30 March 2023
EMA/173313/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Briumvi

International non-proprietary name: ublituximab

Procedure No. EMEA/H/C/005914/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AE	Adverse event of special interest
ANDA	Abbreviated new drug application
ARR	Annualised relapse rate
AUC_{0-t}	Area under the concentration-time curve from time 0 to last time point
BART	Blinded assessment relapse team
B-CLL	B cell chronic lymphocytic leukaemia
CDC	Complement-dependent cytotoxicity
CDI	Confirmed disability impairment
CDP	Confirmed disability progression
C1q	Component 1q
C_{avg} / C_{avg-ss}	Average concentration (at steady state)
CD20	Cluster of differentiation 20
CI	Confidence interval
CL	Systemic clearance
C_{max} , C_{max-ss}	Maximum concentration (at steady state)
C_{min} C_{min-ss}	Minimum concentration (at steady state)
CNS	Central nervous system
DDI	Drug-drug interaction
DMT(s)	Disease modifying treatments
DTL	Drug tolerance level
ECG	Electrocardiogram
EDSS	Expanded disability status scale
EC_{50}	Half maximal efficacy concentration
ECLIA	Electrochemiluminescence immunoassay
ePPND	Enhanced pre- and postnatal development
E-R	Exposure response
FcγRIIIa	Fragment crystallizable gamma receptor 3a
GEE	Generalised estimating equation

GLP	Good laboratory practice
GOF	Goodness of fit
HPC	High positive control
ia	intraarterial
IMPD	Investigational medicinal product dossier
IRAP	Independent relapse adjudication panel
ISR	Incurred sample reanalyses
(m)ITT	(modified) intent-to-treat
IV	Intravenous(ly)
IIV	Inter-individual variability
IRR	Infusion-related reaction
LPC	Low positive controls
mAb	monoclonal antibody
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
NEDA	No evidence of disease activity
NEL	New and enlarging T2 hyperintense lesions
NOAEL	No-observed-adverse-effect level
Q	Inter-compartmental clearance
pcVPCs	Prediction-corrected visual predictive checks
PD	Pharmacodynamics
PK	Pharmacokinetics
popPK	Population pharmacokinetics
pv	perivenous
RMP	Risk management plan
R(R)MS	Relapsing (remitting) multiple sclerosis
RSE	Relative standard error
SAE	Serious adverse event
SDMT	Symbol digit modalities test
SmPC	Summary of product characteristics
TEAE	Treatment emergent adverse event

TK	Toxicokinetics
Vd	Volume of distribution
Vp	Peripheral volume of distribution
Vc	Central volume of distribution
t½	Apparent terminal elimination

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Propharma Group The Netherlands B.V. submitted on 23 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Briumvi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied 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 (see section 5.1).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0317/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0317/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance ublituximab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26 January 2017	EMEA/H/SA/3456/1/2016/II	Valentina Mantua Fernando de Andrés Trelles

The scientific advice pertained to the following *clinical* aspects:

- The use of a population pharmacokinetics approach to characterise drug-demographic and drug-disease interactions was acceptable to CHMP in principle.
- Proposal to conduct 2 identical Phase III studies that was agreed by CHMP
- Primary and secondary efficacy endpoints: primary endpoint of annualised relapse rate (ARR) after 96 weeks of treatment and the secondary endpoints of time to onset of confirmed disability progression (CDP) for at least 12 and 24 weeks were agreed by CHMP
- Use of teriflunomide as comparator was also agreed by CHMP.

1.7. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Ewa Balkowiec Iskra Co-Rapporteur: Armando Genazzani

The application was received by the EMA on	23 November 2021
The procedure started on	24 December 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 March 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	28 March 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 March 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 November 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	03 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 January 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 January 2023

The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 February 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 March 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Briumvi on	30 March 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	30 March 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Multiple sclerosis (MS) is an inflammatory-demyelinating disease of the central nervous system (CNS) that is characterised by inflammation, demyelination, and degenerative changes (National MS Society 2020).

2.1.2. Epidemiology and risk factors

According to the MS International Federation, approximately 2.8 million people worldwide have been diagnosed with MS (Atlas of MS 3rd Edition 2020). In Europe, Germany (303 per 100,000) and Denmark (282 per 100,000) have the highest prevalence. The incidence of MS varies across regions, with rates as high as 8 to 10 new cases per 100,000 in high latitudinal regions.

MS usually begins between 20 and 40 years of age. Rates of MS are 2 to 3 times higher in women than in men and higher in regions that are further from the equator. Comorbidities are frequent in MS and have an adverse influence on outcome and adherence to treatment. MS is one of the most common causes of non-traumatic neurologic disability in young adults, and therefore, the economic impact of MS is quite significant (Wallin et al. 2019, Reich et al. 2018).

2.1.3. Aetiology and pathogenesis

The cause is not known. It is believed that a combination of genetic factors, immune system abnormalities, and environmental factors triggers the disease.

The pathophysiology of RRMS includes a well-described inflammatory component, which predominates earlier in the disease, and a degenerative component for both myelin and neurons, from the beginning of the disease but whose clinical consequences plays a more significant role as time goes on (Compston and Coles 2008, Reich et al. 2018). Approximately 85% of people who develop MS begins with Relapsing Remitting Multiple Sclerosis (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. Without a disease-modifying treatment (DMT), over the course of 2 decades, more than half of untreated patients transitioned to a phase of gradual worsening independent of acute attacks and likely the acute inflammatory changes, known as progressive MS. Progressive forms of MS can be present as the initial disease course in approximately 10% to 15% of patients (Lublin et al. 2020).

2.1.4. Clinical presentation, diagnosis

Previously, MS was classified into 4 clinical subtypes: RRMS, secondary progressive MS, primary progressive MS, and progressive relapsing MS (Lublin and Reingold 1996). 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), 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) (Lublin et al. 2014).

The main clinical feature of RRMS is the relapse defined as the occurrence new symptoms or the worsening of old symptoms, lasting more than 24 hours, and be separated from the previous attack by at least 30 days.

The diagnosis of MS is based on clinical manifestations as well as on findings in paraclinical diagnostic tests including Magnetic Resonance Imaging (MRI) and evaluation of the oligoclonal bands in the cerebrospinal fluid.

2.1.5. Management

A variety of 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 (Greenfield and Hauser 2018, Hauser and Cree 2020).

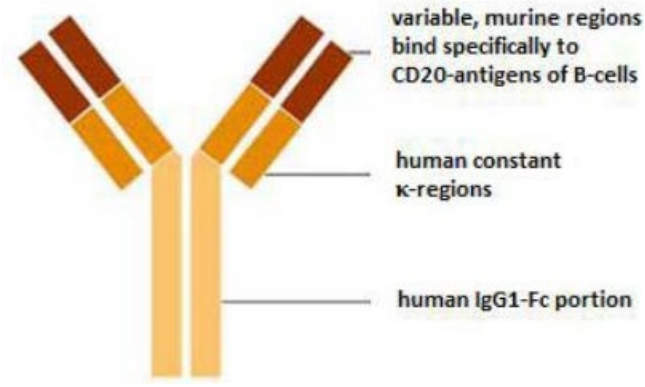
Available DMTs include injectable, oral, and infusion therapies. Monoclonal antibodies for RRMS include natalizumab, ocrelizumab, rituximab (off-label use), ofatumumab, and alemtuzumab. The FDA and EMA have approved two B cell-targeted therapies to treat MS, namely ocrelizumab (OCREVUS [ocrelizumab] USPI 2021, OCREVUS [ocrelizumab] SmPC 2021) and ofatumumab (ALIQOPA™package insert 2017, KESIMPTA [ofatumumab] USPI 2020, KESIMPTA [ofatumumab] SmPC 2021).

2.2. About the product

Ublituximab is a recombinant immunoglobulin (Ig)G1 chimeric monoclonal antibody (mAb) that targets the cluster of differentiation 20 (CD20) antigen expressed on the surface of pre-B and mature B lymphocytes. The mAb has 2 glycosylated heavy and light chains including 16 correctly paired disulfide bonds (12 intrachain and 4 interchain disulfide bonds).

It is composed of a total of 1,322 amino-acids. The human (62.8% of total amino-acids) and murine (37.2%) parts of ublituximab are represented in Figure 1.

Figure 1: Murine and Human Parts of Ublituximab



The murine and human regions come respectively from the following clones:

- CAT 13.6E12 (murine hybridoma, available as ACC 474); and
- T125A2 (human hybridoma, LFB Biotechnologies internal reference).

The measured molecular weight of 147 kDa is consistent with the theoretical molecular weight deduced from the amino acid sequence and the glycosylation of the glycoprotein. It is produced by stable expression in a clone after transfection of the rat myeloma cell line YB2/0.

2.3. Type of application and aspects on development

The applicant requested a centralised scientific advice regarding the clinical development for the treatment of relapsing MS (see above). Further, a Joint Rapporteur MAA Pre-submission Meeting was held in order to discuss the preparation of the marketing authorisation application.

2.4. Quality aspects

2.4.1. Introduction

Ublituximab, the active substance contained in Briumvi, is a chimeric monoclonal antibody produced in a clone of the rat myeloma cell line YB2/0 by recombinant DNA technology.

Briumvi is presented as a concentrate for solution for infusion in a single-use vial containing 150 mg of ublituximab in 6 mL at a concentration of 25 mg/mL. Pack size of 1 vial.

Other ingredients are: sodium chloride, sodium citrate, polysorbate 80, hydrochloric acid, water for injections.

2.4.2. Active Substance

2.4.2.1. General information

Ublituximab is a recombinant IgG1 chimeric monoclonal antibody which binds to CD20. It is a potent B cell depleting antibody with both antibody-dependent cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). The antibody is glycoengineered by its production in the rat cell line YB2/0. This cell line has reduced levels of fucosyl-transferase activity. This feature leads to lower overall levels of fucosylation leading to higher levels of ADCC mediated potency and B-cell depletion.

Ublituximab has two glycosylated heavy and light chains including sixteen correctly paired disulfide bonds (12 intra-chain and 4 inter-chain disulfide bonds). The predominant N-termini species for both the heavy chain (HC) and the light chain (LC) are modified to pyro-Glu and the predominant C-termini of the HCs include C-terminal lysine truncations. The molecular mass of the predominant species is 146781.3 Da (with glycosylation). The amino acid sequence is described in Module 3.2.S.3.1.

A glycosylation site is present on Asn298 of each HC. N-linked glycosylation sites are nearly completely occupied with predominately biantennary agalactosylated (80%), galactosylated (20%), fucosylated and non-fucosylated structures. There are less than 0.5% Man 5 and no significant levels of sialylated or O-linked glycoforms.

Additional post-translational modifications observed include methionine oxidation and asparagine deamidation at low levels at a limited number of sites. The information provided in General Information section is acceptable.

2.4.2.2. Manufacture, characterisation and process controls

Manufacturing process and process controls

The active substance is manufactured at Samsung Biologics Co., Ltd. (SBL), 300 Songo bio-daero, Yeonsu-gu Incheon 21987, Republic of Korea. It was confirmed that all sites involved in manufacture and quality control of the active substance operate in accordance with EU GMP.

The manufacturing process of ublituximab is composed of an upstream cell culture process resulting in the harvest of the cell culture fluid containing ublituximab and a downstream purification and formulation process resulting in the purified antibody. Ublituximab is manufactured at the production bioreactor scale using cell line cultured from the working cell bank (WCB). One vial from the WCB is thawed to generate culture. The culture is expanded through a series of shake flasks and seed bioreactors to meet the inoculum requirements of the production bioreactor. The manufacturing process is described in the dossier 3.2.S.2.2 in sufficient detail – flow charts and narrative descriptions are provided. Comments to the list of process parameters are provided under section 3.2.S.2.4.

Process is typical for a monoclonal antibody and involves upstream process (vial thawing, seed expansion in flasks and seed bioreactors, production in bioreactor, harvest by depth filtration) and downstream process (Protein A affinity chromatography, solvent/detergent (s/d) viral inactivation, cation exchange chromatography (CEX), anion exchange chromatography (AEX), virus removal filtration, and conditioning with ultrafiltration/diafiltration (UF/DF) followed by a final filtration of the bulk material into the final storage container which is frozen). After the addition of the stabilisation buffer, the pool is diluted to a target of 23.5 to 26.5 mg/mL with sodium citrate NaCl, polysorbate 80, pH 6.5 resulting in a ready-to-fill active substance in the formulation buffer.

Virus reduction is achieved with solvent-detergent inactivation, chromatography steps and virus 20 nm nanofiltration steps.

Bioburden-control filtrations (0.2 µm filtrations) occur between several of these steps also for preparation of media and buffers. Bioburden and endotoxin tests are performed routinely throughout the process; bioburden sampling is conducted before 0.2 µm filtration steps (pre-filtration) where possible. Reprocessing is not allowed at any step.

Maximum resins life-time – number of cycles and validated process hold times are provided in the dossier, validation reports to support them are submitted.

Critical process parameters (CPPs) have been identified for both the upstream and downstream process. The choice of CPPs is explained under 3.2.S.2.4 section. The assignment of CPPs is adequately discussed with supporting data.

The total duration of cell culture from vial thaw until harvest is considered critical to define the acceptable maximum culture time according to proven cell line stability and duration of each upstream step is stated. Pool conductivity is not monitored during Protein A step, load conductivity is not monitored during AEX step. This approach is justified by the applicant. Number of diavolumes for UF/DF step is listed as operational parameter, this parameter is classified as CPP. It was further sufficiently clarified how the composition of the solvent/detergent buffer is controlled.

Cleaning and storage procedures for resins and membranes are briefly outlined in 3.2.S.2.2. Information on bed heights, equilibration/elution buffers pH and conductivity are included in the description for chromatography steps.

Control of materials

Raw materials are adequately discussed. All raw materials with the exception of the cells used to recombinantly express ublituximab used in the manufacturing process of ublituximab are of non-animal and non-human origin. Raw materials are listed, all them are NF, Ph.Eur or USP grade. If neither, the in-house specifications are specified. The non-compendial items listed include cell culture media, purification resins, membranes and filters. The in-house specifications for non-compendial raw materials are included in 3.2.S.2.3. Compositions of buffers/media/stock solutions and components are provided in 3.2.S.2.2.

Description of the development of rat myeloma host cell line, YB2/0 is sufficiently described. A list of the animal-derived components used for cell line/bank generation is shown in the dossier. All these materials are subject to EU TSE certification and have been appropriately treated, tested and are from low-risk sources.

The expression vector is 11.1 kb in size and contains five open reading frames for the antibody heavy chain, light chain, Dhfr, NeoR and AmpR genes in the same orientation. The entire construct was verified by sequencing of both DNA strands. The restriction sites (that are shown in the figure provided in the dossier) were used for Southern blot analysis of the integration of the construct. The functional regions of the expression vector are summarised adequately. The resulting expression construct sequence is presented in the dossier – presentation of the development of expression vector is found sufficient.

The production cell line was generated after transfection of the host cell line, selection and screening of transfectants, and then limiting dilution cloning. The clones were screened, production cell line R603-12D11 was selected and adapted to serum free medium. A pre-seed stock (PSS) cell bank was prepared. The description of the generation of production cell line raises no concerns.

Preparation of master cell bank (MCB) and WCB is described in sufficient detail. The MCB and WCB were tested to confirm species identity and safety from adventitious agents in accordance with ICH Q5A requirements. MCB/WCB testing results are provided (for adventitious viruses in 3.2.A.2 section). Genotypic characterisation and testing of the cell banks are in line with ICH Q5D and ICH Q5A.

An end-of-production cell bank (EPCB) was prepared from an ublituximab active substance batch by removing a sample of the culture from the production bioreactor at day 9. The EPCB underwent 14 and 3 population doublings beyond what is typical for the process. The EPCB was genetically characterised alongside the MCB to confirm the genetic stability of the cell line over a period of time sufficient to cover the cell culture commercial manufacturing process plus a margin. Genotypic characterisation and testing of the EPCB bank are in line with ICH Q5D.

A EPCB was also prepared from ublituximab active substance of Process C2 by removing a sample of the culture from the production bioreactor at day 9. The EPCB underwent 22 and 11 population doublings beyond what is typical for the process.

Cell bank storage is addressed and described. A description how stability of the cell banks is routinely monitored is included in 3.2.S.2.3.

Generation of cell line and cell banking system is generally adequately described.

The genetic characterisation and adventitious agent testing results for a EPCB from ublituximab active substance is provided. Summary of analytical methods used to characterise and test MCB and WCBs are provided. The correlation of maximum *in vitro* cell age, qualified passage number and number of cell generations from MCB to which manufacturing process at commercial scale will be limited is clearly declared in 3.2.S.2.3 section. The requirements for establishment and qualification (retesting scheme with acceptance criteria) of future new WCB are provided. The protocol for preparation and qualification of future WCB includes genetic stability.

Control of critical steps and intermediates

Section 3.2.S.2.4 provides a description of the tests, acceptance criteria and action limits for in-process control (IPC) of critical process steps (production bioreactor, s/d and viral filtration) and other process steps employed during manufacture of ublituximab to ensure that process performance and product quality are maintained.

In addition to viral adventitious agents, bioburden and endotoxin are tested at many points in the process using validated assays. Action limits for bioburden and endotoxin testing are provided. Microbial IPCs do not raise objections. Discussion for viral testing is under Module 3.2.A.2

There are no intermediates isolated during the ublituximab manufacturing process.

The control strategy is described (in 3.2.S.2.2 and 3.2.S.2.4) as set of parameters (operational and performance) and controls. The parameters are either CPPs, key process parameters (KPPs) or non-key process parameters. In-process tests are conducted during manufacturing to ensure that the intermediate or final product conforms to its specifications. All parameters are controlled by NORs and ARs (or actions limits).

The applicant described the management of KPPs and CPPs. In the event of an excursion of a CPP from an acceptance range, a deviation is initiated with a formal root cause analysis and impact assessment. CPPs are also subject to required monitoring in the context of a Continued Process Verification (CPV). KPPs are non-critical process parameters that only impact process performance; these are controlled but not subjected to CPV.

As per definition of a parameter - which is not a CPP - its variability is considered to have no impact on a critical quality attribute (CQA). Based on this, the criticality for the following operational parameters was revised to CPPs in the applicant's response. It is also briefly described how excursions from defined action limits are addressed.

No design space is claimed.

The methods for mycoplasma, adventitious viruses and filter integrity testing are provided. The qualification reports that demonstrate the suitability of the in-process analytical methods are included in this section or reference to other sections is provided.

In response to a major objection raised during the procedure, the applicant provided a justification about the selected CQAs and CPPs. Risk assessments were provided. The rationale provided along with the support of scale-down studies (SDM) studies and process characterisation reports presented, is considered adequate to justify the choice of CQAs and CPPs.

Process validation

The process validation strategy for ublituximab is based on a traditional approach that includes the process design, process performance qualification (PPQ) stage and CPV. A risk assessment was performed prior to validation. The risk analysis was based on three rating factors: severity, occurrence and detection. The severity rating factor accounts for the potential impact on CQAs, listed in the dossier. The CQAs were identified in line with ICH Q8, Pharmaceutical Development guideline and ICH Q9. Section 3.2.S.2.6 was updated with the list of declared CQAs.

The upstream process from vial thaw to production bioreactor and harvest of all 4 PPQ batches were successfully executed. PPQ results for four batches are provided. The applicant did not mention any excursions that have occurred during validation.

The upstream and downstream process including all steps described in 3.2.S.2.2. for 4 PPQ batches were successfully executed. All CPPs and IPCs results were within their respective acceptable ranges. Additional and characterisation tests (after consecutive downstream steps) were also performed and results are provided.

The applicant presented data for process parameters for upstream and downstream process. Process parameters were within acceptable ranges. The approach generally conforms to the guideline EMA/CHMP/BWP/187338/2014. The overall approach to validation is acceptable. Process validation results to support the commercial scale (production bioreactor) manufacturing process are provided.

The results from the PPQ runs for in-process bioburden and endotoxin are provided. Results from microbial testing of the PPQ process intermediates, tested using validated bioburden and endotoxin tests, are provided together with hold times acceptance range values. The microbial stability of each in-process pool (singularly) has been validated in the small-scale vessels. Based on the data provided, the maximum hold time for each in-process pool is set. Data from small scale pool hold storage study is in 3.2.S.2.6. Pool hold times for virus filtration filtrate, AEX pool, Protein A pool and clarified harvest pool are considered justified.

A small-scale study was performed to evaluate the lifetime of resins. Each resin will be concurrently validated for use in the ublituximab commercial manufacturing process. To accept the concurrent validation approach for resins, the actions taken in case results do not comply with the defined acceptable ranges. are provided.

There is a lack of a scale down study for the UF/DF membranes. The applicant considers it as low risk. The applicant justified its position in 3.2.S.2.6 section. The criteria for determining acceptance of re-use of the membrane are generic and the same for all antibody processes- e.g. membrane flux, breakthrough, residual contaminating protein and bioburden/endotoxin after cleaning. The methods used at Samsung (SBL) are robust as they leverage multiple product experience. The cleaning step is robust, the loading of the membrane is low, the concentration is low in comparison to other products during the UF steps and the membrane is resistant to fouling. Additionally, at present these membranes have been successfully validated for reuse in other products at SBL for a range of re-uses. As a result, a concurrent validation approach is justified for the membrane lifetime study validation protocol testing and acceptance criteria. This approach is accepted, validation protocol for concurrent validation for membrane lifetime study is provided in 3.2.S.2.5.

It is indicated in the dossier that mixing studies were performed to validate the mixing in the full-scale solution preparation vessels used for solution preparation in the upstream and downstream manufacturing processes. Results of mixing studies are provided to support the operational ranges for mixing.

A chemical stability study was performed to validate the maximum hold time of the buffers used in the downstream process. The maximum hold times of the buffers were based on the last timepoint at which the results met the acceptance criteria. Validation data for buffers can be accepted.

Microbiological data performed to validate the holding times along the manufacturing process have been presented. At commercial scale, the applicant verifies the holding times using “surrogate liquid”.

Hold time for AEX eluate has not been defined. However, acceptable range for diluted neutralised eluate pool hold time during process validation is reported. The applicant has provided a clear table listing all the hold time AR in place for SBL process, along with the validated hold times in the small-scale studies.

To support validation exercise, the applicant has provided: i) Failure modes and effects analysis (FMEA) for upstream and downstream process, reporting identification of CPP and key/non-key parameters, ii) UF/DF Membrane Lifetime and storage studies; iii) Resin life-time study. A high-level tabled summary was included in module 3.2.S.2.6. The small-scale studies were used to challenge the process parameter over the entire range, while full scale data have been obtained working inside the target range.

The active substance manufacturing process has been shown to effectively and consistently remove process-related impurities to acceptable safety levels. For product-related impurities, no significant changes were seen through the downstream manufacturing process (3.2.S.2.5 and 3.S.2.6). The clearance of process-related impurities was consistent across the validation batches with active substance meeting all batch release specifications. The manufacturing-scale data demonstrate consistent removal of product variants to acceptable levels.

Risk assessment for leachables from single-use equipment is presented according to EMA/CHMP/BWP/187338/2014. The analytical procedures for the quantitation of process and product related impurities in in-process and ublituximab samples are validated or qualified according to ICH Q2R1.

Overall, the applicant has provided data to assure that the manufacturing process is appropriately validated and can produce ublituximab batches of consistent quality.

Manufacturing process development

Commercial process C2 is currently run at SBL at bioreactor scale. Process C1 was run in bioreactors. Prior to Process C, Process B1 was first manufactured bioreactors and then bioreactors (Process B2/B3). Process A was manufactured in four sequential bioreactors for early phase material needs. Process A materials were used in non-clinical and phase 1 studies. Process B and C materials were used in all phases of clinical trials and additional nonclinical studies. Changes were made to increase manufacturing scale and productivity and as needed for increased robustness, to fit into equipment at new facilities. Development, processes descriptions and changes between manufacturing processes are transparently described in sufficient detail.

Comparability studies between materials derived from processes A, B and C material has been conducted.

The analytical comparability among ublituximab batches manufactured by different processes have been assessed through batch release testing, extended characterisation and stability programs. Batches used in the pivotal trials RMS-301 and RMS-302 were manufactured by the process B2/B3 and C1. The analytical methodologies used for these batches are those described in 3.2.S.4. Data comparing early process materials, Process A, Process B1, and Process B2 are summarised as well. Stability data comparison for batches from all processes are provided. The applicant concludes that data demonstrate that all ublituximab batches are highly similar. The level of fucosylation in the pivotal trial and commercial materials are different than the earlier materials. The comparability data to evaluate ublituximab quality between batches manufactured by Process B2/B3, Process C1 and Process C2 is provided in 3.2.S.2.6. The investigated batches exhibited comparable physicochemical and biological properties and showed the consistent stability profiles. The applicant's conclusion that Process B2/B3 and Process C1 and C2 yield materials of comparable product quality is accepted.

The batches used in pivotal trials RMS-301 and RMS-302 are clearly listed in Module 3. The choice of batches only from B2/B3 process for comparability study (6.3.2 part of 3.2.S.2.6 section) is justified (not all batches are indicated).

Detailed comparability data for single batches from processes B2/B3, C1 and C2 is provided, in graphical format where applicable.

Several differences are observed across the subsequent process versions, particularly a significant change in the glycosylation profile and in the binding to FcγRIIIa (158V) and ADCC. The differences seen in the level of fucosylation in the pivotal trial material and commercial materials are justified. The applicant discussed the observed difference in fucosylation between the clinical batches and the commercial batches with respect to clinical performance and patient safety. The applicant provided adequate discussion of the observed differences between material from Process B2/B3 and Process C1 and C2. It was also further elaborated which analytical methods were used for analysis (from development stage or commercial) for fucosylation level, FcγRIIIa binding activity and ADCC.

It is noted that the acceptance criterion for cell viability is less for process C2 harvest than for process C1 harvest. The applicant discussed the effect of the prolonged culture in the production bioreactor on the observed significant drop in fucosylation levels on process C2 batches showing apparently no direct correlation to observed ADCC increase and CDC decrease (more pronounced in C2 batches). However, it is still clearly stated that culture duration may influence the fucosylation level.

Overall, the data provided in the responses in support of the above considerations sufficiently reassures about the control of fucosylation levels in process C2-derived material.

The comparability data to evaluate ublituximab quality between batches manufactured by Process B2/B3, Process C1 and Process C2 also reveals differences in glycan levels. These differences are discussed and justified that they do not impact the final conclusion of the comparability study.

Analytical methods used in comparability studies are briefly described. Qualification data for analytical methods used in comparability testing is provided.

A comprehensive comparability study between materials derived from Processes A and B1 and B2 material has been conducted. Comparative batch data comparing Process A and Process B1 are provided. The comparison of the data for Process A and B1 batches shows that the two processes materials are indistinguishable from each other, except for glycan species distribution and relative potency by the CD16 activity assay. The comparison of the data for Process B1 and B2 batches shows that these processes materials are indistinguishable from each other for all attributes. All of the data obtained during these comparison studies are corroborative, and sufficient for the conclusion that ublituximab manufactured in Process A is similar to that from Process B1 and B2.

Data from different process batches and the same stability conditions are compared. Comparison was provided to indicate that all ublituximab process batches have highly similar stability and degradation kinetics. Stability data package is overall acceptable.

The applicant provided data (mean/range result for parameters, conditions, IPCs together with acceptance ranges) for upstream and downstream B2-C2 processes. Process C laboratory-scale development studies were run similarly to the commercial process in a qualified scale down models. It is stated that several process development and characterisation studies in support of acceptance ranges were performed (production bioreactor step, harvest, Protein A chromatography step, s/d, CEX step, AEX step, virus filtration, UF/DF and formulation and filling step). The rationale for setting the acceptance range values and only the references to the underlying supporting characterisation data and documentation are shown. The active substance process control strategy is justified. The potential CPPs for the ublituximab upstream and downstream manufacturing process are evaluated or characterised through process characterisation studies designed to identify the final list of CPPs. The results of the small scale studies (process characterisation studies) supporting the process risk assessment are provided. The impact of investigated process parameters on certain CQAs is shown. Scale-down models' qualification data are provided.

Overall, process control strategy development and comparability data are acceptable. The applicant adequately addressed issues raised during the procedure (Major Objection) regarding observed differences between process versions (e.g. fucosylation levels, see above).

Characterisation

The aim of the structural characterisation was to confirm the primary structure and the higher order structure of ublituximab. The structural and functional attributes of ublituximab are described for the primary reference standard (PRS)). This primary reference standard was produced by the intended commercial Process C. As this primary reference standard was produced by process C1, it is further compared to process C2 and the previous reference standard (process B). Separately, analytical characterisation of process A and B batches are summarised. The molecule heterogeneity was defined and characterised. Various orthogonal analytical techniques were used to characterise the primary structure, carbohydrate structure, mass heterogeneity, disulfide bridge patterns, size heterogeneity, charge heterogeneity, biological functions and degradation pathways. Adequate and sufficient raw data (chromatograms, results) are provided.

Molecular weights of ublituximab were confirmed by intact and reduced mass analysis (LC-MS). Results from the intact mass analyses demonstrated a high level of conformance among the active substance samples. For all analysis, the experimental molecular weight matches the theoretical masses. The analysis verifies the consistency of the primary protein sequence with cDNA. The agalactosylated N-glycan forms are the predominant glycan species. Minor levels of other N-glycans such as the galactosylated glycans are also observed.

The extinction coefficient was established experimentally and the results and conclusions are included.

To verify the amino acid sequence of ublituximab deduced from the DNA sequence, liquid chromatography mass spectrometry (LC-MS) peptide mapping analysis on reduced and alkylated samples was performed. 100% sequence coverage was accomplished for ublituximab combining the two digestions. For all peptides identified, the mass accuracy was within 5 ppm from the theoretical values. In addition to verifying the amino acid sequence of ublituximab, the peptide mapping analysis enabled the detection and relative quantitation of post-translational modifications. Oxidation was identified on several sites. This level of oxidation is similar among the three process batches. Deamidation was observed at multiple asparagine sites The level of deamidation is comparable among the three process batches. Glycosylation was identified on the peptide containing the conserved N-glycosylation site Asn-298 of the heavy chain. The peptide that did not contain a glycosylation modification was also measured. This non-glycosylated peptide was identified at levels around 10% for the three process batches. Primary sequence and post translational modifications data obtained by -MS peptide mapping is found acceptable.

Edman sequencing was used to confirm the N-terminus identity of the earlier reference material and the primary reference standard. The data are sufficient.

The molecular size distribution of reduced and non-reduced ublituximab was investigated by electromobility rate using capillary gel electrophoresis.

A set of characterisation methods was applied to evaluate the higher order structure of ublituximab: circular dichroism, disulfide bond pairing analysis by LC-MS, free sulfhydryl analysis, dynamic light scattering (DSC), size-exclusion chromatography with multi-angle light scattering (SEC-MALS) and analytical ultracentrifugation (AUC).

Characterisation by SEC-MALS and AUC indicate that ublituximab consists of predominantly monomer, along with a small amount of dimer. Low levels of higher order aggregate and fragment were measured.

The unpaired cysteines are quantitated by a colorimetric Ellman's assay. Free thiols are measured at 0.68 mole free thiol/mole ublituximab for the primary reference standard.

Primary and higher order structure have been investigated in sufficient detail.

The charge heterogeneity was quantitatively assessed. icIEF technique were used to show the level and the distribution of the major charge variants. Batch analysis with icIEF demonstrated consistency of this quality attribute. The charge isoforms observed include the main peak, dispersed peaks in the acidic area, and two distinct peaks in the basic area. Ublituximab contains five charge variants: two individual acidic peaks, a main peak, and levels of basic variants. The icIEF method is stability indicating. The increase in the percent acidic species for the degraded samples correlates with decreases in functional binding and potency for all measures.

Analysis of the acidic and basic fractions showed that the enriched acidic and basic species pools all have similar binding and biological activities although the acidic species enriched fraction trends lower for CD20, CDC and ADCC due to both the expected increase in deamidation abundance as well as increased distribution of fucosylated glycoforms during cation exchange chromatography fractionation.

N-linked glycans are enzymatically released from the protein by PNGase F and derivatised by 2-AB, followed by NP chromatography coupled to fluorescence detection. Peak identifications are made based on retention time referencing to glycan standards and has also been confirmed by LC-MS analysis. Batches manufactured by Process B, C.1, and C.2 have comparable levels of galactosylated glycan species. The applicant states that the difference in fucosylated glycan levels has a small impact on the FcγRIIIa binding activity and ADCC activity. Man5 is the only high mannose species observed for all batches and the relative abundance is consistently low.

Ublituximab is an anti-CD20 monoclonal antibody with a wild type human IgG1 Fc domain. Key mechanisms of action of ublituximab include ADCC and CDC, which are facilitated by binding to FcγRIIIa and C1q, in addition to binding to the ligand CD20. The active substance also binds to other Fcγ receptors and FcRN. The binding of Ublituximab to CD20, Fc receptors, and C1q have been characterised through the product development. CD20 binding was also characterised using both FACS assays and an Meso Scale Discovery (MSD) assay. Binding affinities of ublituximab to the entire panel of Fc receptors were characterised using an Octet assay. Binding of ublituximab to FcγRIII 158V and FcγRIII 158F were characterised by surface plasmon resonance. Binding of ublituximab to C1q was characterised by an ELISA assay. More recently, a cell based CD20 binding assay, a surface plasmon resonance based FcγRIIIa binding assay, and an ELISA based C1q binding assay have been optimised and validated. These binding assays use the commercial reference standard RS-117808 as the reference standard and report relative binding potencies. These assays are also in active substance release tests panel. Batch data together with dose dependent response curves are provided in the dossier.

The applicant provided information about the epitope / region recognised by ublituximab on CD20 target, in compliance with relevant guideline (ICH Q6B).

CD20 binding of all batches representing range of clinical experience are comparable whether manufactured by Process B or by Process C1 or by Process C2. The data shows that Process C1 and C2 batches have comparable FcγRIIIa binding activities, and process C batches appear to have consistently higher FcγRIIIa binding activates than the process B batches. This range of FcRIIIa binding activities is representative of clinical experience. Process B and Process C1 batches and Process C2 batches have comparable C1q binding activities. Ublituximab is active *in vitro* in all assay formats and exhibits ADCC, CDC, and ADCP (antibody-dependent cellular phagocytosis) activities. The data shows that Process C batches have higher ADCC activity than the Process B batches, even though the ranges overlap. Process C1 batches and Process C2 batches have comparable ADCC activities. There is an inverse relationship between the ADCC activity and the level of total fucosylated glycans in the range of 40%-60%

fucosylation levels using data generated from the validated KILR ADCC assay. In the range of 20%-40% fucosylation levels, however, ADCC activity seems not to be affected by fucosylation levels. Process B and Process C1 and Process C2 batches have comparable ADCP and B cell depletion activities.

The average of CDC activity seems to shift towards slightly lower levels during the development of the process up to the commercial Process C2, with a trend that appears diametrically opposite to that observed with ADCC. To this regard, the applicant has discussed the correlation between CDC and galactosylation (total and / or sub-species) providing supportive data showing that there is no noticeable correlation between the galactosylation level and the CDC activity for ublituximab. In addition, it is clarified that the galactosylation level is inversely related to G0 and therefore is indirectly controlled by the specification limits of G0.

For release and stability testing, an ADCC KILR assay that uses CD20 expressing Raji cells as target cells (CytoTox Glo is used to quantify cell lysis) has been optimised and validated. As a potency assay, the relative potency is reported using RS-117808 as the primary reference standard. Also other potency assays are included in the active substance specification: CDC activity, CD20 binding activity, FcγIIIRa binding by SPR, C1q binding by ELISA assays. Ublituximab samples were exposed to stress conditions (UV light treatment, high temperatures, low pH, high pH, freeze/ thaw cycling, oxidation, and agitation, using GMP3b (Process B) to evaluate the potential degradation pathways and stability-indicating properties of analytical methods. Dimerisation, backbone cleavage, hinge region disulfide exchange, deamidation and oxidation were identified from these studies as the primary degradation pathways. The glycans remain unaffected by the stress conditions. Forced degraded samples have been characterised for their biological activity by multiple assays. The stressed stability potency testing results also indicate that the degradation process leads to concomitant reduction in activities, including ADCC and CDC activities, as well as binding to CD20, FcγRIII and C1q.

Impurities

Process-related impurities and product-related impurities have been adequately characterised. The information provided in the dossier is acceptable. Overall, the level of characterisation of ublituximab is adequate.

2.4.2.3. Specification

Specifications

The active substance specification include control of identity, purity and impurities and other general tests. Overall the list of tests is in line with ICH Q6B, EMA/CHMP/BWP/532517/2008 and Ph. Eur. Unique method identification numbers are included in specifications.

The overall approach to establish and justify the commercial specifications for ublituximab were based on reference and compendial requirements, the knowledge gained from process development and product characterisation studies which have defined CQAs, an understanding of the manufacturing process capabilities and processing limits, the analytical procedures limitations as confirmed through method validation, and the product stability profile. Statistical analysis was also performed.

The overall approach in the justification of specification is considered acceptable. The specifications reflect approximately 2.5 to 3 standard deviations (SD) of the clinical experience and commercial batch dataset, resulting overall more adequate also in consideration of the consistency of the process.

Module 3.2.S.4 appropriately points the active substance specification for release and shelf-life. However, it is noted that not all the tests proposed in the active substance release specifications are included in

stability studies, where 3 of the 5 potency assays are missing, including CD20 binding. This is generally justified. Reference is made to the finished product stability section.

With regard to the size exclusion high performance liquid chromatography (SEC-HPLC) method, the applicant stated that the acceptable ranges reflect approximately 2.5-3 SD of the commercial datasets and are supported by the clinical experience. The applicant revised attributes grouping in the active substance release and specification.

Regarding the absence of total galactosylated species in the specification, the applicant pointed out that the total galactosylation level is indirectly controlled by the specification limits of G0. The specification range for G0 provides for a narrow range for the control of the total galactosylated species. This is considered acceptable.

Analytical procedures

The applicant describes all analytical procedures used for active substances release and shelf-life analysis. Compendial methods are for appearance, osmolality, pH, bioburden, endotoxin; in-house methods are for: identity by peptide mapping, UV for protein concentration, for purity icIEF, SEC-HPLC, CGE (reduced and non-reduced), hydrophilic interaction ultra-performance liquid chromatography (HILIC-UPLC), two ELISA methods for HCP and Protein A, quantitative polymerase chain reaction (qPCR) for DNA, for potency in-house ADCC, CDC, CD20 Binding Activity, FcγIIIRa binding by SPR, C1q binding by ELISA assays.

