EU Risk Management Plan for Briumvi (ublituximab)

RMP version to be assessed as part of this application:

RMP version number: 1.2

Data lock point for this RMP: 10 October 2023

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Rationale for submitting an updated RMP: Type 1b variation (change of due date for protocol submission); no change to the safety concerns.

Summary of significant changes in this RMP:

- Part I: Product Overview – Table

  New Marketing Authorisation Holder: Neuraxpharm Pharmaceuticals, S.L.

- Part III.2 Additional pharmacovigilance activities:

  TG1101-RMS402 summary: Final Protocol Submission date changed from Q3 to Q4 2023

  TG1101-RMS404 summary: Study Start date corrected from Q1 2023 (erroneously reported) to Q1 2024

- Part III.3 Summary Table of additional Pharmacovigilance activities

  Category 3/ TG1101-RMS402: Final Protocol Submission date changed from Q3 to Q4 2023

  Category 3/ TG1101-RMS404: Study Start date corrected from Q1 2023 (erroneously reported) to Q1 2024

- Annex 2:

  TG1101-RMS402: Final Protocol Submission date changed from Q3 to Q4 2023

  TG1101-RMS404 added

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QPPV signature is kept on file

Table of content

Table of content 2
List of abbreviations 4
Part I: Product Overview 6
Part II: Module SI - Epidemiology of the indication and target population 7
Part II: Module SII - Non-clinical part of the safety specification 10
Part II: Module SIII - Clinical trial exposure 11
Part II: Module SIV - Populations not studied in clinical trials 15
SIV.1 Exclusion criteria in pivotal clinical studies within the development programme 15
SIV.2 Limitations to detect adverse reactions in clinical trial development programmes 22
SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes 23
Part II: Module SV - Post-authorisation experience 23
SV.1 Post-authorisation exposure 23
Part II: Module SVI - Additional EU requirements for the safety specification 24
Part II: Module SVII - Identified and potential risks 24
SVII.1 Identification of safety concerns in the initial RMP submission 24
SVII.2 New safety concerns and reclassification with a submission of an updated RMP 25
SVII.3 Details of important identified risks, important potential risks, and missing information 25
Part II: Module SVIII - Summary of the safety concerns 30
Part III: Pharmacovigilance Plan (including post-authorisation safety studies) 30
III.1 Routine pharmacovigilance activities 30
III.2 Additional pharmacovigilance activities 30
III.3 Summary Table of additional Pharmacovigilance activities 33
Part IV: Plans for post-authorisation efficacy studies 34
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) 34
V.1. Routine Risk Minimisation Measures 35
V.2. Additional Risk Minimisation Measures 36
V.3. Summary of risk minimisation measures 37
Part VI: Summary of risk management plan for Briumvi (ublituximab) 40
II.A List of important risks and missing information 41
II.B Summary of important risks 41
II.C Post-authorisation development plan 46
II.C.1 Studies which are conditions of the marketing authorisation 46
II.C.2 Other studies in post-authorisation development plan 46

Part VII: Annexes **..... 47**

Annex 1 – EudraVigilance Interface **..... 48**

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme **..... 49**

Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan **..... 51**

Annex 4 – Specific adverse drug reaction follow-up forms **..... 52**

Annex 5 – Protocols for proposed and on-going studies in RMP part IV **.... 53**

Annex 6 – Details of proposed additional risk minimisation activities (if applicable) **..... 54**

Annex 7 – Other supporting data (including referenced material) **..... 55**

Annex 8 – Summary of changes to the risk management plan over time **.. 57**

List of abbreviations

Abbreviation	Definition of term
AE	Adverse event
AESI	Adverse Event of Special interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
CI	Confidence interval
CIS	Clinically isolated symptom
CNS	Central nervous system
Covid 19	Corona virus disease 2019
CVA	Cerebrovascular accident
DHO-DH	dihydroorotate dehydrogenase
DMT	Disease modifying therapies
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EMA	European medicines agency
EPAR	European public assessment report
EU	European Union
FDA	(US) Food and Drug Administration
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
GPRD	General Practice Research Database
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IG-E	Immunoglobulin E
IG-G	Immunoglobulin G
INN	International non-proprietary name
INR	International Normalized Ratio
IRR	Infusion-related reactions
MDRD	Modification of Diet in Renal Disease
MS	Multiple Sclerosis
NCI-ODWG	National Cancer Institute-Organ Dysfunction Working Group
NOAEL	No Observable Adverse Effect Level
PASS	Post Authorisation Safety Study
PEG	polyethylene glycol
PIP	paediatric investigation plan
PL	Patient Leaflet

PML	progressive multifocal leukoencephalopathy
PP	primary progressive
PR	progressive relapsing
PSUR	periodic safety update report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RMS	relapsing forms of multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SmPC	summary of product characteristics
SP	secondary progressive
SPMS	secondary progressive multiple sclerosis
TB	tuberculosis
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack

Part I: Product Overview

Table Part I.1 – Product Overview

Active substance **(INN or common name)**	Ublituximab
Pharmacotherapeutic group (ATC Code)	Selective immunosuppressants (L04AA57, requested)
Marketing Authorisation Holder	Neuraxpharm Pharmaceuticals, S.L.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Briumvi
Marketing authorisation procedure	Centralized (EMEA/H/C/005914)
Brief description of the product	Chemical class: IgG1 chimeric monoclonal antibody, glycoprotein
	Summary of mode of action: Ublituximab binds to the trans-membrane antigen CD20 expressed on B-lymphocytes, inducing an immune response that results in the lysis of B cells.
	Important information about its composition: Ublituximab is a glycoengineered murine/human chimeric anti-CD20 monoclonal antibody.
Hyperlink to the Product Information	Module 1.3.1 Briumvi (ublituximab) SmPC
Indication in the EEA	Current: Treatment of adult patients with relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features.
Dosage in the EEA	Current: Initial first dose 150 mg intravenous infusion (150 mg of ublituximab in 6 mL at a concentration of 25 mg/mL), followed by the initial second dose 450 mg intravenous infusion 2 weeks later. Maintenance dose 450 mg intravenous infusion every 24 weeks (treatment interval with a minimum of 5 months).

Pharmaceutical form and strengths	Current: Concentrate for solution for infusion
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication and target population

Relapsing forms of multiple sclerosis (RMS)

Incidence:

A systematic review has comprehensively catalogued the incidence and prevalence of MS across Europe between January 1985 and January 2011. Only a few studies reported countrywide data. The prevalence and incidence of MS are not well documented in many regions of Europe. Incidence and prevalence of MS vary considerably between different ethnic populations (Kingwell E et al., 2013) Multiple sclerosis (MS) typically affects young adults (mean age at onset 30 years), and women are affected more often than men (median estimated female/male ratio is 2.1). Regionally, the average age of onset is 29.2 years in Europe (World Health Organisation, 2008.).

Prevalence:

The global prevalence of MS is estimated at 36 people per 100,000 people (The Multiple Sclerosis International Federation, 2020.). This global estimate has increased from 2.3 million people in 2013 (The Multiple Sclerosis International Federation, 2020.), which is consistent with stated increases in the national prevalence in some countries over this time. Several factors are likely to play an important role in explaining the increase, including improvements in counting methods nationally and globally since 2013, as well as better diagnosis, people with MS living longer and global population growth (9% since 2013). Multiple sclerosis is present in all regions of the world but is notably higher in the European and Americas regions. In the European region, San Marino (337 per 100,000), Germany (303 per 100,000) and Denmark (282 per 100,000) have the highest number of people with MS. San Marino and Germany have the highest prevalence in the world. Europe has an estimated prevalence of 133 per 100,000 inhabitants, followed by the Americas (112 per 100,000), Eastern Mediterranean (30 per 100,000), South-East Asia (9 per 100,000), Africa (5 per 100,000) and Western Pacific (5 per 100,000). The age-standardised (standardised to the 2013 European population) prevalence per 100,000 by different ethnicities was 180, 74 and 29 for the White, Black and South Asian populations, respectively.

Demographics of the population in the proposed indication and risk factors for the disease:

The higher incidence of MS among women observed for the last 4–5 decades was not evident 3–4 generations ago, when the sex ratio was close to unity. Recent studies have shown that the sex ratio in MS is still changing in many countries. For instance, in Japan, the female-to-male ratio has increased from 2.63 in 2001 to 3.57 in 2011. The risk of MS is increasing from south to north in Europe, North America and Japan on the northern hemisphere, and from north so south in Australia and New Zealand on the southern hemisphere (Houzen H et al., 2018; Benjaminsen E et al., 2014). The causes of the sex ratio changes that have occurred in most countries are unclear but are likely to have resulted from

environmental influences or from the consequences of gene–environmental interactions (Scalfari A et al., 2013).

A recent analysis of trends in the sex ratio in MS for individuals born between 1930 and 1989 found a marked increase in Northern Europe (not including the UK) (from 2.09 to 3.77), but only a moderate increase in Southern Europe (from 1.46 to 2.31) (Trojano M, et al 2012). In contrast, a study in Sweden found a mean female-to-male ratio for MS of 2.62, with no clear trend with year of birth for individuals born between 1931 and 1985 (Mackenzie et al., 2014). In the 'Incidence and prevalence of multiple sclerosis in the UK 1990–2010 descriptive study' in the General Practice Research Database (GPRD), the mean female-to-male ratio for MS was 2.4 and there was no trend with time over the 20-year study period (Mackenzie IS et al., 2014).

The mean age of MS diagnosis is 32 years (Walton C et al., 2020). The maximum incidence of MS occurred at age 40 years (women) to 45 years (men) (Mackenzie IS et al., 2014).

