Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Briumvi

Active ingredient: Ublituximab

Sponsor: Accelagen Pty Ltd

March 2026

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ADCC	Antibody dependent cell-mediated cytotoxicity
AEs	Adverse events
ARR	Annualized relapse rate
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration-time curve
CDC	Complement dependent cytotoxicity
CDP	Confirmed disability progression
CL	Clearance
CMI	Consumer Medicines Information
CNS	Central nervous system
DMTs	Disease-modifying therapies
FDA	U.S. Food and Drug Administration
Delegate	The Delegate of the Secretary of the Department of Health, Disability and Ageing who decided the submission under section 25 of the Act.
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
IRAP	Independent Relapse Adjudication Panel
mITT	Modified intention-to-treat
mAbs	monoclonal antibodies
MS	Multiple sclerosis
NEDA	No Evidence of Disease Activity (NEDA
PI	Product Information
PK	Pharmacokinetics
PP	Per protocol
PPMS	Primary Progressive Multiple Sclerosis
RMP	Risk management plan
RMS	Relapsing forms of multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SAEs	Serious adverse events
SDMT	Symbol digit modalities test
TGA	Therapeutic Goods Administration
TEAEs	Treatment emergent adverse events

Product submission

Submission details

Type of submission:	New biological entity
Product names:	Briumvi
Active ingredient:	Ublituximab
Decision:	Approved
Date of decision:	4 June 2025
Approved therapeutic use for the current submission:	Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features
Date of entry onto ARTG:	11 June 2025
ARTG number:	453648
▼*Black Triangle Scheme*	Yes
Sponsor's name and address:	Neuraxpharm Australia Pty Ltd. Suite 3.12. 32 Delhi Road, Macquarie Park, NSW, Australia, 2113
Dose form:	Concentrate for solution for infusion
Strength:	25 mg/ml
Container:	Glass vial
Pack size:	1 or 3 vials
Route of administration:	Intravenous infusion
Dosage:	For information regarding dosage, refer to the Product Information.
Pregnancy category:	**Category C** Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Accelagen Pty Ltd (the sponsor) to register Briumvi (ublituximab) for the following proposed indication:[1]

> *Treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features*

Disease or condition

Multiple sclerosis (MS) is an inflammatory-demyelinating disease of the central nervous system (CNS) that is characterized by inflammation, demyelination, and degenerative changes.[2] Damage to myelin leads to multiple areas of scarring and impacts the messaging within the CNS. The manifestation of neurological symptoms varies with the type and the severity of MS. The cause is not known. It is believed that a combination of genetic factors, immune system abnormalities, and environmental factors triggers the disease.

In 2014, the International Advisory Committee on Clinical Trials of MS revised the MS phenotypes to the following disease-modifier phenotypes: clinically isolated syndrome (not active or active), Relapsing-remitting multiple sclerosis (RRMS; not active or active), and progressive disease (active and with progression; active but without progression; not active with progression; not active and without progression).[3] Relapsing forms of multiple sclerosis (RMS) is a broad term to describe MS types characterised by distinct episodes of worsening neurological function.

Approximately 85% of people who develop MS begins with RRMS, which is characterised by recurrent inflammatory episodes in which autoreactive lymphocytes marginate across the blood brain barrier and enter the CNS, leading to acute injury to myelin, oligodendrocytes, and axons, and potentially causing new or worsening neurologic deficits. Over the course of 2 decades, more than half of untreated patients transitioned to a phase of gradual worsening independent of acute attacks, known as progressive MS. Progressive forms of MS can be present as the initial disease course (Primary Progressive Multiple Sclerosis; PPMS) in approximately 10% to 15% of patients.[4]

Current treatment options

A variety of disease-modifying therapies (DMTs) have been approved by the US FDA and the EMA to treat MS, including RMS. The primary target for the majority of DMTs developed to date has been T cells. Recent immunopathologic and clinical studies have demonstrated that B cells also play a central role in the pathogenesis of the disease, perhaps upstream of the T cell-mediated pathology.[5,6]

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[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] National MS Society. The National Multiple Sclerosis Society. 2020; https://www.nationalmssociety.org

[3] Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, Wolinsky JS, Balcer LJ, Banwell B, Barkhof F, Bebo B Jr, Calabresi PA, Clanet M, Comi G, Fox RJ, Freedman MS, Goodman AD, Inglese M, Kappos L, Kieseier BC, Lincoln JA, Lubetzki C, Miller AE, Montalban X, O'Connor PW, Petkau J, Pozzilli C, Rudick RA, Sormani MP, Stüve O, Waubant E, Polman CH. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014 Jul 15;83(3):278-86. doi: 10.1212/WNL.0000000000000560. Epub 2014 May 28. PMID: 24871874; PMCID: PMC4117366.

[4] Lublin FD, Coetzee T, Cohen JA, Marrie RA, Thompson AJ, on behalf of the International Advisory Committee on Clinical Trials in MS. The 2013 clinical course descriptors for multiple sclerosis. Neurology. 2020;94(24):1088

[5] Greenfield AL, Hauser SL. B-cell Therapy for Multiple Sclerosis: Entering an era. Ann Neurol. 2018;83(1):13-26

[6] Hauser SL, Cree BAC. Treatment of Multiple Sclerosis: A Review. Am J Med. 2020;133(12):1380-1390

Available DMTs include injectable, oral, and infusion therapies. Monoclonal antibodies for RRMS include natalizumab, ocrelizumab, rituximab (off-label use), ofatumumab, and alemtuzumab. The FDA and EMA have approved two B cell-targeted therapies to treat MS, namely ocrelizumab (Ocrevus) and ofatumumab (Aliqopa and Kesimpta). B cell-depleting therapy is highly effective against relapsing forms of the disease and ocrelizumab was the first DMT approved to treat disability worsening in PPMS (Ocrevus).

Clinical rationale

MS is an immune mediated disease in which B cells play a central role in disease pathogenesis. In vivo and in vitro studies demonstrate that B cells contribute to tissue damage in MS through several mechanisms, including the presentation of autoantigens and the production of soluble inflammatory mediators. In addition, B cells can influence the effector function of other immune cells involved in autoimmune responses. In MS, B cells are believed to migrate across the blood–brain barrier, where they undergo antigen driven stimulation, affinity maturation, and clonal expansion within the CNS.[7] B cells also serve as precursors to plasma cells, which secrete autoreactive antibodies that may contribute to demyelinating events within the CNS. Accordingly, therapeutic strategies targeting aberrant B cell mediated autoimmune activity represent a significant advance in the treatment of MS.

Anti CD20 monoclonal antibodies (mAbs) have been developed to selectively deplete CD20 expressing B cells. These agents rapidly and profoundly reduce circulating B cell levels, with depletion typically sustained for approximately 6 to 9 months. CD20 negative cells, including stem cells (pro B cells), many plasmablasts, and terminally differentiated antibody producing plasma cells, are not directly targeted. Pre-clinical studies indicate that B cell depletion within lymphoid tissues and bone marrow is less complete than in the peripheral circulation. The extent to which B cells are effectively depleted from the CNS remains incompletely understood[8].

Several anti CD20 mAbs are used or have been evaluated in the clinical management of MS, with differences in antibody structure and mechanisms of B cell depletion. Rituximab is a chimeric mouse–human mAb originally approved for the treatment of B cell lymphoma and is not approved for MS in the United States or the European Union. Ocrelizumab, a humanized mAb, differs from rituximab in its antibody backbone and mediates B cell depletion through multiple mechanisms, including apoptosis and antibody dependent cellular phagocytosis. Ofatumumab is a humanized mAb that binds a small loop epitope on CD20 and primarily induces B cell depletion through complement dependent cytotoxicity rather than antibody dependent cell mediated cytotoxicity.[9,10]

[7] Hauser SL. The Charcot Lecture | beating MS: a story of B cells, with twists and turns. Multi Scler. 2015;21(1):8-21

[8] Graf JA-O, Mares J, Barnett M, et al. Targeting B Cells to Modify MS, NMOSD, and MOGAD: Part 1. Neurol Neuroimmunol Neuroinflamm. 2020;8(1):e918.

[9] Teeling JL, Mackus Wj Fau - Wiegman LJJM, Wiegman Lj Fau - van den Brakel JHN, et al. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. J Immunol. 2006;177(1):362-371.

[10] Klein C, Lammens A Fau - Schäfer W, Schäfer W Fau - Georges G, et al. Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. MAbs. 2013;5(1):22-33.

Clinical studies evaluating rituximab, ocrelizumab, and ofatumumab in patients with relapsing forms of MS have demonstrated efficacy, including reductions in gadolinium enhancing lesions and annualized relapse rates compared with placebo or active comparators. [11,12,13,14,8, 6]

Ublituximab is a chimeric anti CD20 monoclonal antibody that selectively targets CD20 expressing B cells. Binding of ublituximab to CD20 results in B cell lysis primarily via antibody dependent cell mediated cytotoxicity (ADCC), with a lesser contribution from complement dependent cytotoxicity.

Ublituximab (also referred to as TG-1101) is a glycoengineered mAb that targets a novel epitope on the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ublituximab results in antibody-dependent cellular cytolysis, antibody-dependent cellular phagocytosis, and complement-mediated lysis. Ublituximab is glycoengineered to have a low fucose content in the Fc region which results in increased affinity for the Fc gamma receptor IIIa (or CD16).[15] This increased affinity is associated with potent in vitro ADCC against B cells compared with both rituximab and ofatumumab, particularly of cells that express low levels of CD20.[16,17,18] The enhanced ADCC of ublituximab translates to greater potency and lower doses compared to the non-glycoengineered anti-CD20 mAbs rituximab and ocrelizumab.

Regulatory status

Australian regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. Table 1 summarises these submissions and provides the indications where approved.

[11] Bar-Or A, Calabresi Pa Fau - Arnold D, Arnold D Fau - Markowitz C, et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. Ann Neurol. 2008;63(3):395-400.
[12] Hauser SL, Waubant E Fau - Arnold DL, Arnold Dl Fau - Vollmer T, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008;358(7):676-688.
[13] Kappos L, Li D Fau - Calabresi PA, Calabresi Pa Fau - O'Connor P, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet (London, England). 2011;378(9805):1779-1787.
[14] Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. New England Journal of Medicine. 2017;376(3):221-234.
[15] Le Garff-Tavernier M, Herbi L, de Romeuf C, et al. Antibody-dependent cellular cytotoxicity of the optimized anti-CD20 monoclonal antibody ublituximab on chronic lymphocytic leukemia cells with the 17p deletion. Leukemia. 2014;28(1):230-233
[16] de Romeuf C, Dutertre CA, Le Garff-Tavernier M, et al. Chronic lymphocytic leukaemia cells are efficiently killed by an anti-CD20 monoclonal antibody selected for improved engagement of FcgammaRIIIA/CD16. Br J Haematol. 2008;140(6):635-643.
[17] Bellon A, Sadoun A, Grivel K, et al. Comparison of Cell Lysis Mediated by LFB-R603 with That Mediated by Ofatumumab Against Cells Expressing Low Levels of CD20. Blood. 2011;118(21):3913
[18] Le Garff-Tavernier M, Decocq J Fau - de Romeuf C, de Romeuf C Fau - Parizot C, et al. Analysis of CD16+CD56dim NK cells from CLL patients: evidence supporting a therapeutic strategy with optimized anti-CD20 monoclonal antibodies. Leukemia. 2011;25(1):101-109.