The choice of procedures to measure respective attributes is appropriate. In-house methods descriptions are sufficient (with chromatograms, standard curves, dose response curves and system suitability test (SST) criteria).

In-house methods (release and in-process) have been validated and compendial methods were qualified. The applicant provided sufficient method transfers data. The applicant provided, in addition to the summary of validation criteria and results, the validation reports of experimental methods.

To support the selection of the potency assays and consistent potency control throughout product lifetime, the validation exercise demonstrated that the chosen cell-based potency assays for release and stability testing and relevant acceptance criteria are capable to detect subpotent batches.

Several methods adaptations were introduced during development. However, the data used for the comparability exercise and for setting the specifications were either generated with the same assay or, when the versions of the assays were different, they were appropriately corrected before inclusion. To this regard, the applicant provided adequate information concerning the relevant conversion factors (for cIEF and SEC) derived from the evaluation of multiple active substance lots by means of previous and updated methods in order to ensure both data sets can be evaluated on a consistent basis.

The rationale for the selection of stability-indicating methods, to be included in the stability specification panel, has been provided.

Batch analysis

Batch analysis data has been provided for all batches described in the dossier: from processes A, B1, B2/B3, C1, PPQ and C2 (in summary 66 batches). All batches were within specification and the data is corroborative and consistent across manufacturing runs. A summary of additional methods incorporated to batch assessment as well as changes associated with the historical development and release of the product are provided too.

Reference standard

A two-tiered reference standard programme is proposed from lots representative of production and clinical materials to ensure consistency and continuity of the ublituximab quality.

Preparation, characterisation and qualification of the current PRS is adequately described. The PRS will be used to qualify new working reference standards (WRS).

Primary reference standard is well-characterised and qualified by testing according to the release specification and extensive structural characterisation tests. Results are provided. . The certified standards are monitored via formal stability studies. Sufficient information of the container for reference standards is included. The primary Reference Standard n RS-117808-80 is derived from batch RS-117808 (GMP16) manufactured with process C1. Tests results have been provided with respect to the 5 potency assays to determine potency at active substance release.

The applicant, as requested, tightened the PRS and WRS qualification acceptance criteria for icIEF, N-glycan profile, ADCC, CDC, C1q binding by ELISA and CD20 binding activity.

The applicant also provided the lists extended characterisation tests (and corresponding acceptance criteria) for the qualification of future PRS and WRS.

Container closure

The container closure system (CCS) for ublituximab is Celsius Flexible Freeze Thaw (FFT) bags or equivalent. They are single-use multilayer bags with a product contact layer of EVA (ethylene vinyl acetate) copolymer and an outer layer of EVOH (ethylene vinyl alcohol). Container specification is registered in 3.2.S.6 section.

2.4.2.4. Stability

A preliminary shelf life of 36 months is proposed. Stability programme is in accordance with ICH Q5C.

The stability data for ublituximab include 36-month data for three registration stability studies for the active substance batches manufactured with Process C2. In addition, up to 60 months of stability data for five active substance batches from process C1, B3 and B2, as well as one active substance batch from Process B1 are also presented as supportive studies. All stability results met the acceptance criteria at the intended storage condition. The applicant concluded that overall data support the proposed 36 months of shelf life for commercial ublituximab active substance at the intended storage condition.

No statistical analysis of stability data has been provided, since the proposed commercial active substance shelf life of 36 months is based on actual 36-month long-term intended storage condition data of the three registration batches and no trend was observed on any attribute.

Bioburden and endotoxins are added in future time points in the three registration stability studies (48 and 60 months).

The stability specifications do not include CD20 (see above). Conversely, forced degradation study results experimentally supported that N-glycan method is not stability-indicating.

The supportive stability studies used different container closure system (30mL Nalgene polycarbonate bottles with 25 mL fill) from the registration stability studies (30mL Celsius bags).

Overall, the proposed shelf life of 36 months is agreed.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product

Briumvi is presented as a concentrate for solution for infusion for IV administration. It is a sterile solution containing 150 mg of ublituximab in 6 mL (concentration 25 mg/mL). The final concentration after dilution is approximately 0.6 mg/mL for the first infusion and 1.8 mg/mL for the second infusion and all subsequent infusions.

The CCS is a single-use Type I, colourless glass vial with siliconised chlorobutyl rubber stoppers that contain a barrier film and sealed with aluminum caps with a plastic button.

The finished product excipients are sodium chloride, sodium citrate, polysorbate 80, hydrochloric acid, water for injections.

Ublituximab is a colourless to slightly yellow, clear to opalescent, essentially particle free liquid. Ublituximab active substance is manufactured to include the final formulation excipients and is ready-to-fill during finished product manufacture. The osmolality and pH of the product are compatible with an intravenous route of administration. PS80 is included in the active substance formulation as a stabiliser to prevent IgG aggregation during freezing, storage and thawing of the active substance and manufacturing, storage, and shipping of the finished product.

All excipients comply with USP and Ph. Eur. requirements. No excipient of animal or human origin is used in the formulation of ublituximab.

Pharmaceutical development

Formulation development has been clearly described. Initial formulation development was performed targeting the 10 mg/mL ublituximab concentration (the product concentration chosen for initial clinical trials) with a long-term storage at 5°C for both active substance and finished product. Excipients were chosen based on previous experience with development of IgG1 antibodies. Antibody product quality was evaluated during these initial studies using a variety of physiochemical methods to select the formulation that provided the best product stability under stress conditions such as high temperature, agitation, and oxidation. The development results confirmed the suitability of buffer and excipient. The objective of the 25 mg/mL formulation was to provide a higher product concentration more suitable for frozen storage of active substance and smaller finished product vials. Results from the freeze/thaw and thermal stability studies provide confirmation that the 25 mg/mL formulation is suitable for use at the active substance and finished product intended storage conditions.

Following a major objection during the procedure, the applicant provided a detailed description of manufacturing process development. Obtained results have been summarised in tabular form. Manufacturing process development data is in line with ICH Q8. The applicant amended manufacturing development section with information on the choice of critical parameters impacting product performance and on control of these parameters.

The ublituximab container closure system consists of a Type I borosilicate vial closed with a siliconised rubber stopper. The stopper contains a FluroTec coating on the product contact surface. The flip-off seal consists of aluminium and polypropylene. The container closure system has been discussed and extractable and leachable studies have been performed and the adopted methodology and the selection of used solvents adequately justified. No overfill has been defined. According to the specification each vial should contain ≥6.0 mL of solution.

Ublituximab injection for IV administration is manufactured as sterile single use vials. Vials are washed and depyrogenated prior to use. Stoppers are received ready to use from the supplier. Details on the stopper sterilisation method and cycle have been included in relevant CTD sections. Seals are received ready to sterilise from the supplier and they are steam sterilised at the finished product manufacturer prior to use. Prior to filling in sterile, depyrogenated vials, ublituximab is sterilised by filtration.

Compatibility studies for ublituximab administration have been performed. Ublituximab injection for IV administration was prepared by dilution into different sterile diluents, including normal saline and 5% dextrose. Polyvinyl chloride (PVC) and polyolefin (PO) infusion bags and intravenous lines have been studied. Administration with or without an in-line 0.2 µm filter was tested. Ublituximab is stable up to flow rates of 500 mL/hour.

The applicant has presented data to justify the use of in-line filters.

2.4.3.2. Manufacture of the product and process controls

Manufacturing process and process controls

SBL is responsible for finished product manufacture. Millmount Healthcare, Block 7, City North Business Campus, Stamullen, Co. Meath, Ireland K32 YD60 is responsible for final EU release. It was confirmed that all sites involved in manufacture and quality control of the finished product operate in accordance with EU GMP.

The manufacturing process of the finished product consists of the following steps: Sterilisation/Depyrogenation of Primary Container Closure and Processing Components, Thawing of Active substance, Filtration, Pooling, and Mixing of Active substance, Sterile Filtration, Filling, Stoppering and Capping, Visual Inspection and Bulk Packaging, Labelling and Secondary Packaging.

Manufacturing process as well as its control has been described in sufficient details. Major equipment has been specified.

Process validation

Process validation data have been presented.

It has been stated that holding time studies has been performed on one batch. Other two validation batches were manufactured using parameters within acceptable ranges. Batches used in hold time studies have been clearly characterised.

The manufacturing process and the cleanliness level adopted during filtration, pooling and mixing of the Active substance (Grade C) and during the final sterile filtration and filling operation of the Finished product (Grade A with Grade B background) is found adequate. In fact, active substance Bag Pooling and Sampling as well as active substance Bag Mixing take place in Grade C environment. Once in the mixing bag, the system remains closed with sterile-to-sterile closed-system connectors up to the filling needles in the Grade A RABS. A pre-sterilised disposable transfer line is passed from the Grade B vial filling room to the pooling bag located in Grade D, found acceptable as at this stage the system is closed and aseptic connectors are used.

The process validation on the 4 PPQ lots cover the range for active substance thawing time. The active substance thawing is limited to the thawing time challenged.

The impact of transport on product quality and integrity was assessed through real time shipping validation studies performed at a minimum and maximum shipment load (and storage conditions).

Module 3.2.P.3.5 includes data and summaries of the shipping validation studies performed on the finished product. These studies included shipping of the finished product from the manufacturer, Samsung Biologics in South Korea, to a secondary packaging facility in the United States (US), then on to a storage/distribution depot also in the US. Over the course of shipping, the product was exposed to the challenges associated with both air and ground transportation. The studies involved both minimum and maximum loading conditions and were executed during both summer and winter to challenge environmental temperature extremes. The studies evaluated chemical and biological activity stability of the product through analytical testing following shipping execution. In addition, physical attributes were evaluated which included thermal monitoring, primary container/closure integrity testing, and secondary/tertiary packaging conditions. Data from the studies indicate that the supply chain controls for the shipping of ublituximab were sufficient to protect the product chemical and physical attributes. The risk of product shipping routes to Europe were evaluated.

Overall, finished product process validation is considered satisfactory.

2.4.3.3. Product specification

Specifications

Specifications for the finished product include control of identity, purity and impurity, potency and other general tests. In general, the panel of tests are in line with ICH Q6B.

Detailed justification of the proposed specification has been presented.

The exclusion of CD20 binding from the finished product release specifications was not endorsed, since essential to monitor the 'selectivity of action' of ublituximab (which is key in the mode of action and underlies the cell lysis measured in the ADCC and CDC assays). The applicant revised the specification to include CD20 binding at release. This may be reconsidered once an appropriate amount of data will be collected post-approval by the applicant. Any revision of the specification would require the submission of an appropriate variation application.

No shelf life specification for CD20 binding is included, which is acceptable for the marketing authorisation application and reference is made to the finished product stability section.

The acceptance criteria for appearance in Module 3.2.P.5.1 has been aligned with the Ph. Eur. Monograph as well as the acceptance criteria on colour and opalescence. In addition, the acceptance criteria for extractable Volume have been updated in Module 3.2.P.5.1 to 6.0-6.5 mL.

The applicant provided the description of the characterisation method used to assess the variation of PS80 composition from lot to lot, due to a possible degradation. It was agreed not to include PS80 in the release testing panel for active substance and finished product. However, the applicant will implement and validate an HPLC analytical method to measure PS80 concentration for ublituximab finished product at release and stability (see CHMP Recommendations).

Analytical procedures

Compendial analytical procedures follow the current edition of the referenced pharmacopeia. For non-compendial analytical methods already presented in the active substance section, corresponding reference has been provided, what is acceptable. The container closure integrity test (CCIT), performed by Dye Penetration as IPC for finished product samples, has been described.

Non-compendial methods used for release and stability testing of ublituximab are the same as the non-compendial methods used for release testing of ublituximab. The analytical qualification results provided

in Module 3.2.S.4.3 for ublituximab active substance are also applicable for the finished product. Method validation report for CCIT has been provided.

Characterisation of impurities

Adequate information on potential impurities has been presented. A summary of the outcome of the Risk Analysis on elemental impurities performed in line with ICH Q3D guideline (currently Ph. Eur. requirement) has been provided. A risk assessment concerning the presence of nitrosamine impurities in the product has been submitted by the applicant in Module 1 and the outcome of nitrosamine risk assessment has been also presented in sections 3.2.P.5.5 and 3.2.P.5.6. No issue has been identified and no specific controls are deemed necessary.

Batch analysis

Batch analysis data for over 50 finished product batches have been presented, corresponding to all ublituximab completed GMP and development batches made to date including active substance batches and their corresponding finished product lots.

Reference standard

The reference standards for finished product are the same as used for active substance testing.

Container closure system

The primary packaging consists of a Type I borosilicate vial closed with a siliconised rubber stopper. The outer packaging is cardboard box. Specifications and representative certificates of analyses for each element of primary packaging has been presented. Manufacturers of each component of primary packaging have been defined. The stoppers are steam sterilised and are received only ready to use from the supplier. Details on the stopper sterilisation method and cycle have been provided. Stoppers are steam sterilised by the supplier in an autoclave with a minimum temperature of 121°C for a minimum of 15 minutes (in accordance with Ph. Eur. 5.1.1). The name and address of the site of sterilisation is available.

Analytical procedures used during control of primary packaging have been described.

2.4.3.4. Stability of the product

A shelf life of 3 years when stored at 2-8°C protected from light is claimed.

36 month stability data at 5°C (2-8°C) for three registration stability studies for the 150 mg finished product batches manufactured at SBL from the commercial process, accompanied with 6-month accelerated and stressed stability data (25°C/60% RH and 40°C/75% RH) have been provided. In addition, 36 months of data for ten batches at 5°C (2-8°C), supported by 6-month accelerated and stressed stability data (25°C/60% RH and 40°C/75% RH) have been also presented as supportive studies. The data are trended and compared. Also photostability data have been presented. Photostability data show that the finished product is sensitive to high level of visible light and UV exposure.

Binding assays, particularly towards CD20, are essential to monitor the 'selectivity of action' of ublituximab (which is key in the mode of action and underlies the cell lysis measured in the ADCC and CDC assays). The applicant provided as requested a full panel of data including 5 lots of finished product stored at 5°C for up to 36 months to show that there is no direct indication of CD20 instability at any condition of normal storage or use of the finished product. The data provided do not call for comment and in the context of this MAA it is agreed not to include CD20 binding in the shelf-life specification.

The applicant committed to enlarge the CD20-binding database for finished product release and stability data for the 3 ongoing finished product stability batches, in order to evaluate any change on this attribute and the eventual lack of correlation with ADCC and CDC (see CHMP Recommendations).

Overall, thirty-six months shelf life for ublituximab finished product at the storage condition of 2-8ºC protected from light is considered acceptable.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and subsequently for 8 hours at room temperature.

From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C and subsequently for 8 hours at room temperature, unless dilution has taken place in controlled and validated aseptic conditions.

2.4.3.5. Post approval change management protocol(s)

Not applicable.

2.4.3.6. Adventitious agents

Controlled sourcing of raw materials is the primary defence against introducing causative agents of TSE and BSE in the manufacturing process. The use of animal materials (no animal derived materials except cell line) is compliant with the effective version of EMA/410/01. Active substance and finished product therefore pose minimal/negligible risk for transmission of TSE and BSE.

Extensive testing for endogenous and adventitious viral agents has been conducted for the expression cell lines, MCBs and WCBs and EPCB to ensure that the cell banks are free from detectable adventitious viral contamination.

Bulk harvest is tested for the absence of mycoplasma, adventitious viruses (using several *in vitro* virus assay indicator cell clines). This is in line with ICH Q5A.

Bulk testing is performed on the production bioreactor as an IPC during production of each lot confirmation of the presence of infectious adventitious agent will lead to lot rejection.

The ublituximab purification process includes several steps for virus reduction. Two viral validation studies reports have been provided, both covering the entire manufacturing process. The studies used four model viruses: Xenotropic Murine Leukemia Virus (XMuLV), Minute Virus of Mice (MVM), Reovirus (REO-3), and Pseudorabies Virus (PRV). They cover a range of virus characteristics on scaled-down models including Protein A chromatography, solvent detergent viral inactivation, anion exchange membrane chromatography, and viral filtration. Inhibition, toxicity and interference testing were performed before the study. Scale-down models were also assessed for their representativeness. Virus reduction factors for the four model viruses demonstrate a robust viral clearance capability for the manufacturing process. According to the ICH Q5A guideline, the applicant provided a calculation of estimated particles per dose, considering the limit of detection (LOD) of the transmission electronic microscopy (TEM) method used to reveal any presence of retrovirus-like particles (RVLP). The average endogenous virus-like particles found in the unprocessed bulk samples from three representative runs is reduced to significantly less than 2 particles in a million doses (TEM results).

Overall, these data support that the viral safety of ublituximab finished product for commercial use is according to ICH Q5A.

The applicant provided demonstration of the robustness of viral clearance of reused columns where applicable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The provided Module 3 dossier is well-structured and divided into active substance and finished product parts, followed by Appendices and Regional Information. The dossier was updated satisfactorily following questions asked during the procedure.

No additional issues that would trigger a GMP inspection have been identified during the assessment of the information in the Module 3, all GMP issues were properly addressed.

In response to a major objection raised during the procedure on the active substance process control strategy, the applicant provided a justification about the selected CQAs and CPPs. Risk assessments were provided. The rationale provided along with the support of scale-down studies (SDM) studies and process characterisation reports presented, is considered adequate to justify the choice of CQAs and CPPs.

The applicant adequately addressed comparability issues (Major Objection) raised during the procedure.

Following a major objection raised during the procedure, the applicant provided a detailed description of finished product manufacturing process development. Obtained results have been summarised in tabular format. Manufacturing process development data is in line with ICH Q8. The applicant amended manufacturing development section with information on the choice of critical parameters impacting product performance and on control of these parameters.

The applicant implemented the request to include CD20 binding in the finished product release specifications as part of the control of biological activity.

Recommendations for future quality development have been agreed (see section 2.4.6).

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Briumvi is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Briumvi is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant is recommended to enlarge the CD20-binding database for finished product release and stability data for the 3 ongoing finished product stability batches, in order to evaluate any change on this attribute and the eventual lack of correlation with ADCC and CDC.
- The applicant is recommended to implement and validate an HPLC-CAD method to measure PS80 concentration for ublituximab finished product at release and stability.

2.5. Non-clinical aspects

2.5.1. Introduction

Ublituximab is a recombinant IgG1 chimeric monoclonal antibody which binds to CD20. Ublituximab is produced in the rat cell line YB2/0. This cell line has reduced levels of fucosyl-transferase activity resulting in antibody glycoforms incorporating less fucose content.

This submission document deals with the properties of ublituximab that support its use in the treatment of RMS through IV administration. Moreover, other anti-CD20 mAbs (rituximab, obinutuzumab, ofatumumab and ocrelizumab), some of those (ofatumumab and ocrelizumab) already approved for the treatment of MS, are used as comparators.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

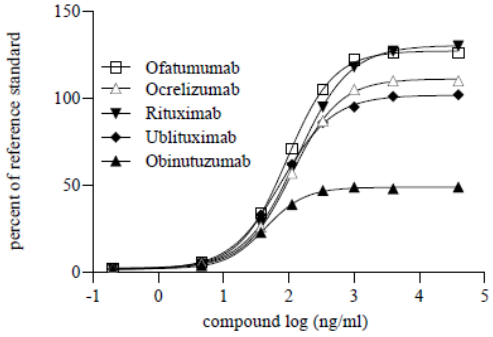
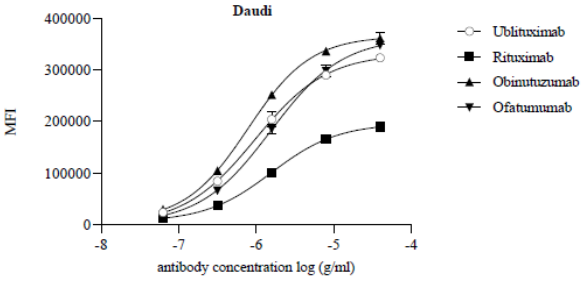
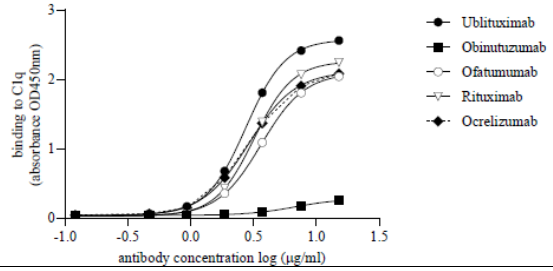
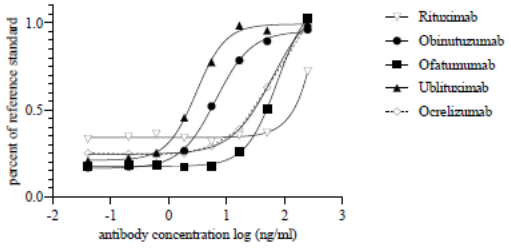
Ublituximab was evaluated in a series of *in vitro* studies that determined the binding and activity of ublituximab primarily using cancer derived cell lines (Table 1). In the majority of these studies, the activity of ublituximab was compared to that of rituximab, the first-in-class anti-CD20 therapeutic mAb, and other anti-CD20 mAbs such as ofatumumab and obinutuzumab. *In vitro* pharmacology studies evaluated target-binding properties, functional activity (i.e., ADCC, antibody-dependent cellular phagocytosis [ADCP], and CDC) in cell-based assays, as well as B-cell depletion in whole blood samples.

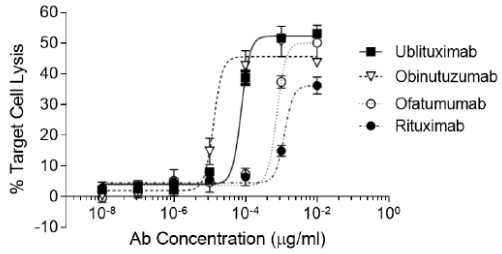
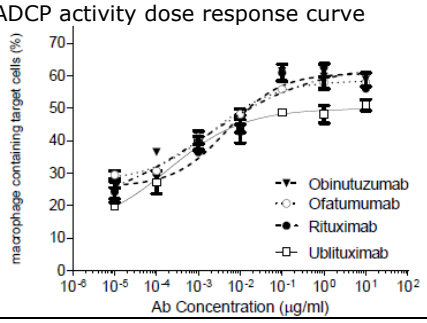
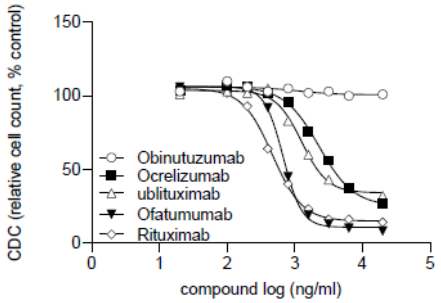
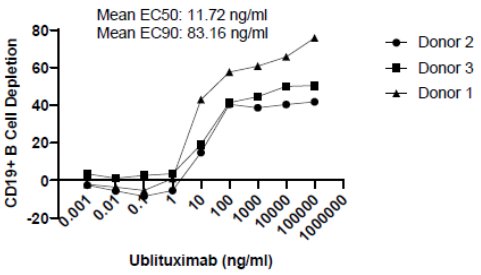
Ublituximab recognises and binds to a novel human epitope on the CD20 antigen that is apparently not targeted by other anti-CD20 mAbs on the market, including ocrelizumab and ofatumumab which are approved for the treatment of RMS. Ublituximab binds to its CD20 target antigen with a low nanomolar affinity that is similar to that of rituximab. The Fc region of ublituximab binds to Fc receptors with a higher affinity than rituximab, conferring a more robust effector cell response than rituximab in measures of ADCC, ADCP, and B-cell depletion. The difference in Fc receptor affinity is especially evident at low antibody concentrations where effector functions triggered by Fc binding demonstrate that ublituximab is more effective than rituximab in promoting target cell lysis.

In measures of ADCC, ublituximab induced higher cytotoxicity when compared to rituximab, ocrelizumab, and ofatumumab. In functional CDC assays, ublituximab results were comparable to those of rituximab at high antibody concentrations but were slightly weaker when submaximal concentrations of antibodies were added. Ublituximab and rituximab mediated ADCP similarly. The reduced levels of fucose in ublituximab glycosylation of the human IgG1-Fc-portion is claimed to be associated to the higher ADCC vs ocrelizumab> ofatumumab> rituximab observed on lymphoblast-like Raji cells and on NK cells.

Both ADCC and CDC contributed to B-cell depletion in whole blood. In whole blood from healthy human donors, ublituximab was more effective in depleting B cells than rituximab and ofatumumab at low concentrations. When high concentrations of the antibodies were tested, ublituximab, rituximab, and ofatumumab generally resulted in similar levels of B-cell depletion.

Table 1: In vitro primary pharmacodynamics studies performed with ublituximab

Type of Study/Study no	**Test system or protocol**	**Noteworthy Findings**
Epitope mapping **R-08-204**	Peptide scanning identified the CD20 epitope recognised by ublituximab as NFIRAHTPYIN IYNCEPANPSEKNSP. The underlined residues are the most important for binding.	
Cell Surface CD20 Binding in Jeko-1 cell line **TGDOC-2020-037: COA_295-8888-090**	The ranking in potency (i.e., the maximum level of binding) of all five antibodies tested was as follows: ofatumumab = rituximab > ocrelizumab = ublituximab > obinutuzumab.	CD20 Binding Dose Response Curves in Jeko-1 Cells 
Cell Surface CD20 Binding in Daudi and Raji cell lines **TGDOC-2020-037: SR5308**	Calculated EC_{50} values were similar for all four antibodies: 0.983, 1.59, 0.793 and 1.57 µg/mL for ublituximab, rituximab, obinutuzumab and ofatumumab, respectively in Daudi cells.	CD20 Binding Dose Response Curves in Daudi and Raji cell 
FcγRIIIa 158V and 158F Binding **TGDOC-2020-037**	Ublituximab had the highest FcγRIII binding affinities compared to the other 4 anti-CD20 antibodies and demonstrated a 4-fold higher affinity than ocrelizumab toward 158Vand 3-fold higher affinity for 158F.	
FcγR Binding **TGDOC- 2020-037: SR16841**	Strong binding of ublituximab to all FcγRIII receptors when compared to other anti-CD20 antibodies.	
C1q Binding **TGDOC-2020-037: COT_295-8888-088**	Obinutuzumab displayed minimal C1q binding whereas the 4 other anti-CD20 antibodies, including ublituximab, showed similar binding activity to C1q.	C1q biding dose response curve 
Functional ADCC assay in KILR CD16a modified T cells **TGDOC-2020-037: COA_295- 8888-091**	Ublituximab and obinutuzumab displayed lower EC_{50} values, corresponding to greater ADCC than ofatumumab, rituximab, and ocrelizumab.	ADCC activity dose response curve 

Type of Study/Study no	Test system or protocol	Noteworthy Findings
Functional ADCC assay in Raji cell line **TGDOC-2020-037: U8228BI200**	In the presence of NK cells from patients with B-CLL, ublituximab was more effective at inducing lysis of Raji cells. Ublituximab EC_{50}=0.1 ng/mL Rituximab EC50=8 ng/mL The degranulation marker CD107a indicated that CLL NK cells were activated more by ublituximab (mean=45.7%) than rituximab (mean=14.1%).	ADCC activity dose response 
Functional ADCP assay in Daudi cell line **TGDOC- 2020-037: U3459BI200**	All antibodies exhibited similar dose-dependent phagocytosis activities with EC_{50} values in the range of 0.331 to 7.64 ng/mL.	ADCP activity dose response curve 
Functional CDC assay in Jeko-1 cell line **TGDOC- 2020-037: COA_295-8888-089**	Rituximab and ofatumumab demonstrated comparable CDC activity and higher than the CDC activity of ublituximab and ocrelizumab.	CDC activity dose response curve 
B-Cell Depletion in Human Donor Whole Blood **TGDOC-2020-037: TD4557**	Ublituximab and obinutuzumab demonstrated greater B cell depletion than ofatumumab, rituximab, and ocrelizumab in 3 human donors.	Ublituximab B-cell depletion in human donor whole blood 

EC_{50}: half maximal efficacy concentration; FcγRIIIa, fragment crystallizable gamma receptor 3a; CD20, cluster of differentiation 20; C1q, component 1q; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; B-CLL: chronic lymphocytic leukaemia

B cell depletion by ublituximab was also observed in *in vivo* mouse models of the clearance of cells derived from a patient suffering from B cell chronic lymphocytic leukaemia (B-CLL). Immunodeficient SCID (B and T cells deficient) and SCID-NOD (B and T cells deficient, deficient in complement activity, showing reduced NK cell and macrophage activity) mice were used.

The assays performed in the SCID mice demonstrated the efficacy of ublituximab administered at 10, 1, 0.1 mg/kg to induce significant clearance of B-CLL cells (> 80%). At the highest dose tested 10 mg/kg,

the activity of ublituximab was comparable with that of rituximab (10 mg/kg). This efficacy could be mediated by several mechanisms: ADCC mediated by NK cells and/or macrophages, CDC or apoptosis.

Ublituximab administered at lower doses of 1 and 0.1 mg/kg probably does not involve the complement pathway as the clearance profile observed in the SCID-NOD mice was comparable to that observed in the SCID mice.

2.5.2.2. Secondary pharmacodynamic studies

The cross-reactivity of ublituximab across a wide range of normal human and cynomolgus monkey tissues was assessed. Monkeys share 97% CD20 protein sequence homology compared with the naturally occurring human sequence.

Ublituximab tissue cross-reactivity was evaluated using validated immunohistochemical staining method. A direct staining method was implemented using an avidin-biotin peroxidase complex to detect bound ublituximab that is complexed with the secondary antibody (goat antihuman IgG biotin). Staining was evaluated using human tissue from tonsil, heart, lymph node, and spleen. Human tonsil was selected as the CD20 positive control tissue, and human heart was selected as the CD20 negative control tissue to be used in the tissue cross-reactivity studies.

Normal human tissues: immunostaining was minimal to moderate in the thymus, tonsil, lymph nodes and spleen, minimal to mild in the small and large intestines and minimal in the prostate, uterus (endometrium) and parotid salivary gland. Ublituximab showed binding to tissues known to express CD20. The distribution of the staining demonstrated that the test item is binding specifically to its target and no other tissues.

Normal cynomolgus monkey tissues: positive staining to ublituximab was observed in lymphoid follicles in the lymph node, lung and spleen. The intensity was graded from mild to moderate and the distribution was considered diffuse in all cases. No specific staining was observed in the rest of the tissues evaluated. Lymphoid follicles are present in the outer cortex of lymph nodes, the splenic white pulp and lymphoid associate tissue. Lymphoid follicles are the site of B cell proliferation. CD20 is a B cell integral protein expressed specifically on B cells. The lack of staining outside the lymphoid follicles indicates the ublituximab is not cross reacting with other tissues evaluated in this study.

2.5.2.3. Safety pharmacology programme

No stand-alone safety pharmacology studies were conducted. As ublituximab demonstrates high specificity for its target, safety pharmacology endpoints, including cardiovascular, CNS and respiratory, were evaluated in cynomolgus monkeys as part of the pivotal 4-week, 13-week and 26-week repeat-dose toxicity studies. Throughout the non-clinical dossier, the applicant refers to ICH S9 guideline. This could be valid for the initial sought indication of ublituximab non-Hodgkin lymphoma. Since the current application is for ublituximab in the treatment of MS, the ICH S6 guideline should be the reference.

There were no observed clinical findings concerning cardiac, respiratory, or CNS safety pharmacology in the general toxicology studies.

2.5.2.4. Pharmacodynamic drug interactions

Due to the high binding specificity of ublituximab to human CD20, a transmembrane protein expressed on the surface of cells of B lineage origin, it is stated to be unlikely that ublituximab is having pharmacodynamic (PD) interactions with co-administered drugs. Ublituximab is recommended as a single-agent treatment.

No non-clinical PD drug-drug interaction (DDI) studies were performed.

2.5.3. Pharmacokinetics

The pharmacokinetics (PK) and toxicokinetics (TK) of ublituximab were assessed in rabbits and in cynomolgus monkeys, respectively. Rabbits and monkeys share a high CD20 protein sequence homology compared with the naturally occurring human CD20 sequence (80% and 97%, respectively). The studies were performed by the intravenous (IV) route which is intended clinical route of ublituximab' s administration.

All bioanalytical methods for the detection of ublituximab and antidrug antibodies were based on ligand-binding assays. The bioanalytical methods were developed and adequately validated. Incurred sample reanalyses (ISR) performed in support of the GLP-compliant toxicology studies No. 20264749, 20083321, 20083322 met predefined reproducibility criteria for all assays in all studies. GLP toxicology studies 32879 and 32880 were conducted in 2009 prior to the adoption of EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** *Guideline on Bioanalytical Method Validation* and therefore ISR was not conducted.

Absorption and Distribution

Single-dose and repeated toxicity studies

In rabbit and monkey single-dose studies, ublituximab demonstrated a bi-compartmental elimination profile. After a single IV administration to male New Zealand rabbits, ublituximab concentrations declined in a bi-exponential fashion. The mean maximum concentration (C_{max}) and area under the concentration-time curve (AUC) from time 0 to 648 hours after dosing ($AUC_{0\text{-}648hr}$) were 261 ug/mL and 14700 ug•hr/mL, respectively. The mean systemic clearance (CL)was 0.8 mL/hr/kg, with an apparent terminal elimination (t½) of 96.5 hours. The mean volume of distribution (Vd) was 100 mL/kg which is approximately 2× the plasma volume.

After a single IV administration to monkeys, the exposure increased in a greater than dose-proportional manner between doses of 0.3 and 10 mg/kg, and in an approximately dose proportional manner between doses of 10 and 100 mg/kg, suggesting target-Mediated Drug Disposition. The male and female average n AUC from time 0 to last time point ($AUC_{0\text{-}t}$) was 80.2, 15000, and 162000 ug•hr/mL, respectively, for 0.3, 10, and 100 mg/kg, while the C_{max} was 6.5, 239, and 2200 ug/mL, respectively. The male and female average CL at 10 mg/kg was 0.660 mL/hr/kg with an t½ of 58.2 hours. The male and female average Vd at 10 mg/kg was 55.1 mL/kg. No evidence of sex effect was observed.

In a 4-week repeat-dose toxicity study, following the weekly IV administration of 10 or 50 mg/kg of ublituximab for 4 weeks, the C_{max} and AUC increased in an approximately dose-proportional manner. On Day 22, the $AUC_{0\text{-}t}$ and C_{max} were increased in a greater than dose-proportional manner. In general, neither drug accumulation nor sex effect was apparent.

In the 13-week repeat-dose toxicity study, following IV administration of 3, 10, or 30 mg/kg ublituximab in 6 doses of 13 weeks, the C_{max} and AUC from time 0 to 144 hours after dosing ($AUC_{0\text{-}144h}$) increased in an approximately dose-proportional manner across the doses. Dose proportionality on Day 78 could not be accurately assessed due to immunogenicity-mediated accelerated clearance. Neither drug accumulation nor sex differences in exposure were apparent.

In the 26-week repeat-dose toxicity study, following weekly IV administration of 30 mg/kg ublituximab for 26 weeks, slight drug accumulation was noted. No sex differences in exposure were apparent.

Enhanced pre- and postnatal development (ePPND)

TK parameters for anti-drug antibody (ADA) positive and ADA negative animals were reported separately to assess the impact of immunogenicity.

ADA positive and ADA negative monkeys had comparable C_{max} values (ranged from 913 to 1203 µg/mL) after the first and seventh doses. The AUC_{0-t} values (ranged from 47100 to 58200 µg•hr/mL) for the ADA positive and ADA negative monkeys were also comparable after the first dose. After the seventh repeat dose, however, the AUC_{0-t} values were decreased in the ADA positive animals compared to those in the ADA negative animals, suggesting accelerated clearance due to the immune response. The drug accumulation ratio ranged from 1.25 to 1.60 in ADA negative animals and from 0.296 to 0.985 in ADA positive animals.

Comparing the exposures to non-pregnant monkeys in the 13-week and 26-week studies, the AUC_{0-t} in the pregnant monkeys after the first dose were approximately 30%higher (55900±8790 in Set A and 52600±6550 in Set B vs. 42900±4420 ug•hr/mL in 13-week study), which may be associated with study variability.

Infant monkeys appeared to have 30% higher ublituximab levels than those of the corresponding mothers, with infant-to-maternal concentration ratios of ublituximab ranging from 3.53 to 10.4 on post-partum day 14.

Distribution

IV administered ublituximab is expected to selectively bind to the CD20 antigen expressed on B cells. The Vd of ublituximab in monkeys varied from dose to dose, ranging from 46.2 to 105 mL/kg, which is approximately 2 times the plasma volume in monkeys.

No conventional distribution studies using radiolabelled ublituximab were conducted in pregnant monkeys (e.g. protein binding or whole-body autoradiography). This is considered acceptable according to ICHS6(R1).

Metabolism

No metabolism studies were performed on ublituximab. Monoclonal antibodies are expected to be metabolised in the same manner as endogenous antibodies. This is acceptable according to ICHS6(R1).

Excretion

Similar to metabolism, modes of excretion are anticipated to be similar to endogenous antibodies (proteolysis protected by Fc-Rn receptor). Studies of excretion is therefore not necessary.

No level of ublituximab was measured in the milk of monkey after parturition in the ePPND study in monkeys.

Pharmacokinetic drug-drug interaction

PK DDI studies with ublituximab were not conducted. Ublituximab does not undergo classical metabolic reactions involving the superfamily of cytochrome P450 (CYP) isoenzymes. Hence, co-medication with CYP isoenzyme substrates, inducers or inhibitors is not expected to result in clinically relevant pharmacokinetics drug interactions. No information currently exists to suggest that CD20 can modulate expression of CYP enzymes or transporter proteins. Since ublituximab is highly specific for CD20 and does not bind to any other proteins/macromolecules, it is highly unlikely that it will either directly or indirectly (by affecting CD20 function) modulate CYP or transporter expression.

Immunogenicity in monkeys

Ublituximab was immunogenic to monkeys. This is expected, since it is a human chimeric monoclonal - antibody homolog and is directed at cell surface marker which undergo internalisation.