The proportion of patients with multiple sclerosis (MS) who develop symptoms before 16 years of age has been variously estimated at between 0.4% and 10.5%. The estimated incidence of paediatric MS was 0.64 per 100 000 person-years with a clear increase from the age group ≤10 (0.09/100 000) to 2.64 per 100 000 in age group 14−15 years. All had relapsing−remitting disease with polysymptomatic onset in half of the cases. Approximately 97% to 99% of the affected children have relapsing-remitting MS, while 85% to 95% of the adults experience such a condition (Inaloo S et al., 2013).

Aging is a significant factor influencing the course of MS. Patients with MS over the age of 65 years are more likely to have a progressive course (primary progressive (PP), 29%; secondary progressive (SP), 26%; or progressive relapsing (PR), 8%) compared to their younger counterparts of whom 57% have relapsing-remitting multiple sclerosis (RRMS) (Sanai SA et al., 2016).

The main existing treatment options:

The current therapeutic approach involves symptomatic treatment, treatment of acute relapses, and disease modifying therapies (DMTs). Symptomatic treatment refers to all therapies applied to improve symptoms and complications caused by the disease. More specific treatments are those that intend to interfere with the pathophysiology of MS, e.g., facilitate remyelination or axonal conductivity. The standard of care for acute relapses is intravenous (IV) methylprednisolone which shortens the duration of a relapse but has no influence on its sequelae.

DMTs aim to modify the course of the disease mainly by suppressing or modulating the immune responses involved in MS pathogenesis. Biological (therapeutic proteins, monoclonal antibodies) and small chemical active substances have been approved for use in this therapeutic context. These therapies aim to prevent relapses, and ultimately, intend to decrease the rate of accumulation of disability. Due to the risks (identified or potential) of opportunistic infections, malignancies, and other systemic adverse drug reactions, several of these treatment options are considered as second-line options, i.e., treatment is restricted to patients with rapidly evolving MS or those who had a suboptimal response to prior therapies.

It is often recommended that patients take a DMT as early as they are diagnosed. Two conceptually different treatment approaches have emerged:

- The 'escalation approach' advocates the first line use of moderately effective DMTs (i.e., classical first-line therapies, e.g., interferons and glatiramer acetate) and a later escalation to high-efficacy therapies only if new disease activity breaks through, i.e., relapses or new lesions as shown by MRI.
- The 'highly effective treatment early approach' advocates initiation of high-efficacy therapies early on (as first-line therapy). Treatment-related risks are weighed against the expected

occurrence of brain damage caused by the disease.

Several DMTs/DMT classes are currently available and approved in the EU (European union) for use in RMS, which vary in their mechanism of action, efficacy, safety, mode of administration and ease of use (**Table II.1.**).

Table II.1. Disease Modifying Therapies (DMTS) for Relapsing Multiple Sclerosis (RMS)

Disease Modifying Therapy for Relapsing Multiple Sclerosis (RMS)	**Mechanism of Action**
alemtuzumab	anti-CD52 monoclonal antibody
cladribine	nucleoside analogue of deoxyadenosine
dimethyl fumarate	modulates Nrf2 transcriptional pathway
fingolimod	modulates sphingosine-1-phosphate (S1P) receptor
(peg) interferon beta	immunomodulatory cytokine
glatiramer acetate	immunomodulatory agent
mitoxantrone	DNA intercalating agent
natalizumab	anti-integrin α4 monoclonal antibody
ocrelizumab	anti-CD20 monoclonal antibody
ofatumumab	anti-CD20 monoclonal antibody
ozanimod	modulates S1P receptor sub-types 1 and 5
ponesimod	modulates S1P receptor sub-type 1
siponimod	modulates S1P receptor sub-types 1 and 5
teriflunomide	inhibits mitochondrial dihydroorotate dehydrogenase (DHO-DH)

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Multiple sclerosis is an acquired idiopathic, inflammatory demyelinating disorder of the CNS in which the myelin sheath is disrupted due to genetic and environmental factors. The attacks are defined as new neurological deficits lasting more than 24 hours that can be associated with an anatomical localisation, in the absence of fever or any infection. Usually, the neurological deficit develops sub-acutely over 2 to 4 weeks, and it usually resolves completely or partially over 6 to 8 weeks, either spontaneously, or after treatment with corticosteroids. Different clinical and pathological subtypes of MS have been identified. In about 80%–85% of patients, there are attacks (relapses), and complete or partial remissions following them, whereas in 10%–15% of patients, there is a slow progressive course without any relapses. Patients suffer a range of symptoms including motor weakness, spasticity, gait and coordination imbalance, sensory dysfunction, vision loss, sexual dysfunction, fatigue, depression, chronic pain, sleep disorders and cognitive impairment (Damal K et al., 2013).

Clinical patterns can be grouped as follows (Lublin FD et al., 2014): clinically isolated symptom (CIS); relapsing-remitting multiple sclerosis (RRMS): Active and non-active RRMS; Progressive MS: Active progressive, active non-progressive, non-active progressive, non-active non-progressive (stable) subtypes. The term "relapsing MS (RMS)" applies to those affected patients with either relapsing-remitting multiple sclerosis (RRMS) or secondary progressive multiple sclerosis (SPMS) with superimposed relapses. Patients with relapsing MS, despite suffering from different MS forms, constitute a common target for current treatment options. There are no clear criteria that mark the transition from RRMS to SPMS.

Although MS is essentially chronic and disabling, long-term disability is not necessarily the immediate cause of death. However, MS does carry the risk of systemic complications in the advanced stages of the disease that may lead to death (Scalfari A et al., 2013). Globally, there were 18,932 deaths (95% CI: 16,577 to 21,033) attributed to MS in 2016. The global age standardised death rates decreased significantly from 1990 to 2016 (change -11.5%; 95% CI: -35.4% to -4.7%) (GBD 2016 Multiple Sclerosis Collaborators, 2019). In 2016, the pooled crude mortality rate was 9.78 per 1,000 person-years (95% CI: 6.81-14.02). Pooled all-cause standardised mortality rate (SMR) per 1,000 person-

years was 2.80 (95% CI: 2.74-2.87), 2.56 (95% CI: 2.47-2.66) in males and 3.06 (95% CI: 2.97-3.17) in females (Manouchehrinia A et al., 2016). The overall mortality rates in population-based French and US MS cohorts were 3.7 and 8.9 per 1,000 person-years, respectively.

Important co-morbidities in the target population:

Certain comorbidities are more prevalent in people with MS. According to a comprehensive systematic review of 249 articles, the most prevalent comorbidities in MS are depression (23.7%), anxiety (21.9%), hypertension (18.6%), hypercholesterolemia (10.9%), and chronic lung disease (10.0%) (Marrie RA et al., 2015). Compared with the general population, vascular comorbidities are shown to be more prevalent in the population with MS, including hypertension, hyperlipidaemia, and ischemic heart disease. A large population-based matched cohort study compared over 12,200 persons with MS registered in the Clinical Practice Research Datalink in England with close to 73,000 controls. Over an 11-year period, patients with MS had a 28% increased risk of acute coronary syndrome, a 59% increased risk of cerebrovascular disease, and a 32% increased risk of any macrovascular disease, which was not completely accounted for by traditional vascular risk factors (Magyari M et al., 2020). MS patients have an increased risk of infection, notably infections of the renal tract, and a two-fold increased risk of hospitalized infections compared with non-MS patients (Persson R et al., 2020).

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

The pharmacokinetic and toxicity profiles of ublituximab were evaluated after single and repeated doses in cynomolgus monkeys. Ublituximab was well tolerated upon weekly dosing for up to 26 weeks at doses of 30 mg/kg/dose in cynomolgus monkeys.

Key ublituximab-related findings in repeat-dose toxicity studies included expected decreases in lymphocyte count and corresponding changes in lymphoid tissue, thymus, spleen, and bone marrow. Treatment-related mortality was observed in 1 female monkey administered with 50 mg/kg ublituximab in the 4-week good laboratory practice (GLP) toxicity study. On Day 20, the female was euthanized after demonstrating clinical signs of marked dehydration, pallor of the lip mucosa, hypothermia, hypoactivity, prostration, body weight loss, and markedly reduced food consumption in the presence of moderate modifications of the hepatic parenchyma. Similarly, body weight loss secondary to decreased food consumption with correlative changes in haematology and clinical chemistry parameters was observed in a male at 50 mg/kg. In comparison, 30 mg/kg ublituximab was well tolerated in monkeys after multiple doses over a 13-week period and over a 26-week period with changes primarily noted in lymphoid tissue.

In general toxicity studies, there were no histopathology changes in reproductive tissues. Ublituximab was not tolerated in pregnant monkeys administered with 30 mg/kg ublituximab during the first, second, and third trimesters of pregnancy. Principal effects included increased foetal and infant loss as well as musculoskeletal- and central nervous system-related foetal abnormalities. Based on these results and a single dose evaluated, there was not a dose level or trimester in which a NOAEL for developmental outcomes could be determined.

Toxicity

- *Key issues identified from acute or repeat-dose toxicity studies*

The pharmacokinetic and toxicity profiles of ublituximab were evaluated after single and repeated doses in cynomolgus monkeys. Ublituximab was well tolerated upon weekly dosing for up to 26 weeks at doses of 30 mg/kg/dose in cynomolgus monkeys.

There were no ublituximab-related changes in body weights, qualitative food consumption, ophthalmic evaluation, veterinary physical examinations and vitals, qualitative ECG parameters, body temperatures, organ weights or macroscopic findings in all animals surviving to scheduled necropsy. The microscopic findings at terminal euthanasia were observed in the mandibular and mesenteric lymph nodes and spleen, which were consistent with the pharmacological activity of ublituximab. Other treatment-related microscopic changes included mononuclear cell infiltration in the central nervous system and eye as well as vascular/perivascular inflammation in various tissues that were potentially related to immune-mediated effects secondary to anti-drug antibody formation associated with the administration of ublituximab.

