised AC-determined NMOSD attack rate was analysed as a secondary endpoint and in AQP4-IgG seropositive patients treated with inebilizumab the result was 0.09.

Immunoglobulin G4-related disease (IgG4-RD)

The efficacy of inebilizumab for the treatment of IgG4-RD was studied in one randomised (1:1), double-blind, multicentre, 52-week placebo-controlled clinical trial that enrolled 135 adult patients with active IgG4-RD. Patients had active disease, defined by clinical, imaging, laboratory or biopsy features, and required treatment in the judgement of the physician. Eligible patients had newly diagnosed or recurrent IgG4-RD that required glucocorticoid (GC) treatment at screening, had a confirmed history of organ involvement at any time in the course of the disease, and met the 2019 ACR/EULAR classification criteria.
All potential flares during the study were assessed by the investigator and subsequently reviewed by a blinded, independent, adjudication committee, who determined whether the flare met one or more of the protocol-defined, organ-specific flare diagnostic criteria. Disease flare was defined as new/worsening signs or symptoms that were positively adjudicated and warranted treatment by the investigator. Absence of alternative diagnoses was required.

Patients received 300 mg IV of inebilizumab or placebo at Days 1, 15 and 183 of the RCP. Patients were at a uniform dose of glucocorticoids (GCs) at the time of randomisation (equivalent to 20 mg prednisone per day) and then began a prespecified taper of 5 mg per day every 2 weeks to discontinuation at the end of 8 weeks. The use of GCs during the trial was permitted for treatment of IgG4-RD flares, and for other purposes including premedication for investigational treatment, oral GC treatment up to 2 weeks, or at a dose of up to 2.5 mg per day of prednisone or equivalent for treatment of adrenal insufficiency. The concomitant use of biologic and non-biologic immunosuppressive agents was prohibited during the trial. Patients who completed the RCP had the option to enrol in an OLP and initiate or continue treatment with inebilizumab.

227 patients were screened for eligibility. Of the 135 enrolled IgG4-RD patients, 68 patients were randomised to receive inebilizumab and 67 were randomised to receive placebo. Baseline demographics and disease characteristics for IgG4-RD patients during the RCP were balanced across the treatment groups (see table 6). Although no comparator was available during the OLP, treated and AC-determined flares in the open-label treatment period were determined.

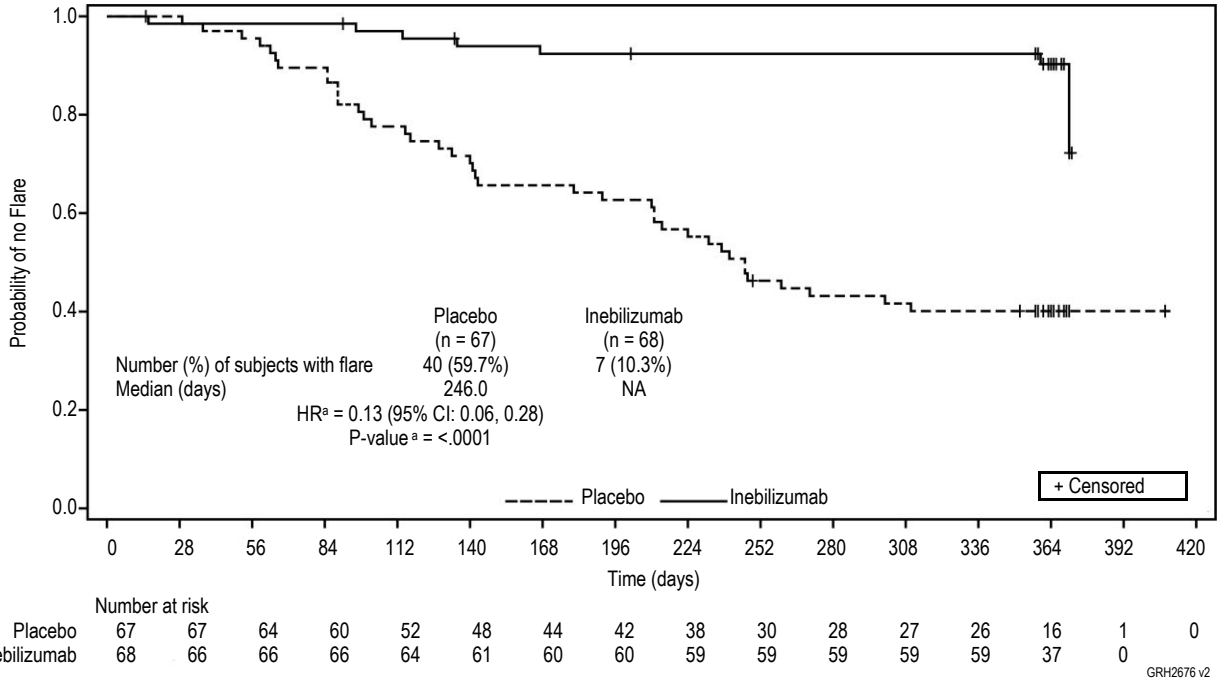
Table 6. Demographics and baseline characteristics of IgG4-RD patients