After a single administration, the incidence of ADA positive was 100% at 0.3 mg/kg, while there was no ADA positive signal observed at 10 and 100 mg/kg.

In the 4-week study, the incidence of monkeys with ADA positive was 100% at 10 mg/kg and 17% at 50 mg/kg.

In the 13-week study, the incidence of ADA positive was 100%, 80%, and 70%, respectively, at 3, 10, and 30 mg/kg/dose.

In the 26-week repeat-dose toxicity study the incidence of ADA positive was 90% (9 out of 10) at 30 mg/kg. The incidence of ADA at specific timepoints was 9 out of 10 animals at Week 4, 6 out of 10 animals at Week 8, and 2 out of 9 animals at Weeks 12, 18 and 26. At Weeks 12, 18, and 26, ADA was seen in the same 2 animals at each timepoint indicating a sustained response that correlated with reduced exposure. All other animals experienced a transient ADA response which did not impact exposure to ublituximab and clearance.

In ePPND study, the incidence of ADA positive in pregnant monkeys ranged from 44% to 100% across treatment Sets A, B and C. In the infant monkeys, the incidence of ADA+ was 25% (2 of 8).

Overall, the finding of ADA positive animals correlated closely with the decreased exposure observed in TK parameters and with the re-emergence of peripheral B cells.

Immunogenicity-mediated accelerated clearance at low doses was observed, which led to exposure reduction. The phenomenon was more profound at the low dose groups (e.g., ≤10 mg/kg) relative to the high dose groups (e.g., ≥30 mg/kg). However, an immune response cannot be ruled out for the high dose groups because high ublituximab concentrations in circulation interfere with the ability of the assay to detect ADA. The immunogenicity observed in non-human primates, however, provides limited value in predicting an immune response against a therapeutic protein in humans.

In toxicity studies, immunogenicity-mediated accelerated clearance at low doses was observed, which led to exposure reduction However, at high dose groups (30 and 50 mg/kg) ublituximab exposure was maintained, allowing for adequate evaluation of ublituximab treatment-related toxicities.

2.5.4. Toxicology

Monkey toxicity studies were all performed according to GLP in France or in USA. Local tolerance study in rabbit and the bacterial reverse mutation assay, were not (entirely) performed under GLP as stated by the applicant; however, since they are not considered pivotal for the marketing authorisation application, this is considerable acceptable.

2.5.4.1. Single dose toxicity

After a single dose of ublituximab administered IV to cynomolgus monkeys at doses of 0.3, 10, or 100 mg/kg, ublituximab was generally well tolerated at all dose levels evaluated. Ublituximab was considered to be well tolerated at the injection sites at all dose-levels tested. No mortality and no relevant clinical signs were observed at any dose-level tested. No effects on body weight or food consumption were noted at any dose-level tested. A dose-related lower white blood cell count mainly due to a dose-related lower lymphocyte count were recorded on day 15 in control and treated animals (pharmacological effect of the test item). A moderate increase of the fibrinogen concentration was observed at the high dose-level in both sexes, but was considered not related to the test item. No blood biochemistry findings were noted on day 15 in any treated group. At necropsy on day 15, lower absolute and relative thymus weights were recorded in males at all dose-levels and in females at 10 or 100 mg/kg, effects consistent with the expected pharmacological effects of the test item.

In animals treated with ublituximab at 0.3 mg/kg, ADA were detected in all of the animals on Day 14. In general, ADA were not detected at doses of 10 or 100 mg/kg on Day 14; however, these results are not reliable due to possible ublituximab interference in the assay.

Immunophenotyping demonstrated significant B-lymphocyte depletion in the peripheral blood, starting at 24 hours after treatment in all 3 ublituximab dose levels. Evaluation of the lymph nodes, spleen, and bone marrow on Day 15 showed a decrease in the proportion of B lymphocytes among the nucleated cells (CD45+) in these tissues in all 3 ublituximab dose levels.

2.5.4.2. Repeat dose toxicity

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. In the 4-week GLP toxicity study treatment-related mortality was observed in 1 female monkey administered with 50 mg/kg. No recovery period was included. This female was euthanised on Day 20 after showing* clinical signs of marked dehydration, pallor of the lip mucosa, hypothermia (body temperature less than 34°C), hypoactivity, prostration, body weight loss starting on Day 15, and markedly reduced food consumption. The clinical deterioration observed in this immuno-depressed animal in the presence of moderate modifications of the hepatic parenchyma led to the premature sacrifice of this animal. Similarly, body weight loss secondary to decreased food consumption with correlative changes in haematology and clinical chemistry parameters was observed at 50 mg/kg.

The no-observed-adverse-effect level (NOAEL) in the 4-week repeat-dose study was 10 mg/kg, with a male and female average $AUC_{0\text{-}168hr}$ of 318 µg•hr/mL and C_{max} of 129 µg/mL on Day 22.

In the 13-week repeat-dose study, ublituximab was tolerated up to 30 mg/kg, which was the highest dose evaluated. Six-month recovery period was included. One female monkey dosed with 10 mg/kg ublituximab was prematurely sacrificed due to suspected spontaneous cardiomyopathy, which was considered unrelated to ublituximab treatment. Histopathological findings in this female were consistent with spontaneous cardiomyopathy. Clinical signs associated with ublituximab administration in the 13-week repeat-dose study included liquid feces in females dosed with 30 mg/kg ublituximab and occasional vomitus following dosing at 3 and 10 mg/kg. 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. The microscopic findings consisted of decreased germinal centre development and decreased size and number of the follicles. The lymphoid follicles located in the cortex of the mandibular and mesenteric lymph nodes and the spleen of affected animals were reduced in size primarily due to a decrease in germinal centre development. The NOAEL was 30 mg/kg, with a male and female combined average AUC of 23400 µg•hr/mL and C_{max} of 556 µg/mL on Day 78.

In the 26-week repeat-dose study, ublituximab was tolerated at 30 mg/kg, which was the only dose evaluated. No recovery period was included. A female monkey dosed with 30 mg/kg was found dead on Day 50 due to pulmonary haemorrhage secondary to ADA related immune-mediated hypersensitivity reaction. Clinical signs associated with ublituximab administration included liquid faeces and 2 instances of infusion related reactions. Microscopic findings consisted of changes in lymphoid tissue consistent with the pharmacologic activity of ublituximab. Additionally, several animals exhibited mononuclear cell infiltration in the CNS and eye as well as vascular/perivascular inflammation in various tissues that were attributed by the study director to an immune-mediated toxicity secondary to ADA formation rather than being indicative of distribution of ublituximab into the CNS. Ublituximab distribution across the blood brain barrier was not assessed in toxicology studies. At 30 mg/kg the male and female average $AUC_{0\text{-}144hr}$ of 74000 µg•hr/mL and C_{max} of 1060 µg/mL on Day 176 (ADA negative animals only), were registered.

2.5.4.3. Genotoxicity

Ublituximab was tested in a GLP bacterial reverse mutation assay to evaluate its mutagenic potential. The ability of ublituximab to induce reverse mutation at selected loci of several strains of S. typhimurium (TA1535, TA1537, TA98, TA100, and TA102) was measured at doses of 0, 1, 3, 10, 30, and 100 µL/plate. Testing was conducted in the presence and absence of an exogenous metabolic activation system using hepatic microsomes from rat livers induced by Aroclor 1254 with a 48-hour incubation period. Ublituximab induced neither toxicity nor precipitation in any strain tested at any dose. The maximum dose retained for the first mutagenicity assay was 100 µL/plate in all strains, either with or without metabolic activation. Ublituximab induced no mutagenic activity in any of the S. typhimurium strains (TA1535, TA1537, TA98, TA100, and TA102) tested, either in the absence or presence of metabolic activation.

2.5.4.4. Carcinogenicity

According to ICH S6(R1) guideline, standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. For ublituximab, conventional carcinogenicity studies are not appropriate because carcinogenicity studies are not feasible in cynomolgus monkey, ublituximab is not pharmacologically active in rodents, and 2-year bioassay is a poor predictor of carcinogenicity risk associated with immunosuppression. Due to the mechanism of action, i.e. immunosuppression, tumour promoting effects of ublituximab cannot be ruled out.

2.5.4.5. Reproductive and developmental toxicity

No dedicated fertility studies were performed. Based on studies of general toxicity in cynomolgus monkeys no concerns on reproductive organotoxicity are expected.

In a ePPND study, IV dosing of 30 mg/kg/week ublituximab in pregnant female monkeys was poorly tolerated. 10 adult females were euthanised early due to deteriorating clinical condition or were found dead after administration of 3 to 6 doses of ublituximab at 30 mg/kg/week (3 animals from Set 2A and 7 animals from Set 2B). Clinical signs observed in multiple animals included bleeding from gums, oral cavity, and/or nasal cavity; ataxia; loss of consciousness/moribundity; and hunched posture. All 10 adult females had systemic changes consistent with an ADA formation, and 9 of the 10 had placental abnormalities that included infarction, perivillous fibrin, and/or retroplacental haematoma that were likely immune mediated and involved in fetal loss.

In first trimester dosing, there were 9 fetal losses and no infant losses. Ublituximab-related placental changes occurred in 3 out of 10 placentas and included diffuse friable texture and dark red gelatinous material accumulation with microscopic correlates of moderate to marked infarcts. These placentas were from females that were euthanised early and were considered a component of the ublituximab-related systemic changes. Fetal loss was directly attributed to the placental changes in 2 animals and secondary to euthanasia of the female for 1 animal. There were no other ublituximab-related effects on fetal macroscopic or microscopic pathology, morphometric measurements, or teratogenic external, visceral, or heart evaluations as applicable.

In second trimester dosing, there were 12 fetal losses and 3 infant losses. Of these losses, 7 were associated with adult females that were euthanised early/found dead, and ublituximab-related placental findings were noted in 6 of the 7 adult females. These findings included gelatinous fetal surface, generalised pallor of the disc, and material accumulation on the maternal surface with histologic correlates of retroplacental haematoma, disc infarct, and perivillous fibrin accumulation. Fetal loss was directly attributed to the placental changes in 4 animals and secondary to euthanasia of the female for

3 animals. There were no other ublituximab-related effects on fetal macroscopic or microscopic pathology, morphometric measurements, or teratogenic external, visceral, or heart evaluations as applicable.

A NOAEL could not be determined due to only one dose level evaluated in this reproductive toxicity on cynomolgus monkeys.

Table 2: Exposure Multiples of Ublituximab between ePPND Study in Monkeys and To-Be-Marketed Human Dose

Species (Study ID)	Dose	Observed Exposure		Safety Multiple	
		AUC µg•hr/mL	C_{max} µg/mL	AUC	C_{max}
Human (population PK report)[c]	450 mg/subject	3000[d]	140	NA	NA
Monkey ePPND (20083322)	30 mg/kg[a]	78000[b]	1180[b]	26×	8.43×

AUC, area under the concentration-time curve; Cmax, maximum concentration; ePPND, enhanced pre- post-natal development study; NA, not applicable.
a Only dose evaluated in the ePPND study.
b Average $AUC_{0\text{-}144hr}$ and C_{max} on GD 63 (Set A) and GD112 (Set B)
d Model-estimated steady state AUC and C_{max}

In toxicity studies, immunogenicity-mediated accelerated clearance at low doses was observed. However in high dose groups (30 and 50 mg/kg) ublituximab exposure was maintained, allowing for adequate evaluation of ublituximab treatment-related toxicities.

Lactation was not an endpoint in ePPND and no ublituximab in mother's milk was measured.

2.5.4.6. Toxicokinetic data

Please refer to PK section

2.5.4.7. Local tolerance

The objective of Study 20070605TL was to assess the local tolerance of ublituximab in New Zealand albino rabbits using the perivenous and intra-arterial routes. Three groups of 5 female rabbits were administered either sodium chloride, formulation buffer (sodium citrate [7.35 g/L], NaCl [9 g/L], and polysorbate 80 [700 mg/L]), or ublituximab once by the pv route and once by the ia route on the same day. Sodium chloride, formulation buffer, and ublituximab were administered as a single pv injection at a volume of 0.5mL and a single ia injection at a volume of 1.042 mL/kg, which corresponded to the 10 mg/kg dose of ublituximab. The ia injections were performed by infusion at a rate of 1 mL/minute.

No mortality or clinical signs were observed in any of the animals. Local signs observed were mainly haematoma upstream from the ia site. Local signs observed with the pv route in animals treated with 0.9% NaCl were mainly erythema, and animals treated with the formulation buffer and ublituximab presented mainly with haematoma. No lesions were seen at the necropsy examination, except erythema and haematoma seen at the injection sites on ears (by ia and pv routes) in all the groups with the comparable occurrence. Histopathology results showed that in the 10 mg/kg-treated group, the ia and pv injections did not cause treatment-related responses.

2.5.5. Ecotoxicity/environmental risk assessment

Ublituximab is comprised of naturally occurring amino acids and is not expected to have any environmental impact. The persistence, bioaccumulation and toxicity are considered unlikely and present a very low risk.

The Predicted Environmental Concentration in the surface water is 0.00225, which is below 0.01 µg/L, and no other environmental concerns are apparent. Therefore, it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients. A Phase II environmental fate/risk assessment is not considered necessary.

2.5.6. Discussion on non-clinical aspects

Ublituximab is a recombinant IgG1 chimeric monoclonal antibody which binds to the pre-B cells, mature and memory B cells surface CD20. It is proposed to be used in the treatment of RMS trough the IV route of administration. Other anti-CD20 mAbs (rituximab, obinutuzumab, ofatumumab and ocrelizumab) some of those (ofatumumab SC and ocrelizumab IV) already approved for the treatment of MS, were used as comparators in the non-clinical evaluation.

Ublituximab is produced in the rat cell line YB2/0 which has reduced levels of fucosyl-transferase activity resulting in antibody glycoforms incorporating less fucose content. The low content of fucose in ublituximab glycosylation of the human IgG1-Fc-portion is claimed to be associated to the higher ADCC vs ocrelizumab> ofatumumab> rituximab observed on lymphoblast-like Raji cells and on NK cells. As regards the potential clinical advantage, it is noted that in clinical trials ublituximab at a lower dose (450 mg) than ocrelizumab (600 mg) demonstrated a lower annualised relapse rate (ARR) and lower rate of participants experiencing confirmed disability progression (CDP). With respect to safety, ublituximab displayed a similar adverse event (AE) profile compared to ocrelizumab.

The applicant has shown that ublituximab binds FcγRIIIa 158V with a dissociation constant value approximately 10-fold lower than FcγRIIIa 158F (64 versus 680 nM), however ublituximab binding to both variants was stronger compared to other anti-CD20 antibodies, and ublituximab is less sensitive to FcγRIIIa polymorphisms clinically than other anti-CD20 antibodies, a trend which has been observed in the clinic. The clinical data from the Phase III Studies of ublituximab (TG1101-RMS301 and TG1101-RMS302) demonstrate the uniform PD effect of CD19+ B-cell depletion in nearly all patients, with absolute counts of CD19+ B cells remaining lower than the limit of normal (<100 cells/µL) for 97.9% to 100% of patients through Week 96. These results demonstrated that FcγRIIIa 158 polymorphisms did not have an impact on the clinical activity of ublituximab.

As regards the lower CDC vs. ADCC contribution in ublituximab pharmacological activity as shown by *in vitro* and *in vivo* studies*, t*he applicant assumes that it is not thought to translate to decreased efficacy and that it may lead overall to a better clinical outcome with improved tolerability, potentially contributing to the ability to infuse ublituximab in 1 hour for the second and subsequent infusion compared to longer infusion times for other anti-CD20.

No *in vivo* MS model was carried out. Although, one model recapitulating all MS pathogenesis features currently does not exist, the experimental autoimmune/allergic encephalomyelitis is recognised as the model which better reflects the autoimmune pathogenesis of MS. However, the feasibility of such a model due to ublituximab cross-reaction with rodent CD20 and its the strong immunogenicity observed in non-human primate studies, is questioned. The performed studies in immunocompromised mice models (SCID and SCID NOD) of the clearance of human B-CLL provide evidence that ublituximab can deplete tumoral B cell. This can be considered a proof of concept, also confirmed in clinical setting.

Monkeys share 97% CD20 protein sequence homology compared with the naturally occurring human sequence. In both normal human and cynomolgus monkey tissues ublituximab showed binding to tissues known to express CD20. The lack of staining outside the lymphoid follicles indicates the ublituximab has low off-target potential.

PK and TK of ublituximab were assessed in non-clinical studies in rabbits (sharing 80% CD20 protein sequence homology) and cynomolgus monkeys. However, the results from the IV administration to male New Zealand rabbits are affected by the non-GLP status and the use of only male rabbit. The rationale for carrying out this study is not completely understood also considering the in the GLP local tolerance study by perivenous and intra-arterial administration in rabbit, only female rabbits were used. All bioanalytical methods of ublituximab and ADA were based on ligand-binding assays. The bioanalytical methods were adequately validated.

The toxicological profile of ublituximab was assessed in cynomolgus monkeys in 4-week single dose study and repeated dose toxicity studies of 4-weeks, 13-week with 6-month recovery period and 26-weeks duration, which also included endpoints of safety pharmacology. The key ublituximab-related findings included expected decreases in lymphocyte count and corresponding changes in lymphoid tissue, thymus, spleen, and bone marrow. Immunosuppression (B cell depletion) is the pharmacological effect of ublituximab. Overall, 30 mg/kg ublituximab was well tolerated in monkeys after multiple doses over a 13-week and a 26-week periods with changes primarily noted in lymphoid tissue. In 26-week repeat-dose toxicity study at the only dose tested was 30 mg/kg, several animals exhibited mononuclear cell infiltration in the CNS and eye as well as vascular/perivascular inflammation in various tissues that were likely related to immune-mediated effects secondary to ADA rather than being indicative of distribution of ublituximab into the CNS. Although distribution across the blood brain barrier was not assessed, the possibility that ublituximab passes the disrupted blood brain barrier, cannot be completely ruled out and accumulation of peripheral immune cells at CNS levels in patients suffering from MS, could occur independently. The postulated peripherally action of ublituximab causing B-cell depletion, is expected to ameliorate the CNS inflammatory status. Moreover, it remains unclear how the peripheral ADA formation could alter the healthy monkey BBB integrity. Moreover, the study does not allow to know the persistence of the observed findings, since no recovery period was added in the study, or the dose-effect relationship, since only one dose was used. Of note, also in dose-repeated toxicity studies with other anti-CD20 monoclonal antibodies, ofatumumab recombinant fully human and ocrelizumab humanised, both approved for the treatment of MS, perivascular inflammatory cell infiltration in the brain and diffuse lymphocytic and plasmacytic cell infiltrates in the choroid and ciliary body of the eyes, were observed. Clinical relevance of mononuclear cell infiltration in monkey brain parenchyma remains uncertain. The issue was not further pursued in the absence of any clinical observations of autoimmune or hypersensitivity reactions in patients with ADA.

The adverse maternal and fetal effects observed in the ePPND study in monkeys treated with only 30 mg/kg ublituximab, were not attributed to a direct effect of ublituximab, but instead were considered secondary to immunogenicity of the test article, resulting in a hypersensitivity response, formation of ADA, and downstream immune-mediated adverse effects on multiple organ systems including placenta.

No information on ublituximab excretion in milk is presented in non-clinical documentation.

However, 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. Adequate wording in section 4.6 is added consistently with other approved anti-CD20 monoclonal antibodies. "Safety in pregnancy and lactation, including foetal risk" are listed as missing information in the RMP.

Ublituximab was immunogenic in monkeys. This is expected, since it is a human chimeric monoclonal antibody and is directed at cell surface marker which undergo internalisation. In toxicity studies,

immunogenicity-mediated accelerated clearance at low doses was observed, which led to exposure reduction. However, at high dose groups (30 and 50 mg/kg) ublituximab exposure was maintained, allowing for adequate evaluation of ublituximab treatment-related toxicities.

Ublituximab is intended for chronic use. The sustained depletion of B-cells might affect the immune system ability to detect and eliminate cancer cells thus leading to an increased risk of developing solid tumours. Although it is agreed that the weight of evidence in the literature does not suggest that B cell depletion plays a driving force in tumour formation and promotion, "malignancies" is reported as important potential risk in other anti-CD20 authorised for the treatment of MS Risk management plan (RMP)s and "Known active malignancy" is included as a contraindication (section 4.3) in the corresponding Summary of Product Characteristics (SmPCs). Also considering the clinical assessment, the same approach is followed for Briumvi.

The CHMP agrees that Ublituximab is comprised of naturally occurring amino acids and is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Based on the available non-clinical data regarding pharmacodynamics, pharmacokinetic and toxicology of ublituximab, the application is considered approvable from a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study identifier	**Study design**	**Treatment**	**Number of Subjects Treated / Study Status**
TG1101-RMS301 (ULTIMATE I)	Randomised, multicentre, double-blinded, double-dummy, active-controlled study to assess the efficacy, safety, and tolerability of ublituximab/oral placebo as compared to teriflunomide/IV placebo in subjects with RMS	Ublituximab + placebo arm: Ublituximab (150 mg/4 h) on Wk 1 D1; IV Ublituximab (450 mg/1 h) on Wk 3 D15, Wk 24, Wk 48, Wk 72; IV Placebo on Wk 1 D1 until last day of Wk 95; QD; PO Teriflunomide + placebo arm: Teriflunomide 14 mg on Wk 1 D1 until last day of Wk 95; QD; PO Placebo on Wk 1 D1 Wk 3 D15, Wk 24, Wk 48, Wk 72; IV	Total: 548 Ublituximab: 273 Teriflunomide: 275 Completed
TG1101-RMS302 (ULTIMATE II)	Randomised, multicentre, double-blinded, double-dummy, active-controlled study to assess the efficacy, safety, and tolerability of ublituximab/oral placebo as compared to teriflunomide/IV placebo in subjects with RMS	Ublituximab + placebo arm: Ublituximab (150 mg/4 h) on Wk 1 D1; IV Ublituximab (450 mg/1 h) on Wk 3 D15, Wk 24, Wk 48, Wk 72; IV Placebo on Wk 1 D1 until last day of Wk 95; QD; PO Teriflunomide + placebo arm: Teriflunomide 14 mg on Wk 1 D1 until last day of Wk 95; QD; PO Placebo on Wk 1 D1, Wk 3 D15, Wk 24, Wk 48, Wk 72; IV	Total: 545 Ublituximab: 272 Teriflunomide: 273 Completed

Study identifier	Study design	Treatment	Number of Subjects Treated / Study Status
TG1101-RMS201	Placebo-controlled, multicentre, dose-finding study in subjects with RMS	Cohort 1: Ublituximab 150 mg/4 h D1, 450 mg/3 h D15, 450 mg/1.5 h Wk 24; IV Placebo 4 h D1, 3 h D15; IV Cohort 1a (after D28, for placebo subjects): Ublituximab 150 mg/4 h D1, 450 mg/3 h D15, 450 mg/1.5 h Wk 24; IV Cohort 2: Ublituximab 150 mg/4 h D1, 450 mg/1.5 h D15, 450 mg/1 h Wk 24; IV Placebo 4 h D1, 1.5 h D15; IV Cohort 2a (after D28, for placebo subjects): Ublituximab 150 mg/4 h D1, 450 mg/1.5 h D15, 450 mg/1 h Wk 24; IV Cohort 3: Ublituximab 150 mg/4 h D1, 450 mg/1 h D15, 600 mg/1 h Wk 24; IV Placebo 4 h D1, 1 h D15; IV Cohort 3a (after D28, for placebo subjects): Ublituximab 150 mg/4 h D1, 450 mg/1 h D15, 600 mg/1 h Wk 24; IV Cohort 4: Ublituximab 150 mg/3 h D1, 600 mg/ 1 h D15, 600 mg/1 h Wk 24; IV Placebo 3 h D1, 1 h D15; IV Cohort 4a (after D28, for placebo subjects): Ublituximab 150 mg/3 h D1, 600 mg/1 h D15, 600 mg/1 h Wk 24; IV Cohort 5: Ublituximab 150 mg/2 h D1, 600 mg/1 h D15, 600 mg/1 h Wk 24; IV Placebo 2 h D1, 1 h D15; IV Cohort 5a (after D28, for placebo subjects): Ublituximab 150 mg/2 h D1, 600 mg/1 h D15, 600 mg/1 h Wk 24; IV Cohort 6: Ublituximab 150 mg/1 h D1, 600 mg/1 h D15, 600 mg/1 h Wk 24; IV Placebo 1 h D1, 1 h D15; IV Cohort 6a (after D28, for placebo subjects): Ublituximab 150 mg/1 h D1, 600 mg/1 h D15, 600 mg/1 h Wk 24; IV	Total: 49 Completed
Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Modelling			
TGTX-PMX-TGl 101-2920	Population pharmacokinetic and exposure-response analysis of efficacy and safety of ublituximab in multiple sclerosis		The PopPK dataset included 591 subjects with RMS including 47 subjects in Study TG 1101-RMS201, 272 subjects in Study TG 1101-RMS301 and 272 subjects in Study TG 110 l-RMS302

2.6.2. Clinical pharmacology

Ublituximab (also referred to as TG-1101) is a recombinant immunoglobulin (Ig)G1 chimeric mAb that targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes.

2.6.2.1. Pharmacokinetics

Analytical methods

Bioanalytical methods were developed, validated and performed to support the clinical development of the ublituximab. Following techniques were developed: Electrochemiluminescence immunoassay (ECLIA) for ublituximab detection in human serum (01128004), ECLIA for ADA detection in human serum (01128007), and cell-based assay for the detection of neutralising anti-TG-1101 antibodies in human serum (01128016). All methods were validated according to the guidelines:

EMEA/CHMP/BMWP/14327/2006 and EMEA/CHMP/EWP/192217/2009. Moreover, the applicant also provided the validation report for teriflunomide (15503ANIA) determination in samples from RMS301 and RMS302 studies.

Validation 01128004 (ublituximab determination)

Validation procedure for the quantification of TG-1101 in human serum using ECLIA was performed. Calibration curve concentrations ranged from 15.63 to 2000 ng/mL. During procedure following parameters were addressed and met the acceptance criteria: selectivity (normal and MS patients sera), sensitivity, intra- and inter-assay accuracy and precision and ruggedness and robustness.

As per storage stability, results for only 686 days were found in the dossier. Upon request, the applicant provided stability at 1044 day (about 34 months), however the LTS period do not cover the period of storage of samples. Following the CHMP request to submit the LTS data covering 45 months i.e. the maximum storage period for samples from studies RMS201, RMS301 and RMS302, the applicant proposed to provide these data post approval by Q3 of 2023 and to formalise this commitment via a Letter of Recommendations as a post-approval measure (**REC**). The proposal is acceptable.

Validation 01128007 (ADA determination)

In the validation report it is reported that the stability of ADA will be set for the following conditions: short-term stability at room temperature for 19 hours and 40 minutes, 6 freeze-thaw stability in human serum, long-term stability in human serum (at -60°C to -80°C for at least 12 months). The applicant proposed to submit the results of the full long stability data (that cover samples in RMS201, RMS301 and RMS302) post approval by Q2 2024 and to formalise this commitment via a letter of recommendations as a post-approval measure (**REC**).

For Study RMS201, post-baseline PK and ADA sample were both available at time points Day 15 and Week24, for study RMS301 and RMS302 on Day15, Weeks 24, 48, 72, 96 and at end of study.

The bioequivalence reports for ADA determination were provided for RMS201 (01128010), RMS301 (01128017) and RMS302 (01128018). The applicant did not initially provide the corresponding ublituximab concentrations for ADA samples.

Nab assay validation (01128016)

The NAb assay was based on a cell-based ADCC assay.

Drug tolerance was determined during validation to be 0.1 µg/mL of TG-1101 at the low positive control (LPC1 0.95 µg/mL and LPC2 1.50 µg/mL) and 1 µg/mL at high positive control (HPC) (50 µg/mL). Haemolysis was not found to interfere with the assay. Lipemia was found to potentially interfere with the assay and cause a false negative result.

The NAb status for each subject in the treatment-emergent ADA (TE-ADA) positive population was considered positive if the subject had at least one post-baseline positive NAb sample. For all other TE-ADA positive subjects, the NAb status was negative. Subjects who were TE-ADA negative were assigned a NAb negative status.

Based on data reported in the BA reports of Nab determinations in the RMS201 (BA report 01128019), RMS301 (BA report 01128020) and RMS302 (BA report 01128021) it is noted that several Nab negative samples had ublituximab concentration above the drug tolerance level (DTL) (0.1 µg/mL) at LPC therefore impacting the reliability of negative results.

- For Study RMS201, 22 samples from 17 of the 34 subjects (50.0% of the ADA positive subjects) had at least 1 sample with TG-1101 concentrations > 0.1 µg/mL (DTL) and were negative for Nab.

- In Study RMS301, 380 samples from 214 of the 237 subjects (90.3% of the ADA positive subjects) had at least 1 sample with TG-1101 concentrations > 0.1 µg/mL (DTL). 2 samples from 1 subject were Nab positive, the remaining samples (378) were considered Nab negative.
- In Study RMS302, 449 samples from 224 of the 242 subjects (92.6% of the ADA positive subjects) had at least 1 sample with TG-1101 concentrations > 0.1 µg/mL (DTL). 4 samples were positive for anti-TG-1101 neutralizing antibodies, the remaining 445 samples were negative for neutralizing antibodies.

As per validation report, lipemia can interfere with Nab determination. In Study RMS301 and RMS302 17 and 10 samples, respectively, showed lipemia potentially impacting the Nab determination.

Teriflunomide determination in plasma (validation number 155037ANIA)

A high-performance liquid chromatographic method for the determination of teriflunomide in human EDTA K2 plasma was validated over an analytical range of 10 to 5000 ng/mL.

The method was validated in accordance to the relevant Guidelines. The BA reports for teriflunomide determination in RMS301 and RMS302 were provided. Samples were stored within the validated stability period; the incurred samples reanalysis was performed according to relevant GL and met the criteria of assay reproducibility. Some samples exceed the Upper Limit of Quantification and were reanalysed using the appropriate dilution scheme.

Population pharmacokinetic (popPK) and exposure-response analysis of efficacy and safety of Ublituximab in Multiple Sclerosis. TGTX-PMX-TGl 101-2920.

Objectives

• Update a previously developed PopPK model for ublituximab using data from subjects with RMS enrolled in Studies TG1101-RMS201, TG1101-RMS301, and TG1101- RMS302 and to assess the impact of potential covariates, including disease, on ublituximab PK

• Characterise E-R safety relationships for ublituximab in subjects with RMS enrolled in Studies TG1101-RMS201, TG1101-RMS301, and TG1101-RMS302 for selected safety endpoints, including infusion-related reaction

• Characterise exposure response (E-R) efficacy relationships for ublituximab in subjects with RMS from Studies TG l 101-RMS301 and TG l 101-RMS302 for the following efficacy endpoints: ARR and total number of gadolinium-enhancing Gadolinium (Gd)-enhancing Tl-lesions by MRI scan at Week 96,

• Evaluate the influence of covariates on significant E-R efficacy and safety relationships for ublituximab,

• Evaluate PopPK and E-R relationships to support a recommended therapeutic dose for subjects with RMS.

Population PK Analysis

The PopPK dataset included 5624 quantifiable ublituximab serum concentrations from 591 subjects with RMS including 47 subjects in Study TG 1101-RMS201, 272 subjects in Study TG 1101-RMS301 and 272 subjects in Study TG 110 l-RMS302. This data was combined with a previous dataset of ublituximab in subjects with haematologic malignancies enrolled in two Phase 1 studies (CD20-0703 and TGTX-1101-101) and one Phase 3 study (UTX-TGR-304). The combined dataset included a total of 7485 quantifiable ublituximab serum concentrations from 895 subjects. During base PopPK model development, an additional 15 outlying concentrations were excluded. The final PopPK model development was based on a dataset including 7470 quantifiable ublituximab serum concentrations from 894 subjects.

PK parameter estimates for a typical subject (defined as a male subject that is ADA negative with a body weight of 73 kg from North America or Western Europe) were as follows: CL was estimated to be 11.6 mL/h, with inter-individual variability (IIV) of 38.1%; Ve was estimated to be 3.18 L(IIV=15.0%); peripheral volume of distribution (Vp) was estimated to be 3.60 L (IIV=21.3%); and inter-compartmental clearance (Q) was estimated to be 11.6 mL/h.

Body weight and ADA were found to be statistically significant predictors of ublituximab CL. Ublituximab CL was modestly increased by 14% in subjects that were ADA positive compared to those had no quantifiable ADA. For the wide range of body weight in the RMS subpopulation (45.1 to 154 kg), CL ranged from 22% lower to 48% higher compared to that for a typical subject with a body weight of 73 kg. In addition at late times (417 d after the start of treatment), CL was reduced by a median of 12.5%.

Body weight, sex and region were found to be a statistically significant predictor of Ve. Subjects from Eastern Europe were found to have slightly higher (10%) Ve than Western Europeans and North Americans and females had slightly lower (7%) Ve than males. For the wide range of body weight in the RMS subpopulation (45.1 to 154 kg), central volume of distribution (Vc) ranged from 19% lower to 38% higher than that for a typical subject with a body weight of 73 kg.

After inclusion of body weight in the model, there was no effect of age, haemoglobin concentration, platelet count, white blood cell count, renal impairment or hepatic impairment on ublituximab PK.

Final Model Evaluation

Model parameters were estimated with relative standard error (RSE) <20% for structural and covariate model parameters and RSE <30% for random effects estimates. Shrinkage was acceptable for CL and Ve (5.32% and 32.6%, respectively) with large shrinkage on Vp (40%).

Key goodness of fit (GOF) diagnostics for the ublituximab final PopPK model suggest satisfactory fit with minimal bias in residuals over time and across predicted concentration values and show good agreement between predicted and observed concentrations.

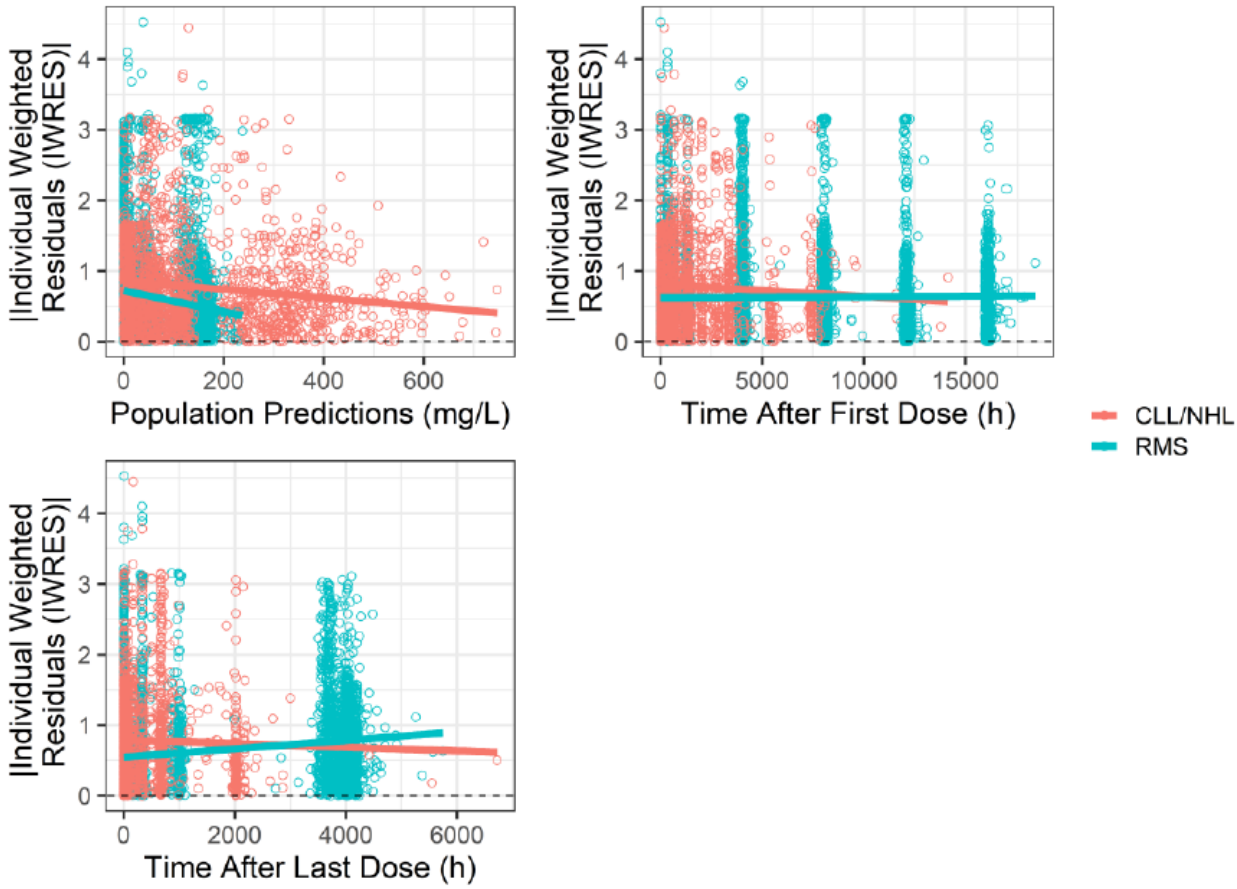
Relative to the base model, ETA - covariate relationships were resolved and no further trends between ETAs (on CL and Ve) and covariates were evident in the RMS subpopulation, suggesting that the model adequately captured significant covariate relationships.

The prediction-corrected visual predictive checks (pcVPCs) stratified by study and overall by time and time after last dose evaluated the ability of the model to reproduce the distribution of the data (Figure 3).

Overall, the pcVPC plots suggest that the model well predicts the central tendency of the observed ublituximab concentrations and adequately captures the range of the data. The relative importance of covariate effects included in the final PopPK model was evaluated with a forest plot of relative changes in exposure ($C_{max\text{-}ss}$, $C_{min\text{-}ss}$, and AUC_{ss}) when covariates were varied one at a time (i.e., univariate analysis). The effects of these covariates, including body weight, sex, region ADA and the fractional change in CL at late times, on ublituximab exposures fell within the range of 0.8 to 1.25 compared to the reference exposure (defined as the exposure for a male subject from North America/Western Europe with a body weight of 73 kg, who is ADA negative and has been on treatment for <416 days. Consequently, none of the covariates were deemed clinically relevant. Furthermore, the covariates did not have a significant impact on the magnitude of IIV on CL or Ve. The combined effects of body weight and ADA reduced IIV by only 2.8%, from 39.2% in the base model to 38.1 % in the final model. Similarly, body weight, sex and region reduced IIV by 18.5% in Ve from 18.4% in the base model to 15.0% in the final model.