- *Reproductive/developmental toxicity*

The pregnancy and foetal outcomes demonstrated increased foetal and infant mortality. Gestation length in the second and third trimester-treated females was also shorter. In 2 infants whose mothers were treated during the second trimester, abnormal external, skeletal, and morphometric findings were observed. There were no ublituximab-related developmental findings in infants whose mothers were treated during the first trimester.

- *Genotoxicity*

Not applicable as per the ICH S6 guideline.

- *Carcinogenicity*

As per the ICH S6 guideline, carcinogenicity studies are generally considered not to be relevant to biotechnology-derived products and were therefore not performed for ublituximab.

Safety pharmacology

In general toxicology studies, there were no observed findings related to the respiratory, cardiovascular or central nervous systems.

Other toxicity-related information or data

Not applicable.

Part II: Module SIII - Clinical trial exposure

In total, in the primary pooled safety population, 545 patients were exposed to ublituximab in two pivotal Phase III clinical studies. These clinical studies had a treatment duration of 96 weeks and a study duration of 120 weeks. The pooled Phase III studies provide comparative results with teriflunomide. This safety dataset is used as the primary data set throughout this RMP:

Study TG1101-RMS301: A Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE I Study)

Study TG1101-RMS302: A Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE II Study)

Supplementary safety analyses included safety data from the 48 subjects included in the Phase II, single-arm, dose-finding study, Study **TG1101-RMS201**, concatenated with its extension study, Study **TG1101-RMS201E**, for the same subjects. The TG1101-RMS201(E) study was not pooled with the TG1101-RMS301 and TG1101-RMS302 studies, as the Phase II studies utilized differing dose levels, a placebo phase, and varying infusion times. In addition, this Phase II study is a single-arm study, so not comparative like the Phase III studies:

Study TG1101-RMS201: A Placebo-Controlled Multi-Center Phase IIa Dose Finding Study of Ublituximab, a Third-Generation Anti-CD20 Monoclonal Antibody, in Patients with Relapsing Forms of Multiple Sclerosis

Study TG1101-RMS201E: An Open Label Extension of the TG1101-RMS201 Trial, for Subjects Currently Enrolled in TG1101-RMS201 Treated with Ublituximab for Relapsing forms of Multiple Sclerosis

Additionally, safety data were taken from an extension study which enrolled subjects from the ublituximab arm and the teriflunomide arm of the pivotal Phase III studies TG1101-RMS301 and TG1101-RMS302:

TG1101-RMS303: An Open Label Extension Study of Ublituximab in Subjects with Relapsing Multiple Sclerosis

Subjects from the pivotal Phase III studies, TG1101-RMS301 and TG1101-RMS302, could roll-over to this extension study. The safety data of the subjects who received ublituximab in one of the Phase III studies and rolled over to this extension study were concatenated as a second safety data analysis (N=545).

Also, safety data was supplemented with data on ublituximab for subjects who had previously received teriflunomide in Studies TG1101-RMS301 and TG1101-RMS302, and who subsequently received ublituximab upon rolling over into Study TG1101-RMS303 (N=328).

Finally, safety data from the 17 oncology/haematology studies (completed and ongoing; single agent and in combination) were taken into account. As these studies enrolled subjects with different indications and treated at different doses, these are only used as supplementary safety information. In these oncology studies, 1475 subjects were exposed to ublituximab single agent or in combination therapy.

In the following tables, only safety data from the RMS studies are discussed, unless explicitly stated.

Table SIII.1 Duration of exposure and dose extent of exposure

	Pooled Pivotal Phase III Studies (RMS301 and RMS302)		**Concatenated* Phase III Studies (includes RMS303)**
	Ublituximab (N=545) n (%)	**Teriflunomide (N=548) n (%)**	**Ublituximab (N=545) n (%)**
Number of infusions*			
Mean (SD)	4.8 (0.62)	4.8 (0.68)	5.9 (1.30)
Median (minimum, maximum)	5.0 (1, 5)	5.0 (1, 5)	6.0 (1, 8)
Number of infusions, n (%)			
1	5 (0.9)	3 (0.5)	5 (0.9)
2	9 (1.7)	16 (2.9)	9 (1.7)
3	11 (2.0)	17 (3.1)	11 (2.0)
4	15 (2.8)	9 (1.6)	15 (2.8)
5	505 (92.7)	503 (91.8)	186 (34.1)
6	-	-	62 (11.4)
7	-	-	240 (44.0)

	Pooled Pivotal Phase III Studies (RMS301 and RMS302)		Concatenated* Phase III Studies (includes RMS303)
	Ublituximab (N=545) n (%)	**Teriflunomide (N=548) n (%)**	**Ublituximab (N=545) n (%)**
8	-	-	17 (3.1)
Total number of started infusions	2644	2637	3237
Total number of completed infusions without interruption, n (%)	2554 (96.6)	2623 (99.5)	3142 (97.1) 9
Total number of completed infusions with interruption, n (%)	75 (2.8)	6 (0.2)	80 (2.5)
Total number of incomplete infusions, n (%)	15 (0.6)	8 (0.3)	15 (0.5)

* Safety data from the Phase III studies RMS301 and RMS302, supplemented with the safety data from the extension study RMS303 from patients who received ublituximab in the studies RMS301 and RMS302.

Taking into account that the second infusion will be given 0.5 months (2 weeks) after the first infusion, and all subsequent infusions given every 6 months, these numbers represent about 18,500 months of patient exposure time.

Table SIII.2 Age group and gender

Age	**Patients (N=545) n (%)**
<38 years	326 (59.8)
≥38 years	219 (40.2)
Total	545 (100)
Gender	**Patients (N=545) n (%)**
Male	200 (36.7)
Female	345 (63.3)
Total	545 (100)

Table SIII.3 Race and ethnic origin

Race	**Patients n (%)**
Black or African-American	8 (1.5)
White	535 (98.2)
Native Hawaiian or Other Pacific Islander	1 (0.2)
Other	1 (0.2)
Total	545 (100)
Ethnic Origin	**Patients n (%)**
Hispanic or Latino	13 (2.4)
Not Hispanic or Latino	524 (96.1)
Not reported	6 (1.1)
Unknown	2 (0.4)

Total	545 (100)

Of the 17 clinical studies in oncology/haematology, 5 studies have been completed, and 12 are ongoing. These subjects receive ublituximab monotherapy (in 3 studies) or ublituximab in combination with other anti-cancer medications, and therefore, are not pooled as part of the core safety population. A brief summary on exposure is given below.

For information, in Table SIII.4, the clinical trial exposure data for ublituximab in the oncology/haematology studies is presented for patients who received the single agent or in any combination.

In these 1475 patients, the ublituximab dose varied, however, most patients (1368 [92.7%]) received 900 mg, which is twice as high as in the RMS studies. The duration of exposure is given here as number of months.

Table SIII.1 Clinical trial exposure in the oncology/haematology studies

Duration of exposure	**Number of subjects (%) N=1475**
<1 month	167 (11.3)
1-<3 months	229 (15.5)
3-<6 months	310 (21.0)
6-<12 months	256 (17.4)
12-<24 months	247 (16.7)
24-<36 months	103 (7.0)
36-<48 months	121 (8.2)
48-<60 months	41 (2.8)
≥60 months	1 (0.1)
Age Group	**Number of subjects (%) N=1475**
18-64	581 (39.4)
65-74	562 (38.1)
75-84	288 (19.5)
≥85	44 (3.0)
Gender	**Number of subjects (%) N=1475**
Male	959 (65.0)
Female	516 (35.0)
Race	**Number of subjects (%) N=1475**

White	1276 (86.5)
Black or African American	63 (4.3)
Native Hawaiian or Other Pacific Islander	1 (0.1)
American Indian or Alaska Native	3 (0.2)
Asian	23 (1.6)
Multiple	4 (0.3)
Other	25 (1.7)
Not Reported/Unknown	80 (5.5)
Ethnicity	**Number of subjects (%) N=1475**
Hispanic or Latino	53 (3.6)
Not Hispanic or Latino	1291 (87.5)
Not Reported	64 (4.3)
Not Reported/Unknown	67 (4.6)

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Pivotal data from studies TG1101-RMS301 and TG1101-RMS302 support the safety and efficacy in the target population (RMS). Patient enrolment in these studies was based on inclusion/exclusion criteria that allowed for evaluation of safety and efficacy while minimising risk for patients and ensuring enrolment of patients considered representative of the target population. The key safety-related exclusion criteria from these studies are presented in Table SIV.1.

Table SIII.1 Key-safety-related exclusion criteria

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale for not including as missing information
Pregnant or nursing	Immunomodulating agents such as the anti-CD20 class of drugs are known to have a potential for embryo-foetal toxicity. Following weekly intravenous administration of ublituximab to pregnant monkeys during the first, second or third trimesters of pregnancy at the maximum clinical dose of 450 mg, foetal loss and external, skeletal and visceral abnormalities in infants were observed.	Yes	
≥ 10 years disease duration from onset with subjects Expanded Disability Status Scale (EDSS) ≤ 2.0	An EDSS of 2 or less with disease duration of at least 10 years would suggest minimal disease activity or progression.	No	These patients are not included in the labelled indication of active relapsing MS.