Characteristic	Placebo N = 67	Inebilizumab N = 68	Overall N = 135
Age (years): mean (standard deviation [SD])	58.2 (12.2)	58.2 (11.5)	58.2 (11.8)
Age ≥ 65 years, n (%)	21 (31.3%)	21 (30.9%)	42 (31.1%)
Sex: Male, n (%)	49 (73.1%)	39 (57.4%)	88 (65.2%)
Disease duration (years): mean (SD)	2.54 (3.06)	2.64 (3.73)	2.59 (3.40)
Ig-G4 manifestation Newly diagnosed	31 (46.3%)	31 (45.6%)	62 (45.9%)
ACR/EULAR Classification Criteria score Mean (SD)	38.3 (11.7)	40.1 (12.1)	39.2 (11.9)
Prior non-glucocorticoid therapy for IgG4-RD Yes	20 (29.9%)	17 (25.0%)	37 (27.4%)
Baseline IgG4-RD Responder Index score Mean (SD)	6.0 (4.0)	5.4 (4.0)	5.7 (4.0)

Results in IgG4-RD patients are presented in figure 2 and table 7.

The study met the primary efficacy endpoint, time to the first treated and AC-determined IgG4-RD flare, which was longer in the inebilizumab group, compared with the placebo group (hazard ratio: 0.13; $p < 0.0001$; see figure 2). The key secondary endpoints were also met with statistical significance (see table 7).

Figure 2. Primary endpoint - Kaplan-Meier plot of time to first treated and AC-determined IgG4-RD flare during the randomised-controlled period



[a] Based on Cox regression method, with placebo as the reference group.

Patients who did not complete the RCP and who did not have a treated and AC-determined flare during the RCP were censored at the time of discontinuation.

Table 7. Key secondary efficacy results in IgG4-RD patients

	Treatment group	
	Inebilizumab N = 68	**Placebo N = 67**
Annualised flare rate for treated and AC-determined IgG4-RD flares	0.10	0.71
Rate ratio (95% CI)[a]	0.14 (0.06, 0.31)	
p-value[a]	< 0.0001	
Proportion of subjects achieving treatment-free, flare-free complete remission at week 52[b]	39 (57.4%)	15 (22.4%)
Odds ratio (95% CI)[c]	4.68 (2.21, 9.91)	
p-value[c]	< 0.0001	
Proportion of subjects achieving corticosteroid-free, flare-free complete remission at week 52[d]	40 (58.8%)	15 (22.4%)
Odds ratio (95% CI)[c]	4.96 (2.34, 10.52)	
p-value[c]	< 0.0001	

[a] Estimated from the negative binomial regression, with placebo as the reference group.
[b] Defined as the lack of evident disease activity (IgG4-RD RI = 0 or investigator's decision) at week 52, no AC-determined flare during the RCP, and no treatment for flare or disease control except the required 8-week GC taper.
[c] Based on logistic regression model, with placebo as the reference group.
[d] Defined as the lack of evident disease activity (IgG4-RD RI = 0 or investigator's decision) at week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC taper.

The mean (SD) total GC use for IgG4-RD disease control per patient was lower in the inebilizumab group compared with the placebo group, with a mean (SD) of 118.25 (438.97) mg prednisone equivalent versus 1384.53 (1723.26) mg prednisone equivalent, respectively during the RCP. The mean (SD) daily GC use during the RCP per patient using GC was 3.34 (2.09) mg prednisone equivalent in the inebilizumab group versus 5.97 (4.20) mg prednisone equivalent in the placebo group. The mean (SD) total GC use during the RCP per patient using GC was 1148.71 (877.92) mg prednisone equivalent in the inebilizumab group versus 2208.65 (1707.56) mg prednisone equivalent in the placebo group.