The applicant submitted the GOF plots separately for the RMS population and for participants with haematologic malignancies (CLL/NHL) (Figure 2). The GOF lines for RMS and CLL/NHL overlap, further supporting the inclusion of all data in the population PK model.

Figure 2: GOF Diagnostics of the Ublituximab Final Model (Run UMS165)



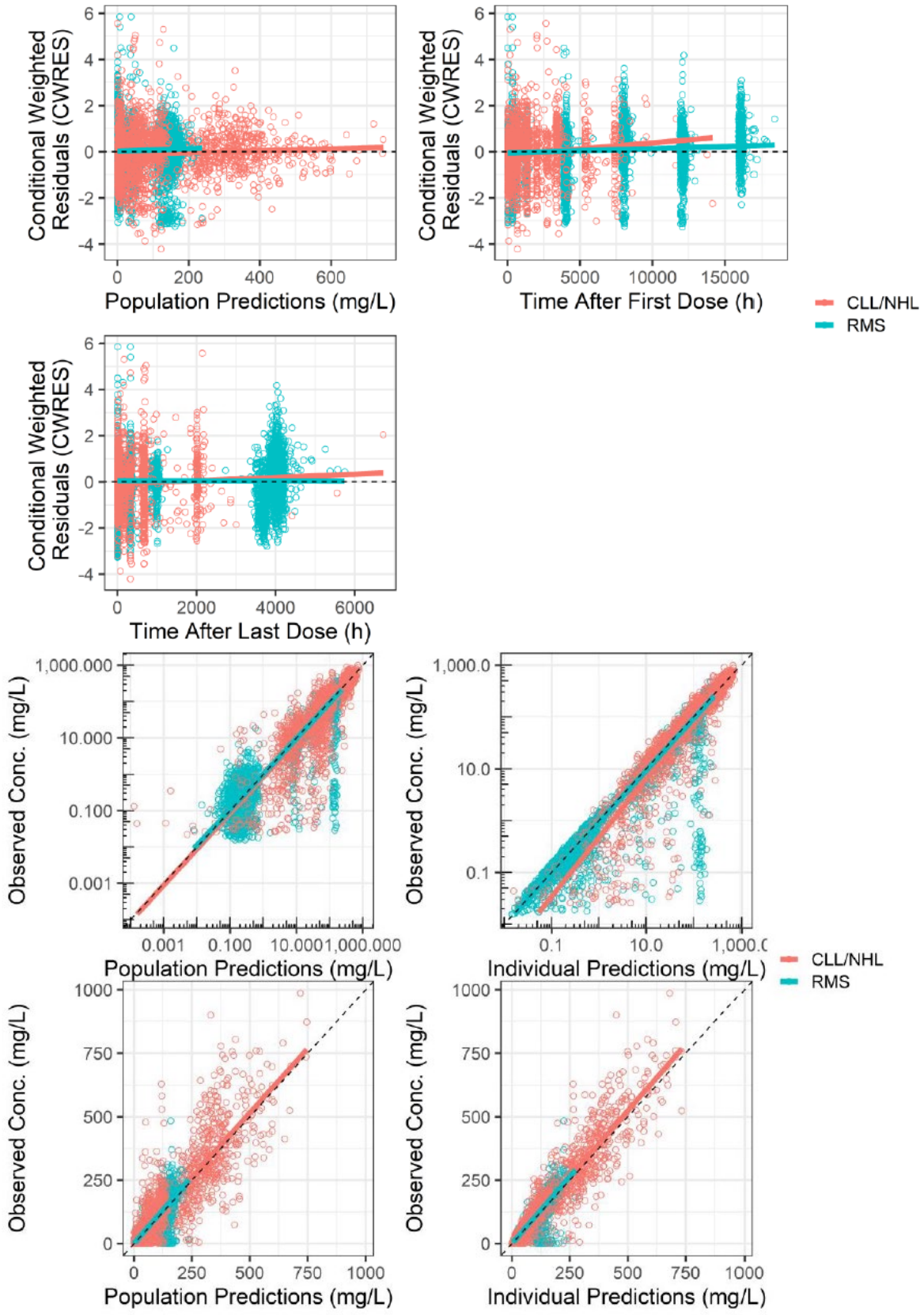
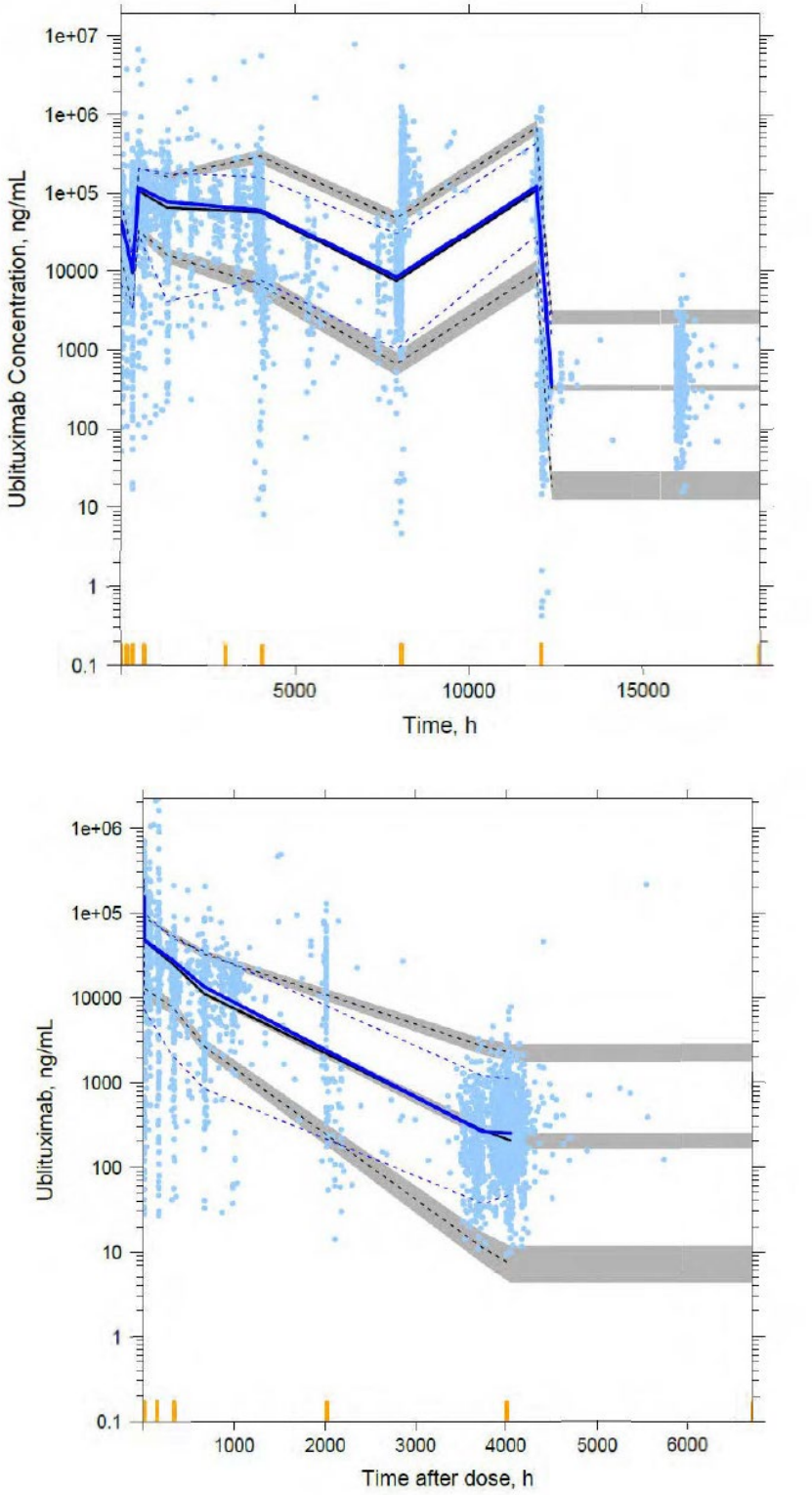

Conditional Weighted Residuals (CWRES)
Population Predictions (mg/L)
Time After First Dose (h)
Time After Last Dose (h)
Observed Conc. (mg/L)
Individual Predictions (mg/L)
CLL/NHL
RMS

Figure 3: pcVPC for the Ublituximab Final PopPK Model (Run UMS165) by Study



pcVPC=prediction-corrected visual predictive check; PI=prediction interval; pred-corr=prediction-corrected; PopPK=population pharrnacokinetic(s).
Note: The blue dots are prediction-corrected observed concentrations; the blue lines are the 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations; and the black lines are the 50th (solid), 5th (dashed), and 95th (dashed) percentiles of simulations. The gray bands are the 95% Pis for the corresponding black lines based on 500 simulations. The short yellow lines indicate bin intervals.

It can be noted that up to approximately 8000 h a lot of prediction-corrected observed concentrations are out of the 5th-95th percentiles of simulation. Furthermore, it can be noted an overprediction of the 5th percentile up to approximately 2000h and then an overprediction.

C_{min-ss} was more variable, varying up to 65% between covariate categories. Although baseline body weight was a statistically significant covariate influencing ublituximab PK, subjects with a body weight of ≥80 kg had slightly decreased C_{max-ss} and average concentration (C_{avg}) at steady state (C_{avg-ss}) compared with subjects with a body weight of <80 kg (geometric mean ratios of Cavg,ss = 0.799, C_{max-ss} =0. 823) while C_{min-ss} was decreased by 44%. As renal impairment was correlated with body weight (R=-0.43), differences in exposures between subjects with normal and mild renal impairment reflected variations in body weight. Similarly, differences in exposures by sex reflected variations in body weight (R=-0.40). ADA demonstrated a modest effect on exposures (geometric mean ratio for C_{max-ss}, C_{avg-ss} and C_{min-ss} = 0.972, 0.859 and 0.621, respectively. These findings suggest that none of the evaluated covariates had a clinically relevant impact on ublituximab exposure.

Predicted Exposure Metrics Based on the Final PopPK Model

The final model of ublituximab was utilised to obtain individual post hoc estimates of PK parameters (AUCss, C_{avg-ss}, C_{max-ss}, and C_{min-ss}) at Week 48 (Table 3).

The geometric mean t½ (90% confidence interval [CI]) was calculated to be 21.8 days (21.4, 22.1 days). Median time to reach steady state was determined to be 15.5 weeks. Accordingly, there was no accumulation for subjects that received the per-protocol regimen of 150 mg ublituximab on Day 1 followed by 450 mg on Day 15, Week 24 and Week 48. The median C_{max} ratio at Week 24 to C_{max} on Day 1 was 3.04 (range 3.00 to 3.42) consistent with the 3-fold increase in the amount of the dose and indicative of no accumulation. Similarly, the C_{max} ratio at Week 48 to Week 24 was 1, indicative of no accumulation.

Table 3: Model-Predicted Ublituximab Exposure Metrics Following the Week 48 Dose Stratified by Dose

Dose	150 mg	450 mg	600 mg
N	7	555	31
AUC_{ss} (μg.d/mL)	1320 (48.4)	3000 (28)	3730 (40.2)
C_{avg} (ng/mL)	3930 (48.4)	8940 (28)	11100 (40.2)
C_{max} (ng/mL)	55700 (29.6)	139000 (15.1)	187000 (16.1)
C_{min} (ng/mL)	88.8 (160)	139 (170)	127 (388)

Based on the final PopPK model, C_{max-ss} and C_{avg-ss} varied by 20% between covariate categories for all covariates of interest. C_{min-ss} was more variable, varying up to 65% between covariate categories. Although baseline body weight was a statistically significant covariate influencing ublituximab PK, subjects with a body weight of 2:80 kg had slightly decreased C_{max-ss} and C_{avg-ss} compared with subjects with a body weight of <80 kg (geometric mean ratios of C_{avg-ss} = 0.799, C_{max-ss} = 0. 823) while C_{min-ss} was decreased by 44%. As renal impairment was correlated with body weight (R=-0.43), differences in exposures between subjects with normal and mild renal impairment reflected variations in body weight. Similarly, differences in exposures by sex reflected variations in body weight (R=-0.40). ADA demonstrated a modest effect on exposures (geometric mean ratio for C_{max-ss}, C_{avg-ss} and C_{min-ss} = 0.972, 0.859 and 0.621, respectively. These findings suggest that none of the evaluated covariates had a clinically relevant impact on ublituximab exposure.

Exposure-Response Efficacy Analysis

A total of 543 subjects with RMS were included in the ublituximab efficacy E-R analyses of ARR (ARR dataset), and total number of Gd-enhancing Tl-lesions per MRI scan at Week 96 (MRI dataset).

Table 4: Summary of Observed Efficacy Endpoints in the Ublituximab Efficacy Exposure-Response Dataset By Study

	TG1101-RMS301 (N = 271)	TG1101-RMS302 (N=272)	Overall (N = 543)
Annualized Relapse Rate			
Mean (SD)	0.107 (0.332)	0.116 (0.336)	0.111 (0.349)
Median [Min, Max]	0 [0, 2.80]	0 [0, 3.07]	0 [0, 3.07]
Total Number of Gadolinium Enhancing T1-Lesions per MRI Scan at Week 96			
Mean (SD)	0.0295 (0.133)	0.0374 (0.194)	0.0335 (0.167)
Median [Min, Max]	0 [0, 1.00]	0 [0, 2.25]	0 [0, 2.25]
Missing	6 (2.2%)	0 (0%)	6 (1.1%)

Table 5: Summary of Observed ARR Endpoint in the Ublituximab Efficacy Exposure-Response Dataset By Quartiles of Exposure Metrics

	Q1 (N=136)	Q2 (N=136)	Q3 (N=135)	Q4 (N=136)	Overall (N=543)
Annualized Relapse Rate					
$C_{max,ss}$ following Week 48 Dose					
Mean (SD)	0.0854 (0.321)	0.0908 (0.354)	0.150 (0.362)	0.120 (0.357)	0.111 (0.349)
Median [Min, Max]	0 [0, 2.32]	0 [0, 3.07]	0 [0, 1.65]	0 [0, 2.80]	0 [0, 3.07]
$C_{min,ss}$ following Week 48 Dose					
Mean (SD)	0.130 (0.409)	0.122 (0.372)	0.0730 (0.230)	0.121 (0.359)	0.111 (0.349)
Median [Min, Max]	0 [0, 2.32]	0 [0, 3.07]	0 [0, 1.10]	0 [0, 2.80]	0 [0, 3.07]
$C_{avg,ss}$ following Week 48 Dose					
Mean (SD)	0.0812 (0.319)	0.148 (0.429)	0.104 (0.291)	0.113 (0.343)	0.111 (0.349)
Median [Min, Max]	0 [0, 2.32]	0 [0, 3.07]	0 [0, 1.65]	0 [0, 2.80]	0 [0, 3.07]
$C_{max,ss}$ following the first dose					
Mean (SD)	0.0854 (0.321)	0.0870 (0.353)	0.154 (0.363)	0.120 (0.357)	0.111 (0.349)
Median [Min, Max]	0 [0, 2.32]	0 [0, 3.07]	0 [0, 1.65]	0 [0, 2.80]	0 [0, 3.07]

Table 6: Summary of Observed Total Number of Gadolinium Enhancing Tl-Lesions per MRI Scan at Week 96 in the Ublituximab Efficacy Exposure-Response Dataset By Quartiles of Exposure Metrics

	Q1 (N=135)	Q2 (N=134)	Q3 (N=134)	Q4 (N=134)	Overall (N=537)
Total Number of Gadolinium Enhancing T1-Lesions per MRI Scan					
$C_{max,ss}$ following Week 48 Dose					
Mean (SD)	0.0222 (0.124)	0.0454 (0.232)	0.0181 (0.100)	0.0485 (0.179)	0.0335 (0.167)
Median [Min, Max]	0 [0, 1.00]	0 [0, 2.25]	0 [0, 0.750]	0 [0, 1.25]	0 [0, 2.25]
$C_{min,ss}$ following Week 48 Dose					
Mean (SD)	0.0185 (0.0948)	0.0181 (0.101)	0.0329 (0.162)	0.0647 (0.255)	0.0335 (0.167)
Median [Min, Max]	0 [0, 0.750]	0 [0, 0.750]	0 [0, 1.25]	0 [0, 2.25]	0 [0, 2.25]
$C_{avg,ss}$ following Week 48 Dose					
Mean (SD)	0.0167 (0.026)	0.0224 (0.112)	0.0466 (0.241)	0.0485 (0.179)	0.0335 (0.167)
Median [Min, Max]	0 [0, 0.750]	0 [0, 1.00]	0 [0, 2.25]	0 [0, 1.25]	0 [0, 2.25]
C_{max} following the first dose					
Mean (SD)	0.0222 (0.124)	0.0454 (0.232)	0.0181 (0.100)	0.0485 (0.179)	0.0335 (0.167)
Median [Min, Max]	0 [0, 1.00]	0 [0, 2.25]	0 [0, 0.750]	0 [0, 1.25]	0 [0, 2.25]

Table 7: Descriptive Statistics of the Ublituximab Exposure Metrics By Quartiles (ARR Dataset)

Exposure	Quantiles	N	Minimum	Geometric Mean	Median	Maximum	SD
$C_{avg,ss}$ following W48 Dose (ng/mL)	Q1	136	2065.9	6225.7	6606.7	7757.4	1123.2
	Q2	136	7760.3	8388.4	8376.2	9060.9	387.31
	Q3	135	9062.6	9808.4	9849.6	10673	483.89
	Q4	136	10697	12344	11917	32796	2854.1
C_{max} following First Dose (ng/mL)	Q1	136	3898.3	36390	37996	41474	4793.9
	Q2	136	41536	44034	44164	46442	1317.4
	Q3	135	46452	48404	48580	50554	1260.8
	Q4	136	50582	54644	53786	74551	4066.0
$C_{max,ss}$ following W48 Dose (ng/mL)	Q1	136	47363	111807	115466	125736	12695
	Q2	136	125831	133563	134117	140663	3999.9
	Q3	135	140925	147126	147626	153836	3962.0
	Q4	136	153882	166717	163628	227648	12892
$C_{min,ss}$ following W48 Dose (ng/mL)	Q1	136	0.019005	32.580	41.480	73.871	20.090
	Q2	136	74.233	104.17	104.06	152.04	22.581
	Q3	135	152.72	223.66	225.96	308.91	46.838
	Q4	136	312.11	524.97	461.37	9782.4	960.59

Table 8: Descriptive Statistics of the Ublituximab Exposure Metrics By Quartiles (MRI Dataset)

Exposure	Quantiles	N	Minimum	Geometric Mean	Median	Maximum	SD
$C_{avg,ss}$ following W48 Dose (ng/mL)	Q1	135	2126.2	6351.2	6647.4	7790.9	1019.9
	Q2	134	7792.4	8417.2	8395.2	9076.1	382.81
	Q3	134	9076.9	9826.2	9854.9	10697	482.58
	Q4	134	10707	12361	11918	32796	2870.2
C_{max} following First Dose (ng/mL)	Q1	135	3898.3	36355	37978	41446	4796.6
	Q2	134	41474	43962	44138	46376	1296.1
	Q3	134	46381	48350	48543	50546	1282.2
	Q4	134	50554	54674	53786	74551	4083.7
$C_{max,ss}$ following W48 Dose (ng/mL)	Q1	135	84540	114070	115890	125850	8443.7
	Q2	134	126270	133680	134140	140660	3913.5
	Q3	134	140920	147130	147650	153840	3976.9
	Q4	134	153880	166830	163630	227650	12939
$C_{min,ss}$ following W48 Dose (ng/mL)	Q1	135	0.019005	32.866	41.783	74.233	20.023
	Q2	134	74.345	105.37	104.52	156.71	23.111
	Q3	134	156.72	225.45	228.48	312.11	46.668
	Q4	134	314.77	528.34	466.47	9782.4	966.95

The relationship between ARR and ublituximab was explored using negative binominal regression. No statistically significant exposure-efficacy relationship (p=0.111) was observed.

Although not statistically significant, exploratory evaluations are shown for C_{max-ss} following the Week 48 dose, as it has the lowest p-value. The model was then used to predict ARR for subjects who received 450 mg every 24 weeks. The 95% CI of the model-predictions across percentiles overlap, suggesting similar treatment benefit across ublituximab exposure groups.

The relationship between the total number of Gd enhancing Tl-lesions per MRI scan at week 96 and ublituximab was explored using negative binominal regression. No statistically significant exposure-efficacy relationship (p=0.273) was observed. Although not statistically significant, exploratory evaluations are shown for C_{avg-ss} as it was the exposure with the lowest p-value.

Absorption

Ublituximab is administered as an IV infusion. No studies with other routes of administration were performed. No food interaction studies were conducted, which is acceptable given the route of administration.

Distribution

The PopPK model-estimated Ve was estimated to be 3.18 L (IIV 16%) and Vp was estimated to be 3.60 L (IIV=21.3%).

Elimination

The PopPK model-estimated systemic clearance was 11.6 mL/h with IIV of 38.1%. The inter compartmental clearance was 11.6 mL/h. The geometric $t_{1/2}$ (90% CI) was calculated to be 21.8 days (21.4, 22.1 days). Time to reach steady state was 15.6 weeks. Ublituximab is expected to be degraded

to small peptides and amino acids by ubiquitous proteolytic enzymes. Thus, classic hepatic metabolism pathways are not involved in the clearance of Ublituximab.

Dose proportionality and time dependencies

Study TGTX1101-101 was a Phase 1 first-in-human dose-escalation study in participants with haematologic malignancies that enrolled 3 to 6 participants at each dose level of 450 mg, 600 mg, 900 mg, and 1200 mg study. Data from this study seems to not support the dose proportionality between 450 mg and 1200 mg.

Upon request, the applicant submitted figures of observed ublituximab plasma concentrations versus time after dose for all studies.

The model-predicted ublituximab concentrations were provided in Table 9.

Table 9: Model-Predicted Ublituximab Exposure Metrics Following the Week 48 Dose Stratified by Dose

Dose	150 mg	450 mg	600 mg
N	7	555	31
AUC_{ss} (μg.d/mL)	1320 (48.4)	3000 (28)	3730 (40.2)
C_{avg} (ng/mL)	3930 (48.4)	8940 (28)	11100 (40.2)
C_{max} (ng/mL)	55700 (29.6)	139000 (15.1)	187000 (16.1)
C_{min} (ng/mL)	88.8 (160)	139 (170)	127 (388)

No accumulation of ublituximab was observed for subjects receiving 150 mg ublituximab on Day 1 followed by 450 mg 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).

Special populations

- **Impaired renal and hepatic function**

No studies with renal or hepatic impaired patients were conducted. The exposures of ublituximab were comparable among subjects with mild (n=101) renal impairment compared to subjects with normal (n=454) renal function. The exposures of ublituximab were comparable among subjects with mild (n=19) or moderate (n=3) hepatic impairment relative to those with normal (n=494) hepatic function, although the number of subjects with hepatic impairment is limited.

- **Gender**

Sex was found to be a statistically significant predictor of Vc. Females had a slightly lower (7%) Vc than males. C_{max} values were not differentiated according to the sex - for males mean C_{max} was 125 ug/ml (90%CI -123, 128) and for females mean C_{max} was 148 ug/mL (90%CI -146, 150). A ratio between male and female C_{max} was 1.18. Sex differences for Vc values seem to be out of clinical significance.

- **Race**

Region was found to be a statistically significant predictor of Ve. Subjects from Eastern Europe were found to have slightly higher (10%) Ve than Western Europeans and North Americans. White/all other participants have mean C_{max} ratio 1.04. Race differences in PK parameters values seem to be out of clinical significance.

- **Weight**

Body weight was found to be statistically significant predictors of ublituximab CL. According to popPK, for the wide range of body weight in the RMS subpopulation (45.1 to 154 kg), CL ranged from 22% lower to 48% higher compared to that for a typical subject with a body weight of 73 kg. In addition at late

times (417 d after the start of treatment), CL was reduced by a median of 12.5%. Mean values for C_{max} for participants weighting above 80 kg was 121 ug/mL (118, 123) and mean values for C_{max} for participants weighting under 80 kg was 147 ug/mL (145, 149). C_{max} ratio between groups of patients weighting above and under 80 kg was 0.823.

Ublituximab CL in the popPK model ranged from 22% lower to 48% higher compared to that for a typical subject with a body weight of 73 kg across the ranges of body weights (median weight 69 kg, range 45.1 to 154.0 kg), however, as observed in the exposure-safety and exposure-efficacy analyses, ublituximab exposure had no impact on safety or efficacy observations in the RMS population.

Endpoints for efficacy (ARR and total number of Gd-enhancing T1-lesions per MRI scan at Week 96) and safety [AEs of special interests (AESI)] were plotted by exposure quartiles and no positive trends were observed in the RMS population Therefore, differences in body weight resulting in slight differences in exposure are not correlated with efficacy or safety responses with ublituximab treatment.

- **Elderly**

Age was not significant predictors of ublituximab popPK and was not deemed clinically relevant. A C_{max} ratio for patients under 35 and above 35 was 0.979. According to the popPK, age was not deemed to be clinically relevant for ublituximab PK.

The oldest enrolled patients in the Phase III programme were 55 years of age but the population database for the ublituximab popPK includes participants with MS (n=593) and with haematologic malignancies (n=338) up to 88 years of age, with 171 participants (18%) ≥65 years of age including 65 patients enrolled in study TG1101-RMS303 as per the cut off of 01 March 2022.

- **Children**

No dedicated PK studies in paediatric population were performed. A PIP has been adopted.

Pharmacokinetic interaction studies

No formal DDI studies have been performed with ublituximab as no drug interactions are expected via cytochrome P450 enzymes, other metabolising enzymes, or transporters.

Pharmacokinetics using human biomaterials

No PK studies with human biomaterial was performed.

Bioequivalence studies

The applicant presented two bioequivalence studies for the bioequivalent teriflunomide product used as active comparator in the pivotal trials TG1101-RMS301 and TG 1101-RMS302, namely Study 150123 and Study 150124. Moreover, the validation report 155037 ANIA dated 29.09.2015 (used for studies 150123 and 150124) has been also submitted.

The two bioequivalent studies 150123 and 150124 were correctly performed in terms of enrolled subjects, wash-out period, sampling. It was declared that were conducted in GCP compliance. The bioanalytical method used to determine teriflunomide concentrations was validated and the validation report as well as the bioanalytical reports were attached in the dossier.

2.6.2.2. Pharmacodynamics

Mechanism of action

Ublituximab is a recombinant chimeric mAb that is specific for the CD20 antigen expressed on the surface of B cells. It is composed of a murine variable region fused onto a human constant region and displays

the typical structure of immunoglobulin G (IgG) 1 consisting of 2 gamma heavy chains and 2 kappa light chains linked with 16 intra- and inter-chain disulfide bridges. It is composed of a total of 1322 amino acids (144 kDa).

With regard to disease pathogenesis, the role of B-cells in autoimmune diseases has been of great priority in both pre-clinical and clinical research in autoimmune diseases, especially in MS. B-cells can form autoantibodies, which can result in pathological immune complex deposition that can activate the complement system as well as initiate acute inflammatory cascade by producing pro-inflammatory cytokines and chemokines. Further, B cells have been shown to regulate the formation and function of T cells, which can aid in the demyelinating events seen with MS.

Primary pharmacology

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 (TG1101-RMS201).

This was a 52-week, placebo-controlled phase 2, dose-finding study of ublituximab in patients with RMS. Primary objectives were to determine the B-cell depletion after ublituximab infusion in RMS patients and determine optimal dose and infusion time for ublituximab in subjects with RMS. The primary efficacy variable was the responder rate of B-cell depletion at Week 4, which was defined as the proportion of subjects who had reduced B-cell depletion by ≥95% at Week 4 (2 weeks after Week 3 Day 15, the second scheduled infusion of ublituximab). Subjects within each cohort received ublituximab on Day 1, Day 15, and Week 24 or placebo on Days 1 and 15. Placebo Patients received ublituximab after completion of week 4. Overall, six cohorts with different dose regimens and infusion times were tested. Total 45 subjects completed the 48-week treatment periods. Mean age across cohorts ranged from 34.3 to 44.9. Most patients enrolled were females 66.7%, and most were White – 81.3%.

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%) (2.2.3.2.). 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 10).

Table 10: CD19+ B-cell Depletion Responder Rate (ITT Population)

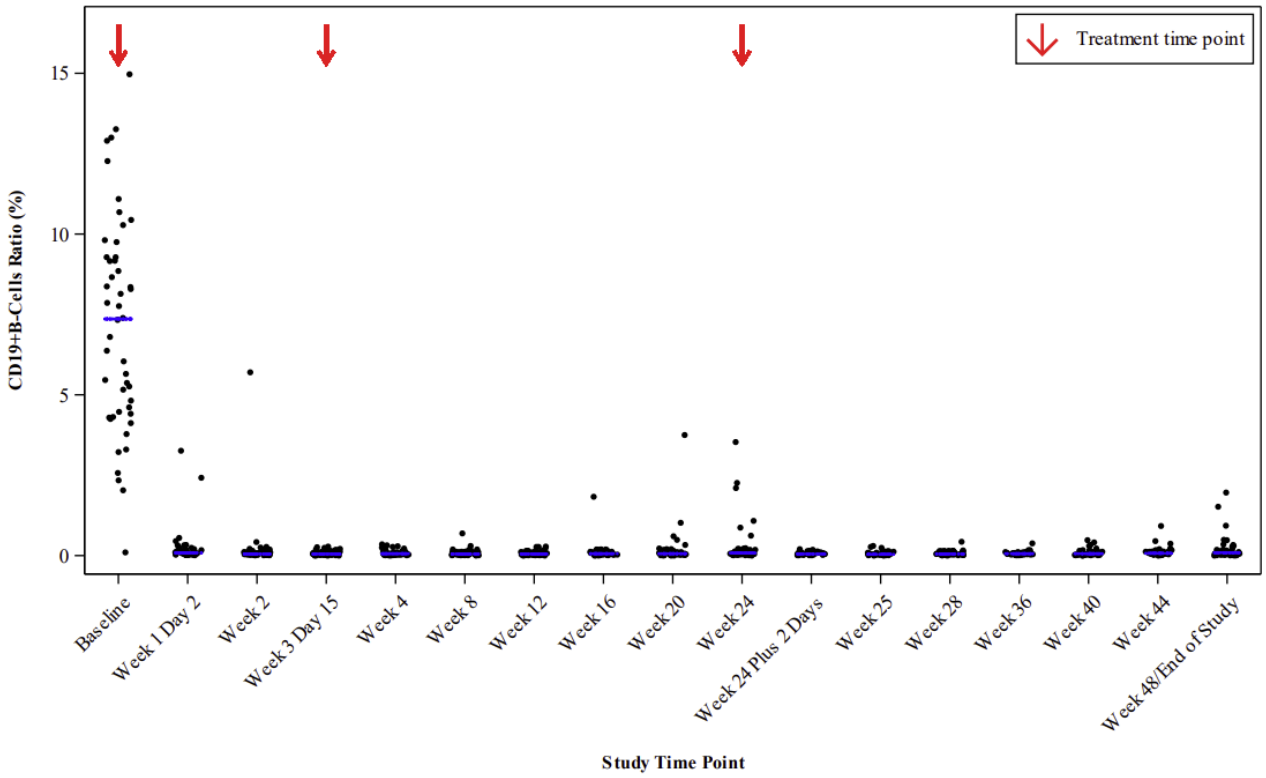
CD19+ B Cell Count (%)	Cohort 1 (N=8)	Cohort 2 (N=8)	Cohort 3 (N=8)	Cohort 4 (N=8)	Cohort 5 (N=8)	Cohort 6 (N=8)	Total (N=48)
Responder rate (%) (95% CI)[a, b]	87.5 (47.35, 99.68)	100 (63.06, 100)	87.5 (47.35, 99.68)	100 (63.06, 100)	100 (63.06, 100)	100 (63.06, 100)	95.8 (85.75, 99.49)

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). b The 95% CI was estimated using the Clopper-Pearson (exact) method.

The median percentage change from baseline in CD19+ B cell count was -98.6% within 24 hours following the first infusion of ublituximab (Week 1 Day 2); B-cell reduction was sustained 2 weeks later at Week 3 Day 15 (immediately prior to the second infusion of ublituximab: -99.1%), at Week 4 (-99.2%), at Week 24 (immediately prior to the third infusion of ublituximab: -98.6%), and also at Week 48/end of study (-98.9%).

The percentage change from baseline in CD19+ B cell count was generally similar across cohorts. Reductions in memory (CD19+CD27+) and naïve (CD19+CD27-) B cells were also observed across all cohorts from Week 1 Day 2 through Week 48/end of study (Figure 4).

Figure 4: CD19+ B Cell Count (%) by Visit (ITT Population)



Phase III: Ublituximab In Multiple Sclerosis Treatment Effects (ULTIMATE I STUDY) - TG1101-RMS301

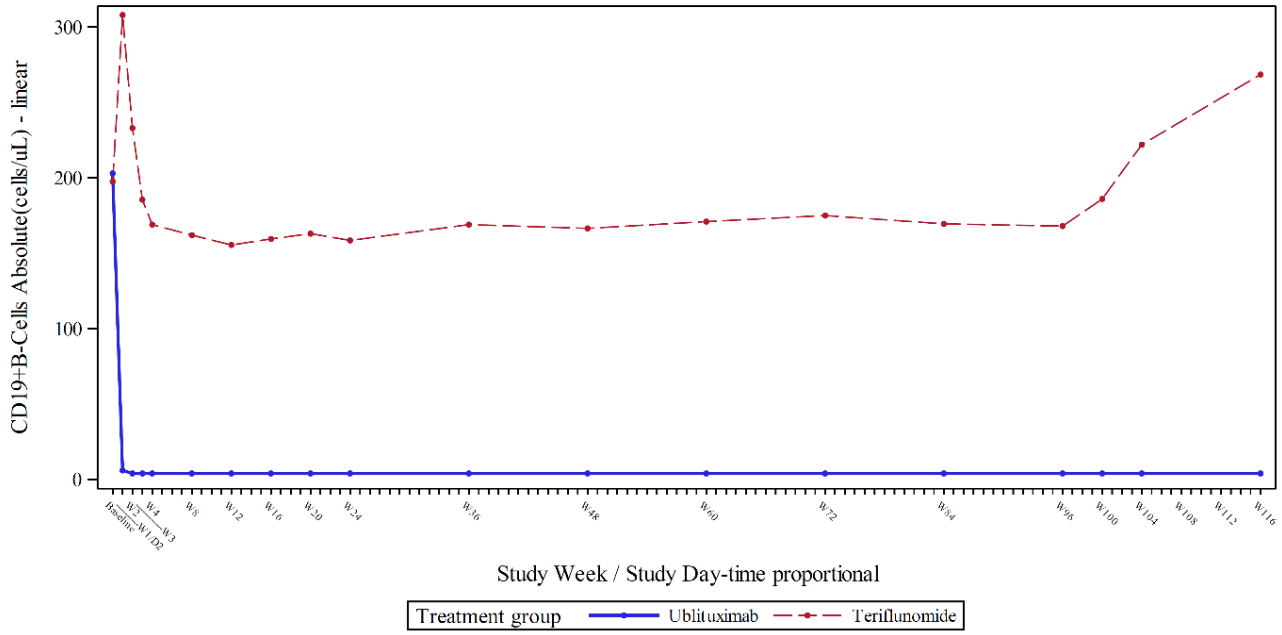
B lymphocyte cell counts (% CD19+ B cells) were tabulated per scheduled time point together with absolute and percentage changes from baseline. Blood collection for CD19+ B-Cell Counts was performed at screening, Days 1, 2, 8, and 15; Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, and 84; and end of study.

Overall, participants in the ublituximab group had a greater decrease in the mean number of CD19+ B cells over the 116-week study period than participants in the teriflunomide group.

The mean number of CD19+ B cells at baseline was similar in both treatment groups (224.9 cells/µL in the ublituximab group and 223.9 cells/µL in the teriflunomide group). Starting at Week 1 Day 2, participants in the ublituximab group had a notable decrease from baseline in the mean number of CD19+ B cells (-216.5 cells/µL [95.46% reduction]), which remained generally consistent through Week 116 (-156.7 cells/µL [78.63% reduction]).

Participants in the teriflunomide group had a slight increase from baseline in the mean number of CD19+ B cells at Week 1 Day 2 (92.6 cells/µL [56.11% increase]) and Week 2 (20.6 cells/µL [15.28% increase]) and fluctuated within <2% through Week 116.