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale for not including as missing information
Current evidence or known history of clinically significant infection including: a. Chronic or ongoing active viral, bacterial, or fungal infectious disease requiring long term systemic treatment such as, but not limited to: PML, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis (TB), or active hepatitis C b. Previous serious opportunistic or atypical infections c. History of positive serology for hepatitis B or hepatitis C or HIV d. Previous diagnosis with a congenital or acquired immunodeficiency (AIDS)	Immunomodulating agents such as the anti-CD20 class of drugs are known to have a potential for immunosuppressive effects that could lead to infection or lead to reactivation of viral opportunistic infections/co-infections.	No	Serious infections, including opportunistic infections, are included as an Important Potential Risk
History of clinically significant CNS trauma (e.g. traumatic brain injury, cerebral contusion, spinal cord compression	CNS trauma could impact interpretability of the study results.	No	Overall, there is a limited number of patients with significant CNS trauma as a comorbidity in the target population to adequately evaluate ublituximab safety in this subset of patients.

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale for not including as missing information
History of liver disease, including but not limited to: a. Known history of active hepatitis B or C any time prior to randomization or known history of active hepatitis A within 3 years prior to randomization b. Presence of chronic liver or biliary disease c. Moderate or severe hepatic impairment defined as Child Pugh Score B or C, respectively, based on measurement of total bilirubin, serum albumin, International Normalized Ratio (INR) and as well as on presence /absence and severity of ascites and hepatic encephalopathy d. Any of the following abnormal laboratory values at screening or first infusion: • ALT/SGPT > 2 X the Upper Limit of Normal (ULN) • AST/SGOT > 2 X ULN	It is unknown if there is an effect of moderate-severely impaired hepatic function on ublituximab elimination and exposure in humans as well as if patients with moderate-severe hepatic impairment would have a different safety profile from patients with normal to mild hepatic impairment.	No	Based on available clinical trial data, there was no clinically meaningful difference or trends observed in safety with ublituximab exposure in patients with mild hepatic impairment relative to patients with normal hepatic function; therefore, the safety profile of patients with moderate or severe hepatic impairment is not anticipated to be different. Ublituximab exposure was comparable in patients with mild or moderate hepatic impairment relative to patients with normal hepatic function.

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale for not including as missing information
History of renal impairment, including, but not limited to: a. Hypoproteinaemia (e.g., in case of severe liver disease or nephrotic syndrome) with serum albumin < 3.0 g/dL b. Severe renal insufficiency requiring renal dialysis	It is unknown if there is an effect of moderate-severely impaired renal function on ublituximab elimination and exposure in humans as well as if patients with moderate-severe renal impairment would have a different safety profile from patients with normal to mild renal impairment.	No	Based on available clinical trial data, there was no clinically meaningful difference or trends observed in safety with ublituximab exposure in patients with mild renal impairment relative to patients with normal renal function; therefore, the safety profile of patients with moderate or severe renal impairment is not anticipated to be different. Ublituximab exposure was comparable in patients with mild renal impairment relative to patients with normal renal function.
Subjects with significantly impaired bone marrow function or significant anaemia, leukopenia, or thrombocytopenia a. Haematocrit < 24% and/or b. Absolute white blood cell count < 4,000 cells/mm3 and/or c. Platelet count < 150,000 cells/mm3 and/or d. Absolute neutrophil ≤ 1,500 cells/mm3	Immunomodulating agents such as the anti-CD20 class of drugs may have a potential for myelosuppressive effects. Patients with a severely impaired bone marrow function at baseline may be more susceptible to developing a serious infection.	No	Serious infections, including opportunistic infections, are included as an Important Potential Risk

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale for not including as missing information
Absolute lymphocyte counts less than 1000/microliter	Immunomodulating agents such as the anti-CD20 class of drugs are known to have a potential for immunosuppressive effects including impairment of bone marrow function.	No	Decreased lymphocyte counts have been observed frequently, however, were mostly mild to moderate in severity and are associated with the intended mechanism of action of ublituximab. Based on these data, patients with significantly low hematological parameters at baseline are not anticipated to have poor outcomes due to ublituximab.

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale for not including as missing information
Any severe and/or uncontrolled medical conditions or other conditions such as: a. Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV) b. QTcF: Female > 450 msec; male > 430 msec c. Angina not well-controlled by medication d. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting in the past 6 months prior to screening	It is unknown if patients with a history of cardiovascular disorders would have a different safety profile from patients without a prior history of cardiovascular complications. Infused anti-CD20s may have a potential for IRR-related hypotension. Therefore, patients with cardiovascular conditions (e.g. CHF) were not included.	No	Overall, there is a limited number of patients with significant cardiovascular disease as a comorbidity in the target population to adequately evaluate ublituximab safety in this subset of patients. Patients with significant cardiovascular conditions could impact interpretability of the study results.
Other significant concurrent, uncontrolled medical condition including, but not limited to, cardiac, renal, hepatic, haematological, gastrointestinal, endocrine, immunodeficiency syndrome, pulmonary, cerebral, psychiatric, or neurological disease.	It is unknown if patients with a history of other significant medical conditions would have a different safety profile from patients without them.	No	These diverse medical conditions may be present as comorbidities in the target population but will likely be limited to adequately evaluate ublituximab safety in these subset of patients.

Criterion	Reason for exclusion	Is it considered to be included as missing information	Rationale for not including as missing information
Lack of immunity to varicella	Immunomodulating agents such as the anti-CD20 class of drugs are known to have a potential for immunosuppressive effects that could lead to infection or lead to reactivation of viral opportunistic infections/co-infections.	No	Serious infections, including opportunistic infections, are included as an Important Potential Risk
Vaccination with live virus within 2 months of randomization	Immunomodulating agents such as the anti-CD20 class of drugs may impair immune response, which may lead to infection by a live virus administered by vaccination.	No	It is recommended in labelling to administer live virus vaccines at least 4 weeks prior to initiation of ublituximab, which is generally in alignment with guidelines for timing of live virus vaccinations with anti-CD20 drug class administration.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The ublituximab clinical development programme for the indication of RMS 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 exposure beyond 96 weeks. Across the 545 subjects who received ublituximab in the two Phase III pivotal RMS studies, the median treatment duration was 72 weeks.

When taking into account the extension study TG1101-RMS303 as well, 505 subjects received ublituximab treatment for >12 months.

The studies in the clinical development programme for oncology/haematology, although the majority of studies is evaluating ublituximab in combination regimens, may provide safety information on rare adverse reactions, adverse reactions with a long latency or those caused by prolonged exposure. Across the 1475 subjects who have received ublituximab in oncology/haematology studies, the treatment duration was between 1 month and > 60 months. The dosages for the oncology/haematology studies differed and were higher (see Table SIII.4).

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure Pooled Pivotal Phase III Studies (RMS301 and RMS302) Ublituximab (N=545)
Pregnant/breastfeeding women	Not included in the clinical development programme; however, 10 patients became pregnant on study in the pivotal studies
Paediatric (patients <18 years)	Not included in the clinical development programme
Elderly (patients >55 years)	0
Patients with relevant comorbidities:	
Patients with renal impairment (all)*	224
Severe (eGFR <30 mL/min)	0
Moderate (eGFR ≥30 to <60 mL/min)	4
Mild (eGFR ≥60 to <90 mL/min)	220
Patients with hepatic impairment (all)*	41
Severe	0
Moderate	3
Mild	38
Patients with cardiovascular impairment	7
Immunocompromised patients	Unknown
Population with relevant different ethnic origin	No ethnicities were excluded
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; NCI-ODWG: National Cancer Institute-Organ Dysfunction Working Group.
*Based on the MDRD equation (renal) and NCI-ODWG criteria (hepatic).

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable as ublituximab is not marketed for any indication in any country.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Ublituximab is not able to pass the blood-brain barrier and is therefore not expected to have a potential for misuse for illegal purposes.

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

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Adverse reactions with minimal clinical impact on patients (in relation to the severity of the indication treated) (mostly Grade 1 to 2 in severity and non-serious):

Respiratory tract infections (upper and lower)

Herpes virus infections

Pain in extremity

Neutropenia

Decreased immunoglobulins

Decreased lymphocytes

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Not applicable

Impaired immunisation response

Impaired immunization response in the setting of ublituximab treatment is unknown based on the data available from the clinical development programme. It is known to prescribers, however, that the mechanism of action of the anti-CD20 class of agents affects the immune system and may have an impact on immunisation response; therefore, it is not considered important for inclusion in the list of safety concerns in the RMP.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Infusion-related reactions

Risk-benefit impact:

Infusion-related reactions in an individual can be impactful (medically important) and may require medical intervention and may lead to discontinuation of the treatment.

Important Potential Risk 1: Serious infections, including opportunistic infections (e.g. PML and HBV reactivation)

Risk-benefit impact:

Serious infections in an individual can be impactful (medically important) and may require medical intervention and may lead to discontinuation of the treatment.

Important Potential Risk 2: Malignancy

Risk-benefit impact:

Malignancy in an individual can be impactful (medically important) and may require medical intervention and may lead to discontinuation of the treatment.

Missing information 1: Long-term safety of ublituximab

Risk-benefit impact:

There has been about 18,500 months of patient exposure time across the 545 ublituximab-treated subjects in the pooled pivotal Phase 3 RMS trials and durations of ublituximab treatment exposure beyond 2 years in 257 of these subjects, in which no clinically significant impact on the risk-benefit balance has been observed. Longer-term safety data on ublituximab is limited to further assess the impact on the risk-benefit balance.