Available data from the OLP, in which patients continued to receive inebilizumab supports a sustained treatment effect of inebilizumab.

Generalized myasthenia gravis (gMG)

The efficacy of inebilizumab for the treatment of gMG was studied in a randomised, double-blind, multicentre, placebo-controlled clinical trial. The RCP was 52 weeks for the anti-AChR-Ab+ population who received 300 mg IV of inebilizumab or placebo at Days 1, 15 and 183. The RCP was 26 weeks for the anti-MuSK-Ab+ population who received 300 mg IV of inebilizumab or placebo at Days 1 and 15. The primary analysis was conducted after week 26 in both populations.

Patients met the following eligibility criteria:
- Presence of autoantibodies against AChR or MuSK
- Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV
- Myasthenia Gravis-Activities of Daily Living (MG-ADL) score between 6 and 10 with > 50% of this score attributed to non-ocular items or an MG-ADL score ≥ 11

- Quantitative Myasthenia Gravis (QMG) score of ≥ 11
- On a stable dose of a corticosteroid or a specified non-steroidal immunosuppressive therapy (NSIST), or a combination of both prior to randomisation.

The stable dose of corticosteroid (> 5 mg/day prednisone or equivalent) was tapered to 5 mg/day (prednisone or equivalent) from week 4 to week 24. Rescue therapy included IVIg and plasma exchange.

Inebilizumab was administered according to the recommended dosage regimen (see section 4.2).

Patients were randomised at a 1:1 ratio; of the 238 enrolled gMG patients, 95 anti-AChR-Ab+ patients and 24 anti-MuSK-Ab+ patients were randomised to receive inebilizumab and 95 anti-AChR-Ab+ patients and 24 anti-MuSK-Ab+ patients were randomised to receive placebo.

Baseline demographics and disease characteristics for gMG patients during the RCP were balanced across the treatment groups (see Table 8).

Table 8. Demographics and baseline characteristics of gMG patients for overall population

Characteristic	**Placebo N = 117**	**Inebilizumab N = 119**	**Overall N = 236**
Age (years): mean (standard deviation [SD])	47.9 (15.0)	47.1 (15.7)	47.5 (15.3)
Age ≥ 65 years, n (%)	16 (13.7)	22 (18.5)	38 (16.1)
Sex: Male, n (%)	52 (44.4)	40 (33.6)	92 (39.0)
Sex: Female, n (%)	65 (55.6)	79 (66.4)	144 (61.0)
Race, (%)			
Asian	46.2	38.7	42.4
Black or African American	2.6	1.7	2.1
White	47.9	58	53
Disease duration (years): mean (SD)	6.73 (7.28)	5.94 (6.96)	6.34 (7.12)
Baseline MG-ADL Score: mean (SD)			
Overall population	9.1 (2.8)	9.0 (2.8)	9.1 (2.8)
AChR+ population	9.3 (2.8)	9.1 (2.7)	9.2 (2.7)
MuSK+ population	8.3 (2.5)	8.8 (3.1)	8.5 (2.8)
Baseline QMG Score: mean (SD)			
Overall population	17.3 (4.2)	16.7 (4.2)	17.0 (4.2)
AChR+ population	17.4 (4.3)	16.9 (4.1)	17.1 (4.2)
MuSK+ population	17.2 (3.9)	16.1 (4.8)	16.7 (4.3)
Number of patients receiving stable immunosuppressant therapy at baseline: n (%)			
Corticosteroid only	68 (58.1)	82 (68.9)	150 (63.6)
NSIST only	9 (7.7)	8 (6.7)	17 (7.2)
Corticosteroid plus 1 NSIST	39 (33.3)	29 (24.4)	68 (28.8)
Acetylcholinesterase inhibitor: n (%)	93 (79.5)	94 (79.0)	187 (79.2)

The results of the primary and key secondary endpoints are presented in Table 9 and Figures 3 to 5.

The efficacy of inebilizumab was measured using the MG-ADL scale, which assesses the impact of gMG on an 8-item questionnaire that focuses on the MG patient's relevant symptoms and functional performance of activities of daily living. Each item is assessed on a 4-point scale where a score of 0

represents normal function and a score of 3 represents the most severe impact by the disease. The total MG-ADL score ranges from 0 to 24, with higher scores indicating more impairment.