Table 1: International regulatory status at the time the TGA considered this submission

Country	Date of submission	Date of Approval or current status	Indication
United States	28 September 2021	28 December 2022	Briumvi is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive
European Economic Area (centralised)	23 November 2021	31 May 2023	Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features
United Kingdom	26 May 2023	23 October 2023	Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features
Switzerland	17 October 2023	In process	Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features

Registration timeline

Table 2 captures the key steps and dates for this submission. This submission was submitted through the TGA's Comparable Overseas Regulator B (COR-B) process. The full dossier was submitted to the TGA.

Table 2: Timeline for Briumvi (ublituximab), submission PM-2024-02503-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2024
Evaluation completed	13 February 2025
Registration decision (Outcome)	4 June 2025
Registration in the ARTG completed	11 June 2025
Number of working days from submission dossier acceptance to registration decision*	101

* The COR-B process has a 175 working day evaluation and decision timeframe.

Assessment overview

Quality evaluation summary

Ublituximab is a recombinant IgG1 chimeric monoclonal antibody directed against the CD20 antigen expressed on pre-B and mature B lymphocytes. The antibody is glycoengineered and produced in the YB2/0 rat myeloma cell line, resulting in reduced core fucosylation and enhanced antibody-dependent cellular cytotoxicity. Complement-dependent cytotoxicity activity is also demonstrated, contributing to effective B-cell depletion. The molecular structure comprises two identical heavy chains and two identical light chains linked by disulfide bonds. The predominant glycosylated species has an approximate molecular mass of 146.8 kDa, which is consistent with expectations for an IgG1 monoclonal antibody.

The finished product is presented as a concentrated solution for intravenous infusion at a strength of 25 mg/mL. Each single-use Type I glass vial contains 150 mg of ublituximab in a 6 mL fill volume. The formulation includes sodium chloride, sodium citrate, polysorbate 80, hydrochloric acid for pH adjustment, and water for injections. All excipients are compendial and comply with USP, Ph. Eur., or NF requirements. No novel excipients are included in the formulation, and no excipient-related quality concerns were identified.

Manufacture of both the drug substance and the finished product is performed by Samsung Biologics Co., Ltd. in the Republic of Korea. Drug substance manufacture comprises fed-batch cell culture followed by harvest and clarification, and purification using a three-step chromatography process consisting of Protein A affinity chromatography, cation exchange chromatography, and anion exchange chromatography. This process is considered appropriate for control of process- and product-related impurities, including host cell proteins and residual DNA. Following purification, the drug substance is formulated, sterile filtered, filled into single-use containers, frozen, and stored at or below −35°C prior to shipment under controlled frozen conditions to the finished product manufacturing site. Extractables and leachables and container compatibility studies were provided and are considered adequate, with no identified safety concerns.

The finished product manufacturing process includes pooling of drug substance, sterile filtration through a 0.2 µm filter, aseptic filling into vials, visual inspection, and refrigerated storage prior to labelling and packaging. Process descriptions, in-process controls, validation data, and batch analysis results across multiple manufacturing campaigns were reviewed and are considered acceptable. No critical deficiencies were identified in relation to the finished product manufacturing process.

Specifications are applied to both the drug substance and the finished product and include tests for identity, purity, potency, impurities, sterility, endotoxins, and bioburden, as appropriate. Biological activity and potency are assessed using a range of validated orthogonal assays, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, CD20 binding, FcγRIIIa binding, and C1q binding. All non-compendial analytical methods have been adequately validated in accordance with ICH guidelines. The proposed specification limits are supported by batch analysis data and are considered suitable to ensure consistent product quality.

Stability data support a shelf life for the drug substance of 36 months when stored at or below −35°C. For the finished product, a shelf life of three years when stored at 2–8°C and protected from light is supported by real-time stability data. In-use stability studies following dilution support storage for up to 24 hours at 2–8°C followed by up to 8 hours at room temperature. Stability studies were conducted in accordance with relevant ICH guidelines.

The finished product is not photostable; however, appropriate light protection measures are described in the labelling. Shelf-life and storage statements are consistent across the Product Information, Consumer Medicine Information, labelling and ARTG documentation.

Labelling includes appropriate storage conditions and handling precautions, including statements that the product is for single use only and contains no antimicrobial preservative, should not be shaken, should not be frozen, must be stored at 2–8°C and protected from light, and must be diluted prior to administration. These statements are considered adequate from a quality perspective.

All manufacturing, testing, storage, packaging, and release sites associated with the drug substance and finished product hold current GMP clearances with acceptable expiry dates. No outstanding GMP compliance issues were identified during the evaluation. Secondary quality assessments addressing sterility assurance, viral safety, transmissible spongiform encephalopathy risk, mycoplasma, endotoxins, and container safety were provided and are considered satisfactory, demonstrating appropriate control and mitigation of potential risks.

Overall, from a quality perspective, the quality data submitted for Briumvi (ublituximab) are considered acceptable. The dossier demonstrates adequate control of the manufacturing process, specifications, analytical methods, stability, and GMP compliance. On the basis of the data reviewed, the evaluator considers that the product is of acceptable and consistent quality and is suitable for registration, subject to use in accordance with the proposed Product Information, labelling, and storage conditions.

Nonclinical evaluation summary

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of biotechnology derived pharmaceutical medicines (ICH S6 [R1]).[19] All pivotal safety-related studies were GLP compliant.

Ublituximab is a recombinant IgG1 chimeric monoclonal antibody which bound to CD20 on cell surface *in vitro* with an EC_{50} value comparable to other anti-CD20 monoclonal antibodies at concentrations well below expected clinical plasma concentrations. Ublituximab showed affinity to FcγRIIIa 158F and 158V allotypes in the nanomolar range. In functional *in vitro* activity assays, ublituximab exhibited dose dependent ADCC, antibody dependent phagocytosis (ADCP), and to a lesser extent complement dependent cytotoxicity (CDC). Ublituximab induced B-cell depletion in whole blood from healthy donors at mean concentrations well below clinical C_{min}. *In vivo*, treatment with ublituximab resulted in complete depletion of B lymphocytes in monkeys and immunodeficient mice models, supporting the proposed clinical indication.

Immunohistochemical assays examining cross-reactivity showed staining of lymphocytes located in various tissues in normal human and monkey tissues. Ublituximab did not bound to non-specific tissues. There was no evidence of off-target effects in the set of repeat-dose toxicity studies.

Specific safety pharmacology parameters (effects on CNS, cardiovascular and respiratory function) were assessed in the repeat-dose toxicity studies and were found to be unremarkable. No adverse effects on cardiovascular, respiratory or CNS function are predicted during clinical use.

Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Half-life values were long in rabbits, monkeys and humans. Tissue distribution and plasma clearance

[19] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals - Scientific guideline. 2011.

were predicted to be limited. The PK studies showed that the monkey is an appropriate animal model for toxicity testing of ublituximab.

In a single dose toxicity study conducted in Cynomolgus monkeys (up to 100 mg/kg IV), all toxicological findings were consistent with the expected pharmacology of ublituximab (decreased weight of the thymus, B-cell depletion, decreased B lymphocytes in the bone marrow, spleen and lymph nodes).

Repeat-dose toxicity studies by the intravenous route were conducted in Cynomolgus monkeys (up to 26 weeks). Maximum exposures (AUC) were generally moderate to very high at highest tested doses. Ublituximab was generally well tolerated in monkeys with the primary findings consistent with the expected pharmacological effect of ublituximab on B-cells. Depletion of B lymphocytes along with decreased follicle size/number and germinal centres in the lymph nodes and spleen were observed at exposures equal to and higher than clinical exposures. Anti-drug antibodies were detected in the repeat-dose toxicity studies. Immune-mediated effects were also seen in various tissues (pulmonary haemorrhage, mononuclear cell infiltration in the central nervous system and eye, and vascular/perivascular inflammation in aorta, epididymis, gall bladder, seminal vesicle, heart, kidney, mesentery, jejunum, stomach and testis) at 30 mg/kg/week (exposure ratio based on AUC = 19). The relevance of these findings to humans is unclear.

Given the protein nature of the drug, the *in vitro* Ames test was not considered relevant. No other genotoxicity studies and no carcinogenicity studies were conducted, which is considered acceptable. No proliferative lesions were seen in the repeat-dose toxicity study.

Fertility and early embryofetal development study was not conducted. Immune-mediated vascular/perivascular inflammation in epididymis and testis was observed at moderate relative exposures. Clinical relevance of these findings is unknown. In an enhanced pre/postnatal study (ePPND) study in cynomolgus monkeys, ublituximab intravenous administration (weekly) to pregnant monkeys led to increased abortions in treated females and the premature sacrifice of pregnant females. Ublituximab treatment resulted in increased fetal and infant mortality, shorter gestation length, and abnormal external, skeletal and morphometric findings. The significant immune-mediated effects on maternal health may have contributed to most of the fetal/infant effects. Ublituximab is likely to cross the blood-placenta barrier. Infants had high serum levels of ublituximab, likely due to gestational exposure. Given the pharmacological action of the drug, a risk for infection in the neonate period exists.

While no effects on some immunological parameters (T-cell dependent antibody response, natural killer cell activity) were seen in treated cynomolgus monkeys at high exposures, given the pharmacological action of the drug, a risk of infections exists in patients.

There are no nonclinical objections to the registration of Briumvi (ublituximab) for the proposed indication.

Clinical evaluation summary

Pharmacology

Bioanalytical methods were developed, validated and performed to support the clinical development of the ublituximab.