Missing information 2: Safety in pregnancy and lactation, including foetal risk

Risk-benefit impact:

The safety profile of ublituximab is not known in pregnant or lactating women due to their exclusion from the RMS clinical studies; therefore, clinical data on the safety of ublituximab in pregnant or lactating women is limited to assess the impact on the risk-benefit balance.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

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

SVII.3.1.1 Important Identified Risk: Infusion-related reactions

Important identified risk: Infusion-related reactions	
Potential mechanisms	Treatment with monoclonal antibodies has been associated with infusion-related reactions, some of which may be severe. Infusion-related reactions (IRRs) are thought to be due to the release of cytokines and/or other chemical mediators. The exact mechanism responsible for infusion-related reactions to monoclonal antibodies is not known, but like the taxanes, these reactions are unlikely to be true type 1 IGE mediated hypersensitivity reactions (Lenz 2007).
Evidence source and strength of evidence	Infusion-related reactions were frequently reported in the RMS clinical studies of ublituximab (TG1101-RMS301, TG1101-RMS302, and TG1101-RMS201) and are a known class effect of anti-CD20 monoclonal antibodies administered as an intravenous infusion. IRR were mostly non-serious and there were no fatal cases.

Important identified risk: Infusion-related reactions	
Characterization of risk	In the pooled analysis of the pivotal Phase III studies, the incidence of an IRR ADR was highest with the first infusion of ublituximab (40.4%) and decreased with subsequent infusions (8.6% with the second infusion, 7.0% with the third, 5.1% with the fourth, and 4.0% with the fifth). The ADRs of IRR had a median onset time and median duration of 1 day. The IRRs were mostly Grade 1 or 2 in severity; only 0.6% of subjects had Grade ≥3 IRRs. The most frequently reported IRRs by preferred term (≥10% of subjects) included pyrexia and headache. Two subjects had serious IRRs (anaphylactic reaction and hypersensitivity) that led to discontinuation of ublituximab and 1 subject had a non-serious IRR that led to discontinuation of ublituximab.
Risk factors and risk groups	Infusion-related reactions occur most often during the first infusion in patients who have not had this type of infusion before.
Preventability	Ublituximab is a medicinal product which is subject to restricted medical prescription. Therefore, health care professionals administering ublituximab must be vigilant for signs and symptoms. The possibility of a delayed reaction, which may occur up to 24 hours after the infusion, should also be considered. Any discomfort experienced by the patient should be notified to the treating physicians immediately. Pre-medication is required to mitigate IRRs. Appropriate medical support should be available for the management of severe reactions such as serious IRRs. Patients should be observed for at least one hour after completion of the first two infusions. Physicians should inform patients that IRRs can occur up to 24 hours after the infusion. The possibility of a delayed reaction, which may occur up to 24 hours after the infusion, should also be considered.
Impact on the risk-benefit balance of the product:	Infusion-related reactions in an individual can be impactful (medically important) and may require medical intervention or may lead to discontinuation of treatment.
Public health impact:	Most patients have only experienced mild to moderate events of IRR that resolved. The physician community is well aware of this risk and IRR management is a routine part of standard care, hence, the impact on public health is considered minimal.

SVII.3.1.2 Important Potential Risk: Serious infections, including opportunistic infections (e.g., PML and HBV reactivation)

Important potential risk: Serious infections, including opportunistic infections (e.g., PML and HBV reactivation)	
Potential mechanisms	The risk of infection, including opportunistic infections, may be associated with the use of any anti-CD20 biological product (including ublituximab), depleting B-cells.
Evidence source and strength of evidence	Non-clinical findings show that ublituximab reduces B and T lymphocytic cells, and thereby may have a resulting immunosuppressant effect attributed to its pharmacologic action. Although serious infections were infrequently reported in the RMS clinical studies (TG1101-RMS301, TG1101-RMS302, and TG1101-RMS201) of ublituximab, 3 fatal infections have occurred, and it is a known class effect of anti-CD20 monoclonal antibodies. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with anti-CD20 antibodies. There was one case of HBV reactivation that occurred in a patient treated with ublituximab in the RMS clinical development program. No cases of PML in the RMS clinical studies of ublituximab have been reported; however, this opportunistic infection has been observed with other anti-CD20 monoclonal antibodies and other MS therapies.
Characterization of risk	In the pooled analysis of the pivotal Phase III studies, serious infections were reported in 5.0% of subjects in the ublituximab group and 2.9% of subjects in the teriflunomide group. The most common TEAEs (≥0.5% of subjects in any group) of serious infections were pneumonia (ublituximab: 0.9%; teriflunomide: 0.4%), COVID-19 pneumonia (ublituximab: 0.7%; teriflunomide: 0.4%), and acute sinusitis (ublituximab: 0.6%; teriflunomide: 0). When excluding subjects with COVID-19 pneumonia, serious infections were reported in 23 of 545 subjects (4.2%) in the ublituximab group and 14 of 548 subjects (2.6%) in the teriflunomide group. Grade ≥3 serious infections were reported in more subjects in the ublituximab group compared to subjects in the teriflunomide group (20 [3.7%] versus 10 [1.8%]). The most common Grade ≥3 TEAEs were pneumonia (ublituximab: 0.7%; teriflunomide: 0.2%) and COVID-19 pneumonia (ublituximab: 0.7%; teriflunomide: 0.2%). Serious infections led to discontinuation of ublituximab in a total of 4 subjects: central nervous system enteroviral infection in 2 subjects and pulmonary tuberculosis and meningoencephalitis viral in 1 subject each. In the ublituximab group, there were 3 fatal infections (encephalitis, pneumonia, and salpingitis). The fatal case of encephalitis was attributed to a post-measles complication, and the fatal case of salpingitis was attributed to a post-procedural complication of an ectopic pregnancy; both events were considered not related to ublituximab. The fatal case of pneumonia was considered related to

Important potential risk: Serious infections, including opportunistic infections (e.g., PML and HBV reactivation)	
	ublituximab.
Risk factors and risk groups	Previous or concomitant medicines that affect the immune system, such as chemotherapy, immunosuppressants or other medicines used to treat multiple sclerosis, can be important contributing factors. In patients with a history of HBV infection, anti-CD20 antibody therapy may trigger HBV reactivation.
Preventability	Ublituximab is a medicinal product subject to restricted medical prescription. Health care professionals administering ublituximab must be vigilant for signs and symptoms of serious infections. HBV screening should be performed in all patients before initiation of treatment with ublituximab. For patients who are HBsAg negative and anti-HBc positive or who are carriers of HBV [HBsAg positive], consult clinicians with expertise in managing hepatitis B regarding monitoring and consideration of HBV antiviral prophylaxis before starting and during treatment with ublituximab.
Impact on the risk-benefit balance of the product:	Serious infections in an individual can be impactful (medically important) and may require medical intervention or may lead to discontinuation of treatment.
Public health impact:	Minimal public health impact is foreseen. Serious infections are a known class effect for antiCD20 monoclonal antibodies and occurred at similar rates in the standard-of-care comparator approved.

SVII.3.1.3 Important Potential Risk: Malignancy

Important potential risk: Malignancy	
Potential mechanisms	The pathogenesis of malignancy with anti-CD20s is not well understood. It is hypothesized that immunosuppressive therapies could result in loss of immune protection against cancer such as via impaired immunosurveillance or activation of the immune system to become pro-tumorigenic (Melamed E 2020).
Evidence source and strength of evidence	A potential risk of malignancy has been observed with another anti-CD20 antibody. A weight of evidence approach (including review of the non-clinical and clinical findings with ublituximab and a comprehensive literature review on the biology, mechanism of action and non-clinical and clinical findings of other anti-CD20 therapies) has not revealed data to suggest that treatment with ublituximab would support or induce proliferation of transformed cells possibly leading to neoplasia.
Characterization of risk	Carcinogenicity studies were not conducted with ublituximab. There were 3 malignancies reported in the ublituximab RMS clinical development programme: 2 serious cases: 1 endometrial stromal sarcoma and 1 uterine cancer in the Phase III studies; and 1 non-

Important potential risk: Malignancy	
	serious case: basal cell carcinoma in the Phase II study. The events were likely idiopathic or etiologically related to the subject's disease state. The exact underlying cause of endometrial stromal sarcoma is currently unknown. All 3 subjects recovered, and all cases were considered not related by the Investigator.
Risk factors and risk groups	No risk factors have been identified.
Preventability	Ublituximab is a medicinal product subject to restricted medical prescription. Health care professionals administering ublituximab must be vigilant for signs and symptoms of malignancies.
Impact on the risk-benefit balance of the product	Malignancy in an individual can be impactful (medically important) and may require medical intervention or may lead to discontinuation of treatment.
Public health impact	Minimal public health impact is foreseen.

SVII.3.2. Presentation of the Missing Information

Missing information: Long-term safety of ublituximab treatment	
Evidence source	The long-term safety of ublituximab has not yet been established. Long-term safety of ublituximab is being further investigated in the TG1101-RMS303 open label extension study of ublituximab in subjects with RMS. There has been about 18,500 months of patient exposure time across the 545 ublituximab-treated subjects in the pooled pivotal Phase 3 RMS trials and durations of ublituximab treatment exposure beyond 2 years in 257 of these subjects.
Population in need of further characterisation/ Anticipated risk/consequence	Further characterisation of patients who have received ublituximab treatment for longer durations of exposure is needed.

Missing information: Safety in pregnancy and lactation, including foetal risk	
Evidence source	The safety of ublituximab in pregnant or lactating women has not been established due to their exclusion from the clinical studies. Based on findings in animal studies and the mechanism of action of ublituximab, ublituximab may cause foetal harm and infant B cell depletion when administered to a pregnant woman. The presence of ublituximab in human milk and its effects on the breastfed child or on milk production have not been investigated.

Missing information: Safety in pregnancy and lactation, including foetal risk	
Population in need of further characterisation/ Anticipated risk/consequence	Although ublituximab is not intended to be used in pregnant or lactating women, considering the demographics of MS patients receiving ublituximab, further characterisation in this patient population is needed.