Figure 5: B Lymphocyte Cell Counts – Median (mITT Population)



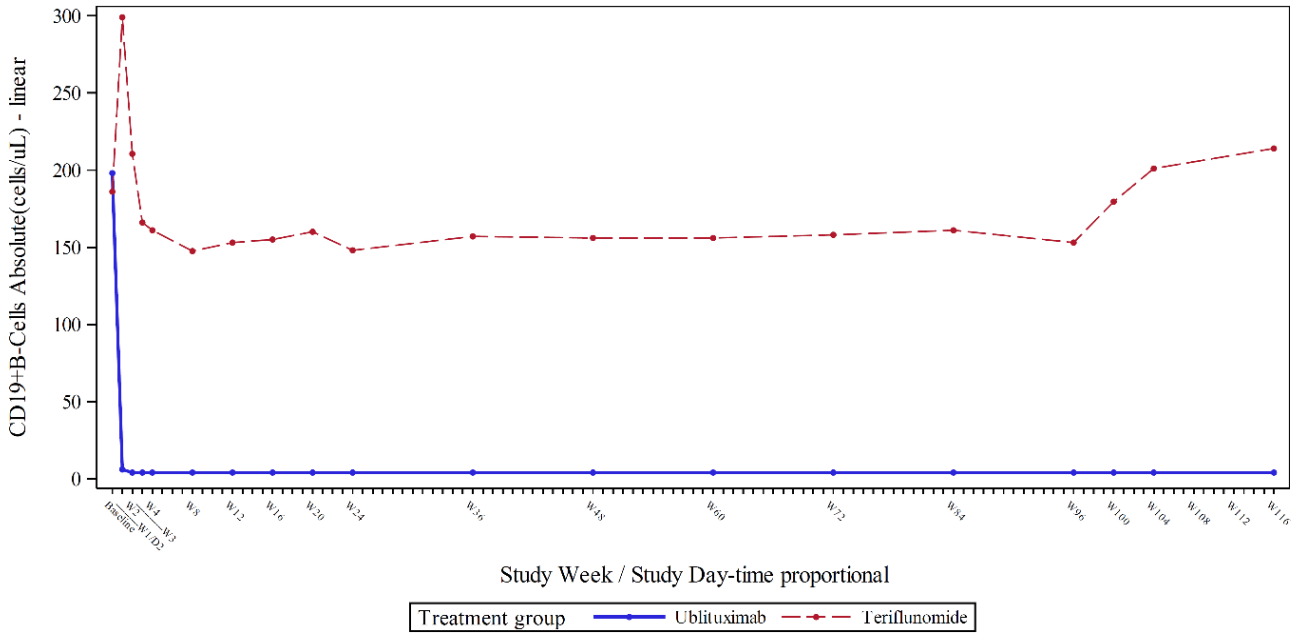
Phase III: Ublituximab In Multiple Sclerosis Treatment Effects (ULTIMATE II STUDY) - TG1101-RMS302

B lymphocyte cell counts (% CD19+ B cells) were tabulated per scheduled time point together with absolute and percentage changes from baseline. Blood collection for CD19+ B-Cell Counts was performed at screening; Days 1, 2, 8, and 15; Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, and 84; and end of study.

The mean number of CD19+ B cells at baseline was similar in both treatment groups (225.0 cells/µL in the ublituximab group and 221.7 cells/µL in the teriflunomide group). Starting at Week 1 Day 2, participants in the ublituximab group had a decrease from baseline in the mean number of CD19+ B cells (-216.4 cells/µL [95.66% reduction]), which remained consistent through Week 116 (-201.3 cells/µL [97.87% reduction]).

Participants in the teriflunomide group had a slight increase from baseline in the mean number of CD19+ B cells at Week 1 Day 2 (108.5 cells/µL [68.25% increase]) and Week 2 (20.9 cells/µL [19.08% increase]) and fluctuated within <2% through Week 116.

Figure 6: B Lymphocyte Cell Counts – Median (mITT Population)



Secondary pharmacology

QT

An electrocardiogram (ECG) assessment was conducted as part of the 4-week, repeat-dose, GLP monkey toxicology study. Ublituximab was administered IV to monkeys (3 per sex per group) at dose levels of 0 (vehicle control), 10, or 50 mg/kg once weekly for 4 weeks. ECG examinations were performed on all animals before the beginning of the treatment period, 60 minutes and 6 hours after the first administration (Day 1), and 6 hours after treatment on Days 8, 15, and 22. These examinations were performed using a Cardiovit AT-6 Schiller instrument and standard leads I, II, and III. In the first instance, the heart rate, PQ and QT intervals, and the QRS-complex duration were determined on lead II. Animals were lightly anesthetised with ketamine hydrochloride.

No ublituximab-related abnormalities in rhythm or waveform morphology were found at any dose level based on comparison of pre-dose and post-dose ECG recordings. There were no ublituximab-related changes in ECG parameters. A few observed qualitative ECG abnormalities were considered incidental findings unrelated to ublituximab treatment. The highest dose evaluated (50 mg/kg) resulted in a mean C_{max} and mean AUC of 1480 µg/mL and 7270 µg*hr/mL, respectively, on Day 22 of the study. ECG assessments were also included in the 13-week and 26-week repeat-dose, GLP monkey toxicology studies with no ublituximab-related changes in ECG parameters in both studies. The highest dose evaluated (30 mg/kg) resulted in a C_{max} and AUC of 1060 µg/mL and 74000 µg*hr/mL, respectively, on Day 176 of the 26-week study.

No dedicated QTc clinical studies were performed. During monkey toxicology study no ublituximab related abnormalities in rhythm or waveform morphology were found at any dose regimen tested, compared to the baseline pre-dose ECG recordings.

Immunogenicity

In Study TG1101-RMS201, TE-ADA was detected in 21 (52.5%) of 40 evaluable subjects at 1 or more timepoints. Among the subjects with a positive TE-ADA response, NAb were only detected in 1 out of 40 subjects (2.5%). While a decrease in B-cell depletion was noted at Week 24 for this subject, B-cell

depletion was similar to the NAb negative population by Week 48. Additionally, there was no impact on ARR or safety for this subject.

In a pooled analysis of Studies TG1101-RMS301 and TG1101-RMS302, TE-ADA was detected in 434 (81.3%) of 534 evaluable subjects at 1 or more timepoints in either study.

No meaningful effect of ADA presence on PK, PD (mean % change in B-lymphocytes), efficacy (ARR) and safety (any TEAE all grades and grade ≥3, AESI all grades, grade ≥3 and infusion related reactions all grades) endpoint was observed.

The applicant analysed the impact of Nab status on secondary efficacy endpoints. No significant differences were observed for Nab-positive and Nab-negative participants. Secondary efficacy outcomes of patients with neutralizing antibody positive (n=34) and neutralizing antibody negative (n=500) status were compared. There was no meaningful impact of neutralizing antibody on secondary efficacy endpoints of ublituximab in Studies TG1101-RMS301 and TG1101-RMS302.

Pharmacodynamic interactions with other medicinal products or substances

No PD interaction studies were performed. Ublituximab is not considered to enhance or reduce the effect of other substances.

Genetic differences in PD response

Genetic profile is not expected to affect PD of ublituximab.

Relationship between plasma concentration and effect

According to the dose finding study (TG1101-RMS201), similar reduction in CD19+ B-cell counts was seen across dose cohorts

2.6.3. Discussion on clinical pharmacology

The PK profile of ublituximab in RMS patients was characterised during clinical studies TG1101-RMS201, TG1101-RMS301, and TG1101-RMS302. Further, a PopPK model was also developed using data from clinical studies TG1101-RMS201, TG1101-RMS301, and TG1101-RMS302 (TGTX-PMX-TGl 101-2920). A covariate impact on PK of ublituximab PK was also assessed.

Bioanalytical methods were developed, validated and performed to support the clinical development of the ublituximab. Following techniques were developed: ECLIA for ublituximab detection in human serum (validation 01128004), ECLIA for ADA detection in human serum (validation 01128007), and cell-based assay for the detection of neutralising anti-TG-1101 antibodies in human serum (validation 01128016). All methods were validated according to the guidelines: EMEA/CHMP/BMWP/14327/2006 and EMEA/CHMP/EWP/192217/2009. There were several concerns pertaining these bioanalytical studies.

As per study No. 01128004, the applicant was asked to justify the reliability between validated and long-term storage conditions for pivotal studies bioanalyses (No. 01128018, No. 01128012, No. 01128013), as only results for 686 days of storage stability were initially provided (Study No. 01128004) and study samples were stored significantly longer. The applicant provided stability at 1044 days (about 34 months), however the LTS period do not cover the period of storage of samples. The applicant committed to provide by Q3 of 2023 long term storage data covering 45 months i.e. the maximum storage period for samples from clinical studies RMS201, RMS301 and RMS302 (**REC**). Further, the applicant was requested to clarify the findings from two cross-site validations presented in this report however it was determined the popPK model for the RMS programme is comprised mostly of data from the validated ELISA method.

As per study No. 01128007, the applicant was requested to provide the long-term stability data. The applicant declared that the assessment is ongoing to cover the entire period of storage for study samples. During the procedure, the applicant submitted an amendment 2 of the validation report including long-term stability at 923 days (~30 months). The data was considered acceptable but to cover the maximum storage period (56 months), data for other 32 months is neededThe applicant committed to provide by Q2 of 2024 the full Long Term Storage data of ADA to cover samples in clinical trials RMS201, RMS301 and RMS302 and to formalise this commitment via the letter of recommendation as a post approval measure (**REC**). This proposal was considered acceptable.

The BA reports for ADA determination were provided for RMS201 (01128010), RMS301 (01128017) and RMS302 (01128018). The applicant did not provide the corresponding ublituximab concentrations for ADA samples, however, for RMS301 and RMS302 it is reported that 2.2% (6 subjects) and 2.9% (8 subjects), respectively, of subjects showed ublituximab concentrations above the PC (100 ng/ml) drug tolerance of 25 µg/ml. Of them, 3 for RMS301 and 6 for RMS302 were ADA negative, but these results are unreliable. Ublituximab concentrations were not available for RMS201 in which 52.2% of subjects were ADA positive, precluding the identification of samples above the drug tolerance level. Upon request, the applicant provided the addendum of ISI report in which for study RMS201, RMS301 and RMS302 all ublituximab and ADA determinations at each timepoint are reported. Only 18 subjects showed ublituximab concentration above the DTL at one (or two) timepoint. However, all these subjects have an alternate ADA-evaluable sample in which the ublituximab concentrations are below the DTL, therefore the conclusions on their ADA status can be considered reliable. Seven subjects were ADA negative at the timepoint in which ublituximab concentrations were above the DTL, however they were classified as TE-ADA since the presence of other available and reliable determinations. Five subjects were ADA negative at the timepoint in which ublituximab concentrations were above the DTL and were not TE-ADA since they were negative at all other reliable timepoints or the subject is ADA positive at baseline. The applicant response was considered acceptable.

As per Nab assay validation (01128016), it was noted that several Nab negative samples had ublituximab concentration above the drug tolerance (0.1 µg/mL) at LPC and lipemia interference therefore impacting the reliability of negative results, however upon further clarification

the impact of these unreliable Nab determinations is considered limited.

The applicant was requested to clarify how many TE-ADA positive participants have been tested for Nab determination and how many Nab negative participants had ublituximab concentrations exceeding the DTL. The majority of samples had ublituximab concentrations above 1000 ng/ml and considering the drug tolerance at HPC (1000 ng/ml), out of a total of 420 Nab negative patients, 35 had ublituximab concentration above DTL at more than 1 trough timepoints and 8 at all timepoints, therefore the last 8 patients are considered not reliable for Nab determination. The impact of these unreliable Nab determinations is considered limited. Overall, in study RMS201, TE-ADA were 21/40 and 1 is Nab positive; in RMS301 and RMS302 TE-ADA were 434/534 of which 34 were Nab positive. The active comparator used in the pivotal trials TG1101-RMS301 and TG 1101-RMS302 was an unlicensed teriflunomide product bioequivalent to Aubagio which, after the conduct of the pivotal trials, received FDA approval through an abbreviated new drug application (ANDA) supported by two bioequivalence studies. The applicant informed that the product received FDA approval (ANDA 209583) on 24 September 2021 and the status remains unchanged. The applicant also clarified that only one active comparator was used throughout both pivotal trials for all sites, countries and subjects. The applicant provided the case study reports of two bioequivalence studies comparing teriflunomide medicinal product provided by TG therapeutics with Aubagio. Giving the lack of several information, the applicant was requested to submit all documentation for the two bioequivalent studies, namely 150123 and 150124. The two bioequivalent studies 150123 and 150124 were correctly performed in terms of enrolled subjects, wash-out period, sampling. It was declared that they were conducted in GCP compliance. The bioanalytical

method used to determine teriflunomide concentrations was validated and the validation report as well as the bioanalytical reports were attached in the dossier. A PopPK model was developed to predict ublituximab PK parameters; estimated Ve and Vp were 3.18 L (IIV=15.0%) and 3.60 L (IIV=21.3%), respectively. The model estimated CL was 11.3 mL/h (IIV of 38.1%). Mean t1/2 was calculated to be 21.8 days. Bodyweight, sex region, and 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. It was noted that C_{min-ss} varies up to 65% between covariate categories in the popPK and the applicant was requested to clarify justify that predicted values are considerate reliable. The applicant clarified that C_{min} was determined 24 weeks after dose administration (>7 half-lives) and at these concentrations a 65% relative difference in covariate categories represents an absolute difference of only 0.082 µg/mL, which is more than 100-fold lower than the C_{avg}. It was agreed that the impact of 65% variability is not clinically relevant. Ublituximab CL in the popPK model ranged from 22% lower to 48% higher compared to that for a typical subject with a body weight of 73 kg across the ranges of body weights (median weight 69 kg, range 45.1 to 154.0 kg), however, as observed in the exposure-safety and exposure-efficacy analyses, ublituximab exposure had no impact on safety or efficacy observations in the RMS population. A overprediction has been observed, possible reason could be the high data variability, also in the observed data, considering the very broad concentration range of predicted data. This makes difficult the prediction of plasma concentrations and its use as base for further analysis, e.g. E-R and product information. In addition, the exposure-response relationship between Ublituximab C_{max-ss} and ARR showed partial overlap making this analysis not useful to individuate the concentration, thus the corresponding dose, responsible for the target ARR. The same is also true for total number of Gd enhancing T1-lesions per MRI scan at week 96.

As per dose proportionality and time dependency, data from study TGTX1101-101 seems to not support the dose proportionality between 450 mg and 1200 mg. In the submitted figures of observed ublituximab plasma concentrations versus time after dose for all studies, doses below 300 mg were almost absent, thus no support for dose ~300 mg As per the model-predicted ublituximab concentrations, exposure data between 450 mg and 600 mg did not show a clear dose-proportionality also considering the high variability. Therefore, the applicant was requested to narrow the range for the dose proportionality between 150 mg and 450 mg in section 5.2 of the SmPC.

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. No studies with renal and hepatic impaired patients were conducted. According to the pop PK data, the PK of ublituximab were not differentiated between the subjects with mild renal impairment and normal renal function and between patients with mild or moderate hepatic impairment and normal hepatic function. The last is additionally supported as ublituximab is expected to be degraded to small peptides and amino acids by ubiquitous proteolytic enzymes that are not restricted to the hepatic tissue. The population database for the ublituximab popPK includes participants with MS and with haematologic malignancies up to 88 years of age, with 171 participants (65 in TG1101-RMS303 as per 01 March 2022 safety update cut-off) ≥65 years of age. The popPK did not show a significant relationship between age and ublituximab exposure. It also did not show a relationship between disease (MS, haematologic malignancies) and ublituximab clearance. Based on the totality of data, it can be agreed that the PK of ublituximab is expected to be the same in older patients with MS. Therefore, no posology adjustment is recommended in patients with MS over 55 years of age. The applicant's argumentation is acceptable.

PD characteristic of ublituximab was developed in clinical studies: TG1101-RMS201, TG1101-RMS301, and TG1101-RMS302. In dose response study TG1101-RMS201, B-cell depletion within target range

(95%) was maintained before ublituximab dosing at Week 24 and was sustained at Week 48 with a similar reduction in CD19+ B-cell counts across dose cohorts (150 mg, 450 mg and 600 mg). Further, a reduction in CD4+ and increased T reg expression was seen. In studies, TG1101-RMS301, and TG1101-RMS302, at week 1 day 2, patients administrated with ublituximab had a significant decrease of CD19 B-cells from baseline (above 95% reduction) and was maintained through week 116.

No meaningful effect of ADA presence on PK, PD efficacy and safety endpoints was observed. No significant differences were observed for Nab-positive and Nab-negative participants. Secondary efficacy outcomes of patients with neutralizing antibody positive (n=34) and neutralizing antibody negative (n=500) status were compared. There was no meaningful impact of neutralizing antibody on secondary efficacy endpoints of ublituximab in Studies TG1101-RMS301 and TG1101-RMS302.

No dedicated QTc clinical studies were performed. During monkey toxicology study no ublituximab related abnormalities in rhythm or waveform morphology were found at any dose regimen tested, compared to the baseline pre-dose ECG recordings.

No PD interaction studies were performed. Ublituximab is not considered to enhance or reduce the effect of other substances. Upon request, the applicant address the potential of PD interaction ins section 4.5 of the SmPC.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology programme is acceptable.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- The applicant should provide by Q3 of 2023 the Long Term Storage data covering 45 months i.e. the maximum storage period for samples from clinical studies RMS201, RMS301 and RMS302.
- The applicant should provide by Q2 of 2024 full Long Term Storage data of ADA to cover samples in clinical trials RMS201, RMS301 and RMS302.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

Study TG1101-RMS201

Methods

Study TG1101-RMS201 was a 52-week, Phase IIa, placebo-controlled, multicentre, dose-finding, cohort-sequential study. The study included 6 treatment cohorts, each with 8 subjects: 6 subjects randomised to receive ublituximab and 2 subjects randomised receive to placebo.

Eligible subjects were 18 to 55 years of age, with a diagnosis of RMS by McDonald criteria 2010, ≥2 relapses in prior 2 years or 1 relapse in the year prior to Screening and/or ≥1 Gd-enhancing lesion, Expanded Disability Status Scale (EDSS) 0 to 5.5 (inclusive), B cell counts ≥5% of total lymphocytes, and neurologic stability ≥30 days prior to Screening and baseline.

Subjects within each treatment cohort received either ublituximab on Days 1, 15, and Week 24 or placebo on Days 1 and 15. Following completion of Day 28 (Week 4), all subjects randomised to receive placebo entered their respective "a" cohort and received active treatment with ublituximab (Table 11). For all 6 cohorts, the first infusion was a single dose of 150 mg of ublituximab ranging from 1 to 4 hours. The second infusion was on Day 15, ublituximab 450 mg ranging from 1 to 3 hours or 600 mg for 1 hour.

The third infusion was on Week 24, ublituximab 450 mg ranging from 1 to 1.5 hours or 600 mg for 1 hour.

Table 11: Dosing Schema for Ublituximab and Placebo in Study TG1101-RMS201 (Dose Range)

Cohort	Randomization	Treatment Period		
	Treatment and Number of Subjects	Day 1/ Infusion Time	Day 15/ Infusion Time	Week 24/ Infusion Time
1	Ublituximab (n=6)	150 mg/4 h	450 mg/3 h	450 mg/1.5 h
	Placebo (n=2)[a]	Placebo/4 h	Placebo/3 h	-
1a	Ublituximab (n=2)[a]	150 mg/4 h	450 mg/3 h	450 mg/1.5 h
2	Ublituximab (n=6)	150 mg/4 h	450 mg/1.5 h	450 mg/1 h
	Placebo (n=2)[a]	Placebo/4 h	Placebo/1.5 h	-
2a	Ublituximab (n=2)[a]	150 mg/4 h	450 mg/1.5 h	450 mg/1 h
3	Ublituximab (n=6)	150 mg/4 h	450 mg/1 h	600 mg/1 h
	Placebo (n=2)[a]	Placebo/4 h	Placebo/1 h	-
3a	Ublituximab (n=2)[a]	150 mg/4 h	450 mg/1 h	600 mg/1 h
4	Ublituximab (n=6)	150 mg/3 h	600 mg/1 h	600 mg/1 h
	Placebo (n=2)[a]	Placebo/3 h	Placebo/1 h	-
4a	Ublituximab (n=2)[a]	150 mg/3 h	600 mg/1 h	600 mg/1 h
5	Ublituximab (n=6)	150 mg/2 h	600 mg/1 h	600 mg/1 h
	Placebo (n=2)[a]	Placebo/2 h	Placebo/1 h	-
5a	Ublituximab (n=2)[a]	150 mg/2 h	600 mg/1 h	600 mg/1 h
6	Ublituximab (n=6)	150 mg/1 h	600 mg/1 h	600 mg/1 h
	Placebo (n=2)[a]	Placebo/1 h	Placebo/1 h	-
6a	Ublituximab (n=2)[a]	150 mg/1 h	600 mg/1 h	600 mg/1 h

Following completion of Day 28 (Week 4), all subjects randomised to receive placebo entered their respective "a" cohort and received active treatment with ublituximab

Baseline assessments were done within 28 days prior to Day 1. MRI scans were performed at Screening and repeated every 24 weeks thereafter (Weeks 24 and 48). In the event that the subject's condition was deteriorating, laboratory evaluations were repeated within 48 hours prior to initiation of the next infusion.

Participants who were in good health with stable disease were allowed to enter the extended open-label phase of the study (Study TG1101-RMS201E) at the end of the study. Almost all participants (45/48) were enrolled in the extended phase of the trial.

Diagnosis of RMS was based on the 2010 McDonald's criteria. Stable disease was measured from the start of the study treatment until the criteria for relapse or progression of disease were met or there was evidence of new radiological activity as assessed by MRI, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

All efficacy analyses were performed using the ITT, intent-to-treat (ITT) and modified ITT (mITT) populations. All hypothesis tests were descriptive and conducted at a 2-sided significance level of 0.05; no multiplicity adjustment was done.

The primary efficacy variable was responder rate of B-cell depletion at Week 4, which was the proportion of subjects who had reduced B-cell depletion by ≥95% at Week 4 (2 weeks after Week 3 Day 15, the second scheduled infusion of ublituximab) in the ITT population.

The following secondary efficacy variables were summarised using descriptive statistics: B-cell reduction (CD19+, memory [CD19+CD27+], and naïve [CD19+CD27-]), number of new Gd-enhancing lesions,

number of new or enlarging T2 lesions, ARR at Week 48, relapse rate reduction [RRR], percentage of relapse-free subjects, and additional immune profiling (CD4+, CD8+, interleukin [IL]10, and Natural Killer cells).

Results

A total of 49 subjects were randomised; of these, 48 subjects received at least 1 dose of ublituximab and were included in the ITT population. One subject in Cohort 4 was discontinued due to an AE and received placebo only. This subject did not receive ublituximab and was not included in the ITT population.

As per the primary efficacy variable, the responder rate (95% CI) of B-cell depletion at Week 4 was 95.8% (85.75%, 99.49%). Table 10 presented the CD19+ B-cell Depletion Responder Rate (ITT Population).

The median percentage change from baseline in CD19+ B-cell count was -98.6% within 24 hours following the first infusion of ublituximab (Week 1 Day 2). The reduction was sustained 2 weeks later at Week 3 Day 15 (immediately prior to the second infusion of ublituximab: -99.1%), and continued with a reduction of -98.9% at Week 48/end of study. Reductions in memory (CD19+CD27+) and naïve (CD19+CD27-) B cells were also observed from Week 1 Day 2 through Week 48/end of study. The applicant did not evaluate B-cell repletion after ublituximab withdrawal.

Within 1 year prior to Screening, the cumulative number of relapses was 71, with an ARR at baseline of 1.48 (Table 12). At the end of study, following cumulative treatment time of 43.33 subject years, the cumulative number of confirmed relapses was 4, and 91.7% of subjects were relapse free. The ARR at the end of study was 0.09, a reduction of 93.76% from baseline.

Table 12: Annualised Relapse Rate in Study TG1101-RMS201 (ITT Population)

Visit Parameter	Total (N=48)
Baseline	
Subject experienced ≥1 relapses in the previous year, n (%)	43 (89.6)
Total number of relapses within 1 year prior to Screening, mean (SD)	1.5 (0.99)
Cumulative number of relapses	71
ARR[a]	1.48
At the end of study	
Duration of treatment (years), mean (SD)	0.90 (0.082)
Cumulative treatment time (subject years)	43.33
Number of confirmed relapses during treatment, mean (SD)	0.1 (0.28)
Cumulative number of confirmed relapses	4
Percent of relapse-free subjects (%) (95% CI)	91.7 (80.02, 97.68)
ARR[b]	0.09
Reduction of ARR from Baseline (%)	93.76

ARR, annualised relapse rate; CI, confidence interval; ITT, intent-to-treat; max, maximum; min, minimum; SD, standard deviation. Note: The 95% CI was estimated using the Clopper-Pearson (exact) method. a The ARR at baseline was calculated as cumulative number of relapses within 1 year prior to Screening/number of subjects in corresponding group. b The ARR at the end of study was calculated as cumulative number of confirmed relapse/cumulative treatment time

The median percentage change from baseline at Week 48/end of study was 1.3% for CD4+, -15.9% for CD8+, 183.7% for IL10, and 3.6% for Natural Killer cells.

The majority of subjects did not have either CDP or confirmed disability impairment (CDI) for at least 24 weeks (77.1%); 3 subjects (6.3%) had CDP for at least 24 weeks, and 8 subjects (16.7%) had CDI for at least 24 weeks.

Thirty-three subjects (68.8%) had no evidence of disease activity (NEDA) from baseline to Week 48; 41 subjects (85.4%) had no evidence of clinical disease activity, and 40 subjects (83.3%) had no evidence of MRI disease activity.

There were several protocol violations and nearly half of them were attributed to a single investigator site (Site CUA with 10 subjects were significant GCP violations and other non-compliance issues occurred. A sensitivity analysis excluding data for 10 subjects from Site CUA showed that there was no meaningful difference in the study population, outcome, or conclusion with or without the 10 subjects from that site. (Table 13). Other major deviations were missed laboratory assessments, inclusion/exclusion criteria not met and protocol violations related with informed consent.

Table 13: Summary of Efficacy With and Without Subjects From Site CUA (ITT Population)

Parameter Statistic	With Subjects From Site CUA (N=48)	Without Subjects From Site CUA (N=38)
Responder rate (%) (95% CI)[a, b]	95.8 (85.75, 99.49)	97.4 (86.19, 99.93)
End of study		
Percent of relapse-free subjects (%) (95% CI)[b]	91.7 (80.02, 97.68)	92.1 (78.62, 98.34)
ARR[c]	0.09	0.09
Reduction of ARR from Baseline (%)	93.76	94.22

ARR, annualised relapse rate; 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). b The 95% CI was estimated using the Clopper-Pearson (exact) method. c The ARR at the end of study was calculated as cumulative number of confirmed relapse/cumulative treatment time

2.6.5.2. Main 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 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

Methods

The pivotal studies TG1101-RMS301 and TG1101-RMS302 had identical design, therefore the methods section is presented together.

- **Study Participants**

Inclusion criteria:

Subjects must meet 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) with 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.

Exclusion criteria

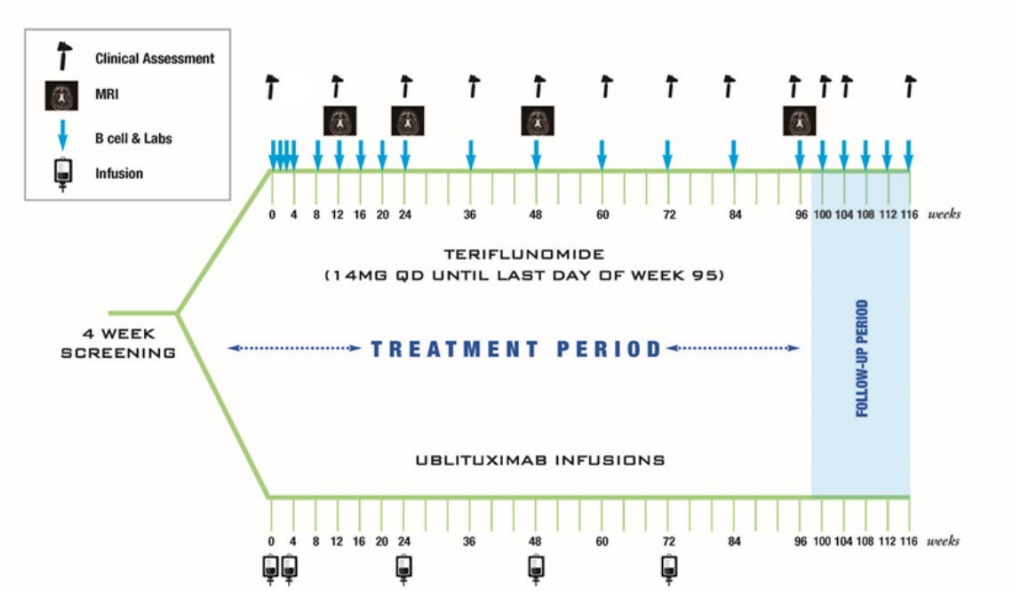
Summarised from the reports:

- Treatment with the following medical products: anti-CD20 / B-cell directed treatment (any time); alemtuzumab (any time); natalizumab (any time); teriflunomide/leflunomide (any time); stem cell transplantation (any time); cladribine (24 months before screening); azathioprine (6 months before screening); S_1P modulators (90 days before screening); IV immunoglobulin and/or plasmapheresis (90 days before screening); glatiramer acetate (30 days before screening), interferons (30 days before screening), dimethyl fumarate (30 days before screening), or glucocorticoids (30 days before screening).
- Patients with MS with ≥ 10 years disease duration from onset and EDSS ≤ 2.0
- Infections including chronic or ongoing active viral, bacterial, or fungal infectious disease requiring long term systemic treatment; opportunistic infections and positive serology for hepatitis B or hepatitis C or HIV.
- History or presence of malignancy.
- Absolute white blood cell count <4,000 cells/mm3 and/or Absolute neutrophil ≤ 1,500 cells/mm^3 and Absolute lymphocyte counts less than 1000/microliter.
- Moderate or severe hepatic impairment defined as Child Pugh Score B or C or severe renal impairment requiring dialysis.

- **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 randomised 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.

Figure 7: Study Design for Study TG1101-RMS301 and TG1101-RMS302



IV, intravenous; MRI, magnetic resonance imaging; QD, once daily. Notes: Ublituximab or IV placebo: Infusions on Week 1 Day 1, Week 3 Day 15, and Weeks 24, 48, and 72. Teriflunomide or oral placebo: Daily starting on Week 1 Day 1 until the last day of Week 95.

Oral study treatment (active or placebo) and infusion regimens (active or placebo) were started on Week 1 Day 1 and continued throughout the treatment period as described in Table 14. The initial ublituximab

infusion was to be administered over 4 hours, with subsequent infusions on Week 3 Day 15 and beyond to be administered over 1 hour.

Table 14: Study Treatment and Dosing Regimen in Study TG1101-RMS301 and –RMS302

	Week 1 Day 1	Week 3 Day 15	Week 24	Week 48	Week 72	Week 96
Ublituximab plus oral placebo	UTX (150 mg/4h)	UTX (450 mg/1h)	UTX (450 mg/1h)	UTX (450 mg/1h)	UTX (450 mg/1h)	-
	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	-

IV, intravenous; QD, once daily; UTX, ublituximab.
* May have been taken in the morning daily. Alternative dosing times were allowed if necessary.

- **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, CDP, NEDA, symbol digit modalities test (SDMT).
- To evaluate the safety of ublituximab/oral placebo, as determined by AEs and SAEs, including MS worsening

- **Outcomes/endpoints**

Primary Endpoint: the primary efficacy variable (per patient) is the number of IRAP-confirmed relapses which started on or after the day of randomisation and up to the day of last study treatment. Then, ARR was defined as the number of Independent Relapse Adjudication Panel (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.

Secondary Endpoints (as per order in hierarchical testing):
1. Total number of Gd-enhancing T1-lesions per MRI scan by Week 96
2. Total number of new and enlarging T2 hyperintense lesions (NEL) per MRI scan by Week 96
3. Time to CDP for at least 12 weeks (12-week CDP) occurring during the 96-week double-blind treatment period*. The time to onset of 12-week CDP was the time to progression defined as an increase in EDSS of at least 1 point higher than the baseline EDSS if the baseline EDSS was ≤5.5 or at least 0.5 higher than the baseline EDSS if the baseline EDSS was >5.5. Disability progression was considered confirmed when the increase in the EDSS score was confirmed at regularly scheduled visits at least 12 or 24 weeks after the initial documentation of neurological worsening (unscheduled visits not included). The "time-to-event" was the time from randomisation to the date of the first measurement of the increased EDSS as required above with confirmed progression. If no event occurred, the time to CDP was regarded as censored at the last scheduled EDSS assessment.

4. Proportion of participants with NEDA from Week 24 to Week 96. A subject with NEDA was defined as a subject without relapses confirmed by the IRAP, without MRI activities (no T1 Gd+ lesions and no new/enlarging T2 lesions), and no 12-week CDP. Any evidence of disease activity from Week 24 to Week 96 was counted as not reaching NEDA (e.g., a Week 24 MRI lesion would count as not reaching NEDA). Any evidence of disease activity before Week 24 was not counted. In case of early termination at any timepoint (including before Week 24), even if an event was not reported before early discontinuation, the subject was considered as not reaching NEDA.

5. Proportion of participants reaching impaired SDMT from baseline to Week 96. Impaired SDMT was defined as a decrease from baseline of at least 4 points at any post-baseline SDMT assessment up to the Week 96 visit.
6. Percentage change in brain volume from baseline to Week 96
* It was analysed using pooled data from the 2 identical studies (TG110--RMS301 and TG1101-RMS302).

Tertiary Endpoints
1. Change in multiple sclerosis functional composite (MSFC) score from baseline to Week 96
2. Time to CDP for at least 24 weeks
3. Time to CDI for at least 12 weeks
4. Time to CDI for at least 24 weeks
5. Health outcomes (MSQoL-54 [inclusive of SF-36]; Fatigue Impact Scale, hospitalisation, steroid use, time out of work). The MSQoL-54 is a multidimensional health-related quality of life measurement that combines generic and MS-specific items into a single assessment.
6. Total volume of Gd-enhancing T1 lesions per MRI scan over the Treatment Period
7. Volume of T2 lesions
8. Volume of hypointense T1 lesions (black holes)
9. Proportion of participants free of disability progression at 24 weeks, 48 weeks, and 96 weeks
10. Proportion of participants with a relapse
11. Time to first confirmed relapse

- **Sample size**

Visit Parameter	Total (N=48)
Baseline	
Subject experienced ≥1 relapses in the previous year, n (%)	43 (89.6)
Total number of relapses within 1 year prior to Screening, mean (SD)	1.5 (0.99)
Cumulative number of relapses	71
ARR[a]	1.48
At the end of study	
Duration of treatment (years), mean (SD)	0.90 (0.082)
Cumulative treatment time (subject years)	43.33
Number of confirmed relapses during treatment, mean (SD)	0.1 (0.28)
Cumulative number of confirmed relapses	4
Percent of relapse-free subjects (%) (95% CI)	91.7 (80.02, 97.68)
ARR[b]	0.09
Reduction of ARR from Baseline (%)	93.76

The sample size for each trial is based on achieving a 40% reduction in ARR with ocrelizumab (another anti-CD20 mAb) based on the results of the OPERA I and II studies. The ARR for teriflunomide was based on the results from the TENERE and TEMSO, which reported an ARR of approximately 29%. Thus, the hypothesised difference for each trial is expected to be a reduction in ARR of approximate of 40% in the ublituximab/ oral placebo group as compared to teriflunomide/IV placebo.

In the TEMSO study, the ARR was 0.319 and to allow for some drift to lower rates and some level of conservative estimates, the applicant hypothesised the teriflunomide/oral placebo ARR would be approximately 0.29 yielding an ARR for ublituximab/placebo of 0.174 requiring 200 subjects per group. Thus, using a two-sided test of the null hypothesis H_0: RR=1.00 vs. the alternative H_a: RR≠1.00 using the m likelihood estimate test statistic in a negative binomial regression model, samples of 220 subjects in the Teriflunomide/oral placebo Group with an average exposure time of 1.75 years and 220 subjects in Ublituximab/placebo Group with an average exposure time of 1.75 years achieves 80% power to detect an event rate ratio of 0.60 when the event rate in the teriflunomide/oral placebo Group (λ1) is 0.29 and the overall Type I error level (alpha) is 0.05 assuming a negative binomial regression distribution for the number of relapses in participants over the 100 weeks of follow-up. To allow for potential losses of up to 10%, this required sample size is increased to 220 per group or a total randomised of 440 per trial.

An independent committee, blinded assessment relapse team (BART) and the DSMB reassessed the sample size for the studies and recommended adding 30 patients per group.

- **Randomisation and Blinding (masking)**

Eligible participants were randomised in a 1:1 ratio to the following treatment arms: ublituximab/oral placebo or teriflunomide/IV placebo. The Investigator accessed an Interactive Web Response System to enroll participants, obtain unique identification numbers, and obtain study drug kit numbers. No stratification factors were utilised in the randomisation process.

These were double-blind, double-dummy studies. All oral study drugs were prepared in identical tablets and containers and all IV study drugs were prepared in identical vials to ensure adequate blinding. All personnel involved with the conduct and interpretation of the study, including the Investigators, study site personnel, and Sponsor were blinded to treatment until after the database was locked and the study was officially unblinded. The unblinding of a participant's treatment was allowed if it was deemed necessary by the Investigator and Medical Monitor to provide immediate medical management.

Relapse determinations by the IRAP were communicated to the treating neurologist, who then notified the participant and updated the eCRF accordingly. The IRAP had no involvement in subsequent participant management decisions. In order to maintain independence and blinding, the examining neurologist did not receive the report. Furthermore, neither the treating neurologist nor the participant could disclose the IRAP decision to the examining neurologist. The treating neurologist, upon receiving the IRAP decision, counseled the participant as described in the protocol. The participant needed to give her/his consent to continue study participation in the event of a confirmed relapse.

- **Statistical methods**

Analysis populations

- Intention-to-Treat (ITT) Population: all randomised participants.
- Modified Intention-to-Treat (mITT) population: all participants in the ITT Population who received at least 1 dose of study drug and had at least 1 baseline and post-baseline efficacy assessment.
- mITT-MRI Population: participants in the mITT Population who had baseline and post-baseline MRI efficacy assessments.

- Per-Protocol (PP) population: all participants in the mITT group who were treated for at least 1.75 years and did not have a major protocol deviation that impacted efficacy analysis.
- PP-MRI Population: all participants in the PP Population who had baseline and post-baseline MRI efficacy assessment.
- Safety Population: all participants who received at least 1 dose of study drug (ublituximab or teriflunomide, with corresponding placebos).
- PK Population: all participants in the Safety Population who had at least 1 baseline and 1 post-baseline PK sample taken.

Primary efficacy endpoint

The primary analysis was performed using the mITT with a negative binomial regression model to accommodate the potential over-dispersed data appropriately. The model included the total number of confirmed relapses with onset between randomisation date and the day of last treatment as response variable, treatment group, EDSS strata (baseline EDSS score ≤3.5 versus >3.5) and region as covariates. In order to account for different treatment durations among subjects, the log transformed standardised treatment duration was included in the model as an "offset" variable for appropriate computation of the ARR. SAS PROC GENMOD was used to assess the overall model with subjects in a repeated statement using a generalised estimating equation (GEE) approach.

For the primary endpoint, different sensitivity analyses were included:

1. All relapses regardless of confirmation: the primary analysis was repeated based on all reported MS relapses (rather than just confirmed ones).