The primary efficacy endpoint was the change from baseline in the MG-ADL score at week 26, in the overall population. A statistically significant difference favoring inebilizumab was observed in the mean change from baseline in MG-ADL total score (-4.3 inebilizumab vs -3.0 for placebo, a difference of -1.3, 95% CI: -2.2, -0.4; p-value: 0.0067). The proportion of patients who received rescue therapy by week 26 was lower in the inebilizumab group compared with placebo (8.4% inebilizumab vs 23.9% placebo).

The key secondary endpoint was the change from baseline in the QMG score at week 26 in the overall population. The QMG score is a 13-item categorical grading system that quantitively measures disease impairment by mainly assessing muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no impairment and a score of 3 represents severe impairment. A total possible score ranges from 0 to 39, where higher scores indicate more severe impairment. A statistically significant difference favoring inebilizumab was observed in the mean change from baseline in QMG total score (-4.9 inebilizumab vs -2.9 placebo, a difference of -2.0, 95% CI: -3.3, -0.7).

Table 9. Change from baseline in MG-ADL and QMG scores at week 26 in adult gMG patients who are Anti-AChR-Ab+ or Anti-MuSK-Ab+

	Overall Population	
	Inebilizumab N = 119	**Placebo N = 117**
MG-ADL Score		
LS Mean	-4.3	-3.0
Difference	-1.3	
95% CI	(-2.2, -0.4)	
p-value	0.0067	
QMG Score		
LS Mean	-4.9	-2.9
Difference	-2.0	
95% CI	(-3.3, -0.7)	
p-value	0.0028	

CI = confidence interval; LS = least square

The proportion of patients who achieved a ≥ 3-point improvement in MG-ADL score at week 26 with no use of rescue therapy between Day 28 and week 26 was 68.7% in the inebilizumab group and 48.2% in the placebo group.

Figure 3. Mean change from baseline in MG-ADL score by week 26 for overall population

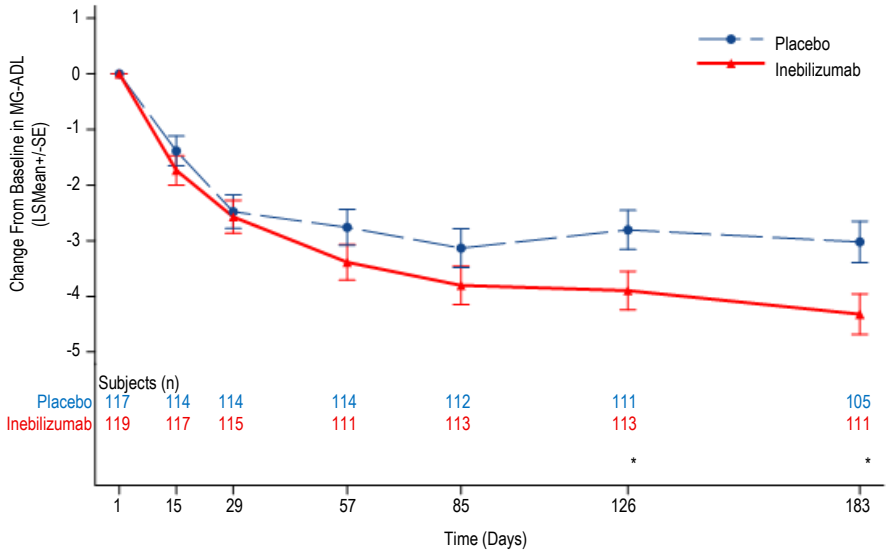
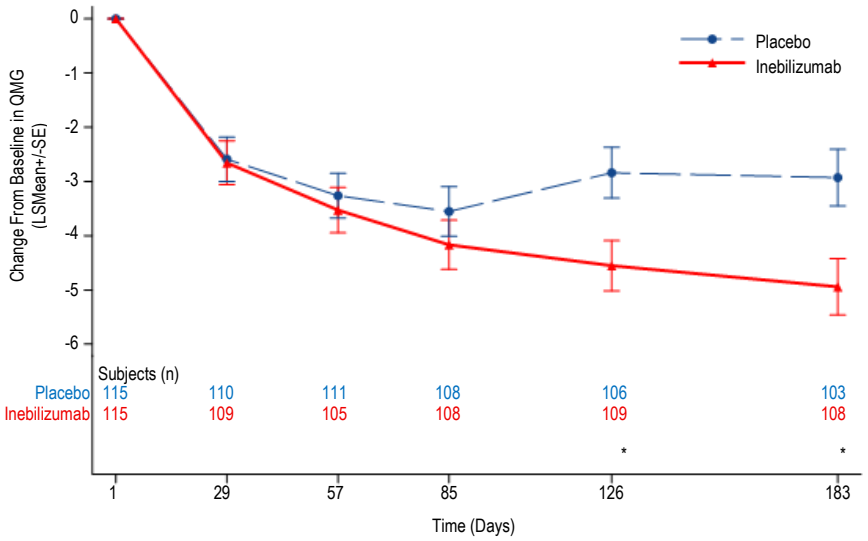
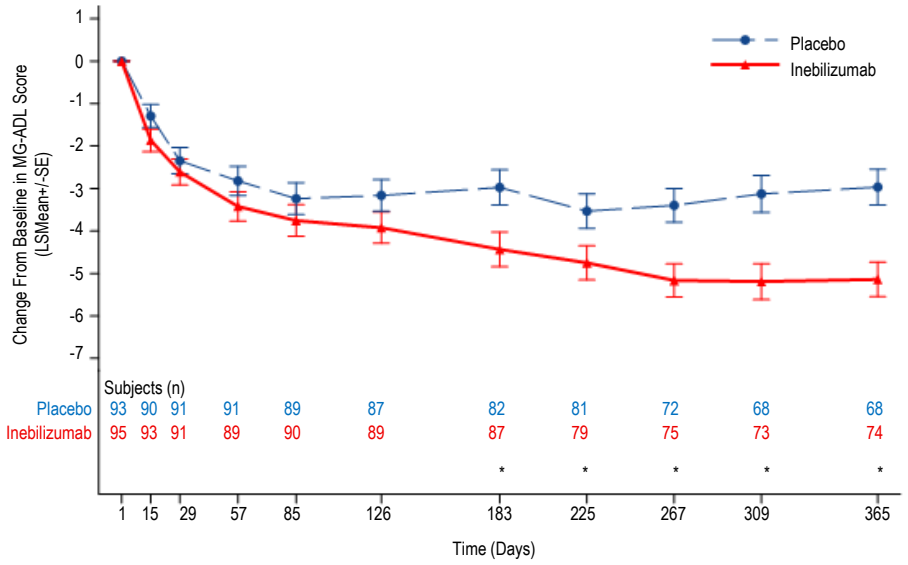


