EUROPEAN UNION RISK MANAGEMENT PLAN

Uplizna® (inebilizumab)

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	3.2
Date:	31 October 2025
Supersedes:	Version 3.1, dated 30 July 2025

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	3.2
Data lock point of this RMP:	10 December 2024
Date of final sign-off:	31 October 2025
Rationale for submitting an updated RMP:	To consolidate the RMP Version 3.1 (submitted within ongoing procedure EMA/VR/0000257358), and RMP Version 2.2 (submitted within CHMP approved procedure EMEA/H/C/005818/II/0012). To update the RMP with data on the proposed indication of generalized myasthenia gravis (gMG).

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Throughout the RMP	• Approved updates for Uplizna® EU RMP Version 2.2 have been consolidated with the proposed Uplizna® EU RMP Version 3.1	Version 3.2, 31 October 2025
Part I: Product(s) Overview	• Included indication of immunoglobulin G4-related disease (IgG4-RD) • Updated to align with the proposed Summary of Product Characteristics (SmPC)	Version 3.2, 31 October 2025
Part II: Safety Specification		
SI: Epidemiology of the Indication(s) and Target Population(s)	Epidemiology for IgG4-RD indication added	Version 3.2, 31 October 2025
SIII: Clinical Trial Exposure	Added the exposure data for the IgG4-RD indication from MITIGATE clinical study	Version 3.2, 31 October 2025
SVII.3.1: Presentation of Important Identified Risks and Important Potential Risks	Included frequency of risk for IgG4-RD indication	
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	• Included indication for each study • Included IgG4-RD patient population to study 20230063 and updated study milestone • Included generalized myasthenia gravis (gMG) patient population to study 20230063 and updated study milestone • Included gMG patient population to study 20230064	Version 3.2, 31 October 2025
Part VII: Annexes		
Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	• Included indication for each study • Updates made according to the changes made above	Version 3.2, 31 October 2025
Annex 7: Other Supporting Data (Including Referenced Material)	• Added references for IgG4-RD indication	Version 3.2, 31 October 2025

Other RMP versions under evaluation: RMP version number: Submitted on: Procedure number:	
Details of the currently approved RMP:	
Version number:	2.2
Approved with procedure:	EMEA/H/C/005818/II/0012
Date of approval (opinion date):	18 September 2025
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind, Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
AChR	acetylcholine receptor
ACR	American college of rheumatology
AIP	autoimmune pancreatitis
anti-AChR-Ab+	anti-acetylcholine receptor antibody positive
anti-MuSK-Ab+	anti-muscle-specific tyrosine kinase antibody positive
AQP4	anti-aquaporin-4
CBC	complete blood count
CD	cluster of differentiation
EEA	European Economic Area
EFD	embryofetal development
EFNS	European Federation of Neurological Societies
eGFR	estimated glomerular filtration rate
EPAR	European Public Assessment Report
EU	European Union
EULAR	European league against rheumatism
FcRn	fragment crystallizable receptor
gMG	generalized myasthenia gravis
HBcAb	hepatitis B core antibody
HBsAG	hepatitis B surface antigen
HBV	hepatitis B virus
HIV-1	human immunodeficiency virus-1
huCD19 Tg	human CD19 transgenic
ICF	informed consent form
IgG1	immunoglobulin G1
IgG4-RD	IgG4-related disease
IV	intravenous
JCV	John Cunningham virus
MAH	Marketing Authorization Holder
MG	myasthenia gravis
MRI	magnetic resonance imaging
MTPC	Mitsubishi Tanabe Pharma Corporation
MuSK	muscle-specific tyrosine kinase
NEMOS	NMO Study Group

Term/Abbreviation	Explanation
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorder
NOAEL	no observed-adverse-effect level
NSF	nephrogenic systemic fibrosis
OLP	open-label period
PBRER	Periodic Benefit Risk Evaluation Report
PI	product information
PL	package leaflet
PML	progressive multifocal leukoencephalopathy
PSUR	periodic safety update report
RCP	randomized-controlled period
RMP	risk management plan
SC	subcutaneous
SmPC	Summary of Product Characteristics
SOC	System Organ Class
US	United States

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Inebilizumab
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	L04AG10
Marketing authorization holder	Amgen Europe B.V
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Uplizna®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Inebilizumab is a monoclonal antibody that specifically binds to cluster of differentiation (CD)19, a cell surface antigen present on pre-B and mature B-cell lymphocytes including plasmablasts, and some plasma cells.
Summary of mode of action	Following cell surface binding to B-lymphocytes, inebilizumab supports antibody-dependent cellular cytolysis and antibody-dependent cellular phagocytosis. B-cells are believed to play a central role in the pathogenesis of neuromyelitis optica spectrum disorder (NMOSD), immunoglobulin G4-related disease (IgG4-RD), and generalized myasthenia gravis (gMG). The precise 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.
Important information about its composition	Inebilizumab is a humanized IgG1 monoclonal antibody produced in Chinese hamster ovary cell line by recombinant DNA technology.

Table 1. Product(s) Overview

Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.
Indication(s) in the EEA	
Current	Uplizna is indicated as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin 4 immunoglobulin G (AQP4-IgG) seropositive.
Proposed	<u>Neuromyelitis optica spectrum disorders (NMOSD)</u> Uplizna is indicated as monotherapy for the treatment of adult patients with NMOSD who are anti-aquaporin 4 immunoglobulin G (AQP4-IgG) seropositive. <u>Immunoglobulin G4-related disease (IgG4-RD)</u> Uplizna is indicated for the treatment of adult patients with active IgG4-RD. <u>Generalized myasthenia gravis (gMG)</u> 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.
Dosage in the EEA	
Current	Initial recommended loading dose is 300 mg (3 vials of 100 mg) intravenous (IV) infusion followed 2 weeks later by a second 300 mg IV infusion. The recommended maintenance dose is 300 mg IV infusion every 6 months.
Proposed	Not applicable.
Pharmaceutical form(s) and strength(s)	
Current	Concentrate for solution for infusion: 100 mg/10 mL (10 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution.
Proposed:	Not applicable.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Neuromyelitis Optica Spectrum Disorder

Incidence	The incidence of NMOSD in Europe is estimated as 0.054 to 0.4 cases per 100 000 per year (Jonsson et al, 2019; Papp et al, 2018; Aboul-Enein et al, 2013; Jacob et al, 2013; Asgari et al, 2011). Worldwide, incidence rates have been reported between 0.039 and 0.73 per 100 000 person-years among adults (Papp et al, 2021).
Prevalence	The prevalence of NMOSD in Europe is estimated as 0.72 to 4.4 cases per 100 000 (Jonsson et al, 2019; Papp et al, 2018; Aboul-Enein et al, 2013; Jacob et al, 2013; Cossburn et al, 2012; Asgari et al, 2011). Worldwide, the prevalence ranges from 0.34 to 10 per 100 000 persons among adults (Papp et al, 2021).
Demographics of population in the proposed indication and risk factors for the disease	NMOSD is a worldwide disease affecting women and men ranging from 3 to 80 years of age (Weinshenker and Wingerchuk, 2017). Middle-aged patients are most commonly affected and the median age of onset of NMOSD in Europe ranges from 30 to 55 years (Aboul-Enein et al, 2013; Cossburn et al, 2012; Asgari et al, 2011). While preadolescent children do not have a sex predilection, after adolescence, women predominate and constitute 70% to 90% of affected individuals with a female to male ratio ranging from 3:1 to 9:1 (Huang et al, 2020; Weinshenker and Wingerchuk, 2017; Asgari et al, 2011; Collongues et al, 2010). The disease is present in all ethnic groups; however, a predilection for non-white individuals has been reported and the highest incidence has been observed in Afro-Caribbean regions where the rate is about 2.5 fold higher than that of the predominantly White population in the United States (US) (Papp et al, 2021; Weinshenker and Wingerchuk, 2017). Similar patterns have been observed in Denmark where higher prevalence was reported in the Asian population 2.47 per 100 000 persons as compared to 1.01 per 100 000 persons for the Caucasian population (Papp et al, 2018). Familial aggregation of neuromyelitis optica (NMO) currently known as NMOSD (Glisson, 2021; Fujihara, 2019) has been reported and constitutes at least 3% of cases (Weinshenker and Wingerchuk, 2017). Genetic predisposition, more specifically the allele HLA-DRB1*03 has been identified as a risk for NMO in the French, Brazilian (NMO-Ig-positive), and Afro-Caribbean populations (Zarei et al, 2018).

Table 2. Summary of Epidemiology of Neuromyelitis Optica Spectrum Disorder

Main existing treatment options	Soliris (eculizumab) was approved for the treatment of NMOSD in adult subjects who are anti-aquaporin-4 (AQP4) antibody positive with a relapsing course of the disease in the United States (June 2019) and European Union (EU) (August 2019) (Alexion, 2019; FDA, 2019; Selmaj and Selmaj, 2019). ENSPRYNG (satralizumab) and Ultomiris (raviluzumab) are indicated for the treatment of NMOSD in adult patients who are AQP4 antibody-positive (Alexion, 2024; Genentech, 2020). Acute NMOSD attacks are generally treated with high-dose corticosteroids or plasma exchange (Glisson, 2021; Trebst et al, 2014; Kimbrough et al, 2012; Sellner et al, 2010). Disability in NMOSD is the result of acute attacks, so the goal of chronic treatment is to reduce the risk of attacks (Sellner et al, 2010). Treatment guidelines developed prior to the performance of randomized, controlled trials were based on limited, uncontrolled studies (Trebst et al, 2014; Sellner et al, 2010). The European Federation of Neurological Societies (EFNS) recommended first-line treatment with azathioprine with or without oral corticosteroids and consideration of rituximab (Sellner et al, 2010). The EFNS recommends consideration of cyclophosphamide, mitoxantrone, mycophenolate mofetil, IV immunoglobulin, methotrexate, or intermittent plasma exchange as options for second-line treatment (Sellner et al, 2010). The German NMO Study Group (NEMOS) recommends azathioprine or rituximab as first-line treatments; mycophenolate mofetil, mitoxantrone, or methotrexate as second-line therapies; and combination therapies or tocilizumab as third-line options (Trebst et al, 2014). However, the efficacy and long-term safety of these drugs in NMOSD have not been rigorously studied.
Natural history of the indicated condition in the untreated population, including mortality and morbidity	NMOSD attacks can be severe and can result in blindness, paralysis, and even death due to neurogenic respiratory failure (Oh and Levy, 2012). Incomplete recovery from attacks is typical, and accumulative disabilities arise from the severity and frequency of attacks. By some estimates, within 5 years, > 50% of patients are blind in one or both eyes or require ambulatory help (Wingerchuk et al, 2007). Historically, mortality in NMO was as high as 30% at 5 years, but a more recent study suggests 9% at 6 years (Kitley et al, 2012). Common symptoms include visual impairment, sensory deficits, weakness, stiffness/spasticity, bowel and bladder dysfunction, gait dysfunction, pain, and mood disorders (Eaneff et al, 2017).
Important comorbidities	NMOSD is commonly associated with other systemic autoimmune diseases, including autoimmune thyroid disease, systemic lupus erythematosus, and Sjogren's syndrome (Huda et al, 2019; Weinshenker and Wingerchuk, 2017). Anxiety disorders, migraine, major depression disorder, and iron deficiency anemia have also been reported (Barzegar et al, 2021).

Table 3. Summary of Epidemiology of Active IgG4-related Disease

Incidence/ Prevalence	There are limited published data on the incidence and prevalence of immunoglobulin G4-related disease (IgG4-RD). Most observational research were cohort studies from single-site global tertiary care centers. Unfortunately, results from these studies are inherently open to referral bias and thus, do not accurately reflect the epidemiology of IgG4-RD in the general population. However, recently, larger population-based studies have been conducted in the US and Japan, generating incidence and prevalence estimates for IgG4-RD. Reliable population-based estimates for incidence/prevalence of IgG4-RD are not available for Europe. A retrospective cohort study, using US population-based claims data reported an incidence of IgG4-RD as 0.78 per 100 000 person-years in 2015 which increased to 1.39 per 100 000 person-years in 2019. The point prevalence on 01 January 2019 was 5.3 per 100 000 persons (Wallace et al, 2023). The reason for this increased incidence/prevalence remains unclear, but could potentially be related to the algorithms/International Classification of Diseases (ICD) codes used or physician's awareness of the disease. In a study from Japan, the incidence of IgG4-RD was estimated to be 2.8 to 10.8 per million population, with a median age of onset of 58 years (Umehara et al, 2012).
Demographics of population in the proposed indication and risk factors for the disease	In the Wallace et al, retrospective cohort study described above, the mean age of patients was 56.5 years with 57.6% female and 66% White (Wallace et al, 2023). Fernández Codina (2015) conducted a retrospective multicenter study in 12 hospitals across Spain, including patients who met the criteria of IgG4-RD diagnosis. Of the 55 patients included in the study, 69.1% were male. Median age at diagnosis was 53 years. There were 54.5% patients in the histologically highly suggestive IgG4-RD group and 45.5% in the probable IgG4-RD group. A study from Germany retrospectively evaluated 46 patients from a tertiary referral center who were diagnosed with IgG4-RD and/or type 1 autoimmune pancreatitis (AIP) according to the International Consensus Diagnostic Criteria or Unifying-AIP criteria between June 2006 and August 2019 (Backhus et al, 2021). Forty-six patients, consisting of 67% men and 33% women, were included in the analysis. The mean age was 54 years (SD ± 16, range 21 to 87). Parente et al (2024) characterized a Portuguese population of patients under rheumatology care, utilizing a national multicenter observational study focused on patients with a clinical lgG4-RD diagnosis (62.5% met the 2019 American college of rheumatology [ACR] / European League Against Rheumatism [EULAR] classification criteria) followed-up in rheumatology departments. Data collected from 30 March 2022 to 20 December 2022 included 24 patients with a mean current age of 59.95 years (SD = ±13.35). The mean age at diagnosis was 56.09 years (SD = ±14.13), and the mean age at the onset of symptoms was 53.96 years (SD = ±14.19). Twelve (50%) patients were male. The most common overall manifestations involved salivary glands (37.5%), followed by orbits, lacrimal glands and aorta (25% each), and pancreas (20.8%). The study documented single organ disease in 6 (25%) patients. There was 1 death (4.2%).

Table 3. Summary of Epidemiology of Active IgG4-related Disease

Demographics of population in the proposed indication and risk factors for the disease (continued)	A retrospective study was conducted by Keller-Sarmiento et al (2024) at San Raffaele Hospital (HSR) in Milan (Italy). Data from 210 patients affected by IgG4-RD were followed at the IgG4-RD Outpatient Clinic of the Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UniRAR) between January 2010 and December 2022. There were 210 patients with IgG4-RD (71% male) included in the study. The mean age at disease onset was 58 years (SD = ± 15). The median (interquartile range [IQR]) serum IgG4 level at the time of diagnosis was 419 mg/di (IQR 139-472). Multiorgan involvement was present in 170 patients (81%). Organs affected by IgG4-RD included pancreas (49%), biliary tract (24%), salivary glands (21%), and retroperitoneum (19%). Of the patients, 41% had pancreato-biliary disease, 20% had retroperitoneal fibrosis/aortitis, 14% had head and neck limited disease, 27% had Mikulicz/Systemic disease. The median follow-up time was 58 months (30 to 94 months).
Main existing treatment options	Currently there are no approved products for the treatment of IgG4-RD. Surgery is one management approach, particularly in organs amenable to excision such as the pancreas, aorta, biliary ducts, and thyroid (Lee et al, 2019) and some patients, particularly those with pancreato-biliary or renal disease, may require stenting for mechanical obstruction. However, interventional procedures are not always curative, and patients undergoing surgical intervention often also receive pharmacological treatment (Lee et al, 2019; Brito-Zeron et al, 2016). Like any surgical procedure, these interventions are associated with some risks, including those related to infection and anesthesia. Glucocorticoids (GCs) are typically used to induce remission in patients with active IgG4-RD and are recommended for this purpose in an international consensus group statement on the management of IgG4-RD (Khosroshahi et al, 2015) and other publications (Okazaki et al, 2022; Tanaka and Stone, 2023; Lanzillotta et al, 2021; Lohr et al, 2020; Omar et al, 2020; Kamisawa et al, 2019; Zhang and Stone, 2019; Brito Zerón et al, 2016). IgG4-RD flares are responsive to GC therapy and a high proportion of patients (> 90%) have clinical response to GC therapy (Abraham and Khosroshahi, 2017; Masaki et al, 2017). Both prospective and retrospective studies demonstrate that, although GCs are effective initially for most patients, disease recurrences during or after GC tapering are common. Between 40% and 76% of patients who had successful treatment with GCs will relapse in the same organ or another, requiring several induction treatments and long tapers (Peng et al, 2024; Abraham and Khosroshahi, 2017; Brito-Zerón et al, 2016). Although used in IgG4-RD in patients experiencing a flare, the toxicity of GCs is a major concern. The deleterious effects of steroids when taken long-term are substantial (Miloslavsky et al, 2017). Furthermore, in some patients, particularly those with comorbidities such as osteoporosis, uncontrolled hypertension, diabetes, glaucoma, and peptic ulcer disease, GCs may be contraindicated (Hodgens and Sharman, 2024).