2. IRAP-confirmed relapses including follow-up: to assess the effects of treatment withdrawals, the primary analysis was repeated using the information on relapses which occur during the period following drug withdrawal to the end of the study period regardless of whether additional treatment were utilised. Relapses which occurred after permanent discontinuation of study medication was included and natural log (time on study in years) rather than the natural log (time on study drug in years) was used as the offset variable in the negative binomial model, which is the primary analysis.

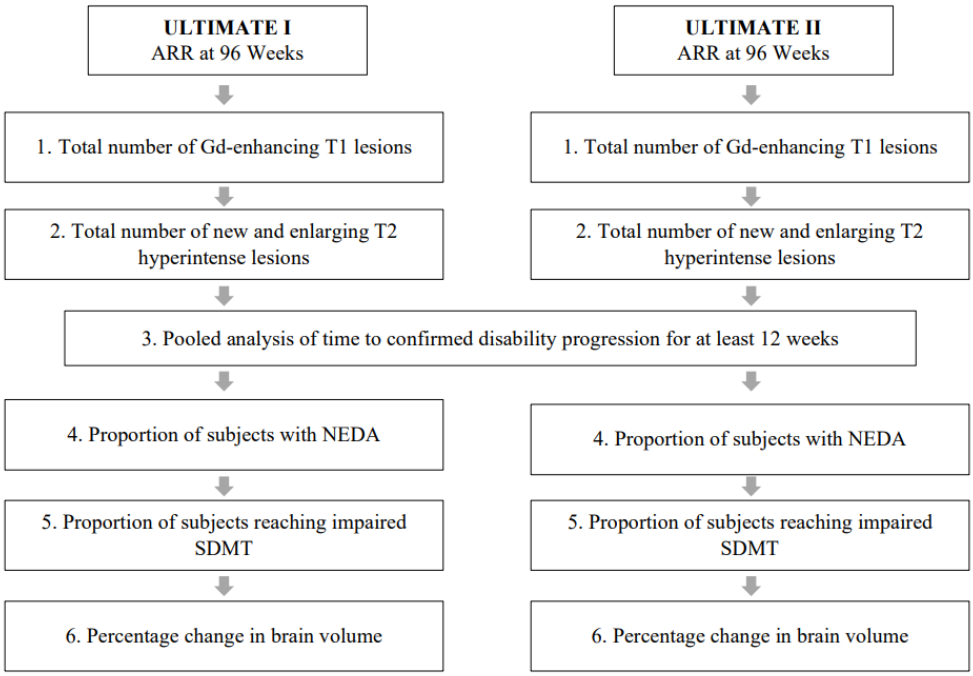
3. Multiple imputation of withdrawn participants: the dropouts from the trial using all participants who provided withdrawal of consent excluding deaths were examined. Multiple imputation was used to impute the expected number of relapses a participant would have had if they had continued to participate in the trial. To perform the imputation, 10 replicates were used since a relapse on treatment is relatively low frequency event. The covariates used to model and predict the imputations included: treatment, region, number of relapses in previous year, baseline EDSS score strata (<3.5, ≥3.5), baseline number of T1 Gd-enhancing lesions, sex and the subject's age at baseline as covariates.

4. A time to relapse analysis using Cox proportional hazards model with first IRAP-confirmed relapse as the primary event was conducted to compare with the primary analysis in a negative binomial model. The Cox proportional hazards model was specified with treatment, region, number of relapses in previous year, baseline EDSS score strata (<3.5, ≥3.5), baseline number of T1 Gd enhancing lesions, sex, and the subject's age at baseline as covariates.

Key secondary efficacy endpoints

Type I error was controlled by using a hierarchical gate-keeping procedure. Once primary endpoint was statistically significant at alpha=0.05, the secondary endpoints were tested in the pre-specified order as indicated in the endpoint section and Figure 8. The CDP key secondary endpoint was considered confirmatory only if all tests for the primary endpoint and secondary endpoints (#1 and #2) before this test were statistically significant (α=0.05) in both studies.

Figure 8: Secondary Efficacy Gatekeeping Testing Procedure



ARR, annualised relapse rate; Gd, gadolinium; NEDA, no evidence of disease activity; SDMT, Symbol Digit Modalities Test.

The treatment group difference for the MRI count variables was assessed using negative binomial regression with an offset based on log-transformed number of post-baseline MRI scans and covariates region, baseline EDSS strata, and corresponding baseline lesion count.

The proportion of subjects who suffered CDP during the study at 2 years and associated 95% CIs for each treatment group were provided. The median time-to-event with 2-sided 95% CIs as well as the proportion of subjects remaining event-free at times of interest was estimated using Kaplan-Meier method.

NEDA rates were compared using logistic regression with the same baseline adjustments as used in the primary endpoint analysis, without treatment duration offset, but including log-transformed baseline MRI counts (T1, unenhancing; T2, Gd-enhancing).

SDMT rates were compared using logistic regression with the same baseline adjustments as used in the primary endpoint analysis, without treatment duration offset, but including log-transformed baseline MRI counts (T1, unenhancing; T2, Gd-enhancing).

The percentage change in brain volume was analysed using a Mixed Model Repeated Measures (MMRM) analysis by fitting percent change from baseline values on the cube root transformed volume from all visits after baseline in the treatment period with scheduled assessments of brain volume.

For secondary outcomes T1 Gd enhancing, T2 NELs, and 12 week CDP, the effects of dropouts and study discontinuations were similarly evaluated as number 3 above.

Further, there were two additional sensitivity analyses performed for the secondary endpoint 12-week CDP: Time to CDP for at least 12 weeks including unconfirmed progression at Week 96 and Time to CDP for at least 12 weeks including all unconfirmed progression

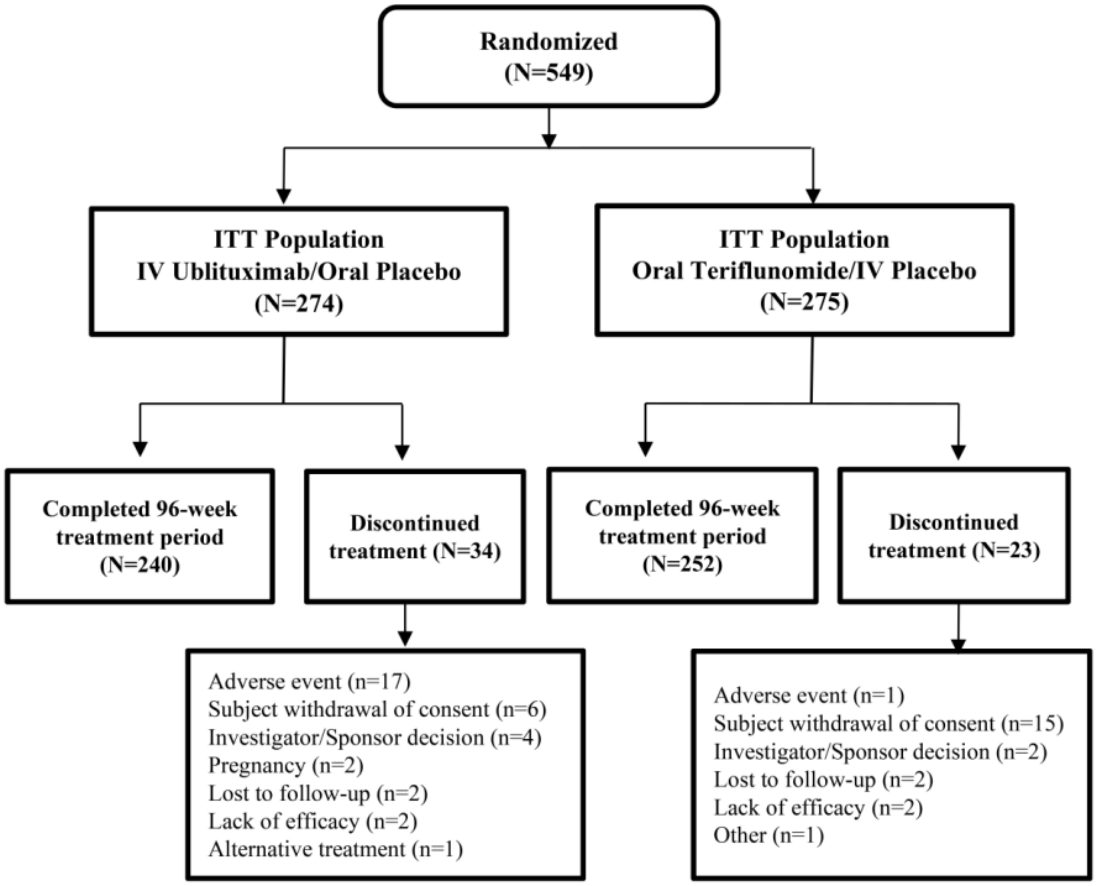
Results

Results from the two pivotal studies are presented separately.

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 ARR and safety/tolerability of ublituximab/oral placebo as compared to teriflunomide/intravenous (IV) placebo in subjects with RMS.

- **Participant flow**

Figure 9: Disposition of Subjects in Study TG1101-RMS301 (ITT Population)



ITT: Intend-to-treat; IV: Intravenous.
The ITT population consisted of all randomised subjects

- **Recruitment**

Study Initiation Date (First Participant First Visit): 19 Sep 2017 (date of informed consent).

Study Completion Date (Last Participant Last Visit): 06 Nov 2020

A database lock date - 23 Nov 2020.

The study TG1101-RMS301 was conducted at 60 study centres in 9 countries in Europe and North America.

- **Conduct of the study**

The study protocol was amended seven times. All amendments applied to both studies RMS301 and RMS 302. Protocol versions 1.0 and 2.0 were not implemented and participants were enrolled in the study beginning with protocol version 2.1. Only 3 protocol versions (3.0, 3.1, and 3.2) were implemented during active enrolment, and the amendments for these protocol versions did not change any inclusion

or exclusion criteria and did not impact the study population. Protocol version 4.0 (17 Jan 2020) primarily implemented important safety guidance on management of infection and introduced the open-label extension Study TG1101-RMS303. Protocol version 5.0 (04 Sep 2020) refined the statistical analysis language to align with the Statistical Analysis Plan (04 Sep 2020) and made minor study procedural and administrative updates. Most of the changes were done to clarify procedural issues. The amendments for these protocol versions did not impact the study population, change the primary or key secondary endpoints, or change the analysis methods. There were no changes after database lock.

With protocol amendment 3.2 (dated 09 February 2018), that specifically applied to Ukraine recruitment sites (10 sites), a change in both studies was introduced as regards the comparator to specify that an unlicensed bioequivalent teriflunomide product was used in place of the marketed reference medical product. The applicant confirmed that there was only one form of the active comparator used throughout both pivotal studies for all sites and participants. The active comparator was an unlicensed teriflunomide product bioequivalent to Aubagio that was under an active IMPD during the conduct of the studies and which, after the conduct of the pivotal trials, received FDA approval through an ANDA.

- **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 was generally similar in the 2 treatment groups: mean time since first MS symptoms (ublituximab: 7.5 years, teriflunomide: 6.8 years), mean time since diagnosis (ublituximab: 4.9 years; teriflunomide: 4.5 years), mean time since most recent relapse (ublituximab: 6.4 months; teriflunomide: 5.8 months), and 1 to 2 relapses in the 1 year prior to Screening (ublituximab: 90.8%, teriflunomide: 91.9%). The majority of subjects had a baseline EDSS of ≤3.5 (ublituximab: 73.8%, teriflunomide: 75.9%). More than half of subjects had no Gd-enhancing lesions at baseline (ublituximab: 56.5%, teriflunomide: 56.9%). In the study, almost exclusively took part the participants with RRMS. There were only 7 (2.6%) and 4 (1.5%) SPMS in the ublituximab and teriflunomide arm respectively.

The percentage of subjects with prior MS treatment was similar in the two treatment groups: MS therapy for at least 1 month (ublituximab: 39.5%, teriflunomide: 39.8%) and MS therapy in the past 5 years (ublituximab: 40.2%, teriflunomide: 40.9%). The most common types of MS therapy (≥10% in any treatment group) were glatiramer acetate (ublituximab: 16.6%, teriflunomide: 13.1%) and interferon beta-1a (ublituximab: 12.2%, teriflunomide: 9.1%). Similar proportions of subjects previously received corticosteroid treatment for relapses in the ublituximab and teriflunomide groups (94.8% and 92.7%, respectively), with a mean time since last dose of corticosteroid treatment for relapse of 8.6 and 7.9 months in the ublituximab and teriflunomide groups, respectively.

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

Table 15 for further details.

Table 15: Extent of Exposure to Intravenous Study Treatment in Study TG1101-RMS301 (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[a], 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

- **Numbers analysed**

The ITT Population consisted of 549 participants overall, with 274 participants in the ublituximab group and 275 participants in the teriflunomide group. One randomised participant did not receive study drug and was excluded from the Safety Population. Four participants were excluded from the mITT Population, which consisted of 545 (99.3%) participants. Ten participants did not have baseline or post-baseline MRI efficacy assessments and were thus excluded from the mITT-MRI Population (N=535).

The 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. Two participants did not have baseline and post-baseline MRI efficacy assessments and were thus excluded from the PP-MRI Population. The PK Population included 531 (96.7%) participants.

- **Outcomes and estimation**

Primary efficacy endpoint

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

Table 16: Annualised 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 are summarised in Table 17 and were consistent with the primary analyses.

Table 17: Sensitivity Analyses: Annualised Relapse Rate in Study TG1101-RMS301 (mITT Population)

Sensitivity Analyses	Ublituximab (N=271)		Teriflunomide (N=274)		Rate Ratio (95%CI)	P-value
	No. of relapses	ARR (LS mean and 95%CI)	No. of relapses	ARR (LS mean and 95%CI)		
IRAP-Confirmed Relapses Including Follow-up	53*	0.070 (0.040, 0.125)**	139*	0.180 (0.119, 0.273)**	0.390 (0.265, 0.575)**	<.0001
Including all participant-reported relapses irrespective of confirmation*	66#	0.205 (0.133, 0.317)##	152#	0.475 (0.359, 0.629)##	0.431 (0.299, 0.623)##	<.0001
Multiple Imputation of Withdrawn Subjects	N/A	0.077 (0.042, 0.138)&	N/A	0.189 (0.124, 0.287)&	0.405 (0.267, 0.616)&	<.0001

ARR, annualised relapse rate; CI, confidence interval; CRS, clinical study report; EDSS, Expanded Disability Status Scale; IRAP, Independent Relapse Adjudication Panel; LS, least squares; mITT, modified intent-to-treat; NA, not applicable.
*Overall, & Cumulative number of IRAP confirmed relapses / Cumulative treatment time.
**GEE (Generalised Estimating Equation model for the relapse count per participant with logarithmic link function, treatment, region and baseline EDSS strata as covariates and log(years on study) as offset.
#Overall, & Cumulative number of participant-reported relapses / Cumulative treatment time.
##GEE (Generalised Estimating Equation model for the relapse count per participant with logarithmic link function, treatment, region and baseline EDSS strata as covariates and log(years of follow-up) as offset.
&GEE (Generalised Estimating Equation 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 applicant analysed the Independent Relapse Adjudication Panel (IRAP)-confirmed relapses in studies RMS301 and RMS302 for severity (Table 18) and recovery (Table 19).

Table 18: The analysis of IRAP-Confirmed Relapses by Worst Severity (mITT Population)

	Ublituximab N=543	Teriflunomide N=546
Participants with No Relapses	**473**	**406**
Participants with Relapses	**70**	**140**
Mild	9.8% (53/543)	17.4% (95/546)
Moderate	2.4% (13/543)	7.9% (43/546)
Severe	0.7% (4/543)	0.4% (2/546)

Relapse severity categorisation (Ramo-Tello et al 2021): Mild: EDSS score increase ≤ 1 point, Moderate: EDSS score increase 1 – 2.5 points, Severe: EDSS score increase >2.5 or more points

Table 19: Recovery Analysis of IRAP-Confirmed Relapses (mITT Population)

	Relapse Recovery (%)* Ublituximab N=543 subjects	Relapse Recovery (%)* Teriflunomide N=546 subjects
Total Number of Relapses (n)	97	213
Full	67% (65/97)	74% (158/213)
Partial	33% (32/97)	26% (55/213)

*Percentage is based on total number of IRAP-confirmed relapses with a defined recovery (full or partial) divided by the number of total IRAP-confirmed relapses during the treatment period

Relapse recovery categorisation (Kantarci et al 2019) – Full recovery: EDSS returns to pre-relapse levels at any timepoint within 24 weeks (+1-week window) of symptom onset, Partial recovery: EDSS remains elevated vs. pre-relapse levels at all timepoints within 24 weeks (+1-week window) of symptom onset

Upon request, the applicant presented the analysis of the partial recovery in relation to EDSS change during treatment. The percentages of partial recovery from relapse with EDSS score increase ≤0.5 (ublituximab 14.7% and teriflunomide 13.0%) and with 1.0 (ublituximab 32.6% and teriflunomide 31.3%) were similar in both treated groups. For relapses with an EDSS increase of 1.5-2.0, the proportion of relapses with partial recovery is more significant for ublituximab (71.4%) versus teriflunomide (36.0%). In contrast, for relapses with EDSS increase ≥2.5, the percent partial recovery is greater for teriflunomide (71.4%) versus ublituximab (50.0%).

Key secondary efficacy endpoints

1. Total Number of Gadolinium-enhancing T1 Lesions per MRI Scan by Week 96

The treatment effect of ublituximab versus teriflunomide was statistically significant in favor of ublituximab (Table 20). Similar findings were reported for the ITT population and for the PP-MRI population.

Table 20: Total Number of Gadolinium-enhancing T1 Lesions per MRI Scan by Week 96 in Study TG1101-RMS301 (mITT-MRI Population)

	Ublituximab (N=265)	Teriflunomide (N=270)
Gadolinium-enhancing lesion count, mean (SD)		
Baseline	2.3 (5.52)	1.6 (3.68)
Week 12	0.1 (0.42)	0.9 (2.37)
Week 24	0.0 (0.13)	0.8 (2.36)
Week 48	0.0 (0.09)	0.9 (2.21)
Week 96	0.0 (0.07)	0.7 (1.55)
Total number of Gadolinium-enhancing T1 lesions per MRI scan per subject		
n	264	269
Mean (SD)	0.030 (0.1335)	0.818 (1.8045)
Median (minimum, maximum)	0.00 (0.00, 1.00)	0.25 (0.00, 18.00)
Negative binomial model[a]		
Least squares means (95% CI)	0.016 (0.008, 0.032)	0.491 (0.355, 0.679)
Ratio: ublituximab / teriflunomide	0.033 (0.019, 0.058)	
Difference: ublituximab - teriflunomide	-0.475 (-0.628, -0.321)	
p value	<0.0001	

CI, confidence interval; modified intent-to-treat; MRI: magnetic resonance imaging; SD, standard deviation.
a GEE (Generalised 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 0.018 (95% CI: 0.009, 0.034) in the ublituximab group and 0.551 (95% CI: 0.391, 0.777) in the teriflunomide group. The treatment effect was statistically significant in favor of ublituximab at a ratio of 0.032 (95% CI: 0.018, 0.056; p<0.0001), corresponding to a reduction of 96.8%.

2. 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 favor of ublituximab (Table 21). Similar findings were reported for the ITT population and for the PP-MRI population.

Table 21: 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[a]		
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 (Generalised 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)

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 or enlarging T2 hyperintense lesions per MRI scan was 0.222 (95% CI: 0.149, 0.330) in the ublituximab group and 2.971 (95% CI: 2.218, 3.979) in the teriflunomide group. The treatment effect was statistically significant in favour of ublituximab at a ratio of 0.075 (95% CI: 0.055, 0.102; p<0.0001), corresponding to a reduction of 92.5%.

3. The 12-week CDP endpoint

For the 12-week CDP endpoint, the pooled analyses using data from Studies TG1101-RMS301 and TG1101-RMS302 are presented together is a section "Analysis performed across trials".

4. Proportion of Subjects With NEDA From Week 24 to Week 96

The treatment effect was numerically in favour of ublituximab (Table 22). Similar findings were reported for the ITT population and for the PP population.

Table 22: 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.

5. 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 23. Similar findings were reported for the ITT population and for the PP population.

Table 23: 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.

6. 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 24. Similar findings were reported for the ITT population and for the PP-MRI population.

Table 24: Percentage in Brain Volume Change From Baseline to Week 96 in Study TG1101-RMS301 (mITT-MRI Population)

	Ublituximab (N=265)	**Teriflunomide (N=270)**
Baseline (mm^3), mean (SD)	1653661.1 (116369.48)	1669997.7 (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	

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.

Tertiary efficacy endpoints

1. Change in MSFC Score From Baseline to Week 96

At baseline, the mean MSFC score was -0.034 for subjects in the ublituximab group and 0.046 for subjects in the teriflunomide group. Subjects in the ublituximab group consistently had a greater mean increase from baseline of the MSFC score than subjects in the teriflunomide group from Week 12 through Week 96. The LS mean for the change from baseline in MSFC score at Week 96 was 0.469 (95% CI: 0.301, 0.638) in the ublituximab group and 0.266 (95% CI: 0.100, 0.432) in the teriflunomide group, with a numerical difference in favour of ublituximab of 0.203 (95% CI: 0.001, 0.405).

2-4. Time to 24-weeks CDP, time to 12-weeks CDI and time to 24-weeks CDI

For the 24-week CDP and 12- and 24-week CDI endpoints, the pooled analyses using data from studies TG1101-RMS301 and TG1101-RMS302 are done.

5. Health outcomes

At baseline, the mean values were similar between the ublituximab and teriflunomide groups for all 12 subscales, the 2 summary physical health subscale, the health distress subscale, and the SF-36 physical functioning, the LS mean differences were in favour of ublituximab at 3.749 (95% CI: 0.651, 6.847), 3.567 (95% CI: 0.122, 7.012), and 1.573 (95% CI: 0.273, 2.872), respectively. For the MSQoL-54 physical health and mental health composite scores, the LS mean differences were numerically in favour of ublituximab at 2.246 (95% CI: -0.162, 4.654) and 2.306 (95% CI: -0.395, 5.007), respectively.

The LS mean differences for the total FIS score and the cognitive dimension, physical dimension, and social dimension subscale scores were -3.788 (95% CI: -8.138, 0.562), -0.520 (95% CI: -1.672, 0.631;), -1.495 (95% CI: -2.763, -0.227), and -1.514 (95% CI: -3.782, 0.754), respectively.

The mean number of days in the hospital due to a suspected MS relapse during the study for all subjects was notably lower in the ublituximab group (0.3 days) than in the teriflunomide group (1.4 days). The LS mean for the number of days in the hospital was 0.125 in the ublituximab group and 0.469 in the teriflunomide group. The ratio of ublituximab versus teriflunomide was statistically significant in favour of ublituximab at 0.266 (95% CI: 0.124, 0.572).

The proportion of subjects with any hospitalisation due to a suspected MS relapse in the ublituximab group (4.8%) was less than half that of subjects in the teriflunomide group (10.6%), corresponding to an odds ratio of 0.386 (95% CI: 0.191, 0.783) in favour of ublituximab, a reduction of 61.4% in the odds of hospital stay.

Considering only IRAP-confirmed relapses treated with steroids, the LS mean for the related ARR was 0.070 in the ublituximab group and 0.170 in the teriflunomide group, with a rate ratio of 0.408 (95% CI: 0.267, 0.623) in favour of ublituximab. About half as many subjects in the ublituximab group (12.9%) received steroids as treatment for IRAP-confirmed relapses compared with subjects in the teriflunomide group (24.1%), corresponding to a difference of -11.2% (95% CI: -17.6%, -4.7%). The odds ratio was in favour of ublituximab at 0.437 (95% CI: 0.275, 0.695)

Over the entire study period for subjects with time-out-of-work diary data (n=162 in the ublituximab group and n=144 in the teriflunomide group), on average, subjects in the ublituximab group missed fewer hours of work (77.48 hours) and smaller percentage of working hours (3.271%) than subjects in the teriflunomide group (104.94 hours and 4.403%, respectively).

6. Total volume of Gd-enhancing T1 lesions per MRI scan over the Treatment Period

The mean total volume of Gd-enhancing T1 lesions per MRI scan at baseline was higher in the ublituximab group (0.213 mL) compared to the teriflunomide group (0.162 mL). The LS mean for the change from

baseline in the cubic root transformed total volume of Gd-enhancing T1 lesions per MRI scan across all post-baseline timepoints was -0.273 (95% CI: -0.298, -0.248) in the ublituximab group and -0.131 (95% CI: -0.155, -0.106) in the teriflunomide group, with a numerical difference in favour of ublituximab of -0.142 (95% CI: -0.166, -0.119).

7. Volume of T2 lesions

The mean total volume of T2 lesions at baseline was slightly higher in the ublituximab group (15.909 mL) than in the teriflunomide group (14.868 mL). Subjects in the ublituximab group had a greater reduction from baseline in the mean total volume of T2 lesions at Weeks 24, 48, and 96 compared with subjects in the teriflunomide group, who had an increase from baseline in the mean total volume of T2 lesions at Weeks 24, 48, and 96. The LS mean for the change from baseline in the cubic root transformed total volume of T2 lesions across all post-baseline timepoints was -0.020 (95% CI: -0.036, -0.003) in the ublituximab group and 0.038 (95% CI: 0.022, 0.054) in the teriflunomide group, corresponding to a numerical difference of -0.058 (95% CI: -0.074, -0.041;) in favour of ublituximab.

8. Volume of hypointense T1 lesions (black holes)

The mean total volume of hypointense T1 lesions at baseline was slightly higher in the ublituximab group (3.326 mL) than in the teriflunomide group (3.112 mL) Subjects in the ublituximab group had a slight increase from baseline in the mean total volume of hypointense T1 lesions at Weeks 24 and 48, and a slight reduction at Week 96, compared with subjects in the teriflunomide group, who had a slight reduction from baseline in the mean total volume of hypointense T1 lesions at Weeks 24 and 48, and an increase at Week 96. The LS mean for the change from baseline in the cubic root transformed total volume of hypointense T1 lesions across all post-baseline timepoints was 0.010 (95% CI: -0.008, 0.027) in the ublituximab group and 0.023 (95% CI: 0.006, 0.040) in the teriflunomide group, corresponding to a difference of -0.013 (95% CI: -0.031, 0.005).

9. Proportion of participants free of disability progression at 24 weeks, 48 weeks, and 96 weeks

The result of this tertiary analysis using data from Studies TG1101-RMS301 and TG1101-RMS302 is presented in the section "Analysis performed across trials".

10. Proportion of participants with a relapse

A greater proportion of subjects in the ublituximab group were free of IRAP-confirmed relapse compared to the teriflunomide group: 96.2% versus 90.8% at 24 weeks, 92.4% versus 83.6% at 48 weeks, and 86.0% versus 74.4% at 96 weeks, respectively.

11. Time to first confirmed relapse

The proportion of subjects in the ublituximab group with at least 1 IRAP-confirmed relapse during treatment was approximately half of that in the teriflunomide group (13.3% versus 24.8%). The time to first IRAP-confirmed relapse for ublituximab and teriflunomide (log-rank test) was numerically in favour of ublituximab with a hazard ratio of 0.50 (95% CI: 0.33, 0.75).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25: Summary of Efficacy for trial TG1101-RMS301

Title: Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE I STUDY)	
Study identifier	TG1101-RMS301, EudraCT Number: 2017-000638-75

Design	120-week Phase III, randomised, multicentre, 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.		
	Duration of screening phase Treatment Period Follow-up period		4 weeks 96 weeks 20 weeks
Hypothesis	Superiority		
Treatments groups	Ublituximab (Arm 1):		• Strength and pharmaceutical dosage form: 15 mL (10 mg/mL) or 6 mL (25 mg/mL) single-use glass vials diluted in 0.9% NaCl for a total volume of 250 mL • Dose: 150 mg on Week 1 Day 1 with an infusion rate of 4 hours, followed by 450 mg on Week 3 Day 15, Week 24, 48, and 72 with an infusion rate of 1 hour • Route of administration: IV infusion
	Placebo (Arm 1):		• Pharmaceutical dosage form: tablet • Dose: 1 tablet daily starting on Week 1 Day 1 until the last day of Week 95 • Route of administration: oral
	Placebo (Arm 2):		• Pharmaceutical dosage form: 15 mL or 6 mL single-use glass vials diluted in 0.9% NaCl for a total volume of 250 mL • Dose: Received on Week 1 Day 1 with an infusion rate of 4 hours, followed by infusion on Week 3 Day 15, Weeks 24, 48, and 72 with an infusion rate of 1 hour • Route of administration: IV infusion
	Teriflunomide (Arm 2):		• Strength and pharmaceutical dosage form: 14 mg tablet • Dose: 1 tablet daily starting on Week 1 Day 1 until the last day of Week 95 • Route of administration: oral
Endpoints and definitions	Primary endpoint	IRAP-confirmed ARR	ARR defined as the number of Independent Relapse Adjudication Panel (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 for participants in that specific treatment group. Participants were treated up to 96 weeks
	Secondary endpoints (in order of hierarchical testing)	1. Total number of Gd-enhancing T1-lesions per MRI scan by Week 96. 2. Total number of new and enlarging T2 hyperintense lesions (NELs) per MRI scan by Week 96. 3. Time to CDP for at least 12 weeks occurring during the 96-week, double-blind Treatment Period.* 4. Proportion of participants with NEDA from Week 24 to Week 96. 5. Proportion of participants reaching impaired SDMT from baseline to Week 96. 6. Percentage change in Brain Volume from baseline to Week 96. * CDP for at least 12 weeks during the 96-week Treatment Period was analysed using pooled data from 2 identical studies (TG1101-RMS301 and TG1101-RMS302).	
Database lock	23 Nov 2020		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis populations	Modified Intention-to-Treat (mITT) population: all participants in the ITT Population who received at least 1 dose of study drug and had at least 1 baseline and post-baseline efficacy assessment. mITT-MRI population: mITT population who have baseline and post-baseline MRI efficacy

	assessments

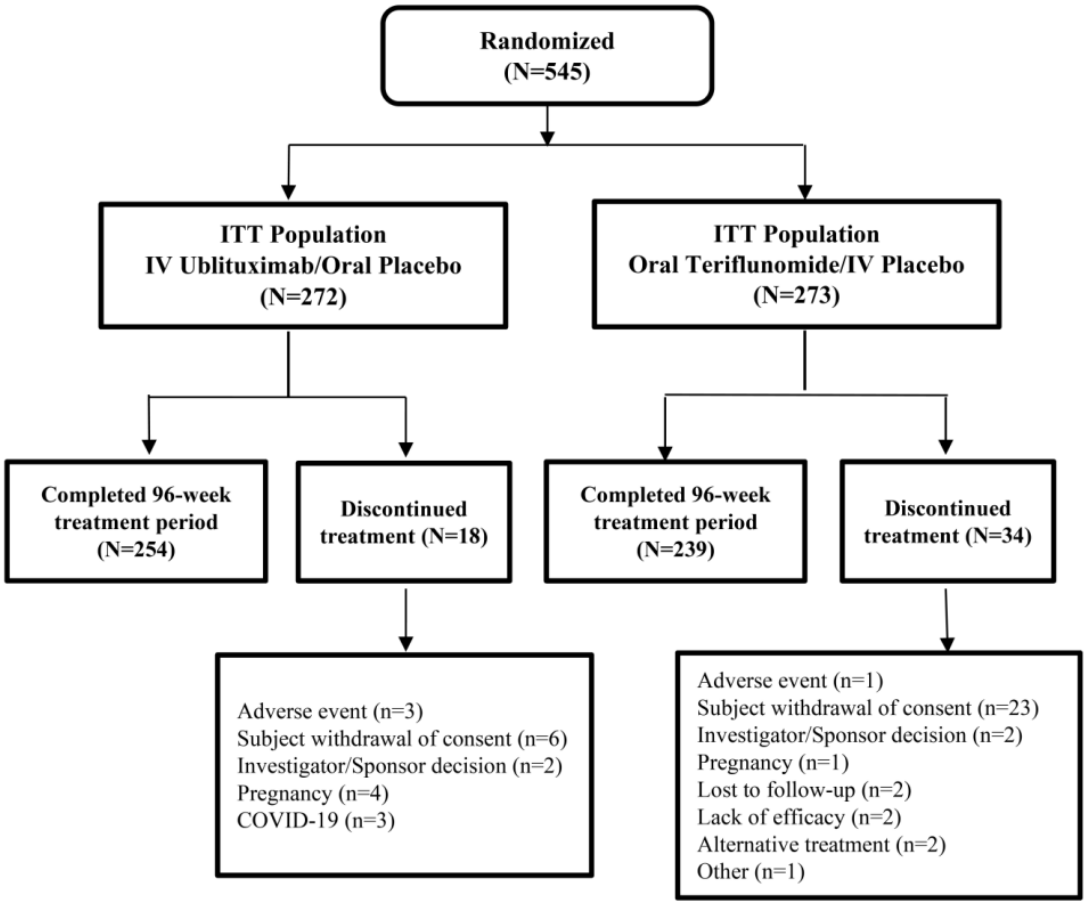
Results	**Primary endpoint: IRAP-confirmed ARR** Cumulative treatment time (subject years) Cumulative number of IRAP confirmed relapses Negative Binomial Model, Least square means (95% CI) Rate Ratio: Ublituximab / Teriflunomide, p-value	**Ublituximab (N=271),mITT** 464.52 44 0.076 (0.042, 0.138)	**Teriflunomide (N=274), mITT** 479.44 111 0.188 (0.124, 0.283) 0.406 (0.268, 0.615), p-value: <.0001
	Total Number of Gadolinium Enhancing T1-Lesions per MRI Scan by Week 96 Negative Binomial Model, Least square means (95% CI) Rate Ratio: Ublituximab / Teriflunomide, p-value	**Ublituximab (N=265), mITT-MRI population** 0.016 (0.008, 0.032)	**Teriflunomide (N=270), mITT-MRI population** 0.491 (0.355, 0.679) 0.033 (0.019, 0.058), p-value: <.0001
	Total Number of New and Enlarging T2 Hyperintense Lesions per MRI Scan by Week 96 Negative Binomial Model, Least square means (95% CI) Rate Ratio: Ublituximab / Teriflunomide, p-value	0.213 (0.144, 0.316)	2.789 (2.136, 3.643) 0.076 (0.056, 0.104), p-value: <.0001
	Time to Confirmed Disability Progression for at Least 12 Weeks Hazard Ratio with 95% CI (Stratified) CDP (12w)- Stratified Log-rank test	**Ublituximab (N=543), pooled two P3 studies**	**Teriflunomide (N=546), pooled two P3 studies** 0.843 (0.504, 1.407) 0.5099
	Proportion of Participants with No Evidence of Disease Activity From Week 24 to Week 96 Number of subjects with No Evidence of Disease Activity, n (%) Logistic Regression, Odds Ratio (95%CI, p-value	**Ublituximab (N=271), mITT** 121 (44.6%)	**Teriflunomide (N=274), mITT** 41 (15.0%) 5.442 (3.536, 8.375) p-value: <.0001 (descriptive only)

	Proportion of participants reaching impaired SDMT from baseline to Week 96. Number of subjects with SDMT impairment, n (%) Logistic Regression, Odds Ratio (95%CI, p-value	**Ublituximab (N=271), mITT** 79 (29.2%)	**Teriflunomide (N=274), mITT** 87 (31.8%) 0.872 (0.603, 1.261) p-value: 0.4669
	Percentage Change in Brain Volume From Baseline to Week 96 Percentage Change from Baseline, mean (SD) MMRM: LS means (95%CI) Difference, p-value	**Ublituximab (N=265), mITT-MRI population** **-**0.596 (0.5769) -0.197 (-0.228, -0.166)	**Teriflunomide (N=270), mITT-MRI population** **-**0.375(0.5564) -0.125 (-0.155, -0.095) -0.072 (-0.107, -0.036), p-value: <.0001 (descriptive only)
Notes: Statistically significant difference was reported for the primary endpoint and 2 secondary endpoints: Total Number of Gadolinium Enhancing T1-Lesions per MRI Scan by Week 96, Total Number of New and Enlarging T2 Hyperintense Lesions per MRI Scan by Week 96. The effect in terms of the remaining secondary endpoints is descriptive only. Sensitivity analyses results show the robustness of the primary analysis.			

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.

- **Participant flow**

Figure 10: 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 randomised subjects

- **Recruitment**

Study Initiation Date (First Participant First Visit): 25 Aug 2017 (date of informed consent).

Study Completion Date (Last Participant Last Visit): 12 Nov 2020

A database lock date - 23 Nov 2020.

The study TG1101-RMS302 was conducted at 50 study centres in 8 countries in Europe and North America.

- **Conduct of the study**

All amendments applied to both studies RMS301 and RMS 302. See study conduction of RMS301 above.

- **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 was generally similar in the 2 treatment groups: mean time since first MS symptoms (ublituximab: 7.3 years, teriflunomide: 7.4 years), mean time since diagnosis (ublituximab:

5.0 years, teriflunomide: 5.0 years), mean time since most recent relapse (ublituximab: 7.8 months, teriflunomide: 6.7 months), and 1 to 2 relapses in the 1 year prior to Screening (ublituximab: 91.2%, teriflunomide: 89.4%). The majority of subjects had a baseline EDSS of ≤3.5 (ublituximab: 80.1%, teriflunomide: 75.7%). About half of subjects had no Gd-enhancing lesions at baseline (ublituximab: 48.2%, teriflunomide: 49.6%). In the study, almost exclusively took part the participants with RRMS. There were only 4 (1.5%) and 5 (1.8%) SPMS in the ublituximab and teriflunomide arm respectively.

The percentage of subjects with prior MS treatment was similar in the 2 treatment groups: MS therapy for at least 1 month (ublituximab: 48.2%, teriflunomide: 42.3%) and MS therapy in the past 5 years (ublituximab: 49.3%, teriflunomide: 43.0%). The most common types of MS therapy (≥10% in any treatment group) were interferon beta-1a (ublituximab: 17.6%, teriflunomide: 15.8%), glatiramer acetate (ublituximab: 14.7%, teriflunomide: 12.5%), and laquinimod (ublituximab: 10.7%, teriflunomide: 11.0%). Similar proportions of subjects previously received corticosteroid treatment for relapses in the ublituximab and teriflunomide groups (93.0% and 89.3%, respectively), with a mean time since last dose of corticosteroid treatment for relapse of 10.3 and 7.3 months in the ublituximab and teriflunomide groups, respectively.