Figure 4. Mean change from baseline in QMG score by week 26 for overall population



Patients who were gMG anti-AChR-Ab+ continued in the RCP until week 52. Results in these patients show that the treatment difference favoring inebilizumab increased over time, compared with placebo. At week 52, in the anti-AChR-Ab+ population, the change from baseline in the MG-ADL score was -5.1 vs -3.0 for inebilizumab and placebo, respectively.

Figure 5. Mean change from baseline in MG-ADL score by week 52 for anti-AChR-Ab+ patients



At the time of primary analysis, in total, 94 patients (79.0%) in the inebilizumab group and 84 patients (70.6%) in the placebo group received any dose of inebilizumab during the OLP. Among patients who initially received inebilizumab during the RCP, continued improvements in MG-ADL and QMG were observed through week 78 of OLP in the anti-AChR-Ab+ and in the anti-MuSK-Ab+ subpopulations, respectively. Among patients who initially received placebo and initiated treatment with inebilizumab during the OLP, improvements in MG-ADL and QMG continued through week 78 of OLP in the anti-AChR-Ab+ and in the anti-MuSK-Ab+ subpopulations, respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with inebilizumab in one or more subsets of the paediatric population in NMOSD, IgG4-RD and gMG (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Inebilizumab is administered as an intravenous infusion. In the NMOSD study, the mean maximum concentration was 108 µg/mL (300 mg, second dose on day 15), and the cumulative area under the curve (AUC) of the 26-week treatment period in which NMOSD patients received two intravenous administrations 2-week apart was 2980 µg×d/mL. In the IgG4-RD study, the mean maximum concentration was 127 µg/mL (300 mg, second dose on day 15), and the cumulative AUC of the 52-week treatment period in which IgG4-RD patients received two intravenous administrations 2 weeks apart, followed by a third dose at week 26 was 4290 µg×d/mL.