Table 3. Summary of Epidemiology of Active IgG4-related Disease

Main existing treatment options (continued)	Moreover, endocrine insufficiency manifests as diabetes mellitus in 26% to 78% of patients with pancreatic involvement (the most common manifestation of IgG4-RD), making this patient population at higher risk for steroid related hyperglycemia (Al-Dhahab et al, 2013). Thus, recurrence of flare, with its attendant risk of progression of disease and of GC treatment toxicity, requires a steroid-sparing treatment approach for the prevention of disease flares and induction of complete remission. Certain traditional immunomodulatory agents have been used for steroid-sparing maintenance therapy in IgG4-RD. These include azathioprine, mycophenolate mofetil, 6-mercaptopurine, methotrexate, tacrolimus, and cyclophosphamide (Khosroshahi et al, 2015; reviewed in Lanzillotta et al, 2020). Retrospective and prospective cohort studies have examined effects of immunomodulatory agents on IgG4-RD, and a meta-analysis of their collected findings suggest possible treatment benefit of the addition of immunomodulatory agents to GC therapy (Omar et al, 2020). However, the efficacy of any of these agents has not been rigorously evaluated in a double-blind, randomized, controlled study, and most of these studies examined immunomodulatory agents in addition to GCs rather than as monotherapy. The cluster of differentiation (CD) 20 targeted B-cell-depleting agent rituximab is also used in IgG4-RD patients; however, evidence for the use of rituximab in IgG4-RD is limited to case reports and case series (Nikolic et al, 2021; Campochiaro et al, 2020; Quattrocchio et al, 2020; Majumder et al, 2018; reviewed in Patel et al, 2023), a meta-analysis (Lanzillotta et al, 2021) and open-label studies. In other autoimmune diseases, rituximab treatment failure is associated with persistence of pathogenic CD19/CD20-B cells that escape depletion by rituximab (Mahevas et al, 2015; Mahevas et al, 2013).
Natural history of the indicated condition in the population, including mortality and morbidity	Immunoglobulin G4-related disease is a rare systemic, chronic immune-mediated disorder that causes fibrosing inflammatory lesions in nearly any organ (Kamisawa, 2022; Maehara et al, 2020; Perugino and Stone, 2020; Zhang and Stone, 2019; Stone et al, 2012). The clinical presentation of IgG4-RD is remarkably heterogenous. The disease usually takes a chronic, relapsing-remitting course and is generally indolent and slowly progressive. The initial clinical presentation is often a mass lesion or organ enlargement that may be mistaken for malignancy. The slow pace of IgG4-RD in many patients allows for parenchymal injury and irreversible organ damage despite relatively few clinical symptoms (Katz et al, 2024). Unchecked, the disease can lead to permanent organ dysfunction, substantial disability, reduced quality of life, and death (Peng et al, 2024; Wallace et al, 2023). Since the initial description in a cohort of Japanese patients with AIP in 2001 (Hamano et al, 2001), IgG4-RD presenting in nearly any organ has been described in male and female patients across the age spectrum and from diverse racial and ethnic backgrounds. However, population-based estimates of the incidence, prevalence, and mortality associated with IgG4-RD remain scarce.

Table 3. Summary of Epidemiology of Active IgG4-related Disease

Natural history of the indicated condition in the population, including mortality and morbidity (continued)	A recent claims database analysis of 524 IgG4-RD cases (Wallace et al, 2023) found a mortality rate of 3.42/100 person-years for IgG4-RD compared to 1.46/100 person-years for the comparator (non-IgG4-RD) group, with an adjusted hazard ratio of 2.51. A second study from 2 UK hospital-based clinics found that patients with IgG4-related pancreatic or biliary disease (common manifestations of IgG4-RD) had 2.1-fold higher odds of death compared with the general population (Huggett et al, 2014). Additional studies also support the increased mortality associated with IgG4-RD (Wallwork et al, 2019), though a single center study based in Japan found no increase in mortality in IgG4-RD patients compared with the general population (Kawahara et al, 2023). This finding may relate to the spectrum and severity of disease reflected in that cohort which was assembled from a single rheumatology department. In the Spanish study Fernández Codina (2015) reported that 47.3% of patients had more than 1 organ affected at presentation. The most frequently affected organs were: retroperitoneum, orbital pseudotumor, pancreas, salivary and lachrymal glands, and maxillary sinuses. Corticosteroids were the mainstay of treatment (83.6%). Eighteen patients (32.7%) required additional immunosuppressive agents. Twenty four (43.6%) patients achieved a complete response and 26 (43.7%) presented a partial response (<50% of regression) after 22 months of follow-up. No deaths were attributed directly to IgG4-RD and malignancy was infrequent. In this large IgG4-RD series reported in Europe, patients were middle-aged males, with histologically probable IgG4-RD. The systemic form of the disease was frequent, involving mainly sites of the head and abdomen. Corticosteroids were an effective first-line treatment, sometimes combined with immunosuppressive agents. Neither fatalities nor malignancies were attributed to IgG4-RD. In the Italian study (Keller-Sarmiento, 2024), 18% of patients enrolled in this study were diagnosed with a solid or hematologic malignancy during their lifetime. The remaining 173 patients did not report a history of cancer.

Table 3. Summary of Epidemiology of Active IgG4-related Disease

Important comorbidities	IgG4-RD is associated with substantial morbidity (Katz et al, 2024; Lanzillotta et al, 2024; Zhang and Stone, 2019). The inflammatory and fibrotic processes of the disease result in acute disability and can lead to permanent organ dysfunction (Wallwork et al, 2019; Evans et al, 2018; Karim et al, 2016; Huggett et al, 2014; Cheuk and Chan, 2010). For example, IgG4-RD affecting the head and neck may result in orbital myositis, uveitis, scleritis, sialadenitis, chronic nasorhinosinusitis, Riedel's thyroiditis, and supraglottic stenosis (Wallwork et al, 2019; Evans et al, 2018; Karim et al, 2016; Huggett et al, 2014; Cheuk and Chan, 2010). Furthermore, involvement of the chest can manifest as parenchymal lung disease, pleural disease, pericarditis, coronary arteritis, fibrosing mediastinitis, and aortitis. Abdominal and pelvic manifestations include AIP type I, sclerosing cholangitis, sclerosing mesenteritis, retroperitoneal fibrosis and aortitis, tubulointerstitial nephritis, membranous glomerulonephritis, and prostatitis. Finally, pituitary, and central nervous system involvement can result in hypophysitis and hypertrophic pachymeningitis (Katz et al, 2024; Lanzillotta et al, 2024; Zhang and Stone, 2019). Irreversible organ damage is observed in approximately 60% of IgG4-RD patients at the time of diagnosis (Wallace et al, 2020; Abraham and Khosroshahi, 2017). The association between cancer and IgG4-RD is evolving, with some studies showing an association (Keller-Sarmiento, 2024, Wallace 2024) while others show no significant increase in cancer incidence or morbidity/mortality in the IgG4-RD population (Fernández Codina, 2015).

Table 4. Summary of Epidemiology of Generalized Myasthenia Gravis (gMG)

Incidence/ Prevalence	Myasthenia gravis (MG) is a rare, chronic, autoimmune neuromuscular condition (Lehnerer et al, 2022; Finnis and Jayawant, 2011). Global incidence and prevalence of MG has been rising steadily and consistently over the past several decades. A global systematic literature review examined 35 studies up to 2007 and determined the incidence rate of MG varied from 1.7 to 21.3, with a global rate of 5.3 per million. A follow-up study added an additional 29 studies up to 2019 and determined that depending on the geographic location, the global prevalence of MG ranges between 1.5 to 17.9 per million. This indicates an estimate of 56 000 to 123 000 patients in Europe (Bubuioc et al, 2021; Carr et al, 2010). A retrospective epidemiological study to determine the incidence and prevalence of MG in the province of Ourense (Galicia, Spain), identified 80 cases of MG, with a prevalence of 260 per 1 000 000 population (95% CI: 202.7, 316.4), rising to 517.9 per 1 000 000 population in those aged ≥ 65 (95% CI: 363.2, 672.9). Cumulative incidence in the study period was 15.4 per 1 000 000. Early onset (≤ 50 years) was recorded in 29.1% of cases (Garcia Estevez et al, 2023). A large, 4-year prospective cohort study of all known patients with new-onset MG in the East Midlands of the United Kingdom reported the incidence standardized to the 2011 England population was 17.3 per 1 000 000 (95% CI: 10.4, 28.2) and to the 2011 European population was 16.37 per 1 000 000 (95% CI: 9.75, 27.07) (Maddison et al, 2019). A retrospective study assessing incidence, prevalence, and treatment patterns in Germany over 10 years based on medical claims data covering 6.1 million insured persons showed that between 2011 and 2020, the prevalence of MG increased from 15.7 to 28.2 per 100 000. The age-adjusted incidence rate was 2.8 per 100 000 within the study period (95% CI: 2.43, 3.22) (Wartmann et al, 2023). A nationwide register-based study on the current incidence and prevalence of MG and MG subgroups in Sweden showed that in 2016, the incidence of MG in Sweden was 2.9 per 100 000 (95% CI: 2.5, 3.2 per 100 000) and the crude prevalence was 36.1 per 100 000 (95% CI: 34.9, 37.3) (Westerberg and Punga, 2020). A recent study analyzed US Census claims data representing over 300 million patients in all regions of the US, which estimated an overall incidence and prevalence of MG for 2021 of 3.1 per 100 000 (with similar estimates for males and females [3.2 versus 3.1 per 100 000, respectively]) and prevalence of 37 per 100 000 (with similar estimates for males and females [37.3 and 36.7, respectively]) (Rodrigues et al, 2024). Another recent US study utilized two Truven Health MarketScan databases, which included a sample of approximately 20 million commercially insured and Medicare recipients, plus 10 million Medicaid recipients. Overall, estimated prevalence was estimated at 320.2 cases per million (32.0/100 000) (Ye et al, 2024). Additional studies in Asia showed a prevalence rate of MG ranging from 12.99 per 100 000 in 2014 in Korea to a lower prevalence of 2.19 to 11.07 per 100 000 in China (Dresser et al, 2021; Fang et al, 2020; Lee et al, 2016; Park et al, 2016). In a survey-based retrospective analysis of several medical departments in Japan (7745) for 2017, with 2708 survey forms returned the number of patients with MG in Japan was 29 210 (95%CI: 26 030, 32 390). The prevalence was 23.1 per 100 000 (95% CI: 20.5, 25.6) (Yoshikawa et al, 2022).

Table 4. Summary of Epidemiology of Generalized Myasthenia Gravis (gMG)

Demographics of population in the indication and risk factors for the disease	Incidence rates have a bimodal distribution in women, with peaks around ages 30 and 50. In men, the incidence increases steadily with age, with the highest rates between age 60 and 89 (Carr et al, 2010). Women are more commonly affected before age 40, with a female:male ratio of 3:1 for early-onset MG. In the fifth decade of life, women and men are equally affected, while men have a higher proportion after age 50, with a male:female ratio of 3:2 (Ciafaloni, 2019). Around 10% of cases are pediatric (< 18 years old) (Phillips, 2003). MG can affect people of all race and ethnic backgrounds and is slightly more prevalent in patients of African ancestry (Alshekhlee et al, 2009; Oh et al, 2009; Phillips et al, 1992). Furthermore, MG phenotype may vary depending on the ethnic background. In a retrospective study from South Africa, black patients were more likely to have treatment-resistant ophthalmoplegia and ptosis than white patients, whereas white patients were more likely to develop treatment refractory gMG (Heckmann et al, 2007). The age at diagnosis was 17 years higher in Caucasians than non-Caucasians in another cohort of patients with ocular MG (Peragallo et al, 2016). A US study found that MG started earlier and had a more severe phenotype in African Americans than in Caucasians (Oh et al, 2009). The seronegative African Americans had a higher percent of muscle -specific kinase (MuSK) seropositivity (50% versus 17% in the white patients). Patients of Asian ancestry have higher rates of MuSK antibodies compared to Caucasians and individuals of African ancestry (Boldingh et al, 2017; Abukhalil et al, 2015). MuSK-associated MG is also more prevalent among those living in latitudes closer to the equator (Dresser et al, 2021; Oh et al, 2009; Deymeer et al, 2007). In most patients no precipitating factors prior to disease onset can be identified, but infections, stress, trauma, metabolic derangements, medications (eg, penicillamine), and pregnancy have all been implicated in a minority (Grob et al, 2008).
Main existing treatment options	Anticholinesterase inhibitors and immunosuppressive therapies are standard of care for MG and have reduced mortality and improved quality of life (Evoli and Damato, 2023). Approximately 85% to 90% of MG patients respond to these therapies; however, efficacy has limited durability and there are side-effects associated with long-term use that lead to reduced quality of life (Urban et al, 2018). Additionally, compared to anti-acetylcholine receptor antibody positive (anti-AChR-Ab+) patients, anti-muscle-specific tyrosine kinase antibody positive (anti-MuSK-Ab+) patients often have a poorer response to standard therapies such as anticholinesterase inhibitors, and are more likely to remain steroid dependent, despite the addition of other immunosuppressive agents (Gilhus et al, 2019). CD20-specific B cell-depleting therapies, such as rituximab, have been investigated as a potential therapy for anti-AChR-Ab+ and anti-MuSK-Ab+ MG (Nowak et al, 2022; Piehl et al, 2022; Fichtner 2020b). While rituximab is efficacious in anti-MuSK-Ab+ MG with > 95% of patients reaching stable or pharmacological remission, similar levels of efficacy are not observed in anti-AChR-Ab+ MG patients (~56% of patients experience relapse within approximately 3 years post-treatment) (Fichtner 2020b; Yi et al, 2018).

Table 4. Summary of Epidemiology of Generalized Myasthenia Gravis (gMG)

Main existing treatment options (continued)	Further, 2 recently completed placebo-controlled, randomized clinical trials demonstrate diverging conclusions regarding the efficacy of rituximab (BeatMG and RINOMAX) resulting in uncertainty about efficacy (Nowak et al, 2022; Piehl et al, 2022). More recently, several therapeutics targeting the complement pathway (eculizumab/Soliris®, ravulizumab/Ultomiris®, and zilucoplan/Zilbrysq®) have been approved for the treatment of anti-AChR-Ab+ generalized MG only, because immunoglobulin G4 (IgG4) antibodies associated with anti-MuSK-Ab+ generalized MG do not activate complement (Evoli and Damato, 2023). Other therapies targeting the neonatal fragment crystallizable receptor (FcRn) have also been approved for use in the treatment of either anti-AChR- Ab+ generalized MG (efgartigimod alfa/Vyvgart®) or both anti-AChR-Ab+ and anti-MuSK- Ab+ generalized MG subgroups (rozanolixizumab-noli/Rystiggo®) (Evoli and Damato, 2023). FcRn inhibitors reduce the overall levels of circulating pathogenic autoantibodies by inhibiting the IgG salvage mechanism, but do not directly target the B cells responsible for producing the pathogenic autoantibodies.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Most patients with MG first present with ocular symptoms. Of these, 12% to 80% will develop generalized disease, with approximately 90% of cases doing so within the 2 to 3 years after diagnosis (Mittal et al, 2011; Grob et al, 2008). With improved treatments, disease severity tends to lessen after the first 5 years of illness (Grob et al, 2008). Most patients with MG will experience at least 1 exacerbation of symptoms throughout the course of their illness. These exacerbations may be triggered by an infection (commonly an upper respiratory tract infection), a reduction in dose of medications used to treat myasthenia, the use of high-dose steroids (within the first 10 to 14 days) in severe or bulbar MG, administration of medications known to aggravate myasthenia, warmer ambient temperatures, or emotional stress (Hehir and Silvestri, 2018). MG exacerbation (worsening of myasthenic weakness) includes symptoms of worsened double vision, slurred speech, increased arm weakness, falling, unsteady walking, and difficulty swallowing. A severe exacerbation of MG is known as a myasthenic crisis, and it can be life-threatening. Symptoms of a myasthenic crisis include respiratory failure, severe bulbar muscle weakness, upper airway obstruction, and severe dysphagia with aspiration (Darer et al, 2024; Stetefeld and Schroeter, 2019; Jani-Acsadi and Lisak, 2007). MG crisis occurs in approximately 15% to 20% of patients and is more likely to occur early on in the disease course, usually within the first 3 years following diagnosis (Jani-Acsadi and Lisak, 2007). Approximately 30% of patients with anti-MuSK MG experience an MG crisis; almost 70% of these crises occur within 6 months of symptom onset (Evoli and Padua, 2013). MG crisis treatment is aimed at identifying and treating any underlying precipitants, protection of the airway and mechanical ventilation until strength improves, and often plasmapheresis or possibly IV immunoglobulin (Sanders et al, 2016; Barth et al, 2011; Gajdos et al, 1997). The average duration of intubation is 5 days (Carr et al, 2014). The mortality rate in myasthenic crisis is less than 5% and is usually caused by complications of hospitalization and treatment (Carr et al, 2014).

Table 4. Summary of Epidemiology of Generalized Myasthenia Gravis (gMG)

Natural history of the indicated condition in the untreated population including mortality and morbidity	Remission in MG can occur either with or without the need for continued treatment (Jaretzki et al, 2000). In early studies examining the course of MG, it was found that approximately 20% of patients experience a complete or nearly complete remission lasting at least 6 months (Grob,1958; Grob, 1953). Follow-up studies suggest a long-term remission rate of about 10% (Grob et al, 2008). Any residual weakness tends to be confined to the orbicularis oculi and although most patients have 1 remission, as many as 5% may have 2 to 4 remissions throughout the course of their disease. Most remissions occur in the first year following diagnosis but can occur much later and the average interval between disease onset and remission is 4 years. Remission is more common in juvenile and female patients (Grob et al, 2008). The mortality rate of MG has dramatically declined from the early 20th century after the availability of acetylcholine esterase inhibitors, immunosuppressants, IV immunoglobulin and advanced respiratory care. However, the mortality rate from the disease remains at 5% to 9%, being slightly higher in males than females (Grob et al, 2008). Using the US Nationwide Inpatient Sample (NIS) database for the years 2000 to 2005, the overall in-hospital mortality rate was estimated as 2.2%, but higher in those with MG crisis (4.7%), with the main predictors of death being older age and the presence of respiratory failure (Dresser et al, 2021; Alshekhlee et al, 2009).
Important comorbidities	High rates of comorbidities were observed in patients with MG in a US retrospective observational cohort study utilizing de-identified patient data (from 2006 to 2019) from the IQVIA insurance claims database. Data for 3516 patients with MG were identified (51.2% male; mean age [standard deviation], 55.8 [13.9]; age range, 18 to 84 years). The most prevalent comorbidities were cardiovascular and endocrine disorders, including hypertension (41.9%), hyperlipidemia (37.1%), fatigue (24.8%), uncomplicated diabetes (18.2%), cerebrovascular disease (17.6%) and hypothyroidism (15.4%). Chronic pulmonary disease (13.5%) and sleep disorders (13.2%) were also common comorbidities (Basoff et al, 2023).

Part II: Module SII - Nonclinical Part of the Safety Specification

Nonclinical evaluation demonstrated that inebilizumab specifically recognizes human CD19 and has poor or no cross-reactivity to CD19 expressed on cells from nonhuman primates, rodents, or rabbits. Therefore, the human CD19 transgenic (huCD19 Tg) mouse was selected as the relevant animal model for testing the pharmacology and safety (toxicity) testing of inebilizumab.