Individual results for study samples (inform that most of the results are above curve range (reaching even 400,000ng/mL). According to the population pharmacokinetic (PopPK) modelling results, ublituximab pharmacokinetics (PK) showed linear mode over the dose range

150 to 600mg in subjects with RMS. Estimated central volume of distribution $(V)_c$ and peripheral volume of distribution (V_p) were 3.18 L (inter-individual variability[IIV] = 15.0%) and 3.60 L (IIV = 21.3%), respectively. The model estimated clearance (CL) was 11.3mL/h (IIV of 38.1%). Mean $t_{1/2}$ was calculated to be 21.8 days. No accumulation of ublituximab during the proposed regimen in RMS (dosing every 24 weeks) was shown.

Bodyweight, sex region, and anti-drug antibodies (ADA) presence were found to be significant covariates of ublituximab PK. These covariates had a modest effect on exposures (all results contained within the 0.8 to 1.25 exposure ratio), and they are not supposed to be clinically relevant. Age, baseline haemoglobin, platelet count and white blood cell count, renal impairment and hepatic impairment were not found to be significant predictors of ublituximab PK. Bodyweight was found to be a statistically significant predictors of ublituximab CL. A modest effect of body weight on ublituximab exposure was seen.

No accumulation of ublituximab was observed for subjects receiving 150mg ublituximab on Day 1 followed by 450mg on Day 15, Week 24 and Week 48 (C_{max} ratio at week 24 to Day 1 was 3.04; C_{max} ratio at week 48 to week 24 was 1).

No special population studies were performed to characterise PK parameters of ublituximab. According to the PopPK, body weight, sex, region, and ADA were significant covariates of ublituximab PK. None of them seems clinically relevant, and no dose adjustment needs to be implemented.

The oldest patients enrolled were 56 years old. In the Summary of Product Characteristics (SmPC)[20], the Sponsor states that: “Based on the limited data available, no posology adjustment is needed in patients over 55 years of age”.

Dose response study TG1101-RMS201

52-week, Phase IIa, placebo-controlled, multicenter, dose-finding, cohort sequential study. The study included 6 treatment cohorts, each with 8 subjects: 6 subjects randomized to receive ublituximab and 2 subjects randomized receive to placebo.

The responder rate (95% CI) of B-cell depletion 2 weeks after Week 3 Day 15, the second scheduled infusion of ublituximab, was 95.8% (85.75%, 99.49%). The responder rate (95% CI) of B-cell depletion was 100% (63.06%, 100%) for Cohorts 2, 4, 5, and 6 and 87.5% (47.35%, 99.68%) for Cohorts 1 and 3.

Table 3: CD19+ B-cell Depletion Responder Rate (ITT Population)

Cohort	Cohort 1 (N=8)	Cohort 2 (N=8)	Cohort 3 (N=8)	Cohort 4 (N=8)	Cohort 5 (N=8)	Cohort 6 (N=8)	Total (N=48)
Responder rate (%) (95% CI)*	87.5 (47.35, 99.68)	100 (63.06, 100)	87.5 (47.35, 99.68)	100 (63.06, 100)	100 (63.06, 100)	100 (63.06, 100)	95.8 (85.75, 99.49)

CD, cluster of differentiation; CI, confidence interval; ITT, intent-to-treat. A responder was defined as subjects with ≥95% peripheral CD19+ B cell depletion from baseline within 2 weeks after the second ublituximab infusion (Week 3 Day 15). The 95% CI was estimated using the Clopper–Pearson (exact) method.

[20] https://www.ema.europa.eu/en/documents/product-information/briumvi-epar-product-information_en.pdf

Efficacy

Pivotal studies

TG1101-RMS301 (ULTIMATE I): a 120-week, Phase III, randomized, multicenter, double-blinded, double-dummy, active-controlled study that was primarily designed to assess the annualized relapse rate (ARR) and safety/tolerability of ublituximab/oral placebo as compared to teriflunomide/intravenous (IV) placebo in subjects with RMS.

TG1101-RMS302 (ULTIMATE II): a 120-week, Phase III, randomized, multicenter, double-blinded, double-dummy, active-controlled study to assess the ARR and safety/tolerability of Ublituximab/oral placebo compared to teriflunomide/IV placebo in subjects with RMS.

Both pivotal studies TG1101-RMS301 and TG1101-RMS302 had identical design (Figure 1 and Table 4).

Inclusion criteria

Subjects met the following inclusion criteria to be eligible for participation in this study: patients with 18-55 years of age diagnosed as having RMS (McDonald criteria 2010[21]) with Expanded Disability Status Scale (EDSS) between 0 and 5.5 (inclusive) at screenings and active disease as defined by ≥2 relapses in prior 2 years or 1 relapse in the year prior to screening and/or ≥1 Gd enhancing lesion. As per mechanism of action, B cell counts ≥5% of total lymphocytes was required

Treatments

Subjects were screened up to 4 weeks (28 days) before the first dosing date of study medication (ublituximab/oral placebo or teriflunomide/IV placebo). Qualified subjects were randomized in a 1:1 ratio to receive either ublituximab/oral placebo on Week 1 Day 1, Week 3 Day 15, and Weeks 24, 48, and 72 or teriflunomide/IV placebo (14 mg, daily starting on Week 1 Day 1 until the last day of Week 95). Upon cessation of study treatment, the subjects were followed for another 20 weeks to enable teriflunomide elimination monitoring.

[21] Polman C, Reingold S, Banwell B et al. Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria. Ann Neurol. 2011;69(2):292-302. doi:10.1002/ana.22366

Figure 1. Study Design for Study TG1101-RMS301 and TG1101-RMS302

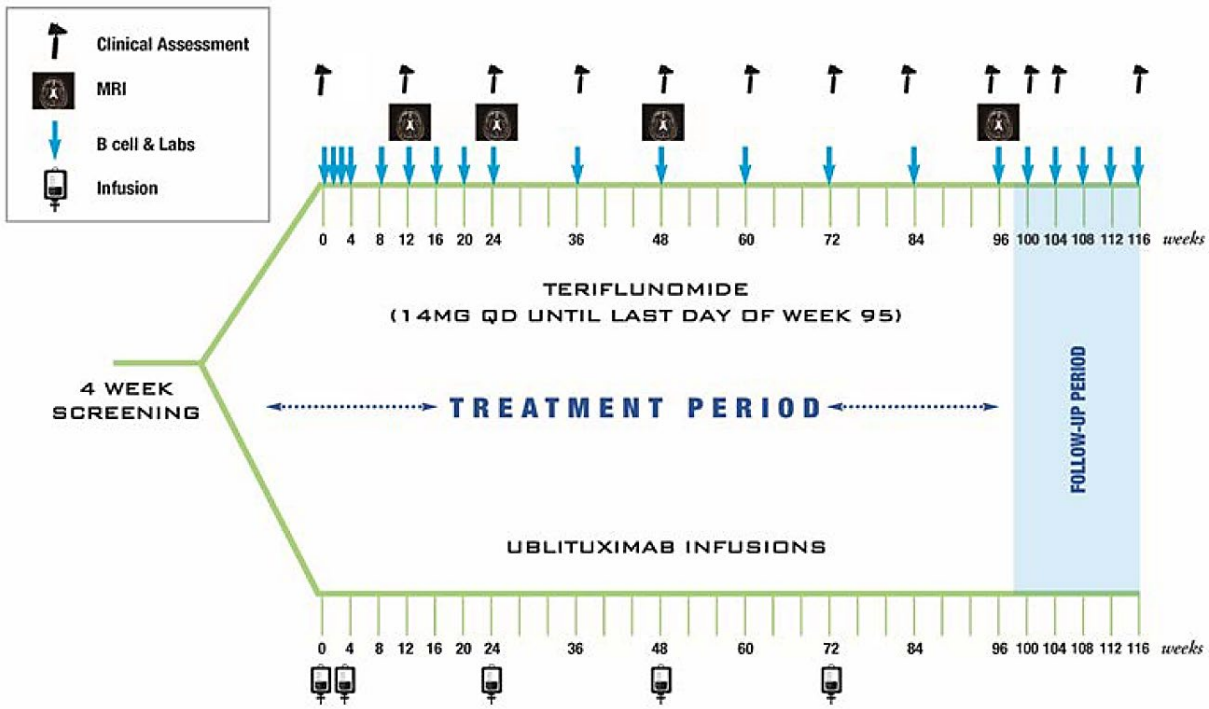


Table 4. Study Treatment and Dosing Regimen in Study TG1101-RMS301 and – RMS302

Treatment arm	Week 1 Day 1	Week 3 Day 15	Week 24	Week 48	Week 72	Week 96
Ublituximab plus oral placebo	UTX (150 mg/4 h)	UTX (450 mg/1 h)	UTX (450 mg/1 h)	UTX (450 mg/1 h)	UTX (450 mg/1 h)	–
	Oral placebo QD* from Week 1 Day 1 until last day of Week 95					
Teriflunomide plus placebo infusion	Teriflunomide (14 mg) QD* from Week 1 Day 1 until last day of Week 95					
	Infusion placebo	Infusion placebo	Infusion placebo	Infusion placebo	Infusion placebo	–

Objectives

Primary objective: to determine the ARR in participants with RMS after 96 weeks (approximately 2 years with a year equal to 365.25 days) treatment with IV infusion of ublituximab/oral placebo compared to 14 mg oral teriflunomide/IV placebo.

Secondary objectives

To examine the effects of ublituximab/oral placebo as compared to teriflunomide/IV placebo on MRI parameters, confirmed disability progression (CDP), No Evidence of Disease Activity (NEDA), symbol digit modalities test (SDMT).

To evaluate the safety of ublituximab/oral placebo, as determined by adverse events (AEs) and serious adverse events (SAEs), including MS worsening.

Primary endpoint

The primary efficacy variable (per patient) is the number of Independent Relapse Adjudication Panel (IRAP)-confirmed relapses which started on or after the day of randomization and up to the day of last study treatment. Then, ARR was defined as the number of IRAP-confirmed relapses per participant year. The estimate of ARR for a treatment group was the total number of relapses

for participants in the respective treatment group divided by the sum of treatment duration (in years) in that specific treatment group. Participants were treated up to 96 weeks.