In the gMG study, the mean maximum concentration (300 mg, second dose on day 15) was 126 µg/mL for the anti-AChR-Ab+ subpopulation (n = 90) and 159 µg/mL for the anti-MuSK-Ab+ subpopulation (n = 20). The cumulative AUC of the 26-week treatment period in which anti-AChR-Ab+ patients (n = 82) received two intravenous administrations 2 weeks apart was 3120 µg×d/mL. The cumulative AUC of the 26-week treatment period in which anti-MuSK-Ab+ patients (n = 17) received two intravenous administrations 2 weeks apart was 3740 µg×d/mL. Additionally, the cumulative AUC of the 52-week treatment period in which anti-AChR-Ab+ patients (n = 84) received two intravenous administrations 2 weeks apart, followed by a third dose at week 26 was 4240 µg×d/mL.

Distribution

Based on population pharmacokinetic analysis, the estimated typical central and peripheral volume of distribution of inebilizumab was 2.95 L and 2.57 L, respectively.

Biotransformation

Inebilizumab is a humanised IgG1 monoclonal antibody that is degraded by proteolytic enzymes widely distributed in the body.

Elimination

In adult patients with NMOSD, IgG4-RD and gMG, the terminal elimination half-life was approximately 18 days. From population pharmacokinetic analysis, the estimated inebilizumab systemic clearance of the first-order elimination pathway was 0.19 L/day. At low pharmacokinetic exposure levels, inebilizumab was likely subject to the receptor (CD19)-mediated clearance, which decreased with time presumably due to the depletion of B cells by inebilizumab treatment.

Special populations

Paediatric population

Inebilizumab has not been studied in adolescents or children.

Elderly

Based on population pharmacokinetic analysis, age did not affect inebilizumab clearance.

Gender, race

A population pharmacokinetic analysis indicated that there was no significant effect of gender and race on inebilizumab clearance.

Renal impairment

No formal clinical studies have been conducted to investigate the effect of renal impairment on inebilizumab. Due to the large molecular weight and hydrodynamic size of an IgG monoclonal antibody, inebilizumab is not expected to be filtered through the glomerulus. From population pharmacokinetic analysis, inebilizumab clearance in patients with varying degrees of renal impairment was comparable to patients with normal estimated glomerular filtration rate.

Hepatic impairment

No formal clinical studies have been conducted to investigate the effect of hepatic impairment on inebilizumab. In clinical studies, no subjects with severe hepatic impairment have been exposed to inebilizumab. IgG monoclonal antibodies are not primarily cleared via the hepatic pathway; change in hepatic function is, therefore, not expected to influence inebilizumab clearance. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (AST, ALP, and bilirubin) had no clinically relevant effect on inebilizumab clearance.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Inebilizumab was evaluated in a combined fertility and embryo-foetal development study in female and male huCD19 Tg mice at intravenous doses of 3 and 30 mg/kg. There was no effect on

embryo-foetal development, however, there was a treatment-related reduction in fertility index at both tested doses. The relevance of this finding to humans is unknown. Additionally, there was a decrease in B-cell populations at the site of B-cell development in foetal mice born to inebilizumab-treated animals as compared to the offspring of control animals, suggesting that inebilizumab crosses the placenta and depletes B cells.

Only sparse toxicokinetic samples were collected in the combined fertility and embryo-foetal development study; based on first dose maximum concentration (C_{max}), the exposure multiples of 3 and 30 mg/kg in female huCD19 Tg mice were 0.4-fold and 4-fold, respectively for the 300 mg clinical therapeutic dose.

In a pre-/postnatal development study in transgenic mice, administration of inebilizumab to maternal animals from gestation day 6 to lactation day 20 resulted in depleted B-cell populations in offspring at postnatal day 50. B-cell populations in offspring recovered by postnatal day 357. The immune response to neoantigen in offspring of animals treated with inebilizumab was decreased relative to offspring of control animals, suggestive of impairment of normal B-cell function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Sodium chloride
Trehalose dihydrate
Polysorbate 80 [E433]
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

5 years

Shelf life after dilution

The prepared infusion solution should be administered immediately. If not administered immediately, store up to 24 hours in a refrigerator at 2°C to 8°C or 4 hours at room temperature prior to the start of the infusion.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL of concentrate in a Type 1 glass vial with an elastomeric stopper and a mist gray flip-off aluminium seal.

Pack size of 3 vials.

6.6 Special precautions for disposal

Preparation of infusion solution

Prior to the start of the intravenous infusion, the prepared infusion solution should be at room temperature between 20°C and 25°C.

The concentrate should be visually inspected for particulate matter and discolouration. The vial should be discarded if the solution is cloudy, discoloured, or it contains discrete foreign particulate matter.