Table 5. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity		
• Key issues identified from acute or repeat-dose toxicity studies	Completed nonclinical toxicology studies with the huCD19 Tg mouse model demonstrated that there were no adverse effects after a single IV dose (up to 50 mg/kg), 5 weekly IV doses (up to 36.6 mg/kg), or 13 or 26 weekly IV doses (up to 30 mg/kg). The only findings from these toxicology studies were related to the pharmacologic action of B-cell depletion. The no observed-adverse-effect level (NOAEL) for repeated inebilizumab IV injection is at least 36.6 mg/kg/week for up to 1 month and 30 mg/kg/week for multiple IV doses up to 6 months. Treatment with inebilizumab resulted in the expected pharmacological depletion of total B lymphocytes in peripheral blood of adult mice. A 13 week repeat-dose study to compare the toxicity of weekly subcutaneous (SC) to IV administration of inebilizumab (3 or 30 mg/kg SC; 30 mg/kg IV comparator) showed findings during the dosing phase that were similar to those identified in the previous repeat-dose toxicology studies. During the recovery phase, an increased incidence of background bronchiolo-alveolar adenomas (benign) was noted in the 30 mg/kg IV group only.	Given that this finding is isolated to 1 study and was not observed in the longer duration, 26-week chronic toxicity study (which also included a 30 mg/kg IV group), and a lifetime study in male huCD19 Tg mice that determined bronchiolo-alveolar adenomas occur at a background incidence, the finding is not considered to represent a risk to patients.

Table 5. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity (continued)		
• Reproductive/ developmental toxicity	The only treatment-related findings in a study on fertility and embryofetal development (EFD) in huCD19 Tg mice was a reduction in fertility index and the number of mice that were pregnant/number of mice in cohabitation. Importantly, there was no inebilizumab impact on EFD. There was evidence that inebilizumab crosses the placenta and depletes B-cells in the progeny of dosed animals; however, there were no adverse consequences of this B-cell depletion in the fetuses. An IV study on the effects of inebilizumab on pre- and post-natal development, including maternal function in mice, was conducted to determine the potential adverse effects of maternal test article exposure (implantation to weaning) on pregnancy, parturition, and lactation of the maternal animals as well as on the growth, viability, development, and immune function of the F1 neonates. Reproductive performance of the F1 generation was also assessed. Results showed no adverse effects on the F0 dams, F1 growth, survival, or reproductive development and performance, and F2 fetuses at any dosage level. The NOAEL for F0 maternal, F1 systemic and reproductive, and F2 embryo/fetal developmental toxicity was considered to be 30 mg/kg/dose, the highest dose level evaluated. F1 pups did show a diminished antibody response to antigen challenge at both inebilizumab dose levels after B-cells had repopulated. Accordingly, the NOAEL for F1 development and immunotoxicity could not be determined.	Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B-cell-depleting antibodies during pregnancy. Blood disorders, particularly decrease in B cell levels in fetal and newborns exposed to inebilizumab in pregnant women is an important potential risk in the RMP (Table 29). Women of childbearing potential should use highly effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab and for 6 months after the last administration of inebilizumab. The use of inebilizumab in women during breastfeeding 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 breastfed child cannot be excluded during this short period. Afterwards, inebilizumab could be used during breastfeeding if clinically needed. However, if the patient was treated with inebilizumab up to the last few months of pregnancy, breastfeeding can be started immediately after birth.

Part II: Module SIII - Clinical Trial Exposure

Table 6. Total Subject Exposure to Inebilizumab in Myasthenia Gravis Clinical Trials by Duration Any Inebilizumab Analysis Set

	Exposure to Inebilizumab by Duration							
Indication	1 – 183 days n (subj-yrs)	184 – 365 days n (subj-yrs)	366 – 548 days n (subj-yrs)	549 – 730 days n (subj-yrs)	731 – 913 days n (subj-yrs)	914 – 1095 days n (subj-yrs)	> 1095 days n (subj-yrs)	Total n (subj-yrs)
Myasthenia Gravis	21 (6.06)	45 (33.78)	34 (42.70)	54 (94.69)	19 (42.89)	23 (63.00)	11 (37.43)	207 (320.55)

n = number of subjects exposed to inebilizumab
Note: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 90.
Data cut-off 01 September 2024.
Source: /userdata/stat/amg335/meta/rmp/analysis/rmp_l_hzn_2025/Programs/t_rmp_all_ex1.sas

Table 7. Total Subject Exposure to Inebilizumab in Myasthenia Gravis Clinical Trials by Age Group and Gender
Any Inebilizumab Analysis Set

	Adults (18 to 64 years) n (subj-yrs)	Elderly People (≥ 65 years) n (subj-yrs)
Male		
Myasthenia Gravis	61 (85.30)	17 (27.35)
Female		
Myasthenia Gravis	116 (190.53)	13 (17.37)

n = number of subjects exposed to inebilizumab
Note: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 90.
Data cut-off 01 September 2024.
Source: /userdata/stat/amg335/meta/rmp/analysis/rmp_l_hzn_2025/Programs/t_rmp_all_ex2.sas

Table 8. Total Subject Exposure to Inebilizumab in Myasthenia Gravis Clinical Trials by Product and Race
Any Inebilizumab Analysis Set

	White n (subj-yrs)	Black or African American n (subj-yrs)	Asian n (subj-yrs)	Native Hawaiian or Other Pacific Islander n (subj-yrs)	Other n (subj-yrs)	Missing/Unknown n (subj-yrs)	Total n (subj-yrs)
Myasthenia Gravis	112 (177.50)	4 (6.96)	86 (128.85)	0 (0.0)	3 (3.21)	2 (4.03)	207 (320.55)

n = number of subjects exposed to inebilizumab
Note: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 90.
Data cut-off 01 September 2024.
Source: /userdata/stat/amg335/meta/rmp/analysis/rmp_l_hzn_2025/Programs/t_rmp_all_ex3.sas

Table 9. Total Subject Exposure to Inebilizumab in Myasthenia Gravis Clinical Trials by Product and Ethnic Group
Any Inebilizumab Analysis Set

	Hispanic/Latino n (subj-yrs)	Non-Hispanic/Latino n (subj-yrs)	Missing/Unknown n (subj-yrs)	Total n (subj-yrs)
Myasthenia Gravis	18 (27.42)	188 (291.41)	1 (1.72)	207 (320.55)

n = number of subjects exposed to inebilizumab
Note: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 90.
The Ethnic Group will be based on the categories collected in each study.
Data cut-off 01 September 2024.
Source: /userdata/stat/amg335/meta/rmp/analysis/rmp_l_hzn_2025/Programs/t_rmp_all_ex4.sas

Table 10. Total Subject Exposure to Inebilizumab in IgG4-RD Clinical Trials by Duration
Any Inebilizumab Analysis Set

	Exposure to Inebilizumab by Duration							
Indication	1 – 183 days n (subj-yrs)	184 – 365 days n (subj-yrs)	366 – 548 days n (subj-yrs)	549 – 730 days n (subj-yrs)	731 – 913 days n (subj-yrs)	914 – 1095 days n (subj-yrs)	> 1095 days n (subj-yrs)	Total n (subj-yrs)
IgG4-RD	16 (4.42)	33 (24.85)	25 (31.99)	19 (34.18)	14 (32.10)	5 (14.09)	0 (0.0)	112 (141.64)

IgG4-RD = immunoglobulin G4-related disease; n = number of subjects exposed to inebilizumab; OLP = open-label period; RCP = randomized-controlled period; sbj-yrs = subject-years
Note: Duration of the exposure is defined as the last inebilizumab dose date -1st inebilizumab dose date + 90.
Data cut-off for IgG4-RD MITIGATE study: 09 April 2024 for the RCP and 09 February 2024 for the OLP.
Source: G:\BPSApp\bps\workspace\UPLIZNA\Adhoc\RMP\Programs\t_rmp_ex1.sas

Table 11. Total Subject Exposure to Inebilizumab in IgG4-RD Clinical Trials by Age Group and Gender
Any Inebilizumab Analysis Set

	Adults (18 to 64 years) n (subj-yrs)	Elderly People (≥ 65 years) n (subj-yrs)
Male		
IgG4-RD	48 (62.72)	23 (23.95)
Female		
IgG4-RD	32 (44.96)	9 (10.01)

IgG4-RD = immunoglobulin G4-related disease; n = number of subjects exposed to inebilizumab; OLP = open-label period; RCP = randomized-controlled period; sbj-yrs = subject-years
Note: Duration of the exposure is defined as the last inebilizumab dose date -1st inebilizumab dose date + 90.
Data cut-off for IgG4-RD MITIGATE study: 09 April 2024 for the RCP and 09 February 2024 for the OLP.
Source: G:\BPSApp\bps\workspace\UPLIZNA\Adhoc\RMP\Programs\t_rmp_ex2.sas

Table 12. Total Subject Exposure to Inebilizumab in IgG4-RD Clinical Trials by Product and Race
Any Inebilizumab Analysis Set

	White n (subj-yrs)	Black or African American n (subj-yrs)	Asian n (subj-yrs)	Native Hawaiian or Other Pacific Islander n (subj-yrs)	Other n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
IgG4-RD	40 (45.65)	0 (0.0)	60 (79.71)	1 (0.76)	5 (5.75)	6 (9.77)	112 (141.64)

IgG4-RD = immunoglobulin G4-related disease; n = number of subjects exposed to inebilizumab; OLP = open-label period; RCP = randomized-controlled period; sbj-yrs = subject-years
Note: Duration of the exposure is defined as the last inebilizumab dose date -1st inebilizumab dose date + 90.
Data cut-off for IgG4-RD MITIGATE study: 09 April 2024 for the RCP and 09 February 2024 for the OLP.
Source: G:\BPSApp\bps\workspace\UPLIZNA\Adhoc\RMP\Programs\t_rmp_ex3.sas

Table 13. Total Subject Exposure to Inebilizumab in IgG4-RD Clinical Trials by Product and Ethnic Group
Any Inebilizumab Analysis Set

	Hispanic/Latino n (subj-yrs)	Non-Hispanic/Latino n (subj-yrs)	Missing/Unknown n (subj-yrs)	Total n (subj-yrs)
IgG4-RD	11 (14.07)	95 (117.80)	6 (9.77)	112 (141.64)

IgG4-RD = immunoglobulin G4-related disease; n = number of subjects exposed to inebilizumab; OLP = open-label period; RCP = randomized-controlled period; sbj-yrs = subject-years
Note: Duration of the exposure is defined as the last inebilizumab dose date -1st inebilizumab dose date + 90.
The Ethnic Group will be based on the categories collected in each study.
Data cut-off for IgG4-RD MITIGATE study: 09 April 2024 for the RCP and 09 February 2024 for the OLP.
Source: G:\BPSApp\bps\workspace\UPLIZNA\Adhoc\RMP\Programs\t_rmp_ex4.sas

Table 14. Total Subject Exposure to Inebilizumab in All Clinical Trials by Indication and Duration
Any Inebilizumab Analysis Set

Indication	Exposure to Inebilizumab by Duration							
	1-183 days n (subj-yrs)	184-365 days n (subj-yrs)	366-548 days n (subj-yrs)	549-730 days n (subj-yrs)	731-913 days n (subj-yrs)	914-1095 days n (subj-yrs)	>1095 days n (subj-yrs)	Total n (subj-yrs)
Neuromyelitis optica spectrum disorder	13 (2.91)	8 (6.25)	7 (8.49)	6 (10.58)	33 (75.35)	33 (88.27)	125 (523.82)	225 (715.68)
Immunoglobulin G4-related disease	16 (4.42)	33 (24.85)	25 (31.99)	19 (34.18)	14 (32.10)	5 (14.09)	0 (0.0)	112 (141.64)
Myasthenia Gravis	21 (6.06)	45 (33.78)	34 (42.70)	54 (94.69)	19 (42.89)	23 (63.00)	11 (37.43)	207 (320.55)
Total	50 (13.39)	86 (64.88)	66 (83.18)	79 (139.46)	66 (150.34)	61 (165.36)	136 (561.25)	544 (1177.86)

n = number of subjects exposed to inebilizumab
IgG4-RD = immunoglobulin G4-related disease; MG = myasthenia Gravis; NMOSD = neuromyelitis optica spectrum disorder; OLP = open-label period; RCP = randomized-controlled period
Note: For NMOSD: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 60.
For IgG4-RD and MG: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 90.
Data cut-off: For gMG MINT study: 01 September 2024; for IgG4-RD MITIGATE study: 09 April 2024 for the RCP and 09 February 2024 for the OLP.
Source: /userdata/stat/amg335/meta/rmp/analysis/rmp_l_hzn_2025/Programs/t_rmp_all_ex1.sas

Table 15. Total Subject Exposure to Inebilizumab in All Clinical Trials by Age Group and Gender
Any Inebilizumab Analysis Set

	Adults (18 to 64 years) n (subj-yrs)	Elderly People (≥ 65 years) n (subj-yrs)
Male		
Neuromyelitis optica spectrum disorder	20 (64.36)	1 (2.70)
Immunoglobulin G4-related disease	48 (62.72)	23 (23.95)
Myasthenia Gravis	61 (85.30)	17 (27.35)
Total	129 (212.38)	41 (54.00)
Female		
Neuromyelitis optica spectrum disorder	195 (626.33)	9 (22.28)
Immunoglobulin G4-related disease	32 (44.96)	9 (10.01)
Myasthenia Gravis	116 (190.53)	13 (17.37)
Total	343 (861.82)	31 (49.66)
Total		
Neuromyelitis optica spectrum disorder	215 (690.69)	10 (24.99)
Immunoglobulin G4-related disease	80 (107.68)	32 (33.96)
Myasthenia Gravis	177 (275.83)	30 (44.72)
Total	472 (1074.20)	72 (103.67)

n = number of subjects exposed to Inebilizumab
IgG4-RD = immunoglobulin G4-related disease; MG = myasthenia Gravis; NMOSD = neuromyelitis optica spectrum disorder; OLP = open-label period; RCP = randomized-controlled period
For NMOSD: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 60.
For IgG4 and MG: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 90.
Data cut-off: For gMG MINT study: 01 September 2024; for IgG4-RD MITIGATE study: 09 April 2024 for the RCP and 09 February 2024 for the OLP.
Source: /userdata/stat/amg335/meta/rmp/analysis/rmp_l_hzn_2025/Programs/t_rmp_all_ex2.sas

Table 16. Total Subject Exposure to Inebilizumab in All Clinical Trials by Product and Race
Any Inebilizumab Analysis Set

Indication	White n (subj-yrs)	Black or African American n (subj-yrs)	Asian n (subj-yrs)	Native Hawaiian or Other Pacific Islander n (subj-yrs)	Other n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
Neuromyelitis optica spectrum disorder	120 (386.71)	19 (59.35)	46 (153.44)	0 (0.0)	40 (116.18)	0 (0.0)	225 (715.68)
Immunoglobulin G4-related disease	40 (45.65)	0 (0.0)	60 (79.71)	1 (0.76)	5 (5.75)	6 (9.77)	112 (141.64)
Myasthenia Gravis	112 (177.50)	4 (6.96)	86 (128.85)	0 (0.0)	3 (3.21)	2 (4.03)	207 (320.55)
Total	272 (609.85)	23 (66.31)	192 (362.00)	1 (0.76)	48 (125.15)	8 (13.79)	544 (1177.86)

n = number of subjects exposed to Inebilizumab
IgG4-RD = immunoglobulin G4-related disease; MG = myasthenia Gravis; NMOSD = neuromyelitis optica spectrum disorder; OLP = open-label period; RCP = randomized-controlled period
For NMOSD: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 60.
For IgG4 and MG: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 90.
Data cut-off: For gMG MINT study: 01 September 2024; for IgG4-RD MITIGATE study: 09 April 2024 for the RCP and 09 February 2024 for the OLP.
Source: /userdata/stat/amg335/meta/rmp/analysis/rmp_l_hzn_2025/Programs/t_rmp_all_ex3.sas

Table 17. Total Subject Exposure to Inebilizumab in All Clinical Trials by Product and Ethnic Group
Any Inebilizumab Analysis Set

Indication	Hispanic/Latino n (subj-yrs)	Non-Hispanic/Latino n (subj-yrs)	Missing/Unknown n (subj-yrs)	Total n (subj-yrs)
Neuromyelitis optica spectrum disorder	40 (124.45)	185 (591.23)	0 (0.0)	225 (715.68)
Immunoglobulin G4-related disease	11 (14.07)	95 (117.80)	6 (9.77)	112 (141.64)
Myasthenia Gravis	18 (27.42)	188 (291.41)	1 (1.72)	207 (320.55)
Total	69 (165.94)	468 (1000.44)	7 (11.49)	544 (1177.86)

n = number of subjects exposed to Inebilizumab
IgG4-RD = immunoglobulin G4-related disease; MG = myasthenia Gravis; NMOSD = neuromyelitis optica spectrum disorder; OLP = open-label period; RCP = randomized-controlled period
For NMOSD: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 60.
For IgG4 and MG: Duration of the exposure is defined as the last inebilizumab dose date - 1st inebilizumab dose date + 90.
Note: the Ethnic Group will be based on the categories collected in each study.
Data cut-off: For gMG MINT study: 01 September 2024; for IgG4-RD MITIGATE study: 09 April 2024 for the RCP and 09 February 2024 for the OLP.
Source: /userdata/stat/amg335/meta/rmp/analysis/rmp_l_hzn_2025/Programs/t_rmp_all_ex4.sas

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 18. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subject is pregnant or breastfeeding, or planning to become pregnant	The safety of the drug in this population is unknown.	Yes	Not applicable.
Subjects concomitantly receiving other immunosuppressive and B-cell-depleting agents[a]	The combination of multiple immunosuppressive agents could theoretically increase the risk of infection.	Yes	Not applicable.
Hypersensitivity to the active substance or to any of the excipients	To ensure that the evaluation of the safety profile in clinical studies was not affected by pre-existing hypersensitivity to the product.	No	Inebilizumab is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients.
Subjects with moderate to severe renal impairment[b]	Subjects with renal impairment are at increased risk for nephrogenic systemic fibrosis (NSF) when exposed to IV gadolinium-based contrast agents. Gadolinium-enhanced magnetic resonance imaging (MRI) was a required protocol procedure for the NMOSD study; therefore, subjects with renal impairment in this study were excluded to avoid risk of NSF.	No	The exclusion of subjects with renal impairment was related to study procedures and not to the drug. The drug is not renally metabolized, so it is reasonable to consider use in patients with renal impairment.