Most subjects received 5 infusions that were >50% complete. See Table 26 for further details.

Table 26: 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
[a]>50% complete, only participants with at least one infusion are represented in this summary

- **Numbers analysed**

The ITT Population consisted of 545 participants overall, with 272 participants in the ublituximab group and 273 participants in the teriflunomide group. No participants were excluded from the Safety Population. One participant was excluded from the mITT Population, which consisted of 544 (99.8%) participants. Six participants did not have baseline or post-baseline MRI efficacy assessments and were thus excluded from the mITT-MRI Population.

The PP Population included 460 (84.4%) participants with 86.8% of subjects in the ublituximab group and 82.1% of participants in the teriflunomide group. One participant did not have baseline and post-

baseline MRI efficacy assessments and was thus excluded from the PP-MRI Population. The PK Population included 538 (98.7%) participants from the Safety Population.

- **Outcomes and estimation**

Primary efficacy endpoint

The treatment effect of ublituximab versus teriflunomide was statistically significant in favour of ublituximab (Table 27). Similar findings were reported for the ITT population and the PP population.

Table 27: Annualised 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 covariates and log (years of treatment) as offset.

The results for the three sensitivity analyses for the mITT population are summarised in Table 28 and were consistent with the primary analyses.

Table 28: Sensitivity Analyses: Annualised Relapse Rate in Study TG1101-RMS302 (mITT Population)

	Ublituximab (N=272)		Teriflunomide (N=272)			
Sensitivity Analyses	**No. of relapses****	**ARR (LS mean and 95%CI)***	**No. of relapses****	**ARR (LS mean and 95%CI)**	**Rate Ratio (95%CI)**	**P-value**
IRAP Confirmed Relapses Including Follow-up	61[*]	0.094 (0.054, 0.166)[**]	122[*]	0.190 (0.122, 0.296)[**]	0.494 (0.331, 0.740)[**]	0.0006
Including all subject-reported relapses irrespective of confirmation*	75[#]	0.174 (0.105, 0.288)[##]	115[#]	0.277 (0.186, 0.411)[##]	0.630 (0.428, 0.928)[##]	0.0193
Multiple Imputation of Withdrawn Subjects	N/A	0.090 (0.048, 0.171)[&]	N/A	0.181 (0.109, 0.299)[&]	0.500 (0.323, 0.773)[&]	<.0001

ARR, annualised relapse rate; CI, confidence interval; IRAP, Independent Relapse Adjudication Panel; LS, least squares; mITT, modified intent-to-treat; NA, not applicable.
*Overall, & Cumulative number of IRAP confirmed relapses / Cumulative treatment time.
**GEE (Generalised Estimating Equation model for the relapse count per participant with logarithmic link function, treatment, region and baseline EDSS strata as covariates and log(years on study) as offset.

#Overall, & Cumulative number of participant-reported relapses / Cumulative treatment time.
##GEE (Generalised Estimating Equation model for the relapse count per participant with logarithmic link function, treatment, region and baseline EDSS strata as covariates and log(years of follow-up) as offset.
&GEE (Generalised Estimating Equation 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.

Key secondary efficacy endpoints

1. 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 29). Similar findings were reported for the ITT population and for the PP-MRI population.

Table 29: 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 (Generalised 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%.

2. 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 30). Similar findings were reported for the ITT population and for the PP-MRI population.

Table 30: Total Number of New and Enlarging T2 Hyperintense Lesions per MRI Scan by Week 96 in Study TG1101-RMS302 (mITT-MRI Population)

	Ublituximab (N=272)	Teriflunomide (N=267)
T2 lesion count		
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)
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[a]		
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 (Generalised 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)

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%.

3. The 12-week CDP endpoint

For the 12-week CDP endpoint, the pooled analyses using data from Studies TG1101-RMS301 and TG1101-RMS302 are presented together is a section "Analysis performed across trials".

4. Proportion of Subjects With NEDA From Week 24 to Week 96

The treatment effect was numerically in favour of ublituximab (Table 31). Similar findings were reported for the ITT population and for the PP population.

Table 31: 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[a], 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[a], n (%)	155 (57.0)	241 (88.6)
Logistic regression[b]		
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.

4. 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 32. Similar findings were reported for the ITT population and for the PP population.

Table 32: 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 unenhancing, T2, Gad enhancing) as covariates
p-value is nominal as the 12-week CDP was not statistically significant.

6. 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 33. Similar findings were reported for the ITT population and for the PP-MRI population.

Table 33: 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.

Tertiary efficacy endpoints

1. Change in MSFC Score From Baseline to Week 96

At baseline, the mean MSFC score was -0.026 for subjects in the ublituximab group and 0.026 for subjects in the teriflunomide group. Subjects in the ublituximab group consistently had a greater mean increase from baseline of the MSFC score than subjects in the teriflunomide group from Week 12 through Week 96. The LS mean for the change from baseline in MSFC score at Week 96 was 0.521 (95% CI: 0.342, 0.701) in the ublituximab group and 0.275 (95% CI: 0.093, 0.456) in the teriflunomide group, with a numerical difference in favour of ublituximab of 0.246 (95% CI: 0.044, 0.448).

2-4. Time to 24-weeks CDP, time to 12-weeks CDI and time to 24-weeks CDI

For the 24-week CDP and 12- and 24-week CDI endpoints, the pooled analyses using data from Studies TG1101-RMS301 and TG1101-RMS302 are done.

5. Health outcomes

Mean baseline values were similar between the ublituximab and teriflunomide groups for all 12 subscales, the 2 summary scores, and the single-item measures. For the MSQoL-54 physical health composite score, the LS mean difference was numerically in favour of ublituximab at 2.891 (95% CI: 0.551, 5.232). For the physical health, role limitations due to physical problems, and energy subscales, the LS mean differences were numerically in favour of ublituximab at 3.238 (95% CI: 0.289, 6.187), 7.170 (95% CI: 1.065, 13.276), and 3.455 (95% CI: 0.699, 6.211), respectively. For the change in health single-item measure, the LS mean difference was numerically in favour of ublituximab at 6.052 (95% CI: 1.994, 10.110). For the SF-36 physical functioning, SF-36 role physical, and SF-36 vitality, the LS mean differences were numerically in favour of ublituximab at 1.357 (95% CI: 0.120, 2.594), 2.028 (95% CI: 0.301, 3.756), and 1.590 (95% CI: 0.263, 2.917), respectively.

The LS mean differences for the total FIS score and the cognitive dimension, physical dimension, and social dimension subscale scores were -2.423 (95% CI: -6.733, 1.887), -0.203 (95% CI: -1.344, 0.939;), -1.131 (95% CI: -2.387, 0.126), and -1.144 (95% CI: -3.364, 1.077), respectively.

The mean number of days in the hospital due to a suspected MS relapse during the study for all subjects was lower in the ublituximab group (0.9 days) than in the teriflunomide group (1.7 days). The LS mean for the number of days in the hospital was 0.663 in the ublituximab group and 1.417 in the teriflunomide group. The ratio of ublituximab versus teriflunomide was numerically in favour of ublituximab at 0.468 (95% CI: 0.233, 0.938). The proportion of subjects with any hospitalisation due to a suspected MS relapse was lower in the ublituximab group (7.7%) than in the teriflunomide group (12.5%), corresponding to an odds ratio of 0.582 (95% CI: 0.327, 1.035) in favour of ublituximab.

Considering only IRAP-confirmed relapses treated with steroid, the LS mean for the related ARR was 0.059 in the ublituximab group and 0.122 in the teriflunomide group, with a rate ratio of 0.480 (95% CI: 0.303, 0.759) in favour of ublituximab.

Less than half as many subjects in the ublituximab group (11.0%) received steroids as treatment for IRAP-confirmed relapses compared with subjects in the teriflunomide group (25.4%), corresponding to a difference of -14.3% (95% CI: -20.7%, -8.0%). The odds ratio was numerically in favour of ublituximab at 0.360 (95% CI: 0.222, 0.585),

Over the entire study period for subjects with time-out-of-work diary data (n=167 in the ublituximab group and n=151 in the teriflunomide group), on average, subjects in the ublituximab group missed slightly more hours of work (128.38 hours) but smaller percentage of working hours (4.092%) than subjects in the teriflunomide group (95.23 hours and 4.688%, respectively).

6. Total Volume of Gadolinium-enhancing T1 Lesions per MRI Scan Over the Treatment Period

The mean total volume of Gd-enhancing T1 lesions per MRI scan at baseline was slightly lower in the ublituximab group (0.234 mL) and the teriflunomide group (0.257 mL). The LS mean for the change from baseline in the cubic root transformed total volume of Gd-enhancing T1 lesions per MRI scan across all post-baseline timepoints was -0.332 (95% CI: -0.357, -0.307) in the ublituximab group and -0.181 (95% CI: -0.207, -0.156) in the teriflunomide group, with a numerical difference in favour of ublituximab of -0.151 (95% CI: -0.174, -0.128).

7. Volume of T2 Lesions

The mean total volume of T2 lesions at baseline was slightly lower in the ublituximab group (14.701 mL) than in the teriflunomide group (15.341 mL). Subjects in the ublituximab group had a reduction from baseline in the mean total volume of T2 lesions at Weeks 24, 48, and 96 compared with subjects in the teriflunomide group, who had an increase from baseline in the mean total volume of T2 lesions at Weeks 24, 48, and 96. The LS mean for the change from baseline in the cubic root transformed total volume of T2 lesions across all post-baseline timepoints was -0.026 (95% CI: -0.041, -0.012) in the ublituximab group and 0.037 (95% CI: 0.022, 0.052) in the teriflunomide group, corresponding to a numerical difference of -0.063 (95% CI: -0.078, -0.048) in favour of ublituximab.

8. Volume of Hypointense T1 Lesions

The mean total volume of hypointense T1 lesions at baseline was slightly lower in the ublituximab group (3.235 mL) than in the teriflunomide group (3.578 mL). Subjects in the ublituximab group had a greater reduction from baseline in the mean total volume of hypointense T1 lesions at Weeks 24, 48, and 96, compared with subjects in the teriflunomide group, who had a slight decrease from baseline in the mean total volume of hypointense T1 lesions at Weeks 24 and 48 and a slight increase at Week 96. The LS mean for the change from baseline in the cubic root transformed total volume of hypointense T1 lesions across all post-baseline timepoints was 0.003 (95% CI: -0.014, 0.020) in the ublituximab group and

0.018 (95% CI: 0.000, 0.036) in the teriflunomide group, corresponding to a difference of -0.015 (95% CI: -0.033, 0.003).

9. Proportion of participants free of disability progression at 24 weeks, 48 weeks, and 96 weeks

The result of this tertiary analysis using data from Studies TG1101-RMS301 and TG1101-RMS302 is presented in the section "Analysis performed across trials".

10. Proportion of Subjects With a Relapse

A greater proportion of subjects in the ublituximab group were free of IRAP-confirmed relapse compared with subjects in the teriflunomide group: 92.6% versus 90.7% at 24 weeks, 90.0% versus 82.2% at 48 weeks, and 87.4% versus 72.1% at 96 weeks, respectively.

11. Time to First Confirmed Relapse

The proportion of subjects in the ublituximab group with at least 1 IRAP-confirmed relapse during treatment was approximately half of that in the teriflunomide group (12.5% versus 26.5%). The time to first IRAP-confirmed relapse for ublituximab and teriflunomide (log-rank test) was numerically in favour of ublituximab with a hazard ratio 0.43 (95% CI: 0.28, 0.65).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 34: Summary of Efficacy for trial TG1101-RMS302

Title: Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE II STUDY)		
Study identifier	TG1101-RMS302, EudraCT Number: 2017-000639-15	
Design	120-week Phase III, randomised, multicentre, 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.	
	Duration of screening phase Treatment Period Follow-up period	4 weeks 96 weeks 20 weeks
Hypothesis	Superiority	
Treatments groups	Ublituximab (Arm 1):	• Strength and pharmaceutical dosage form: 15 mL (10 mg/mL) or 6 mL (25 mg/mL) single-use glass vials diluted in 0.9% NaCl for a total volume of 250 mL • Dose: 150 mg on Week 1 Day 1 with an infusion rate of 4 hours, followed by 450 mg on Week 3 Day 15, Week 24, 48, and 72 with an infusion rate of 1 hour • Route of administration: IV infusion
	Placebo (Arm 1):	• Pharmaceutical dosage form: tablet • Dose: 1 tablet daily starting on Week 1 Day 1 until the last day of Week 95 • Route of administration: oral
	Placebo (Arm 2):	• Pharmaceutical dosage form: 15 mL or 6 mL single-use glass vials diluted in 0.9% NaCl for a total volume of 250 mL • Dose: Received on Week 1 Day 1 with an infusion rate of 4 hours, followed by infusion on Week 3 Day 15, Weeks 24, 48, and 72 with an infusion rate of 1 hour • Route of administration: IV infusion
	Teriflunomide (Arm 2):	• Strength and pharmaceutical dosage form: 14 mg tablet • Dose: 1 tablet daily starting on Week 1 Day 1 until the last day of Week 95 • Route of administration: oral

Endpoints and definitions	Primary endpoint	IRAP-confirmed ARR	ARR defined as the number of Independent Relapse Adjudication Panel (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 for participants in that specific treatment group. Participants were treated up to 96 weeks
	Secondary endpoints (in order of hierarchical testing)	1. Total number of Gd-enhancing T1-lesions per MRI scan by Week 96. 2. Total number of new and enlarging T2 hyperintense lesions (NELs) per MRI scan by Week 96. 3. Time to CDP for at least 12 weeks occurring during the 96-week, double-blind Treatment Period.* 4. Proportion of participants with NEDA from Week 24 to Week 96. 5. Proportion of participants reaching impaired SDMT from baseline to Week 96. 6. Percentage change in Brain Volume from baseline to Week 96. * CDP for at least 12 weeks during the 96-week Treatment Period was analysed using pooled data from 2 identical studies (TG1101-RMS301 and TG1101-RMS302).	
Database lock	23 Nov 2020		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis populations	Modified Intention-to-Treat (mITT) population: all participants in the ITT Population who received at least 1 dose of study drug and had at least 1 baseline and post-baseline efficacy assessment. mITT-MRI population: mITT population who have baseline and post-baseline MRI efficacy assessments

Results	**Primary endpoint: IRAP-confirmed ARR**	**Ublituximab (N=272),mITT**	**Teriflunomide (N=272), mITT**
	Cumulative treatment time (subject years)	485.90 53	465.70
	Cumulative number of IRAP confirmed relapses	25	102
	Negative Binomial Model, Least square means (95% CI)	0.091 (0.049, 0.169)	0.178 (0.109, 0.291)
	Rate Ratio: Ublituximab / Teriflunomide, p-value		0.509 (0.330, 0.784), p-value: 0.0022
	Total Number of Gadolinium Enhancing T1-Lesions per MRI Scan by Week 96	**Ublituximab (N=272), mITT-MRI population**	**Teriflunomide (N=267), mITT-MRI population**
	Negative Binomial Model, Least square means (95% CI)	0.009 (0.004, 0.017)	0.250 (0.162, 0.385)
	Rate Ratio: Ublituximab / Teriflunomide, p-value		0.035 (0.019, 0.064), p-value: <.0001
	Total Number of New and Enlarging T2 Hyperintense Lesions per MRI Scan by Week 96	**Ublituximab (N=272), mITT-MRI population**	**Teriflunomide (N=267), mITT-MRI population**
	Negative Binomial Model, Least square means (95% CI)	0.282 (0.200, 0.397)	2.831 (2.128, 3.767)
	Rate Ratio: Ublituximab / Teriflunomide, p-value		0.100 (0.073, 0.136), p-value: <.0001
	Time to Confirmed Disability Progression for at Least 12 Weeks	**Ublituximab (N=543), pooled two P3 studies**	**Teriflunomide (N=546), pooled two P3 studies**
	Hazard Ratio with 95% CI (Stratified)		0.843 (0.504, 1.407)
	CDP (12w)- Stratified Log-rank test		0.5099

	Proportion of Participants with No Evidence of Disease Activity From Week 24 to Week 96 Number of subjects with No Evidence of Disease Activity, n (%) Logistic Regression, Odds Ratio (95%CI, p-value	**Ublituximab (N=272), mITT** 117 (43.0%)	**Teriflunomide (N=272), mITT** 31 (11.4%) 7.946 (4.917, 12.841) p-value: <.0001 (descriptive only)
	Proportion of participants reaching impaired SDMT from baseline to Week 96. Number of subjects with SDMT impairment, n (%) Logistic Regression, Odds Ratio (95%CI, p-value	**Ublituximab (N=272), mITT** 79 (29.0%)	**Teriflunomide (N=272), mITT** 86 (31.6%) 0.862 (0.596, 1.246) p-value: 0.4290
	Percentage Change in Brain Volume From Baseline to Week 96 Percentage Change from Baseline, mean (SD) MMRM: LS means (95%CI) Difference, p-value	**Ublituximab (N=272), mITT-MRI population** -0.642 (0.56) -0.194 (-0.225, -0.164)	**Teriflunomide (N=267), mITT-MRI population** -0.576(0.5988) -0.176 (-0.207, -0.146) -0.018 (-0.053, 0.017) p-value: 0.3108
Notes: Statistically significant difference was reported for the primary endpoint and 2 secondary endpoints: Total Number of Gadolinium Enhancing T1-Lesions per MRI Scan by Week 96, Total Number of New and Enlarging T2 Hyperintense Lesions per MRI Scan by Week 96. The effect in terms of the remaining secondary endpoints is descriptive only. Sensitivity analyses results show the robustness of the primary analysis.			

2.6.5.3. Clinical studies in special populations

In the clinical study programme took part subjects aged 18 -55 years old. There is no data regarding older patients.

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

1. Time to Confirmed Disability Progression for at Least 12 Weeks (secondary endpoint)

The analyses of 12-week CDP were based on pooled data from Studies TG1101-RMS301 (ULTIMATE I) and TG1101-RMS302 (ULTIMATE II). The proportion of subjects free of CDP for at least 12 weeks at 24, 48, and 96 weeks was low in the ublituximab group and similar to the teriflunomide group (

Table 35). The time to CDP for at least 12 weeks was not statistically significant using a stratified log-rank test (

Table 35).

Table 35: Time to Confirmed Disability Progression for at Least 12 Weeks in Studies TG1101-RMS301 and TG1101-RMS302 Pooled (mITT Population)

	Pooled	
	Ublituximab (N=543)	**Teriflunomide (N=546)**
Number of subjects with CDP for at least 12 weeks, n (%)	28 (5.2)	32 (5.9)
Number of subjects without CDP for at least 12 weeks, n (%)	515 (94.8)	514 (94.1)
Proportion free of CDP (12 weeks), % (95% CI)[a]		
At 24 weeks	98.5 (97.0, 99.2)	99.1 (97.7, 99.6)
At 48 weeks	97.2 (95.3, 98.3)	96.9 (95.0, 98.1)
At 96 weeks	94.6 (92.3, 96.3)	93.8 (91.3, 95.5)
CDP for at least 12 weeks – unstratified log-rank test[a] (p value)	0.5753	
Hazard ratio (95% CI), unstratified[b]	0.865 (0.521, 1.437)	
CDP for at least 12 weeks – stratified log-rank test[a,c] (p value)	0.5099	
Hazard ratio (95% CI), stratified[b,c]	0.843 (0.504, 1.407)	

CDP, confirmed disability progression; CI, confidence interval; mITT, modified intent-to-treat.
For Kaplan-Meier estimates, the quartiles (including median) were not reached and the 95% CI of quartiles were not estimable.
Participants were at risk until Week 84; disability progression which occurred first at Week 96 could not be confirmed.
[a] Estimated by Kaplan-Meier method.
[b] Hazard ratio is estimated using Cox regression model with treatment group as covariate.
[C] The stratification factors include region, baseline EDSS, and study

The sensitivity analyses for this secondary endpoint are presented in Table 36.

Table 36: Sensitivity Analyses: Time to Confirmed Disability Progression for at Least 12 Weeks in Studies TG1101-RMS301 and TG1101-RMS302 Pooled (mITT Population)

Sensitivity Analyses	Ublituximab (N=543)		Teriflunomide (N=546)		Hazard Ratio[b,c] (95% CI)	Log-rank p value
	Number of Subjects With Progression	Median Weeks[a] (95% CI)[b]	Number of Subjects With Progression	Median Weeks[a] (95% CI)[b]		
Multiple imputation	NA	-	NA	-	0.575 (0.368, 0.899)	0.0265
Including unconfirmed progressions at Week 96	30	-	40	105.6 (-, -)	0.753 (0.465, 1.218)	0.2446
Including all unconfirmed progressions	83	109.0 (106.3, -)	138	107.0 (103.3, 109.1)	0.586 (0.443, 0.774)	0.0001

CDP, confirmed disability progression; CI, confidence interval; mITT, modified intent-to-treat.
For Kaplan-Meier estimates, the quartiles (including median) were not reached and the 95% CI of quartiles were not estimable.
[a] Estimated by Kaplan-Meier method.
[b] Hazard ratio is estimated using Cox regression model with treatment group as covariate.
[C] The stratification factors include region, baseline EDSS, and study

2. Time to Confirmed Disability Progression for at Least 24 Weeks (tertiary endpoint)

The proportion of subjects with CDP for at least 24 weeks using the pooled data was 18 subjects (3.3%) in the ublituximab group and 26 subjects (4.8%) in the teriflunomide group, with similar numbers of subjects free of CDP for at least 24 weeks (525 subjects [96.7%] and 520 subjects [95.2%], respectively, in the ublituximab and teriflunomide groups). The hazard ration for the CDP confirmed at 24 weeks using a stratified log-rank test was 0.657 [95% CI: 0.358, 1.205].

3. Time to Confirmed Disability Improvement for at Least 12 Weeks and 24 Weeks (tertiary endpoints)

The proportion of subjects who achieved CDI for at least 12 weeks using the pooled data was higher in the ublituximab group compared with the teriflunomide group. The difference between treatment groups for time to CDI for at least 12 weeks was in favour of ublituximab using a stratified log-rank test (hazard ratio: 2.158 [95% CI: 1.406, 3.313]). Similar results were seen for the proportion of subjects who achieved CDI for at least 24 weeks (

Table 37).

Table 37: Time to Confirmed Disability Improvement in Studies TG1101-RMS301 and TG1101-RMS302 Pooled (mITT Population)

	Pooled	
	Ublituximab (N=543)	**Teriflunomide (N=546)**
Time to CDI for at least 12 weeks		
Number of subjects with CDI for at least 12 weeks, n (%)	65 (12.0)	33 (6.0)
Number of subjects without CDI for at least 12 weeks, n (%)	478 (88.0)	513 (94.0)
CDI for at least 12 weeks – unstratified log-rank test[a] (p value)	0.0009	
Hazard ratio (95% CI), unstratified[b]	2.008 (1.321, 3.053)	
CDI for at least 12 weeks – stratified log-rank test[a,c] (p value)	0.0003	
Hazard ratio (95% CI), stratified[b,c]	2.158 (1.406, 3.313)	
Time to CDI for at least 24 weeks		
Number of subjects with CDI for at least 24 weeks, n (%)	52 (9.6)	28 (5.1)
Number of subjects without CDI for at least 24 weeks, n (%)	491 (90.4)	518 (94.9)
CDI for at least 24 weeks – unstratified log-rank test[a] (p value)	0.0062	
Hazard ratio (95% CI), unstratified[b]	1.879 (1.187, 2.974)	
CDI for at least 24 weeks – stratified log-rank test[a,c] (p value)	0.0026	
Hazard ratio (95% CI), stratified[b,c]	2.031 (1.269, 3.248)	

CDI, confirmed disability improvement; CI, confidence interval; mITT, modified intent-to-treat.
Participants were at risk until Week 84; disability progression which occurred first at Week 96 could not be confirmed.
For Kaplan-Meier estimates, the quartiles (including median) were not reached and the 95% CI of quartiles were not estimable.
[a] Estimated by Kaplan-Meier method.
[b] Hazard ratio is estimated using Cox regression model with treatment group as covariate.
[C] The stratification factors include region, baseline EDSS, and study

A sensitivity analysis of CDI for at least 12 weeks was performed using pooled data from subjects in Studies TG1101-RMS301 and TG1101-RMS302, stratified by baseline EDSS strata (≤3.5, >3.5). A durable improvement of CDI was defined as when the EDSS score at the end of study was not higher than the baseline EDSS score.

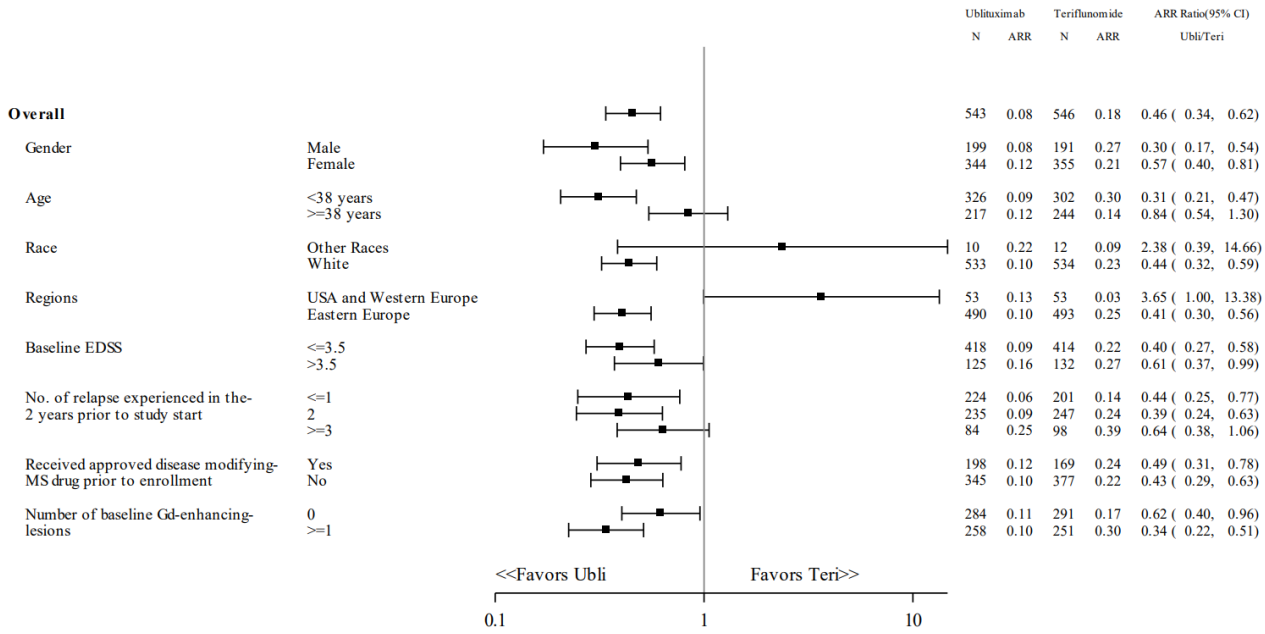
Of the subjects who achieved CDI for at least 12 weeks, more subjects in the ublituximab group than in the teriflunomide group had durable improvement (11.4% versus 5.7%), with a difference in favour of ublituximab. The observation was also true in each of the baseline EDSS stratum.

4. Subgroup analyses.

Subgroup analyses by gender (male, female), race (White, other race), age category (<38 years, ≥38 years), region (USA and Western Europe, Eastern Europe), baseline EDSS strata (≤3.5, >3.5), number of relapses experienced in the 2 years prior to study start (≤1, 2, and ≥3), received approved disease-modifying MS drug prior to enrollment (Yes, No), and number of baseline Gd-enhancing lesions (0, ≥1) were performed for the primary efficacy variable (ARR [IRAP confirmed]) using the pooled data in Studies TG1101-RMS301 and TG1101-RMS302.

Similar results were reported in most of the subgroup analyses of ARR, the primary efficacy endpoint The LS mean for the ARR was similar for subjects aged ≥38 years (0.12 versus 0.14) and higher in the ublituximab group than in the teriflunomide group for subjects of other races (0.22 versus 0.09); however, the number of subjects of other races was small (n=22) (Figure 11).

Figure 11: Forest Plot of Annualised Relapse Rate Subgroup Analysis in Studies TG1101-RMS301 and TG1101-RMS302 Pooled (mITT Population)



ARR, annualised relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd, Gadolinium; ISE, Integrated Summary of Efficacy; mITT, modified intent-to-treat; MS, multiple sclerosis; USA, United States of America.
Notes: Rate ratios were based on a GEE model with logarithmic link function, treatment, region, and baseline EDSS strata as covariate and log (years of treatment) as offset for overall. Subgroups used the same model but excluded region and baseline EDSS strata as covariates.

For subjects in the USA and Western Europe region, the number of subjects was small (n=106) for ARR analysis, and the LS mean for ARR was higher in the ublituximab group than in the teriflunomide group (0.127 versus 0.035). Of note, for the ublituximab group, the ARR of 0.127 was similar to the ARR of 0.102 in the Eastern Europe region and the ARR of 0.084 in the overall mITT population. For the teriflunomide group, the ARR of 0.035 in USA and Western Europe was considerably lower than the ARR of 0.250 in Eastern Europe, the ARR of 0.20 observed in previous studies with teriflunomide (

Table 38).

Table 38: Annualised Relapse Rate (IRAP Confirmed) by Region and Treatment Group in Studies TG1101-RMS301 and TG1101-RMS302 Pooled (mITT Population)

Region	Ublituximab			Teriflunomide		
	N	Relapses	ARR (95% CI)	N	Relapses	ARR (95% CI)
USA and Western Europe	53	10	0.127 (0.063, 0.256)	53	3	0.035 (0.012, 0.104)
Eastern Europe	490	87	0.102 (0.078, 0.133)	493	210	0.250 (0.211, 0.296)
Overall	543	97	0.084 (0.054, 0.128)	546	213	0.183 (0.133, 0.251)

ARR, annualised relapse rate; CI, confidence interval; IRAP, Independent Relapse Adjudication Panel; mITT, modified intent-to-treat; USA, United States of America.

Further, consistent results were seen for key secondary endpoints in both regions. Compared with teriflunomide, ublituximab reduced Gd-enhancing T1 lesions by 90% in the USA and Western Europe Region and 96% in the Eastern Europe Region (Table 39) and reduced new and enlarging T2 lesions by 78% in the USA and Western Europe Region and 91% in the Eastern Europe Region (Table 40).

Table 39: Analysis of Number of Gd-enhancing T1 lesions (mITT-MRI population)

Region	Ublituximab		Teriflunomide		Rate Ratio (ublituximab/ teriflunomide) (95% CI)	p-value
	N	Number of Lesions per MRI scan (95% CI)	N	Number of Lesions per MRI scan (95% CI)		
USA and Western Europe	53	0.025 (0.008, 0.084)	52	0.248 (0.150, 0.411)	0.102 (0.027, 0.387)	0.0008
Eastern Europe	484	0.034 (0.022, 0.054)	485	0.906 (0.743, 1.105)	0.038 (0.023, 0.062)	<.0001
Overall	537	0.034 (0.022, 0.052)	537	0.845 (0.696, 1.025)	0.040 (0.025, 0.064)	<.0001

Number of GD-enhancing T1 Lesions per MRI scan is the LS mean from GEE model for total number of gadolinium-enhancing T1 lesions with logarithmic link function, treatment as independent variable, Study as covariates and an offset based on the log-transformed number of post-baseline MRI scans.

Table 40: Analysis of Number of New/Enlarging T2 Hyperintense Lesions (mITT-MRI Population)

Region	Ublituximab		Teriflunomide		Rate Ratio (ublituximab/ teriflunomide) (95% CI)	p-value
	N	Number of Lesions per MRI scan (95% CI)	N	Number of Lesions per MRI scan (95% CI)		
USA and Western Europe	53	0.365 (0.182, 0.734)	52	1.677 (1.110, 2.532)	0.218 (0.098, 0.485)	0.0002
Eastern Europe	484	0.428 (0.351, 0.521)	485	4.750 (4.081, 5.528)	0.090 (0.070, 0.115)	<.0001
Overall	537	0.422 (0.349, 0.510)	537	4.469 (3.855, 5.180)	0.094 (0.074, 0.120)	<.0001

Number of New and Enlarging T2 Hyperintense Lesions per MRI scan is the LS mean from GEE model for total number of new and enlarging T2 hyperintense lesions with logarithmic link function, treatment as independent variable, Study as covariate and an offset based on the log-transformed number of post-baseline MRI scans

The applicant position is that the results for the ublituximab treatment group, including ARR, are highly consistent between the two regions. The perceived diminished trend in performance of ublituximab relative to teriflunomide therefore is a result of the over-performance of teriflunomide in the USA and Western Europe region likely due to large variability of small number of subjects in the region, potentially with rather favourable baseline characteristics. According to the applicant, the prognosis observed across the important baseline characteristics was noticeably better for teriflunomide-treated subjects in USA and Western Europe than in Eastern Europe. Thus, the applicant concluded the low ARR of 0.035 in the teriflunomide group in USA and Western Europe is unlikely to be representative of ARR in patients treated with teriflunomide.

Upon request, the applicant provided efficacy analysis for the primary endpoint and the two first secondary endpoints by disease activity in line with EMA guidelines (EMA/CHMP/771815/2011, Rev. 2). The analysis of baseline values for baseline disease activity indicates that the proportion of patients with highly active disease (having ≥2 relapses in the prior year and ≥1 Gd-enhancing lesion) is slightly lower in the US and Western Europe than in Eastern Europe for teriflunomide (Table 41). In the analysis of efficacy by disease activity, better results were found for those with non-highly active MS but the difference is particularly prominent for participants in the teriflunomide arm (Table 42).

Table 41: Baseline Disease Activity by Region

Study arm	**Teriflunomide**		**Ublituximab**	
Region	**USA and Western Europe (N=53)**	**Eastern Europe (N=493)**	**USA and Western Europe (N=53)**	**Eastern Europe (N=490)**
Active Disease	48 (90.6%)	418 (84.8%)	46 (86.8%)	409 (83.5%)
Highly Active Disease	5 (9.4%)	75 (15.2%)	7 (13.2%)	81 (16.5%)

Table 42: Analysis by Disease Activity Intensity

	Ublituximab	**Teriflunomide**	**Rate Ratio (95% CI) (ublituximab/ teriflunomide)**	**p-value**
ARR				
Active	0.096 (0.072, 0.127)	0.186 (0.154, 0.225)	0.513 (0.364, 0.722)	0.0001
Highly active	0.145 (0.089, 0.236)	0.496 (0.357, 0.690)	0.292 (0.162, 0.527)	<0.0001
Gd-enhancing T1 Lesions				
Active	0.012 (0.007, 0.021)	0.381 (0.288, 0.504)	0.031 (0.019, 0.050)	<0.0001
Highly active	0.038 (0.016, 0.092)	0.875 (0.477, 1.607)	0.044 (0.019, 0.098)	<0.0001
New/Enlarging T2 Lesions				
Active	0.204 (0.151, 0.274)	2.414 (1.951, 2.987)	0.084 (0.065, 0.109)	<0.0001
Highly active	0.568 (0.336, 0.959)	6.367 (3.825, 10.599)	0.089 (0.060, 0.132)	<0.0001

Criteria for highly active disease (HAD) defined as >=2 relapses in prior year and >=1 Gd-enhancing lesion at baseline

2.6.5.5. Supportive studies

Long-term efficacy is being evaluated in two currently ongoing extension studies, Studies TG1101-RMS201E and TG1101-RMS303. No efficacy data is available at the time of the MAA.

Study TG1101-RMS201E is an open-label, extension study for subjects who have completed the 48-week treatment period in Study TG1101-RMS201 and were in good health with stable disease. The primary objective of this study is to evaluate the safety, tolerability, and long-term efficacy outcomes of ublituximab treatment in subjects continuing treatment after completion of Study TG1101-RMS201. All subjects receive ublituximab 450 mg infusion over 1 hour administered every 24 weeks. The efficacy endpoints are ARR and CDP. As of the cutoff date of 23 Nov 2020, 43 subjects have been enrolled and received at least 1 dose of ublituximab. Forty-three out of 48 (90%) subjects enrolled in Study TG1101-RMS201 continued ublituximab treatment in the extension Study TG1101-RMS201E.

Study TG1101-RMS303 is a 172-week, open-label, extension study for subjects who have completed the 96-week double blind treatment period of Studies TG1101-RMS301 or TG1101-RMS302. The objective of the study is to evaluate the long-term safety and efficacy of ublituximab therapy in subjects with RMS. All subjects receive 150 mg of ublituximab infusion over 4 hours on Day 1 of Week 1, 450 mg of ublituximab infusion over 1 hour on Day 15 of Week 3, and on Weeks 24, 48, 72, 96, 120, 144, and 168 or until physician or subject decision to withdraw prior to this time. The efficacy endpoints are as follows: ARR, MRI parameters (T1 Gd-enhancing, T1 hypointense lesions, T2 lesions, and brain atrophy), CDP and CDI, NEDA, cognition (evaluated by SDMT), and function (evaluated by MSFC). As of the cutoff date of 23 Nov 2020, 642 subjects have been enrolled and received at least 1 dose of ublituximab, and 39 of the 642 subjects have received >3 infusions (Week 24). As of 23 Jun 2021, 850 out of 985 (86%) subjects enrolled in Studies TG1101-RMS301 or TG1101-RMS302 continued ublituximab treatment or rolled over from the teriflunomide arm to receive ublituximab treatment in the extension Study TG1101-RMS303.

Ukraine represents a main Country for number of recruitment centres involved in the ongoing study RMS303. The applicant has commented on the integrity of this study considering the unfortunate historical events currently affecting that area, and provided reassurance that the ongoing war in Ukraine has not impacted data collection for the pivotal trials while only minimally impacting on patient retention for long-term data collection.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Demonstration of the clinical efficacy of ublituximab was based on three studies: one phase IIa (dose finding) and two pivotal phase III studies.

Study TG1101-RMS201 was a 52-week, Phase IIa, placebo-controlled, multicentre, dose-finding, cohort-sequential study in subjects with RMS.