Part II: Module SVIII - Summary of the safety concerns

Table S0.IIIII.1 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infusion-related reactions
Important potential risks	Serious infections, including opportunistic infections (e.g., PML and HBV reactivation) Malignancy
Missing information	Long-term safety of ublituximab treatment Safety in pregnancy and lactation, including foetal risk

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires: Potential progressive multifocal leukoencephalopathy (PML)

Other forms of routine pharmacovigilance activities: Suspected cases of progressive multifocal leukoencephalopathy (PML) will be escalated for further review, assessment and adjudication. The adjudication process will include internal neurologist(s)/neurology expert(s) with MS experience and external experts, e.g., infectious disease specialists, neurologists and neuroradiologists, as needed**.** To perform the adjudication, all facets of a case will be reviewed in detail, including patient background and characteristics, medical history, concomitant medications, diagnostic tests, clinical course, laboratory tests, treatment and outcome.

III.2 Additional pharmacovigilance activities

TG1101-RMS402 summary

Study short name and title:

TG1101-RMS402, A long-term observational study of the safety and effectiveness of ublituximab in patients with relapsing multiple sclerosis

Rationale and study objectives:

To characterise the long-term safety of ublituximab treatment in RMS patients

Primary Objective

- To assess the incidence of serious infections and malignancies in ublituximab-treated relapsing MS patients observed longitudinally

Study design:

This is a prospective, observational, non-interventional, multi-centre, global study with safety data and outcomes collected as part of standard clinical practice.

Study population:

Cohorts of approximately 2,300 ublituximab-treated patients with RMS and 700 other DMT-treated patients with RMS will be enrolled.

Milestones:

Final Protocol submission: Q4 2023; Interim Reports: annually beginning one year after the launch of Briumvi in any EU country; Final Report submission: one year following study completion

TG1101-RMS403 summary

Study short name and title:

TG1101-RMS403, A registry study of pregnancy and infant outcomes in patients treated with ublituximab.

Rationale and study objectives:

To characterise the safety of ublituximab use in pregnancy, including maternal, foetal and neonate/infant outcomes, in female patients with relapsing forms of multiple sclerosis.

Primary Objectives

To estimate the incidence of major congenital malformations in foetuses/infants born to ublituximab-exposed pregnant women with MS.

Study design:

This is an observational registry study designed to evaluate maternal, foetal and neonate/infant outcomes resulting from ublituximab exposure prior to (approximately 6 months before last menstrual period prior to becoming pregnant) and during pregnancy in female participants with RMS. Infants born to ublituximab-exposed mothers will be evaluated for one-year post-partum. Additional study populations of pregnant patients not exposed to ublituximab will be used as a comparison cohort.

Study population:

The prospectively planned study populations include (a) a cohort with a target sample size of 100 live births in female participants with RMS with ublituximab exposure within 6 months of their LMP or anytime during pregnancy and (b) an internal control cohort with a target sample size of 100 live births in female participants with RMS not exposed to ublituximab, who may be treated with an approved DMT or no DMT, enrolled as a comparison cohort. A third population (c) is a healthy control cohort.

Milestones:

Final Protocol submission: 03/2024; Study Start: 06/2024, Interim Reports: annually beginning in 03/2025; Study Finish: 03/2035, Final Report submission: 03/2036

TG1101-RMS404 summary

Study short name and title:

TG1101-RMS404, A study to characterize the safety of Briumvi use in Pregnant Patients with Multiple Sclerosis using Data from an Administrative Healthcare Claims Database

Rationale and study objectives:

To characterise the safety of ublituximab use in pregnancy, including maternal, foetal and neonate/infant outcomes, in female patients with relapsing forms of multiple sclerosis.

Primary Objectives

To estimate the incidence of major congenital malformations in foetuses/infants born to ublituximab-exposed pregnant women with MS.

Study design:

This is a retrospective analysis utilizing secondary data of pregnant women with MS who received ublituximab from 6 months prior to the first day of the estimated last menstrual period (LMP) or up to and including the end of pregnancy, as well as their infants.

Study population:

The study will analyse data for pregnant women with MS who have received at least one prescription for ublituximab within 6 months prior to estimated LMP, who have uninterrupted coverage in the database, and who have a linked infant or record of other birth outcome. This study will use a case-control design and include a matched control group of patients with MS who did not receive ublituximab as a comparator to those who received ublituximab.

Milestones:

Final Protocol submission: 03/2024; Study Start: Q1 2024, Interim Reports: annually beginning in 03/2025; Study Finish: 03/2035, Final Report submission: 03/2036

TG1101-RMS303 summary

Study short name and title:

TG1101-RMS303 Open Label Extension Study of Ublituximab in Subjects with Relapsing Multiple Sclerosis

Rationale and study objectives:

Extension study of TG1101-RMS301 and TG1101-RMS302 to evaluate the long-term safety and efficacy of ublituximab treatment in subjects with relapsing forms of MS

Study design:

Open-label extension study

Study population:

This is an open-label extension study for subjects who previously completed studies TG1101-RMS301 and TG1101-RMS302.

Milestones:

Final Report submission: estimated Q1 2029

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities:				
A long-term observational study of the safety and effectiveness of ublituximab in patients with relapsing multiple sclerosis (TG1101-RMS402) Planned	To assess the incidence of serious infections and malignancies in relapsing MS participants treated with ublituximab compared with other disease-modifying treatments (DMTs) observed longitudinally. To evaluate the long-term safety of ublituximab compared to other DMTs in patients with relapsing forms of multiple sclerosis in a real world setting To assess long-term effectiveness of ublituximab compared with other DMTs in participants with relapsing forms of MS.	Long-term safety of ublituximab treatment; serious infections, including opportunistic infections; and malignancy	Updated proposal	07 Jul 2023
			Final Protocol submission	Q4 2023
			Interim Report Submissions	Annually beginning one year after the launch of Briumvi in any EU country
			Final report submission	One year following study completion
A registry study of pregnancy and infant outcomes in patients treated with ublituximab (TG1101-RMS403)	To characterise the safety of ublituximab use in pregnancy, including maternal, foetal and neonate/infant outcomes, in female patients with relapsing forms of multiple sclerosis	Safety of ublituximab in pregnant women, including infants exposed to ublituximab during pregnancy	Updated proposal	07 Jul 2023
			Final Protocol submission	Q1 2024
			Study Start	06/2024
			Interim report submissions	Annually beginning in 03/2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Planned			Study Finish	03/2035
			Final report submission	03/2036
A study to characterize the safety of Briumvi use in pregnant patients with multiple sclerosis using data from an administrative healthcare claims database (TG1101-RMS404) Planned	To characterise the safety of ublituximab use in pregnancy, including maternal, foetal and neonate/infant outcomes, in female patients with relapsing forms of multiple sclerosis	Safety of ublituximab in pregnant women, including infants exposed to ublituximab during pregnancy	Updated proposal	07 Jul 2023
			Final Protocol submission	Q1 2024
			Study Start	Q1 2024
			Interim report submissions	Annually beginning in 03/2025
			Study Finish	03/2035
			Final report submission	03/2036
Conducted voluntarily by marketing authorisation holder:				
Open-label extension study of ublituximab in subjects with relapsing multiple sclerosis (TG1101-RMS303) Ongoing	Extension study of TG1101-RMS301 and TG1101-RMS302 to evaluate the long-term safety and efficacy of ublituximab treatment in subjects with relapsing forms of MS	Long-term safety of ublituximab treatment; serious infections, including opportunistic infections; and malignancy	Final report submission	Estimated Q1 2029

Part IV: Plans for post-authorisation efficacy studies

There are no plans for post-authorisation efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Infusion-related reactions (important identified risk)	Routine risk communication: *SmPC: Sections 4.2, 4.4, 4.8* *PL: Sections 2, 3, 4* Routine risk minimisation activities recommending specific clinical measures: *SmPC: Section 4.2, Pre-medication is required to mitigate infusion-related reactions.* *SmPC Section 4.2, Appropriate resources should be available to manage severe infusion reactions.* *SmPC Section 4.4, Observe patients for at least one hour after the first two infusions. Patients should be informed infusion reaction can occur up to 24 hours.* Other risk minimisation measures beyond the Product Information: *Legal status: Ublituximab is a medicinal product subject to restricted medical prescription.*
Serious infections, including opportunistic infections (e.g., PML and HBV reactivation) (important potential risk)	Routine risk communication: *SmPC: Sections 4.3, 4.4, 4.8* *PL: Sections 2, 4* Routine risk minimisation activities recommending specific clinical measures: *SmPC: Section 4.3 and 4.4, Delay administration with an active infection until resolved.* *SmPC: Section 4.4, Physicians should monitor for early signs or symptoms of PML. If suspected, withhold, and perform appropriate diagnostic evaluation. If PML is confirmed, permanently discontinue ublituximab.* *SmPC: Section 4.4, Hepatitis B virus screening should be performed before initiation of treatment with ublituximab. Patients with positive hepatitis serology should be referred to a liver disease expert before start of treatment and should be monitored. Patients with an active Hep B virus should not be treated with ublituximab.* Other risk minimisation measures beyond the Product Information: *Legal status: Ublituximab is a medicinal product subject to restricted medical prescription.*
Malignancy (important potential risk)	Routine risk communication:

	SmPC: Section 4.3 *PL: Section 2* Routine risk minimisation activities recommending specific clinical measures: *SmPC: Section 4.3, Patients with a known active cancer should not be treated with ublituximab.* Other risk minimisation measures beyond the Product Information: *Legal status: Ublituximab is a medicinal product subject to restricted medical prescription.*
Long-term safety of ublituximab treatment (missing information)	Routine risk communication: *None* Routine risk minimisation activities recommending specific clinical measures: *None* Other risk minimisation measures beyond the Product Information: *Legal status: Ublituximab is a medicinal product subject to restricted medical prescription.*
Safety in pregnancy and lactation, including foetal risks (missing information)	Routine risk communication: *SmPC: Sections 4.4, 4.6, 5.3* *PL: Section 2* Routine risk minimisation activities recommending specific clinical measures: *SmPC: Section 4.6, Women of childbearing potential should use effective contraception while receiving ublituximab and for at least 4 months after the last infusion.* *SmPC: Section 4.6, For activities during breastfeeding while on ublituximab.* *SmPC: Section 4.4, In infants of mothers treated with ublituximab during pregnancy, vaccines administration should be discussed with a qualified specialist.* Other risk minimisation measures beyond the Product Information: *Legal status: Ublituximab is a medicinal product subject to restricted medical prescription.*

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Infusion-related reactions (important identified risk)	Routine risk minimisation measures: <u>Communication:</u> *SmPC: Sections 4.2, 4.4, 4.8* *PL: Sections 2, 3, 4* <u>Specific clinical measures:</u> *SmPC: Section 4.2 and PL: Section 3, where advice is given on pre-medication and having appropriate resources available to manage severe infusion reactions* *SmPC: Section 4.4, observe patients for at least one hour after the first two infusions* *SmPC: Section 4.4 and PL: Section 4: patients should be informed infusion reaction can occur up to 24 hours* <u>Subject to restricted medical prescription.</u> Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Serious infections, including opportunistic infections (e.g., PML, HBV reactivation) (Important potential risk)	Routine risk minimisation measures: <u>Communication:</u> *SmPC: Sections 4.3, 4.4, 4.8* *PL: Sections 2, 4* <u>Specific clinical measures:</u> *SmPC: Sections 4.3 and 4.4 and PL: Section 2, delay administration with an active infection until resolved* *SmPC: Section 4.4 and PL: Section 2, monitor signs or symptoms of PML; withhold*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *PML targeted follow-up questionnaire* Additional pharmacovigilance activities: *Post-authorisation long-term safety study (TG1101-RMS402)*

Safety concern	Risk minimisation activities	Pharmacovigilance activities
	if suspected PML and perform appropriate diagnostic evaluation including MRI; permanently discontinue if PML confirmed *SmPC: Sections 4.3 and 4.4 and PL: Section 2, hepatitis B virus screening prior to initiation; consult liver disease expert for positive hepatitis serology* Subject to restricted medical prescription. Additional risk minimisation measures: *None*	
Malignancy (Important potential risk)	Routine risk minimisation measures: Communication: *SmPC: Section 4.3* *PL: Section 2* Specific clinical measures: *SmPC: Section 4.3 and PL Section 2, patients with a known active cancer should not be treated with ublituximab* Subject to restricted medical prescription. Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Post-authorisation long-term safety study (TG1101-RMS402)*
Long-term safety of ublituximab treatment (Missing information)	Routine risk minimisation measures: Communication: *None* Specific clinical measures: *None* Subject to restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Post-authorisation long-term safety study (TG1101-RMS402)*

Safety concern	Risk minimisation activities	Pharmacovigilance activities
	Additional risk minimisation measures: *None*	
Safety in pregnancy and lactation, including foetal risks (Missing information)	Routine risk minimisation measures: <u>Communication:</u> *SmPC: Sections 4.4, 4.6, 5.3* *PL: Section 2* <u>Specific clinical measures:</u> *SmPC: Section 4.6 and PL: Section 2, contraception for at least 4 months after last infusion in women of childbearing potential* *Refer to SmPC Section 4.6 and PL Section 2 for activities during breastfeeding while on ublituximab.* *Refer to SmPC Section 4.4 and PL Section 2 for activities required in case that an infant is exposed in utero to ublituximab.* <u>Subject to restricted medical prescription.</u> Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Post-authorisation pregnancy safety studies (TG1101-RMS403 and TG1101-RMS404)*

Part VI: Summary of risk management plan for Briumvi (ublituximab)

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

Briumvi's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Briumvi should be used.

This summary of the RMP for Briumvi should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 Briumvi's RMP.

I. The medicine and what it is used for

Briumvi is authorised for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see SmPC for the full indication). It contains ublituximab as the active substance and it is given by intravenous infusion. Ublituximab is a glycoengineered murine/human chimeric anti-CD20 monoclonal antibody that targets an epitope of the B-lymphocyte antigen CD20 expressed on the cell membranes of lymphocytes.

Further information about the evaluation of Briumvi's benefits can be found in Briumvi's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/briumvi

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised 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 patient (e.g., with or without prescription) can help to minimise its risks.

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

In addition to these measures, information about adverse events is collected continuously and regularly analysed, 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 Briumvi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Briumvi are risks that need special risk management activities to further investigate or minimise 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 Briumvi. 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 (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Infusion-related reactions
Important potential risks	Serious infections, including opportunistic infections (e.g., PML and HBV reactivation) Malignancy
Missing information	Long-term safety of ublituximab treatment Safety in pregnancy and lactation, including foetal risks

II.B Summary of important risks

Important identified risk: Infusion-related reactions	
Evidence for linking the risk to the medicine	TG1101-RMS301, TG1101-RMS302, TG1101-RMS201 and their extension studies.
Risk factors and risk groups	Infusion-related reactions occur most often during the first infusion in patients who have not had this type of infusion before.
Risk minimisation measures	**Routine risk communication:** SmPC: Sections 4.2, 4.4, 4.8 PL: Section 2, 3, 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Treatment with other medicines such as a corticosteroid and antihistamine to mitigate possible side effects such as infusion-related reactions are required before each infusion; medicines used to reduce fever may also be

	used. • Appropriate medical support should be available for the management of severe reactions such as serious infusion related reactions. • Patients should be observed for at least one hour after completion of the first two infusions of ublituximab for any symptom of infusion-related reaction. Physicians should inform patients that an infusion-related reaction can occur up to 24 hours after the infusion. Sections 4.2 and 4.4 of the SmPC include more detailed information. **Other risk minimisation measures beyond the Product Information:** ***Medicine's legal status*:** Ublituximab is a medicinal product subject to restricted medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Serious infections, including opportunistic infections (e.g., PML and HBV reactivation)	
Evidence for linking the risk to the medicine	TG1101-RMS301, TG1101-RMS302, TG1101-RMS201 and their extension studies. Opportunistic infections including PML and HBV reactivation are a class risk for anti-CD20 monoclonal antibodies; however, no cases of PML have been observed in the RMS studies with ublituximab.
Risk factors and risk groups	Previous or concomitant medicines that affect the immune system, such as chemotherapy, immunosuppressants or other medicines used to treat multiple sclerosis, can be important contributing factors. In patients with a history of hepatitis B virus (HBV) infection, anti-CD20 antibody therapy may trigger HBV reactivation.
Risk minimisation measures	**Routine risk communication:** SmPC: Sections 4.3, 4.4, 4.8 PL: Sections 2, 4 **Routine risk minimisation activities recommending specific clinical measures to**

Important potential risk: Serious infections, including opportunistic infections (e.g., PML and HBV reactivation)	
	address the risk: • Administration of ublituximab must be delayed in patients with an active infection until the infection is resolved. • For progressive multifocal leukoencephalopathy (PML; a very rare and life-threatening brain infection), physicians should be alerted for the early signs and symptoms which can include any new onset or worsening of neurological signs or symptoms. If PML is suspected, dosing with ublituximab must be withheld and an appropriate diagnostic evaluation should be performed. Magnetic Resonance Imaging (MRI) findings may be apparent before clinical signs or symptoms. If PML is confirmed, ublituximab must be discontinued permanently. • Hepatitis B virus screening should be performed before initiation of treatment with ublituximab as per local guidelines because patients with active Hepatitis B virus infection should not be treated with ublituximab. Patients with positive serology (blood serum diagnostic); carriers of Hepatitis B virus should be referred to a liver disease expert before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. Sections 4.3 and 4.4 of the SmPC include more detailed information **Other risk minimisation measures beyond the Product Information:** ***Medicine's legal status*:** Ublituximab is a medicinal product subject to restricted medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Post-authorisation long-term safety study (TG1101-RMS402)

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	A potential risk of malignancy has been observed with another anti-CD20 antibody. A weight of evidence approach (including review of the non-clinical and clinical findings with ublituximab and a comprehensive literature review on the biology and mechanism of action) has not revealed data to suggest that treatment with ublituximab would support or induce proliferation of transformed cells possibly leading to neoplasia.
Risk factors and risk groups	No risk factors have been identified.
Risk minimisation measures	**Routine risk communication:** SmPC: Section 4.3 **Routine risk minimisation measures:** Patients should be asked whether they have an active cancer because patients with a known active cancer should not be treated with ublituximab. **Other risk minimisation measures beyond the Product Information:** ***Medicine's legal status*:** Ublituximab is a medicinal product subject to restricted medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Post-authorisation long-term safety study (TG1101-RMS402)

Missing information: Long-term safety of ublituximab treatment	
Risk minimisation measures	**Routine risk communication:** None **Routine risk minimisation activities recommended specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** ***Medicine's legal status*:** Ublituximab is a medicinal product subject to

Missing information: Long-term safety of ublituximab treatment	
	restricted medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Post-authorisation long-term safety study (TG1101-RMS402) Open Label Extension Study of ublituximab in subjects with Relapsing MS (TG1101-RMS303)
Missing information: Safety in pregnancy and lactation, including foetal risks	
Risk minimisation measures	**Routine risk communication:** SmPC: Sections 4.4, 4.6, 5.3 PL: Section 2 **Routine risk minimisation measures:** • Women of childbearing potential should be instructed that they should use contraception while receiving ublituximab and for at least 4 months after the last infusion of ublituximab. • It is unknown whether ublituximab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, ublituximab could be used during breast-feeding if clinically needed. • In infants of mothers treated with ublituximab during pregnancy, live or live-attenuated vaccines should not be administered before the recovery of B-cell counts has been confirmed. Measuring CD19-positive B-cell levels in neonates and infants prior to vaccination is recommended. Inactivated vaccines may be administered as indicated prior to recovery from B-cell depletion, however, assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted. The safety and timing of vaccination should be discussed with the infant's physician. Sections 4.4 and 4.6 of the SmPC includes more detailed information. **Other risk minimisation measures beyond the**

Missing information: Long-term safety of ublituximab treatment	
	Product Information: ***Medicine's legal status*:** Ublituximab is a medicinal product subject to restricted medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Post-authorisation pregnancy and infant outcomes safety studies (TG1101-RMS403 and TG1101-RMS404)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ublituximab.