Table 18. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subject has positive test for hepatitis C serology	To reduce the risk of worsening hepatitis C infection	No	Unlike for hepatitis B, B-cell depleting agents have not been associated with reactivation of hepatitis C once it is cured.
Chronic hepatitis B infection	To reduce the risk of hepatitis B reactivation	No	The risk of latent Hepatitis B virus (HBV) reactivation has been observed with other B-cell depleting antibodies and as such it is a potential risk with inebilizumab covered under the important potential risk of viral reactivation and opportunistic infections (Table 26).

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[a] Applicable to NMOSD study only
[b] In the NMOSD study, subjects with an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 were excluded, in the IgG4 RD study, subjects with eGFR < 30 mL/min/1.73 m^2 were excluded, and in the gMG study, subjects with eGFR < 45 mL/min/1.73 m^2 were excluded.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 19. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program. Cumulatively, 7 pregnancies were reported from study sources in which subjects were exposed to inebilizumab prior to or during pregnancy (5 maternal exposure and 2 paternal exposure). Of these, 2 resulted in normal live birth, 3 were lost to follow-up, 1 resulted in full-term delivery (Not Otherwise Specified), and 1 resulted in a spontaneous abortion (Not Otherwise Specified).
Breastfeeding women	Not included in the clinical development program. No breastfeeding women have been exposed.
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in the clinical development program.
Patients with severe renal impairment	Not included in the clinical development program.
Patients with cardiovascular impairment	No specific analyses of cardiovascular function were performed, but these patients were not excluded from the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Approximately 13% of subjects (69/544 subjects) in the clinical study program were Hispanic/Latino. Half (50%) of the subjects in the clinical study program were white. There were 35% Asian subjects, 4% Black subjects, and < 1% Native Hawaiian or other Pacific Islander in the clinical study program. The remaining 10% of subjects were of other or missing/unknown race.

Table 19. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	
Age < 18 years	Not included in the clinical development program.
Age ≥ 65 years	There were 72 subjects aged ≥ 65 years included in the clinical development program (30 subjects in the gMG clinical study, 32 subjects in the IgG4-RD clinical study, and 10 subjects in the NMOSD clinical study).

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes), and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country and are converted to a monthly estimate of patient time and, when feasible, patient count using region and product specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

Postmarketing patient exposure estimates are reported overall and for the following geographic regions: EU/EEA, Switzerland, US, and Other (countries, not otherwise specified, where Amgen is the Marketing Authorization Holder). Patient exposure estimates for countries where marketing authorization is held by Amgen's licensing partners, such as Japan and neighboring countries, are obtained directly from these companies, may be based on a different set of assumptions, and are reported under a separate paragraph or table in this document.

Estimates of postmarketing patient exposure by age and sex are not yet available for inebilizumab.

SV.1.2 Exposure

The cumulative number of patients exposed (or patient-years of exposure) to inebilizumab through commercial distribution is shown in Table 20 below.

Table 20. Estimated Number of Patient-years of Exposure to Inebilizumab, by Region, in the Postmarketing Setting

Country	Cumulative[a] Number of Patient-years
US	1759
Canada	17
EU/EEA	245
Austria	12
France	60
Germany	136
Italy	22
Poland	1
Spain	14
Switzerland	2
Other	
Brazil	42
Total	2064

EU/EEA = European Union/European Economic Area; US = United States
[a] Cumulatively from launch through 10 December 2024
Note: Numbers may not add to the total due to rounding.

Cumulatively from launch through 10 December 2024, there has been 1 early access program case reported.

In addition, cumulatively from launch through 10 December 2024, there has been an estimated 1 patient-year of exposure to inebilizumab in Saudi Arabia through a patient requested supply program.

Postauthorization Use From Business Partners

Cumulatively through 10 December 2024, there has been an estimated 737 patient-years of exposure to inebilizumab in Mitsubishi Tanabe Pharma Corporation (MTPC) territories (Japan).

Cumulatively through 31 December 2024, there has been an estimated 3152 patient-years of exposure to inebilizumab in Hansoh territories (China).

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 21. Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Arthralgia: The rate of arthralgia was numerically higher in the inebilizumab group than the placebo group (9.8% versus 3.6%) during the randomized-controlled period (RCP). The rate of arthralgia was lower in the open-label period (OLP) than in the RCP (4.3% for the inebilizumab/inebilizumab group subjects and 5.9% for the placebo/inebilizumab group subjects). A serious adverse event of arthralgia occurred in 1 of 225 (0.4%) subjects treated with inebilizumab. There is no known biological mechanism for a potentially higher rate of arthralgia with inebilizumab. The rationale for not including it in the list of safety concerns in the RMP is that the clinical impact on patients is low relative to the seriousness of NMOSD.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 22. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Important Identified Risks	
Infusion reaction	Infusion reactions are a general risk associated with biologics and have been observed in patients treated with inebilizumab. Symptoms associated with infusion reactions can include dyspnea, reduced blood pressure, rash, fever, and gastrointestinal symptoms. Most serious infusion reactions in inebilizumab-treated patients have been observed in oncology studies. In the RCP of the NMOSD trial infusion reactions were observed in 9.2% of inebilizumab-treated patients and 10.7% of placebo-treated patients. Amongst the 264 study subjects with autoimmune diseases who have been exposed to inebilizumab, a serious infusion reaction has been observed in 1 (0.38%) subject (migraine that required hospitalization for treatment). The risk of infusion reaction is reduced by pre-treating patients with a corticosteroid (methylprednisolone 100 mg IV or similar), an antihistamine (diphenhydramine 25 to 50 mg orally or similar), and an anti-pyretic (paracetamol 500 to 650 mg orally or similar). The drug should be administered by staff familiar with recognizing and treating infusion reactions, and equipment and medications used for treating such reactions should be available. Risk-benefit impact: Serious infusion reactions can include dyspnea, reduced blood pressure, rash, fever, and gastrointestinal symptoms, and may necessitate medical intervention and/or interruption or discontinuation of treatment. It is anticipated that the important identified risk of infusion reaction can be adequately managed by the risk minimization measures in the SmPC, described above. Therefore, the risk of infusion reaction is not expected to meaningfully impact the benefit-risk profile of Uplizna.
Neutropenia	Neutropenia was reported as an adverse event at a low rate in the inebilizumab group (2.3% vs 0% in placebo during the RCP; 2.2% in the Any Inebilizumab population). Of the 5 adverse event cases of neutropenia observed in the Any Inebilizumab population, 3 were Grade 1 (mild) in severity with onset at 1 to 3 months post Dose 2 of inebilizumab; one was Grade 2 (moderate) in severity with onset approximately 2 weeks post Dose 2 of inebilizumab; and one was Grade 3 (severe) in severity with onset 6 months after Dose 3 of inebilizumab. By analysis of laboratory results in the RCP, a neutrophil level of 1.0 to 1.5 x 10^9/L was observed in 6.9% of inebilizumab-treated patients versus 1.8% of placebo-treated patients. A neutrophil level of 0.5 to 1.0 x 10^9/L was observed in 1.7% of inebilizumab-treated patients versus 0% of placebo-treated patients. Mean percent change from baseline at Week 28 in neutrophil levels was similar between the treatment groups (0.87% for inebilizumab, 1.1% placebo).

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Abbreviations and footnotes are defined on the last page of this table

Table 22. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Neutropenia (continued)	Neutropenia was generally transient, and no subject with laboratory-defined Grade 2 or higher neutropenia experienced a serious infection. Neutropenia has been observed with other B-cell-depleting monoclonal antibodies and may be a class effect. Risk-benefit impact: Events of neutropenia in inebilizumab-treated subjects were mild or moderate, were generally transient, and were not associated with serious infections. Therefore, the impact of this important identified risk on the benefit-risk profile of Uplizna is expected to be low.
Important Potential Risks	
Serious Infections, Viral Reactivation, and Opportunistic Infections	During the RCP of Study 1155, similar proportions of subjects in both treatment groups had infections, while a greater proportion of subjects in the placebo group (10.7%) had opportunistic infections than in the inebilizumab group (2.9%). Rates of serious infection were low in both groups (3.8% for placebo and 1.7% for inebilizumab). Risk of serious infection is mitigated by determining whether there is an active infection prior to every infusion and delaying administration of inebilizumab in patients with an active infection until the infection resolves. Hepatitis B virus (HBV) reactivation has been observed with other B-cell-depleting antibodies and as such is a potential risk with inebilizumab. No cases of HBV reactivation were reported during inebilizumab clinical trials; however, subjects with chronic HBV infection were excluded from clinical studies. To mitigate against the potential risk of HBV reactivation, the SmPC specifies that HBV screening should be performed in all patients before initiating treatment with inebilizumab. Patients with active HBV infection should not be administered inebilizumab, and patients otherwise at risk for HBV reactivation should consult with liver disease experts before initiating and during inebilizumab treatment. Concomitant use of inebilizumab with immunosuppressive agents, including systemic corticosteroids, may increase the risk of infection. For this reason and as specified in the SmPC, the potential risk of additive immune system effects should be taken into consideration if inebilizumab is co-administered with immunosuppressive therapies. The safety of immunization with live or live-attenuated vaccines following inebilizumab dosing has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during inebilizumab treatment and until B-cell repletion. Risk-benefit impact: Serious and/or opportunistic infections can lead to hospitalization, prolongation of hospitalization, or can be life-threatening. Inebilizumab treatment was not associated with an increased risk of serious infections in subjects with NMOSD. It is anticipated that the important potential risk of serious infections can be adequately managed with the risk minimization measures described in the SmPC, described above. Therefore, the risk of serious infections is not considered to meaningfully impact the benefit-risk profile of Uplizna.

Abbreviations and footnotes are defined on the last page of this table

Table 22. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Important Potential Risks (continued)	
Progressive Multifocal Leukoencephalopathy (PML)	Progressive multifocal leukoencephalopathy is an opportunistic infection caused by the John Cunningham virus (JCV) that typically only occurs in patients who are immunocompromised. Progressive multifocal leukoencephalopathy is listed as a Special warning and precaution for drugs that deplete B-cells by targeting the CD20 molecule (rituximab, ocrelizumab, ofatumumab, and obinutuzumab). As of 2008, 57 cases of PML have been reported following rituximab therapy in patients with hematologic malignancies, systemic lupus erythematosus, rheumatoid arthritis, idiopathic autoimmune pancytopenia, and immune thrombocytopenia (Carson et al, 2009). In the clinical trials evaluating ofatumumab for the treatment of chronic lymphocytic leukemia, one case of PML was reported (Wierda et al, 2010). Relative risk for PML associated with rituximab and other B-cell-depleting therapies is difficult to establish due to the small number of such reports and because they are observed in populations with considerable confounding risk factors such as lymphopenia, history of immunosuppression, and as yet unestablished incidence rates of PML in various diseases (background PML risk). Relative risk for rituximab-associated PML in the rheumatoid arthritis population was estimated at 1:25 000 based on 5 cases in a population estimated at 129 000 (Clifford et al, 2011). To date, no PML cases have been reported with rituximab in NMO. The background incidence rate of PML in the NMO population is unknown. One case of PML reported in the literature describes an NMO patient who developed PML after treatment with azathioprine (Flanagan et al, 2013). No confirmed case of PML has been reported in any inebilizumab study. In Study 1155, one subject in the inebilizumab group died from hospital-acquired, ventilator-associated pneumonia following the development of new brain lesions. Brain MRI and cerebrospinal fluid testing for JCV (2 negative reports from reference laboratories and 1 positive report from a local laboratory) did not provide sufficient information to reach a clear diagnosis, but PML was part of the differential diagnosis for the lesions. The subject's family did not consent to an autopsy; therefore, no brain sample could be collected for analysis. The Investigator considered the events related to investigational product. Following review of this case with numerous experts, the opinion of Viela Bio is that the available data could not establish definitively the cause of the subject's brain lesions. The differential diagnosis of these brain lesions includes PML, acute disseminated encephalomyelitis, and atypical NMOSD relapse.

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Abbreviations and footnotes are defined on the last page of this table

Table 22. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Important Potential Risks (continued)	
Progressive Multifocal Leukoencephalopathy (PML) (continued)	The risk of PML for inebilizumab is considered to be low based on experience with similar B-cell-depleting therapies. Due to the nature of the disease, NMOSD patients are frequently monitored for signs and symptoms of underlying central nervous system disease, and therefore are already being monitored for clinical manifestations of PML. MRI findings may be apparent before clinical signs or symptoms. At the first sign or symptom suggestive of PML, inebilizumab should be withheld and appropriate diagnostic evaluation performed. Risk-benefit impact: PML is a serious opportunistic infection that can result in hospitalization or death. In the 1 case of 'probable PML' (verbatim term)/'progressive multifocal leukoencephalopathy' (Preferred Term) reported in the OLP, which was associated with a fatal treatment-emergent serious adverse event of pneumonia, a definitive diagnosis could not be established, but the differential diagnosis included PML, acute disseminated encephalomyelitis, or atypical NMOSD attack. Viela Bio's assessment concluded that this case does not change the benefit-risk of inebilizumab for attack prevention treatment in NMOSD. The important potential risk of PML is anticipated to be sufficiently rare as not to meaningfully impact the benefit-risk profile of Uplizna.
Malignancy	A review of data describing malignancy risk in a similar class of treatments, CD20+ B-cell-depleting therapies, found that the safety profile of rituximab, including use in patients with autoimmune disease, suggests no increase in the risk of breast cancer or other malignancies (Gelfand et al, 2017). An increased number of malignancies (including breast cancers) have been observed in clinical trials in ocrelizumab-treated subjects compared with control groups; however, the incidence was within the background rate expected for a multiple sclerosis population (OCREVUS US Prescribing Information, 2017). In Study 1155, there was no evidence to suggest an increased risk of malignancy in subjects treated with inebilizumab. One subject had a treatment-emergent serious adverse event in the System Organ Class (SOC) 'Neoplasms benign, malignant and unspecified (including cysts and polyps)' in the RCP. The subject was in the placebo group and had a treatment-emergent serious adverse event of Breast cancer tumor. Based on the totality of evidence, it has not been established that B-cell depletion increases the risk of malignancy. However, the possible risk for the development of solid tumors cannot be excluded at this time. Further data are needed before any relationship with inebilizumab or a similar class of treatment can be concluded.

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Abbreviations and footnotes are defined on the last page of this table

Table 22. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Important Potential Risks (continued)	
Malignancy (continued)	Risk-benefit impact: Cancer is among the leading causes of death worldwide. Inebilizumab treatment was not associated with an increased risk of malignancy in subjects with NMOSD. Therefore, the important potential risk of malignancy is not considered to meaningfully impact the benefit-risk profile of Uplizna.
Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women	A review of data describing risk of administering a similar class of treatments, CD20+ B-cell-depleting therapies, during pregnancy highlighted that their use is relatively contraindicated because of potential harm to the developing fetus and infant (Gelfand et al, 2017). It has been reported that infants whose mothers were treated with B-cell-depleting monoclonal antibodies subsequently experienced transient B-cell depletion and peripheral lymphocytopenia. Nonclinical pregnancy studies in primates support the potential harm of these therapies, as demonstrated by severe decreases in B-cells in the neonates, renal toxicity, testicular toxicity, lymphoid follicle formation in the bone marrow, and perinatal deaths. Study 1155 eligibility criteria excluded lactating or pregnant females or females who intend to become pregnant anytime from signing the informed consent form (ICF) through the study plus 6 months following last dose of investigational product. Three pregnancies occurred in inebilizumab-exposed subjects in Study 1155. In all cases, there were no complications during the pregnancy or delivery, and there were no reported birth defects in the baby. Risk-benefit impact: There is no evidence of any risks associated with inebilizumab use in subjects with NMOSD. However, as a precautionary measure, it is preferable to avoid the use of inebilizumab in women of childbearing potential not using contraception and during pregnancy, unless the potential benefit to the mother outweighs the potential risk to the fetus. Therefore, the important potential risk of use during pregnancy is not considered to meaningfully impact the benefit-risk profile of Uplizna.
Missing Information	
Safety in patients ≥ 65 years	Patients ≥ 65 years of age were not excluded from the NMOSD clinical study, but an insufficient number (n = 10) were enrolled to enable a full evaluation of the safety and efficacy in this population. A population pharmacokinetic analysis indicated that there was no significant effect of age on inebilizumab clearance. Risk-benefit impact: Insufficient data are available to evaluate the safety and efficacy of Uplizna in patients ≥ 65 years. Routine pharmacovigilance procedures will be utilized to monitor for unexpected adverse events in adults ≥ 65 years.

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Abbreviations and footnotes are defined on the last page of this table

Table 22. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Missing Information (continued)	
Use in pregnancy and breastfeeding	Inebilizumab use in pregnancy and breastfeeding was not permitted in the NMOSD clinical study because inebilizumab safety during pregnancy or breastfeeding is unknown. Three pregnancies were reported in inebilizumab-exposed NMOSD subjects with conception at approximately 2.5, 3, and 0.5 months following their previous dose of inebilizumab in Study 1155. One pregnancy was uncomplicated and resulted in delivery of a healthy infant. One pregnancy was complicated by Candida vulvovaginitis and bacterial vaginosis; the pregnancy resulted in a healthy infant born by Cesarean section. One pregnancy resulted in delivery via Cesarean section due to oligohydramnios and breech position. No abnormalities or health problems in the children were noted. The SmPC recommends that women of childbearing potential should use contraception while receiving inebilizumab and for 6 months after the last infusion of inebilizumab. There is no known exposure of inebilizumab in breastfeeding women. Risk-benefit impact: Inebilizumab is a humanized 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. The full risks are not known and use in pregnancy and breastfeeding is not recommended.
Patients concomitantly receiving other immunosuppressive agents	Uplizna has not been studied in patients receiving chronic concomitant immunosuppressive medications. Risk-benefit impact: Chronic use of other immunosuppressive medications together with Uplizna could theoretically increase the risk of infection.