The study included 6 treatment cohorts, each with 8 subjects: 6 subjects randomised to receive ublituximab and 2 subjects randomised receive to placebo. The primary efficacy variable was responder rate of B-cell depletion at Week 4, which was the proportion of subjects who had reduced B-cell depletion by ≥95% at Week 4 in the ITT population. There were 48 patients overall in the study, which, when subdivided into individual study subgroups, resulted in very small populations in each subgroup. There were several protocol violations and nearly half of them were attributed to a single investigator site (Site CUA) with 10 subjects (20% of all study participants) were significant GCP violations and other non-compliance issues occurred. No differences were shown concerning the observed results in a sensitivity analysis without the subgroup mentioned above. Other major deviations were missed laboratory

assessments but they were not directly related to ublituximab measures. The major deviations with informed consent were associated with re-consent timing after protocol amendments.

According to the applicant, the optimal dose and infusion time of ublituximab were determined as follows: Day 1 (first infusion): 150mg infused over 4 hours, Day 15 (second infusion): 450mg infused over 1 hour, Week 24 (third infusion) and subsequent infusions: 450 mg infused over 1 hour. During the procedure, the applicant was requested to further justify it because the proposed dose regimen (4h/1h/1h) was not tested as such in the phase II study. The applicant explained that the proposed posology is based on the drug regimen used in the Phase III Studies TG1101-RMS301 and TG1101-RMS302. This regimen most closely aligns to Cohort 2 in the Phase II Study RMS201 with the exception of the infusion time for the second ublituximab dose (Day 15). The infusion time of 1 hour was evaluated in subsequent cohorts and ultimately selected as the Phase III dose. The explanation was considered sufficient.

During the procedure, the applicant was requested to provide a rationale for the use of B-lymphocyte reduction criteria of more than 95% as a PD therapeutic target for optimal clinical effect. In most cases, the administration of ublituximab successfully achieved an almost complete reduction in B-lymphocyte levels. However, using only a relative parameter is not fully justified, as an absolute reduction in B-lymphocyte levels appears to be more important for suppression. Pooled data from RMS301 & RMS302 show participants enrolled across all arms (N = 1089) had a median (IQR) B-cell count of 195 (147 – 269) at baseline. Therefore, 95% depletion from these baseline values corresponds to a median (IQR) of 10 (7 – 13) cells/μL in terms of absolute B-cell count. The applicant claimed that this reduction is within the range of B-cell depletion of other anti-CD20. However, while the lower threshold is within this range, the median reduction is slightly higher. However, given the efficacy of ublituximab confirmed in pivotal studies, the magnitude of B-lymphocyte reduction is sufficient.

Participants who were in good health with stable disease were allowed to enter the extended open-label phase of the study (Study TG1101-RMS201E) at the end of the study. The 'stability' criteria themselves were subjectively assessed by the investigators, which is questionable. However, there were no cases of unstable disease in patients participating in the RMS201 trial, and almost all participants (45/48) took part in the extended phase of the trial.

Studies TG1101-RMS301 and TG1101-RMS302 were 120-week, Phase III, randomised, multicentre, double-blind, double-dummy, active-controlled studies with identical study designs.

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 randomised 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 randomisation 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 absolutely 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 randomised. 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 primary analysis of the primary endpoint was performed using a negative binomial model instead of the standard poisson model to avoid overdispersion (i.e. when variance is higher than mean value).This is acceptable. The applicant 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 pre-specified 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 applicant 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.

With protocol amendment 3.2 (dated 09 February 2018), that specifically applied to Ukraine recruitment sites (10 sites), a change in both studies was introduced as regards the comparator to specify that an unlicensed bioequivalent teriflunomide product was used in place of the marketed reference medical product. The applicant confirmed that there was only one form of the active comparator used throughout both studies for all sites and participants. The active comparator was an unlicensed teriflunomide product bioequivalent to Aubagio that was under an active IMPD during the conduct of the studies and which, after the conduct of the pivotal trials, received FDA approval through an ANDA.

A significant number of major protocol deviations was observed in the studies. The most frequent major deviation was “study procedure or assessment”. The applicant 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.

Upon request, the applicant 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.

Efficacy data and additional analyses

Study TG1101-RMS201 was a 52-week, Phase IIa, placebo-controlled, multicentre, dose-finding, cohort-sequential study in subjects with RMS.

In the RMS201 study, ublituximab (irrespective on the dose) led to rapid peripheral CD19+ B-cell depletion. The primary endpoint was met with an overall 95.8% responder rate of B-cell depletion at Week 4. There was >95% median depletion in all treated subjects within 24 hours of receiving the initial dose of 150 mg ublituximab and ≥98% median depletion in all treated subjects by Week 4. Moreover, B-cell depletion within the 95% target range was largely maintained before ublituximab dosing at Week 24 and was sustained at Week 48. In most cases, the administration of ublituximab successfully achieved an almost complete reduction in B-lymphocyte levels. On brain imaging parameters, most ublituximab-treated subjects showed no evidence of clinical or MRI disease activity during the 48-week treatment period (85.4% and 83.3%, respectively). The ARR was reduced by 93.76% from baseline, and 91.7% of subjects remained relapse-free on-study. Moreover, 93.8% of subjects had no 24-week CDP, including 16.7% of subjects who showed CDI for at least 24 weeks.

In the study, all schemes tested led to profound B-lymph depletion, and no significant differences were shown between them. All tested clinical efficacy parameters were not analysed in separate subgroups but in the whole population.

Studies TG1101-RMS301 and TG1101-RMS302 were 120-week, Phase III, randomised, multicentre, double-blind, double-dummy, active-controlled studies with identical study designs.

The primary endpoint was met in both pivotal studies. A statistically significant reduction in ARR for ublituximab compared to teriflunomide was demonstrated. Ublituximab, compared to teriflunomide, significantly reduced ARR by 59.4% (rate ratio: 0.406 [95% CI: 0.268, 0.615]; p<0.0001) in Study TG1101-RMS301 and by 49.1% (rate ratio: 0.509 [95% CI: 0.330, 0.784]; p=0.0022) in Study TG1101-RMS302. The primary efficacy results of ARR in the two studies were consistent. Pre-sensitivity analyses provided consistent results. The applicant analysed the Independent Relapse Adjudication Panel (IRAP)-confirmed relapses in studies RMS301 and RMS302 for severity and recovery. The majority of the relapses were mild or moderate and results appear to be comparable from the point of view of the severity of relapses. Among subjects who had a relapse, the partial recovery was to some extant higher in the ublituximab group (33% vs. 26%). According to the definition, the partial recovery EDSS remains elevated vs. pre-relapse levels at all time-points within 24 weeks (+1-week window) of symptom onset. The applicant presented the results of the partial recovery in relation to the EDSS change and it can be concluded that the risk of partial recovery is similar in both treatment arms.

Secondary efficacy endpoints were tested in a hierarchical manner. A statistically significant difference between ublituximab and teriflunomide was reported for the secondary efficacy endpoint of total number of Gd-enhancing T1 lesions per MRI scan at Week 96 and the secondary efficacy endpoint of total number of new or enlarging T2 hyperintense lesions per MRI scan at Week 96. The proportion of subjects with CDP for at least 12 weeks was slightly lower for ublituximab compared to teriflunomide but did not reach the level of statistical significance. The effect on the disability progression (CDP) was not demonstrated, probably due to the low incidence of the CDP (about 5%) in both study arms. Therefore, results from subsequent secondary outcomes (proportion of subjects with NEDA from Week 24 to Week 96, proportion

of subjects reaching impaired SDMT from baseline to Week 96 and percentage change in brain volume from baseline to Week 96) should be treated as an exploratory only. Overall, the secondary and tertiary endpoints generally supported the results of the analysis performed for primary endpoint.

In the clinical studies with ublituximab there was very limited number of patients with SPMS with superimposed relapses. In line with EMA guideline (EMA/CHMP/771815/2011, Rev. 2), it is reasonable to assume that relapses in RRMS and SPMS have the same underlying inflammatory pathophysiology and therefore efficacy on relapses in RRMS patients may be extrapolated to efficacy on relapses in SPMS. Therefore, it is considered acceptable to extrapolate the study results on disease activity to the whole RMS population.

Upon, the applicant clarified how many patients were DMT treatment naïve in both studies. While the proportion of treatment-naive patients was very well balanced in Study TG1101-RMS301 (59.1 vs 59.8%), the proportion of patients who received DMT was higher in the teriflunomide group (57.0% vs 50.7%) in Study TG1101-RMS302. However, the primary endpoint analysis (ARR) shows that the effect of ublituximab was similar in both studies (0.076 - TG1101-RMS301 and 0.091 - TG1101-RMS302), and therefore it can be agreed the applicant position that differences in the proportion of treatment-naive patients did not translate into differences in effect size.

Subgroup analysis of ARR yielded similar results for most of the subgroups, however, the limited number of relapses observed across both studies precluded interpretability, particularly for smaller subgroups.

The concern on study result generalizability due to the poor representativeness of the Western Countries (9.7% of the total population), is further reinforced by results by region, showing the opposite behaviour of the ARR in response to treatment relative to the comparator between USA/Western Europe and East Europe. In the analysis of ARR performed for the pooled data from both pivotal studies, the number of relapses in the ublituximab group was similar in both regions. It may be agreed that the results for the ublituximab treatment group, including ARR, are highly consistent between the two regions. Conversely, the ARR result for the teriflunomide treatment group in the USA and Western Europe Region (ARR=0.035) is low and an outlier based on previous teriflunomide studies [(ASCLEPIOS studies the ARR for teriflunomide was 0.22 and 0.25 respectively] as well as the ARR that was observed in the larger Eastern Europe subgroup of studies TG1101-RMS301 and TG1101-RMS302. Although acknowledging the limited numerosity of the Western patients, the trend is clearly differentiated from their counterpart in Eastern Europe. The applicant's justification relies on the different performance of the control arm observed in the two geographical areas, with a higher efficacy of teriflunomide in USA/Western Europe than in Eastern Europe. The claimed more favourable conditions, within Western countries, of patients assigned to teriflunomide in comparison to the ublituximab group, is regarded as the underlying explanation. Contrarily to the applicant's position, it should be noted that more favourable baseline disease characteristics in USA/Western Europe compared to their co-respective in Eastern Europe were observable in both treatment arms, not just the teriflunomide group. Part of the problem with the results obtained was that the applicant did not apply stratification by region This limitation was acknoledged by the applicant who stated that the chance of baseline imbalances is higher between each region subgroup since the study randomisation was not stratified by region, which could be more impactful on smaller subgroup such as the USA and Western Europe subgroup. In this regard, the applicant recognised that the sample size and number of relapses in the USA and Western Europe Region were rather small, accounting for less than 10% of the overall population, and only 3.5% of the study relapses across the two studies. Small sample sizes are subject to greater chance of random findings and more prone to cofounding by baseline imbalances with known or unknown factors.

However, analysis of baseline values for baseline disease activity indicates that the proportion of patients with highly active disease is slightly lower in the US and Western Europe than in Eastern Europe for teriflunomide (9.4% vs 15.2%). This was further confirmed in the analysis of differences in the efficacy

of teriflunomide in participants with active vs highly active disease (better results for patients who are not highly active disease).

In the analysis of the number of enhancing Gd+ foci, it is worth noting that a higher number of lesions per scan was observed in patients treated with teriflunomide. This effect remains in discordance with the frequency of relapses. The analysis indicates that for patients in the US and Western European region using ublituximab, a higher incidence of relapses (ARR) is simultaneously associated with a lower number of enhancing foci compared to teriflunomide. Even considering the low number of patients, this lack of correlation of ARR with the number of foci is puzzling. The applicant informed that such an observation had been documented in the literature as the clinicoradiological paradox (Chard & Trip 2017). The phenomenon probably arises due to the high sensitivity of MRI assessments in capturing changes in lesions, which contrasts with the less sensitive and more subjective EDSS scoring system. It should be noted, however, that the clinicoradiological paradox mainly refers to the discrepancy between MRI and disability score, this latter mainly related to phenomena of biological redundancy and neuroplasticity rather than either Gd-enhancing T1 or new Enlarging T2 Hyperintense lesions. It remains unclear the herein reported observation of dissociation between relapses and MRI foci, given their underlying common pathological features. In any case, the issue specifically concerns the control arm, and therefore it can be considered a marginal aspect of concern.

In addition to the already mentioned inconsistency in results by region, lack of superiority of ublituximab over teriflunomide was detected also for race and age. For the primary endpoint (ARR), the limited sample size in the "Other Race" subgroup does not allow for definitive conclusions to be drawn. The benefit on ARR appeared stronger in younger age (-69%) group than older age group (-16%), which was mainly driven by different ARR estimates in the teriflunomide arm (higher in younger age). Similar trends for both age groups were observed for T1/T2-lesions.

2.6.7. Conclusions on the clinical efficacy

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

2.6.8. Clinical safety

The primary safety evaluation for ublituximab compared to teriflunomide is based on pooled safety data from the 2 pivotal studies. A supplementary safety evaluation for ublituximab in RMS is based on pooled analyses of the 2 pivotal studies concatenated with data from Study TG1101-RMS303 for the same subjects. An additional supplementary safety evaluation is based on safety data from Study TG1101-RMS201 concatenated with data from Study TG1101 RMS201E for the same subjects.

Ublituximab is being studied in a variety of patient populations, both as a single agent and in combination with other agents. To date, over 2,500 subjects have been exposed to ublituximab across all indications, including approximately 600 subjects with RMS.

2.6.8.1. 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

In the pooled analysis of the pivotal Phase 3 studies, the median number of infusions was 5. In ublituximab group 92,7% of subjects (505 patients) received 5 infusions. Out of 545 participants in TG1101-RMS301 and TG1101-RMS302, 494 completed the 96-week treatment period. The main reasons for discontinuation in these patients were withdrawal of consent and AE. Of these 494 participants, 481 (97%) completed the 20-week follow-up period or enrolled in the RMS301 extension study. Only 13 of 494 (2.6%) participants discontinued from the study following completion of the 96-week treatment period. Reasons for discontinuation included 9 participants declining participation in RMS303 and 4 participants with COVID-19 logistical restrictions or other reasons. As per 01 Mar 2022, 422 participants out of the 545 (77.4% %) included in the pivotal trials had enrolled in RMS303 Following rollover to Study TG1101-RMS303, 52 subject (9.5%) discontinued mainly due to AEs or withdrawal of consent.

In concatenated Phase 2 Studies, a total of 45 subjects (93.8%) completed the 48-week treatment period in Study TG1101 RMS201 and enrolled in the extension study, Study TG1101 RMS201E. As of the data cutoff date of 01 March 2022, 28 subjects (58.3%) were still on treatment and 20 subjects (41.7%) prematurely discontinued study treatment. The most common reason for discontinuation of study treatment was withdrawal by subject together with death and switched to a different disease-modifying therapy.

2.6.8.2. Adverse events

As per 20 November 2020, in the pooled analysis of the pivotal Phase III studies, the incidence of at least 1 TEAE 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.

As per 20 November 2020, in the concatenated Phase III studies, these percentages were similar to the percentages reported in the parent studies: any TEAE: 89.7% versus 89.2%, TEAEs of Grade ≥3: 23.5% [12 additional subjects reporting TEAEs of Grade ≥3 in the extension study] versus 21.3%, serious TEAEs: 11.9% versus 10.8%, TEAEs leading to discontinuation of study treatment: 4.8% versus 4.2%, and treatment-emergent AESIs: 65.0% versus 63.9%.

As per 20 November 2020, in the pooled analysis of the pivotal Phase III studies, 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 were 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 were 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.

As per 20 November 2020, in the concatenated Phase III studies, treatment-related 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.

At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, 809 (83.1%) had at least 1 TEAE, 272 had at least 1 TEAEs of Grade ≥3, 167 (17.1%) had at least 1 serious TEAEs, 55 (5.6%) had at least 1 TEAE leading to treatment discontinuation and 22 had any TEAE with an outcome of death. The risk of infusion-related reactions is considered an important identified risk and the risk of serious infections remains an important potential risk for ublituximab in RMS. No new safety concerns or risks were identified from this safety update.

2.6.8.3. Serious adverse event/deaths/other significant events

As per 20 November 2020, in the pooled analysis of the pivotal Phase III studies, 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.

As per 20 November 2020, in the concatenated Phase III studies, serious TEAEs were reported in 6 additional subjects (11.9% versus 10.8% in the parent studies). These included COVID-19 pneumonia in 4 subjects; tibia fracture and fibula fracture in 1 subject; and uterine leiomyoma and vaginal haemorrhage in 1 subject. In addition, 2 subjects with serious TEAEs (complicated appendicitis and deep vein thrombosis) in the parent study had new serious TEAEs (salpingitis/peritonitis/salpingo oophoritis and COVID-19 pneumonia, respectively) in the extension study, Study TG1101-RMS303.

At 01 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). The applicant provided detailed analysis of COVID-19 impact on patients 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 factors for fatal COVID-19-related adverse events.

As per 20 November 2020, in the concatenated Phase II studies, serious TEAEs were reported in 11 subjects (22.9%). For 2 subjects, the serious TEAE was considered possibly related to ublituximab (cellulitis and colitis). One pregnancy case led to permanent discontinuation of ublituximab. At 01 March 2022, out of the 48 participants included in the Ublituximab Update Safety set of phase III trials, serious TEAEs were reported in 17 subjects with six additional participants who had new serious case of COVID-19 or COVID-19 pneumonia

<u>Infusion-related reaction (IRR)</u>

Investigator-reported IRRs

As per 20 November 2020, in the pooled analysis of the pivotal Phase III studies, the percentage of subjects with Investigator-reported 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.

As per 20 November 2020, in the concatenated Phase III studies, 5 additional subjects had Investigator-reported IRRs (48.6% versus 47.7% in the parent studies). Investigator-reported IRRs started within 24 hours of infusion in 264 of 265 subjects (99.6%).

IRR based on the AESI category

As per 20 November 2020, for ublituximab-treated subjects, the incidence of IRR based on the AESI category was 48.3% and did not differ meaningfully from the incidence of Investigator reported IRR (47.7%). The most commonly reported TEAE signs and symptoms associated with IRR AESI category (≥5% of ublituximab-treated subjects) were headache (10.3%), pyrexia (9.7%), chills (8.1%), and influenza-like illness (6.2%). The corresponding Investigator-reported rates were pyrexia (9.5%), chills (7.9%), headache (7.5%), and influenza-like illness (5.9%).

As per 20 November 2020, in the concatenated Phase III studies, the percentage of subjects with IRRs as AESIs was similar to the parent studies (49.2% versus 48.3%).

At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, 389 (39.9%) had at least one IRR with 12 IRR of Grade ≥3. The most commonly reported TEAE signs and symptoms were similar to the ones already reported as of cut-off of 20 November 2020.

Cytopenias / Lymphopenia

As per 20 November 2020, in the pooled analysis of the pivotal Phase III studies, cytopenias as 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%).

As per 20 November 2020, in the pooled analysis of the pivotal Phase III studies, Grade ≥3 TEAEs associated with lymphocyte count included lymphocyte count decreased (ublituximab: 5.5%; teriflunomide: 0) and lymphopenia (ublituximab: 4.0%; teriflunomide: 0.5%). In the ublituximab group, 1 subject had a serious TEAE of lymphocyte count decreased, and 1 subject had a Grade 3 TEAE of lymphopenia that led to discontinuation of study treatment. No new Grade ≥3 TEAEs of lymphopenia or lymphocyte count decreased were reported in the concatenated Phase III studies.

At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, 222 (22.8%) had at least one episode of cytopenia with 102 of Grade ≥3. Lymphopenia and Lymphocyte count decreased were reported in 70 (24 of Grade ≥3) and 56 (30 of Grade ≥3) participants, respectively.

Malignancies

As per 20 November 2020, 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.

As per 20 November 2020, in the concatenated Phase III studies, an additional TEAE of oophorectomy (Grade 2 and not serious) in the malignancies AESI category was reported in the extension study in the same subject who had a TEAE of endometrial stromal sarcoma in the parent study.

As per 20 November 2020, the overall incidence (95% CI) of malignancies in the ublituximab group was 0.4 (0.04, 1.32) with an incidence rate of 0.24 per subject-year.

At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, malignancies as AESIs were reported in 5 subjects (0.5%) including the three mentioned cases and two additional cases of pseudomyxoma peritonei and splenectomy.

Serious infections

As per 20 November 2020, 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).

At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, serious infections were reported in 130 of which 117 were of Grade ≥3. The most commonly reported infection was COVID-19 pneumonia.

Treatment-emergent Opportunistic Infections

As per 20 November 2020, 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 were reported in 2 subjects in the ublituximab group (chronic hepatitis B and meningoencephalitis viral) and 1 subject in the teriflunomide group (septic shock).

As per 20 November 2020, in the concatenated Phase III studies, the percentage of subjects with treatment-emergent opportunistic infections (any grade) was similar to the parent studies (12.8% versus 11.9% in the parent studies).

At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, treatment emergent opportunistic infections were reported in 8.9% of participants.

Deaths

As per 20 November 2020, in the pooled analysis of the pivotal Phase III studies, TEAEs with an outcome of death were reported in 3 subjects (0.6%) in the ublituximab group (encephalitis, pneumonia, and salpingitis). There were no TEAEs with an outcome of 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.

At 01 March 2022, out of the 974 participants included in the Ublituximab Safety Update set of phase III trials, 22 TEAE with an outcome of death were reported. The additional 19 cases of death were due to COVID-19 related events.

As per 20 November 2020, no deaths were reported in Studies TG1101-RMS201 or TG1101-RMS201E. At 01 March 2022, out of the 48 participants included in the Ublituximab Update Safety set of phase II trials, three deaths were reported due to COVID-19-related events.

2.6.8.4. Laboratory findings

As per 20 November 2020, the most notable laboratory abnormalities were low lymphocyte count (91% of patients treated with ublituximab at Week 1), which is expected given the intended mechanism of action of ublituximab. Of note, at Week 2 only 7.8% of ublituximab treated patients reported low lymphocyte count. In the pivotal studies, the overall incidence of the liver function abnormalities in patients treated with ublituximab was low (0.6% experienced ALT ≥10xULN and 0.4% experienced AST ≥10xULN). In only one subject from ublituximab group ALT value did not normalise before or after the end of the study.

Other laboratory parameters did not show any consistent abnormalities or clinically relevant differences compared to active control group.

2.6.8.5. Safety in special populations

Patients aged 18-55 years were included in the pivotal studies, hence, the safety profile is not known for other age groups. The safety profile was comparable between patients ≥38 years of age and < 38 years of age with a higher incidence of any TEAEs in younger subjects (93.9% vs 83.6%). Moreover, higher incidence of any TEAEs and serious TEAEs was reported in female subjects compared to male subjects. However, the observed differences by gender and age are not considered clinically meaningful.

No conclusions regarding differences by race can be made due to very limited number of patients of other than White race included in the pivotal studies.

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.

Out of the total 545 participants who received ublituximab in the Phase III studies, 220 had mild renal impairment (GFR ≥60 mL/min and <90 mL/min), 4 had moderate renal impairment (GFR <60 mL/min) at baseline and no patients had severe renal impairment (GFR <30 mL/min). There were no clinically meaningful differences observed TEAEs, SAEs, drug discontinuations, AESI and deaths in participants receiving ublituximab with mild renal impairment compared to normal renal function. No analysis of safety profile in patients with moderate renal impairment was feasible due to the fact that only 4 ublituximab-treated participants had moderate renal impairment.

Use of ublituximab during pregnancy may cause fetal 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.

2.6.8.6. Immunological events

The immunogenicity of ublituximab in subjects with RMS was evaluated in clinical studies through the assessment of ADA and characterisation of ADA positive clinical samples for potential neutralizing activity. The immunogenicity of ublituximab and the potential impact on the clinical profile was characterised in the three RMS clinical studies TG1101-RMS201, TG1101-RMS301, and TG1101-RMS302.

The 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.

The applicant presented analysis indicating that the presence of TE-ADA or NAb did not impact efficacy and safety of ublituximab as indicated in section 5.1 of the SmPC.

2.6.8.7. Safety related to drug-drug interactions and other interactions

No formal DDI studies have been performed, as no drug interactions are expected via cytochrome P450 enzymes, other metabolising enzymes or transporters.

The safety of immunisation with live or live-attenuated vaccines, following ublituximab therapy has not been studied.

2.6.8.8. Discontinuation due to adverse events

As per 20 November 2020, 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 ADRs 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 ADR that led to discontinuation of study treatment. In the concatenated Phase III studies, TEAEs led to discontinuation of study treatment in 3 additional subjects (COVID-19 pneumonia) and all TEAEs were serious. At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, 55 (5.6%) 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, one subject discontinued ublituximab treatment in Study TG1101-RMS201 due to pregnancy. At 01 March 2022, out of the 48 participants included in the Ublituximab Update Safety set of phase II trials, one additional participant discontinued treatment due to a TEAE of COVID-19.

2.6.8.9. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

The primary source of safety data in the RMS target population consists of the two identical pivotal randomised, 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 applicant 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 applicant has provided data about the timing of infections and the timing of the events of cytopenia or hypogammaglobulinaemia. Apparently, it emerges that most infection events did not happen in proximity of reduced values of neutrophils, lymphocytes or immunoglobulins.

The applicant 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 applicant 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 applicant 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 applicant provided detailed analysis of COVID-19 impact on patients 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 factors 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 new born.

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.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Section 4.8 of the SmPC include dedicated subsections for IRR, infection and laboratory abnormalities including immunoglobulins decreased, lymphocytes and neutrophils.

2.6.10. Conclusions on the clinical safety

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

2.7. Risk Management Plan

2.7.1. Safety concerns

***Table 43**: 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

2.7.2. Pharmacovigilance plan

Table 44: 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	Q3 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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
A registry study of pregnancy and infant outcomes in patients treated with ublituximab (TG1101-RMS403) 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	06/2024
			Interim report submissions	Annually beginning in 03/2025
			Study Finish	03/2035
			Final report submission	03/2036
A study to characterise 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 2023
			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

2.7.3. Risk minimisation measures

Table 45: 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: Communication: *SmPC: Sections 4.2, 4.4, 4.8* *PL: Sections 2, 3, 4* Specific clinical measures: *SmPC: Section 4.2 and PL: Section 3, where advice is given on pre-medication and having appropriate resources*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimisation activities	Pharmacovigilance activities
	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* Subject to restricted medical prescription. Additional risk minimisation measures: *None*	
Serious infections, including opportunistic infections (e.g., PML, HBV reactivation) (Important potential risk)	Routine risk minimisation measures: Communication: *SmPC: Sections 4.3, 4.4, 4.8* *PL: Sections 2, 4* Specific clinical measures: *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 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*	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)*
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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None*

Safety concern	Risk minimisation activities	Pharmacovigilance activities
	Subject to restricted medical prescription. Additional risk minimisation measures: *None*	Additional pharmacovigilance activities: *Post-authorisation long-term safety study (TG1101-RMS402)*
Safety in pregnancy and lactation, including foetal risks (Missing information)	Routine risk minimisation measures: Communication: *SmPC: Sections 4.4, 4.6, 5.3* *PL: Section 2* Specific clinical measures: *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.* 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 pregnancy safety studies (TG1101-RMS403 and TG1101-RMS404)*

2.7.4. Conclusion

The CHMP and PRAC consider that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28 December 2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Briumvi (ublituximab) is included in the additional monitoring list as containing a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

MS is a chronic disease of the CNS characterised by inflammation, demyelination, and axonal/neuronal destruction, ultimately leading to severe disability. In a majority of patients (up to 85%), the disease starts with a relapsing and remitting form of MS, and recovery from each relapse may often be incomplete and lead to the accumulation of disability.

3.1.2. Available therapies and unmet medical need

An increasing number of DMTs approved in RMS are available, with different efficacy and safety profile, different modes of action, and different routes of administration. Ublituximab will join the DMD targeting B-cells to prevent acute inflammatory activity in MS.

3.1.3. Main clinical studies

The pivotal studies that characterise the efficacy and safety of ublituximab in RMS are Study TG1101-RMS301 and Study TG1101-RMS302 (two identical Phase III, 120-week, randomised, multicentre, global, double-blinded, double-dummy, active-controlled studies). These studies were primarily designed to assess the ARR and safety and tolerability of ublituximab/oral placebo compared to teriflunomide/IV placebo in subjects with RMS.

Efficacy data from Study TG1101-RMS201, a Phase IIa, 52-week, dose-ranging, placebo-controlled, multicentre study, are used as supportive information for the efficacy of ublituximab in RMS.

3.2. Favourable effects

Ublituximab, compared to teriflunomide, significantly reduced ARR by 59.4% (rate ratio: 0.406 [95% CI: 0.268, 0.615]; p<0.0001) in Study TG1101-RMS301 and by 49.1% (rate ratio: 0.509 [95% CI: 0.330, 0.784]; p=0.0022) in Study TG1101-RMS302. In addition, ublituximab in comparison to

teriflunomide caused the significant reduction of the mean number of Gd-enhancing T1 lesions by 96.7% (ratio: 0.033 [95% CI: 0.019, 0.058]; p<0.0001) by Week 96 in Study TG1101-RMS301 and reduction by 96.5% (ratio: 0.035 [95% CI: 0.019, 0.064]; p<0.0001) by Week 96 in Study TG1101-RMS302. Similarly, the ublituximab administration reduced the mean number of new and enlarging T2 hyperintense lesions. It caused reduction by 92.4% (ratio: 0.076 [95% CI: 0.056, 0.104]; p<0.0001) by Week 96 in Study TG1101-RMS301 and reduction by 90.0% (ratio: 0.100 [95% CI: 0.073, 0.136]; p<0.0001) by Week 96 in Study TG1101-RMS302.

3.3. Uncertainties and limitations about favourable effects

In the clinical studies with ublituximab there was a very limited number of patients with SPMS with superimposed relapses. In line with EMA guideline (EMA/CHMP/771815/2011, Rev. 2), it is reasonable to assume that relapses in RRMS and SPMS have the same underlying inflammatory pathophysiology and therefore efficacy on relapses in RRMS patients may be extrapolated to efficacy on relapses in SPMS.

The proportion of subjects with 12-week CDP was low and similar in both treatment groups (28 subjects [5.2%] in the ublituximab group and 32 subjects [5.9%] in the teriflunomide group). The time to CDP for at least 12 weeks was not statistically significant using a stratified log-rank test (hazard ratio: 0.843 [95% CI: 0.504, 1.407; p=0.5099]). The proportion of subjects with 24-week CDP for at least 24 weeks using the pooled data was 18 subjects (3.3%) in the ublituximab group and 26 subjects (4.8%) in the teriflunomide group. Similarly 24-week CDP was not nominally significant using a stratified log-rank test (hazard ratio: 0.657 [95% CI: 0.358, 1.205]; p=0.1716). The limited number of CDP events in both studies precluded the ability to detect a statistically significant difference. As the 12-week CDP was the third endpoint in the hierarchy for controlling for multiplicity, results from other secondary endpoints could only be considered as exploratory. Nevertheless, only NEDA was nominally significant in both pivotal trials and it is already a composite or clinical and imaging markers of inflammatory activity.

With 9.6% of patients recruited in USA/Western Europe between the two pivotal trials and a subgroup analysis by region showing inconsistency in results between areas, with a more favourable profile of teriflunomide in Western Countries, generalisability of the results towards the EU was extensively discussed during the procedure. Nevertheless, 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. Further, in the analysis of ARR performed for the pooled data from both pivotal studies, the number of relapses in the ublituximab group was similar in both regions. Then, it may be agreed that the results for the ublituximab treatment group, including ARR, are highly consistent between the two regions. Conversely, the ARR result for the teriflunomide treatment group in the USA and Western Europe Region (ARR=0.035) is low and an outlier based on previous teriflunomide studies as well as the ARR that was observed in the larger Eastern Europe subgroup of studies TG1101-RMS301 and TG1101-RMS302. Finally, it was concluded that results could be extrapolated to EU population.

3.4. Unfavourable effects

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

As per 20 November 2020, in the pooled analysis of the pivotal Phase III studies, cytopenias as AESIs 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. At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, 222 (22.8%) had at least one IRR. had at least one

episode of cytopenia with 102 of Grade ≥3. Lymphopenia and Lymphocyte count decreased were reported in 70 (24 of Grade ≥3) and 56 (30 of Grade ≥3) participants, respectively.

IRR (e.g. pyrexia, chills, headache, influenza-like illness myalgia) were quite common with ublituximab (5% of patients in the pivotal studies). As per 20 November 2020, in the pooled analysis of the pivotal Phase III studies, for ublituximab-treated subjects, the incidence of IRR based on the AESI category was 47.7% in. At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, 389 (39.9%) had at least one IRR.

Overall, there seems to be a higher risk of fatal and serious infection AEs with ublituximab compared to the active comparator. As per 20 November 2020, 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. At 01 March 2022, out of the 974 participants included in the Ublituximab Update Safety set of phase III trials, serious infections were reported in 130 of which 117 were of Grade ≥3. The most common TEAEs were pneumonia in particular in the context of COVID-19 disease.

As per 20 November 2020, in the pooled analysis of the pivotal Phase III studies, three patients died in the ublituximab arm (vs none in the comparator).Of these events, only one case (the pneumonia) was considered related to ublituximab by the applicant or Investigator. However, the other two cases recognised an infective component as important step in their pathogenesis. Therefore, considering the possibility of ublituximab-induced immunosuppression, the hypothesis that the two other cases of infections are both not related to the treatment cannot be easily dismissed. At 01 March 2022, out of the 974 participants included in the Ublituximab Safety Update set of phase III trials, 22 TEAE with an outcome of death were reported. The additional 19 cases of death were due to COVID-19 related events.

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). From these, only 34 subjects included in Studies TG1101-RMS301 and one TG1101-RMS302 were NAb positive. The applicant presented analysis indicating that the presence of TE-ADA or NAb did not impact, efficacy and safety of ublituximab.

3.5. Uncertainties and limitations about unfavourable effects

Patients >55 years old were not enrolled in the study: thus safety data are missing in this relevant subgroup. Moreover, this subpopulation has an intrinsically higher cancer risk of malignancy: considering that ublituximab is a substance, in principle, able to impair the physiologic cancer immunosurveillance, there are, thus, uncertainties about the risk of malignancy (particularly in the older population). Hence, malignancy has been included as important potential risk.

Although from the presented analysis, the presence of TE-ADA or NAb does not appear to impact PD, efficacy and safety of ublituximab, potential influence on the efficacy and safety of ublituximab administered in the subsequent relapses in patients previously treated with ublituximab remains unknown.

3.6. Effects Table

Table 46: Effects Table for Ublituximab in RMS

Effect	Short Description	Unit	Ublituximab	Teriflunomide	Uncertainties/ Strength of evidence	References
Favourable Effects						
ARR	Annualised relapse rate. Number of confirmed MS relapses in a year		0.089 (0.068, 0.115)	0.232 (0.196, 0.275)	0.382 (0.280, 0.520), p<0.0001	1
MRI T1 Gd+	Total number of Gd-enhancing T1 lesions per MRI scan per subject		0.013 (0.008, 0.022)	0.382 (0.293, 0.498)	0.035 (0.022, 0.054) p <0.0001	1
MRI T2	Total number of new and enlarging T2 hyperintense lesions per MRI scan per subject		0.244 (0.185, 0.322)	2.790 (2.272, 3.426)	0.088 (0.070, 0.110) p<0.0001	1
Unfavourable Effects						
IRR AE (any grade)		%	48.3	13.1		Pivotal Phase 3 studies
Lymphopenia		%	9.7	1.1		Pivotal Phase 3 studies
Lymphocyte count decreased		%	9.0	1.8		Pivotal Phase 3 studies
TE-ADA		%	81.3	N/A		Pivotal Phase 3 studies
Serious infections		%	5.0	2.9		Pivotal Phase 3 studies
Cytopenias (Grade ≥ 3)		%	12.1	2.4		Pivotal Phase 3 studies

IRR – infusion-related reactions.
1.- the Pooled Analysis of Studies TG1101-RMS301 and TG1101-RMS302 (mITT Population)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Ublituximab, in comparison to teriflunomide, significantly decreased the risk of relapses in RMS patients, as demonstrated in both pivotal trials. The risk reduction was high and the relative risk reduction was about 50%. The impact of the treatment on the MRI variables was also significant. The reduction of the mean number of Gd-enhancing T1 lesions or the mean number of new and enlarging T2 hyperintense lesions was high, exceeding 90%. On the other hand, the proportion of subjects with 12- or 24-week CDP was low and similar in both treatment groups.

From the safety perspective, in line with the safety profile described for other anti-CD20 mAbs, the main safety issues of ublituximab are known and includes the risk of IRR, cytopenias and infections. There seems to be a higher risk of fatal and serious infection AEs with ublituximab compared to the active comparator. At the present time, possible correlations between infections (including CNS and Covid-19 infections) and cytopenia and hypogammaglobulinemia cannot be excluded.

3.7.2. Balance of benefits and risks

Although ublituximab demonstrated a significant impact on the ARR and MRI markers of acute inflammatory activity, the analysis did not show a significant impact on the CDP. The applicant claims that the lack of the effect may be a result of the limited number of CDP events in both studies that preclude the ability to detect a statistically significant difference. This explanation can be followed.

On top of underrepresentation of USA / Western Europe populations in both pivotal trials, results from subgroup analysis casted doubts about the generalisability of the results towards an EU population. In the analysis of ARR performed for the pooled data from both pivotal studies, the number of relapses in the ublituximab group was similar in both regions. Hence it may be agreed that the results for the ublituximab treatment group, including ARR, are highly consistent between the two regions. Conversely, the ARR result for the teriflunomide treatment group in the USA and Western Europe Region (ARR=0.035) is low and an outlier based on previous teriflunomide studies as well as the ARR that was observed in the larger Eastern Europe subgroup of studies TG1101-RMS301 and TG1101-RMS302. In fact, analysis of baseline values for baseline disease activity indicates that the proportion of patients with highly active disease was slightly lower in the US and Western Europe than in Eastern Europe for teriflunomide (9.4% vs 15.2%). This was further confirmed in the analysis of differences in the efficacy of teriflunomide in participants with active vs highly active disease (better results for patients who are not highly active disease). Consequently, it was agreed that the ARR observed in the Western European and US populations is lower than usual and finally it was agreed that efficacy results could be reasonably extrapolable to EU populations.

3.8. Conclusions

The overall benefit/risk balance of Briumvi is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Briumvi is favourable in the following indication(s):

> 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 (see section 5.1).

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

New active substance status

Based on the CHMP review of the available data, the CHMP considers that ublituximab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.