Results

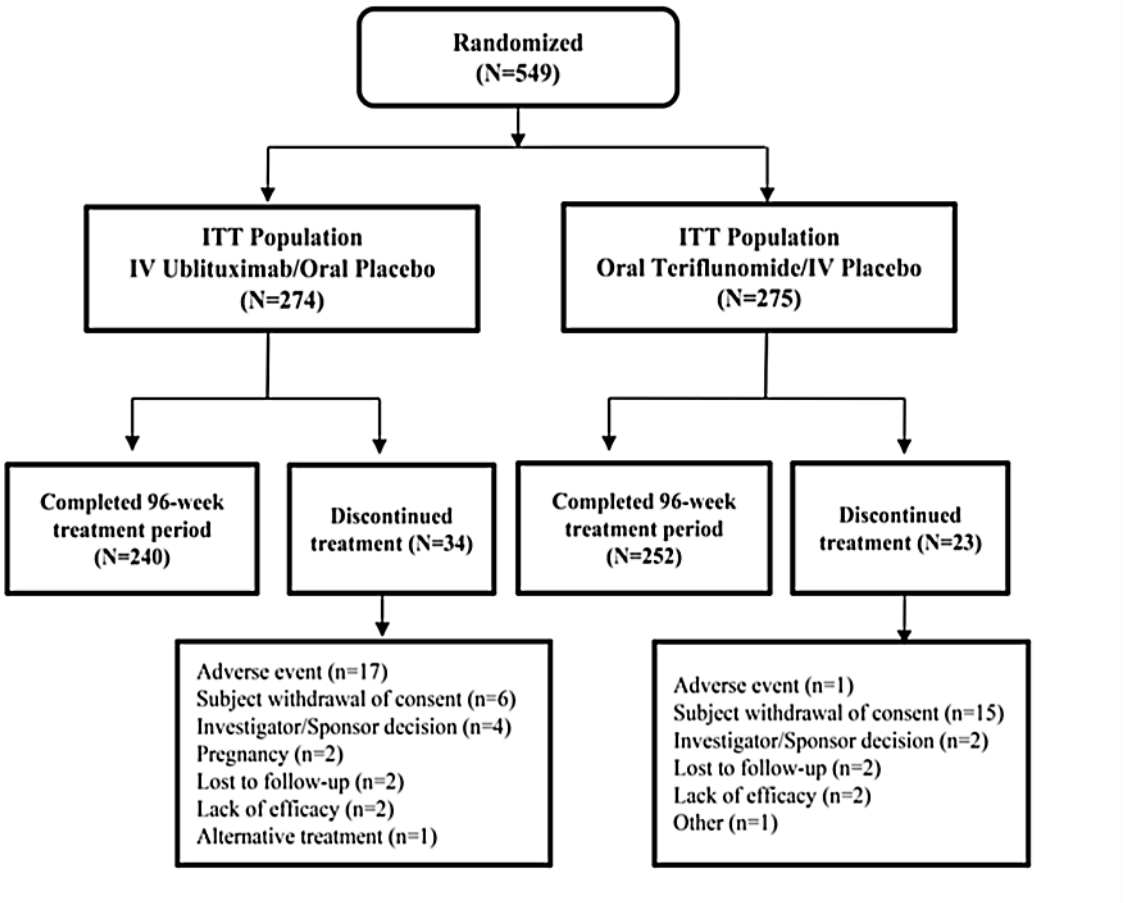
Results from the two pivotal studies are presented separately.

TG1101-RMS301 (ULTIMATE I)

120-week, Phase III, randomized, multicenter, double-blinded, double-dummy, active-controlled study that was primarily designed to assess the ARR and safety/tolerability of ublituximab/oral placebo as compared to teriflunomide/intravenous (IV) placebo in subjects with RMS (Figure 2).

Participant flow

Figure 2: Disposition of Subjects in Study TG1101-RMS301 (ITT Population)



Baseline data

The demographics and disease characteristics were similar for subjects in the ublituximab and teriflunomide groups. For the ublituximab group, the median (range) age was 36.0 (18 to 55) years, 61.3% of subjects were female, 97.4% of subjects were White, 95.9% of subjects were not Hispanic or Latino, and 90.4% of subjects were from Eastern Europe. For the teriflunomide group, the median (range) age was 36.5 (18 to 55) years, 65.3% of subjects were female, 97.1% of subjects were White, 97.1% of subjects were not Hispanic or Latino, and 88.7% of subjects were from Eastern Europe.

The MS disease history and the percentage of subjects with prior MS treatment were similar in the two treatment groups.

Table 5: Extent of Exposure to Intravenous Study Treatment in Study TG1101-RMS301 (Modified intention-to-treat [mITT] Population)

	Ublituximab (N=271)	Teriflunomide (N=274)
Number of infusions		
Mean (SD)	4.8 (0.71)	4.9 (0.59)
Median (minimum, maximum)	5.0 (1, 5)	5.0 (1, 5)
Number of infusions, n (%)		
1	3 (1.1)	2 (0.7)
2	7 (2.6)	4 (1.5)
3	7 (2.6)	7 (2.6)
4	8 (3.0)	4 (1.5)
5	246 (90.8)	257 (93.8)
Percentage of planned total dose (ublituximab or placebo) taken		
Mean (SD)	95.4 (16.28)	96.7 (13.61)
Median (minimum, maximum)	100.0 (7.7, 100.0)	100.0 (7.7, 100.0)

mITT, modified intent-to-treat; SD, standard deviation.

Note: Ublituximab treatment in the Ublituximab group; Placebo in the Teriflunomide group.

*≥50% complete, only participants with at least one infusion are represented in this summary.

Outcomes and estimation

The ITT Population consisted of 549 participants overall, with 274 participants in the ublituximab group and 275 participants in the teriflunomide group. The per protocol (PP) population included 467 (85.1%) participants, with 83.2% of subjects in the ublituximab group and 86.9% of participants in the teriflunomide group.

Primary efficacy endpoint

The treatment effect of ublituximab versus teriflunomide was statistically significant in favour of ublituximab. Similar findings were reported for the ITT population and the PP population.

Table 6. Annualized Relapse Rate (IRAP Confirmed) in Study TG1101-RMS301 (mITT Population)

	Ublituximab (N=271)	Teriflunomide (N=274)
Duration of treatment[a] (years)		
Mean (SD)	1.7 (0.37)	1.8 (0.31)
Cumulative treatment time[b] (subject years)	464.52	479.44
Number of IRAP-confirmed relapses during treatment[a]		
Mean (SD)	0.162 (0.4507)	0.405 (0.8166)
Cumulative number of IRAP-confirmed relapses[b]	44	111
Raw annualized relapse rate[c]	0.09	0.23
Negative binomial model[d]		
Least squares means (95% CI)	0.076 (0.042, 0.138)	0.188 (0.124, 0.283)
Rate ratio: ublituximab / teriflunomide	0.406 (0.268, 0.615)	
Difference: ublituximab − teriflunomide	−0.111 (−0.166, −0.056)	
p value	<0.0001	

CI, confidence interval; IRAP, Independent Relapse Adjudication Panel: mITT, modified intent-to-treat; SD, standard deviation.

a. Per subject
b. Overall
c. Cumulative number of IRAP-confirmed relapses / Cumulative treatment time
d. GEE model for the relapse count per participant with logarithmic link function, treatment, region, and baseline EDSS strata as covariates and log (years of treatment) as offset.

The results for the three sensitivity analyses for the mITT population including Annualized Relapse Rate, the analysis of IRAP-Confirmed Relapses by worst severity recovery and analysis of IRAP-confirmed relapses were consistent with the primary analyses.

Key secondary efficacy endpoints

Total number of gadolinium-enhancing t1 lesions per MRI Scan by Week 96

The treatment effect of ublituximab versus teriflunomide was statistically significant in favour of ublituximab (Table 7). Similar findings were reported for the ITT population and for the PP-MRI population.

Table 7. Total Number of Gadolinium-enhancing T1 Lesions per MRI Scan by Week 96 in Study TG1101- RMS301 (mITT-MRI Population)

	Ublituximab (N=271)	Teriflunomide (N=274)
Duration of treatment[a] (years)		
Mean (SD)	1.7 (0.37)	1.8 (0.31)
Cumulative treatment time[b] (subject years)	464.52	479.44
Number of IRAP-confirmed relapses during treatment[a]		
Mean (SD)	0.162 (0.4507)	0.405 (0.8166)
Cumulative number of IRAP-confirmed relapses[b]	44	111
Raw annualized relapse rate[c]	0.09	0.23
Negative binomial model[d]		
Least squares means (95% CI)	0.076 (0.042, 0.138)	0.188 (0.124, 0.283)
Rate ratio: ublituximab / teriflunomide	0.406 (0.268, 0.615)	
Difference: ublituximab − teriflunomide	−0.111 (−0.166, −0.056)	
p value	<0.0001	

Cl, confidence interval; modified intent-to-treat; MRI: magnetic resonance imaging; SD, standard deviation.
a GEE (Generalized Estimating Equation) model with logarithmic link function, covariates treatment, region, baseline EDSS strata, baseline number of lesions (0/21) and an offset based on the log-transformed number of post-baseline MRI scans)

Total number of new and enlarging t2 hyperintense lesions per MRI Scan by Week 96

The treatment effect of ublituximab versus teriflunomide was statistically significant in favour of ublituximab (Table 8). Similar findings were reported for the ITT population and for the PP-MRI[22] population.

A sensitivity analysis of the total number of new and enlarging T2 hyperintense lesions per MRI scan at Week 96 using multiple imputation showed similar results.

[22] all participants in the Per-Protocol Population who had baseline and post-baseline MRI efficacy assessments.

Table 8. Total Number of New and Enlarging T2 Hyperintense Lesions per MRI Scan by Week 96 in Study TG1101-RMS301 (mITT-MRI Population)

	Ublituximab (N=265)	Teriflunomide (N=270)
T2 lesion count, mean (SD)		
Baseline	63.8 (38.21)	60.5 (37.14)
New or enlarging T2 lesion count, mean (SD)		
Week 24	1.0 (2.14)	4.4 (10.00)
Week 48	0.0 (0.23)	3.5 (7.68)
Week 96	0.0 (0.13)	4.6 (8.59)
Total number of new and enlarging T2 hyperintense lesions per MRI scan per subject		
n	260	267
Mean (SD)	0.351 (0.7256)	4.279 (7.6766)
Median (minimum, maximum)	0.00 (0.00, 7.00)	1.33 (0.00, 58.33)
Negative binomial model		
Least squares means (95% CI)	0.213 (0.144, 0.316)	2.789 (2.136, 3.643)
Ratio: ublituximab / teriflunomide	0.076 (0.056, 0.104)	
Difference: ublituximab - teriflunomide	-2.576 (-3.272, -1.881)	
p value	<0.0001	

CI, confidence interval; modified intent-to-treat; MRI: magnetic resonance imaging; SD, standard deviation

a. GEE (Generalized Estimating Equation) model with logarithmic link function, covariates treatment, region, baseline EDSS Strata, baseline number of lesions (0≥1) and an offset based on the log-transformed number of post-baseline MRI scans)

Proportion of subjects with NEDA from week 24 to week 96

The treatment effect was numerically in favour of ublituximab (Table 9). Similar findings were reported for the ITT population and for the PP population.