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ICF = informed consent form; IgG1 = immunoglobulin G1; IV = intravenous; HBV = hepatitis B virus; NMOSD = neuromyelitis optica spectrum disorder; OLP = open-label period; RCP = randomized-controlled period; SmPC = Summary of Product Characteristics

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Table 23. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Reclassification of Safety Concerns		
Important identified risks		
Infusion reaction	Infusion reaction has been renamed to infusion-related reactions	To align with the Preferred Term of Infusion-related reaction
Important potential risks		
Serious infections, viral reactivation, and opportunistic infections	Serious infections, viral reactivation, and opportunistic infections, previously classified as an important potential risk has been reclassified to the following: • Important identified risk: Infections, including serious infections • Important potential risk: Viral reactivation and opportunistic infections	During the randomized-controlled period (RCP) of the inebilizumab immunoglobulin G4-related disease (IgG4-RD) and generalized myasthenia gravis (gMG) clinical study, there was an imbalance in 'all infections' and 'serious infections' observed; however, the rate of opportunistic infections was balanced between the inebilizumab group and placebo group. One case of viral reactivation was reported. The imbalance did not appear to be impacted by age (< 65 versus ≥ 65) and Covid-19 related infections.
Removal of Safety Concerns		
Important Identified risks		
Neutropenia	Neutropenia, previously an important identified risk, has been removed from the list of safety concerns	As the risk of 'Infections, including serious infections' has been added to the list of safety concerns, the risk of neutropenia is considered to be duplicated. The analysis of treatment-emergent adverse events and laboratory data in the gMG study did not show an increased incidence of neutropenia or neutrophil count decreased.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 24. Important Identified Risk: Infusion-related Reactions

Potential mechanisms	Infusion-related reactions are a general risk associated with infusion of foreign proteins such as biologics and have been observed with inebilizumab.
Evidence source(s) and strength of evidence	This risk was identified based on data from clinical studies, post-marketing data, and scientific literature.
Characterization of the risk	
Frequency	<u>gMG</u> In the phase 3, randomized, double-blind, multicenter, placebo-controlled Study 20230049 (MINT; previously Study VIB0551.P3.S1), 12 of 119 inebilizumab-treated subjects (10.1%) and 7 of 119 placebo-treated subjects (5.9%) had infusion-related reactions in the RCP of the study, as of the primary analysis data cut-off of 28 May 2024 (risk difference: 4.2% [95% CI: -2.9%, 11.7%]). In the any inebilizumab analysis set (N = 207), as of the supplemental analysis data cut-off of 01 September 2024, 20 subjects (9.7%; 95% CI: 6.0%, 14.5%) had infusion-related reactions, one of which was serious. <u>IgG4-RD</u> In the phase 3, randomized, double-blind, multicenter, placebo-controlled Study 20230068 (MITIGATE; previously VIB0551.P3.S2), 5 of 68 inebilizumab-treated subjects (7.4%) and 10 of 67 placebo-treated subjects (14.9%) had infusion-related reactions in the RCP of the study (risk difference -7.6% [95% confidence interval [CI]: -19.0%, 3.3%]). In the any inebilizumab analysis set (N = 112), 11 subjects (9.8%; 95% CI: 5.01%, 16.89%) had infusion-related reactions, one of which was serious, resulting in hospitalization. <u>NMOSD</u> In the RCP of Study 1155, 9.2% of subjects treated with inebilizumab and 10.7% of subjects treated with placebo had infusion-related reaction events. In the any inebilizumab analysis set of Study 1155 (N = 225), 28 subjects (12.4%; 95% CI: 8.4%, 17.5%) had infusion-related reaction events.
Severity	Grade 3 and Grade 4 infusion-related reactions have been reported in inebilizumab clinical studies. Most infusion-related reactions in the inebilizumab clinical studies were mild or moderate in severity.
Reversibility	All infusion-related reactions observed in clinical studies were reversible and most subjects recovered from the event.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 24. Important Identified Risk: Infusion-related Reactions

Long-term outcomes	Study data from > 3 years showed a decrease in infusion-related reactions observed over time. No long-term effects are expected after resolution of the infusion-related reactions.
Impact on quality of life	Infusion-related reactions may lead to hospitalization and in some cases may require interruption or discontinuation of inebilizumab.
Risk factors and risk groups	There are no identified risk factors for infusion-related reactions. Infusion-related reactions were more common during the first infusion than during subsequent infusions.
Preventability	The risk of infusion reaction-related is mitigated by premedication with a corticosteroid (eg, methylprednisolone 80 mg to 125 mg or equivalent) approximately 30 minutes prior to each inebilizumab infusion, an antihistamine (eg, diphenhydramine 25 to 50 mg or equivalent), and an antipyretic (eg, paracetamol 500 to 650 mg orally or equivalent). Inebilizumab should be administered under the supervision of a physician experienced in the treatment of NMOSD, IgG4-RD, or gMG and with access to appropriate medical support to manage potential severe reactions such as serious infusion-related reactions.
Impact on the risk-benefit balance of the product	It is anticipated that the important identified risk of infusion-related reactions can be adequately managed by the risk minimization measures in the SmPC, described above. Therefore, the risk of infusion-related reactions is not expected to meaningfully impact the benefit-risk profile of inebilizumab.
Public health impact	In the NMOSD, IgG4-RD, and gMG clinical studies, most of the infusion-related reactions were mild to moderate and all events resolved. The rate of infusion-related reactions associated with inebilizumab was lower than what has been reported from other B-cell depleting agents (eg, rituximab). Therefore, the public health impact of this risk is expected to be low.

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CI = confidence interval; gMG = generalized myasthenia gravis; IgG4-RD = immunoglobulin G4-related disease; IV = intravenous; NMOSD = neuromyelitis optica spectrum disorder; RCP = randomized-controlled period; SmPC = Summary of Product Characteristics

Table 25. Important Identified Risk: Infections, Including Serious Infections

Potential mechanisms	Inebilizumab causes reduction in peripheral blood lymphocyte count and immunoglobulin 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.
Evidence source(s) and strength of evidence	This risk was identified based on data from clinical studies and postmarketing data.
Characterization of the risk	
Frequency	<u>gMG</u> In Study 20230049, 51 of 119 inebilizumab-treated subjects (42.9%) and 43 of 119 placebo-treated subjects (36.1%) had infection events in the RCP of the study (risk difference: 6.7 [-5.7%, 18.9%]), as of the primary analysis data cut-off of 28 May 2024. In the RCP, 7 of 119 inebilizumab-treated subjects (5.9%) and 5 of 119 placebo-treated subjects (4.2%) had serious infection events (risk difference: 1.7 [-4.4%, 8.0%]). A Grade 5, fatal infection event (septic shock and pneumonitis) was reported in 1 of 119 inebilizumab-treated subjects (0.8%) and no placebo-treated subjects in the RCP of the study (risk difference 0.8% [-2.3%, 4.6%]). In the any inebilizumab analysis set (N = 207), 91 subjects (44.0%; 95% CI: 37.1%, 51.0%) had infection events, as of the supplemental analysis data cut-off of 01 September 2024. Of these, 15 subjects (7.2%; 95% CI: 4.1%, 11.7%) had serious infection events. <u>IgG4-RD</u> In Study 20230068 (MITIGATE; previously VIB0551.P3.S2), 51 of 68 inebilizumab-treated subjects (75.0%) and 36 of 67 placebo-treated subjects (53.7%) had infection events in the RCP of the study (risk difference 21.3% [5.2%, 36.4%]). Serious infection events were reported in 4 of 68 inebilizumab-treated subjects (5.9%) and no placebo-treated subjects in the RCP of the study (risk difference 5.9% [0.3%, 14.2%]). In the Any inebilizumab analysis set (N = 112), 79 subjects (70.5%; 95% CI: 61.18%, 78.77%) had infection events. Of these, 9 subjects (8.0%; 95% CI: 3.74%, 14.71%) had serious infection events. <u>NMOSD</u> In the RCP of Study 1155, 39.1% of subjects treated with inebilizumab and 41.1% of subjects treated with placebo had infection events. Serious infection events were reported in 1.1% of subjects treated with inebilizumab and 3.6% of subjects treated with placebo had serious infection events. In the any inebilizumab analysis set of Study 1155 (N = 225), 74.7% of subjects had infection events. Serious infection events were reported in 11.1% of subjects.
Severity	Most infection events were mild or moderate in severity.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 25. Important Identified Risk: Infections, Including Serious Infections

Reversibility	The infection events were generally transient.
Long-term outcomes	No long-term outcome is expected after resolution of the infection.
Impact on quality of life	Impact on quality of life can be variable depending on the severity of the infections; however, recovery can be achieved with appropriate and timely intervention.
Risk groups or risk factors	Concomitant use of inebilizumab with immunosuppressive agents, including systemic corticosteroids, may increase the risk of infection. Use of inebilizumab in patients with known immunodeficiencies may increase the risk of infection.
Preventability	The SmPC advises that the patient's recent (ie, within 6 months) complete blood count (CBC) including differentials and immunoglobulins should be obtained before initiation of inebilizumab, and assessments of these tests are recommended periodically during treatment and after discontinuation 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 are also instructed to promptly report symptoms of infection to their physician. Treatment discontinuation should be considered if a patient develops recurrent infections if immunoglobulin levels indicate immune compromise. Inebilizumab is contraindicated in patients who have a severe active infection and in patients who are in a severely immunocompromised state. Vaccination with live or live-attenuated vaccines is not recommended during inebilizumab treatment and until B-cell repletion. The potential for increased immunosuppressive effects should be considered if combining inebilizumab with other immunosuppressants.
Impact on the risk-benefit balance of the product	The risk of infection, including serious infection has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling.
Public health impact	Most of the infections associated with inebilizumab were nonserious and resolved without clinical complication or sequelae. No significant increase in mortality and morbidity has been observed in subjects with infections associated with inebilizumab. Therefore, the public health impact is considered low.

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CBC = complete blood count; CI = confidence interval; gMG = generalized myasthenia gravis; IgG4-RD = immunoglobulin G4-related disease; NMOSD = neuromyelitis optica spectrum disorder; RCP = randomized-controlled period.

Table 26. Important Potential Risk: Viral Reactivation and Opportunistic Infections

Potential mechanisms	Reduction of levels of CD19+ B-cells has the potential to induce immunosuppression and potentially increase the risk of opportunistic infections. B-cell depletion with other monoclonal antibodies has been observed to increase the risk of HBV reactivation in patients with chronic hepatitis B infection. Hepatitis B virus reactivation has been observed with other B cell-depleting antibodies and as such is a potential risk with inebilizumab.
Evidence source(s) and strength of evidence	This potential risk was identified based on data from clinical studies, postmarketing data and scientific literature.
Characterization of the risk	
Frequency	<u>gMG</u> In Study 20230049, 1 of 119 inebilizumab-treated subjects (0.8%) and 2 of 119 placebo-treated subjects (1.7%) had opportunistic infection events in the RCP of the study (risk difference -0.8%; 95% CI: -5.2%, 3.1%), as of the primary analysis data cut-off of 28 May 2024. In the any inebilizumab analysis set (N = 207), 2 subjects (1.0%) had opportunistic infection events (1 serious event and 1 nonserious), as of the supplemental analysis data cut-off of 01 September 2024. One subject (0.5%) had HBV reactivation (nonserious). <u>IgG4-RD</u> In Study 20230068 (MITIGATE; previously VIB0551.P3.S2), 2 of 68 inebilizumab-treated subjects (2.9%) and 1 of 67 placebo-treated subjects (1.5%) had opportunistic infection events in the RCP of the study (risk difference 1.4% [-5.3%, 8.8%]). In the any inebilizumab analysis set (N = 112), 3 subjects (2.7%) had opportunistic infection events; no opportunistic infection events were serious. No subjects had a viral reactivation event. <u>NMOSD</u> During the RCP of Study 1155, no subject had an opportunistic infection. In the any inebilizumab analysis set of Study 1155 (N = 225), 2 subjects (0.8%) had an opportunistic infection event (1 serious event and 1 nonserious). No cases of viral reactivation were reported.
Severity	Most events were mild or moderate in severity.
Reversibility	Reversibility will depend on the nature and the severity of the infections; however, most events were generally transient.
Long-term outcomes	No long-term outcome is expected after resolution of the infection.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 26. Important Potential Risk: Viral Reactivation and Opportunistic Infections

Impact on quality of life	Impact on quality of life can be variable depending on the severity of the infections. Reactivation of latent infections and development of opportunistic infections may cause a range of symptoms from minor to serious or life-threatening; however, recovery can be achieved with appropriate and timely intervention.
Risk factors and risk groups	Patients with serologic evidence of HBV infection (hepatitis B surface antigen positive [HBsAg+] or anti-hepatitis B core antibody positive [HBcAb+]) are at risk for HBV reactivation if they receive immunosuppressive therapy. The safety of immunization with live or live-attenuated vaccines following inebilizumab dosing has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during inebilizumab treatment and until B-cell repletion.
Preventability	The SmPC advises that the patient's recent (ie, within 6 months) CBC including differentials and immunoglobulins should be obtained before initiation of inebilizumab, and assessments of these tests are recommended periodically during treatment and after discontinuation until B-cell repletion. Prior to every infusion, it should be determined whether there is a clinically significant infection. In case of infection, inebilizumab should be delayed until the infection resolves. Patients are also instructed to promptly report symptoms of infection to their physician. Treatment discontinuation should be considered if a patient develops a serious opportunistic infection if immunoglobulin levels indicate immune compromise. The potential for increased immunosuppressive effects should be considered if combining inebilizumab with other immunosuppressants. Prior to initiation of inebilizumab treatment patients should be screened for HBV infection. Patients with active hepatitis due to HBV who are HBsAg+ or HBcAb+ should not be administered inebilizumab. For patients who are chronic carriers of HBV (HbsAg+), a liver disease expert should be consulted before starting inebilizumab and during treatment. Inebilizumab is contraindicated in patients with active chronic infection such as hepatitis B infection. 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. Inebilizumab is contraindicated in patients with active or untreated latent tuberculosis. Vaccination with live or live-attenuated vaccines is not recommended during inebilizumab treatment and until B-cell repletion.
Impact on the risk-benefit balance of the product	The risk of viral reactivation and opportunistic infection has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 26. Important Potential Risk: Viral Reactivation and Opportunistic Infections

Public health impact	Based on inebilizumab clinical study data from subjects with NMOSD, IgG4-RD, and gMG, results have not confirmed a definitive association with an increased risk of viral reactivation and opportunistic infections. Most opportunistic infection cases reported were generally transient and mild to moderate in severity. Therefore, the public health impact is considered low.

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CBC = complete blood count; gMG = generalized myasthenia gravis; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IgG4-RD = immunoglobulin G4-related disease; NMOSD = neuromyelitis optica spectrum disorders; RCP = randomized-controlled period; SmPC = Summary of Product Characteristics.

Table 27. Important Potential Risk: Progressive Multifocal Leukoencephalopathy (PML)

Potential mechanisms	The potential mechanism of PML occurring in patients treated with B-cell-depleting monoclonal antibodies is not well understood. Progressive multifocal leukoencephalopathy is considered to be a potential risk for inebilizumab based on experience from other drugs with a similar mechanism of action, ie, B-cell depletion.
Evidence source(s) and strength of evidence	This potential risk was identified based on 1 unconfirmed case from clinical study data and scientific literature. In this 1 unconfirmed case, the subject died following the development of new brain lesions, for which a definitive diagnosis could not be established, though the differential diagnosis included an atypical NMOSD relapse, PML, or acute disseminated encephalomyelitis.
Characterization of the risk	
Frequency	No confirmed case of PML has been reported in any inebilizumab study. <u>NMOSD</u> In Study 1155, 1 subject (0.4%) in the inebilizumab group died from hospital-acquired, ventilator-associated pneumonia following the development of new brain lesions. Brain MRI and cerebrospinal fluid testing for John Cunningham virus (JCV) did not provide sufficient information to reach a clear diagnosis, but PML was part of the differential diagnosis for the lesions. Relative risk for PML associated with B-cell-depleting therapies is difficult to establish due to the small number of such reports and because they are observed in populations with considerable confounding risk factors such as lymphopenia, history of immunosuppression, and as yet unestablished incidence rates of PML in various diseases (background PML risk).
Severity	The 1 unconfirmed case of PML was fatal.
Reversibility	Reversal of PML may be achieved by using plasma exchange to accelerate the removal of therapeutic agents that put patients at risk for PML; however, the outcome of PML depends on the severity of the underlying disease and treatment received.
Long-term outcomes	No data on long-term outcomes are available.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 27. Important Potential Risk: Progressive Multifocal Leukoencephalopathy (PML)

Impact on quality of life	Typical symptoms associated with PML are diverse, progress over days to weeks, and usually lead to severe disability or death.
Risk factors and risk groups	Risk factors for PML include autoimmune conditions, such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus, treatment with biological therapies that allow for JCV reactivation, human immunodeficiency virus-1 (HIV-1) infections, lymphopenia, and history of immunosuppression (National Institute of Neurological Disorders and Stroke, 2024).
Preventability	There are no known factors that can prevent PML. The SmPC recommends to suspend inebilizumab treatment at the first sign or symptom suggestive of PML and to evaluate further, including consultation with a neurologist, MRI scan preferably with contrast, cerebrospinal fluid testing for JCV DNA, and with repeat neurological assessments to be considered. If confirmed, inebilizumab treatment should be discontinued. A history of PML is a contraindication in the SmPC.
Impact on the risk-benefit balance of the product	No confirmed cases of PML have been observed in inebilizumab-treated subjects.
Public health impact	The risk of PML with inebilizumab treatment is considered to be low based on experience with similar B-cell-depleting therapies. Therefore, the public health impact is considered low.

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HIV-1 = human immunodeficiency virus-1; JCV = John Cunningham virus; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder; PML = progressive multifocal leukoencephalopathy; RCP = randomized-controlled period; SmPC = Summary of Product Characteristics.

Table 28. Important Potential Risk: Malignancy

Potential mechanisms	Immunomodulatory drugs may increase the risk of malignancy by suppressing anti-tumor immune response.
Evidence source(s) and strength of evidence	This potential risk was identified based on data from clinical studies, postmarketing data and scientific literature.
Characterization of the risk	
Frequency	gMG In Study 20230049, no subjects in the RCP of the study had a malignancy event, as of the primary analysis data cut-off of 28 May 2024. In the any inebilizumab analysis set (N = 207), 2 subjects (1.0%; 95% CI: 0.1%, 3.4%) had a malignancy event (squamous cell carcinoma of the cervix and clear cell renal cell carcinoma), as of the supplemental analysis data cut-off of 01 September 2024. IgG4-RD In Study 20230068 (MITIGATE; previously VIB0551.P3.S2), 2 of 68 inebilizumab-treated subjects (2.9%) and 1 of 67 placebo-treated subjects (1.5%) had malignancy events in the RCP of the study. In the Any inebilizumab analysis set (N = 112), 4 subjects (3.6%; 95% CI: 0.098%, 8.89%) had a malignancy event. NMOSD In Study 1155, 1 subject in the placebo treatment group in the RCP had a malignancy event (breast cancer tumor). In the any inebilizumab analysis set of Study 1155 (N = 225), 3 subjects (1.3%; 95% CI: 0.3%, 3.9%) had malignancy events.
Severity	The malignancy events ranged from mild to life-threatening.
Reversibility	Reversibility will depend on the nature and severity of the malignancy.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	The impact on quality of life depends on the nature and severity of the malignancy.
Risk factors and risk groups	Immunomodulatory medicinal products may increase the risk of malignancy. On the basis of limited experience with inebilizumab in NMOSD, IgG4-RD, and gMG, the current data do not confirm an increased risk of malignancy. However, the possible risk for the development of solid tumors cannot be excluded.
Preventability	There are no known factors that can prevent malignancy. Active malignancies is a contraindication in the SmPC.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 28. Important Potential Risk: Malignancy

Impact on the risk-benefit balance of the product	Cancer is among the leading causes of death worldwide. Inebilizumab treatment has not been confirmed to be associated with an increased risk of malignancy in subjects with NMOSD, IgG4-RD, and gMG. Therefore, the important potential risk of malignancy is not considered to meaningfully impact the benefit-risk profile of inebilizumab.
Public health impact	Based on inebilizumab clinical study and postmarketing data in subjects with NMOSD, IgG4-RD, and gMG, results have not confirmed a definitive association with an increased risk of malignancy. Therefore, the public health impact is considered low.