- The vial should not be shaken.
- The vial should be stored upright.
- Obtain an intravenous bag containing 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. Do not use other diluents to dilute inebilizumab as their use has not been tested.
- Use only a 21-gauge or smaller bore needle (e.g., 22 or 23-gauge) to puncture the vial stopper. Do not use vial spikes or closed system transfer devices, as these may damage the stopper and compromise vial integrity.
- Withdraw 10 mL of Uplizna from each of the 3 vials contained in the carton and transfer a total of 30 mL into the 250 mL intravenous bag. Mix diluted solution by gentle inversion. Do not shake the solution.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1602/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 April 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

AstraZeneca Pharmaceuticals LP
Frederick Manufacturing Center (FMC)
633 Research Court
Frederick, MD 21703 USA

Name and address of the manufacturers responsible for batch release

Horizon Therapeutics Ireland DAC
Pottery Road
Dun Laoghaire
Co. Dublin
A96 F2A8
Ireland

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Uplizna in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Uplizna is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Uplizna have access to/are provided with the following educational package:

- A **patient card**

The **patient card** shall contain the following key messages:

- Information that inebilizumab treatment may increase the risk of infections, including serious infections, viral reactivation, opportunistic infections, and PML
- A warning message on seeking early medical care in case of signs and symptoms of infection and PML
- A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency that the patient is receiving inebilizumab
- Contact details of treating physician/centre
- Cross-reference to the Package Leaflet

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Uplizna 100 mg concentrate for solution for infusion
inebilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 10 mL contains 100 mg of inebilizumab (10 mg/mL)

After dilution, the final concentration of the solution to be infused is 1.0 mg/mL.

3. LIST OF EXCIPIENTS

Histidine, histidine hydrochloride monohydrate, polysorbate 80, sodium chloride, trehalose dihydrate, and water for injections.

See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
3 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Must be diluted before use.
Read the package leaflet before use.
Do not shake.
Store vials upright.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf life after dilution:
Administer the prepared infusion solution immediately. If not administered immediately, store up to 24 hours in a refrigerator at 2°C to 8°C or 4 hours at room temperature prior to the start of the infusion.

Discard date:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original carton to protect from light.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1602/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

GLASS VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Uplizna 100 mg sterile concentrate
inebilizumab
For IV use after dilution.

2. METHOD OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg/mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Uplizna 100 mg concentrate for solution for infusion
inebilizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- Your doctor will give you a patient card, which contains important safety information you need to be aware of before and during your treatment with Uplizna.

What is in this leaflet

1. What Uplizna is and what it is used for
2. What you need to know before you are given Uplizna
3. How Uplizna is given
4. Possible side effects
5. How to store Uplizna
6. Contents of the pack and other information

1. What Uplizna is and what it is used for

Uplizna contains the active substance inebilizumab and belongs to a class of medicines called monoclonal antibodies. It is a protein that targets antibody-producing cells in the immune system (the body's natural defences) called B cells.

Uplizna is used to treat adults with:
- Neuromyelitis optic spectrum disorder (NMOSD), a rare condition which affects the nerves of the eye and spinal cord. The condition is thought to be due to the immune system mistakenly attacking the nerves in the body. Uplizna is given to patients with NMOSD whose B cells produce antibodies against aquaporin-4, a protein that plays an important role in nerve function.
- Immunoglobulin G4-related disease (IgG4-RD), a rare condition which affects multiple organs in the body. The condition is due to the immune system damaging the body's own tissues. Patients with IgG4-RD may have high levels of a specific type of antibody called IgG4. B cells producing IgG4 build up in affected tissues and contribute to organ damage.
- Generalized myasthenia gravis (gMG), a rare condition where the immune system attacks and damages muscle cells causing muscle weakness throughout the body. Patients with gMG produce IgG autoantibodies against specific proteins, which disrupt or block communication between nerves and muscles.

2. What you need to know before you use Uplizna

Do not use Uplizna

- if you are **allergic to inebilizumab** or any of the other ingredients of this medicine (listed in section 6).
- if you are suffering from a severe active infection such as hepatitis B.
- if you have active or untreated latent tuberculosis.

- if you have a history of progressive multifocal leukoencephalopathy (PML), an uncommon but serious brain infection caused by a virus.
- if you have been told that you have severe problems with your immune system.
- if you have cancer.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before you are given Uplizna if you:
- have or think you have an infection.
- have ever taken, take, or plan to take medicines that affect your immune system, or other treatments for your condition. These medicines could increase your risk of getting an infection.
- have ever had **hepatitis B** or are a carrier of the hepatitis B virus.
- have ever had **hepatitis C** or are a carrier of the hepatitis C virus.
- have had a recent vaccination or are scheduled to receive any vaccinations. You should receive any required vaccines at least 4 weeks before you start treatment with Uplizna.