Table 9. Proportion of Subjects With NEDA From Week 24 to Week 96 for Study TG1101-RMS301 (mITT Population)

	Ublituximab (N=271)	Teriflunomide (N=274)
Number of subjects with NEDA[a], n (%)	121 (44.6)	41 (15.0)
Difference (%) ublituximab – teriflunomide (95% CI)	29.7 (22.4, 37.0)	
Number of subjects with any evidence of disease activity or terminated early[a], n (%)	150 (55.4)	233 (85.0)
Logistic regression[b]		
Odds ratio: ublituximab / teriflunomide (95% CI)	5.442 (3.536, 8.375)	
p value	<0.0001	

CI, confidence interval; modified intent-to-treat; NEDA, no evidence of disease activity.
a. Denominator is the number of participants in the analysis population.
b. Logistic regression model with treatment, region, baseline EDSS strata, and log-transformed baseline MRI counts (T1 unenhancing, T2, Gad enhancing) as covariates p-value is nominal as the 12-week CDP was not statistically significant.

Proportion of subjects reaching impaired SDMT From baseline to week 96

The treatment effect for the number of subjects with impaired SDMT is shown in Table 10.

Similar findings were reported for the intention to treat (ITT) population and for the PP population.

Table 10. Proportion of Subjects Reaching Impaired Symbol Digit Modalities Test From Baseline to Week 96 in Study TG1101-RMS301 (mITT Population)

	Ublituximab (N=271)	Teriflunomide (N=274)
Number of subjects with SDMT impairment[a], n (%)	79 (29.2)	87 (31.8)
Risk difference (%): ublituximab – teriflunomide	−2.6 (−10.3, 5.1)	
Number of subjects without SDMT impairment[a], n (%)	192 (70.8)	187 (68.2)
Logistic regression[b]		
Odds ratio: ublituximab / teriflunomide (95% CI)	0.872 (0.603, 1.261)	
p value	0.4669	

CI, confidence interval; modified intent-to-treat; SDMT, symbol digit modalities test.
a Denominator is the number of participants in the analysis population.
b Logistic regression model with treatment, region, baseline EDSS strata, and log-transformed baseline MRI counts (T1 unenhancing, T2, Gad enhancing) as covariates
p-value is nominal as the 12-week CDP was not statistically significant.

Percentage change in brain volume from baseline to week 96

In the ublituximab group, the mean percentage change from Baseline in brain volume demonstrated increased brain atrophy at Weeks 24, 48, and 96 In the teriflunomide group, the mean percentage change from Baseline in brain volume increased slightly at Week 24 and then demonstrated increased brain atrophy at Weeks 48 and 96. The LS mean for the percentage change of the cube root transformed volume from Baseline to Week 96 for ublituximab versus teriflunomide is shown in Table 11. Similar findings were reported for the ITT population and for the PP-MRI population.

Table 11: Percentage in Brain Volume Change from Baseline to Week 96 in Study TG1101-RMS301 (mITTMRI Population)

	Ublituximab (N=265)	Teriflunomide (N=270)
Baseline (mm^3), mean (SD)	165366.1 (116369.48)	169997.7 (109684.30)
Percentage change from Baseline, mean (SD)		
Week 24	-0.142 (0.3910)	0.070 (0.4201)
Week 48	-0.357 (0.4843)	-0.108 (0.5074)
Week 96	-0.596 (0.5769)	-0.375 (0.5564)
MMRM[a]		
LS means (95% CI)	-0.197 (-0.228, -0.166)	-0.125 (-0.155, -0.095)
LS means: ublituximab − teriflunomide (95% CI)	-0.072 (-0.107, -0.036)	
p value	<0.0001	

Cl, confidence interval; mITT, modified intent-to-treat; MRI, magnetic resonance imaging; LS least squares; MRMM Mixed Model Repeated Measures; SD, standard deviation.
A MMRM (Mixed Model Repeated Measures) of the percentage changes of the cube root transformed volume from baseline. The model includes treatment, region, baseline EDSS strata, visit, treatment-by-visit interaction, and baseline volume (cube root transformed) as covariates and an unstructured covariates matrix.
p-value is nominal as the 12-week CDP was not statistically significant.

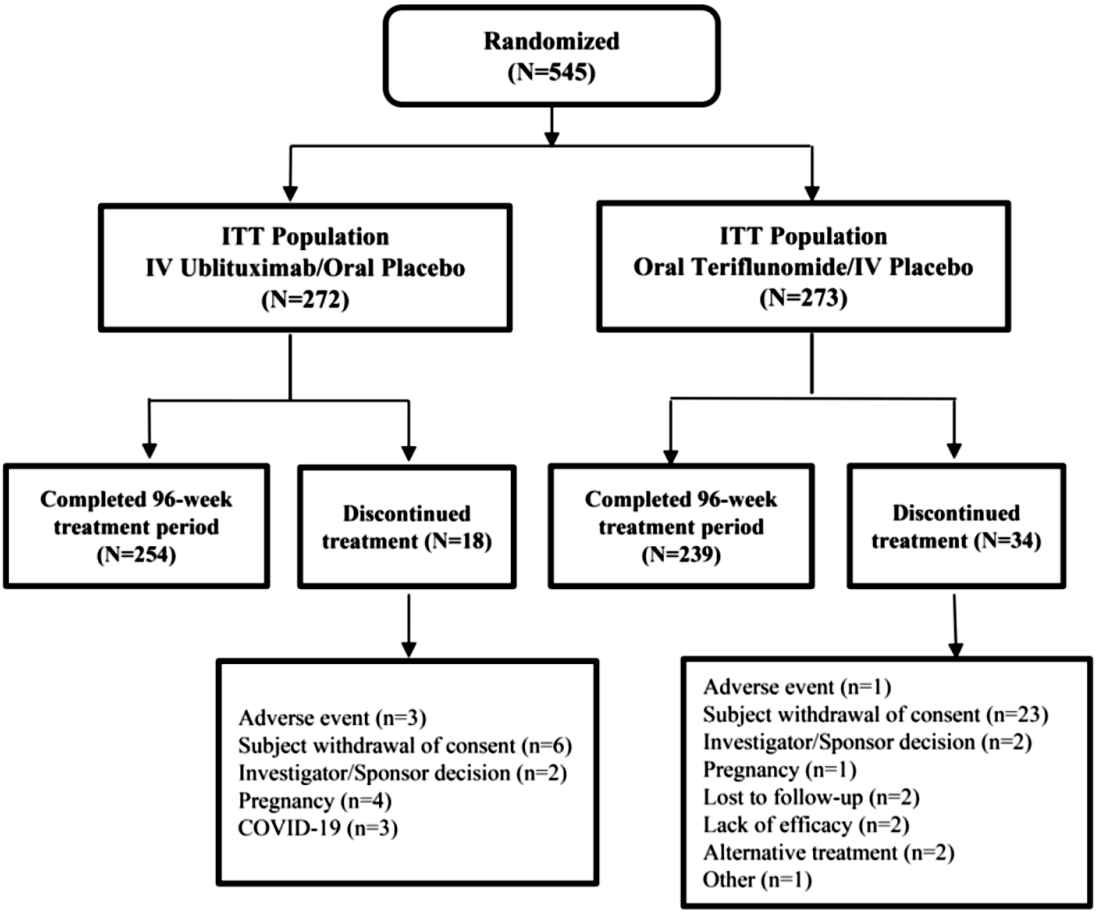
Study TG1101-RMS302 (ULTIMATE II)

120-week Phase III, randomized, multicenter, double-blinded, double-dummy, active-controlled study that is primarily designed to assess the ARR and safety/tolerability of ublituximab (TG-

1101; UTX)/oral placebo as compared to teriflunomide/IV placebo in participants with RMS. Conducted at 50 study centres in 8 countries in Europe and North America (Figure 3).

Participant flow

Figure 3: Disposition of Subjects in Study TG1101-RMS302 (ITT Population)



ITT: Intend-to-treat; IV: Intravenous; COVID-19, coronavirus infection 2019. The ITT population consisted of all randomized subjects

Baseline data

The demographics and disease characteristics were similar for subjects in the ublituximab and teriflunomide groups. For the ublituximab group, the median (range) age was 33.0 (18 to 55) years, 65.4% of subjects were female, 98.9% of subjects were White, 96.3% of subjects were not Hispanic or Latino, and 90.1% of subjects were from Eastern Europe. For the teriflunomide group, the median (range) age was 36.0 (18 to 55) years, 64.7% of subjects were female, 98.5% of subjects were White, 96.3% of subjects were not Hispanic or Latino, and 91.9% of subjects were from Eastern Europe.

The MS disease history and the percentage of subjects with prior MS treatment was similar in the 2 treatment groups.

Most subjects received 5 infusions that were >50% complete.

Table 12: Extent of Exposure to Intravenous Study Treatment in Study TG1101-RMS302 (mITT Population)

	Ublituximab (N=272)	Teriflunomide (N=272)
Number of infusions		
Mean (SD)	4.9 (0.38)	4.8 (0.71)
Median (minimum, maximum)	5.0 (2, 5)	5.0 (1, 5)
Number of infusions[a], n (%)		
1	0	1 (0.4)
2	2 (0.7)	10 (3.7)
3	4 (1.5)	10 (3.7)
4	7 (2.6)	5 (1.8)
5	259 (95.2)	246 (90.4)
Percentage of planned total dose (ublituximab or placebo) taken		
Mean (SD)	98.4 (8.75)	95.2 (16.53)
Median (minimum, maximum)	100.0 (30.8, 103.5)	100.0 (7.7, 103.5)

mITT, modified intent-to-treat; SD, standard deviation.
Note: Ublituximab treatment in the Ublituximab group, Placebo in the Teriflunomide group
3>50% complete, only participants with at least one infusion are represented in this summary

Outcomes and estimation

Primary efficacy endpoint

The treatment effect of ublituximab versus teriflunomide was statistically significant in favour of ublituximab. Similar findings were reported for the ITT population and the PP population.