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CI = confidence interval; gMG = generalized myasthenia gravis; IgG4-RD = immunoglobulin G4-related disease; NMOSD = neuromyelitis optica spectrum disorder; RCP = randomized-controlled period

Table 29. Important Potential Risk: Blood Disorders, Particularly Decrease in B-Cell Levels in Fetal and Newborns Exposed to Inebilizumab in Pregnant Women

Potential mechanisms	Inebilizumab may cross the placenta and deplete B-cells in the fetus. A review of data describing the risk of administering a similar class of treatments (CD20+ B-cell-depleting therapies) during pregnancy highlighted that their use is relatively contraindicated because of potential harm to the developing fetus and infant (Gelfand et al, 2017). It has been reported that infants whose mothers were treated with B-cell-depleting monoclonal antibodies subsequently experienced transient B-cell depletion and peripheral lymphocytopenia. Nonclinical pregnancy studies in primates support the potential harm of these therapies, as demonstrated by severe decreases in B-cells in the neonates, renal toxicity, testicular toxicity, lymphoid follicle formation in the bone marrow, and perinatal deaths. Inebilizumab nonclinical studies showed evidence that inebilizumab crosses the placenta and depletes B-cells in the progeny of inebilizumab-administered huCD19 Tg mice; however, there were no adverse consequences of this B-cell depletion in the fetuses.
Evidence source(s) and strength of evidence	This potential risk was identified based on data from nonclinical animal studies and class effect with B-cell-depleting therapies from scientific literature and clinical study data.
Characterization of the risk	
Frequency	No clinical study cases of blood disorders have been reported in fetuses or newborns.
Severity	Not applicable.
Reversibility	No data is available for B-cell depletion and repletion in newborns exposed to inebilizumab in pregnant women.
Long-term outcomes	No data on long-term outcomes are available.
Impact on quality of life	No data are currently available on the impact on quality of life for this risk.
Risk factors and risk groups	Fetuses and newborns may be at risk of blood disorders as inebilizumab may cross the placenta and deplete B-cells.
Preventability	The SmPC advises that women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab and for 6 months after the last infusion of inebilizumab.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 29. Important Potential Risk: Blood Disorders, Particularly Decrease in B-Cell Levels in Fetal and Newborns Exposed to Inebilizumab in Pregnant Women

Impact on the risk-benefit balance of the product	Based on the risk mitigation advice included in the SmPC, the important potential risk of use during pregnancy is not considered to meaningfully impact the benefit-risk profile of inebilizumab.
Public health impact	Based on inebilizumab clinical study and postmarketing data in subjects with NMOSD, IgG4-RD, and gMG, results have not confirmed a definitive association with an increased risk of blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women, the public health impact is considered low.

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gMG = generalized myasthenia gravis; IgG4-RD = immunoglobulin G4-related disease; NMOSD = neuromyelitis optica spectrum disorder; SmPC = Summary of Product Characteristics

SVII.3.2 Presentation of the Missing Information

Table 30. Missing Information: Safety in Patients ≥ 65 Years

Evidence source	Reduction of levels of CD19+ B-cells has the potential to induce immunosuppression and potentially increase the risk of infections. Due to immunosenescence, older patients have an increased risk of infection, malignancy, and autoimmune disorders. Therefore, it is anticipated that the use of inebilizumab in older patients may have an increased risk for infections, malignancies, and other autoimmune conditions than younger patients. A population pharmacokinetic analysis indicated that there was no significant effect of age on inebilizumab clearance.
Population in need of further characterization	Subjects ≥ 65 years of age were not excluded from the NMOSD clinical study but an insufficient number (n = 10) were enrolled in the NMOSD clinical study. In the IgG4-RD study, 32 subjects ≥ 65 years of age were included. The limited number of subjects within the older age subgroup does not allow for a full evaluation of the safety and efficacy in this population.

IgG4-RD = immunoglobulin G4-related disease; NMOSD = neuromyelitis optica spectrum disorder

Table 31. Missing Information: Use in Pregnancy and Breastfeeding

Evidence source	Inebilizumab is a humanized IgG1 monoclonal antibody and immunoglobulins are known to cross the placental barrier. Human IgG is excreted in human milk, and the potential for absorption of inebilizumab to lead to B-cell depletion in the breastfed infant is unknown. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B-cell depleting antibodies during pregnancy. Inebilizumab nonclinical studies showed evidence that inebilizumab crosses the placenta and depletes B-cells in the progeny of inebilizumab-administered huCD19 Tg mice; however, there were no adverse consequences of this B-cell depletion in the fetuses.
Population in need of further characterization	No studies of inebilizumab have been conducted in pregnant women. Pregnant women and women planning to become pregnant were not eligible to participate in clinical studies with inebilizumab. The SmPC advises that women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab and for at least 6 months after the last infusion of inebilizumab. The data on pregnancy exposure from clinical studies of inebilizumab are insufficient to inform on the drug-associated risk. There are no data on the presence of inebilizumab in human milk, the effects on a breastfed infant, or the effects on milk production. Study 20230064 (previously VIB0551.P4.S4) is an ongoing, global observational pregnancy safety study in women with NMOSD and gMG exposed to inebilizumab during pregnancy. This registry is being conducted to better characterize how inebilizumab commercial product (Uplizna) may affect pregnancy and infant outcomes.

gMG = generalized myasthenia gravis; IgG1 = immunoglobulin G1; NMOSD = neuromyelitis optica spectrum disorder; SmPC = Summary of Product Characteristics.

Table 32. Missing Information: Patients concomitantly receiving other immunosuppressive agents

Evidence source	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.
Population in need of further characterization	Inebilizumab has not been studied in patients receiving chronic concomitant immunosuppressive medications.

Part II: Module SVIII - Summary of the Safety Concerns

Table 33. Summary of Safety Concerns

Important identified risks	• Infusion-related reactions • Infections, including serious infections
Important potential risks	• Viral reactivation and opportunistic infections • Progressive multifocal leukoencephalopathy (PML) • Malignancy • Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women
Missing information	• Safety in patients ≥ 65 years • Use in pregnancy and breastfeeding • Patients concomitantly receiving other immunosuppressive agents

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 34.

Table 34. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
• Progressive Multifocal Leukoencephalopathy (PML)	Progressive Multifocal Leukoencephalopathy (PML)	A specific adverse reaction follow-up questionnaire in line with standard diagnostic criteria will be utilized in order to further characterize this risk.
• Uplizna® Initial Pregnancy Questionnaire (Mother) • Uplizna® Initial Pregnancy Questionnaire (Father) • 6 to 8 Weeks Post Due Date Questionnaire (Mother) • 6 to 8 Weeks Post Due Date Questionnaire (Father) • Six and Twelve Month Infant Questionnaire • Uplizna® Breastfeeding Questionnaire	Use in Pregnancy and Breastfeeding	In order to collect relevant medical and safety information and to further evaluate the missing information regarding Use in pregnancy and breastfeeding, specific adverse reaction follow-up questionnaires are utilized.

III.2 Additional Pharmacovigilance Activities

Table 35. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Study 20257092 (Previously VB-4149) CorEvitas SPHERES (Synergy of Prospective Health & Experimental Research for Emerging Solutions) Registry for Neuromyelitis Optica Spectrum Disorder (NMOSD) (NMOSD indication) Category 3	To prospectively study the natural history of NMOSD and the comparative effectiveness and comparative safety of approved and off-label medications used in the treatment of NMOSD, as well as to systematically evaluate the burden for patients with this disease and to describe treatment utilization patterns. Adverse events of special interest (Targeted Events) including the important risks and missing information such as serious infections, malignancies, severe hypersensitivity reactions/anaphylaxis, and pregnancy will be evaluated.	Prospective, observational research study for patients with NMOSD under the care of a licensed neurologist.	Adult (≥ 18 years) patients with NMOSD under the care of a licensed neurologist.	Final Study Report: December 2028

Table 35. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Study 20230064 (Previously VIB0551.P4.S4) An Observational Pregnancy Safety Study in Women with Neuromyelitis Optica Spectrum Disorder (NMOSD) and Generalized Myasthenia Gravis (gMG) Exposed to UPLIZNA® During Pregnancy (NMOSD indication: ongoing; gMG indication: planned) Category 3	The registry is conducted to better characterize how inebilizumab commercial product (UPLIZNA) may affect pregnancy and infant outcomes. The specific objectives are: • To assess pregnancy and birth safety outcomes in female patients with NMOSD and gMG, exposed to UPLIZNA during pregnancy as defined by receipt of any dose during pregnancy or within 6 months preceding conception. • To describe major congenital malformations, minor congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births, if they occur, in women with gestational exposure to UPLIZNA.	Prospective, observational pregnancy study (registry) to monitor female patients who were exposed to UPLIZNA (inebilizumab-cdon) during pregnancy.	The study population will consist of patients who have been exposed to inebilizumab during pregnancy, as defined by receipt of any dose during pregnancy or within 6 months preceding conception and have signed an ICF.	• Interim study report: July 2026 • Final study report: July 2033

Table 35. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study of Outcomes for Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD), IgG4-related Disease (IgG4-RD), and generalized myasthenia gravis (gMG) Treated With inebilizumab in Europe. (NMOSD indication: ongoing; IgG4-Rd and gMG indications: planned) Category 3	To assess characteristics, treatment patterns and safety outcomes in patients diagnosed with NMOSD, IgG4-RD, and gMG who initiate treatment with inebilizumab. Specific objectives are: • To describe demographic, clinical and treatment characteristics of patients at the time of first inebilizumab treatment • To describe inebilizumab treatment patterns in the first 12 months following treatment initiation in terms of dosing, duration of treatment, frequency of drug discontinuation, switching, and use of add-on therapies • To quantify the incidence of adverse events of special interest, including serious infections, opportunistic infections, hepatitis B reactivations, serious infusion-related reactions, and malignancies.	Retrospective, observational research study for patients with NMOSD, IgG4-RD, and gMG exposed to inebilizumab.	The study population will consist of adult (≥ 18 years) patients with NMOSD, IgG4-RD, and gMG who initiate treatment with inebilizumab.	• Protocol submission: March 2022. • Final study report: December 2032

Table 35. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Study 20230115 (Previously HZNP-UPL-401) A safety study of NMOSD patients receiving inebilizumab following closure of the open-label period N-MOMENTUM Study (NMOSD indication) Category 3	To understand the long-term effects of inebilizumab by collecting safety, laboratory, and other data from patients receiving long-term treatment with inebilizumab, and following discontinuation of inebilizumab.	International, open-label, uncontrolled.	NMOSD patients who received inebilizumab during the now-completed phase 3 study CD-IA-MEDI-551-1155 (N-MOmentum, as well as new NMOSD patients at participating sites).	• Protocol submission: March 2022 • Final Study Report: August 2028

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III.3 Summary Table of Additional Pharmacovigilance Activities

Table 36. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 20230064 (Previously VIB0551.P4.S4) An Observational Pregnancy Safety Study in Women with Neuromyelitis Optica Spectrum Disorder (NMOSD) and Generalized Myasthenia Gravis (gMG) Exposed to UPLIZNA (NMOSD indication: ongoing; gMG indication: planned) Ongoing	The registry is conducted to better characterize how inebilizumab commercial product (UPLIZNA) may affect pregnancy and infant outcomes. The specific objectives are: • To assess pregnancy and birth outcomes in female patients with NMOSD and gMG, exposed to inebilizumab commercial product (UPLIZNA) during pregnancy as defined by receipt of any dose during pregnancy or within 6 months preceding conception. • To describe major congenital malformations, minor congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births, if they occur, in women with gestational exposure to UPLIZNA.	• Use in pregnancy and breastfeeding • Blood disorders particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women	Protocol submission Interim study report Final study report	October 2021 July 2026 July 2033

Table 36. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 20257092 (Previously VB-4149) CorEvitas SPHERES (Synergy of Prospective Health & Experimental Research for Emerging Solutions) Registry for Neuromyelitis Optica Spectrum Disorder (NMOSD) (NMOSD indication) Ongoing	To prospectively study the natural history of NMOSD and the comparative effectiveness and comparative safety of approved and off-label medications used in the treatment of NMOSD, as well as to systematically evaluate the burden for patients with this disease and to describe treatment utilization patterns. Adverse events of special interest (Targeted Events) including the important risks and missing information such as serious infections, malignancies, severe hypersensitivity reactions/anaphylaxis, and pregnancy will be evaluated.	• Infusion-related reactions • Infections, including serious infections • Viral reactivation, and opportunistic infections • PML • Malignancy • Blood disorders particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women • Use in pregnancy and breastfeeding • Patients concomitantly receiving other immunosuppressive agents • Safety in patients ≥ 65 years	First Patient In Final study report	June 2021 December 2028

Table 36. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study of Outcomes for Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD), Immunoglobulin G4-related disease, and Generalized Myasthenia Gravis (gMG)Treated With inebilizumab in Europe (NMOSD indication: ongoing; IgG4-RD and gMG indications: planned) Ongoing	• To describe demographic, clinical and treatment characteristics of patients at the time of first inebilizumab treatment • To describe inebilizumab treatment patterns in the first 12 months following treatment initiation in terms of dosing, duration of treatment, frequency of drug discontinuation, switching, and use of add-on therapies • To quantify the incidence of adverse events of special interest, including serious infections, opportunistic infections, hepatitis B reactivations, serious infusion-related reactions, and malignancies.	• Infusion-related reactions • Infections, including serious infections • Viral reactivation and opportunistic infections • PML • Malignancy • Patients concomitantly receiving other immunosuppressive agents • Safety in patients ≥ 65 years • Use in pregnancy and breastfeeding	Protocol submission Final study report	March 2022 December 2032

Table 36. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 20230115 (Previously HZNP-UPL-401) A safety study of NMOSD patients receiving inebilizumab following closure of the open-label period N-MOMENTUM Study (NMOSD indication) Ongoing	• To understand the long-term effects of inebilizumab. • To assess specific safety, laboratory, and other measures in patients with NMOSD, during long-term treatment with inebilizumab and following its discontinuation.	• Infusion-related reactions • Infections, including serious infections • Viral reactivation, and opportunistic infections • PML • Malignancy • Use in pregnancy and breastfeeding • Patients concomitantly receiving other immunosuppressive agents • Safety in patients ≥ 65 years	Protocol submission Final study report	March 2022 August 2028

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned postauthorization efficacy studies for inebilizumab.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 37. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Infusion-related reactions	Routine risk communication: • SmPC Section 4.2, Section 4.4, Section 4.8, Section 5.1, PL Section 2, PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to receive treatment under the supervision of a physician experienced with NMOSD, IgG4-RD, or gMG and with access to appropriate medical support to manage potential severe reactions such as serious infusion-related reactions is provided in SmPC Section 4.2 • Recommendations to use prophylaxis medications (corticosteroid, antihistamine, and antipyretic) prior to each inebilizumab infusion is provided in SmPC Section 4.2 and Section 4.4 Other risk minimization measures beyond the PI: • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only
Infections, including serious infections	Routine risk communication: • SmPC Section 4.2, Section 4.3, Section 4.4, Section 4.5, Section 4.8, PL Section 2, PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations to obtain a recent (ie, within 6 months) CBC including differentials and immunoglobulins before initiation of inebilizumab and periodically during treatment and after discontinuation until B-cell repletion and to determine if there is a clinically significant infection prior to treatment are provided in SmPC Section 4.2 and Section 4.4 • Recommendation for treatment discontinuation in the case of serious infections and recurrent infections is included in SmPC Section 4.4 Other risk minimization measures beyond the PI: • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 37. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks	
Viral reactivation and opportunistic infections	Routine risk communication: • SmPC Section 4.2, Section 4.3, Section 4.4, Section 4.5, Section 4.8, PL Section 2, PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations to obtain a recent (ie, within 6 months) CBC including differentials and immunoglobulins before initiation of inebilizumab and periodically during treatment and after discontinuation until B-cell repletion and to determine if there is a clinically significant infection prior to treatment are provided in SmPC Section 4.2 and Section 4.4 • Recommendation for HBV screening and evaluation for active tuberculosis and test for latent infection before administration of inebilizumab is included in SmPC Section 4.2 • Recommendation for treatment discontinuation in the case of serious opportunistic infection or recurrent infections is included in SmPC Section 4.4 Other routine risk minimization measures beyond the PI: • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only
Progressive multifocal leukoencephalopathy (PML)	Routine risk communication: • SmPC Section 4.3, Section 4.4, PL Section 2 and Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to evaluate further at the first sign or symptom suggestive of PML, including consultation with a neurologist, MRI scan preferably with contrast, cerebrospinal fluid testing for JCV DNA, with repeat neurological assessments to be considered is included in SmPC Section 4.4 • Recommendation for treatment suspension if signs and symptoms of PML should occur and to discontinue treatment if PML is confirmed is included in SmPC Section 4.4 Other routine risk minimization measures beyond the PI: • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting. • Legal status: prescription only

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 37. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks (continued)	
Malignancy	Routine risk communication: • SmPC Section 4.3, Section 4.4, PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the PI: • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only
Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women	Routine risk communication: • SmPC Section 4.4, Section 4.6, Section 5.3 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations on monitoring newborns for B-cell depletion and to not administer live or live-attenuated vaccines before confirming recovery of B-cell counts in the infant are included in SmPC Section 4.4 and Section 4.6 • Recommendations that women of childbearing potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab during treatment and for 6 months after the last dose of treatment are included in SmPC Section 4.4 and Section 4.6 • Recommendation to consider consulting with a qualified specialist to assess whether a protective immune response has been mounted is included in SmPC Section 4.4 Other routine risk minimization measures beyond the PI: • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only
Missing Information	
Safety in patients ≥ 65 years	Routine risk communication: • SmPC Section 4.2, Section 5.2 Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the PI: • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only

Footnotes, including abbreviations, are defined on the last page of the table.