Infusion-related reactions
Uplizna can cause infusion-related reactions, which can include headache, feeling sick (nausea), sleepiness, shortness of breath, fever, muscle pain, rash, palpitations or other symptoms. Treatment may be interrupted or stopped if symptoms occur.

Children and adolescents
This medicine should not be given to children and adolescents because it has not been studied in this population.

Other medicines and Uplizna
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before you are given this medicine.

Pregnancy
Uplizna should not be used during pregnancy as the medicine may pass the placenta and affect the baby. If you are able to get pregnant you should use birth control (contraception) continuously once you start receiving Uplizna. If your doctor recommends stopping treatment, continue your contraception until 6 months after your last infusion.

Breast-feeding
It is not known if Uplizna passes into breast milk. If you are breast-feeding, talk to your healthcare provider about the best way to feed your baby if you start treatment with Uplizna.

Driving and using machines
Uplizna is not expected to impact your ability to drive or use machines.

Uplizna contains sodium
This medicine contains 48 mg sodium (main component of cooking/table salt) in each infusion. This is equivalent to 2% of the recommended maximum daily dietary intake of sodium for an adult.

Uplizna contains polysorbate
This medicine contains 1 mg of polysorbate 80 per vial which is equivalent to 0.1 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Uplizna is given

Uplizna is given by a drip (infusion) into a vein under the supervision of a doctor experienced in treating patients with your condition.

The recommended dose is 300 mg.

The first dose is followed 2 weeks later by a second dose, and after that a dose every 6 months.

You will be given other medicines half an hour to an hour before the infusion, to reduce the risk of side effects. A doctor or nurse will monitor you during the infusion and for an hour afterward.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss the possible side effects with you and explain the risks and benefits of Uplizna prior to treatment.

Serious side effects

The most **serious side effects** are infusion-related reactions and infections (see section 2). These side effects may happen any time during treatment or even after your treatment has ended. You may experience more than one side effect at the same time. If you have an infusion-related reaction or infection, call or see your doctor right away.

Other side effects

Very common (may affect more than 1 in 10 people)

- bladder infection
- infection in the nose, throat, sinuses, and/or lungs
- common cold (nasopharyngitis)
- flu
- joint pain
- back pain
- immunoglobulins decreased
- lower-than-normal number lymphocyte (a form of white blood cells) in the blood (lymphopenia)
- reaction to the Uplizna infusion (see Infusion-related reactions, above)
- headache

Common (may affect up to 1 in 10 people)

- lower-than-normal number neutrophil (a form of white blood cells) in the blood, sometimes occurring 4 weeks or more after the latest dose of Uplizna (neutropenia; late-onset neutropenia)
- swollen sinuses usually caused by an infection
- pneumonia (lung infection)
- cellulitis, a potentially serious bacterial skin infection
- shingles (herpes zoster, a painful, blistering rash in one part of the body)
- muscle pain (myalgia)
- fever (pyrexia)
- cough

Uncommon (may affect up to 1 in 100 people)

- infection in the blood (sepsis), an unusually severe response to an infection
- progressive multifocal leukoencephalopathy (PML), an uncommon but serious brain infection caused by a virus
- abscess (an infection under the skin usually caused by bacteria)
- bronchiolitis, an infection of the airways caused by a virus

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Uplizna

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date, which is stated on the carton after "EXP". The expiry date refers to the last day of that month.
Store in a refrigerator at 2°C to 8°C.
Store in the original carton to protect from light.
Do not freeze.
Do not use this medicine if you notice particulate matter and discolouration.

6. Contents of the pack and other information

What Uplizna contains

- The active substance is inebilizumab.
- Each vial contains 100 mg of inebilizumab.
- The other ingredients are histidine, histidine hydrochloride monohydrate, polysorbate 80, sodium chloride, trehalose dihydrate, and water for injections.

What Uplizna looks like and contents of the pack

Uplizna 100 mg concentrate for solution for infusion is a clear to slightly opalescent, colourless to slightly yellow solution supplied as one carton containing 3 vials.

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4817 ZK Breda
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Manufacturer
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Manufacturer
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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.