Table 13: Annualized Relapse Rate (IRAP Confirmed) in Study TG1101-RMS302 (mITT Population)

	Ublituximab (N=272)	Teriflunomide (N=272)
Duration of treatment[a] (years)		
Mean (SD)	1.8 (0.20)	1.7 (0.37)
Cumulative treatment time[b] (subject years)	485.90	465.70
Number of IRAP confirmed relapses during treatment[a]		
Mean (SD)	0.195 (0.5848)	0.375 (0.7334)
Cumulative number of IRAP confirmed relapses[b]	53	102
Raw annualized relapse rate[c]	0.11	0.22
Negative binomial model[d]		
Least squares means (95% CI)	0.091 (0.049, 0.169)	0.178 (0.109, 0.291)
Rate ratio: ublituximab / teriflunomide	0.509 (0.330, 0.784)	
Difference: ublituximab – teriflunomide	−0.087 (−0.148, −0.027)	
p value	0.0022	

CI, confidence interval; IRAP, Independent Relapse Adjudication Panel; mITT, modified intent-to-treat; SD, standard deviation.
a. Per subject
b. Overall
c. Cumulative number of IRAP-confirmed relapses / Cumulative treatment time
d. GEE model for the relapse count per participant with logarithmic link function, treatment, region, and baseline EDSS strata as covariate and log (years of treatment) as offset.
The results for the three sensitivity analyses for the mITT population including the Annualized Relapse Rate were consistent with the primary analyses.

Key secondary efficacy endpoints

Total number of gadolinium-enhancing T1 lesions per MRI scan by week 96

The treatment effect of ublituximab versus teriflunomide was statistically significant in favour of ublituximab (Table 14). Similar findings were reported for the ITT population and for the PP-MRI population.

Table 14: Total Number of Gadolinium-enhancing T1 Lesions per MRI Scan by Week 96 in Study TG1101- RMS302 (mITT-MRI Population)

	Ublituximab (N = 272)	Teriflunomide (N = 267)
Gadolinium-enhancing lesion count, mean (SD)		
Baseline	2.6 (5.77)	2.4 (5.44)
Week 12	0.1 (0.67)	1.0 (3.70)
Week 24	0.0 (0.15)	0.8 (2.38)
Week 48	0.0 (0.06)	0.7 (1.88)
Week 96	0.0 (0.00)	0.7 (1.79)
Total number of Gadolinium-enhancing T1 lesions per MRI scan per subject		
n	272	267
Mean (SD)	0.037 (0.1939)	0.882 (2.2144)
Median (minimum, maximum)	0.00 (0.00, 2.25)	0.25 (0.00, 23.00)
Negative binomial model[a]		
Least squares means (95% CI)	0.009 (0.004, 0.017)	0.250 (0.162, 0.385)
Ratio: ublituximab / teriflunomide	0.035 (0.019, 0.064)	
Difference: ublituximab – teriflunomide	−0.241 (−0.347, −0.135)	
p value	<0.0001	

CI, confidence interval; modified intent-to-treat; MRI: magnetic resonance imaging; SD, standard deviation.
a. GEE (Generalized Estimating Equation) model with logarithmic link function, covariates treatment, region, baseline EDSS strata, baseline number of lesions (0/≥1) and an offset based on the log-transformed number of post-baseline MRI scans)

Sensitivity analysis of the total number of Gd-enhancing T1 lesions per MRI scan at Week 96 using multiple imputation showed similar results. The LS mean for the number of Gd-enhancing T1 lesions per MRI scan was 0.009 (95% CI: 0.005, 0.018) in the ublituximab group and 0.276 (95% CI: 0.180, 0.424) in the teriflunomide group. The treatment effect was statistically significant in favour of ublituximab at a ratio of 0.033 (95% CI: 0.018, 0.060; p<0.0001), corresponding to a reduction of 96.7%.

Total number of new and enlarging T2 hyperintense lesions per MRI scan by week 96

The treatment effect of ublituximab versus teriflunomide was statistically significant in favour of ublituximab (Table 15). Similar findings were reported for the ITT population and for the PP-MRI population.

Table 15. Total Number of New and Enlarging T2 Hyperintense Lesions per MRI Scan by Week 96 in Study TG1101-RMS302 (mITT-MRI Population)

T2 lesion count	Ublituximab (N=272)	Teriflunomide (N=267)
Baseline, mean (SD)	65.3 (41.23)	63.8 (41.36)
New or enlarging T2 lesion count, mean (SD)		
Week 24	1.4 (3.39)	5.1 (9.15)

T2 lesion count	Ublituximab (N=272)	Teriflunomide (N=267)
Week 48	0.0 (0.12)	3.0 (5.14)
Week 96	0.0 (0.14)	5.2 (9.03)
Total number of new and enlarging T2 hyperintense lesions per MRI scan per subject		
n	269	259
Mean (SD)	0.498 (1.1454)	4.662 (7.7407)
Median (minimum, maximum)	0.00 (0.00, 9.33)	2.00 (0.00, 52.00)
Negative binomial model		
Least squares means (95% CI)	0.282 (0.200, 0.397)	2.831 (2.128, 3.767)
Ratio: ublituximab / teriflunomide	0.100 (0.073, 0.136)	
Difference: ublituximab − teriflunomide	−2.549 (−3.313, −1.786)	
p value	<0.0001	

CI, confidence interval; modified intent-to-treat; MRI: magnetic resonance imaging; SD, standard deviation.
a. GEE (Generalized Estimating Equation) model with logarithmic link function, covariates treatment, region, baseline EDSS strata, baseline number of lesions (0/21) and an offset based on the log-transformed number of post-baseline MRI scans).

A sensitivity analysis of the total number of new and enlarging T2 hyperintense lesions per MRI scan at Week 96 using multiple imputation showed similar results. The LS mean for the number of new and enlarging T2 hyperintense lesions per MRI scan was 0.292 (95% CI: 0.208, 0.412) in the ublituximab group and 3.041 (95% CI: 2.256, 4.098) in the teriflunomide group. The treatment effect was statistically significant in favour of ublituximab at a ratio of 0.096 (95% CI: 0.070, 0.131; p<0.0001), corresponding to a reduction of 90.4%.

Proportion of subjects with NEDA from week 24 to week 96

The treatment effect was numerically in favour of ublituximab (Table 16). Similar findings were reported for the ITT population and for the PP population.

Table 16: Proportion of subjects with no evidence of disease activity from week 24 to week 96 for study TG1101-RMS302 (mITT Population)

	Ublituximab (N=272)	Teriflunomide (N=272)
Number of subjects with NEDA, n (%)	117 (43.0)	31 (11.4)
Difference (%): ublituximab – teriflunomide (95% CI)	31.6 (24.6, 38.6)	
Number of subjects with any evidence of disease activity or terminated early, n (%)	155 (57.0)	241 (88.6)
Logistic regression		
Odds ratio: ublituximab / teriflunomide (95% CI)	7.946 (4.917, 12.841)	
p value	<0.0001	

CI confidence interval; modified intent-to-treat; NEDA, no evidence of disease activity.
a. Denominator is the number of participants in the analysis population.
b. Logistic regression model with treatment, region, baseline EDSS strata, and log-transformed baseline MRI counts (T1 unenhancing, T2, Gad enhancing) as covariates
P-value is nominal as the 12-week CDP was not statistically significant.

Proportion of subjects reaching impaired symbol digit modalities test from baseline to week 96

The treatment effect for the number of subjects with impaired SDMT is shown in Table 17. Similar findings were reported for the ITT population and for the PP population.

Table 17: Proportion of subjects reaching impaired symbol digit modalities test from baseline to week 96 for study TG1101-RMS302 (mITT Population)

	Ublituximab (N = 272)	Teriflunomide (N = 272)
Number of subjects with SDMT impairment[a], n (%)	79 (29.0)	86 (31.6)
Risk difference (%): ublituximab – teriflunomide	−2.6 (−10.3, 5.1)	
Number of subjects without SDMT impairment[a], n (%)	193 (71.0)	186 (68.4)
Logistic regression[b]		
Odds ratio: ublituximab / teriflunomide (95% CI)	0.862 (0.596, 1.246)	
p value	0.4290	

CI, confidence interval; modified intent-to-treat; SDMT, symbol digit modalities test.
a Denominator is the number of participants in the analysis population.
b Logistic regression model with treatment, region, baseline EDSS strata, and log-transformed baseline MRI counts (T1 unenhanang, T2, Gad enhancing) as covariates
p-value is nominal as the 12-week CDP was not statistically significant.

Percentage change in brain volume from baseline to week 96

In the ublituximab group, the mean percentage change from Baseline in brain volume demonstrated increased brain atrophy at Weeks 24, 48, and 96. In the teriflunomide group, the mean percentage change from Baseline in brain volume increased slightly at Week 24 and then demonstrated increased brain atrophy at Weeks 48 and 96. The LS mean for percentage change of the cube root transformed volume from Baseline at Week 96 for ublituximab versus teriflunomide are shown in Table 18. Similar findings were reported for the ITT population and for the PP-MRI population.

Table 18. Percentage in Brain Volume Change from Baseline to Week 96 in Study TG1101-RMS302 (mITT-MRI Population)

	Ublituximab (N=272)	Teriflunomide (N=267)
Baseline (mm^3), mean (SD)	1679927.3 (93579.97)	1668710.7 (100037.37)
Percentage change from Baseline, mean (SD)		
Week 24	-0.150 (0.3975)	0.027 (0.3957)
Week 48	-0.357 (0.4302)	-0.177 (0.4440)
Week 96	-0.642 (0.5600)	-0.576 (0.5988)
MMRM[a]		
LS means (95% CI)	-0.194 (-0.225, -0.164)	-0.176 (-0.207, -0.146)
LS means ublituximab − teriflunomide (95% CI)	-0.018 (-0.053, 0.017)	
p value	0.3108	

CI, confidence interval; mITT. modified intent-to-treat; MRI, magnetic resonance imaging; LS least squares; MRMM Mixed Model Repeated Measures; SD, standard deviation.
a MMRM (Mixed Model Repeated Measures) of the percentage changes of the cube root transformed volume from baseline. The model includes treatment, region, baseline EDSS strata, visit, treatment-by-visit interaction, and baseline volume (cube root transformed) as covariates and an unstructured covariance matrix.
p-value is nominal as the 12-week CDP was not statistically significant.

Safety

The primary safety evaluation for ublituximab compared to teriflunomide is based on pooled safety data from the 2 pivotal studies.

Patient exposure

In total 545 patients with RMS have been exposed to ublituximab in two completed pivotal studies for 72 weeks.

As per cutoff date of 01 March 2022, the total number of participants exposed to ublituximab in phase III trials was 974 participants reflecting the newly rolled over participants from the teriflunomide arm of the parent studies now being treated with ublituximab. In addition, 48 subjects have been exposed in a completed Phase 2 study for 24 weeks

Adverse events

In the pooled analysis of the pivotal Phase III studies (cut off 20Nov 2020), the incidence of at least 1 treatment emergent adverse events (TEAEs) was similar in subjects in the ublituximab and teriflunomide groups (89.2% and 91.4%, respectively). More subjects in the ublituximab group than subjects in the teriflunomide group reported TEAEs of Grade ≥3 (21.3% versus 14.1%), TEAEs of Grade 4 (2.2% versus 0.7%) , serious TEAEs were reported in 10.8% of subjects in the ublituximab group and 7.3% of subjects in the teriflunomide group, TEAEs leading to discontinuation of study treatment were reported in 4.2% of subjects in the ublituximab group and 0.7% of subjects in the teriflunomide group and TEAEs leading to death were reported in 0.6% of subjects in the ublituximab group and none of the subjects in the teriflunomide group.