Table 37. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Missing information (continued)	
Use in pregnancy and breastfeeding	Routine risk communication: • SmPC Section 4.4 and Section 4.6, and PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations that women of childbearing potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab during treatment and for 6 months after the last dose of treatment are included in SmPC Section 4.4, Section 4.6, PL Section 2 Other routine risk minimization measures beyond the PI: • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only
Patients concomitantly receiving other immunosuppressive agents	Routine risk communication • SmPC Section 4.4 and Section 4.5, and PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations to consider the potential for increased immunosuppressive effects in the presence of concomitant immunosuppressive therapy are included in SmPC Section 4.4 and Section 4.5 Other routine risk minimization measures beyond the PI: • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only

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CBC = complete blood count; HBV = hepatitis B virus; IV = intravenous; IgG4-RD = immunoglobulin G4-related disease; JCV = John Cunningham virus; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder; PI = Product Information; PL = Package Leaflet; PML = progressive multifocal leukoencephalopathy; SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimization Measures

Table 38. Additional Risk Minimization Measure: Educational Material: Patient Card

Objectives	To provide patients/caregivers with educational information on the following safety areas of interest: • Infections, including serious infections, • Viral reactivation and opportunistic infections • PML The goal of this information is to educate patients about the risks while using inebilizumab by communicating important risks of PML, infections, including serious infections, viral reactivation and opportunistic infections, and of the clinical symptoms that should promptly lead patients to seek medical attention.
Rationale for the additional risk minimization activity	To increase the understanding of safe and effective use of inebilizumab.
Target audience and planned distribution path	Target audience: Patients who are either currently being treated with inebilizumab, or to who therapy with inebilizumab is proposed. Distribution path: Dissemination of the educational materials to healthcare professionals (HCP) involved in treatment with inebilizumab.
Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness of the materials will be evaluated and monitored based on outcome indicators. Outcome indicators are assessed by monitoring the adverse events related to the safety areas of interest recorded in the safety database. The results of the monitoring of the risk minimization measures will be included in each Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER).
Evaluation of the effectiveness of risk minimization activities	Not yet assessed (IgG4-RD and gMG). Cumulatively, as of 10 December 2024, an increase in the severity or frequency of occurrence of PML, serious infections, viral reactivation, or opportunistic infections has not been observed (NMOSD).

V.3 Summary of Risk Minimization Measures

Table 39. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Infusion-related reactions	Routine risk minimization measures: • SmPC Section 4.2, Section 4.4, Section 4.8, Section 5.1 • PL Section 2 and Section 4 • Recommendation to receive treatment under the supervision of a physician experienced with NMOSD, IgG4-RD, or gMG and with access to appropriate medical support to manage potential severe reactions such as serious infusion-related reactions is provided in SmPC Section 4.2 • Recommendations to use prophylaxis medications (corticosteroid, antihistamine, and antipyretic) prior to each inebilizumab infusion are provided in SmPC Section 4.2 and 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

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Table 39. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Infections, including serious infections	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4, 4.5, and 4.8. • PL Section 2 and Section 4 • Recommendations to obtain a recent (ie, within 6 months) CBC including differentials and immunoglobulins before initiation of inebilizumab and periodically during treatment and after discontinuation until B-cell repletion and to determine if there is a clinically significant infection prior to treatment are provided in SmPC Section 4.2 and Section 4.4 • Recommendation for treatment discontinuation in the case of serious infections and recurrent infections is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only Additional risk minimization measures: • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Table 39. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Viral reactivation and opportunistic infections	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4, 4.5, and 4.8 • PL Section 2 and Section 4 • Recommendations to obtain a recent (ie, within 6 months) CBC including differentials and immunoglobulins before initiation of inebilizumab and periodically during treatment and after discontinuation until B-cell repletion and to determine if there is a clinically significant infection prior to treatment are provided in SmPC Section 4.2 and Section 4.4 • Recommendation for HBV screening and evaluation for active tuberculosis and test for latent infection before administration of inebilizumab is included in SmPC Section 4.2 • Recommendation for treatment discontinuation in the case of serious opportunistic infection or recurrent infections is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Table 39. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Progressive multifocal leukoencephalopathy	Routine risk minimization measures: • SmPC Section 4.3 and 4.4 • PL Sections 2 and 4 • Recommendation to evaluate further at the first sign or symptom suggestive of PML, including consultation with a neurologist, MRI scan preferably with contrast, cerebrospinal fluid testing for JCV DNA, with repeat neurological assessments to be considered is included in SmPC Section 4.4 • Recommendation for treatment suspension if signs and symptoms of PML should occur and to discontinue treatment if PML is confirmed is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402 Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)
Malignancy	Routine risk minimization measures: • SmPC Sections 4.3 and 4.4 • PL Section 2 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Table 39. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women	Routine risk minimization measures: • SmPC Sections 4.4, 4.6, and 5.3 • Recommendations on monitoring newborns for B-cell depletion and to not administer live or live-attenuated vaccines before confirming recovery of B-cell counts in the infant are included in SmPC Section 4.4 and Section 4.6 • Recommendations that women of childbearing potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab during treatment and for 6 months after the last dose of treatment are included in SmPC Section 4.4 and Section 4.6 • Recommendation to consider consulting with a qualified specialist to assess whether a protective immune response has been mounted is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230064 (Previously VIB0551.P4.S4) Pregnancy Registry (NMOSD and gMG indications)

Table 39. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Safety in patients ≥ 65 years	Routine risk minimization measures: • SmPC Sections 4.2 and 5.2 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)
Use in pregnancy and breastfeeding	Routine risk minimization measures: • SmPC Sections 4.4 and 4.6 • PL Section 2 • Recommendations that women of childbearing potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab during treatment and for 6 months after the last dose of treatment are included in SmPC Section 4.4 and Section 4.6, and PL Section 2 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire Additional pharmacovigilance activities: • Study 20230064 (Previously VIB0551.P4.S4) Pregnancy Registry (NMOSD, IgG4-RD, and gMG indications) • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Table 39. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information (continued)		
Patients concomitantly receiving other immunosuppressive agents	Routine risk minimization measures: • SmPC Sections 4.4 and 4.5 • PL Section 2 • Recommendations to consider the potential for increased immunosuppressive effects in the presence of concomitant immunosuppressive therapy are included in SmPC Section 4.4 and Section 4.5 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

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CBC = complete blood count; gMG = generalized myasthenia gravis; IgG4-RD = immunoglobulin G4-related disease; IV = intravenous; JCV = John Cunningham virus; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder; PL = Package Leaflet; PML = progressive multifocal leukoencephalopathy; SmPC = Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for inebilizumab is presented below.

Summary of Risk Management Plan for Uplizna® (inebilizumab)

This is a summary of the risk management plan (RMP) for Uplizna. The RMP details important risks of Uplizna, how these risks can be minimized, and how more information will be obtained about Uplizna's risks and uncertainties (missing information).

Uplizna's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Uplizna should be used.

This summary of the RMP for Uplizna should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Uplizna's RMP.

I. The Medicine and What it is Used for

Uplizna is authorized for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD), immunoglobulin G4-related disease (IgG4-RD), and generalized myasthenia gravis (gMG) (see SmPC for the full indication). It contains inebilizumab as the active substance and it is given by intravenous administration.

Further information about the evaluation of Uplizna's benefits can be found in Uplizna's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/uplizna

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Uplizna, together with measures to minimize such risks and the proposed studies for learning more about Uplizna's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Uplizna, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Uplizna is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Uplizna are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Uplizna. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Infusion-related reactions • Infections, including serious infections
Important potential risks	• Viral reactivation and opportunistic infections • Progressive multifocal leukoencephalopathy (PML) • Malignancy • Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women
Missing information	• Safety in patients ≥ 65 years • Use in pregnancy and breastfeeding • Patients concomitantly receiving other immunosuppressive agents

II.B. Summary of Important Risks

Important identified risk: Infusion-related Reactions	
Evidence for linking the risk to the medicine	This risk was identified based on data from clinical studies, post marketing data, and scientific literature.
Risk factors and risk groups	There are no identified risk factors for infusion-related reactions. Infusion-related reactions were more common during the first infusion than during subsequent infusions.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, Section 4.4, Section 4.8, and Section 5.1 • PL Section 2 and Section 4 • Recommendation to receive treatment under the supervision of a physician experienced with NMOSD, IgG4-RD, or gMG and with access to appropriate medical support to manage potential severe reactions such as serious infusion-related reactions is provided in SmPC Section 4.2 • Recommendations to use prophylaxis medications (corticosteroid, antihistamine, and antipyretic) prior to each inebilizumab infusion are provided in SmPC Section 4.2 and 4.4 • Clinical setting: Intravenous (IV) product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study See Section II.C of this summary for an overview of the postauthorization development plan (NMOSD indication)

Important identified risk: Infections, Including Serious Infections	
Evidence for linking the risk to the medicine	This risk was identified based on data from clinical studies and postmarketing data.
Risk factors and risk groups	Concomitant use of inebilizumab with immunosuppressive agents, including systemic corticosteroids, may increase the risk of infection. Use of inebilizumab in patients with known immunodeficiencies may increase the risk of infection.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, Section 4.3, Section 4.4, Section 4.5, and Section 4.8 • PL Section 2 and Section 4 • Recommendations to obtain a recent (ie, within 6 months) complete blood count (CBC) including differentials and immunoglobulins before initiation of inebilizumab and periodically during treatment and after discontinuation until B cell repletion and to determine if there is a clinically significant infection prior to treatment are provided in SmPC Section 4.2 and Section 4.4 • Recommendation for treatment discontinuation in the case of serious infections and recurrent infections is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only Additional risk minimization measures: • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication) See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Viral Reactivation and Opportunistic Infections	
Evidence for linking the risk to the medicine	This potential risk was identified based on data from clinical studies, postmarketing data, and scientific literature.
Risk factors and risk groups	Patients with serologic evidence of hepatitis B virus (HBV) infection (hepatitis B surface antigen positive [HBsAg+] or anti hepatitis B core antibody positive [HBcAb+]) are at risk for HBV reactivation if they receive immunosuppressive therapy. The safety of immunization with live or live-attenuated vaccines following inebilizumab dosing has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during inebilizumab treatment and until B-cell repletion.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, Section 4.3, Section 4.4, Section 4.5, and Section 4.8 • PL Section 2 and Section 4 • Recommendations to obtain a recent (ie, within 6 months) complete blood count including differentials and immunoglobulins before initiation of inebilizumab and periodically during treatment and after discontinuation until B-cell repletion and to determine if there is a clinically significant infection prior to treatment are provided in SmPC Section 4.2 and Section 4.4 • Recommendation for HBV screening and evaluation for active tuberculosis and test for latent infection before administration of inebilizumab is included in SmPC Section 4.2 • Recommendation for treatment discontinuation in the case of serious opportunistic infection or recurrent infections is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication) See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Progressive Multifocal Leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	This potential risk was identified based on 1 unconfirmed case from clinical studies and scientific literature. In this 1 unconfirmed case, the subject died following the development of new brain lesions, for which a definitive diagnosis could not be established, though the differential diagnosis included an atypical NMOSD relapse, PML, or acute disseminated encephalomyelitis.
Risk factors and risk groups	Risk factors for PML include autoimmune conditions, such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus, treatment with biological therapies that allow for John Cunningham virus (JCV) reactivation, human immunodeficiency virus (HIV)-1 infections, lymphopenia, and history of immunosuppression (National Institute of Neurological Disorders and Stroke. Progressive Multifocal Leukoencephalopathy. 2024. Accessed September 2024 from https://www.ninds.nih.gov/health-information/disorders/progressive-multifocal-leukoencephalopathy).
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.3 and 4.4 • PL Section 2 and Section 4 • Recommendation to evaluate further at the first sign or symptom suggestive of PML, including consultation with a neurologist, magnetic resonance imaging (MRI) scan preferably with contrast, cerebrospinal fluid testing for JCV DNA, with repeat neurological assessments to be considered is included in SmPC Section 4.4 • Recommendation for treatment suspension if signs and symptoms of PML should occur and to discontinue treatment if PML is confirmed are included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication) See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This potential risk was identified based on data from clinical studies, postmarketing data, and scientific medical literature.
Risk factors and risk groups	Immunomodulatory medicinal products may increase the risk of malignancy. On the basis of limited experience with inebilizumab in NMOSD, IgG4-RD, and gMG, the current data do not confirm an increased risk of malignancy. However, the possible risk for the development of solid tumors cannot be excluded.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.3 and 4.4 • PL Section 2 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD, and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication) See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women	
Evidence for linking the risk to the medicine	This potential risk was identified based on data from non-clinical study animal studies and class effect with B-cell-depleting therapies from scientific literature and clinical study data.
Risk factors and risk groups	Fetuses and newborns may be at risk of blood disorders as inebilizumab may cross the placenta and deplete B-cells.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4, 4.6, and 5.3 • Recommendations on monitoring newborns for B-cell depletion and to not administer live or live-attenuated vaccines before confirming recovery of B-cell counts in the infant are included in SmPC Section 4.4 and Section 4.6 • Recommendations that women of childbearing potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab during treatment and for 6 months after the last dose of treatment are included in SmPC Section 4.4 and Section 4.6 • Recommendation to consider consulting with a qualified specialist to assess whether a protective immune response has been mounted is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230064 (previously VIB0551.P4.S4) Pregnancy Registry (NMOSD and gMG indications) See Section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Safety in patients ≥ 65 years	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 and Section 5.2 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication) See Section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Use in pregnancy and breastfeeding	
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4 and 4.6 • PL Section 2 • Recommendations that women of childbearing potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab during treatment and for 6 months after the last dose of treatment are included in SmPC Section 4.4 and Section 4.6 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20230064 (Previously VIB0551.P4.S4) Pregnancy Registry (NMOSD and gMG indications) • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication) See Section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Patients concomitantly receiving other immunosuppressive agents	
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4 and 4.5 • PL Section 2 • Recommendations to consider the potential for increased immunosuppressive effects in the presence of concomitant immunosuppressive therapy are included in SmPC Section 4.4 and Section 4.5 • Clinical setting: IV product that can only be administered in an infusion center or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD, IgG4-RD and gMG indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication) See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of inebilizumab.

II.C.2. Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Study 20257092 (Previously VB-4149) CorEvitas SPHERES (Synergy of Prospective Health & Experimental Research for Emerging Solutions) Registry for Neuromyelitis Optica Spectrum Disorder (NMSOD) (NMOSD indication)	To prospectively study the natural history of NMOSD and the comparative effectiveness and comparative safety of approved and off-label medications used in the treatment of NMOSD, as well as to systematically evaluate the burden for patients with this disease and to describe treatment utilization patterns. Adverse events of special interest (Targeted Events) including the important risks and missing information such as serious infections, malignancies, severe hypersensitivity reactions/anaphylaxis, and pregnancy will be evaluated.
Study 20230064 (Previously VIB0551.P4.S4) Pregnancy Registry Study An Observational Pregnancy Safety Study in Women with Neuromyelitis Optica Spectrum Disorder (NMOSD) and Generalized Myasthenia Gravis (gMG) Exposed to UPLIZNA® during Pregnancy. (NMOSD and gMG indications)	The registry is conducted to better characterize how inebilizumab commercial product (UPLIZNA) may affect pregnancy and infant outcomes. The specific objectives are: • To assess pregnancy and birth outcomes in female patients with NMOSD, exposed to inebilizumab commercial product (UPLIZNA) during pregnancy as defined by receipt of any dose during pregnancy or within 6 months preceding conception. • To describe major congenital malformations, minor congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births, if they occur, in women with gestational exposure to UPLIZNA.
Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study Real-World Observational Study of Outcomes for Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD), IgG4-related Disease (IgG4-RD), and Generalized Myasthenia Gravis (gMG) Treated With inebilizumab in Europe (NMOSD, IgG4-RD, and gMG indications)	The specific objectives are: • To describe demographic, clinical and treatment characteristics of patients at the time of first inebilizumab treatment • To describe inebilizumab treatment patterns in the first 12 months following treatment initiation in terms of dosing, duration of treatment, frequency of drug discontinuation, switching, and use of add-on therapies • To quantify the incidence of adverse events of special interest, including serious infections, opportunistic infections, hepatitis B reactivations, serious infusion-related reactions, and malignancies.
Study 20230115 (Previously HZNP-UPL-401) Postauthorization Safety Study A safety study of NMOSD patients receiving inebilizumab following closure of the open-label period N-MOMENTUM Study (NMOSD indication)	• To understand the long-term effects of inebilizumab • To assess specific safety, laboratory, and other measures in patients with NMOSD, during long-term treatment with inebilizumab and following its discontinuation.