II.C.2 Other studies in post-authorisation development plan

Long-term surveillance of ublituximab-treated patients with multiple sclerosis

Purpose of the study:

- to characterise the long-term safety of ublituximab in RMS patients, with a primary objective to estimate the incidence rates of serious infections and malignancies.

A registry study of pregnancy and infant outcomes in patients treated with ublituximab

Purpose of the study:

- to further characterise the safety of ublituximab in RMS patients when used during pregnancy, including follow-up of infants exposed to ublituximab during pregnancy.

A study to characterize the safety of Briumvi use in pregnant patients with multiple sclerosis using data from an administrative healthcare claims database

Purpose of the study:

- to characterize the safety of Briumvi use in pregnant patients with multiple sclerosis and their infants using data from an administrative healthcare claims database

Open Label Extension Study of ublituximab in subjects with Relapsing MS

Purpose of the study:

- to evaluate the long-term safety and efficacy of ublituximab treatment in subjects with relapsing forms of MS for subjects previously treated in studies TG1101-RMS301 and TG1101-RMS302

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface 48
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme 49
Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan 51
Annex 4 - Specific adverse drug reaction follow-up forms 52
Annex 5 - Protocols for proposed and on-going studies in RMP part IV 53
Annex 6 - Details of proposed additional risk minimisation activities (if applicable)..... 54
Annex 7 - Other supporting data (including referenced material) 55
Annex 8 – Summary of changes to the risk management plan over time..... 57

Annex 4 – Specific adverse drug reaction follow-up forms

Specific Adverse Event Follow-Up Questionnaire – Potential progressive multifocal leukoencephalopathy (PML)

Form instructions are located on the final page of the form.

Section 1: Background Information

Information for the person completing this form	
Name:	**Health Care Professional (HCP):** ☐ Yes ☐ No
Relationship to patient:	Title (e.g., MD, RN):
Company Name: ☐ N/A	
Company Case Number (if applicable): ☐ N/A	
Address:	
Email:	
Phone #:	Fax #:

Patient Information		
	Ht (in):	Wt (lb):
Date of Birth or Age:	Sex (assigned at birth): ☐ Male ☐ Female ☐ Undifferentiated ☐ Decline to answer	

Briumvi (ublituximab) Use	
Has the patient taken Briumvi (ublituximab)? ☐ Yes ☐ No	Indication/Diagnosis for Use:
	Initially Prescribed Dose:
	Current Dose: If current dose differs from initially prescribed dose, please explain why:
	Usage Dates from: Click or tap to enter a date. to Click or tap to enter a date. Frequency of Dose: Usage Status: ☐ Ongoing ☐ Discontinued ☐ N/A

Section 2: Relevant Medical History

Multiple Sclerosis (MS)	
Does the patient have a diagnosis of multiple sclerosis? ☐ Yes ☐ No	Specific diagnosis:
	Date of first diagnosis: Click or tap to enter a date.
	If relapsing MS, provide the date of the last relapse? Click or tap to enter a date.

Autoimmune Disorders	
Does the patient have an autoimmune disorder diagnosis? ☐ Yes ☐ No	Specific diagnosis:
	Date of first diagnosis: Click or tap to enter a date.
	Outcome: ☐ Recovered ☐ Ongoing

Hematological Malignancies	
Does the patient have any hematological malignancies? ☐ Yes ☐ No	Specific diagnosis:
	Date of first diagnosis: Click or tap to enter a date.
	Outcome: ☐ Recovered ☐ Ongoing

History of CNS Infections ☐ **N/A**	
Specific Diagnosis and Pathogen:	Date: Click or tap to enter a date.
Specific Diagnosis and Pathogen:	Date: Click or tap to enter a date.

Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS) ☐ **N/A**		
☐ HIV	Date of first diagnosis: Click or tap to enter a date.	☐ Past ☐ Current
☐ AIDS	Date of first diagnosis: Click or tap to enter a date.	☐ Past ☐ Current

Transplants (HSCT or Solid Organ) ☐ **N/A**	
Specific Diagnosis:	Date: Click or tap to enter a date.
Specific Diagnosis:	Date: Click or tap to enter a date.

Other Relevant Medical History (e.g. CNS lymphoma or other CNS disorders) ☐ **N/A**
Details:

Section 3: Relevant Prior or Concomitant Medications

If the patient was taking any prior or concomitant medications associated with or known to increase the risk of PML, please provide details below.

(E.g., natalizumab, prednisolone, dimethyl fumarate, fludarabine, rituximab, brentuximab vedotin, fingolimod, or ocrelizumab)

Medication	Indication	Dose/Unit	Route	Frequency	Start Date	Continuing? (Y/N)	Date of Last Dose / Stop Date
					Click or tap to enter a date.		Click or tap to enter a date.
					Click or tap to enter a date.		Click or tap to enter a date.
					Click or tap to enter a date.		Click or tap to enter a date.

Please list any additional relevant concomitant medications (e.g. other immunosuppressants) below:

Section 4: PML Diagnosis Details

Associated Neurological Signs or Symptoms (select all that apply)

☐ Difficulty speaking	☐ Difficulty with memory or thinking	☐ Difficulty with vision or reading
☐ Headache	☐ Loss of coordination	☐ Seizure
☐ Sensory loss	☐ Weakness in the arms or legs	☐ Other

Imaging Scan(s)

Magnetic resonance imaging (MRI) performed: ☐ Yes ☐ No	Date Performed: Click or tap to enter a date.
	Gadolinium: ☐ Used ☐ Not Used
	Results of scan:
	Are MRI results consistent with a PML diagnosis? ☐ Yes ☐ No ☐ Inconclusive

Section 4: PML Diagnosis Details

Computerized tomography (CT) performed: ☐ Yes ☐ No	Date Performed: Click or tap to enter a date. Results of scan: Are CT results consistent with a PML diagnosis? ☐ Yes ☐ No ☐ Inconclusive
Cerebrospinal Fluid (CSF) PCR Test	
CSF for JC Virus (JCV) test performed: ☐ Yes ☐ No	Date Performed: Click or tap to enter a date. JC Virus Result: ☐ Positive ☐ Negative ☐ Unknown Results of CSF PCR Test: Are CSF test results consistent with a PML diagnosis? ☐ Yes ☐ No ☐ Inconclusive
Brain Biopsy	
Brain biopsy performed: ☐ Yes ☐ No	Date Performed: Click or tap to enter a date. Histopathologic Triad: ☐ Positive ☐ Negative ☐ Inconclusive ☐ Not Assessed Immunohistochemistry or electron microscopy: ☐ Positive ☐ Negative ☐ Inconclusive ☐ Not Assessed Results of Biopsy: Are biopsy results consistent with a PML diagnosis? ☐ Yes ☐ No ☐ Inconclusive
Additional Testing	
Physical Examination: ☐ Yes ☐ No	Date Performed: Click or tap to enter a date. Results of exam:
Other relevant testing used to aid in PML diagnosis: ☐ Yes ☐ No	Test Performed: Date Performed: Click or tap to enter a date. Results of test:
Was a specialist consulted? ☐ Yes ☐ No If yes, provide a summary of the consultation notes:	

Section 5: Pertinent Laboratory Test Results

Provide details of the laboratory tests including normal range, as available (select all that apply)

Section 5: Pertinent Laboratory Test Results

Test Performed	Test Name	Normal Range (include units)	Test dates and results with units (if available, include baseline value)[1]
☐	Neutrophils		
☐	Basophils		
☐	Eosinophils		
☐	Lymphocytes		
☐	$CD4^+$ T cell count		
☐	$CD8^+$ T lymphocytes		
☐	CD19+ B cell count		
☐	B lymphocytes		
☐	Immunoglobulin M		
☐	Immunoglobulin G		
☐	Blood anti-JCV antibody		
☐	JCV DNA in urine		
☐			
☐			

[1] Please specify if result is from CSF or blood/serum.

Section 6: All Other Contributing Factors

If applicable, please discuss any other factors that may have contributed to the PML diagnosis (that have not been previously specified above):

Form Instructions

- Access to completed forms, and information contained therein, must be restricted to authorized parties.
- Completed forms must be protected at all times and securely stored.
- Printing of completed forms should be limited to only those instances where absolutely necessary, and only in a secure manner (i.e., do not execute remote printing, ensure printed form is immediately retrieved by authorized party, etc.).
- Electronic transmissions (e-mail, electronic file transfer, etc.) of completed forms, and information contained therein, must be adequately secured and protected from unauthorized access or disclosure.
- Confirm the accuracy of recipient(s) e-mail address(es) or other electronic destination, prior to transmission.

Send form using either secure email (preferred) or fax to TGTX Pharmacovigilance and Drug Safety at:
Email: TGTXSafety@ubc.com
US Fax #: 1-877-778-1887
Outside of US Fax #: +800 (24) 25 26 27

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not applicable.