The most common TEAEs (≥10% of subjects in any group) were headache (ublituximab: 34.3%; teriflunomide: 26.6%), nasopharyngitis (ublituximab: 18.3%; teriflunomide: 17.9%), pyrexia (ublituximab: 13.9%; teriflunomide: 4.9%), nausea (ublituximab: 10.6%; teriflunomide: 7.8%), diarrhoea (ublituximab: 8.1%; teriflunomide: 10.6%), and alopecia (ublituximab: 3.5%; teriflunomide: 15.3%). The percentage of subjects with TEAEs related to study treatment was higher in the ublituximab group compared to the teriflunomide group (66.4% versus 50.0%). The most common TEAEs related to study treatment (≥10% of subjects in any group) were headache (ublituximab: 11.2%; teriflunomide: 5.5%), pyrexia (ublituximab: 10.5%; teriflunomide: 1.8%), and alopecia (ublituximab: 2.9%; teriflunomide: 14.8%). The most common TEAEs of Grade ≥3 was lymphocyte count decreased (ublituximab: 5.5%; teriflunomide: 0) and lymphopenia (ublituximab: 4.0%; teriflunomide: 0.5%), which was attributable to the intended mechanism of action of ublituximab. All other TEAEs of Grade ≥3 was reported in ≤2% of subjects in either treatment group. Two TEAEs of Grade 4 (anaphylactic reaction and CNS enteroviral infection) were considered serious and led to discontinuation of ublituximab treatment.

TEAEs were reported in 4 additional subjects (67.2% of subjects versus 66.4% of subjects in the parent studies). No new TEAEs related to study treatment were reported in ≥10% of subjects. An additional Grade 4 TEAE of neutropenia was reported in 1 subject.

Serious adverse event/deaths/other significant events

In the pooled analysis of the pivotal Phase III studies (cut off 20Nov 2020), serious TEAEs were reported in 59 subjects (10.8%) in the ublituximab group and 40 subjects (7.3%) in the teriflunomide group. No serious TEAEs (by PT) were reported in ≥1% of subjects in either treatment group. Serious TEAEs reported in 3 or more subjects included events of coronavirus

infection 2019 (COVID-19) pneumonia, pneumonia, and acute sinusitis in the ublituximab group and neurological symptom and pyelonephritis acute in the teriflunomide group.

At 1 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, 167 (17.1%) had at least 1 serious TEAEs. The increased incidence of serious TEAEs was driven by COVID-19 pneumonia (80 participants).

As per 20 November 2020, in the pooled Phase III studies, serious TEAEs were reported in 6 additional subjects (11.9% versus 10.8% in the parent studies).

Infusion-related reactions

Pooled analysis of the pivotal Phase III studies, the percentage of subjects with Investigator-reported Infusion-related reactions (IRRs) was higher in the ublituximab group as expected with the infusion of an anti-CD20 monoclonal antibody compared to the teriflunomide group (47.7% versus 12.2%). The most common Investigator-reported IRRs by PT (≥5% of subjects in any group) were pyrexia (ublituximab: 9.5%; teriflunomide: 0.7%), chills (ublituximab: 7.9%; teriflunomide: 0.5%), headache (ublituximab: 7.5%; teriflunomide: 2.2%), influenza-like illness (ublituximab: 5.9%; teriflunomide: 0.9%), and IRR (ublituximab: 5.0%; teriflunomide: 0.5%). Investigator-reported IRRs of Grade ≥3 occurred in 15 subjects (2.8%) in the ublituximab group and 1 subject (0.2%) in the teriflunomide group. Lymphocyte count decreased (1.7%) was the most common Investigator-reported IRR of Grade ≥3 in the ublituximab group. The majority of the

Investigator-reported IRRs started within 24 hours of infusion.

Cytopenias / Lymphopenia

In the pooled analysis of the pivotal Phase III studies, cytopenias as adverse events of special interest (AESIs) were reported in 25.7% of subjects in the ublituximab group and were of Grade ≥3 in 12.1% of subjects. In the concatenated Phase III studies, the percentage of subjects with cytopenias as AESIs was similar to the parent studies (any grade: 26.8% versus 25.7%; Grade ≥3: 12.7% versus 12.1%).

Malignancies

In the pooled analysis of the pivotal Phase III studies, malignancies as AESIs were reported in 2 subjects (0.4%) in the ublituximab group and 1 subject (0.2%) in the teriflunomide group. The TEAEs of endometrial stromal sarcoma and uterine cancer in the ublituximab group were considered SAEs. Neither of the events led to permanent discontinuation of study treatment.

Serious infections

In the pooled analysis of the pivotal Phase III studies, serious infections as AESIs 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) in the serious infections AESI category 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).

Treatment-emergent opportunistic infections

In the pooled analysis of the pivotal Phase III studies, the incidence of potential treatment emergent opportunistic infections was similar in subjects in the ublituximab and teriflunomide groups (11.9% and 10.4%, respectively). The most common TEAEs (≥2% of subjects in any group) were oral herpes (ublituximab: 3.1%; teriflunomide: 3.3%) and influenza (ublituximab:

2.6%; teriflunomide: 2.7%). The treatment-emergent opportunistic infections of Grade ≥3 was reported in 2 subjects in the ublituximab group (chronic hepatitis B and meningoencephalitis viral) and 1 subject in the teriflunomide group (septic shock).

Deaths

In the pooled analysis of the pivotal Phase III studies, deaths were reported in 3 subjects (0.6%) in the ublituximab group (encephalitis, pneumonia, and salpingitis). There were no death in the teriflunomide group. The event of pneumonia was considered possibly related to ublituximab. The other two events were considered not related to ublituximab.

Immunological events

Immunological events were evaluated through the assessment of ADA and characterization of ADA positive clinical samples for potential neutralizing activity. incidence of TE-ADA in Study TG1101-RMS201 was 52.5% (21/40) but only 1 was Nab positive. The incidence of TE-ADA in Studies TG1101-RMS301 and TG1101-RMS302 was 78.0% and 84.4% in each study, respectively, and was 81.3% (434/534) with only 34 subjects being NAb positive. in the pooled data from both studies.

Discontinuation due to adverse events

In the pooled analysis of the pivotal Phase III studies, the incidence of TEAEs leading to study treatment discontinuation was higher in the ublituximab group compared to the teriflunomide group (4.2% versus 0.7%). The adverse drug reactions leading to discontinuation in the ublituximab group were anaphylactic reaction, hypersensitivity, IRR, myalgia and tracheobronchitis (1 subject each). Anaphylactic reaction was the only Grade ≥3 adverse drug reaction that led to discontinuation of study treatment.

Risk management plan

Accelagen Pty Ltd has submitted EU-RMP version 1.2 (dated 20 November 2023; Data lock point 10 October 2023) and Australia specific annex version 0.1 (dated 6 June 2024) in support of this application. The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Table 19: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infusion-related reactions	✓	None	✓	None
Important potential risks	Serious infections, including opportunistic infections (e.g., PML and HBV reactivation)	✓§	✓*	✓	None
	Malignancy	✓	✓*	✓	None
Missing information	Long-term safety of ublituximab treatment	✓	✓*‡	✓	None

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Safety in pregnancy and lactation, including foetal risk	✓	✓†	✓	None

*Post-authorisation long-term safety study (TG1101-RMS402)
†Post-authorisation pregnancy safety studies (TG1101-RMS403 and TG1101-RMS404)
‡Open-label extension study (TG1101-RMS303)
§ PML targeted follow-up questionnaire

Risk-benefit analysis

Overview

This is a COR-B Category 2 submission to register new biological entity based on EMA reports. There have been several post-approval changes that have been approved in the EU.

Studies 301 (ULTIMATE I) and 302 (ULTIMATE II) provided pivotal efficacy and safety data. Both are 120-week, Phase III, randomized, multicentre, double-blinded, double-dummy, active-controlled study that was primarily designed to assess the Annualized relapse rate (ARR) and safety/tolerability of ublituximab/oral placebo as compared to teriflunomide/IV placebo in participants with RMS.

Efficacy

Subjects enrolled in each pivotal study were 18 to 55 years of age (inclusive) and with at least 1 relapse in the previous year, at least 2 relapses in the previous 2 years, or had the presence of a T1 Gad-lesion in the previous year. Subjects were also required to have an EDSS score from 0 to 5.5 at Baseline. Both studies were conducted in the USA and Europe. The vast majority of patients (RMS301 - 89.5%, RMS302 – 91.0%) were recruited in study centres located in Eastern Europe (Russia, Ukraine, Belarus, Georgia).

Participants were randomized in a 1:1 ratio to the following treatment arms: ublituximab/oral placebo or teriflunomide/IV placebo. The choice of teriflunomide as active comparator is appropriate. The randomization processes in both studies were not stratified. While it can be agreed that for studies involving a large group of patients, performing stratification is not necessary, stratification in pivotal studies of DMT for MS is often used in particular with regard to the region or baseline disability in order to avoid imbalance in factors that may be important determinants of treatment effectiveness. In fact, lack of stratification, resulted in a certain degree of imbalance in baseline characteristics between the two treatment groups, especially in USA and Western Europe with a small subset of population (around 10%). Given that results for different regions may differ significantly from each other due to many factors, this may have been justified. However, relevant variables indicating disease characteristics at baseline, such as EDSS score and T1/T2 lesions count, were included as covariates in the statistical analysis models.

The centralised assignment of clinical endpoints, together with a separate role for the local treating and examining neurologists implemented early in both studies (version 2.0 and 2.1 both dated before first study recruitment), constitute appropriate strategy for mitigation of accidental treatment unblinding associated to the different mechanism of action of ublituximab and teriflunomide and consequent distinct effect on clinical and laboratory parameters. Further,

a central MRI reading has been performed in both trials, reassuring not only the consistent imaging analysis across centres but also the unblinded estimation of the MRI-based endpoints.

The sample size assumptions based on clinical trial results for ocrelizumab and teriflunomide were considered reasonable. The studies allowed for interim sample size reassessment when 210 of the 220 participants have been randomized. The BART estimated the ARR in each group based on the pooled population ARR and recommended adding 30 participants per group. As the reassessment of the sample size seems to be based on the pooled population ARR, done by an independent committee, and almost at the end of the studies, the integrity of the studies is not considered questioned.