PART VII: ANNEXES

Table of Contents

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

Follow-up forms

Follow-up Form Title	Date of Follow-up Version
Progressive Multifocal Leukoencephalopathy (PML)	12 March 2025
Uplizna® Initial Pregnancy Questionnaire (Mother)	23 June 2025
Uplizna® Initial Pregnancy Questionnaire (Father)	23 June 2025
6 to 8 Weeks Post Due Date Questionnaire (Mother)	16 September 2015
6 to 8 Weeks Post Due Date Questionnaire (Father)	16 September 2015
Six and Twelve Month Infant Questionnaire	16 September 2015
Uplizna® Breastfeeding Questionnaire	23 June 2025

AMGEN®

Report of Suspected UPLIZNA-Associated Adverse Event: Progressive Multifocal Leukoencephalopathy (PML)

Date of this Report (dd/mm/yyyy) | AER #

1. PATIENT DETAILS (Please indicate dates as (dd/mm/yyyy)

Patient Initials (Confidential) | Hosp/ID no. (Confidential)

Age at time of event _____

Date of birth _____

Gender ☐ Male ☐ Female

Adverse event description: _____

Start date _____ End date _____

2. UPLIZNA THERAPY (Please indicate dates as dd/mm/yyyy)

IV dose (mg) _____ Frequency _____
(eg, initial loading dose followed by 2nd loading dose 2 weeks later, then every 6 months from the first infusion)

Start date _____ Stop date _____ Resume date _____ (if applicable) Last dose date _____ (before adverse event)

Batch # _____ Lot # _____ Batch/Lot # unknown ☐

Indication for Treatment (include date of diagnosis):

☐ Neuromyelitis optica spectrum disorder _____ ☐ Myasthenia Gravis _____

☐ Immunoglobulin G4-related disease _____ ☐ Other (specify) _____

3. CLINICAL SIGNS AND SYMPTOMS (Check all that apply, provide dates of onset/resolution if available as dd/mm/yyyy)

Neurological manifestations:

☐ Cognitive dysfunction _____ ☐ Hemiparesis _____ ☐ Visual deficit _____

☐ Dysarthria _____ ☐ Ataxia _____ ☐ New onset seizure _____

☐ Memory impairment _____ ☐ Aphasia _____ ☐ Recent changes in behavior, personality, or mood _____

☐ Any other abnormal findings (specify) _____

4. MRI AND LABORATORY INVESTIGATIONS (Check all that apply, provide dates if available as dd/mm/yyyy)

Brain MRI performed ☐ Yes ☐ No (date) _____

Results _____

Brain biopsy performed ☐ Yes ☐ No (date) _____

Histopathological results _____

CSF (cerebrospinal fluid) analysis ☐ Yes ☐ No (date) _____

CSF cell count and differential _____

Total protein _____ Oligoclonal bands _____ Myelin basic protein _____

Assay kit used for JC virus DNA copy by PCR ☐ Yes ☐ No (date) _____

JC viral DNA copy number analysis by PCR _____

Additional CSF samples available to be provided to Amgen? ☐ Yes ☐ No
(If yes, Amgen will contact you to make arrangements to transport the sample.)

5. MEDICAL HISTORY (Check all that apply. Specify diagnosis and date of diagnosis (dd/mmm/yyyy). If needed, add details in Additonal Information section.)

☐ Prior immunomodulatory therapy _____

☐ Malignancy _____ ☐ HIV infection _____

☐ Organ transplantation _____ ☐ Other autoimmune disorders _____

6. CONCOMITANT MEDICATION

Drug Name/Brand	Indication	Start Date (dd/mmm/yyyy)	End Date (dd/mmm/yyyy)	Dose/Units (eg,mg/day)

7. ADDITIONAL INFORMATION

8. ADVERSE EVENT FINAL OUTCOME/SEQUELAE

REPORTER Name: _____

☐ Physician ☐ Pharmacist ☐ Nurse ☐ Other (specify) _____

Address: _____

City: _____ State/Province: _____

Country: _____ Postal Code: _____

Email: _____ Phone/Fax: _____ (with country code)

Signature: _____ Title/Organization _____

RETURN TO AMGEN VIA SECURE EMAIL OR FAX

AMGEN

Safety Database # _____

UPLIZNA®
INITIAL PREGNANCY QUESTIONNAIRE (MOTHER)

You may return completed form to Amgen Office Fax or Email:

_____

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other_____ Parent exposed to product? ☐ Mother ☐ Father

Name _____Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

*Did the patient sign the *Authorization for Release of Pregnancy Related Medical Information*? ☐ Yes ☐ No

Section 2 – Mother Current Pregnancy Information

Mother's Initials: _____

Age: _____years

Number of fetuses_____

Date of birth: (if permitted to provide by local laws)

Day_____Month_____Year_____

Date of last menstrual period:

Day_____Month_____Year_____

Estimated date of delivery:

Day_____Month_____Year_____

Relevant Laboratory Tests & Procedu res

Test Name	Test Date (dd/mm/yyyy)	Test Result

Section 3 – Mother Prenatal Medication History

Please list all medications (prescription and over-the-counter [include vitamins, herbal medications, etc.) and vaccines, taken by the **mother within 3 months prior to or during pregnancy**.

UPLIZNA® Therapy (please indicate dates as dd/mm/yyyy)**:**

IV dose_____ (mg) Frequency_____ (eg, initial loading dose followed by 2nd loading dose 2 weeks later, then every 6 months from first infusion)

Start Date_____Stop date_____Resume date (if applicable)_____Last dose date_____

Batch #_____Lot #_____ ☐ Batch/Lot # unknown

Indication for Treatment (Include date of diagnosis)**:**

☐ Neuromyelitis optica spectrum disorder _____ ☐ Myasthenia Gravis _____

☐ Immunoglobulin G4-related disease_____ ☐ Other (specify) _____

List any other medications used within 3 months prior to or during the pregnancy:

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yyyy)	Date Drug Stopped (dd/mm/yyyy)	Indication for Treatment

AMGEN

UPLIZNA® INITIAL PREGNANCY QUESTIONNAIRE (MOTHER) *continued*

Safety Database #

Section 4 – Pregnancy Complication and Adverse Event Information

If the **mother** experienced any pregnancy complications (e.g. preeclampsia, gestational diabetes, placenta previa, etc.) please complete the following:

Pregnancy Complication or Adverse Event	**Date the Complication or Event Started** (dd/mm/yyyy)	**Date the Complication or Event Resolved** (dd/mm/yyyy)	**Outcome** (for example: resolved, not resolved, unknown, other, etc.)

Section 5 – Mother Relevant Medical History

Please provide pertinent medical history:

☐ hypertension ☐ seizure ☐ diabetes ☐ difficulty conceiving ☐ asthma ☐ thyroid dysfunction ☐ other_____

Please describe any additional factors that may have an impact on the outcome of this pregnancy, including relevant medical or family history, mother's occupation, illnesses during pregnancy etc. Please specify other disorders including familial birth defects/genetic/chromosomal disorders, etc.:

Section 6 – Mother Substance Use

Substance use (Including 9 months prior to the pregnancy or during pregnancy)	**Yes** or **No**	**Specify product used and concentration** (alcohol by volume [ABV], proof, %, mg)	**Frequency** (daily, weekly, monthly, other)	**Amount** (e.g., number of cigarettes, ounces of alcohol, number of edibles per day/week)	**Substance use duration** in relation to the pregnancy (weeks, months, years)	**Substance use stopped** in relation to the pregnancy (weeks, months, years)	**Date substance was last used if not stopped** (dd/mm/yyyy)
Tobacco use (cigarettes, cigars, pipe, smokeless tobacco, electronic cigarettes, other)							
Alcohol (beer, wine, hard liquor, spirits, other)							
Recreational and Illicit drugs (marijuana, synthetic cannabinoids, cocaine, heroin, other)							

Section 7 – Mother Previous Obstetrical (Pregnancy) History

Please provide the number of pregnancies after treatment with an Amgen product was initiated. Include the pregnancy outcome for each of these pregnancies and any additional relevant details:

Number of pregnancies and outcome details:

☐ Normal healthy baby: _____

☐ Stillbirth: _____

☐ Baby with birth defect: _____

☐ Outcome unknown: _____

☐ Miscarriage: _____

☐ Abortion (induced for medical reason): _____

☐ Abortion (induced for non-medical [voluntary] reason): _____

❑ Other (specify outcome) or any significant additional information:

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Safety Database #

UPLIZNA® INITIAL PREGNANCY QUESTIONNAIRE (MOTHER) *continued*

Section 8 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

Pregnancy Outcome (check the appropriate box below):

☐ Live birth
☐ Number of infants_____(1: single, 2: twins, etc.)
(If multiple births: Please provide all information for each infant in the additional information text box below:)

If live birth: Gender: ☐ Male ☐ Female

Length: _____cm/inches Birth weight: _____gram/lb

Head circumference: _____cm/inches

Did the baby have any complications/medical problems/ congenital anomalies (birth defects)? ☐ Yes ☐ No
If yes, please provide specific information on the medical problem:

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
☐ Due to health issue (mother or baby)
☐ For voluntary reason
☐ Other (please specify):_____

Please confirm if there were there any tests done or results given for the baby/fetus? ☐ Yes ☐ No
If yes, please provide the details below.

Additional Information on pregnancy outcome and/or test/results:

Section 9 – Reporter Signature (can be digital or manual)

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____

Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs.
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider for the pregnancy/delivery:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider who is prescribing the Amgen product:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider for the child:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

AMGEN

UPLIZNA®
INITIAL PREGNANCY QUESTIONNAIRE (FATHER)

Mother Safety Database # _____

You may return completed form to Amgen Office Fax or Email:

_____

Section 1 – Reporter Information

Reporter: ☐ Father ☐ Health Care Professional ☐ Other _____

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

*Did the father sign the Authori*zation for Release of Medical Information*? ☐ Yes ☐ No

Section 2 – Father Medication Information

UPLIZNA® Therapy (please indicate dates as dd/mm/yyyy)**:**

IV dose_____ (mg) Frequency_____ (eg, initial loading dose followed by 2nd loading dose 2 weeks later, then every 6 months from first infusion)

Start Date_____ Stop date_____ Resume date (if applicable)_____ Last dose date_____

Batch #_____ Lot #_____ ☐ Batch/Lot # unknown

Day_____ Month _____ Year _____

Indication for Treatment (Include date of diagnosis)**:**

☐ Neuromyelitis optica spectrum disorder _____ ☐ Myasthenia Gravis _____

☐ Immunoglobulin G4-related disease_____ ☐ Other (specify) _____

Father's initials:_____ Age: _____

Father's pertinent medical history (cardiac conditions, rheumatoid arthritis, cancer, hypertension, etc.):

AMGEN

UPLIZNA® INITIAL PREGNANCY QUESTIONNAIRE (FATHER)

Mother Safety Database # _____

Section 3 – Father Substance Use

Substance use (Including 9 months prior to/during the partner's pregnancy)	**Yes** or **No**	**Specify product used and concentration** (alcohol by volume [ABV], proof, %, mg)	**Frequency** (daily, weekly, monthly, other)	**Amount** (e.g., number of cigarettes, ounces of alcohol, number of edibles per day/week)	**Substance use duration** prior to/during the partner's pregnancy (weeks, months, years)	**Substance use stopped** prior to/during the partner's pregnancy (weeks, months, years)	**Date substance was last used if not stopped** (dd/mm/yyyy)
Tobacco use (cigarettes, cigars, pipe, smokeless tobacco, electronic cigarettes, other)							
Alcohol (beer, wine, hard liquor, spirits, other)							
Recreational and Illicit drugs (marijuana, synthetic cannabinoids, cocaine, heroin, other)							

Section 4 – Current Partner's Pregnancy Outcome (for Live Birth)

☐ Number of infants_____(1: single, 2: twins, etc.)

Multiple births: Please provide all information for each multiple birth infant in the additional information text box below*:

Gender: ☐ Male ☐ Female Birth weight: _____gram/lb

Length: _____cm/inches Head circumference: _____cm/inches

Did the baby have any complications/medical problems/congenital anomalies (birth defects)? ☐ Yes ☐ No

If yes, please provide specific information on the medical problem*:* *Additional information on pregnancy outcome:

Section 5 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____

Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs.
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider who is prescribing the Amgen product:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider for the Child:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

AMGEN®

Safety Database #

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other _____

Any change in the reporter contact information? ☐ Yes ☐ No If yes, please provide updated contact information:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

Section 2 – Mother Prenatal Medication History

Please provide any additional medication information for medicines used during your pregnancy not previously reported. For example, if you resumed or discontinued the Amgen Product or any other medications during the pregnancy (include vitamins, folic acid, herbal medications, and vaccines).

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Section 3 – Mother Pregnancy Complications and/or Adverse Event Information

Pregnancy Complication or Adverse Event (e.g. preeclampsia, gestation diabetes)	Date the Complication or Event Started (dd/mm/yy)	Date the Complication or Event Resolved (dd/mm/yr)	Outcome (for example: resolved, not resolved, unknown, other, etc.)

AMGEN®

Safety Database # _____

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER) *continued*

Section 4 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

Pregnancy Outcome (please check the appropriate box below)

☐ Live birth
- ☐ Number of infants_____(1: single, 2: twins, etc.)
  (If multiple births: Please provide all information for each infant in the additional information text box below:)

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
- ☐ Due to health issue (mother or baby)
- ☐ For voluntary reason
- ☐ Other (please specify):_____

If live birth: Gender: ☐ Male ☐ Female

Length: _____cm/inches Birth weight: _____gram/lb Head circumference: _____cm/inches

Did the baby have any complications/medical problems/congenital anomalies (birth defects)? ☐ Yes ☐ No
If yes, please provide specific information below.

Additional Information on pregnancy outcome:

Section 5 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____

Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider for the pregnancy/delivery:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider who is prescribing the Amgen product:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider for the child:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

AMGEN®

Mother Safety Database #

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (FATHER)

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Father ☐ Health Care Professional ☐ Other_____

Any change in the reporter contact information? ☐ Yes ☐ No If yes, please provide updated contact information:

Name _____Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

Section 2 – Father Medication History

If you have changed the dose, frequency of the Amgen product you are taking during your partner's pregnancy, please provide this information below.

Amgen Medications	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment
Resumed, if applicable						

Section 3 – Current Pregnancy Outcome (for Live Birth)

☐ Number of infants_____(1: single, 2: twins, etc.)
Multiple births: Please provide all information for each multiple birth infant in the additional information text box below*:

Gender: ☐ Male ☐ Female Birth weight: _____gram/lb

Length: _____cm/inches Head circumference: _____cm/inches

Did the baby have any complications/medical problems/ congenital anomalies (birth defects)? ☐ Yes ☐ No

If yes, please provide specific information on the medical problem*:*

*Additional multiple birth information:

Section 4 – Reporter Signature

Signature of person completing questionnaire: _____Date: _____

Please print name: _____

Title: _____

Mother Safety Database # _____

Infant Safety Database # _____

AMGEN®

SIX AND TWELVE MONTH INFANT QUESTIONNAIRE

You may return completed form to Amgen Office Fax or Email:

_____

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Father ☐ Health Care Professional (HCP) ☐ Other_____

Section 2 – Infant Healthcare Provider (HCP) Information

May Amgen contact the HCP for medical information regarding your child? ☐ Yes ☐ No

If yes, please provide contact information:

Name _____ Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

Section 3 – Infant Medical Health Information

List any other medications/drugs (include vitamins and over-the-counter medications taken by the child)

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Has the infant had any abnormal screening tests? ☐ Yes ☐ No If yes, please explain:

Has the infant followed growth curves and developmental milestones as expected for chronological age?

☐ Yes ☐ No If no, please explain:

Has the infant had any illnesses or persistent health problems? ☐ Yes ☐ No If yes, please explain:

Section 4 – Reporter Signature

Signature of person completing questionnaire: _____Date: _____

Please print name: _____Title and specialty if HCP_____

AMGEN

Mother Safety Database # _____

Infant Safety Database # _____

UPLIZNA® BREASTFEEDING QUESTIONNAIRE

You may return completed form to Amgen Office Fax or Email:

_____

Section 1 – Reporter Information

Reporter: ☐ Patient ☐ Health Care Professional (HCP) ☐ Other_____

Name _____Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

*Did the patient sign the Authorization for Release of Medical Information? ☐ Yes ☐ No

Section 2 – Mother Demographic Information

Mother's initials: _____ **Age:** _____ **Date of birth** (if permitted by local laws): Day ____ Month_____Year_____

Section 3 – Mother Medication Information

UPLIZNA® Therapy (please indicate dates as dd/mm/yyyy)**:**

IV dose_____ (mg) Frequency_____ (e.g., initial loading dose followed by 2nd loading dose 2 weeks later, then every 6 months from first infusion)

Start Date_____Stop date_____Resume date (if applicable)_____Last dose date_____

Batch #_____Lot #_____ ☐ Batch/Lot # unknown

Is the mother continuing to take Uplizna® while breastfeeding? ☐ Yes ☐ No

If no, please provide the date when Uplizna® was discontinued or the mother stopped breastfeeding:

Day_____ Month _____ Year _____

Indication for Treatment (Include date of diagnosis)**:**

☐ Neuromyelitis optica spectrum disorder _____ ☐ Myasthenia Gravis _____

☐ Immunoglobulin G4-related disease_____ ☐ Other (specify) _____

List any other medications/drugs (include vitamins, herbals, and vaccines) the Mother used while breastfeeding

Medications/Drugs	**Dose**	**Route** (e.g. oral, subcutaneous)	**Frequency** (e.g. daily, weekly)	**Date drug started** (dd/mm/yyyy)	**Date drug stopped** (dd/mm/yyyy)	**Indication for treatment**

Section 4 – Mother Medical Information

Mother's pertinent medical information (e.g. arthritis, hypertension, thyroid dysfunction, etc.):

UPLIZNA® BREASTFEEDING QUESTIONNAIRE
(continued)

Mother Safety Database # _____

Infant Safety Database # _____

Section 5 – Mother Substance Use

Substance use (Including 9 months prior to the pregnancy, during pregnancy, and during breastfeeding)	**Yes** or **No**	**Specify product used and concentration** (alcohol by volume [ABV], proof, %, mg)	**Frequency** (daily, weekly, monthly, other)	**Amount** (e.g., number of cigarettes, ounces of alcohol, number of edibles per day/week)	**Substance use duration** in relation to the pregnancy/ breastfeeding (weeks, months, years)	**Substance use stopped** in relation to the pregnancy/ breastfeeding (weeks, months, years)	**Date substance was last used if not stopped** (dd/mm/yyyy)
Tobacco use (cigarettes, cigars, pipe, smokeless tobacco, electronic cigarettes, other)							
Alcohol (beer, wine, hard liquor, spirits, other)							
Recreational and Illicit drugs (marijuana, synthetic cannabinoids, cocaine, heroin, other)							

Section 6 – Infant Medical Information

Does the infant currently have any health issues? ☐ Yes ☐ No If yes, provide current health details and treatment provided: _____

_____

Is the infant gaining weight and developing normally? ☐ Yes ☐ No If no, please specify:

_____

_____

Section 7 – Infant Medication Information

Medications/Drugs	**Dose**	**Route** (e.g., oral, subcutaneous)	**Frequency** (e.g., daily, weekly	**Date drug started** (dd/mm/yyyy)	**Date drug stopped** (dd/mm/yyyy)	**Indication for treatment**

Section 8 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____ Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your child's HCP.
May Amgen contact your child's HCP? ☐ Yes ☐ No

Health Care Provider for the child:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

Annex 6. Details of Proposed Additional Risk Minimization Activities

Draft key messages of the additional risk minimization measures

Prior to launch of Uplizna in each Member State, the Marketing Authorization Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, 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:

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 and 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/center
- Cross-reference to the Package Leaflet