These studies were primarily designed to assess the efficacy and safety/tolerability of ublituximab/oral placebo compared to teriflunomide/IV placebo in subjects with RMS. The primary endpoint (ARR) and secondary endpoints including measurements of MRI inflammatory activity and disability progression were acceptable.

The Sponsor included sensitivity analysis for the primary endpoint to explore efficacy for all relapses regardless of confirmation, IRAP-confirmed relapses during follow-up and multiple imputation of withdrawn participants. This is acceptable. Type I error was controlled in this study by using a hierarchical gate-keeping procedure. Once primary endpoint was statistically significant at alpha=0.05, the secondary endpoints were tested in a prespecified order. This is acceptable.

While there were 7 protocol amendments, only three protocol versions (3.0, 3.1, and 3.2) were implemented during active enrolment and the Sponsor position that the amendments for these protocol versions did not change any inclusion or exclusion criteria and did not impact the study population can be agreed.

A significant number of major protocol deviations was observed in the studies. The most frequent major deviation was “study procedure or assessment”. The Sponsor clarified that protocol deviations were anticipated in trials of this size, complexity, and duration, and there is no single root cause driving the major protocol deviations recorded in TG1101-RMS301 and TG1101-RMS302. Common causes of study procedure and assessment deviations were due to scheduling conflicts, staff availability or turnover, changes in protocol procedures, and subject compliance with protocol requirements. A significant proportion of study procedure and assessment deviations were related to compliance with the pregnancy test procedure requirement. Further, the TG1101-RMS301 and TG1101-RMS302 studies recorded a significant number of deviations due to the COVID-19 pandemic. These deviations primarily reflect a site’s inability to complete study visits within the protocol-defined window or complete individual study assessments as required, generally due to local travel restrictions or quarantine periods for staff, participants, or even participant family members. The explanations of the reasons for the major protocol deviations in the pivotal studies seem sufficient.

The Sponsor provided a breakdown of the reasons for discontinued participation in Study TG1101-RMS301 [ublituximab (6.2%) in comparison to teriflunomide group (0.4%)], with a distinction made regarding the causes. Of note was the higher rate of discontinuation of study participation in the arm taking ublituximab, but both frequency and reasons varied.

Overall, Briumvi can be considered approvable for a clinical efficacy perspective.

Safety

The primary source of safety data in the RMS target population consists of the two identical pivotal randomized, double blind, 2-arm, active controlled Phase 3 studies TG1101-RMS302 and TG1101-RMS302. In total 545 subjects with RMS treated with ublituximab were included in the

primary safety evaluation. In two pivotal studies, 90.6% of patients from ublituximab group completed the 96-week treatment period. The main reasons for discontinuation in these patients were withdrawal of consent and AE. Supplementary safety data were obtained from a single arm, dose finding Phase 2 study and two ongoing extension studies. In total 1022 patients were exposed to ublituximab in Phase 3 and Phase 2 studies. 974 patients are exposed to ublituximab in the extension Study TG1101-RMS303 as per cut-off of 01 March 2022.

Patients up to 55 years of age were included in the pivotal III studies. 63% of subjects were female, 98% were White. Both groups were well balanced with respect to age, sex and race. In concatenated Phase 2 studies patients between 20 and 56 years of age were included (the media age was 42.5 years). The majority of participants were female (66.7%). Overview of AEs in main safety data did not indicate an imbalance between ublituximab and teriflunomide in incidence of at least 1 TEAEs. However, a higher number of patients from ublituximab group experienced TEAE of Grade ≥3 compared to teriflunomide treated patients. Nevertheless, the disproportion was mainly related to the higher incidence of TEAEs of lymphocyte decrease and lymphopenia, which could be expected, given the mechanism of action of ublituximab. The analysis of the relationship between the duration of exposure and incidence of any TEAEs showed that the highest incidence of TEAEs was reported during the exposure period of 0 to <6 months. The analysis performed did not show an increase in the incidence of serious TEAEs reported during ≥18 months.

The most common TEAEs reported during the pivotal Phase 3 studies were headache, nasopharyngitis, pyrexia, nausea, diarrhoea and alopecia. The incidence of pyrexia was substantially higher in subjects treated with ublituximab compared to teriflunomide (13.9% vs 4.9%) but the Sponsor clarified that 75% of events resolved within 3.5 days.

The overall incidence of serious TEAEs in the pooled pivotal studies was comparable between both ublituximab and teriflunomide groups. As per 20 November 2020 cut-off, serious TEAEs reported in 3 or more subjects in the ublituximab group included events of COVID-19 pneumonia, acute sinusitis, pneumonia. 7 additional serious TEAEs were reported in the concatenated Phase 3 studies (4 cases of COVID-19 pneumonia, tibia and fibula fracture in 1 subject and uterine leiomyoma and vaginal haemorrhage in 1 subject). One additional case of COVID-19 pneumonia and one case of salpingitis/peritonitis/salpingo-oophoritis) were reported in the extension study TG1101-RMS303.

In line with the safety profile described for other anti-CD20 mAbs, the main safety issues with of ublituximab are the risk of IRR and infections.

Serious infections were reported in 5% of subjects from ublituximab group compared to 2.9% of patients from teriflunomide group in the pooled analysis of the pivotal studies as per 20 November 2020 cut-off date. The incidence of potential treatment-emergent opportunistic infections was comparable between both groups (11.9% in ublituximab group and 10.4% in teriflunomide group) as per 20 November 2020 cut-off date.

A risk of cytopenia is a known TEAEs associated with the use of any anti-CD20 biological product depleting B cells. As per 20 November 2020 cut-off in the pooled analysis of the pivotal Phase 3 studies, cytopenias were reported in 25.7% of subjects in the ublituximab group compared to 9.3% in teriflunomide group. In 12.1% of subjects treated with ublituximab, cytopenias of Grade ≥3 were reported (lymphocyte count decreased – 5.5%; lymphopenia – 4%). Neutropenia was observed in 2% of patients treated with ublituximab in the pivotal Phase 3 studies. The Sponsor has provided data about the timing of infections and the timing of the events of cytopenia or hypogammaglobulinemia. Apparently, it emerges that most infection events did not happen in proximity of reduced values of neutrophils, lymphocytes or immunoglobulins.

The Sponsor provided detailed analysis of cases of serous and fatal infections, CNS infections, COVID-19 infections and malignancies. Generally, patients reporting had more comorbidities and a history of prior infections. No correlation between infections and cytopenia/hypogammaglobulinemia was identified. The Sponsor clarified that two subjects who experienced serious CNS enteroviral infections had normal immunoglobulins, neutrophils and lymphocyte counts. The incidence of COVID-19 was comparable between the two arms with serious cases in 0.7% ublituximab-treated patients and 0.4% teriflunomide-treated patients as per 20 November 2020 cut-off date.

The sponsor has presented updated safety data based on a data cut-off date of 01 March 2022. Overall, the incidence and the pattern of TEAEs, serious TEAEs, AESIs was consistent with that observed in data provided in the initial submission as per 20 November cut-off date. The risk of IRR remained as an important identified risk and the risk of serious infections as an important potential risk for ublituximab in RMS. No new safety concerns or risks were identified from this safety update. The Sponsor provided detailed analysis of COVID-19 impact on patient's safety. Overall, no definitive trend in baseline characteristics or disease history for participants who had any COVID-19-related adverse events was observed. However, age and obesity were confirmed as a risk factor for fatal COVID-19-related adverse events.

As per 20 November 2020 cut-off date, AEs leading to withdrawal were reported in 4.2% of patients treated with ublituximab in the pivotal studies. The AEs were anaphylactic reaction, hypersensitivity, IRR, myalgia and tracheobronchitis. At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, 55 had at least 1 TEAE leading to treatment discontinuation. The most common TEAE leading to discontinuation of ublituximab treatment was COVID-19 pneumonia.

As per 20 November 2020 cut-off date, three deaths were reported in the pivotal studies in the ublituximab group (encephalitis, pneumonia and salpingitis). The event of pneumonia was considered possibly related to ublituximab. In the other two fatal events it is not possible to exclude a causative/permissive role of ublituximab-induced immunosuppression; for the information provided, the encephalitis case was due to measles infection in an apparently unvaccinated patient, and in the salpingitis case the fatal outcome could have been linked to a delay in seeking medical assistance. At 01 March 2022, out of the 974 participants included in the Ublituximab Safety Update phase III set, 22 cases of TEAE with an outcome of death were reported. The additional 19 cases of death were due to COVID-19 related events.

No differences in safety profile with respect to hepatic impairment at baseline was reported. However, it is noted that a very limited number of patients with moderate hepatic impairment and no patients with severe hepatic impairment at baseline were included.

There were no clinically meaningful differences observed in TEAE, SAE, drug discontinuations, AESI and deaths in participants receiving ublituximab with mild renal impairment compared to normal renal function. Since only 4 subjects with moderate renal impairment were included in the studies, no analysis of ublituximab safety profile was possible.

Use of ublituximab during pregnancy may cause foetal harm and may cause infant B-cell depletion. There were 14 cases of pregnancy reported (including 3 cases of pregnancy of the subject's partner) in the ublituximab clinical development program. One case of spontaneous abortion and 3 cases with an unknown outcome were reported. The outcome of 5 pregnancies were full-time delivery of a healthy newborn.

It is noted that a substantial number of subjects exposed to ublituximab developed TE-ADA (81.3% in the pooled analysis of the pivotal studies and 52.5% in Study TG1101-RMS201). 34 subjects included in Studies TG1101-RMS301 and one TG1101-RMS302 were NAb positive. However, there is no impact on efficacy and safety as indicated in section 5.1 of the SmPC.

The overall safety profile of ublituximab appears acceptable. Ublituximab can be considered approvable from a clinical safety perspective.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Briumvi (ublituximab) for the following indication:

> *Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features*

Specific conditions of registration

Briumvi (Ublituximab) is to be included in the Black Triangle Scheme. The PI and CMI for Briumvi must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

The Briumvi EU-Risk Management Plan (RMP) (version 1.2, dated 20 November 2023, data lock point 10 October 2023), with Australia-Specific Annex (ASA) (version 0.2, dated 14 January 2025), included with submission PM-2024-02503-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Laboratory testing & compliance with Certified Product Details (CPD)

- All batches of Briumvi ublituximab 150 mg/6 mL concentrated injection for infusion vial supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

Certified product details

- The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

- A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website:

Certified Product Details guidance [for the form]

Certified Product Details form [for the CPD guidance]

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication #