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APPLICATION NUMBER:

761238Orig1s000

CLINICAL REVIEW(S)

Clinical Review
 Laura Baldassari, MD, MHS
 BLA 761238
 Ublituximab-xiiy (Briumvi)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761238
Priority or Standard	Standard
Submit Date(s)	09/28/2021
Received Date(s)	09/28/2021
PDUFA Goal Date	12/28/2022
Division/Office	Division of Neurology 2, Office of Neuroscience
Reviewer Name(s)	Laura Baldassari, MD, MHS
Review Completion Date	11/11/2022
Established/Proper Name	Ublituximab-xiiy
(Proposed) Trade Name	Briumvi
Applicant	TG Therapeutics
Dosage Form(s)	150mg/6mL (25 mg/mL) single-dose vial
Applicant Proposed Dosing Regimen(s)	First infusion: 150mg IV infusion Second infusion (2 weeks later): 450mg IV infusion Subsequent infusions (every 6 months): 450mg IV infusion
Applicant Proposed Indication(s)/Population(s)	Briumvi (ublituximab-xiiy) is a CD20-directed cytolytic antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

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Glossary

AC	advisory committee
AE	adverse event
ALC	absolute lymphocyte count
ANC	absolute neutrophil count
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EDSS	Expanded Disability Status Scale
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LP	lumbar puncture

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MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MS	multiple sclerosis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PML	progressive multifocal leukoencephalopathy
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RMS	Relapsing forms of multiple sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Ublituximab-xiiy (TG1101) is a recombinant IgG1 chimeric, glycoengineered monoclonal antibody targeting the CD20 antigen, leading to lysis of B-cells. Ublituximab-xiiy targets a novel epitope of CD20 that is not bound by ofatumumab or ocrelizumab. [REDACTED] (b) (4) [REDACTED] and therefore result in greater antibody-dependent cellular cytotoxicity (ADCC) than rituximab and ocrelizumab.

Two anti-CD20 monoclonal antibodies, ocrelizumab (Ocrevus) and ofatumumab (Kesimpta), are approved for the treatment of relapsing forms of multiple sclerosis (RMS) in adults. Ocrelizumab is also approved for the treatment of primary progressive multiple sclerosis. The precise mechanism by which anti-CD20 therapies exert therapeutic effects in multiple sclerosis is unknown, but is presumed to involve binding to CD20 on B-lymphocytes, which leads to cytolysis via ADCC and/or complement-mediated lysis.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Two adequate and well-controlled, identical Phase 3 trials provided substantial evidence that treatment with ublituximab-xiiy administered intravenously (IV) at an initial dose of 150mg, then 450mg on Day 15, and 450mg every 6 months thereafter, reduces the frequency of relapses in comparison to treatment with teriflunomide in patients with relapsing forms of MS. Treatment with ublituximab-xiiy significantly reduced the frequency of new MRI lesions (both gadolinium-enhancing and new/enlarging T2 lesions) in comparison to teriflunomide. However, ublituximab-xiiy did not demonstrate benefit compared to teriflunomide in terms of 3-month confirmed disability progression.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Two adequate and well-controlled, identical Phase 3 trials in adults with RMS provided substantial evidence that treatment with ublituximab-xiiy significantly reduces annualized relapse rate and the frequency of new MRI lesions (both gadolinium-enhancing and new/enlarging T2 lesions) in comparison to teriflunomide. However, ublituximab-xiiy did not demonstrate benefit compared to teriflunomide in terms of 12-week confirmed disability progression. These findings represent clinically relevant benefits that justify a moderate safety risk, similar to other anti-CD20 therapies approved for RMS. The risks associated with ublituximab-xiiy treatment were consistent with those observed with other anti-CD20 therapies, including infections (including serious and fatal infections), infusion related reactions, reduction in IgM, cytopenias, and reduction in immunoglobulins (particularly IgM). Opportunistic infections and reduction in IgG were not observed in controlled RMS trials of ublituximab-xiiy; however, longer-term experience is needed to fully assess these risks. Therefore, based on available data, the risk profile appears manageable and consistent with other anti-CD20 therapies, and justifies the benefit of treatment with ublituximab-xiiy in patients with RMS.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	- Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, and neurodegenerative disease affecting the central nervous system. - Relapsing forms of MS are defined by the occurrence of clinical relapses, which are events characterized by new onset neurological symptoms associated with disability, from which there is variable recovery. Relapsing forms of MS include clinically isolated syndrome, relapsing remitting MS, and active secondary progressive MS. - The prevention of relapses is paramount to the treatment of patients with relapsing forms of MS, in order to prevent new neurological symptoms that can lead to disability.	Treatment of relapsing forms of multiple sclerosis is intended to reduce the frequency of clinical relapses. Clinical relapses can be permanently disabling and reduce quality of life.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are over twenty products approved for treatment of relapsing forms of MS. • Currently approved MS therapeutics have demonstrated efficacy in reducing the risk of clinical relapse, which is presumed to be related to immunomodulatory mechanisms of action that impact the neuroinflammatory aspect of the disease.	Treatment of relapsing forms of multiple sclerosis generally involves immunomodulation intended to reduce the frequency of clinical relapse. Many therapies approved for the treatment of relapsing forms of MS are labeled to prevent accumulation of disability.
Benefit	• Two adequate and well-controlled, identical Phase 3 trials in adults with RMS provided substantial evidence that treatment with ublituximab-xiiy significantly reduces annualized relapse rate and the frequency of new MRI lesions (both gadolinium-enhancing and new/enlarging T2 lesions) in comparison to teriflunomide. • Ublituximab-xiiy did not demonstrate benefit compared to teriflunomide in terms of 12-week confirmed disability progression.	There is substantial evidence that treatment of RMS with ublituximab-xiiy provides a clinically meaningful benefit (i.e., reduction of relapses).
Risk and Risk Management	• A major risk of ublituximab-xiiy is that of infection. Serious and fatal infections occurred in ublituximab-xiiy-treated patients during the controlled trials. Serious infections also have been reported with other anti-CD20 therapies approved for RMS, and the relative risk compared to teriflunomide appears similar to that observed in controlled trials for ublituximab-xiiy. • Ongoing clinical surveillance and monitoring of immunoglobulins may be able to mitigate the risk of more serious infections. • Infusion-related reactions, including some serious reactions, were observed. Patients will be required to receive premedication with corticosteroids and an antihistamine, and remain under observation post-infusion.	The risk of treatment of RMS with ublituximab-xiiy appears consistent with that of other anti-CD20 therapies approved for RMS. Infusion related reactions appear manageable with required premedication and post-infusion monitoring. The demonstrated benefit appears to justify the risks.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
x	Clinical outcome assessment (COA) data, such as	
	☐ Patient reported outcome (PRO)	
	☐ Observer reported outcome (ObsRO)	
x	Clinician reported outcome (ClinRO)	Expanded Disability Status Scale (EDSS); see Sec 6.1.1, Study Design, Study Endpoints
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
	☐ Input informed from participation in meetings with patient stakeholders	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, and neurodegenerative disorder affecting the central nervous system. The cause of MS is unknown, but is hypothesized to be related to a complex interaction of genetic and environmental risk factors.^{1,2} MS is the most common cause of non-traumatic neurologic disability in young adults, and it is estimated that approximately 1 million people in the United States have MS.³ Disease manifestations can be diverse, and include weakness, incoordination, visual impairment, sensory loss, gait dysfunction, fatigue, cognitive impairment, and bowel/bladder dysfunction.

Relapsing forms of MS are defined by the occurrence of clinical relapses, which are events characterized by new onset neurological symptoms associated with disability, from which there is variable recovery. Relapsing forms of MS include clinically isolated syndrome, relapsing remitting MS (RRMS), and active secondary progressive MS. The prevention of relapses is paramount to the treatment of patients with relapsing forms of MS; relapses degrade the quality of life in patients with MS, and prevention of relapses prevents new neurological symptoms that can lead to disability.

Relapsing-remitting MS is the most common MS phenotype, as it accounts for approximately 85% of MS cases at symptom onset.⁴ Patients with RRMS present with clinical relapses, from which there is a spectrum of recovery. The median age of RRMS onset is approximately 28 to 30 years.⁵⁻⁷ In general, the frequency of relapse decreases over time,^{8,9} with an estimate of relapse decrease by 17% for every 5 years of disease duration.⁸ The decrease in relapse risk is thought to be more pronounced in patients with older age of onset.

Over time, the majority of patients with RRMS transition from predominantly inflammatory to more neurodegenerative driving forces of the disease, with development of secondary progressive MS (SPMS).¹⁰ The transition to SPMS is an age-dependent process,¹¹⁻¹³ and it is estimated that approximately 30 to 40% of patients with SPMS have relapses superimposed upon this typical gradual decline.^{6,14} The time from RRMS diagnosis to SPMS conversion is age of onset-dependent, and ranges from 18.9 to 20 years for all patients per several natural history studies.^{8,12,15,16} Generally, the younger a patient is at the time of RRMS onset, the longer the disease duration prior to SPMS conversion. However, several studies have demonstrated that patients who receive MS treatments have substantially decreased risk of and delayed conversion to SPMS compared to patients in the pre-treatment era.¹⁷⁻²³ Additionally, use of some therapies approved to treat MS has been shown to delay reaching disability milestones.^{17,20-22}

2.2. Analysis of Current Treatment Options

There are over 20 products approved for treatment of relapsing forms of MS, including clinically isolated syndrome, relapsing remitting MS, and active secondary progressive MS (Table 1). Currently approved MS therapeutics have demonstrated efficacy in reducing the risk of clinical relapse, which is presumed to be related to immunomodulatory mechanisms of action that impact the neuroinflammatory aspect of the disease.

Table 1 (Reviewer). FDA-Approved Treatments for Relapsing Forms of Multiple Sclerosis

Product Name	Relevant Indication (Current)	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety Issues
Interferon beta-1b (Betaseron)	Relapsing forms of MS ¹	1993	SC every other day	ARR ² 0.9 vs. placebo 1.31	Injection site reactions, hepatotoxicity, depression
Interferon beta-1a (Avonex)	Relapsing forms of MS	1996	IM weekly	ARR 0.67 vs. placebo 0.82	Injection site reactions, hepatotoxicity, depression
Glatiramer acetate (Copaxone)	Relapsing forms of MS	1996	SC daily or three times a week	Relapse rate 0.6/2 years vs. placebo 2.4 in Study 1	Injection site reactions, lipoatrophy
Mitoxantrone (Novantrone)	SPMS, progressive relapsing, or worsening RRMS	2000	IV q 3 months, duration limited by cardiotoxicity	Reduction in # relapses (0.4 and 0.73 vs. 1.2 placebo) in study 1; reduction in Gd+ T1 lesions, ARR, EDSS change in Study 2	Leukemia, cardiotoxicity
Interferon beta-1a (Rebif)	Relapsing forms of MS	2002	SC three times a week	29 to 32% reduction in # relapses over 2 years vs. placebo	Injection site reactions, hepatotoxicity, depression
Natalizumab (Tysabri)	Relapsing forms of MS	2004	IV every 4 weeks	67% reduction in ARR vs. placebo	PML, hepatotoxicity
Interferon beta-1b (Extavia)	Relapsing forms of MS	2009	SC every other day	ARR 0.9 vs. placebo 1.31	Injection site reactions, hepatotoxicity, depression
Fingolimod (Gilenya)	Relapsing forms of MS, ages ≥10 years	2010	PO daily	ARR 0.18 vs 0.4 placebo; 0.16 vs. 0.33 Avonex	Macular edema, infection, bradycardia, respiratory effects, liver injury
Teriflunomide (Aubagio)	Relapsing forms of MS	2012	PO daily	22 to 36% reduction in ARR vs. placebo	Hepatotoxicity, peripheral neuropathy, teratogenicity
Dimethyl fumarate (Tecfidera)	Relapsing forms of MS	2013	PO twice daily	44 to 53% reduction in ARR vs. placebo	Lymphopenia, GI effects, flushing

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Product Name	Relevant Indication (Current)	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety Issues
Peginterferon beta-1a (Plegridy)	Relapsing forms of MS	2014	SC every 2 weeks	36% ARR reduction vs. placebo	Injection site reactions, hepatotoxicity, depression
Alemtuzumab (Lemtrada)	Relapsing remitting and active SPMS, patients who have failed ≥ 2 other MS treatments	2015	IV, 3 to 5 days 1 year apart	49 to 55% ARR reduction vs interferon beta-1a	Serious and fatal autoimmune conditions, infusion reactions, stroke, malignancy
Ocrelizumab (Ocrevus)	Relapsing forms of MS; PPMS	2017	IV every 6 months	46 to 47% ARR reduction vs. interferon beta-1a	Infusion-related reactions, infection, possible breast cancer
Monomethyl fumarate (Bafiertam)	Relapsing forms of MS	2018	PO twice daily	See Tecfidera (505(b)(2))	Lymphopenia, GI effects, flushing
Siponimod (Mayzent)	Relapsing forms of MS	2019	PO daily	55% ARR reduction vs. placebo	Macular edema, infection, bradycardia, respiratory effects, liver injury
Cladribine (Mavenclad)	Relapsing forms of MS (excluding CIS), in patients who have failed another MS treatment	2019	2 PO courses 1 year apart	58% ARR reduction vs. placebo	Malignancies, teratogenicity, lymphopenia, infections, hematologic toxicity, liver injury
Diroximel fumarate (Vumerity)	Relapsing forms of MS	2019	PO twice daily	See Tecfidera (505(b)(2))	Lymphopenia, GI effects, flushing
Ozanimod (Zeposia)	Relapsing forms of MS	2020	PO daily	38 to 48% ARR reduction vs. interferon beta-1a	Macular edema, infection, bradycardia, respiratory effects, liver injury
Ofatumumab (Kesimpta)	Relapsing forms of MS	2020	SC every 4 weeks	51 to 59% ARR reduction vs. Teriflunomide	Infections, injection-related reactions, reduction in immunoglobulins, fetal risk
Ponesimod (Ponvory)	Relapsing forms of MS	2021	PO daily	30.5% ARR reduction vs. Teriflunomide	Macular edema, infection, bradycardia, respiratory effects, liver injury
Fingolimod ODT (Tascenso ODT)	Relapsing forms of MS	2021 (TA)	PO daily	See Gilenya (505(b)(2))	Macular edema, infection, bradycardia, respiratory effects, liver injury

¹Relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease

²ARR: Annualized relapse rate

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ublituximab-xiiv is not approved for any indication in the United States. IND (b) (4) for ublituximab for the treatment of (b) (4), along with IND 116762 for umbralisib, was placed on partial hold on 1/13/2022 due to concerns regarding mortality, serious adverse events, and questionable benefit of the combination of ublituximab and umbralisib. Under this partial hold, no new subjects were to be enrolled in the specified trials, and current subjects were required to be reconsented.

BLA 761207 for ublituximab and umbralisib for the treatment of chronic lymphocytic leukemia was withdrawn by the applicant prior to a planned Advisory Committee that was convened due to a mortality signal believed to be associated with umbralisib.

3.2. Summary of Presubmission/Submission Regulatory Activity

Original IND (IND 127265) submission: 10/16/2015

Study TG1101-RMS201 was placed on full clinical hold due to unreasonable and significant risk of illness or injury to human subjects. The review team's concern was related to monitoring and management of infusion-related reactions, as well as the applicant's proposal for determination of dose tolerability. A complete response to clinical hold was submitted on 2/3/2016, and the study was allowed to proceed on 2/16/2016.

Meeting Request regarding Phase 3 trial design: 4/27/2016 (written responses issued 7/8/2016)

Special Protocol Agreement (SPA) Initial Submissions: 9/23/2016 (Study TG1101-RMS301) and 4/26/2017 (Study TG1101-RMS302)

Between 2016 and 2017, multiple SPA resubmissions occurred due to non-agreement.

SPA Agreement: 7/29/2017

Between 2017 and 2020, the applicant submitted multiple SPA amendments, the most recent of which was agreed to by the Division on 4/9/2020.

Pre-BLA meeting: 4/6/2021

Pediatric initial study plan agreement: 5/21/2021 (full waiver)

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BLA 761238 submission: 09/28/2021

Of note, the Division had several concerns related to safety and safety reporting in the context of the ublituximab-xiiy IND. Serious infections and deaths were reported in the RMS development program in 2019, which prompted the Division to request that the applicant update the informed consent documents and Investigator's Brochure, re-consent subjects, and inform investigators of the risk of life-threatening and serious infections on 12/18/2019.

Subsequently, the Division raised concerns due to the delayed reporting of a death in the ublituximab-xiiy development program in February of 2020, which prompted a For Cause inspection by the Office of Scientific Investigations (OSI) in January of 2021. This inspection did not result in any citations. However, the inspection found that the applicant did not have a formal standard operating procedure for assessing safety during the Phase 3 trials, and that a rationale for assessing relatedness to study treatment was unclear (which was also noted by the Data Safety Monitoring Board).

The IND annual report submitted 7/21/2020 indicated the death of a 22 year-old woman due to salpingitis, but no safety report was submitted to the IND. A letter was sent to the applicant on 8/25/2020 regarding IND safety reporting requirements, including the submission of safety reports for all serious infections and deaths, regardless of the applicant's causality determination.

The applicant identified hepatitis B reactivation as an important potential risk of ublituximab-xiiy, and sent a Dear Investigator Letter regarding this risk dated 11/2/2020, which was submitted to the Division on 11/3/2020. The applicant revised this letter following Division feedback, then resubmitted to the Division on 11/20/2020. This revision indicated that "investigators should consider rescreening any subjects with RMS deemed to be at high risk of hepatitis B infection."

3.3. Foreign Regulatory Actions and Marketing History

Ublituximab-xiiy is not approved or marketed anywhere in the world for any indication. The Division is not aware of any foreign regulatory actions taken for the ublituximab-xiiy IND.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Please refer to the OSI review by Cara Alfaro, PharmD. Four sites were inspected for Studies
CDER Clinical Review Template
Version date: September 6, 2017 for all NDAs and BLAs

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TG1101-RMS301 and TG1101-RMS302. Several potential unblinding events, particularly related to unblinded MRI reports containing MS pathology being available to the clinical site and treating neurologist, were identified. The Division sent an Information Request for further information on these potential unblinding events. Please refer to Sections 6.1.2 and 6.2.2 for further discussion.

4.2. Product Quality

Please refer to the Chemistry, Manufacturing, and Control (CMC) review.

4.3. Clinical Microbiology

Please refer to the CMC/Microbiology review.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the Nonclinical review.

4.5. Clinical Pharmacology

Please refer to the Clinical Pharmacology review. Please note that Studies TG1101-RMS301 and TG1101-RMS302 utilized bioequivalent teriflunomide as the active comparator. Determination of the bioequivalence of teriflunomide utilized in these studies and marketed teriflunomide (Aubagio) is deferred to Clinical Pharmacology.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 2 (Reviewer). Clinical Trials Relevant to RMS Indication

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
TG1101-RMS301	NCT03277261	Phase 3, randomized, multicenter, double-blind, double-dummy, active-controlled study of ublituximab-xiiy versus bioequivalent teriflunomide	Day 1: 150mg IV over 4 hours Day 15: 450mg IV over 1 hour Weeks 24, 48, 72: 450mg IV over 1 hour	ARR	96 weeks treatment/120 weeks follow-up	549	RMS	60 centers in 9 countries (Europe and North America)
TG1101-RMS302	NCT03277248	Phase 3, randomized, multicenter, double-blind, double-dummy, active-controlled study of ublituximab-xiiy versus bioequivalent teriflunomide	Day 1: 150mg IV over 4 hours Day 15: 450mg IV over 1 hour Weeks 24, 48, 72: 450mg IV over 1 hour	ARR	96 weeks treatment/120 weeks follow-up	545	RMS	50 centers in 8 countries (Europe and North America)
<i>Studies to Support Safety</i>								
TG1101-RMS201E	NCT03381170	Open-label, single-arm extension study	450mg over 1 hour every 24 weeks	Safety	192 weeks	45	RMS	9 centers in the United States
TG1101-RMS303	NCT04130997	Open-label, single-arm extension study; May include patients from TG1101-RMS201E.	Day 1: 150mg IV over 4 hours Day 15: 450mg IV over 1 hour (301/302 patients only) Weeks 24, 48, 72, 96, 120, 144, 168: 450mg IV over 1 hour	Safety	172 weeks	642	RMS	TG1101-RMS301 and TG1101-RMS302 study sites

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		<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>						
TG1101-RMS201	NCT02738775	Placebo-controlled, multicenter, dose-finding, sequential study. Patients who were assigned to placebo received ublituximab-xiiy following completion of Week 4.	6 dosing cohorts (6 UTX, 2 PBO each) with varying dose and infusion time at Day 1, Day 15, and Week 24. Day 1: 150mg/4 hours, 150mg/3 hours, 150mg/2 hours, or 150mg/1 hour Day 15: 450mg/1 hour, 450mg/1.5 hours, 450mg/3 hours, or 600mg/1 hour Week 24: 450mg/1 hour, 450mg/1.5 hours, or 600mg/1 hour	% patients with ≥95% CD19+ B-cell reduction within 2 weeks after Day 15 infusion (i.e., at Week 4)	52 weeks	49	RMS	9 centers in the United States

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5.2. Review Strategy

The efficacy portion of this review was focused on two pivotal trials, TG1101-RMS301 and TG1101-RMS302. These double-blind trials were of identical design, conducted under Special Protocol Agreements, and utilized bioequivalent teriflunomide as a comparator. The treatment duration of 96 weeks, with 120-week follow-up, is adequate to support an indication for both reduction in annualized relapse rate (ARR), the primary endpoint, and 12- and 24-week confirmed disability progression. These trials will be analyzed separately for their primary endpoint, ARR, and pooled for analysis of 12- and 24-week confirmed disability progression, which was an *a priori* decision. The results of Study TG1101-RMS201 will be discussed as supportive evidence of efficacy.

The safety portion of this review will focus on the double-blind portion of the Phase 3 Studies TG1101-RMS301 and TG1101-RMS302, as well as their open-label extension (TG1101-RMS303). The results of Study TG1101-RMS201 and its open label-extension, TG1101-RMS201E, will be discussed as well. The applicant's Integrated Summary of Safety was separated into Phase 2 and Phase 3 datasets, as previously agreed upon by the Division. Please refer to Section 8.1 for further details regarding the safety review strategy.

Dr. Rui Li, Senior Clinical Analyst, performed several of the reported safety analyses in conjunction with this reviewer.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study TG1101-RMS301

6.1.1. Study Design

Overview and Objective

Study TG1101-RMS301 ("ULTIMATE I") was one of two identical randomized controlled trials (RCTs) whose objective was to assess the efficacy and safety of ublituximab-xiiy compared to bioequivalent teriflunomide as treatment for relapsing forms of MS. Studies TG1101-RMS301 and TG1101-RMS302 were conducted under a Special Protocol Agreement.

The primary objective of the study was to determine the Annualized Relapse Rate (ARR) in subjects with RMS after 96 weeks (approximately 2 years with a year equal to 365.25 days) treatment with IV infusion of ublituximab-xiiy/oral placebo compared to 14 mg oral teriflunomide/IV placebo.

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Secondary objectives were to examine the effects of ublituximab-xiiy/oral placebo as compared to teriflunomide/IV placebo on the following:

1. MRI parameters,
2. Confirmed Disability Progression,
3. No Evidence of Disease Activity (NEDA),
4. Symbol Digit Modality Test (SDMT), and
5. Safety of ublituximab-xiiy/oral placebo, as determined by adverse events (AEs) and serious adverse event (SAEs), including MS worsening.

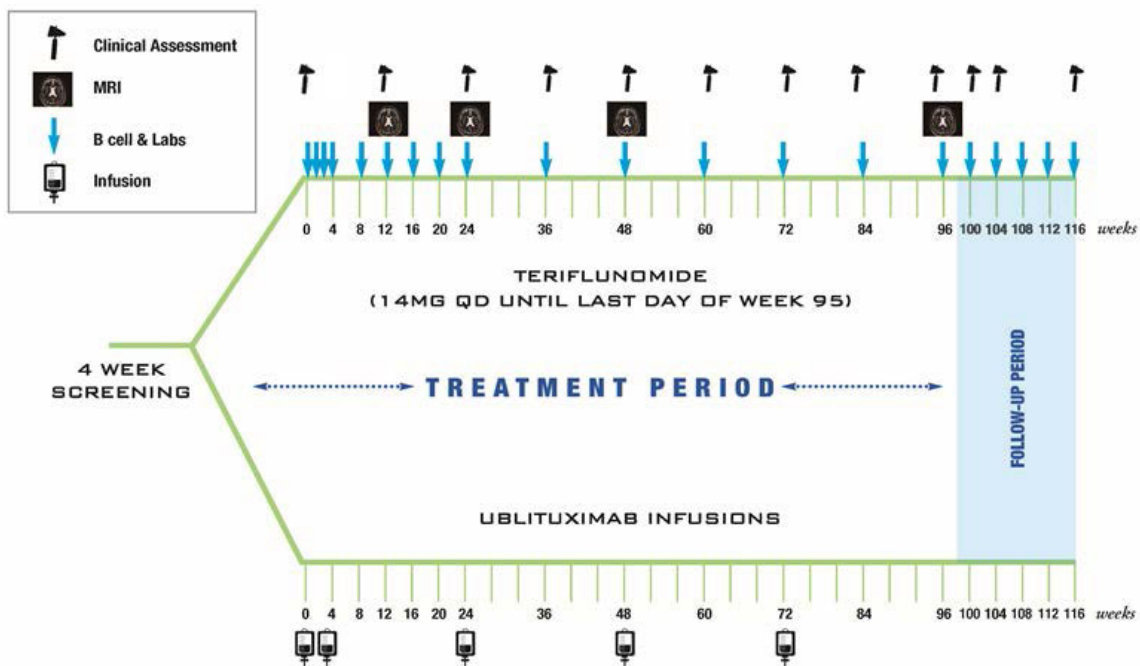
Trial Design

Study TG1101-RMS301 was a 120-week, Phase 3, randomized, multicenter, double-blind, double-dummy, active controlled study, designed to evaluate the efficacy and safety of ublituximab-xiiy compared to bioequivalent teriflunomide in patients with relapsing forms of MS per 2010 McDonald Criteria. Patients were required to have at least 2 relapses in the prior 2 years, or 1 relapse in the prior year and/or at least 1 gadolinium-enhancing lesion. Patients were randomized 1:1 to receive treatment with either ublituximab-xiiy or teriflunomide (with oral or IV placebo, respectively), for 96 weeks (last ublituximab-xiiy infusion at Week 72). Double-blind period follow-up continued until 120 weeks. Upon completion of the double-blind treatment period, patients could consent to participation in the 172-week open label extension study, TG1101-RMS303.

The study schematic for Study TG1101-RMS301 is presented in Figure 1. The study consisted of a Screening Period of up to 4 weeks, a 96-week Double-blind Treatment Period, and a Follow-Up Period of 20 weeks.

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Figure 1 (Applicant). Studies TG1101-RMS301 and TG1101-RMS302 Study Schematic



Source: Applicant's Clinical Study Report, Studies TG1101-RMS301 and TG1101-RMS302

Blinding

Study TG1101-RMS301 utilized a double-dummy design, where patients assigned ublituximab-xiiy received oral placebo, and patients assigned teriflunomide received IV placebo. Teriflunomide and oral placebo were identical in appearance, and were supplied in identical boxes. Ublituximab-xiiy and IV placebo were provided in unit boxes containing either 15mL or 6mL vials, respectively, to the study site.

The Independent Relapse Adjudication Panel (IRAP), which was responsible for confirmation of relapses to be included in the primary efficacy analysis, was blinded. Study staff, including the examining and treating neurologists, were blinded to treatment assignment. Additionally, the examining neurologist was blinded to the treating neurologist's assessments, and vice-versa. MRIs were reviewed by a centralized reading center blinded to treatment assignment and any clinical information.

The protocol also incorporated a Blinded Assessment Relapse Team (BART) that reassessed sample size when 210 out of the 220 participants in each arm were randomized. The Data Safety Monitoring Board (DSMB) reviewed unblinded safety data.

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Key Eligibility Criteria

Please refer to Section 13.2 for full eligibility criteria.

Key Inclusion Criteria

1. Age 18 to 55 years
2. Diagnosis of relapsing MS per 2010 McDonald Criteria
3. ≥ 2 relapses in prior 2 years or 1 relapse in the year prior to screening and/or ≥ 1 Gd enhancing lesion
4. Documented MRI of brain with abnormalities consistent with MS
5. Active disease
6. EDSS 0-5.5 (inclusive) at screening
7. B cell counts $\geq 5\%$ of total lymphocytes
8. Neurologic stability ≥ 30 days prior to screening and baseline

Key Exclusion Criteria

1. Prior treatment with any of the following:
 - a. Anti-CD20 or other B-cell directed treatment
 - b. Alemtuzumab
 - c. Natalizumab
 - d. Teriflunomide
 - e. Leflunomide
 - f. Stem cell transplantation
2. Prior DMT exposure within months of screening:
 - a. 24 months with cladribine
 - b. 6 months with daclizumab, azathioprine, methotrexate, or cyclophosphamide
 - c. 90 days with fingolimod, or experimental S1P modulators, IV immunoglobulin, and plasmapheresis
 - d. 30 days with glatiramer acetate, interferons, dimethyl fumarate, laquinimod or glucocorticoids
3. Diagnosis of primary progressive MS
4. Disease duration ≥ 10 years from onset with EDSS ≤ 2.0
5. Contraindications to MRI, gadolinium, or teriflunomide
6. Evidence or known history of clinically significant infection (e.g., PML, tuberculosis, hepatitis C, hepatitis B, HIV/AIDS)
7. History of liver disease
8. History of renal impairment
9. Laboratory abnormalities
 - a. Absolute lymphocyte count $< 1,000/\mu\text{L}$

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- b. Absolute white blood cell count <4,000 cells/mm³
 - c. Platelets <150,000 cells/mm³
 - d. Absolute neutrophil count ≤1,500 cells/mm³
10. Lack of immunity to varicella based VZV IgG level at screening
11. History or presence of malignancy, lymphoproliferative disease, or history of total lymphoid irradiation or bone marrow transplantation

Study Treatment

Dose Regimen

Subjects were randomized to receive either ublituximab-xiiy/PO placebo or teriflunomide 14mg daily/IV placebo for a 96-week double-blind treatment period. The dosing regimen, including ublituximab-xiiy dose and infusion times, are presented in Table 3.

Table 3 (Applicant). Study TG1101-RMS301 Dosing Regimen

	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 the last day of Week 95					
Teriflunomide plus placebo infusion	Teriflunomide (14 mg) QD* from Week 1 Day 1 until the last day of Week 95					
	Infusion Placebo	Infusion Placebo	Infusion Placebo	Infusion Placebo	Infusion Placebo	

Source: Study TG1101-RMS301 Protocol Version 5.0 (9/4/2020)

All subjects were required to undergo an accelerated elimination procedure at Week 100 or at the time of early treatment withdrawal. Plasma concentration of teriflunomide was measured in all subjects prior to (Week 96) and following (Week 116) the accelerated elimination procedure to assess compliance and maintain the study blind.

Management of Infusion-Related Reactions

Due to the known risk of infusion-related reactions, subjects received pre-medication 30 to 60 minutes prior to each study infusion with an antihistamine (diphenhydramine 50 mg or equivalent; administered orally), and a corticosteroid (dexamethasone 10-20 mg or equivalent; administered orally). Subjects could also receive prochlorperazine (or another antiemetic agents at Treating Neurologist/PI discretion if inadequate) for prevention or treatment of nausea/vomiting.

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The protocol indicates that symptomatic infusion reactions may be treated at the discretion of the treating physician, including but not limited to oral acetaminophen 650mg, corticosteroids, antihistamines, oxygen, and bronchodilators. Due to the potential for infusion-related hypotension, the protocol instructs investigators to consider withholding anti-hypertensive medications for 24 hours prior to study infusion.

Relapse Assessment and Treatment

Subjects who experienced new or worsening neurologic symptoms were instructed to contact the Treating Neurologist within 48 hours of symptom onset. Within 7 days of the subject reporting the suspected relapse to the Treating Neurologist, the subject will be scheduled for a study visit and assessed by both the Treating and Examining Neurologist independently. Relapse assessments included neurological and physical examination, concomitant medications, safety assessment, and Expanded Disability Status Scale (EDSS, by the examining neurologist). The treating neurologist will be blinded to the examining neurologist's EDSS assessment. After the completion of the examining neurologist's assessment, the treating neurologist may initiate relapse treatment with IV methylprednisolone 1g daily for 3 to 5 days.

The results of the treating and examining neurologists' assessments were then sent to the Independent Relapse Adjudication Panel (IRAP) for confirmation. Relapses were confirmed if a subject experienced either a ≥ 2 point increase on one or 1 point increase on 2 or more of the appropriate Functional Systems (which correspond to the patient's symptoms), or a ≥ 0.5 point increase in EDSS (unless EDSS was 0, which requires an increase of at least 1 point) from the previous assessment. Additionally, relapses are defined in the protocol as "new or worsening neurological symptoms lasting ≥ 24 hours with the absence of fever, injury, infection or adverse reactions to medications and accompanied by new neurological findings upon examination by the Examining Neurologist." Relapses were also to be preceded by neurological stability for at least 30 days.

The protocol required all subjects who experience an IRAP-confirmed or Treating Neurologist medically-confirmed relapse to be reconsented within 6 weeks to continue trial participation.

Study Assessments

The schedule of assessments is summarized in Table 4.

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Table 4 (Reviewer). Study TG1101-RMS301 and TG1101-RMS302 Schedule of Assessments

Week	Screening	Baseline	Double-Blind Treatment Period																		Early W/D	Unsched. Relapse			
	-4 to 0	1 (D1)	1 (D2)	2	3	4	8	12	16	20	24	36	48	60	72	84	96	100	104	108	112	116			
Ublituximab-xiiy/placebo infusion		X			X						X	X	X	X											
EDSS, MSFC, and neurological examination	X	X						X			X	X	X	X	X	X	X							X	X
MRI	X							X			X	X					X							X	
Blood collection for B lymphocyte cell counts (% CD19+ B cells)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X
Quantitative immunoglobulins		X			X						X	X		X		X								X	X
Adverse events (CTCAE v4.03)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
12-lead ECG	X	X			X						X	X		X										X	
Routine safety labs (CBC, CMP, UA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X
Subject phone consult																					X	X			

W/D: Withdrawal; Unsched: Unscheduled

Source: Adapted from Study TG1101-RMS301 Protocol Version 5.0 (9/4/2020)

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Disability

Time to 12-week confirmed disability progression (CDP) was a key secondary endpoint for Study TG1101-RMS301, and was evaluated utilizing EDSS assessments performed by the Examining Neurologist at screening, Day 1, Weeks 12, 24, 36, 48, 60, 72, 84, and 96. Disability progression was defined as an increase of ≥ 1.0 point from the baseline EDSS, not attributable to another etiology, when the baseline EDSS was ≤ 5.5 , and ≥ 0.5 when the baseline EDSS was > 5.5 . Confirmation of disability progression occurs when this increase in EDSS is recorded at the subsequent regularly scheduled study visit.

Brain MRI

Brain MRIs were obtained with and without gadolinium contrast in all patients at screening, Weeks 12, 24, 48, 96, and at early withdrawal (if an MRI was not obtained within 30 days). MRIs were evaluated locally for safety reasons, and were formally read by a centralized, blinded reading center for efficacy endpoints. MRI reports provided to the Treating Neurologist only indicated non-MS pathology.

Study Endpoints

The primary efficacy endpoint was ARR, defined as the number of IRAP-confirmed relapses per subject year. The estimate of ARR for a treatment group was the total number of relapses for subjects in the respective treatment group divided by the sum of treatment duration for subjects in that specific treatment group. Subjects were treated up to 96 weeks.

Key secondary efficacy endpoints were:

- 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.
- Time to Confirmed Disability Progression (CDP) for at least 12 weeks occurring during the 96-week double-blind treatment period. This analysis utilized pooled data from the two identical studies, TG1101-RMS301 and TG1101-RMS302.
- Proportion of subjects with No Evidence of Disease Activity (NEDA) from Week 24 to Week 96.
- Proportion of subjects reaching impaired Symbol Digit Modalities Test (SDMT) from baseline to Week 96.
- Percentage change in Brain Volume from baseline to Week 96.

Statistical Analysis Plan

Analysis Population

The Intention-to-Treat (ITT) population was defined as all randomized subjects, analyzed by

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randomized treatment group. The ITT population was only utilized for sensitivity analyses of key efficacy endpoints.

The modified Intention-to-Treat (mITT) population was defined as all subjects in the ITT population who received at least one dose of study medication and had at least one baseline and post-baseline efficacy assessment. The primary efficacy analyses were conducted in the mITT population.

The Per-Protocol population was defined as all subjects in the mITT population who were treated for at least 1.75 years and did not have a major protocol deviation that impacted efficacy analysis.

The Safety Population included all subjects who received at least one dose of study drug. All safety analyses were conducted in the Safety Population.

Primary Endpoint

The primary efficacy endpoint, ARR, was defined as the number of relapses (protocol-defined and IRAP-confirmed) per subject-year (with a year equal to 365.25 days) in the mITT population. This analysis was conducted using a negative binomial regression model to account for potential overdispersion, adjusted for EDSS stratum (baseline EDSS ≤ 3.5 versus > 3.5) and clinic region. The model evaluated the total number of confirmed relapses with onset between the date of randomization and the day of last study treatment, by treatment group. Log-transformed standardized treatment duration (randomization to date of last treatment before early withdrawal or completion of Week 96 assessment) was included in the model as an offset variable. This strategy resulted in a rate ratio with 95% confidence intervals to facilitate comparison of ARR between ublituximab-xiiy and teriflunomide.

Key Secondary Endpoints

Key secondary endpoints, listed above in order, were analyzed in a hierarchical approach using a step-down procedure. Again, the mITT population was utilized for each analysis.

The total numbers of gadolinium-enhancing T1-lesions and new or enlarging T2 hyperintense lesions per MRI scan were calculated as the sum of the number of lesions at Weeks 12, 24, 48, and 96, divided by the number of MRIs performed. These count data were analyzed using negative binomial regression, with offset based on time on study, and covariates of region, baseline EDSS stratum, and baseline MRI lesion counts.

As mentioned above, time to 12-week CDP analysis utilized pooled data from Studies TG1101-RMS301 and TG1101-RMS302. The applicant also analyzed time to 24-week CDP, as well as 12-

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and 24-week confirmed disability improvement (CDI) as tertiary analyses. Time to event analyses were conducted using Kaplan-Meier methods, which reported a median time to event with 95% confidence intervals.

NEDA was defined as having no IRAP-confirmed relapses, MRI activity (no gadolinium-enhancing T1 or new/enlarging T2 hyperintense lesions), or 12-week CDP. The proportion of subjects with NEDA between Weeks 24 and 96 was compared using logistic regression, adjusted for region, baseline EDSS stratum, and baseline MRI lesion counts.

Impairment on SDMT was defined as a decrease from baseline of at least 4 points on any post-baseline assessment, up to the Week 96 visit. The proportion of subjects who experienced impaired SDMT was compared using logistic regression, adjusted for region, baseline EDSS stratum, and log-transformed baseline MRI lesion counts.

Percent brain volume change comparing ublituximab-xiiy- and teriflunomide-treated subjects was analyzed using linear mixed effects models with covariates region, baseline EDSS stratum, and baseline brain volume.

Protocol Amendments

There were 8 protocol amendments to the original Protocol TG1101-RMS301 from 4/14/2017, which are summarized in Table 5.

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Table 5 (Reviewer). Study TG1101-RMS301 Protocol Amendments

Protocol Version	Date	Changes	Patients randomized
1.0	4/14/2017	N/A	0
2.0	6/7/2017	• A sentence was added to include additional analysis of relapses from a more specific timeframe. The sentence reads as follows: "Relapses that occur after study drugs are withdrawn will be assessed over the remainder of the study period and this data will be utilized as part of additional sensitivity analysis (described in the statistical plan) as long as the subject has not withdrawn their consent to be in the trial." • The interface between IRAP and the study sites have been updated to as follows: "IRAP adjudicates each case based on all available data provided for that case and members are not permitted to contact the site or the Sponsor for additional information." • The change in EDSS score for defining progression of disability has been updated to state as follows: "...if a subject experiences at least 1.0 point increase on the EDSS when a baseline score is <5.5..." • The assessment tables now stipulates EDSS must be assessed 1 day prior to randomization. • Intent-to-treat definition was updated in the body of the protocol. • Now included is a hierarchy analysis, sensitivity analysis for secondary endpoints and participants who withdraw from study. • The timeframe of relapse assessment was further defined. • Interim sample size reassessment for relapses was further defined.	0
2.1	7/26/2017	• Examining and Treating Neurologists will act independently. Any scores from evaluations performed by either the Examining or Treating Neurologist will not be shared.	5
3.0	8/3/2017	• Updated Sections 7.2.1.3 and 7.2.1.4 to reflect changes in AEs as reported in the revised Investigator's Brochure (Version 5.0; dated 01 Aug 2017).	296
3.1	10/20/2017	• AEs will be reported using version 4.03 of the National Cancer Institute grading system. • FS scale scores should correspond to the participant's symptoms. • For relapses, participants must re-consent only if they have a confirmed relapse. • Re-consenting criteria will be based on the Treating Neurologist's discretion and the criteria in Appendix C.	141

		• Treatment Schema has been updated to reflect additional MRI scan at Week 12. • Malignancy has been added to the list of discontinuation reasons. • All participants at Week 116 will be counseled by the treating team to have their teriflunomide plasma concentration re-measured prior to attempting to become pregnant or trying to impregnate their female partner. • The Treating Neurologist will perform MSFC and SDMT assessments. • BART will reassess sample size when 210 out of 220 participants in each arm have been randomized. • The use of medical equivalents, when those listed in Section 4.4 and Sections 7.5.2.1 are not available, can be used at the Investigator’s Discretion for Supportive Care Guidelines. • Section 5.2.1 actions taken per grade have been updated. • EDSS scores assessed by the Examining Neurologist is not to be shared with the Treating Neurologist and the Principal Investigator, if they act as the Treating Neurologist. • Liver enzymes will be recorded using a Grading System. • Section 7.5.2.4 now describes updated information regarding second infusion interruptions. • AEs, including pregnancies and medically confirmed deaths, will be followed beginning from the day the consent form is signed until 20 weeks after discontinuation. • Protocol-defined events of special interest (Section 9.10.6) have been updated. • The DSMB will be comprised of at least 3 MDs not including the chair. • Appendix A has been updated to reflect the following: pregnancies are to be followed for 20 weeks after the last study drug was administered, women of childbearing potential must have a negative serum pregnancy test within 5 days prior to initiating treatment, males must not donate sperm for 20 weeks following the last study drug administered, the pregnant participant/male participant’s partner will be asked to provide consent to allow the pregnancy to be followed up for the full duration (or until termination) and 6 months post birth. • Appendix F has been updated to reflect newly provided time of collection for PK samples.	
3.2	2/9/2018	(Ukraine only) • Clarification of the exclusion criteria to avoid potential misinterpretation • Clarification regarding the active comparator to confirm bioequivalent teriflunomide product is used in the study	107

		• Clarification on MRI and PK windows	
4.0	1/17/2020	• Clarification of the exclusion criteria to avoid potential misinterpretation; deleted criterion number 18 and revised 5, 14, and 23. • Clarification regarding the active comparator to confirm that a bioequivalent teriflunomide product is used in the study. • Clarification on MRI and PK windows. • Advise participants to seek immediate medical help and inform the Investigator if they experience signs or symptoms of an infection. • Provide information on TG1101-RMS303 which is the Open-Label Extension of TG1101-RMS301 and TG1101-RMS302.	0
5.0	9/4/2020	• Updated Secondary Endpoints. • Removed volume of T1 hypointense lesions, • Changed volume of T2 lesions to number of new/enlarging T2 hyperintense lesions • Changed “brain volume changes” to percentage change in brain volume from baseline to Week 96 • Removed percentage of subjects free of disability progression at 6 months, 1 year, and 2 years • Removed percentage of subjects with relapse and time to first relapse • Provided clarification/correction for Exclusion Criteria 13b, 15, 21. • Specified timing of teriflunomide elimination procedure post discontinuation from study treatment. • Clarified that participants who terminate early can enter the 20-week Follow-up Period but must sign the Early Termination ICF. • Refined procedures for pregnancy confirmation and added wording regarding counseling regarding teratogenicity. • Clarified site team roles and responsibilities including Treating Neurologist, Examining Neurologist, Radiologist, and Clinical Coordinator. • Updated DSMB composition and review procedures. • Clarified teriflunomide alternative dosing times are allowed if necessary. • Clarified time window for administration of pre-medication on infusion days. • Defined Treating Neurologist Medically Confirmed relapses.	0

		• Added requirement to re-consent participants upon Treating Neurologist medically confirmed relapse. • Updated reference timepoint for participants re-consenting after confirmed relapse. • Clarified the definition of disability progression. • Clarified disability is a post-hoc analysis. • Clarified AE follow-up if participant discontinues from study. • Added guidance to assessments during dosing delay due to lab abnormalities and suspected relapse. • Further defined procedure timing in Schedule of Assessments in tables 5, 6, 7. • Clarified urine pregnancy is required in 20-week Follow-up Period. • Clarified window for PK sampling. • Clarified requirement to collect blood sample for teriflunomide concentration at Early Withdrawal from Treatment Visit. • Clarified requirement to collect urine sample at Early Withdrawal from Treatment Visit and Unscheduled Relapse Visit. • Clarified requirement to draw blood sample for B lymphocyte cell count at Early Withdrawal from Treatment Visit and Unscheduled Relapse Visit. • Clarified MRI window if early withdrawal from study. • Clarified that MRI reports with only non-MS pathology will be provided to Treating Neurologist after randomization. • Clarified participant-reported outcomes (FIS, MSQoL) are done at Early Withdrawal from Treatment Visit. • Clarified time windows for recording of ECG and vital signs pre- and post-infusion. • Clarified starting time for teriflunomide elimination procedure for participants who withdraw from treatment. • Reiterated that no Disease Modifying Therapy is permitted during the 20-week Follow-up Period. • Clarified that urine pregnancy testing is mandatory for female participants of childbearing potential at each visit during the Follow-up Period. • Clarified that teriflunomide drug concentration testing is performed at Week 116 but not shared with sites and participants.	

		• Updated the Comprehensive Adverse Events and Potential Risks profile of teriflunomide and ublituximab. • Clarified timing of teriflunomide concentration, includes early withdrawal from treatment visit and Week 116. • Provided definition of IRRs and that they will be analyzed separately. • Updated ublituximab/IV placebo infusion interruption procedure. • Clarified infusion delay process due to relapse. • Updated definitions of ITT, mITT, and PP Populations. • Clarified definition of ublituximab/IV placebo treatment exposure. • Specified that primary statistical analysis will be done once all participants have completed Week 96. • Listed and clarified all pooled analysis. • Further defined Treatment-Emergent AEs. • Clarified that hospitalizations due to the underlying disease (MS disease progression) and due to relapse do not have to be reported as SAE. • Replaced protocol list of AESIs with reference to valid IB. • Updated the requirement for sites to have procedures in place to ensure study conduct. • Specified pregnancy does not require a report on study medication relatedness. • Defined female participants with hysterectomy as not considered women of childbearing potential.	

Source: Applicant's protocol amendments; Applicant's response to Information Request, received 1/24/22

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6.1.2. Study Results

Compliance with Good Clinical Practices

The Clinical Study Report submitted by the applicant states that the study was conducted in compliance with Good Clinical Practice guidelines, and in accordance with the protocol and “consensus ethical principles originating or derived from the Declaration of Helsinki.”

Financial Disclosure

The applicant provided Form 3454 indicating that there were no financial arrangements with investigators whereby the value of compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a). No investigators had significant disclosed interest or were missing disclosure information for Study TG1101-RMS301. See Section 13.3.

Patient Disposition

In Study TG1101-RMS301, 646 subjects were screened, 97 were screen failures, and 549 were enrolled and randomized. The ITT population included 549 subjects (274 ublituximab-xiiy, 275 teriflunomide), the mITT population included 545 subjects (271 ublituximab-xiiy, 274 teriflunomide). One subject was randomized to the ublituximab-xiiy group but discontinued the study due to withdrawal of consent in the setting of difficult IV placement prior to receiving treatment.

Overall, 492 (89.6%) subjects completed the 96-week double blind treatment period (240 [87.6%] ublituximab-xiiy, 252 [91.6%] teriflunomide), and 437 (79.6%) subjects completed the follow-up period through Week 120 (219 [79.9%] ublituximab-xiiy, 218 [79.3%] teriflunomide). Reasons for premature study drug discontinuation in the ITT population are delineated by treatment group in Table 6.

Reviewer comment: Premature study discontinuations due to adverse events were more frequent in the ublituximab-xiiy group compared to the teriflunomide group (6.2% versus 0.4%, respectively).

The safety population included 548 treated subjects, 273 who received ublituximab-xiiy and 275 who received teriflunomide.

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Table 6 (Reviewer). Study TG1101-RMS301 Reasons for Study Drug Discontinuation (ITT Population)

	Ublituximab-xiiy (n = 274)	Teriflunomide (n = 275)	Total (n = 549)
Completed double-blind treatment period	240 (87.6)	252 (91.6)	492 (89.6)
Premature discontinuation of study drug	34 (12.4)	23 (8.4)	57 (10.4)
Adverse event	17 (6.2) ¹	1 (0.4)	18 (3.3)
Subject withdrawal of consent	6 (2.2)	15 (5.5)	21 (3.8)
Investigator/Sponsor decision	4 (1.5)	2 (0.7)	6 (1.1)
Lost to Follow-up	2 (0.7)	2 (0.7)	4 (0.7)
Lack of efficacy	2 (0.7)	2 (0.7)	4 (0.7)
Pregnancy	2 (0.7)	0 (0)	2 (0.4)
Alternative treatment	1 (0.4)	0 (0)	1 (0.2)
Other	0 (0)	1 (0.4) ²	1 (0.2)

¹Including 2 deaths; ²DSTERM was "Planning on expanding family"; values presented as n (%)

Source: Study TG1101-RMS301, Applicant's Clinical Study Report, Table 12; DCTREAS in ITTFL=Y, by TRT01P in ADSL

Protocol Violations/Deviations

Major protocol deviations occurred at a relatively similar frequency in both treatment groups for the ITT population (39.1% for ublituximab-xiiy and 45.1% for teriflunomide) (Table 7). An Information Request was sent to the applicant on 2/10/2022 requesting a summary table of protocol deviations, with a response received on 3/4/2022. This reviewer was not able to replicate the applicant's analysis. Therefore, the values presented in Table 7 reflect this reviewer's manual recoding of major protocol deviations in the ITT population.

Table 7 (Reviewer). Study TG1101-RMS301 Major Protocol Deviations (ITT Population)

Category	Deviation	Ublituximab-xiyy (N = 274) N (%)	Teriflunomide (N = 275) N (%)
All	Any major deviation	107 (39.1)	124 (45.1)
Informed consent	Any major deviation	11 (4.1)	13 (4.7)
Inclusion/Exclusion Criteria	Excl Cr #8 (≥10 year disease duration if EDSS ≤2.0)	1 (0.4)	1 (0.4)
	Excl Cr #12 (History of CNS trauma)	1 (0.4)	2 (0.7)
	Excl Cr #13 (History of liver disease)	6 (2.2)	1 (0.4)
	Excl Cr #17 (Platelet count)	1 (0.4)	1 (0.4)
	Excl Cr #17 (WBCs, neutrophils)	0 (0)	1 (0.4)
	Excl Cr #19 (QTc)	0 (0)	1 (0.4)
Study medication	Excluded concomitant medication	4 (1.5)	9 (3.3)
	Randomized subject received incorrect treatment ¹	0 (0)	2 (0.7)
	Received steroids outside of relapse	3 (1.1)	7 (2.5)
Study procedure or assessment	Study visit occurred outside of specified window	44 (16.1)	33 (12.0)
	Pregnancy test not performed or out of window	33 (12.0)	30 (10.9)
	Safety laboratory not performed	31 (11.3)	29 (10.5)
	MRI performed outside of specified window	11 (4.0)	18 (6.5)
	MRI not performed	5 (1.8)	4 (1.5)
	EDSS not completed	7 (2.6)	7 (2.5)
	Relapse assessment not performed per protocol	3 (1.1)	9 (3.3)
	Blinding	Unblinding of investigator/staff	6 (2.2)
Subject visit completion or timing	Study visit missed	4 (1.5)	11 (4.0)
	Visit not completed or delayed due to COVID-19 ¹	22 (8.0)	19 (6.9)
Safety reporting	Serious adverse event reporting delay	3 (1.1)	5 (1.8)
	AESI reporting delay	0 (0)	1 (0.4)

Source: ADDV, DVCAT = MAJOR, ITTFL=Y, Summary of manually recoded DVTERM by USUBJID and TRT01A

¹According to Applicant's Response to Information Request, received 3/4/22

Reviewer comment: The number of major protocol violations that occurred is concerning, but the frequency appeared similar in both treatment groups. Potential unblinding events most commonly involved the treating neurologist being unblinded to MRI or EDSS. Please refer to the OSI Review. The safety laboratories not performed were most frequently pregnancy testing.

One subject (Subject ID (b) (6)) experienced a major protocol deviation in which the ECRF/IXRS was not utilized for randomization, and the study nurse chose the treatment assignment as ublituximab-xiyy. The subject received ublituximab-xiyy on Week 1 Day 1, the PI identified the error, and the subject was randomized to teriflunomide, which was started on Week 1 Day 2. An Information Request was sent to the applicant on 2/10/22 regarding this

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deviation due to its serious nature, and the applicant responded on 3/4/22.

Per the applicant, this subject was the first randomized at this site, and despite training, the study nurse “unintentionally circumvented the study centralized randomization process...and manually dispensed one ublituximab-xiiy/placebo kit...and one teriflunomide/placebo kit.” This subject was infused with the ublituximab-xiiy/placebo kit and sent home with the teriflunomide/placebo kit. The next day, the site “discovered the subject had not been randomized in IWRS (Rave) and immediately contacted the subject...The subject reported taking 2 tablets of teriflunomide/placebo from the kit. The applicant was notified, the site was immediately re-trained...and the site was instructed to randomize the subject into IWRS (Rave) the same day.” Following discussion, the applicant and medical monitor decided that the subject be discontinued from the study after the Week 2 Day 8 visit, and this subject is not included in the per protocol population.

The applicant’s investigation indicated that the root cause of this deviation was “the study nurse’s lack of prior experience or sufficient familiarity with the centralized randomization process.” The applicant took corrective and preventative actions, including retraining of staff at this study site and on-site assistance with the site’s second randomization. The applicant indicated that no additional deviations related to randomization procedures occurred at this site, and that no other protocol deviations related to circumventing centralized randomization occurred in Studies TG1101-RMS301 or TG1101-RMS302.

Reviewer comment: This protocol deviation involved study staff circumventing the centralized randomization mechanism and dispensing both ublituximab-xiiy and teriflunomide kits, which is extremely concerning. However, it appears to be an isolated incident per the applicant’s response to Information Request.

Table of Demographic Characteristics

Demographic characteristics for the mITT population are presented in Table 8. Most subjects were female, Caucasian, non-Hispanic, between 30 and 40 years of age, and from Eastern Europe. Overall, the treatment groups appeared to be balanced in terms of demographic characteristics.

Table 8 (Reviewer). Study TG1101-RMS301 Demographics, mITT Population

	Ublituximab-xiiy (N=271) n (%)	Teriflunomide (N=274) n (%)	Total (N=545) n (%)
Sex			
Male	105 (38.8)	95 (34.7)	200 (36.7)
Female	166 (61.3)	179 (65.3)	345 (63.3)
Age (years)			
Mean (SD)	36.2 (8.4)	37.0 (9.6)	36.6 (9.1)
Median (IQR)	36.0 (13.0)	36.5 (15.0)	36.0 (14.0)
Min, max	18, 55	18, 55	18, 55
Age Group			
≥ 18 to < 30 years	66 (24.4)	62 (22.6)	128 (23.5)
≥ 30 to < 40 years	114 (42.1)	101 (36.9)	215 (39.5)
≥ 40 years	91 (33.6)	111 (40.5)	202 (37.1)
Race			
White	264 (97.4)	266 (97.1)	530 (97.3)
Black or African American	6 (2.2)	6 (2.2)	12 (2.2)
Other	0 (0)	2 (0.7)	2 (0.4)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0 (0)	1 (0.2)
Asian	0 (0)	0 (0)	0 (0)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Ethnicity			
Not Hispanic or Latino	260 (95.9)	266 (97.1)	526 (96.5)
Hispanic or Latino	7 (2.6)	2 (0.7)	9 (1.7)
Not reported/Unknown	4 (1.5)	6 (2.2)	10 (1.8)
Region			
United States	23 (8.5)	25 (9.1)	48 (8.8)
Rest of World	248 (91.5)	249 (90.9)	497 (91.2)
Eastern Europe	245 (90.4)	243 (88.7)	488 (89.5)
Western Europe	3 (1.1)	6 (2.2)	9 (1.7)
Canada	0 (0)	0 (0)	0 (0)
South America	0 (0)	0 (0)	0 (0)
Asia	0 (0)	0 (0)	0 (0)
Africa	0 (0)	0 (0)	0 (0)

Source: ADSL for TG1101-RMS301, MITTFL=Y; Tabulated by TRT01A

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline clinical characteristics and disease characteristics for the mITT population are presented in Table 9, Table 10, Table 11, and Table 12. The treatment groups appeared to be similar in terms of height, weight, BMI, and prevalence of renal and hepatic impairment.

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The treatment groups also appeared to be similar in terms of MS disease characteristics, including time since last relapse, time since diagnosis, prior MS treatments, prevalence of gadolinium-enhancing lesions, and T1/T2 lesion characteristics.

Table 9 (Reviewer). Study TG1101-RMS301 Baseline Clinical Characteristics, mITT Population

	Ublituximab-xiiy (N=271)	Teriflunomide (N=274)	Total (N=545)
Height (cm)			
Mean (SD)	170.3 (8.8)	169.7 (9.0)	170.0 (8.9)
Median (IQR)	169.0 (12.0)	168.5 (13.0)	169.0 (12.0)
Min, max	150, 198	147, 192	147, 198
Weight (kg)			
Mean (SD)	71.2 (16.7)	71.7 (17.7)	71.4 (17.2)
Median (IQR)	69.0 (23.0)	69.5 (25.0)	69.0 (24.0)
Min, max	43, 135	41, 135	41, 135
BMI (kg/m ²)			
Mean (SD)	24.4 (5.0)	24.8 (5.1)	24.6 (5.1)
Median (IQR)	23.4 (6.6)	23.6 (7.2)	23.6 (7.0)
Min, max	16.5, 48.1	13.4, 41.7	13.4, 48.1
Hepatic impairment ¹ (n (%))			
Normal	246 (90.8)	252 (92.0)	498 (91.4)
Mild (Total bilirubin >ULN and ≤1.5x ULN or ALT>ULN or AST>ULN)	24 (8.9)	20 (7.3)	44 (8.1)
Moderate (Total bilirubin >1.5x ULN and ≤3x ULN)	1 (0.4)	2 (0.7)	3 (0.6)
Renal Impairment ² (n (%))			
Normal	162 (59.8)	170 (62.0)	332 (60.9)
Mild (GFR ≥60 ml/min & <90 ml/min)	107 (39.5)	101 (36.9)	208 (38.2)
Moderate (GFR ≥90 ml/min & <60 ml/min)	2 (0.7)	3 (1.1)	5 (0.9)

¹Hepatic impairment as defined by HEPIMP in ADSL

²Renal impairment as defined by RENIMP in ADSL

Source: ADSL for TG1101-RMS301, MITTFL=Y; Tabulated by TRT01A

Reviewer Comment: Though subjects with hepatic or renal impairment were to be excluded from the protocol (See Section 13.2), subjects with mild and moderate hepatic and/or renal impairment (as defined by laboratory values provided in the Table) were included.

Table 10 (Reviewer). Study TG1101-RMS301 Disease Characteristics, mITT Population

	Ublituximab-xiiy (N=271)	Teriflunomide (N=274)	Total (N=545)
Time since MS diagnosis (years)			
Mean (SD)	4.9 (5.2)	4.5 (5.0)	4.7 (5.1)
Median (IQR)	2.9 (6.0)	2.5 (5.9)	2.7 (6.0)
Min, max	0.07, 27.5	0.04, 25.7	0.04, 27.5
Time since last relapse (months)			
Mean (SD)	6.4 (6.9)	5.8 (3.5)	6.1 (5.4)
Median (IQR)	5.0 (4.8)	5.0 (4.7)	5.0 (4.7)
Min, max	0.95, 100.3	1.3, 27.0	0.95, 100.3
# relapses in year prior to screening			
Mean (SD)	1.3 (0.6)	1.4 (0.7)	1.3 (0.7)
Median (IQR)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)
Min, max	0, 4	0, 4	0, 4
0 (n (%))	11 (4.1)	8 (2.9)	19 (3.5)
1 (n (%))	178 (65.7)	173 (63.1)	351 (64.4)
2 (n (%))	68 (25.1)	79 (28.8)	147 (27.0)
3 (n (%))	13 (4.8)	10 (3.7)	23 (4.2)
≥4 (n (%))	1 (0.4)	4 (1.5)	5 (0.9)
# relapses in 2 years prior to screening			
Mean (SD)	1.8 (1.0)	2.0 (1.1)	1.9 (1.0)
Median (IQR)	2.0 (1.0)	2.0 (1.0)	2.0 (1.)
Min, max	0, 7	0, 11	0, 11
Baseline EDSS (EDSS)			
Mean (SD)	3.0 (1.2)	2.9 (1.2)	2.9 (1.2)
Median (IQR)	3.0 (2.0)	3.0 (1.5)	3.0 (2.0)
Min, max	0, 5.5	0, 6 ¹	0, 6
≤3.5 (n (%))	200 (73.8)	208 (75.9)	408 (74.9)
>3.5 (n (%))	71 (26.2)	24.1 (66)	137 (25.1)

¹One subject (ID (b) (6)) with baseline EDSS of 6 had a screening EDSS of 4.0 and therefore was included in the trial; Inclusion criteria state EDSS 0 to 5.5.

Source: ADSL for TG1101-RMS301, MITTFL=Y; Tabulated by TRT01A

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Table 11 (Reviewer). Study TG1101-RMS301 Prior MS Treatments, mITT Population

	Ublituximab-xiiy (N=271) n (%)	Teriflunomide (N=274) n (%)	Total (N=545) n (%)
Prior MS Treatment			
Corticosteroids	257 (94.8)	254 (92.7)	511 (93.8)
Interferon beta	53 (19.6)	49 (17.9)	102 (18.7)
Glatiramer acetate	45 (16.6)	36 (13.1)	81 (14.9)
Laquinimod	19 (7.0)	22 (8.0)	41 (7.5)
Dimethyl fumarate	8 (3.0)	7 (2.6)	15 (2.8)
Fingolimod	5 (1.8)	2 (0.7)	7 (1.3)
IVIg	2 (0.7)	4 (1.5)	6 (1.1)
Ozanimod	1 (0.4)	5 (1.8)	6 (1.1)
Daclizumab	0 (0)	4 (1.5)	4 (0.7)
Diroximel fumarate	2 (0.7)	0 (0)	2 (0.4)
Amiselimod	1 (0.4)	0 (0)	1 (0.2)
Investigational Drug	0 (0)	2 (0.7)	2 (0.4)
Plasmapheresis	1 (0.4)	0 (0)	1 (0.2)
Received appropriate MS treatment ¹	92 (34.0)	82 (29.9)	174 (31.9)
Previous corticosteroid treatment for relapse ²	257 (94.8)	254 (92.7)	511 (93.8)

¹APDMTFL in ADSL; ²PRCSREFL in ADSL

Source: ADCM for TG1101-RMS301, MITTFL=Y, CMCAT = "MS TREATMENT HISTORY"; Manually recoded CMTRT, tabulated by TRT01A

Table 12 (Reviewer). Study TG1101-RMS301 Baseline MRI Characteristics, mITT Population

	Ublituximab-xiiy (N=270)	Teriflunomide (N=272)	Total (N=542)
Gadolinium-enhancing lesions			
Mean (SD)	2.3 (5.5)	1.6 (3.7)	1.9 (4.7)
Median (IQR)	0 (2.0)	0 (2.0)	0 (2.0)
Min, max	0, 37	0, 40	0, 40
Present (n (%))	117 (43.2)	116 (42.3)	233 (42.8)
Absent (n (%))	153 (56.5)	156 (56.9)	309 (56.7)
T1 lesion count			
Mean (SD)	36.2 (30.2)	33.3 (30.8)	34.7 (30.5)
Median (IQR)	29.0 (40.0)	25.0 (38.8)	27.0 (40.0)
Min, max	0, 148	0, 202	0, 202
T2 lesion count			
Mean (SD)	64.1 (38.6)	60.4 (37.0)	62.3 (37.8)
Median (IQR)	55.0 (52.5)	54.0 (45.0)	54.5 (48.0)
Min, max	2, 220	5, 248	2, 248
T2 lesion volume (mL)			
Mean (SD)	15.9 (16.0)	14.9 (15.8)	15.4 (15.9)
Median (IQR)	9.9 (16.4)	9.9 (15.6)	9.9 (16.1)
Min, max	0.4 (89.8)	0.5, 131.6	0.4, 131.6

Source: ADSL for TG1101-RMS301, MITTFL=Y; Tabulated by TRT01A

Reviewer comment: Baseline MRI characteristics were missing for 3 subjects, 2 on teriflunomide and 1 on ublituximab-xiiy. The ublituximab-xiiy group had a higher mean gadolinium-enhancing lesion count at baseline compared to teriflunomide, but the median number was similar between the groups.

General medical history for subjects enrolled in Study TG1101-RMS301 was reviewed as well. There did not appear to be any clinically meaningful differences between the treatment groups. Ongoing medical disorders (defined by ONGOFL=Y) occurring in >5% of subjects in either treatment group are presented in Table 13.

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Table 13 (Reviewer). Study TG1101-RMS301 Concurrent Medical Disorders Reported in >5% of Either Treatment Group, mITT Population

		Ublituximab-xiiy (N=271) n (%)	Teriflunomide (N=274) n (%)
System Organ Class	Dictionary-Derived Term ¹		
Musculoskeletal and connective tissue disorders	Osteochondrosis	20 (7.4)	19 (6.9)
	Intervertebral disc protrusion	10 (3.7)	16 (5.8)
	Back pain	3 (1.1)	14 (5.1)
Eye disorders	Myopia	28 (10.3)	23 (8.4)
	Retinal vascular disorder	20 (7.4)	17 (6.2)
Gastrointestinal disorders	Chronic gastritis	22 (8.1)	23 (8.4)
Psychiatric disorders	Depression	17 (6.3)	22 (8.0)
Vascular disorders	Hypertension	19 (7.0)	28 (10.2)

¹MHDECOD in ADMH; Source: Study TG1101-RMS301, ADMH, where MITTFL=Y, ONGOFL=Y, by TRT01A; Applicant's CSR Table 14.1.5.1

Reviewer comment: No major or clinically relevant differences in medical history were observed between the treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Treatment compliance by treatment group in the mITT population, according to the Applicant, is summarized in Table 14. Overall, compliance with IV and oral study treatment was similar between the groups.

Table 14 (Applicant). Study TG1101-RMS301 Summary of Percentage Compliance with Study Treatments, mITT Population

	Ublituximab-xiiy (N=273)		Teriflunomide (N=275)	
	IV Compliance (%)	PO Compliance (%)	IV Compliance (%)	PO Compliance (%)
Mean (SD)	94.8 (17.9)	98.8 (5.2)	96.5 (14.2)	100.00 (12.9)
Median	100	100	100	100
Min, Max	7.7, 100	26.3, 103.3	7.7, 100	76.7, 307.5

Source: Applicant's CSR, Tables 42 and 43

An Information Request was sent to the applicant on 2/10/2022 due to concerns regarding reported compliance with oral study treatment >100%, particularly one subject (b) (6) who had a calculated compliance of 307%. The applicant responded on 3/4/2022, and indicated CDER Clinical Review Template

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that these values were related to minor discrepancies between two data sources used for this information, and missing treatment end dates.

Per the Applicant's CSR, IV compliance <80% occurred in 9.2% (n = 25) of subjects on ublituximab-xiiy and 6.5% (n = 18) of subjects on teriflunomide. Oral treatment compliance <80% occurred in 1.5% (n = 4) of subjects on ublituximab-xiiy and 0.7% (n = 2) subjects on teriflunomide.

Concomitant Medications

Per the applicant's CSR, the most commonly utilized concomitant medications were those intended for infusion pre-medication (dexamethasone and diphenhydramine) and MRI contrast (Table 15).

Table 15 (Reviewer). Study TG1101-RMS301, Selected Concomitant Medications Used by **≥5%** of Either Treatment Group of mITT Population

	Ublituximab-xiiy (N=271) n (%)	Teriflunomide (N=274) n (%)
Infusion pre-medication		
Dexamethasone	253 (93.4)	258 (94.2)
Diphenhydramine hydrochloride	137 (50.6)	135 (49.3)
Diphenhydramine	119 (44.0)	112 (40.9)
Cetirizine	17 (6.3)	17 (6.2)
Paracetamol	19 (7.0)	5 (1.8)
MRI Gadolinium-based Contrast	264 (97.4)	270 (98.5)
Antibiotics		
Amoxicillin trihydrate; clavulanate potassium	17 (6.3)	18 (6.6)
Azithromycin	10 (3.7)	14 (5.1)
Other medications		
Paracetamol (all indications)	101 (37.3)	49 (17.9)
Baclofen	15 (5.5)	18 (6.6)
Ibuprofen	54 (19.9)	60 (21.9)
Vitamin D and analogues	53 (19.6)	55 (20.1)

Source: ADCM where mITTFL=Y, ONTRTFL=Y, categories based on CMINDC; Applicant's CSR (Table 18)

According to the applicant's CSR, the most commonly utilized follow-up medications were cholestyramine (86.3% ublituximab-xiiy, 84.7% teriflunomide) and gadobutrol (52.0% ublituximab-xiiy, 58.0% teriflunomide). Methylprednisolone use is discussed in below. Otherwise, concomitant medication usage appeared to be similar between the treatment groups.

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Rescue Medication Use

The CMINDC variable in the ADCM dataset also indicated treatment for an MS relapse (“MS Relapse Treatment”), and the SCORTFL variable indicated systemic corticosteroids. Per these flags, 39 subjects on ublituximab-xiiy (14.4%) and 72 on teriflunomide (26.3%) received systemic corticosteroids for relapse treatment.

The Applicant’s CSR also indicates that methylprednisolone was utilized as a follow-up medication in 4.4% of ublituximab-xiiy subjects and 7.3% of teriflunomide subjects. However, the indication and dose is not accounted for in these summary statistics.

Reviewer comment: The lower frequency of steroid use in the ublituximab-xiiy group is expected, as this group experienced fewer relapses.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was Annualized Relapse Rate (ARR), which the applicant calculated as a group ARR utilizing treatment duration in years (STDURY) and number of IRAP-confirmed clinical relapses. The ARR for the ublituximab-xiiy group was 0.09, and for the teriflunomide group was 0.23, for an ARR ratio of 0.41 (95% CI 0.28 to 0.59, $p = 2.098e-07$) (Table 16). These results indicate a statistically significant treatment effect of ublituximab-xiiy in relapse reduction compared to teriflunomide.

Table 16 (Reviewer). Study TG1101-RMS301, Summary of Confirmed Relapses and Annualized Relapse Rate

	Ublituximab-xiiy (N=271)	Teriflunomide (N=274)	Ratio (if applicable)
Number (%) of patients who experienced confirmed relapse	36 (13.3)	68 (24.8)	
Number of confirmed relapses experienced per patient during DBT (n (%))			
0	235 (86.7)	206 (75.2)	
1	29 (10.7)	38 (13.9)	
2	6 (2.2)	19 (6.9)	
3	1 (0.4)	9 (3.3)	
4	0 (0)	2 (7.3)	
Number of confirmed relapses experienced per patient during DBT			
Mean (SD)	0.16 (0.5)	0.41 (0.8)	
Median (IQR)	0 (0)	0 (0)	
Min, Max	0, 3	0, 4	
DBT Duration (years) ¹			
Mean (SD)	1.71 (0.4)	1.75 (0.3)	
Median (IQR)	1.82 (0.02)	1.82 (0.02)	
Min, Max	0.003, 1.92	0.003, 1.90	
Group ARR			
Sum DBT Duration (years)	464.52	479.44	
Sum DBT Relapses	44	111	
ARR	0.09	0.23	0.41 (95% CI 0.28 to 0.59) ²

¹Treatment duration per STDURY; ²Calculated using package rateratio.test (version 1.0-2) in RStudio (version 1.1.456)

Reviewer Comment: Reviewer calculations for unadjusted ARR are consistent with those presented by the applicant. The applicant also presented an analysis with LS mean for ARR calculated using negative binomial regression of 0.076 (95% CI 0.042, 0.138) for the ublituximab-xiiy group and 0.188 (95% CI 0.124, 0.283) for the teriflunomide group. The rate ratio was 0.406 (95% CI 0.268, 0.615, p <0.001). Please refer to the statistical review for replication of these adjusted results.

As demonstrated in Table 16, the double-blind treatment exposure was similar between treatment groups at both the individual and group levels. The percentage of patients who experienced a confirmed relapse during double-blind treatment was higher in the teriflunomide group (24.8%) compared to ublituximab-xiiy (13.3%). The mean (SD) number of confirmed

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relapses experienced per patient was higher in the teriflunomide group (0.41 (0.8)) compared to ublituximab-xiiy (0.16 (0.5)).

The applicant also conducted 3 sensitivity analyses for ARR, specifically calculations of ARRs using IRAP-confirmed relapses including follow-up, all relapses irrespective of confirmation, and multiple imputation of withdrawn subjects. These analyses yielded ARR ratios ranging from 0.39 to 0.43 and remained statistically significant, indicating robustness of the primary endpoint in these circumstances.

Data Quality and Integrity

There were no issues regarding the quality of the efficacy data submitted. Please refer to the Protocol Deviations discussion earlier in this section regarding protocol violations that raised concerns regarding data integrity. Please also refer to the OSI review by Cara Alfaro, PharmD.

Efficacy Results – Secondary and other relevant endpoints

Gadolinium-enhancing lesions

The first key secondary efficacy endpoint was the total number of gadolinium-enhancing lesions on brain MRI by Week 96. The mITT-MRI population included subjects who had baseline and post-baseline MRI efficacy assessments (ublituximab-xiiy n = 265, teriflunomide n = 270). Please refer to Table 12 for a summary of baseline gadolinium-enhancing lesions per treatment group.

Per the applicant's analysis, both treatment groups had a mean number of 3.8 MRIs. Ublituximab-xiiy-treated subjects had a lower number of gadolinium-enhancing lesions than those on teriflunomide on all post-baseline MRIs. At Week 96, the mean (SD) total number of gadolinium-enhancing lesions per MRI scan was 0.03 (0.1) for the ublituximab-xiiy group and 0.82 (1.8) for the teriflunomide group (Table 17). The applicant's analysis yielded a rate ratio for the total number of gadolinium-enhancing lesions per MRI scan of 0.033 (95% CI 0.019 to 0.058, p < 0.0001), indicating a statistically significant reduction of gadolinium-enhancing lesions with ublituximab-xiiy compared to teriflunomide.

Table 17 (Reviewer). Study TG1101-RMS301, Gadolinium-Enhancing Lesions, mITT-MRI Population

	Ublituximab-xiiy (N=265)	Teriflunomide (N=270)
Total # Gadolinium-enhancing lesions per MRI by Week 96		
Mean (SD)	0.03 (0.1)	0.82 (1.8)
Median	0	0.25
Min, Max	0, 1.0	0, 18.0
Total # gadolinium-enhancing lesions per subject by Week 96		
Mean (SD)	0.1 (0.5)	3.0 (6.4)
Median	0	1.0
Min, Max	0, 4	0, 54

Source: Applicant's Study TG1101-RMS301 CSR, Tables 22 and 14.2.2.1.1

Please refer to the biostatistics review for replication of these efficacy findings.

New or enlarging T2 lesions

The second key secondary efficacy endpoint was the total number of new or enlarging T2 hyperintense lesions per brain MRI by Week 96.

Per the applicant's analysis, both treatment groups had a mean number of 2.8 MRIs. Ublituximab-xiiy-treated subjects had a lower mean number of new/enlarging T2 hyperintense lesions than those on teriflunomide on all post-baseline MRIs. At Week 96, the total mean (SD) total number of new/enlarging T2 hyperintense lesions per MRI scan was 0.35 (0.7) for the ublituximab-xiiy group and 4.28 (7.7) for the teriflunomide group (Table 18). The applicant's analysis yielded a rate ratio for the total number of new/enlarging T2 hyperintense lesions per MRI scan of 0.076 (95% CI 0.056, 0.104; $p < 0.0001$), indicating a statistically significant reduction of new/enlarging T2 hyperintense lesions with ublituximab-xiiy compared to teriflunomide.

Reviewer comment: Based upon the ADMRI dataset, it appears that the Week 12 MRI was not included in the analysis for new/enlarging T2 hyperintense lesions. However, the difference in the number of MRIs used for each endpoint is not explained in the protocol or Clinical Study Report. An Information Request was sent on 3/28/2022, with a response received on 5/5/2022. The applicant indicated that per protocol, the Week 12 MRI would only be used for gadolinium-enhancing lesion-related endpoints.

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Table 18 (Reviewer). Study TG1101-RMS301, New/Enlarging T2 Hyperintense Lesions, mITT-MRI Population

	Ublituximab-xiiy (N=265)	Teriflunomide (N=270)
Total # new/enlarging T2 lesions per MRI by Week 96		
Mean (SD)	0.35 (0.7)	4.3 (7.7)
Median	0	1.3
Min, Max	0, 7	0, 58.3
Total # new/enlarging T2 lesions per subject by Week 96		
Mean (SD)	1.0 (2.1)	11.8 (20.7)
Median	0	4.0
Min, Max	0, 21	0, 175

Source: Applicant's Study TG1101-RMS301 CSR, Tables 24 and 14.2.2.2.1

Please refer to the biostatistics review for replication of these efficacy findings.

Reviewer comment: Overall, the key secondary efficacy endpoints support a clinically significant treatment effect of ublituximab-xiiy over teriflunomide. The results of the MRI lesion analyses are expected, consistent with other highly effective treatments for RMS, and are congruent with the relapse-related findings of the primary efficacy analysis.

Confirmed Disability Progression (12-week)

Please refer to efficacy results presented in Section 6.3.2 for the pre-specified pooled analysis of Studies TG1101-RMS301 and TG1101-RMS302 for 12-week confirmed disability progression.

Other Secondary Efficacy Endpoints

Three other secondary efficacy endpoints that are not accepted clinical endpoints, but are considered supportive of the primary efficacy finding, were analyzed by the applicant (i.e., were not replicated by this reviewer).

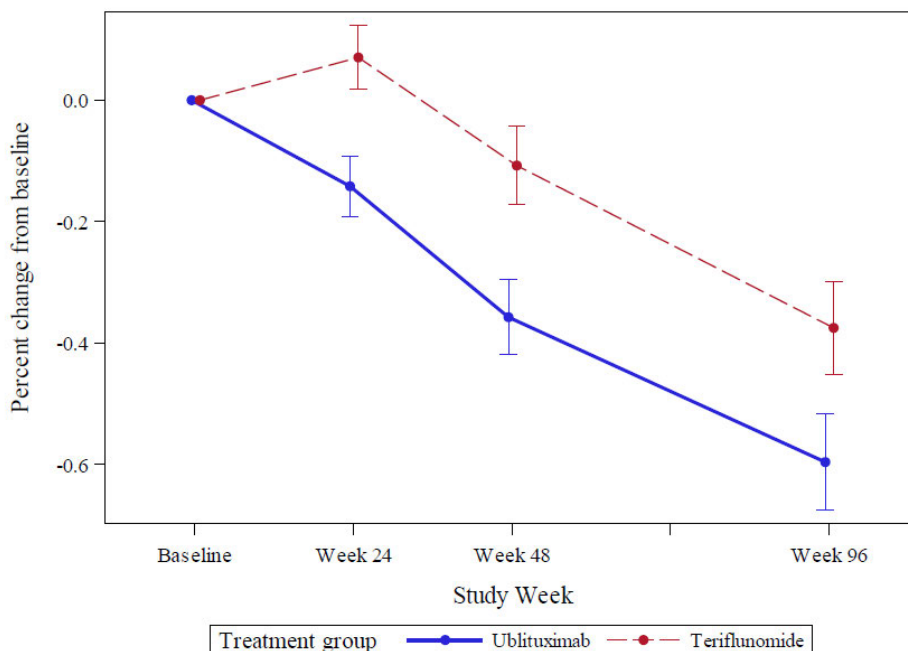
The applicant compared the proportion of subjects with No Evidence of Disease Activity (NEDA) from Week 24 to Week 96. NEDA was defined as having no IRAP-confirmed relapses, MRI activity (either gadolinium-enhancing or new/enlarging T2 lesions), or 12-week CDP between Weeks 24 and 96. Subjects receiving ublituximab-xiiy were more likely to achieve NEDA (44.6%, n = 121) compared to those receiving teriflunomide (15.0%, n = 41), with a statistically significant odds ratio of 5.44 (95% CI 3.54 to 8.38, p<0.0001) in favor of ublituximab-xiiy.

The applicant also compared the proportion of subjects reaching impairment on the Symbol Digit Modalities Test (SDMT) from baseline to Week 96, defined as a decrease from baseline of at least 4 points at any post-baseline assessment. The applicant's analysis did not indicate a

statistically significant difference in the proportion of subjects reaching impaired SDMT between the ublituximab-xiiy and teriflunomide groups; the odds ratio was 0.87 (95% CI 0.60 to 1.26, $p = 0.47$), and the proportion of subjects reaching impaired SDMT in the ublituximab-xiiy group was 29.2%, compared to 31.8% in the teriflunomide group.

Finally, the applicant compared percentage change in brain volume from baseline to Week 96 between the treatment groups in the mITT-MRI population, defined as subjects who had baseline and post-baseline MRI efficacy assessments. As demonstrated in Figure 2, brain volume increased slightly at Week 24 in the teriflunomide group, then declined at a rate similar to that of the ublituximab-xiiy group through Week 96. The applicant performed a mixed model repeated measures analysis, which indicated that the percentage change of the cube root transformed volume from baseline at Week 96 was significantly higher in the teriflunomide group compared to ublituximab-xiiy (i.e., in favor of teriflunomide; LS means [ublituximab-xiiy – teriflunomide] -0.072, 95% CI -0.107 to -0.036, $p < 0.0001$).

Figure 2 (Applicant). Study TG1101-RMS301, Mean Percentage Change in Brain Volume



Source: Figure 14.2.9

Abbreviations: See Section 4.

Note: Mean and the 95% Wald Confidence Intervals are displayed.

Source: Applicant's CSR for Study TG1101-RMS301, Figure 8

Dose/Dose Response

Not applicable, as a single dose was studied in Study TG1101-RMS301.

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Durability of Response

Though the trial was not designed to evaluate durability of response, there did not appear to be a higher frequency of relapse later in the double blind treatment period, suggesting a durable response to ublituximab-xiiy in the setting of B-cell depletion.

Persistence of Effect

Again, the trial was not designed to evaluate persistence of effect, but most patients in the ublituximab-xiiy group appeared to experience B-cell depletion through the end of the double blind treatment period, during which multiple doses of ublituximab-xiiy were administered (See Section 8.4.6). Therefore, the data suggests that there is not a meaningful loss of effect of ublituximab-xiiy over time.

Additional Analyses Conducted on the Individual Trial

Confirmed and Unconfirmed Relapses

Overall, 218 confirmed and unconfirmed relapses occurred across both treatment groups in this study, 152 (69.8%) in the teriflunomide group and 66 (30.3%) in the ublituximab-xiiy group. The rate of IRAP confirmation was similar in both treatment groups, 66.7% (44/66 relapses) in the ublituximab-xiiy group and 73.0% (111/152) in the teriflunomide group. Relapse severity was not captured in the eCRF, and therefore was not able to be tabulated for this review.

The unadjusted group ARR for both confirmed and unconfirmed relapses was 0.14 in the ublituximab-xiiy group versus 0.32 in the teriflunomide group, with an ARR ratio of 0.45 (95% CI 0.33 to 0.60). The percentage of subjects who experienced either a confirmed or unconfirmed relapse was lower in the ublituximab-xiiy group (17.3%) compared to teriflunomide (31.4%). Additionally, the mean (SD) number of relapses (either confirmed or unconfirmed) was lower in the ublituximab-xiiy group (0.24 (0.6)) compared to teriflunomide (0.55 (1.0)).

These relapse data are summarized in Table 19.

Table 19 (Reviewer). Study TG1101-RMS301, Summary of Confirmed and Unconfirmed Relapses

	Ublituximab-xiiy (N=271)	Teriflunomide (N=274)	Ratio (if applicable)
Number (%) of patients who experienced confirmed or unconfirmed relapse	47 (17.3)	86 (31.4)	
Number of confirmed or unconfirmed relapses experienced per patient during DBT (n (%))			
0	224 (82.7)	188 (68.6)	
1	33 (12.2)	47 (17.2)	
2	9 (3.3)	21 (7.7)	
3	5 (1.8)	11 (4.0)	
4	0 (0)	5 (1.8)	
5	0 (0)	2 (0.7)	
Number of confirmed or unconfirmed relapses experienced per patient during DBT			
Mean (SD)	0.24 (0.6)	0.55 (1.0)	
Median (IQR)	0 (0)	0 (1.0)	
Min, Max	0, 3	0, 5	
Number (%) of suspected relapses confirmed during DBT	44 (66.7)	111 (73.0)	
Group ARR (confirmed and unconfirmed)			
Sum DBT Duration (years)	464.52	479.44	
Sum DBT Relapses	66	152	
ARR	0.14	0.32	0.45 (95% CI 0.33 to 0.60) ¹

¹Calculated using package `rateratio.test` (version 1.0-2) in RStudio (version 1.1.456)

Change from Baseline EDSS

Change from baseline EDSS was calculated for each patient during the double blind treatment period, regardless of treatment duration, and results are summarized in Table 20. The mean and median changes from baseline were similar between the treatment groups, but more subjects experienced EDSS improvement (31.4%) on ublituximab-xiiy compared to those on teriflunomide (20.4%).

Table 20 (Reviewer). Study TG1101-RMS301, Change in EDSS During Double Blind Treatment

	Ublituximab-xiiy (N=271)	Teriflunomide (N=274)
Mean (SD ¹ , n)	-0.12 (0.7)	0.12 (0.7)
Median (IQR ² , n)	0 (0.5)	0 (0.5)
Min, max	-2.0, 3.5	-2.5, 4.0
n (%) with worsening EDSS	37 (13.7)	70 (25.5)
n (%) with improving EDSS	85 (31.4)	56 (20.4)
n (%) with stable EDSS	149 (55.0)	148 (54.0)

¹SD: Standard deviation; ²IQR: interquartile range

6.2. Study TG1101-RMS302

6.2.1. Study Design

Overview and Objective

Study TG1101-RMS302 ("ULTIMATE II") was one of two identical randomized controlled trials (RCTs) whose objective was to assess the efficacy and safety of ublituximab-xiiy compared to bioequivalent teriflunomide as treatment for relapsing forms of MS. Please refer to Section 6.1 for Study TG1101-RMS302 trial design information.

Trial Design

Study TG1101-RMS302 was identical in design to that of Study TG1101-RMS301. Refer to Section 6.1.

Study Endpoints

Study TG1101-RMS302 was identical in design to that of Study TG1101-RMS301. Refer to Section 6.1.

Statistical Analysis Plan

Study TG1101-RMS302 was identical in design to that of Study TG1101-RMS301. Refer to Section 6.1.

Protocol Amendments

The protocols for Studies TG1101-RMS301 and TG1101-RMS302 were identical, and protocol amendments were made simultaneously. Please refer to Section 6.1.2 and Table 5. The number of patients randomized under each version of the protocol for TG1101-RMS302 is presented in Table 21.

Table 21 (Reviewer). Study TG1101-RMS302 Protocol Amendments

Protocol Version	Date	Patients Randomized
1.0	4/14/2017	0
2.0	6/7/2017	2
2.1	7/26/2017	7
3.0	8/3/2017	210
3.1	10/20/2017	183
3.2	2/9/2018	143
4.0	1/17/2020	0
5.0	9/4/2020	0

Source: Applicant's response to Information Request, received 1/24/22

6.2.2. Study Results

Compliance with Good Clinical Practices

The Clinical Study Report submitted by the applicant states that the study was conducted in accordance with the protocol and "consensus ethical principles originating or derived from the Declaration of Helsinki and in compliance with all ICH GCP guidelines."

Financial Disclosure

The applicant provided Form 3454 indicating that there were no financial arrangements with investigators whereby the value of compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a). No investigators had significant disclosed interest or were missing disclosure information for Study TG1101-RMS302. See Section 13.3.

Patient Disposition

In Study TG1101-RMS302, 629 subjects were screened, 84 were screen failures, and 545 were enrolled and randomized. The ITT population included 545 subjects (272 ublituximab-xiiy, 273 teriflunomide), the mITT population included 544 subjects (272 ublituximab-xiiy, 272 teriflunomide). All randomized subjects were exposed to study treatment.

Overall, 493 (90.5%) subjects completed the 96-week double blind treatment period (254 [93.4%] ublituximab-xiiy, 239 [87.5%] teriflunomide), and 386 (70.8%) subjects completed the follow-up period (199 [73.2%] ublituximab-xiiy, 187 [68.5%] teriflunomide). Premature study drug discontinuation occurred in 52 (9.5%) subjects overall (18 [6.6%] ublituximab-xiiy and 34 [12.5%] teriflunomide). Reasons for premature study drug discontinuation in the ITT population are delineated by treatment group in Table 22.

Reviewer comment: Premature study discontinuations due to adverse events were more frequent in the ublituximab-xiyy group compared to the teriflunomide group (1.1% versus 0.4%, respectively), but discontinuations were more common in the teriflunomide group overall.

The safety population included 545 treated subjects, 272 who received ublituximab-xiyy and 273 who received teriflunomide.

Table 22 (Reviewer). Study TG1101-RMS302 Reasons for Study Drug Discontinuation (ITT Population)

	Ublituximab-xiyy (n = 272) N (%)	Teriflunomide (n = 273) N (%)	Total (n = 545)
Completed double-blind treatment period	254 (93.4)	239 (87.5)	493 (90.5)
Premature discontinuation of study drug	18 (6.6)	34 (12.5)	52 (9.5)
Subject withdrawal of consent	6 (2.2)	23 (8.4)	29 (5.3)
Pregnancy	4 (1.5)	1 (0.4)	5 (0.9)
Adverse event	3 (1.1) ¹	1 (0.4)	4 (0.7)
Investigator/Sponsor decision	2 (0.7)	2 (0.7)	4 (0.7)
COVID-19	3 (1.1)	0 (0)	3 (0.6)
Lost to Follow-up	0 (0)	2 (0.7)	2 (0.4)
Lack of efficacy	0 (0)	2 (0.7)	2 (0.4)
Alternative treatment	0 (0)	2 (0.7)	2 (0.4)
Other	0 (0)	1 (0.4) ²	1 (0.2)

¹Including 1 death; ²DSTERM was "occurrence relapse"

Source: Study TG1101-RMS302, Applicant's Clinical Study Report, Table 12; DCTREAS in ITTFL=Y, by TRT01P in ADSL

Protocol Violations/Deviations

Major protocol deviations occurred at a higher frequency in the ublituximab-xiyy group (43.0%) compared to the teriflunomide group (34.8%) (Table 23). An Information Request was sent to the applicant on 2/10/2022 requesting a summary table of protocol deviations, with a response received on 3/4/2022. This reviewer was not able to replicate the applicant's analysis. Therefore, the values presented in Table 23 reflect this reviewer's manual recoding of major protocol deviations in the ITT population.

Table 23 (Reviewer). Study TG1101-RMS302 Major Protocol Deviations (ITT Population)

Category	Deviation	Ublituximab-xiiy (N = 272) N (%)	Teriflunomide (N = 273) N (%)
All	Any major deviation	117 (43.0)	95 (34.8)
Informed consent	Any	15 (5.5)	12 (4.4)
Inclusion/Exclusion Criteria	Incl Cr #6 (EDSS 0-5.5)	1 (0.4)	0 (0)
	Excl Cr #5 (Glucocorticoids within 30 days)	1 (0.4)	1 (0.4)
	Excl Cr #8 (≥ 10 year disease duration if EDSS ≤ 2.0)	2 (0.7)	0 (0)
	Excl Cr #13 (History of liver disease)	4 (1.5)	4 (1.5)
	Excl Cr #17 (Platelet count)	4 (1.5)	1 (0.4)
	Excl Cr #17 (WBCs, neutrophils)	2 (0.7)	0 (0)
	Eligibility criteria not fully assessed	4 (1.5)	0 (0)
Study medication	Excluded concomitant medication	5 (1.8)	3 (1.1)
	Randomized subject received incorrect treatment ¹	3 (1.1)	2 (0.7)
	Received steroids outside of relapse	6 (2.2)	4 (1.5)
Study procedure or assessment	Study visit occurred outside of specified window	44 (16.2)	34 (12.5)
	Safety laboratory not performed	27 (9.9)	20 (7.3)
	Pregnancy test not performed or out of window	26 (9.6)	19 (7.0)
	MRI performed outside of specified window	21 (7.7)	19 (7.0)
	MRI not performed	4 (1.5)	3 (1.1)
	EDSS not completed	6 (2.2)	5 (1.8)
	Relapse assessment not performed per protocol	7 (2.6)	0 (0)
Blinding	Unblinding of investigator/staff	6 (2.2)	4 (1.5)
Subject visit completion or timing	Study visit missed	9 (3.3)	4 (1.5)
	Visit not completed or delayed due to COVID-19 ¹	27 (9.9)	23 (8.4)
Safety reporting	Serious adverse event reporting delay	2 (0.7)	7 (2.6)
	AESI reporting delay	0 (0)	0 (0)

Source: ADDV, DVCAT = MAJOR, ITTFL=Y, Summary of manually recoded DVTERM by USUBJID and TRT01A

¹According to Applicant's Response to Information Request, Received 3/4/22

Reviewer comment: The number of major protocol violations that occurred is concerning, and major protocol deviations occurred at a higher frequency in the ublituximab-xiiy group, despite being of similar frequency in Study TG1101-RMS301. Potential unblinding events all involved the treating neurologist being unblinded to MRI or EDSS. Please refer to the OSI Review. Violations where the relapse assessment was not performed per protocol indicated that the assessment was not performed within the protocol-specified window. The safety laboratories not performed were most frequently pregnancy testing (listed separately).

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Table of Demographic Characteristics

Demographic characteristics for the mITT population are presented in Table 24. Similar to Study TG1101-RMS301, most subjects were female, Caucasian, non-Hispanic, between 30 and 40 years of age, and from Eastern Europe. Overall, the treatment groups appeared to be balanced in terms of demographic characteristics.

Table 24 (Reviewer). Study TG1101-RMS302 Demographics, mITT Population

	Ublituximab-xiiy (N=272) n (%)	Teriflunomide (N=272) n (%)	Total (N=544) n (%)
Sex			
Male	94 (34.5)	96 (35.3)	190 (34.9)
Female	178 (65.4)	176 (64.7)	354 (65.1)
Age (years)			
Mean (SD)	34.5 (8.8)	36.2 (9.0)	35.3 (8.9)
Median (IQR)	33.0 (13.0)	36.0 (13.0)	35.0 (14.0)
Min, max	18, 55	18, 55	18, 55
Age Group			
≥ 18 to < 30 years	88 (32.4)	65 (23.9)	153 (28.1)
≥ 30 to < 40 years	105 (38.6)	109 (40.1)	214 (39.3)
≥ 40 years	79 (29.0)	98 (36.0)	177 (32.5)
Race			
White	269 (98.9)	268 (98.5)	537 (98.7)
Black or African American	2 (0.7)	3 (1.1)	5 (0.9)
Other	1 (0.4)	1 (0.4)	2 (0.4)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	0 (0)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Ethnicity			
Not Hispanic or Latino	262 (96.3)	262 (96.3)	524 (96.3)
Hispanic or Latino	6 (2.2)	3 (1.1)	9 (1.7)
Not reported/Unknown	4 (1.5)	7 (2.6)	11 (2.0)
Region			
United States	17 (6.3)	19 (7.0)	36 (6.6)
Rest of World	255 (93.8)	253 (93.0)	508 (93.4)
Eastern Europe	245 (90.0)	250 (91.9)	495 (91.0)
Western Europe	10 (3.7)	3 (1.1)	13 (2.4)
Canada	0 (0)	0 (0)	0 (0)
South America	0 (0)	0 (0)	0 (0)
Asia	0 (0)	0 (0)	0 (0)
Africa	0 (0)	0 (0)	0 (0)

Source: ADSL for TG1101-RMS302, MITTFL=Y; Tabulated by TRT01A

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline clinical characteristics and disease characteristics for the mITT population are presented in Table 25, Table 26, Table 27, and Table 28. Similar to Study TG1101-RMS301, the treatment groups appeared to be similar in terms of height, weight, BMI, and prevalence of renal impairment. Hepatic impairment at baseline, particularly moderate impairment, appeared to be more frequent in the teriflunomide group.

The treatment groups also appeared to be similar in terms of MS disease characteristics, including time since last relapse, time since diagnosis, prior MS treatments, prevalence of gadolinium-enhancing lesions, and T1/T2 lesion characteristics.

Table 25 (Reviewer). Study TG1101-RMS302 Baseline Clinical Characteristics, mITT Population

	Ublituximab-xiiy (N=272)	Teriflunomide (N=272)	Total (N=544)
Height (cm) ¹			
Mean (SD)	170.1 (8.6)	170.2 (8.6)	170.2 (8.6)
Median (IQR)	169.0 (12.0)	169.0 (12.0)	169.0 (12.0)
Min, max	152, 202	150, 194	150, 202
Weight (kg)			
Mean (SD)	70.2 (17.3)	69.1 (15.0)	69.6 (16.2)
Median (IQR)	67.0 (23.0)	67.0 (21.0)	67.0 (22.0)
Min, max	42, 137	38, 125	38, 137
BMI (kg/m ²) ¹			
Mean (SD)	24.2 (5.3)	23.8 (4.6)	24.0 (5.0)
Median (IQR)	22.7 (6.5)	23.1 (5.5)	23.0 (5.8)
Min, max	16.5, 48.8	15.4, 43.3	15.4, 48.8
Hepatic impairment ² (n (%))			
Normal	256 (94.1)	246 (90.4)	502 (92.3)
Mild (Total bilirubin >ULN and ≤1.5x ULN or ALT>ULN or AST>ULN)	14 (5.2)	21 (7.7)	35 (6.4)
Moderate (Total bilirubin >1.5x ULN and ≤3x ULN)	2 (0.7)	5 (1.8)	7 (1.3)
Renal Impairment ³ (n (%))			
Normal	159 (58.5)	144 (52.9)	303 (55.7)
Mild (GFR ≥60 ml/min & <90 ml/min)	111 (40.8)	127 (46.7)	238 (43.8)
Moderate (GFR ≥90 ml/min & <60 ml/min)	2 (0.7)	1 (0.4)	3 (0.6)

¹Height and BMI values were missing for 7 ublituximab-xiiy- and 1 teriflunomide-treated subjects

²Hepatic impairment as defined by HEPIMP in ADSL

³Renal impairment as defined by RENIMP in ADSL

Source: ADSL for TG1101-RMS302, MITTFL=Y; Tabulated by TRT01A

Table 26 (Reviewer). Study TG1101-RMS302 Clinical Characteristics, mITT Population

	Ublituximab-xiiy (N=272)	Teriflunomide (N=272)	Total (N=544)
Time since MS diagnosis (years)			
Mean (SD)	5.0 (5.6)	5.0 (5.2)	5.0 (5.4)
Median (IQR)	3.2 (6.9)	3.7 (7.1)	3.3 (7.0)
Min, max	0.05, 28.3	0.06, 30.1	0.05, 30.1
Time since last relapse (months)			
Mean (SD)	7.8 (9.7)	6.7 (5.9)	7.2 (8.1)
Median (IQR)	5.9 (5.8)	5.2 (5.3)	5.6 (5.6)
Min, max	1.6, 93.0	1.3, 60.3	1.3, 93.0
# relapses in year prior to screening			
Mean (SD)	1.3 (0.7)	1.2 (0.7)	1.3 (0.7)
Median (IQR)	1.0 (1.0)	1.0 (0)	1.0 (1.0)
Min, max	0, 4	0, 4	0, 4
0 (n (%))	16 (5.9)	15 (5.5)	31 (5.7)
1 (n (%))	182 (66.9)	192 (70.6)	374 (68.8)
2 (n (%))	66 (24.3)	51 (18.8)	117 (21.5)
3 (n (%))	4 (1.5)	12 (4.4)	16 (2.9)
≥4 (n (%))	4 (1.5)	2 (0.7)	6 (1.1)
# relapses in 2 years prior to screening			
Mean (SD)	1.8 (0.9)	1.8 (0.9)	1.8 (0.9)
Median (IQR)	2.0 (1.0)	2.0 (1.0)	2.0 (1.0)
Min, max	0, 7	0, 7	0, 7
Baseline EDSS			
Mean (SD)	2.8 (1.3)	3.0 (1.2)	2.9 (1.3)
Median (IQR)	2.5 (1.5)	3.0 (1.5)	3.0 (1.5)
Min, max	0, 5.5	0, 5.5	0, 5.5
≤3.5 (n (%))	218 (80.2)	206 (75.7)	424 (77.9)
>3.5 (n (%))	54 (19.9)	66 (24.3)	120 (22.1)

Source: ADSL for TG1101-RMS302, MITTFL=Y; Tabulated by TRT01A

Table 27 (Reviewer). Study TG1101-RMS302 Prior MS Treatments, mITT Population

	Ublituximab-xiiy (N=272) n (%)	Teriflunomide (N=272) n (%)	Total (N=544) n (%)
Prior MS Treatment			
Corticosteroids	253 (93.0)	243 (89.3)	496 (91.2)
Interferon beta	71 (26.1)	58 (21.3)	129 (23.7)
Glatiramer acetate	40 (14.0)	33 (12.1)	73 (13.4)
Laquinimod	29 (10.7)	30 (11.0)	59 (10.8)
Daclizumab	6 (2.2)	8 (2.9)	14 (2.6)
Dimethyl fumarate	3 (1.1)	5 (1.8)	8 (1.5)
IVIg	5 (1.8)	1 (0.4)	6 (1.1)
Fingolimod	2 (0.7)	3 (1.1)	5 (0.9)
Ozanimod	1 (0.4)	3 (1.1)	4 (0.7)
Mitoxantrone	2 (0.7)	0 (0)	2 (0.4)
AIN457 (Secukinumab)	0 (0)	1 (0.4)	1 (0.2)
ATX-MS-1467	1 (0.4)	0 (0)	1 (0.2)
Azathioprine	0 (0)	1 (0.4)	1 (0.2)
Diroximel fumarate	0 (0)	1 (0.4)	1 (0.2)
INT131	0 (0)	1 (0.4)	1 (0.2)
Methotrexate	0 (0)	1 (0.4)	1 (0.2)
Plasmapheresis	1 (0.4)	0 (0)	1 (0.2)
Vatelizumab	0 (0)	1 (0.4)	1 (0.2)
Received appropriate MS treatment ¹	106 (39.0)	87 (32.0)	193 (35.5)
Previous corticosteroid treatment for relapse ²	253 (93.0)	243 (89.3)	496 (91.2)

¹APDMTFL in ADSL; ²PRCSREFL in ADSL

Source: ADCM for TG1101-RMS302, MITTFL=Y, CMCAT = "MS TREATMENT HISTORY"; Manually recoded CMTRT, tabulated by TRT01A

Table 28 (Reviewer). Study TG1101-RMS302 Baseline MRI Characteristics, mITT Population

	Ublituximab-xiiy (N=272)	Teriflunomide (N=270)	Total (N=542)
Gadolinium-enhancing lesions			
Mean (SD)	2.6 (5.8)	2.5 (5.5)	2.5 (5.6)
Median (IQR)	1.0 (3.0)	0.5 (2.0)	1.0 (3.0)
Min, max	0, 61	0, 46	0, 61
Present (n (%))	141 (51.8)	135 (50.0)	276 (50.9)
Absent (n (%))	131 (48.2)	135 (50.0)	266 (49.1)
T1 lesion count			
Mean (SD)	38.6 (31.9)	39.1 (35.4)	38.8 (33.7)
Median (IQR)	31.5 (44.0)	28.0 (41.3)	29.0 (42.0)
Min, max	1, 186	0, 172	0, 186
T2 lesion count			
Mean (SD)	65.3 (41.2)	64.0 (41.2)	64.7 (41.2)
Median (IQR)	56.5 (48.0)	53.5 (46.3)	55.0 (48.0)
Min, max	4, 232	9, 219	4, 232
T2 lesion volume (mL)			
Mean (SD)	14.7 (13.5)	15.7 (17.5)	15.2 (15.6)
Median (IQR)	11.0 (15.0)	9.6 (17.0)	10.3 (15.8)
Min, max	0.5, 83.1	0.5, 123.1	0.5, 123.1

Source: ADSL for TG1101-RMS302, MITTFL=Y; Tabulated by TRT01A

Reviewer comment: Baseline MRI characteristics were missing for 2 subjects on teriflunomide.

General medical history for subjects enrolled in Study TG1101-RMS302 was reviewed as well. Ongoing medical disorders (defined by ONGOFL=Y) occurring in >5% of subjects in either treatment group are presented in Table 29.

Table 29 (Reviewer). Study TG1101-RMS302 Concurrent Medical Disorders Reported in >5% of Either Treatment Group, mITT Population

		Ublituximab-xiiy (N=272) n (%)	Teriflunomide (N=272) n (%)
System Organ Class	Dictionary-Derived Term ¹		
Musculoskeletal and connective tissue disorders	Osteochondrosis	22 (8.1)	28 (10.3)
	Intervertebral disc protrusion	13 (4.8)	5 (1.8)
Eye disorders	Back pain	9 (3.3)	14 (5.1)
	Myopia	32 (11.8)	29 (10.7)
Gastrointestinal disorders	Retinal vascular disorder	30 (11.0)	23 (8.5)
	Chronic gastritis	22 (8.1)	21 (7.7)
Respiratory, thoracic, and mediastinal disorders	Paranasal cyst	16 (5.9)	14 (5.1)
Psychiatric disorders	Depression	14 (5.1)	7 (2.6)
Vascular disorders	Hypertension	18 (6.6)	19 (7.0)

¹MHDECOD in ADMH; Source: Study TG1101-RMS302, ADMH, where MITTFL=Y, ONGOFL=Y, by TRT01A; Applicant's CSR Table 14.1.5.1

Reviewer comment: No major or clinically relevant differences in medical history were observed between the treatment groups. These data were also consistent with that observed in Study TG1101-RMS301.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Treatment compliance by treatment group in the mITT population, according to the applicant, is summarized in Table 30. Overall, compliance with IV and oral study treatment was similar between the groups.

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Table 30 (Applicant). Study TG1101-RMS302 Summary of Percentage Compliance with Study Treatments, Safety Population

	Ublituximab-xiiy (N=272)		Teriflunomide (N=273)	
	IV Compliance (%)	PO Compliance (%)	IV Compliance (%)	PO Compliance (%)
Mean (SD)	98.4 (8.8)	98.7 (4.6)	94.9 (17.0)	98.1 (7.2)
Median	100	99.9	100	99.8
Min, Max	30.8, 103.5	69.8, 110.9	7.7, 103.5	6.3, 100.7

Source: Applicant's CSR, Tables 42 and 43

An Information Request was sent to the applicant on 2/10/2022 due to concerns regarding reported compliance with study treatment >100%. The applicant responded on 3/4/2022, and indicated that these values were related to minor discrepancies between two data sources used for this information.

Per the Applicant's CSR, IV compliance <80% occurred in 4.4% (n = 12) of subjects on ublituximab-xiiy and 9.9% (n = 27) of subjects on teriflunomide. Oral treatment compliance <80% occurred in 2.2% (n = 6) of subjects on ublituximab-xiiy and 2.9% (n = 8) subjects on teriflunomide.

Concomitant Medications

Per the applicant's CSR, the most commonly utilized concomitant medications were those intended for infusion pre-medication (dexamethasone and diphenhydramine) and MRI contrast (Table 31).

Table 31 (Reviewer). Study TG1101-RMS302, Selected Concomitant Medications Used by $\geq 5\%$ of Either Treatment Group of mITT Population

	Ublituximab-xiiy (N=272) n (%)	Teriflunomide (N=272) n (%)
Infusion pre-medication		
Dexamethasone	249 (91.5)	260 (95.6)
Diphenhydramine	125 (46.0)	19 (7.0)
Diphenhydramine hydrochloride	80 (29.4)	96 (35.3)
Cetirizine	39 (14.3)	38 (14.0)
Dimenhydrinate	25 (9.2)	24 (8.8)
Paracetamol	30 (11.0)	16 (5.9)
Methylprednisolone	17 (6.3)	7 (2.6)
MRI Gadolinium-based Contrast	272 (100.0)	269 (98.9)
Antibiotics/Antivirals		
Amoxicillin trihydrate; clavulanate potassium	32 (11.8)	26 (9.6)
Azithromycin	27 (9.9)	21 (7.7)
Acyclovir	17 (6.3)	6 (2.2)
Other medications		
Paracetamol (all indications)		
Baclofen	21 (7.7)	10 (3.7)
Ibuprofen	87 (32.0)	68 (25.0)
Vitamin D and analogues	65 (23.9)	66 (24.3)

Source: ADCM where mITTFL=Y, ONTRTFL=Y, categories based on CMINDC; Applicant's CSR (Table 18)

According to the applicant's CSR, the most commonly utilized follow-up medications were cholestyramine (90.1% ublituximab-xiiy, 86.8% teriflunomide) and gadobutrol (54.8% ublituximab-xiiy, 51.8% teriflunomide). Methylprednisolone use is discussed in below as a rescue medication. Otherwise, concomitant medication usage appeared to be similar between the treatment groups.

Rescue Medication Use

The CMINDC variable in the ADCM dataset also indicated treatment for an MS relapse ("MS Relapse Treatment"), and the SCORTFL indicated systemic corticosteroids. Per these flags, 32 subjects on ublituximab-xiiy (11.8%) and 71 on teriflunomide (26.1%) received systemic corticosteroids for relapse treatment.

The applicant's CSR also indicates that methylprednisolone was utilized as a follow-up medication in 2.6% of ublituximab-xiiy subjects and 5.1% of teriflunomide subjects. However, the indication and dose is not accounted for in these summary statistics.

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Reviewer comment: The lower frequency of steroid use in the ublituximab-xiiy group is expected, as this group experienced fewer relapses.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was Annualized Relapse Rate (ARR), which the applicant calculated as a group ARR utilizing treatment duration in years (STDURY) and number of IRAP-confirmed clinical relapses. The unadjusted group ARR for the ublituximab-xiiy group was 0.11, and for the teriflunomide group was 0.22, for an ARR ratio of 0.50 (95% CI 0.35, 0.70, $p = 3.355e-05$) (Table 32). These results indicate a statistically significant treatment effect of ublituximab-xiiy in relapse reduction compared to teriflunomide.

Table 32 (Reviewer). Study TG1101-RMS302, Summary of Confirmed Relapses and Annualized Relapse Rate

	Ublituximab-xiiy (N=272)	Teriflunomide (N=272)	Ratio (if applicable)
Number (%) of patients who experienced confirmed relapse	34 (12.5)	72 (26.5)	
Number of confirmed relapses experienced per patient during DBT (n (%))			
0	238 (87.5)	200 (73.5)	
1	20 (7.4)	50 (18.4)	
2	10 (3.7)	16 (5.9)	
3	3 (1.1)	5 (1.8)	
4	1 (0.4)	0 (0)	
5	0 (0)	1 (0.4)	
Number of confirmed relapses experienced per patient during DBT			
Mean (SD)	0.19 (0.6)	0.38 (0.7)	
Median (IQR)	0 (0)	0 (1.0)	
Min, Max	0, 4	0, 5	
DBT Duration (years) ¹			
Mean (SD)	1.79 (0.2)	1.71 (0.4)	
Median (IQR)	1.82 (0.02)	1.82 (0.01)	
Min, Max	0.25, 1.92	0.04, 2.15	
Group ARR			
Sum DBT Duration (years)	485.90	465.70	
Sum DBT Relapses	53	102	
ARR	0.11	0.22	0.50 (95% CI 0.35, 0.70) ²

¹Treatment duration per STDURY; ²Calculated using package rateratio.test (version 1.0-2) in RStudio (version 1.1.456)

Reviewer Comment: Reviewer calculations for unadjusted ARR are consistent with those presented by the applicant. The applicant also presented an analysis with LS mean for ARR calculated using negative binomial regression of 0.091 (95% CI 0.049, 0.169) for the ublituximab-xiiy group and 0.178 (95% CI 0.109, 0.291) for the teriflunomide group. The ARR rate ratio was 0.509 (95% CI 0.330, 0.784, p=0.0022). Please refer to the statistical review for replication of these adjusted results.

As demonstrated in Table 32, the double-blind treatment exposure was similar between treatment groups at both the individual and group levels. The percentage of patients who experienced a confirmed relapse during double-blind treatment was higher in the teriflunomide group (26.5%) compared to ublituximab-xiiy (12.5%). The mean (SD) number of confirmed

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relapses experienced per patient was higher in the teriflunomide group (0.38 (0.7)) compared to ublituximab-xiiy (0.19 (0.6)).

The applicant also conducted 3 sensitivity analyses for ARR, specifically calculations of ARR using IRAP-confirmed relapses including follow-up, all relapses irrespective of confirmation, and multiple imputation of withdrawn subjects. These analyses yielded ARR ratios ranging from 0.49 to 0.63 and remained statistically significant, indicating robustness of the primary endpoint in these circumstances.

Data Quality and Integrity

There were no issues regarding the quality of the efficacy data submitted. Please refer to the Protocol Deviations discussion earlier in this section regarding protocol violations that raised concerns regarding data integrity. Please also refer to the OSI review by Cara Alfaro, PharmD.

Efficacy Results – Secondary and other relevant endpoints

Gadolinium-enhancing lesions

The first key secondary efficacy endpoint was the total number of gadolinium-enhancing lesions on brain MRI by Week 96. The mITT-MRI population included subjects who had baseline and post-baseline MRI efficacy assessments (ublituximab-xiiy n = 272, teriflunomide n = 267). Please refer to Table 28 for a summary of baseline gadolinium-enhancing lesions per treatment group.

Per the applicant's analysis, ublituximab-xiiy-treated subjects had a mean of 3.8 MRIs and teriflunomide treated subjects had a mean of 3.7 MRIs. Similar to the results of Study TG1101-RMS301, ublituximab-xiiy-treated subjects had a lower number of gadolinium-enhancing lesions than those on teriflunomide on all post-baseline MRIs. At Week 96, the mean (SD) total number of gadolinium-enhancing lesions per MRI scan was 0.04 (0.2) for the ublituximab-xiiy group and 0.88 (2.2) for the teriflunomide group (Table 33). The applicant's analysis yielded a rate ratio for the total number of gadolinium-enhancing lesions per MRI scan of 0.035 (95% CI 0.019 to 0.064, $p < 0.0001$), indicating a statistically significant reduction of gadolinium-enhancing lesions with ublituximab-xiiy compared to teriflunomide.

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Table 33 (Reviewer). Study TG1101-RMS302, Gadolinium-Enhancing Lesions, mITT-MRI Population

	Ublituximab-xiiy (N=272)	Teriflunomide (N=267)
Total # Gadolinium-enhancing lesions per MRI by Week 96		
Mean (SD)	0.04 (0.2)	0.88 (2.2)
Median	0	0.25
Min, Max	0, 2.25	0, 23.0
Total # gadolinium-enhancing lesions per subject by Week 96		
Mean (SD)	0.1 (0.8)	3.1 (6.6)
Median	0	1.0
Min, Max	0, 9	0, 75

Source: Applicant's Study TG1101-RMS302 CSR, Tables 22 and 14.2.2.1.1

Please refer to the biostatistics review for replication of these efficacy findings.

New or enlarging T2 lesions

The second key secondary efficacy endpoint was the total number of new or enlarging T2 hyperintense lesions per brain MRI by Week 96.

Per the applicant's analysis, ublituximab-xiiy-treated subjects had a mean of 2.9 MRIs and teriflunomide treated subjects had a mean of 2.8 MRIs. Ublituximab-xiiy-treated subjects had a lower mean number of new/enlarging T2 hyperintense lesions than those on teriflunomide on all post-baseline MRIs. At Week 96, the total mean (SD) total number of new/enlarging T2 hyperintense lesions per MRI scan was 0.50 (1.1) for the ublituximab-xiiy group and 4.66 (7.7) for the teriflunomide group (Table 34). The applicant's analysis yielded a rate ratio for the total number of new/enlarging T2 hyperintense per MRI scan of 0.100 (95% CI 0.073, 0.136; $p < 0.0001$), indicating a statistically significant reduction of new/enlarging T2 hyperintense lesions with ublituximab-xiiy compared to teriflunomide.

Table 34 (Reviewer). Study TG1101-RMS302, New/Enlarging T2 Hyperintense Lesions, mITT-MRI Population

	Ublituximab-xiiy (N=272)	Teriflunomide (N=267)
Total # new/enlarging T2 lesions per MRI by Week 96		
Mean (SD)	0.50 (1.1)	4.66 (7.7)
Median	0	2.0
Min, Max	0, 9.3	0, 52.0
Total # new/enlarging T2 lesions per subject by Week 96		
Mean (SD)	1.4 (3.4)	12.5 (18.7)
Median	0	5.0
Min, Max	0, 28.0	0, 102.0

Source: Applicant's Study TG1101-RMS302 CSR, Tables 24 and 14.2.2.2.1

Please refer to the biostatistics review for replication of these efficacy findings.

Reviewer comment: Overall, the key secondary efficacy endpoints support a clinically significant treatment effect of ublituximab-xiiy over teriflunomide. The results of the MRI lesion analyses are expected, consistent with other highly effective treatments for RMS, and are congruent with the relapse-related findings of the primary efficacy analysis.

Confirmed Disability Progression (12-week)

Please refer to efficacy results presented in Section 6.3.2 for the pre-specified pooled analysis of Studies TG1101-RMS301 and TG1101-RMS302 for 12-week confirmed disability progression.

Other Secondary Efficacy Endpoints

Three other secondary efficacy endpoints that are not accepted clinical endpoints, but are considered supportive of the primary efficacy finding, were analyzed by the applicant (i.e., were not replicated by this reviewer).

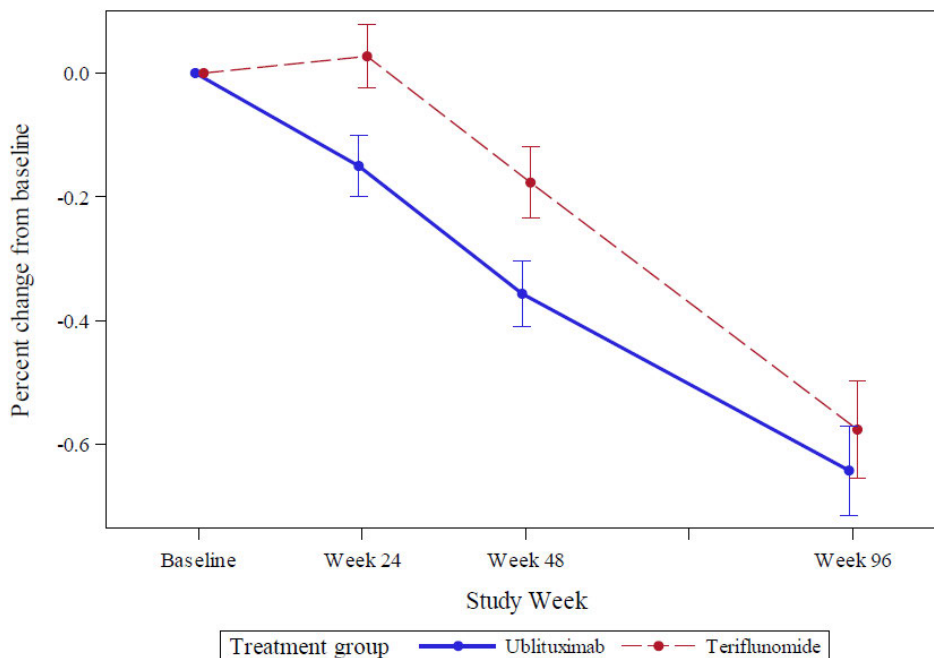
The applicant compared the proportion of subjects with NEDA from Week 24 to Week 96. NEDA was defined as having no IRAP-confirmed relapses, MRI activity (either gadolinium-enhancing or new/enlarging T2 lesions), or 12-week CDP between Weeks 24 and 96. Subjects receiving ublituximab-xiiy were more likely to achieve NEDA (43.0%, n = 117) compared to those receiving teriflunomide (11.4%, n = 31), with a statistically significant odds ratio of 7.95 (95% CI 4.92 to 12.84, p<0.0001) in favor of ublituximab-xiiy.

The applicant also compared the proportion of subjects reaching impairment on the Symbol Digit Modalities Test (SDMT) from baseline to Week 96, defined as a decrease from baseline of at least 4 points at any post-baseline assessment. Similar to the results of Study TG1101-

RMS302, the applicant's analysis did not indicate a statistically significant difference in the proportion of subjects reaching impaired SDMT between the ublituximab-xiiy and teriflunomide groups; the odds ratio was 0.87 (95% CI 0.60 to 1.25, $p = 0.43$), and the proportion of subjects reaching impaired SDMT in the ublituximab-xiiy group was 29.0%, compared to 31.6% in the teriflunomide group.

Finally, the applicant compared percentage change in brain volume from baseline to Week 96 between the treatment groups in the mITT-MRI population, defined as subjects who had baseline and post-baseline MRI efficacy assessments. As demonstrated in Figure 3, and similar to the results of Study TG1101-RMS301, brain volume increased slightly at Week 24 in the teriflunomide group, then declined at a rate similar to that of the ublituximab-xiiy group through Week 96. The applicant performed a mixed model repeated measures analysis, which indicated that the percentage change of the cube root transformed volume from baseline at Week 96 was not statistically significant different in the teriflunomide group compared to ublituximab-xiiy (LS means [ublituximab-xiiy – teriflunomide] -0.018, 95% CI -0.053 to 0.017, $p=0.3108$).

Figure 3 (Applicant). Study TG1101-RMS302, Mean Percentage Change in Brain Volume



Source: [Figure 14.2.9](#)

Abbreviations: See Section 4.

Note: Mean and the 95% Wald Confidence Intervals are displayed.

Source: Applicant's CSR for Study TG1101-RMS302, Figure 8

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Dose/Dose Response

Not applicable, as a single dose was studied in Study TG1101-RMS302.

Durability of Response

Though the trial was not designed to evaluate durability of response, there did not appear to be a higher frequency of relapse later in the double blind treatment period, suggesting a durable response to ublituximab-xiiy in the setting of B-cell depletion.

Persistence of Effect

Again, the trial was not designed to evaluate persistence of effect, but most patients in the ublituximab-xiiy group appeared to experience B-cell depletion through the end of the double blind treatment period, during which multiple doses of ublituximab-xiiy were administered (See Section 8.4.6). Therefore, the data suggests that there is not a meaningful loss of effect of ublituximab-xiiy over time.

Additional Analyses Conducted on the Individual Trial

Confirmed and Unconfirmed Relapses

Overall, 190 confirmed and unconfirmed relapses occurred across both treatment groups in the double-blind treatment period, 115 (60.5%) in the teriflunomide group and 75 (39.5%) in the ublituximab-xiiy group. The rate of IRAP confirmation was lower in the ublituximab-xiiy group (70.7% (53/75 relapses)) compared to the teriflunomide group (88.7% (102/115 relapses)). Again, relapse severity was not captured in the eCRF, and therefore was not able to be tabulated for this review.

Reviewer comment: An Information Request regarding the higher rate of relapse confirmation in the teriflunomide group was sent to the applicant on 3/28/2022. The applicant responded 5/5/2022, indicating that a review of patient profiles yielded no evidence that data provided to the IRAP could be unblinding for teriflunomide, except for one case of alopecia. This response was considered reasonable.

The unadjusted group ARR for both confirmed and unconfirmed relapses was 0.15 in the ublituximab-xiiy group versus 0.25 in the teriflunomide group, with an ARR ratio of 0.63 (95% CI 0.46 to 0.84; p = 0.002). The percentage of subjects who experienced either a confirmed or unconfirmed relapse was lower in the ublituximab-xiiy group (17.3%) compared to teriflunomide (28.3%). Additionally, the mean (SD) number of relapses (either confirmed or unconfirmed) was lower in the ublituximab-xiiy group (0.28 (0.7)) compared to teriflunomide (0.42 (0.8)).

These relapse data are summarized in Table 35.

Table 35 (Reviewer). Study TG1101-RMS302, Summary of Confirmed and Unconfirmed Relapses

	Ublituximab-xiiy (N=272)	Teriflunomide (N=272)	Ratio (if applicable)
Number (%) of patients who experienced confirmed or unconfirmed relapse	47 (17.3)	77 (28.3)	
Number of confirmed or unconfirmed relapses experienced per patient during DBT (n (%))			
0	225 (82.7)	195 (71.7)	
1	29 (40.3)	50 (18.4)	
2	11 (4.0)	19 (7.0)	
3	5 (1.8)	6 (2.2)	
4	1 (0.4)	1 (0.4)	
5	1 (0.4)	1 (0.4)	
Number of confirmed or unconfirmed relapses experienced per patient during DBT			
Mean (SD)	0.28 (0.7)	0.42 (0.8)	
Median (IQR)	0 (0)	0 (1.0)	
Min, Max	0, 5	0, 5	
Number (%) of suspected relapses confirmed during DBT	53 (70.7)	102 (88.7)	
Group ARR (confirmed and unconfirmed)			
Sum DBT Duration (years)	485.90	465.70	
Sum DBT Relapses	75	115	
ARR	0.15	0.25	0.63 (95% CI 0.46 to 0.84) ¹

¹Calculated using package `rateratio.test` (version 1.0-2) in RStudio (version 1.1.456)

Change from Baseline EDSS

Change from baseline EDSS was calculated for each patient during the DBT period, regardless of DBT duration, and results are summarized in Table 36. The proportions of patients with EDSS worsening, improvement, and stability were similar between the treatment groups, which differed from the observation in Study TG1101-RMS301 that more subjects on ublituximab-xiiy experienced EDSS improvement.

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Table 36 (Reviewer). Study TG1101-RMS302, Change in EDSS During Double Blind Treatment

	Ublituximab-xiiy (N=272)	Teriflunomide (N=271)
Mean (SD ¹ , n)	-0.06 (0.7)	0.07 (0.7)
Median (IQR ² , n)	0 (0)	0 (0)
Min, max	-3.0, 3.0	-3.0, 3.0
n (%) with worsening EDSS	44 (16.2)	52 (19.2)
n (%) with improving EDSS	57 (21.0)	53 (19.6)
n (%) with stable EDSS	171 (62.9)	166 (61.3)

¹SD: Standard deviation; ²IQR: interquartile range

6.3. Pooled Studies TG1101-RMS301 and TG1101-RMS302

6.3.1. Study Design

Studies TG1101-RMS301 and TG1101-RMS302 were identical in design. Refer to Section 6.1. The pooled study population was only utilized to evaluate the key secondary efficacy endpoint time to 12-week confirmed disability progression.

6.3.2. Study Results

Compliance with Good Clinical Practices

Refer to Sections 6.1 and 6.2.

Financial Disclosure

Refer to Sections 6.1 and 6.2.

Patient Disposition

Refer to Sections 6.1 and 6.2.

Protocol Violations/Deviations

Refer to Sections 6.1 and 6.2.

Demographic and Baseline Disease Characteristics

The demographics and baseline disease characteristics of the pooled population did not differ significantly from the individual RMS studies (Table 37).

Table 37 (Reviewer). Studies TG1101-RMS301 and TG1101-RMS302 Subject Characteristics, mITT Population

	Pooled		TG1101-RMS301		TG1101-RMS302	
	Ublituximab-xiiy (N=543)	Teriflunomide (N=546)	Ublituximab-xiiy (N=271)	Teriflunomide (N=274)	Ublituximab-xiiy (N=272)	Teriflunomide (N=272)
Sex (n (%))						
Male	199 (36.7)	191 (35.0)	105 (38.8)	95 (34.7)	94 (34.5)	96 (35.3)
Female	344 (63.4)	355 (65.0)	166 (61.3)	179 (65.3)	178 (65.4)	176 (64.7)
Age (years)						
Mean (SD)	35.3 (8.6)	36.6 (9.3)	36.2 (8.4)	37.0 (9.6)	34.5 (8.8)	36.2 (9.0)
Median (IQR)	35.0 (14.0)	36.0 (14.0)	36.0 (13.0)	36.5 (15.0)	33.0 (13.0)	36.0 (13.0)
Min, max	18, 55	18, 55	18, 55	18, 55	18, 55	18, 55
Race (n (%))						
White	533 (98.2)	534 (97.8)	264 (97.4)	266 (97.1)	269 (98.9)	268 (98.5)
Black or African American	8 (1.5)	9 (1.7)	6 (2.2)	6 (2.2)	2 (0.7)	3 (1.1)
Other	1 (0.2)	3 (0.6)	0 (0)	2 (0.7)	1 (0.4)	1 (0.4)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Region (n (%))						
United States	40 (7.4)	44 (8.1)	23 (8.5)	25 (9.1)	17 (6.3)	19 (7.0)
Rest of World	503 (92.6)	502 (91.9)	248 (91.5)	249 (90.9)	255 (93.8)	253 (93.0)
Time since MS diagnosis (years)						
Mean (SD)	5.0 (5.4)	4.7 (5.1)	4.9 (5.2)	4.5 (5.0)	5.0 (5.6)	5.0 (5.2)
Median (IQR)	3.0 (6.4)	2.8 (6.7)	2.9 (6.0)	2.5 (5.9)	3.2 (6.9)	3.7 (7.1)
Min, max	0.05, 28.3	0.04, 30.1	0.07, 27.5	0.04, 25.7	0.05, 28.3	0.06, 30.1
Baseline EDSS						
Mean (SD)	2.9 (1.3)	2.9 (1.2)	3.0 (1.2)	2.9 (1.2)	2.8 (1.3)	3.0 (1.2)
Median (IQR)	3.0 (1.5)	3.0 (1.5)	3.0 (2.0)	3.0 (1.5)	2.5 (1.5)	3.0 (1.5)
Min, max	0, 5.5	0, 6	0, 5.5	0, 6	0, 5.5	0, 5.5
# Gadolinium-enhancing lesions (baseline)						
Mean (SD)	2.4 (5.6)	2.0 (4.7)	2.3 (5.5)	1.6 (3.7)	2.6 (5.8)	2.5 (5.5)
Median (IQR)	0 (2.0)	0 (2.0)	0 (2.0)	0 (2.0)	1.0 (3.0)	0.5 (2.0)
Min, max	0, 61	0, 46	0, 37	0, 40	0, 61	0, 46
# Relapses in year prior to screening						
Mean (SD)	1.3 (0.7)	1.3 (0.7)	1.3 (0.6)	1.4 (0.7)	1.3 (0.7)	1.2 (0.7)
Median (IQR)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	1.0 (0)
Min, max	0, 4	0, 4	0, 4	0, 4	0, 4	0, 4
Prior treatment for MS (n (%))	198 (36.5)	169 (31.0)	92 (34.0)	82 (29.9)	106 (39.0)	87 (32.0)

Source: ADSL for TG1101-RMS301 and TG1101-RMS302, MITTFL=Y; Tabulated by TRT01A

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Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Refer to Sections 6.1 and 6.2.

Efficacy Results – Primary Endpoint

Refer to Sections 6.1 and 6.2. The primary endpoints for these trials, ARR, were analyzed separately.

Data Quality and Integrity

Refer to Sections 6.1 and 6.2.

Efficacy Results – Secondary and other relevant endpoints

These pooled studies were utilized for analysis of time to 12-week CDP only. Analysis and replication of 12-week CDP endpoint is deferred to the Biostatistics reviewer.

Per the applicant's analysis, 12-week CDP occurred in 5.2% of subjects in the ublituximab-xiiy group (n = 28) and 5.9% in the teriflunomide group (n = 32). For time to 12-week CDP, the applicant's analysis indicated a non-statistically significant hazard ratio of 0.843 (95% CI 0.504 to 1.407; p = 0.5099).

The applicant also analyzed time to 24-week CDP, which also yielded non-significant results (hazard ratio 0.657, 95% CI 0.358 to 1.205, p = 0.1716).

Reviewer comment: The applicant analyzed time to 12- and 24-week confirmed disability improvement (CDI) as an exploratory endpoint, and reported statistically significant hazard ratios in favor of ublituximab-xiiy for both endpoints. However, given the non-significant findings in 12- and 24-week CDP, a significant finding in CDI is not relevant. Additionally, this lack of significance on CDP endpoints may be related to the fact that teriflunomide is known to have an effect on CDP, so it would likely be difficult to achieve superiority to teriflunomide on CDP in the context of this trial design. Ublituximab-xiiy could be non-inferior to teriflunomide in terms of CDP, but it is not possible to determine this given the study design.

Dose/Dose Response

Not applicable.

Durability of Response

Refer to Sections 6.1 and 6.2.

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Persistence of Effect

Refer to Sections 6.1 and 6.2.

Additional Analyses Conducted on the Individual Trial

Not applicable.

6.4. Study TG1101-RMS201

6.4.1. Study Design

Overview and Objective

Study TG1101-RMS201 was a Phase 2a, 52-week, placebo-controlled, dose-finding, multicenter, sequential cohort study evaluating ublituximab-xiiy in subjects with relapsing MS. Data from this study was submitted to the BLA to support the data from Studies TG1101-RMS301 and TG1101-RMS302.

The primary objectives of the study were to:

1. Determine the level of B-cell depletion by ublituximab-xiiy in subjects with RMS
2. Determine the optimal dose and infusion time for ublituximab-xiiy in subjects with RMS

The secondary objectives were to:

1. Examine the effect of ublituximab-xiiy on the development of new gadolinium-enhancing lesions and new or enlarging T2 lesions at 24 and 48 weeks.
2. Evaluate the percent of relapses in ublituximab-xiiy-treated RMS subjects
3. Determine immunogenicity
4. Evaluate the safety of ublituximab-xiiy, as determined by adverse events and serious adverse events, including MS worsening

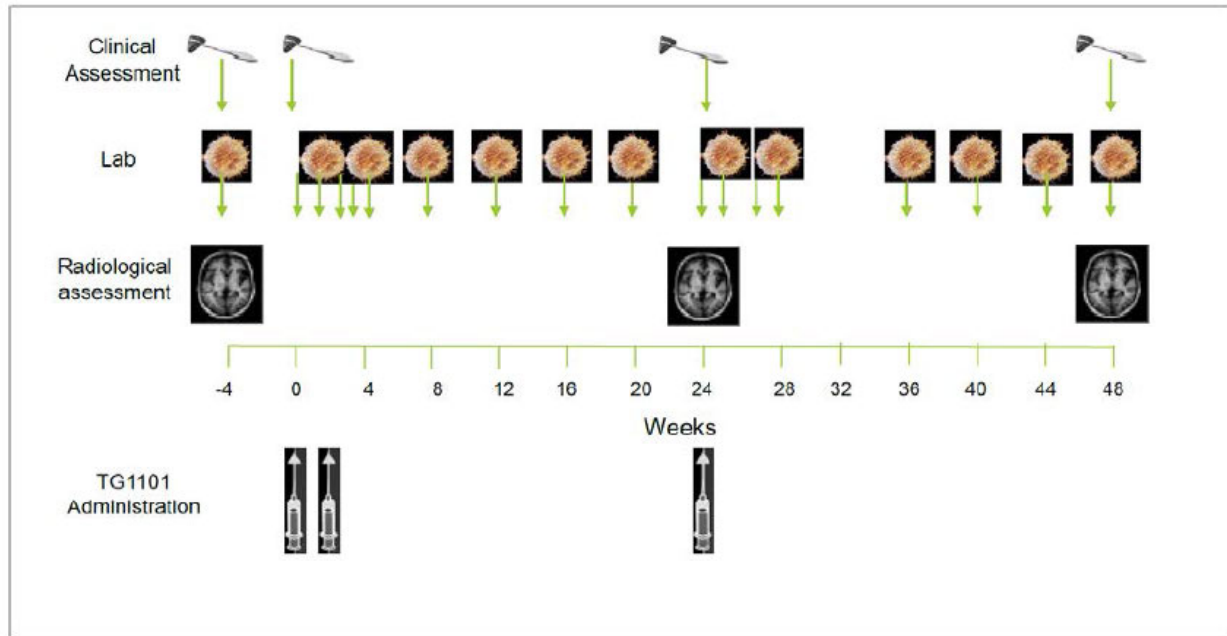
Trial Design

Study TG1101-RMS201 was a Phase 2a, 52-week, placebo-controlled, dose-finding, multicenter, sequential cohort study evaluating the pharmacodynamics, efficacy, and safety of ublituximab-xiiy in subjects with relapsing MS.

The study schematic for Study TG1101-RMS201 is presented in Figure 4. The study consisted of a screening period of up to 4 week and a 48-week double-blind treatment period. Subjects who remained stable at the end of the double-blind treatment period were able to enter the open-label extension study, Study TG1101-RMS201E.

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Figure 4 (Applicant). Study TG1101-RMS201 Study Schematic



Source: Applicant's Clinical Study Report, Study TG1101-RMS201

The study included 6 treatment cohorts with 8 subjects each (6 randomized to ublituximab-xiiy, and 2 to placebo), which are further described in the *Study Treatment* section below.

Key Eligibility Criteria

Key Inclusion Criteria

1. Age 18 to 55 years
2. Diagnosis of RMS per 2010 McDonald Criteria
3. ≥ 2 relapses in prior 2 years or 1 relapse in year prior to screening and/or ≥ 1 gadolinium-enhancing lesion
4. Active disease
5. EDSS 0 to 5.5 (inclusive)
6. B-cell counts $\geq 5\%$ of total lymphocytes
7. Neurological stability ≥ 30 days prior to screening and baseline
8. Contraception requirements

Key Exclusion Criteria

1. Treatment with anti-CD20 or B-cell directed treatment within last 12 months
2. Any previous treatment with alemtuzumab
3. Treatment with teriflunomide within 12 months (unless accelerated elimination procedure completed ≥ 90 days prior to screening)

4. Treatment with natalizumab or fingolimod within 90 days of screening
5. Treatment with glatiramer acetate, interferons, dimethyl fumarate, or glucocorticoids within 30 days of screening
6. Pregnant or nursing
7. ≥ 10 years disease duration if EDSS ≤ 2.0
8. Current evidence or history of infection including PML, tuberculosis, hepatitis B, hepatitis C, or HIV
9. Absolute neutrophil count or platelet count outside normal range
10. Absolute lymphocyte count $< 1000/\mu\text{L}$
11. Lack of immunity to varicella as determined by screening
12. Vaccination with live virus within 2 months of randomization

Study Treatment

The study included 6 treatment cohorts with 8 subjects each (6 randomized to ublituximab-xiiy, and 2 to placebo). Subjects randomized to ublituximab-xiiy received ublituximab-xiiy on Days 1, 15, and Week 24. Subjects randomized to placebo received placebo on Days 1 and 15, then switched to ublituximab-xiiy at Week 24. Each treatment cohort differed in dose and infusion time, and these parameters are described in Table 38.

Table 38 (Applicant). Study TG1101-RMS201 Dosing Regimen

Cohort	Randomization		Treatment Period	
	Subjects and treatment	Day 1/ infusion time	Day 15/ infusion time	Week 24/ infusion time
1	Placebo (n=2) ^b	Placebo / 4h	Placebo / 3h	-
	UTX (n=6)	150 mg / 4h	450 mg / 3h	450 mg / 1.5h
2	Placebo (n=2) ^b	Placebo / 4h	Placebo / 1.5h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1.5h	450 mg / 1h
3	Placebo (n=2) ^b	Placebo / 4h	Placebo / 1h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1h	600 mg / 1h
4	Placebo (n=2) ^b	Placebo / 3h	Placebo / 1h	-
	UTX (n=6)	150 mg / 3h	600 mg / 1h	600 mg / 1h
5	Placebo (n=2) ^b	Placebo / 2h	Placebo / 1h	-
	UTX (n=6)	150 mg / 2h	600 mg / 1h	600 mg / 1h
6	Placebo (n=2) ^b	Placebo / 1h	Placebo / 1h	-
	UTX (n=6)	150 mg / 1h	600 mg / 1h	600 mg / 1h

^a Additional cohorts may be evaluated at doses ranging from 25 mg up to 900 mg to further elucidate the level of B-cell depletion and recovery parameters in subjects with RMS

^b Following completion of Day 28, all placebo subjects will enter their respective "a" cohort and receive active treatment as described in Table 2 below. Further, the study evaluation table (section 7) will be restarted for these patients upon the initiation of active treatment with ublituximab-xiiy

Source: Study TG1101-RMS201 Protocol Version 8.0 (Table 1)

Subjects randomized to placebo began to receive ublituximab-xiiy after Day 28, starting a

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dosing regimen and infusion time identical to that of patients who initially received ublituximab-xiiy in their treatment cohort.

The protocol provided guidelines for infusion rate reduction or delay in the setting of severe infusion-related reactions. The protocol required that subjects have normal absolute neutrophil and platelet counts prior to ublituximab-xiiy infusion, as well as AST/ALT <5x ULN. Ublituximab-xiiy was held for up to 48 hours to allow normalization of lab values, and if normalization did not occur, the subject was withdrawn from the study.

Study Assessments

The schedule of assessments is summarized in Table 39.

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Table 39 (Reviewer). Study TG1101-RMS201 Schedule of Assessments

	Screening	Baseline																
Week	-4 to 0	1 (D1)	1 (D2)	2	3 (D15)	4	8	12	16	20	24	24 (2 days post-dose)	25	28	36	40	44	48
Ublituximab-xiiy/placebo infusion		X			X						X							
EDSS and neurological assessment	X	X									X							X
MRI	X										X							X
Blood collection for immunological assays	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantitative immunoglobulins		X						X			X				X			X
Adverse events (CTCAE v4.0)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X			X						X							
Routine safety labs (CBC, CMP, UA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: Adapted from Study TG1101-RMS201 Protocol Version 8.0 (10/10/2017)

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Relapse Assessment

The protocol defined relapses as “the occurrence of new or worsening neurological symptoms attributable to MS, immediately preceded by a stable or improving neurological state of at least 30 days,” that persist for more than 24 hours in the absence of fever, and are accompanied by objective neurological worsening consistent with an increase ≥ 0.5 on the EDSS (if baseline EDSS > 1.0) or an increase ≥ 1.0 on the EDSS (if baseline EDSS=0).

Relapse assessment was conducted by the treating investigator at each study visit. Subjects who experienced MS relapse was treated with intravenous methylprednisolone 1g daily for up to 5 days, and underwent an MRI 10 days after steroid treatment completion. Additionally, subjects were reconsented following a protocol-defined relapse.

Brain MRI

Brain MRIs with and without gadolinium contrast administration were obtained at screening, Week 24, and Week 48. Subjects who received placebo also underwent brain MRI at Week 4 (prior to the start of ublituximab-xiiy treatment). MRIs were evaluated locally for safety and non-MS pathology, and a report was provided to the treating physician.

Reviewer comment: The method for quantification of gadolinium-enhancing or new/enlarging T2 lesions is not described in the study protocol. The protocol does not mention central reading of MRIs for efficacy endpoints, but a “Central radiology group” at Icahn School of Medicine at Mount Sinai is included in the list of study personnel (Section 6 of CSR).

Study Endpoints

The primary endpoint was responder rate at Week 4, where responders were defined as subjects who experience $\geq 95\%$ B-cell depletion.

Reviewer comment: The applicant clarified via Information Request that the values utilized to determine the responder rate were percentage of CD19+ B-cells, rather than an absolute CD19+ B-cell count. The use of a percentage in this context is not appropriate, and it is therefore not possible to interpret the primary endpoint of this study. Additionally, the applicant indicated that absolute CD19+ B-cell count was not collected as part of this study, other than at the screening visit, so it is not possible to perform an appropriate analysis using absolute CD19+ B-cell count.

Secondary efficacy endpoints were:

- Number of new Gd-enhancing lesions at 24 and 48 weeks

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- Number of new or enlarging T2 lesions at 24 and 48 weeks
- Annualized relapse rate (ARR)
- Relapse rate reduction (RRR)
- Percent of relapse free subjects
- Reduction in B cells (CD19+), memory (CD19+CD27+) and naïve (CD19+CD27-) B cells at baseline, day 1 (pre dose) and 2; week 2; Day 15 (pre-dose); week 4 and every 4 weeks thereafter until the next infusion at week 24 (pre-dose and 2 days post-dose) 25, 28, 36, 40, 44 and 48
- To examine sustained B-cell reduction during the first and third infusions
- Additional immune profiling (CD4+, CD8+, IL10 and NK cells) at baseline, day 1 (pre dose) and 2; week 2, Day 15 (pre-dose); week 4 and every 4 weeks thereafter until the next infusion at week 24 (pre-dose and 2 days post dose) 25, 28, 36, 40, 44 and 48
- PK (ADME) profile of ublituximab-xiiy at day 1 (pre-dose); week 2; day 15 (pre-dose); weeks 4, 24 (pre-dose), and 25

Statistical Analysis Plan

Analysis Populations

The Intention-to-Treat population was defined as all registered subjects who received at least one dose of ublituximab-xiiy. The primary efficacy analysis was conducted in the ITT population.

The modified Intention-to-Treat (mITT) population was defined as all subjects who received ublituximab-xiiy and had one baseline and post-baseline MRI.

The safety population was defined as all subjects who received at least one dose of ublituximab-xiiy.

Primary Endpoint

The primary efficacy analysis (proportion of subjects who experienced $\geq 95\%$ B-cell depletion at Week 4) was conducted in the ITT population. The proportion of responders was presented, along with 95% confidence intervals.

Key Secondary Endpoints

Each secondary endpoint was summarized for all subjects using descriptive statistics. No comparisons were made between subjects randomized to ublituximab-xiiy or initial placebo.

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Protocol Amendments

There were 9 protocol amendments to the original Protocol TG1101-RMS201 from 9/17/2015, which are summarized in Table 40.

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Table 40 (Reviewer). Study TG1101-RMS201 Protocol Amendments

Protocol Version	Date	Changes	Patients randomized
1.0	9/17/2015	N/A	1
1.1	10/30/2015	12 Lead ECG will be performed pre- and post-dose on any day of infusion - Instead of 1.5T MRI, the study sites can use MRI machines ≥ 1.5 T	0
2.0	1/22/2016	- Further defined the unit of B cell count as a percentage of CD19+ - In synopsis, directed the investigator to section 7.1.1 for complete listing of laboratory assessments - Further defined PK and anti-drug- antibody (antibodies developed against ublituximab) collection instructions in trial synopsis and section 7.1.1, and added analysis time points at weeks 4, 16, and 48 - Quantitative immunoglobulin defined as IgA, IgM, IgG in section 7.1.1 - Treatment and subject enrollment scheme was amended with the addition of a placebo arm during the first 28 days. Following completion of Day 28, all placebo subjects will enter their respective "x" cohort and receive active treatment in Table 2 below. Cohort sizes were expanded to include 8 patients, of which 2 will be on placebo. Study title changed to include "Placebo-Controlled" in the title - Added two additional PK analysis time points at weeks 4 and 25 - Added fibrinogen level testing - Added a rescue clause in case subjects experience an MS relapse during the study - Excluded subjects vaccinated with live virus within 2 months of randomization - Added requirement for skilled personnel and adequate equipment at all sites to provide emergency treatment should subjects experience anaphylaxis, hypotension or respiratory distress - Changed directions for infusion interruptions: If there is a second interruption of treatment due to IRR (infusion related reaction) symptoms, ublituximab infusion must be stopped. The treating physician may decide whether to attempt completion of the infusion on a second day - The local radiologists will now review all MRI to identify any new clinically relevant abnormal MRI findings that are not consistent with the diagnosis of MS, with particular attention to the possibility of progressive multifocal leukoencephalopathy, and provide a report of the MRI to the treating physician. Further, physicians must obtain expert evaluations of brain MRI images of subjects with suspected opportunistic CNS infections including PML - Changed Per Protocol (PP) population to modified intent-to-treat population (mITT)	1

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		• Change in primary efficacy measure (% B cell depletion) to >95% • Delete cohort 4 • Possible cohort expansion to include 25 – 900 mg ublituximab	
2.1	3/14/2016	• Change the premedication requirement to the following: Pre-medicate approximately 30 minutes prior to each dose of ublituximab with an antihistamine (diphenhydramine 50 mg or equivalent), and corticosteroid (dexamethasone 10-20mg or equivalent). Oral acetaminophen, 650 mg (or equivalent; only used for intervention) should be restricted to patient who experience fever or pyrexia after week 1 dose, or as clinically warranted and additional medication (which needs to be documented) may be used at discretion of the physician if adverse reactions occur.	0
3.0	5/23/2016	• Modifications to EDSS assessment instructions to require the following: EDSS will be assessed based on a slightly modified neurological examination as fatigue will not contribute to the EDSS assessment • Will exclude subjects previously treated with alemtuzumab • Revised exclusion criteria for subjects previously treated with teriflunomide to the following: • Patients treated with teriflunomide within 12 months prior to screening. Exceptions will be subjects who have undergone accelerated/rapid elimination with oral activated charcoal or oral cholestyramine ≥ 90 days of screening	12
4.0	6/17/2016	• Section 8.1.1 was updated to include the most recent adverse event information related to sponsor study drugs	7
5.0	10/20/2016	• Added another cohort (cohort 4) to the study • In the evaluation table: Weeks 8 and beyond, collections/assessments may occur ±2 days from specified time points	4
6.0	12/13/2016	• Revised original cohort 4 to smaller number of subjects and after initial infusion time • Added 2 other cohorts (cohorts 5 and 6) to the study	18
7.0	4/24/2017	• Addition of relapse assessment into the study evaluation table in section 7. • Added the option for subjects completing the 48 week study, and fulfilling entry criteria, to enter into an open label extension study (this will be submitted as separate protocol: TG1101-RMS201E). This is mentioned in Synopsis: Study Duration, Section 4 (Duration of Therapy), Section 7 (Study Evaluation Table), and Section 7.1 (Overview).	5
8.0	10/10/2017	• Include information regarding a new vial size and concentration for ublituximab	0

Source: Applicant's response to Information Request, received 1/24/22

6.4.2. Study Results

Compliance with Good Clinical Practices

The Clinical Study Report submitted by the applicant states that the study was conducted in compliance with Good Clinical Practice guidelines, outlined in the International Council for Harmonisation E6 Tripartite Guideline and 21 CFR 312.

However, one site (Site CUA, which enrolled 10 subjects) was identified as having “significant Good Clinical Practice violations and other non-compliance issues” by the applicant. Subjects were transferred to Site WLA. Please refer to further discussion of these events under the *Protocol Violations/Deviations* section below. The applicant therefore conducted sensitivity analyses to assess the impact on study data.

Financial Disclosure

The applicant provided Form 3454 indicating that there were no financial arrangements with investigators whereby the value of compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a). No investigators had significant disclosed interest or were missing disclosure information for Study TG1101-RMS201. The applicant was not able to obtain disclosure information for one sub-investigator, and a form of Due Diligence was submitted with Form 3454. The explanation indicated that the sub-investigator did not complete a financial disclosure form prior to leaving the institution, and was added to an updated Form 1572 after trial initiation. See Section 13.3.

Patient Disposition

Fifty-six subjects signed informed consent, and 49 were randomized. Thirty-six subjects were randomized to ublituximab-xiiy, and 13 to placebo. Of the 13 subjects randomized to placebo, 12 were subsequently treated with ublituximab-xiiy; one subject was treated with placebo only and discontinued study participation due to an adverse event (low absolute lymphocyte count). Therefore, the placebo safety population included 13 subjects, and the ITT and safety (ublituximab-xiiy) populations included 48 subjects.

Forty-five subjects completed the treatment period (48 weeks) as planned. Three subjects (6.3%) prematurely discontinued study participation due to withdrawal by subject (n = 1), pregnancy (n = 1), and “missing” (n = 1).

Protocol Violations/Deviations

According to the applicant, 32 subjects (66.7%) experienced a major protocol deviation. The reasons for major protocol deviations included missing laboratory assessments (41.7%),

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inclusion/exclusion criteria not met (25.0%), informed consent (18.8%; delayed reconsenting), study procedures (12.5%), and investigational product compliance (8.3%).

As mentioned previously, one site (Site CUA, which enrolled 10 subjects) was identified as having “significant Good Clinical Practice violations and other non-compliance issues” by the applicant. An audit certificate was provided with this submission, indicating that an Investigator Site Audit was performed between 9/26/2017 and 9/28/2017. All 10 subjects enrolled at this site experienced major protocol violations, including screening B-cell count not being performed (100%), missing screening labs (30%), informed consent violations (40%), inclusion/exclusion criteria violations (40%), other labs missing (30%), and violations of trial procedures (30%, for example, study visits not done). Two subjects with a history of tuberculosis were enrolled in the trial, one subject with hepatitis C antibody positivity was enrolled, and one subject with prior rituximab use was enrolled.

Reviewer comment: The major protocol violations reported at Site CUA are concerning and have significant potential to affect the validity of trial results since 20.8% of the ITT population was enrolled at that site. The applicant conducted a sensitivity analysis excluding subjects from this site, the results of which are discussed below.

Table of Demographic Characteristics

Demographic characteristics for the ITT population (all subjects treated with ublituximab-xiiy) are presented in Table 41. Most subjects were female, Caucasian, non-Hispanic, and ≥40 years of age. All subjects were from the United States.

Table 41 (Reviewer). Study TG1101-RMS201 Demographics, ITT Population

	Initial Ublituximab-xiiy (N=36) n (%)	Initial Placebo ¹ (N=12) n (%)	All Ublituximab-xiiy (N=48) n (%)
Sex			
Male	26 (72.2)	6 (50.0)	16 (33.3)
Female	10 (27.8)	6 (50.0)	32 (66.7)
Age (years)			
Mean (SD)	40.2 (10.1)	37.1 (8.3)	39.4 (9.7)
Median (IQR)	44.0 (14.8)	37.0 (16.0)	42.5 (15.0)
Min, max	20, 56	27, 49	20, 56
Age Group			
≥ 18 to < 30 years	7 (19.4)	4 (33.3)	11 (22.9)
≥ 30 to < 40 years	9 (25.0)	2 (16.7)	11 (22.9)
≥ 40 years	20 (55.6)	6 (50.0)	26 (54.2)
Race			
White	30 (83.3)	9 (75.0)	39 (81.3)
Black or African American	4 (11.1)	3 (25.0)	7 (14.6)
Other	2 (5.6)	0 (0)	2 (4.2)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	0 (0)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Ethnicity			
Not Hispanic or Latino	29 (80.6)	10 (83.3)	39 (81.3)
Hispanic or Latino	7 (19.4)	2 (16.7)	9 (18.8)
Region			
United States	36 (100.0)	12 (100.0)	48 (100.0)
Rest of World	0 (0)	0 (0)	0 (0)

¹One patient initially received placebo and withdrew from the study due to an adverse event, and therefore was not included in the ITT population (did not receive ublituximab-xiiy)

Source: ADSL for TG1101-RMS201, ITTFL=Y; Tabulated by TRT01A

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline clinical characteristics and disease characteristics for the ITT population are presented in

Table 42 and Table 43, respectively. The initial placebo and initial ublituximab-xiiy groups appeared to be similar in terms of height, weight, BMI, time since diagnosis, and time since last relapse. The placebo group had more relapses in the year prior to screening, but interpretation of this difference is limited by small sample size of this group. Additionally, per the applicant's CSR, most subjects (62.5%) had no gadolinium-enhancing lesions at baseline.

Table 42 (Reviewer). Study TG1101-RMS201 Clinical Characteristics (ITT Population)

	Initial Ublituximab-xiiy (N=36)	Initial Placebo ¹ (N=12)	All Ublituximab-xiiy (N=48)
Height (cm)			
Mean (SD)	169.6 (9.4)	172.3 (8.4)	170.3 (9.1)
Median (IQR)	167.6 (14.6)	172.4 (11.7)	168.5 (13.9)
Min, max	154.9, 190.5	157.5, 185.4	154.9, 190.5
Weight (kg)			
Mean (SD)	90.1 (23.7)	90.3 (23.3)	90.2 (23.4)
Median (IQR)	94.4 (35.9)	87.3 (38.9)	91.3 (36.4)
Min, max	54.4, 145.1	60.9, 129.3	54.4, 145.1
BMI (kg/m ²)			
Mean (SD)	31.2 (7.2)	30.4 (7.4)	31.0 (7.2)
Median (IQR)	31.0 (10.1)	28.3 (10.9)	30.5 (10.1)
Min, max	17.7, 48.7	20.6, 45.7	17.7, 48.7

¹One patient initially received placebo and withdrew from the study due to an adverse event, and therefore was not included in the ITT population (did not receive ublituximab-xiiy)

Source: ADSL for TG1101-RMS201, ITTFL=Y; Tabulated by TRT01A

Table 43 (Reviewer). Study TG1101-RMS201 Disease Characteristics, ITT Population

	Initial Ublituximab-xiiy (N=36)	Initial Placebo ¹ (N=12)	All Ublituximab-xiiy (N=48)
Time since MS diagnosis (years)			
Mean (SD)	7.6 (7.6)	8.3 (9.8)	7.8 (8.0)
Median (IQR)	3.8 (13.0)	5.2 (14.4)	4.3 (13.1)
Min, max	0.15, 25.9	0.21, 30.0	0.15, 30.0
Time since last relapse (months)			
Mean (SD)	5.8 (5.2)	6.1 (7.3)	5.8 (5.8)
Median (IQR)	4.1 (3.5)	3.5 (4.3)	3.9 (3.7)
Min, max	1.7, 28.3	1.8, 26.7	1.7, 28.3
# relapses in year prior to screening			
Mean (SD)	1.2 (0.7)	2.3 (1.3)	1.5 (1.0)
Median (IQR)	1.0 (1.0)	2.0 (2.0)	1.0 (1.0)
Min, max	0, 3	1, 5	0, 5
Baseline EDSS (EDSS)			
Mean (SD)	2.5 (1.3)	2.4 (1.4)	2.5 (1.3)
Median (IQR)	2.5 (1.4)	2.3 (1.9)	2.5 (1.5)
Min, max	0, 6	1, 6	0, 6
≤3.5 (n (%))	32 (88.9)	11 (91.2)	43 (89.6)
>3.5 (n (%))	4 (11.1)	1 (8.3)	5 (10.4)

¹One patient initially received placebo and withdrew from the study due to an adverse event, and therefore was not included in the ITT population (did not receive ublituximab-xiiy)

Source: ADSL for TG1101-RMS201, ITTFL=Y; Tabulated by TRT01A

Per the applicant's CSR, 62.5% of subjects in the ITT population had received any MS therapy in the past 5 years. The most commonly used MS therapies in the 5 years prior to trial enrollment were dimethyl fumarate (25.0%), fingolimod (25.0%), glatiramer acetate (18.8%), natalizumab (18.8%), interferon beta-1a (14.6%), and interferon beta-1b (6.3%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Per the applicant's CSR, in the safety population, 93.8% of subjects received all 3 planned infusions of ublituximab-xiiy; 6.3% of subjects completed 2 infusions.

Concomitant Medications

Per the applicant's CSR, the most commonly utilized concomitant medications in the ITT population were diphenhydramine hydrochloride (58.3%), vitamin D (45.8%), methylprednisolone (41.7%), diphenhydramine (39.6%), ibuprofen (39.6%), paracetamol

(39.6%), and dexamethasone (29.2%).

Per the applicant's CSR, the most commonly utilized follow-up medications in the ITT population were glucocorticoids (31.3%, specifically methylprednisolone [18.8%], methylprednisolone sodium succinate [6.3%], and prednisone [4.2%]), vitamin D (58.3%), ibuprofen (33.3%), multivitamins (27.1%), diphenhydramine (25.0%), vitamin B12 (22.9%), gabapentin (22.9%), paracetamol (20.8%), and baclofen (20.8%).

Rescue Medications

The ADCM dataset contained a CSRELF variable, which served as a flag for corticosteroid therapy for MS relapse. However, all rows with CSRELF=Y were either prophylactic corticosteroids used for infusion pre-medication (100mg IV methylprednisolone), asthma treatment, or prior corticosteroid relapse treatment.

Reviewer comment: It does not appear that any subjects enrolled in this study received corticosteroids for relapse. However, the CSR indicates that 4 confirmed relapses occurred in this study. The reason for this discrepancy is not clear.

Efficacy Results – Primary Endpoint

The primary endpoint was the B-cell responder rate (defined as B-cell depletion $\geq 95\%$) in the ITT population at Week 4. B-cell depletion was based upon the CD19+ B-cell ratio, which is not considered interpretable. Absolute CD19+ B-cell count should have been used to determine B-cell depletion and calculate a responder rate.

Reviewer comment: The applicant clarified via Information Request that the values utilized to determine the responder rate were percentage of CD19+ B-cells, rather than an absolute CD19+ B-cell count. The use of a percentage in this context is not appropriate, and it is therefore not possible to interpret the primary endpoint of this study. Additionally, the applicant indicated that absolute CD19+ B-cell count was not collected as part of this study, other than at the screening visit, so it is not possible to perform an appropriate analysis using absolute CD19+ B-cell count.

As mentioned previously, one site (Site CUA, which enrolled 10 subjects) was identified as having "significant Good Clinical Practice violations and other non-compliance issues" by the applicant. The applicant therefore conducted sensitivity analyses to assess the impact to study data, and found that there were no meaningful differences in the results with inclusion of this site.

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Data Quality and Integrity

One site (Site CUA, which enrolled 10 subjects) was identified as having “significant Good Clinical Practice violations and other non-compliance issues” by the applicant. Subjects were transferred to Site WLA. The applicant therefore conducted sensitivity analyses to assess the impact to study data.

Otherwise, no issues regarding data quality or integrity were identified.

Efficacy Results – Secondary and other relevant endpoints

Secondary efficacy endpoints were not reviewed in detail for this study. The applicant indicated that 4 confirmed relapses occurred during the study, and that 91.7% of subjects were relapse-free at the end of the study.

Dose/Dose Response

Though this study involved administration of multiple doses of ublituximab-xiiy, the issues with the primary endpoint (CD19+ B-cells) preclude evaluation of a dose response. This study was not designed to evaluate a potential dose response for clinical endpoints.

Durability of Response

The design of this study was not intended to evaluate durability of response. Therefore, this section is not applicable.

Persistence of Effect

The design of this study was not intended to evaluate persistence of effect. Therefore, this section is not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Both Studies TG1101-RMS301 and TG1101-RMS302 met their primary efficacy endpoint, annualized relapse rate, demonstrating a significant reduction in ARR in subjects who received ublituximab-xiyy compared to those on teriflunomide (Table 44). The ARR ratio for ublituximab-xiyy compared to teriflunomide was 0.41 for Study TG1101-RMS301 and 0.50 for Study TG1101-RMS302.

Table 44 (Reviewer). Summary of Efficacy Results, Studies TG1101-RMS301 and TG1101-RMS302

	Study TG1101-RMS301			Study TG1101-RMS302		
	Ublituximab-xiyy (N=271)	Teriflunomide (N=274)	Ratio	Ublituximab-xiyy (N=272)	Teriflunomide (N=272)	Ratio
Unadjusted group ARR	0.09	0.23	0.41 (95% CI 0.28 to 0.59)	0.11	0.22	0.50 (95% CI 0.35, 0.70)
Number (%) of patients who experienced confirmed relapse	36 (13.3)	68 (24.8)	NA	34 (12.5)	72 (26.5)	NA
Total # gadolinium-enhancing lesions per subject per MRI by Week 96						
Mean (SD)	0.03 (0.1)	0.82 (1.8)	0.033 (95% CI 0.019 to 0.058)	0.04 (0.2)	0.88 (2.2)	0.035 (95% CI 0.019 to 0.064)
Total # new/enlarging T2 lesions per MRI by Week 96						
Mean (SD)	0.35 (0.7)	4.3 (7.7)	0.076 (95% CI 0.056, 0.104)	0.50 (1.1)	4.66 (7.7)	0.100 (95% CI 0.073, 0.136)

7.1.2. Secondary and Other Endpoints

Both Studies TG1101-RMS301 and TG1101-RMS302 met their key secondary efficacy endpoints, total number of gadolinium-enhancing lesions and new/enlarging T2 hyperintense lesions, demonstrating a significant reduction in MRI lesions in subjects who received ublituximab-xiyy compared to those on teriflunomide (Table 44). However, a significant effect on 12- and 24-week CDP was not demonstrated across the pooled studies.

Other secondary endpoints discussed in Sections 6.1.2 and 6.2.2 are not accepted clinical endpoints, but are considered supportive of the primary efficacy finding. These endpoints included the proportion of subjects with NEDA from Week 24 to 96, the proportion of subjects reaching impaired SDMT from baseline to Week 96, and percentage change in brain volume from baseline to Week 96. Ublituximab-xiyy was statistically superior to teriflunomide in terms

of the NEDA endpoint, but not SDMT or brain volume endpoints.

7.1.3. Subpopulations

Subgroup analysis for ARR was conducted by the applicant and Xiang Ling, PhD, FDA Statistical Reviewer. According to the FDA Statistical Review, the rate ratio for ARR was generally similar across subgroups based on sex and age category (Table 45). The subpopulation analysis by region did suggest benefit of teriflunomide over ublituximab-xiiy in the US/Western Europe population, which contradicted the main analysis, but this analysis is limited by small sample size. There is no biological plausibility for a differential effect of an anti-CD20 therapy in the US/Western Europe population compared to an Eastern European population. The Statistical Review also indicated that this result was inconclusive and likely limited by small sample size. Meaningful subpopulation analysis by race was precluded by the small number of non-Caucasian participants enrolled in the clinical studies.

Table 45 (Reviewer). Annualized Relapse Rate Subgroup Analysis

	Study TG1101-RMS301					Study TG1101-RMS302				
	Ublituximab-xiiy		Teriflunomide		Rate Ratio	Ublituximab-xiiy		Teriflunomide		Rate Ratio
	N	ARR	N	ARR		N	ARR	N	ARR	
Sex										
Female	166	0.104	179	0.175	0.594	178	0.093	176	0.179	0.523
Male	105	0.038	95	0.188	0.201	94	0.085	96	0.172	0.493
Region										
US & Western Europe	26	0.281	31	0.046	6.137	27	0.255	22	0.024	10.84
Eastern Europe	245	0.100	243	0.285	0.350	245	0.118	250	0.257	0.458
Age Category										
<38 yrs.	150	0.079	146	0.336	0.235	176	0.083	156	0.206	0.401
≥38 yrs.	121	0.075	128	0.082	0.907	96	0.101	116	0.135	0.750

Source: Statistical Review by Xiang Ling, PhD

7.1.4. Dose and Dose-Response

Not applicable, as one dose was studied in the pivotal trials.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Ublituximab-xiiy appears to have a relatively rapid onset of clinical effects, as subjects on ublituximab-xiiy experienced a rapid depletion in CD19+ B-cells, reduction in MRI lesion activity, and few relapses. As discussed in the sections above, these studies were not designed to

evaluate duration and durability of efficacy effects, but it appears that the B-cell depletion associated with ublituximab-xiiy, which is presumed to result in its clinical benefit on relapses, was durable throughout the study.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are no specific considerations for the benefit in the postmarket setting.

7.2.2. Other Relevant Benefits

There are no additional relevant benefits.

7.3. Integrated Assessment of Effectiveness

Ublituximab-xiiy demonstrated clear, statistically significant, and robust efficacy findings on ARR, gadolinium-enhancing lesions, and new/enlarging T2 hyperintense lesions compared to teriflunomide.

8. Review of Safety

8.1. Safety Review Approach

The safety review will focus on the double-blind portion of the Phase 3 Studies TG1101-RMS301 and TG1101-RMS302, as well as their open-label extension (TG1101-RMS303). The results of Study TG1101-RMS201 and its open label-extension, TG1101-RMS201E, will be discussed as well. The applicant's Integrated Summary of Safety was separated into Phase 2 and Phase 3 datasets, as previously agreed upon by the Division.

Following Division feedback at the pre-BLA meeting, the definition of a treatment-emergent adverse event (TEAE) was revised to "AEs with an onset on, or after the first dose of study medication or with an onset prior to the first dose of study medication that increases in severity on, or after the first dose of study medication

The applicant-provided datasets were initially evaluated by the Office of Computational Science (OCS) JumpStart team, and no major issues were identified. Dr. Rui Li, Senior Clinical Analyst, performed several of the reported safety analyses in conjunction with this reviewer.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

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The overall number of RMS subjects exposed to any ublituximab-xiyy dose and the duration of exposure are provided in Table 46; the safety database includes 964 subjects who received ublituximab-xiyy. Five-hundred and seven subjects were exposed to the proposed clinical dose regimen of ublituximab-xiyy for one year or more (Table 47).

Table 46 (Reviewer). Overall Exposure to Ublituximab-xiyy

Safety Database for the Study Drug			
Individuals exposed to any treatment in this development program for the indication under review N=1512			
Clinical Trial Groups	Ublituximab-xiyy (n=964)	Teriflunomide (n= 548)	Placebo (n= 0)
Healthy volunteers	0	0	0
Controlled trials conducted for this indication (Studies TG1101-RMS201, TG1101-RMS301 and TG1101-RMS302)	593	548	13
All other trials conducted for this indication (TG1101-RMS201E, TG1101-RMS303) ¹	371	0	0

¹ For Study TG1101-RMS303, only subjects who switched to ublituximab-xiyy from teriflunomide; Subjects in TG1101-RMS201 were all treated with ublituximab-xiyy during the main study period and therefore were not counted also for the extension study.
 Source: Applicant's response to Information Request received on 5/5/2022

Table 47 (Reviewer). Exposure to Ublituximab-xiyy by Duration, ISS

Dosage	Number of patients exposed to ublituximab-xiyy				
	≥ 1 dose	≥ 6 months	≥ 12 months	≥18 months	≥ 24 months
<i>Proposed dosing regimen</i>	868	522	507	319	316
<i>Other dosing regimens</i>	48	43	40	39	38

Source: Applicant's response to Information Request received on 5/5/2022, data cutoff 11/23/2020

Per the 120 Day Safety Update, the median number of ublituximab-xiyy infusions among subjects who received ublituximab-xiyy in the parent study increased from 6.0 (range 1 to 8) to 8.0 (range 1 to 9). As of the 120 Day Safety Update, 260 subjects who received ublituximab-xiyy in the parent study had received 8 infusions, and 14 received 9 infusions (reflecting up to 4 years of exposure). Among subjects who received teriflunomide in the double-blind treatment period, the median number of infusions was 3 (range 1 to 5), and 68.4% of subjects received at least 3 infusions. In the Phase 2 studies (TG1101-RMS201 and RMS201E), the median number of infusions was 10.

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8.2.2. Relevant characteristics of the safety population

The demographic characteristics of the pooled, controlled safety population from Studies TG1101-RMS301 and TG1101-RMS302 are listed in Table 48. The characteristics are well balanced by treatment group and typical of an RMS population.

Table 48 (Reviewer). Studies TG1101-RMS301 and TG1101-RMS302, Pooled Demographic Characteristics (Safety Population)

	Ublituximab-xiiy (N=545) n (%)	Teriflunomide (N=548) n (%)	Total (N=1093) n (%)
Sex			
Female	345 (63.3)	356 (65.0)	701 (64.1)
Male	200 (36.7)	192 (35.0)	392 (35.9)
Age (years)			
Mean (SD)	35.4 (8.6)	36.6 (9.3)	36.0 (9.0)
Median (IQR)	35.0 (14.0)	36.0 (14.0)	36.0 (14.0)
Min, max	18, 55	18, 55	18, 55
Age Group			
≥ 18 to < 30 years	154 (28.3)	127 (23.2)	281 (25.7)
≥ 30 to < 40 years	219 (40.2)	210 (38.3)	429 (39.3)
≥ 40 years	172 (31.6)	211 (38.5)	383 (35.0)
Race			
White	535 (98.2)	536 (97.8)	1071 (98.0)
Black or African American	8 (1.5)	9 (1.6)	17 (1.6)
Other	1 (0.2)	3 (0.6)	4 (0.4)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0 (0)	1 (0.1)
Asian	0 (0)	0 (0)	0 (0)
American Indian or Alaska Native	0 (0)	0 (0)	(0)
Ethnicity			
Not Hispanic or Latino	524 (96.2)	530 (96.7)	1054 (96.4)
Hispanic or Latino	13 (2.4)	5 (0.9)	18 (1.7)
Not reported/Unknown	8 (1.5)	13 (2.4)	21 (1.9)
Region			
United States	40 (7.3)	44 (8.0)	84 (7.7)
Rest of World	505 (92.7)	504 (92.0)	1009 (92.3)
Eastern Europe	492 (90.3)	495 (90.3)	987 (90.3)
Western Europe	13 (2.4)	9 (1.6)	22 (2.0)
Canada	0 (0)	0 (0)	0 (0)
South America	0 (0)	0 (0)	0 (0)
Asia	0 (0)	0 (0)	0 (0)
Africa	0 (0)	0 (0)	0 (0)

Source: ADSL for TG1101-RMS301 and TG1101-RMS302, SAFFL=Y; Tabulated by TRT01A

8.2.3. Adequacy of the safety database

The ublituximab-xiiy RMS trial safety database is adequately sized with a sufficient number of patients treated for an appropriate duration to assess safety. The demographic characteristics of the RMS trial patients were similar to the intended treatment population, although there

were limited patients in the extremes of ages and in race groups other than White.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The level of clinically relevant details provided in narratives submitted with this BLA was limited. Review of pertinent events required reference to CRFs and information previously submitted to the IND (specifically the response to Information Request regarding serious infections, submitted to IND 127265 on 12/5/2019, SDN 103). Additionally, Information Requests sent to the applicant on 2/22/2022 and 3/8/2022 requested revised SAE narratives, as the Patient Profiles that the applicant referenced also did not provide an adequate level of detail. Specifically, the applicant was asked to revise narratives that include a "chronological, detailed, and integrated account of clinical symptoms, laboratory results, radiology results, as well as the subject's clinical course." The applicant responded on 3/25/2022 for ublituximab-xiiy-treated subjects and on 4/1/2022 for teriflunomide-treated subjects. This information, which was considered a Major Amendment because it contained new information that obligated additional review time, is incorporated into the narratives discussed in Section 8.4.2.

The application of CTCAE severity grading in these trials was also problematic. In Study TG1101-RMS301, 25 of 59 SAEs were rated as CTCAE Grade 1 (n = 6) or 2 (n = 19), which is not appropriate, as SAEs by definition are considered Grade 3 or above. In Study TG1101-RMS302, 33 of 59 SAEs were rated as CTCAE Grade 1 (n = 8) or 2 (n = 25). An Information Request was sent to the applicant on 3/28/2022 to request an explanation for the discrepant CTCAE grading for SAEs designated as < Grade 3. The applicant responded on 5/5/2022, indicating that AE grading was provided by Study Investigators, and that training and guidance regarding such reporting and grading was provided by the applicant. Additionally, the applicant stated that in some countries, hospitalization is standard for access to care, so hospitalization may trigger an AE to be considered serious per the protocol definition, but did not contribute to the severity grading of the AE. In some cases, the applicant was not able to confirm investigator grading based on available information. The applicant indicated that SAEs designated as Grade 1 or 2 was relatively balanced across the treatment arms (50% ublituximab-xiiy and 48% teriflunomide).

The applicant subsequently conducted a sensitivity analysis in response to this IR, in order to determine whether the overall safety conclusions would change if all Grade 1 or 2 SAEs were considered Grade 3. With this updated grading, the percentage of subjects receiving ublituximab-xiiy who experienced a $\geq$ Grade 3 TEAE under the Infections and Infestations SOC increased from 3.7% to 5.0% (versus 2.0% to 3.1% for teriflunomide). The overall safety conclusions did not appear to be affected.

Reviewer comment: We acknowledge the applicant's explanation for the discrepancies,

but upon review, we disagree with the assigned severity of these events based on inconsistency with established CTCAE severity definitions. However, it does not appear that the overall safety conclusions would change based upon this issue.

Additionally, for both deaths and SAEs related to infections, the applicant consistently assessed causality as not related to ublituximab-xiiy, even though infection is a known risk of other anti-CD20 monoclonal antibody therapies and therefore would be presumed to be a risk with ublituximab-xiiy. The data submitted in this BLA do provide adequate evidence of ublituximab-xiiy acting as an immune suppressant. This lack of attribution was especially evident with serious cases of COVID-19, as the applicant attributed the events to “exposure to infected contacts in the novel COVID-19 pandemic” in safety reports submitted to IND 127265 and did not acknowledge a role of ublituximab-xiiy in the severity of infection or interference with vaccine response.

Reviewer comment: Infections are a known risk with immunosuppressant treatment such as ublituximab-xiiy, and the lack of insight from the applicant regarding this relationship was concerning. This clinical safety review concludes that ublituximab-xiiy is an immune suppressant and that labeling should enumerate the risk of infection with ublituximab-xiiy.

8.3.2. Categorization of Adverse Events

8.3.3. Routine Clinical Tests

Routine hematologic tests included complete blood counts (CBC) with differential, including white blood cell, absolute neutrophil, and lymphocyte counts. Absolute CD19+ B-cell counts were regularly assessed in Studies TG1101-RMS301 and 302, but not TG1101-RMS201. Clinical chemistry included basic metabolic panels (BMP), liver function testing (AST, ALT, bilirubin, ALP), amylase, and lipase. Total IgG and IgM were collected at regular intervals. Timing of key safety assessments is provided in Table 4.

8.4. Safety Results

8.4.1. Deaths

Study TG1101-RMS301

Two deaths occurred in Study TG1101-RMS301, both in the ublituximab-xiiy group (0.7%).

1. Subject (b) (6) was a 32 year-old woman with no medical history receiving ublituximab-xiiy who experienced the SAEs measles and encephalitis (“acute encephalitis of infectious-allergic etiology [post-measles, post-rubella]”) and died on (b) (6). She

received ublituximab-xiyy on [REDACTED] (b) (6)

She was hospitalized [REDACTED] (b) (6) after developing the SAE measles on [REDACTED] (b) (6) (Study Day 365). Her symptoms initially included generalized weakness and rhinorrhea, then on [REDACTED] (b) (6) she developed rash, fever, headache, cough, and conjunctivitis leading to hospitalization due to measles. Chest X-ray was normal. She was also diagnosed with acute bronchitis.

She was vaccinated against measles during childhood per local standards, but no further vaccinations were administered in adulthood and no antibody titers were measured.

Treatment for this SAE [REDACTED] (b) (6) included ceftriaxone, dexamethasone, furosemide, metoclopramide hydrochloride, sorbitol, fluconazole, unspecified herbal and traditional medicine, and tobramycin. The event was considered recovered/resolved on [REDACTED] (b) (6) and the subject was discharged from the hospital.

She then experienced an investigator-confirmed MS relapse on [REDACTED] (b) (6) which was characterized by left sided weakness and ataxia, gait ataxia, and left hand muscle cramps ("hyperkinesia of the left hand") beginning on [REDACTED] (b) (6). She presented for an unscheduled study visit on [REDACTED] (b) (6), at which time the treating neurologist confirmed a relapse.

Brain MRI was notable for "microfocal brain lesion, which was characteristic of demyelinating disease, stable disease type, non-active phase. In the centrum semiovale, multiple demyelinating lesions from 3 mm to 11 mm were detected in the periventricular brain white matter. Some lesions were T1 hypointense lesions, which indicates that they are old. Similar lesions with indistinct boundaries were noted in the infratentorial region at the level of the middle cerebellar peduncles and in the dorsal region of the pons. Following IV contrast, no signs of pathological gadolinium contrast uptake were detected."

She was treated for this MS relapse from [REDACTED] (b) (6) with methylprednisolone. On [REDACTED] (b) (6), she experienced tonic-clonic seizures with loss of consciousness and was hospitalized. She underwent lumbar puncture, and CSF analysis results were "colorless, transparent, protein 0.166, chlorides 138, glucose 3.8, and cytosin 3." Her neurological examination was notable for end-gaze horizontal nystagmus on left gaze, diplopia, left-sided spasticity, and "involuntary compulsive movement of the left limbs and occasional clonic seizures." EEG on [REDACTED] (b) (6) revealed "irritations effects, signs of convulsive readiness of the brain and high threshold of excitability."

Due to her worsening condition and suspicion of encephalitis, she was transferred to another hospital on [REDACTED] (b) (6). She was noted to be conscious, oriented to time and place,

and had "compulsive movements of the left limbs." Repeat lumbar puncture on [REDACTED] (b) (6) was notable for pink and cloudy CSF, with a neutrophilic pleocytosis (22, units not provided), "RBCs per whole field of view," protein "0.495g" (presumably g/L, normal), glucose 4.0 mmol/L (normal), negative HSV-1/2, CMV, EBV, and Parvovirus B19. She worsened despite receiving antiviral therapy.

She was transferred to another hospital on [REDACTED] (b) (6) due to worsening condition and seizures, and was noted to have tonic-clonic seizures every 10 minutes. Progressive multifocal leukoencephalopathy (PML) was suspected, but brain MRI was not performed due to severe seizures. She was also diagnosed with left sided pneumonia, hydrothorax, and mediastinitis on [REDACTED] (b) (6) then bilateral pneumonia on [REDACTED] (b) (6).

She became comatose on [REDACTED] (b) (6), and repeat CSF was collected for JCV testing. She began treatment with IVIg on [REDACTED] (b) (6). She remained comatose and required mechanical ventilation. She experienced dermatitis of the face and cheilitis of unclear etiology. CSF JCV PCR was negative on [REDACTED] (b) (6). Measles virus PCR was negative (presumably CSF) on [REDACTED] (b) (6). Rubella IgM was negative, and IgG was positive on [REDACTED] (b) (6).

Laboratory evaluations during this hospitalization [REDACTED] (b) (6) were notable for leukocytosis (WBC 18.1 x10⁹/L), lymphopenia (ALC 0.4 x10⁹/L), and IgG 28.58 g/L (2858 mg/dL, likely elevated post-IVIg).

Non-serious concomitant TEAEs during this event included breast disorder (since [REDACTED] (b) (6)), dyskinesia, respiratory failure, pneumonia aspiration, pleurisy, dermatitis, cheilitis, amylase increased, sinus tachycardia, pericardial effusion, arteriosclerotic retinopathy, and dermal cyst. Treatment for this SAE [REDACTED] (b) (6) included diazepam, mannitol, furosemide, valproic acid, acyclovir, dexamethasone, IVIg, fluconazole, omeprazole, cefepime, trazodone, clemastine fumarate, prednisolone, pantoprazole, thiopental sodium, valaciclovir, nadroparin, paracetamol, imipenem, levetiracetam, methimazole, pRBCs, diclofenac, acetazolamide, and amiodarone. She also experienced the AE bilateral inferior pneumonia (aspiration) on [REDACTED] (b) (6), for which she received amikacin, ceftazidime, and linezolid.

Her condition continued to worsen, pneumonia worsened on chest X-ray, and she required artificial ventilation on [REDACTED] (b) (6). She died on [REDACTED] (b) (6). She was ultimately diagnosed with post-measles encephalitis (Preferred Term: encephalitis, verbatim term: "acute encephalitis of infectious-allergic etiology (post-measles, post-rubella)"). Autopsy findings included acute meningoencephalitis (possibly of measles, rubella etiology), bilateral interstitial giant cell pneumonia, disseminated intravascular coagulation, bilateral fibrinous pleuropneumonia, encephalomalacia, bilateral hydrothorax, and hydropericarditis. The direct cause of death was reported as "total encephalomalacia...having developed due to

brain coma and continuous artificial ventilation therapy.”

The investigator assessed the event encephalitis at not related to study drug.

Reviewer comment: Please note that the narrative provided in the BLA submission lacked many relevant clinical details, and some of the information reported above was provided in a Response to Information Request regarding serious infections under IND 127265, received on 12/5/2019 (SDN 103), then via Response to Information Request under this BLA received on 3/31/2022.

The timing of her encephalitis presentation a few weeks following measles raises suspicion for post-measles acute disseminated encephalomyelitis (ADEM), as measles encephalitis typically occurs within a few days of the rash. In contrast, subacute sclerosing panencephalitis (SSPE) presents years after the initial infection. Post-measles ADEM occurs in up to 1 in 1000 measles cases, and is associated with up to 25% mortality.²⁴ However, the lack of gadolinium enhancement on brain MRI is slightly atypical for ADEM, but may be confounded by recent steroid administration for a presumed MS relapse. Patients with ADEM generally have lymphocytic pleocytosis and elevated protein, but this patient was noted to have neutrophilic pleocytosis and normal protein.

Giant cell interstitial pneumonia is a rare complication of measles that can develop in immunocompromised patients.

This event is unusually severe and unexpected for an otherwise healthy young woman with RMS. Post-measles encephalitis/ADEM is a definite possibility, but atypical features raise suspicion for other infectious or autoimmune etiologies. It is likely that ublituximab-xiyy contributed to the patient's immunocompromised status and therefore is likely associated with the initiation and severity of this event.

2. Subject (b) (6) was a 22 year-old woman with no medical history receiving ublituximab-xiyy who experienced the SAEs ectopic pregnancy and salpingitis (“left-sided purulent salpingitis”) and died on (b) (6). She received ublituximab-xiyy on (b) (6)

She was found to have ectopic pregnancy in (b) (6), resulting in hospitalization following ultrasound on (b) (6). She underwent left-sided tubotomy and salpingostomatoplasty, and the event was reported recovered/resolved upon hospital discharge on (b) (6). She was also noted to have anemia at the time, with hemoglobin 90 g/L.

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Per the MedWatch reports (UA-PSI-2020- (b) (6), UA-PSI-2020- (b) (6) and UA-PSI-2020- (b) (6) submitted to IND 127265 on (b) (6) (SDN 195) in response to an Information Request, it appears that this subject did not return for her post-surgical 1-month follow-up. She developed left lower abdominal pain, nausea, vomiting, fever, and constipation in early (b) (6), and her condition deteriorated leading to hospitalization.

On (b) (6), she was hospitalized for salpingitis and infected post-surgical wound, with infiltrate of the abdominal cavity, partial intestinal obstruction, and "endogenic intoxication." She received treatment with broad spectrum antibiotics, and underwent left-sided tubotomy and abscess drainage, then three repeat laparotomies (b) (6) (b) (6)). Treatment included ceftriaxone, metronidazole, ciprofloxacin, fluconazole, furosemide, paracetamol, morphine, cefotaxime, prednisolone, gentamicin, amikacin, and meropenem. She died on (b) (6).

Autopsy on (b) (6) indicated that the cause of death was "sepsis, toxicosis, perforation of the sigmoid colon and small intestine, peritonitis, pelvioperitonitis, abdominal abscesses and left-sided purulent salpingitis." Left-sided purulent salpingitis was listed as the main cause of death, and the other findings were listed as complications. Bilateral abscess-forming lower lobe pneumonia, septic splenic hyperplasia, and cachexia were also documented.

The investigator assessed the event at not related to study drug.

Reviewer comment: Again, this event is unusually severe and unexpected for an otherwise healthy young woman with RMS. Though the lack of post-surgical follow-up likely contributed to evolution to severe infection, immunosuppression from ublituximab-xiyy likely also contributed to the development and severity of infection.

Please note that the narrative provided in the BLA submission lacked many relevant clinical details, and the information reported above was provided in a Response to Information Request under IND 127265, received on 8/25/2020 (SDN 195), then a Response to Information Request for this BLA received on 3/31/2022.

Study TG1101-RMS302

One death occurred in Study TG1101-RMS302 in a subject receiving ublituximab-xiyy. Subject (b) (6) was a 36 year-old man with a history of chronic sinusitis and maxillary sinus cyst (since 2016) who experienced the SAE pneumonia (verbatim term "bilateral purulent pneumonia with confluent foci") and died on (b) (6). He received ublituximab-xiyy on (b) (6).

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He experienced the SAE pneumonia (Grade 5) on [REDACTED] (b) (6) (Study Day 476) after presenting with cough and fever. He experienced shortness of breath, decreased exercise tolerance, and elevated body temperature for 7 to 10 days prior to hospitalization. He was hospitalized on [REDACTED] (b) (6), following outpatient treatment with azithromycin, due to dyspnea, cyanosis, and diffuse edema. Vital signs included blood pressure of 90/60 mmHg and heart rate of 115 bpm. Other ongoing TEAEs included prostatitis, pulmonary edema, hydrothorax, gastric ulcer, pancreatitis hemorrhagic, tracheobronchitis, and left ventricular hypertrophy. Laboratory results were notable for leukocytosis (WBC 13.4 x 10⁹/L) and elevated ESR of 22 mm/msec.

Treatment for this SAE included azithromycin, paracetamol, arginine, meldonium, meropenem, enoxaparin, digoxin, epinephrine, dexamethasone, metronidazole, and electrolyte solutions. Despite treatment, his condition worsened.

He died on [REDACTED] (b) (6) and the autopsy listed the direct cause of death as pulmonary and cardiac insufficiency as a complication of bilateral purulent pneumonia with confluent foci. Autopsy findings included bilateral purulent pneumonia with confluent foci, purulent tracheobronchitis, edema and swelling of the brain matter, "parenchymatous degeneration and venous congestion of internal organs, pulmonary edema, bilateral hydrothorax, acute gastric ulcers, and fine-focal hemorrhagic edematous pancreatitis."

The investigator assessed this event as possibly related to ublituximab-xiiy.

Reviewer comment: Again, this event is unusually severe and unexpected for an otherwise healthy young man with RMS. Immunosuppression from ublituximab-xiiy likely also contributed to the development and severity of infection.

Please note that the narrative provided in the BLA submission lacked many relevant clinical details (e.g., autopsy findings, symptoms), and the information reported above was provided in a Response to Information Request under IND 127265, received on 8/25/2020 (SDN 195), then a Response to Information Request for this BLA received on 3/31/2022.

Study TG1101-RMS303

As of the cutoff date for this BLA submission (11/23/2020), no subjects in Study TG1101-RMS303 had died.

Study TG1101-RMS201

No deaths occurred in Study TG1101-RMS201.

Study TG1101-RMS201E

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As of 10/29/2021, one subject in Study TG1101-RMS201E (Subject (b) (6)), a 45 year-old man treated with ublituximab-xiiy from (b) (6) died due to COVID-19 pneumonia. He was treated with ublituximab-xiiy on (b) (6)

He was vaccinated against COVID-19 on (b) (6). He developed fever, myalgias, and malaise following exposure to an infected contact on (b) (6), then was diagnosed with COVID-19 on (b) (6). He was noted to have a productive cough with intermittent hemoptysis. He was treated with steroids and a monoclonal antibody infusion. He continued to worsen and experienced hypoxia with oxygen saturations between 80 to 90%. He was hospitalized on (b) (6) with worsening dyspnea, hypoxia (oxygen saturation 81%), and bradycardia. Chest CT showed a “possible left upper lobe segmental pulmonary embolus considered possibly chronic and extensive bilateral ground-glass opacities likely representing multifocal pneumonia, which was considered secondary to the COVID-19 infection.”

He was discharged on home oxygen, but then on (b) (6) he was rehospitalized due to fever and hypoxia. He was diagnosed with acute respiratory failure, pulmonary embolus, and cryptogenic organizing pneumonia. Chest X-ray showed worsening infiltrates. He was also found to have bilateral lower extremity deep vein thrombosis. He stabilized and was discharged on (b) (6), but on (b) (6) he returned and chest CT showed worsening infiltrates. He required BiPAP for respiratory support, then a ventilator on (b) (6). He died on (b) (6). An autopsy was not performed, but the cause of death was listed as multi organ dysfunction syndrome, septic shock, acute respiratory distress syndrome, and COVID-19 pneumonia.

The event was not considered related to ublituximab-xiiy per the Investigator.

Reviewer comment: *Immunosuppression from ublituximab-xiiy likely also contributed to the development and severity of infection. Please refer to Section 8.5.7 for discussion of COVID-19.*

120-Day Safety Update and Information Requests

Per the 120-day Safety Update (data cutoff date of 5/1/2021), 6 additional subjects died, all due to COVID-19 pneumonia.

An Information Request requesting updated mortality data was sent to the applicant on 10/29/2021. The applicant responded on 11/8/2021, indicating that as of 10/29/2021, 10 subjects in Study TG1101-RMS303 and 1 subject in Study TG1101-RMS201E receiving ublituximab-xiiy died due to COVID-19 or COVID-19 pneumonia. Please refer to COVID-19 discussion in Section 8.5.7.

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A final Information Request requesting updated mortality data was sent to the applicant on 7/28/2022. The applicant responded on 8/18/2022, indicating that as of 8/13/2022, 24 total deaths occurred since the BLA cutoff date. All deaths were due to COVID-19-related events, and occurred in 4 subjects in Study TG1101-RMS201E and 20 subjects in Study TG1101-RMS303.

Please refer to Section 8.5.7 for discussion of COVID-19.

8.4.2. Serious Adverse Events

Study TG1101-RMS301

Treatment-emergent SAEs in Study TG1101-RMS301 are summarized by System Organ Class (SOC) and Preferred Term (PT) in Table 49. Selected narratives for patients treated with ublituximab-xiyy are discussed below.

Table 49 (Reviewer). Study TG1101-RMS301 Serious Adverse Events by Primary System Organ Class and Preferred Term

	Ublituximab-xiyy (N = 273) n (%)	Teriflunomide (N = 275) n (%)
Total Subjects with any SAE	31 (11.4)	19 (6.9)
Infections and infestations	15 (5.5)	6 (2.2)
COVID-19 pneumonia	2 (0.7)	1 (0.4)
Pneumonia	3 (1.1)	0 (0.0)
Central nervous system enteroviral infection	2 (0.7)	0 (0.0)
Urinary tract infection	0 (0.0)	2 (0.7)
Appendicitis	1 (0.4)	0 (0.0)
Bacterial infection	0 (0.0)	1 (0.4)
Bullous erysipelas	1 (0.4)	0 (0.0)
Encephalitis	1 (0.4)	0 (0.0)
Lyme disease	0 (0.0)	1 (0.4)
Measles	1 (0.4)	0 (0.0)
Meningoencephalitis viral	1 (0.4)	0 (0.0)
Peritonsillar abscess	1 (0.4)	0 (0.0)
Pulmonary tuberculosis	1 (0.4)	0 (0.0)
Pyelonephritis acute	0 (0.0)	1 (0.4)
Salpingitis	1 (0.4)	0 (0.0)
Upper respiratory tract infection	1 (0.4)	0 (0.0)
Nervous system disorders	3 (1.1)	5 (1.8)
Neurological symptom	1 (0.4)	4 (1.5)
Acoustic neuritis	0 (0.0)	1 (0.4)
Dizziness	1 (0.4)	0 (0.0)
Presyncope	1 (0.4)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (0.7)	3 (1.1)
Back pain	0 (0.0)	1 (0.4)
Intervertebral disc disorder	0 (0.0)	1 (0.4)

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	Ublituximab-xiiy (N = 273) n (%)	Teriflunomide (N = 275) n (%)
Muscular weakness	0 (0.0)	1 (0.4)
Musculoskeletal chest pain	1 (0.4)	0 (0.0)
Myalgia	1 (0.4)	0 (0.0)
Injury, poisoning and procedural complications	4 (1.5)	0 (0.0)
Concussion	1 (0.4)	0 (0.0)
Femoral neck fracture	1 (0.4)	0 (0.0)
Infusion related reaction	1 (0.4)	0 (0.0)
Patella fracture	1 (0.4)	0 (0.0)
Psychiatric disorders	2 (0.7)	1 (0.4)
Affective disorder	1 (0.4)	0 (0.0)
Mental disorder	1 (0.4)	0 (0.0)
Psychotic disorder	0 (0.0)	1 (0.4)
Gastrointestinal disorders	1 (0.4)	1 (0.4)
Oesophageal achalasia	0 (0.0)	1 (0.4)
Pancreatitis chronic	1 (0.4)	0 (0.0)
Immune system disorders	2 (0.7)	0 (0.0)
Anaphylactic reaction	1 (0.4)	0 (0.0)
Hypersensitivity	1 (0.4)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	2 (0.7)
Ovarian cyst ruptured	0 (0.0)	1 (0.4)
Uterine haemorrhage	0 (0.0)	1 (0.4)
Skin and subcutaneous tissue disorders	0 (0.0)	2 (0.7)
Angioedema	0 (0.0)	1 (0.4)
Rosacea	0 (0.0)	1 (0.4)
Blood and lymphatic system disorders	1 (0.4)	0 (0.0)
Neutropenia	1 (0.4)	0 (0.0)
Endocrine disorders	0 (0.0)	1 (0.4)
Hyperthyroidism	0 (0.0)	1 (0.4)
General disorders and administration site conditions	0 (0.0)	1 (0.4)
Asthenia	0 (0.0)	1 (0.4)
Investigations	1 (0.4)	0 (0.0)
Lymphocyte count decreased	1 (0.4)	0 (0.0)
Pregnancy, puerperium, and perinatal conditions	1 (0.4)	0 (0.0)
Ectopic pregnancy	1 (0.4)	0 (0.0)
Renal and urinary disorders	1 (0.4)	0 (0.0)
Tubulointerstitial nephritis	1 (0.4)	0 (0.0)
Surgical and medical procedures	1 (0.4)	0 (0.0)
Medical device removal	1 (0.4)	0 (0.0)
Vascular disorders	1 (0.4)	0 (0.0)
Varicose vein	1 (0.4)	0 (0.0)

Source: ADAE where SAFFL=Y, TRTEMFL=Y, AESER=Y; AESOC and AEDECOD by TRT01A

Serious Infections

- Two fatal infection-related SAEs (salpingitis, measles and encephalitis) are discussed in Section 8.4.1.

- Subject (b) (6) (a 32 year-old woman receiving ublituximab-xiyy) experienced the SAE central nervous system enteroviral infection (Grade 4, "life-threatening infectious meningoencephalomyelitis of enteroviral origin") on (b) (6). She began treatment with ublituximab-xiyy on (b) (6), and received subsequent infusions on (b) (6).

She reported onset of myalgia, subjective fever, and allodynia on (b) (6) followed by chills, fever, paresthesia, nausea, vomiting, oscillopsia, and diplopia on (b) (6). She was hospitalized on (b) (6). Neurological examination was notable for diplopia, dysarthria, pseudodystonia of the right arm, and propriospinal myoclonus. EEG "confirmed subcortical symptoms." She improved with diazepam and carbamazepine, and also received IVIg acyclovir, and ribavirin. MRI demonstrated "basal and parietal meningitis," and CSF enterovirus PCR was positive. She then "had a low level of consciousness with no response to verbal or painful stimuli" on (b) (6), but regained consciousness on (b) (6). She had neurological improvement and was discharged on (b) (6) with intensive rehabilitation. As of (b) (6), she was improving. The event was reported as recovered/resolved with sequelae on (b) (6). Ublituximab-xiyy was permanently discontinued. The investigator considered this event as possibly related to ublituximab-xiyy.

- Subject (b) (6) (a 37 year-old woman receiving ublituximab-xiyy) experienced the SAE meningoencephalitis viral (Grade 3, "viral meningoencephalitis") on (b) (6). She began treatment with ublituximab-xiyy on (b) (6), and received subsequent infusions on (b) (6). Approximately 2 months after her most recent infusion, she developed fever, vomiting, headaches and weakness. She was hospitalized for viral meningoencephalitis on (b) (6). MRI demonstrated "[a visible irregular area in the left central cerebellar peduncle] with slightly increased signal intensity...which may be consistent with recent demyelination lesions...[and] very numerous motion artifacts." New MS lesions were noted by the treating physician. No signs of meningeal infiltration were noted, so a diagnosis of encephalitis was considered. CSF was notable for lymphocytic pleocytosis (75 cells/ μ L, 97%), elevated protein 90 mg/dL, and "high glucose." CSF Lyme IgG/M were negative. PML was considered in the differential, and JCV IgG testing was "borderline positive" and less than a result from (b) (6). However, CSF was not tested for JCV PCR due to lack of availability at the site. Subsequent lumbar punctures (LPs) were performed on (b) (6), and meningitis panels were negative. Tick-borne encephalitis IgG/M were negative. All infectious studies were negative. Previous TEAEs included lymphocyte count decreased (ALC $0.3 \times 10^9/L$ on (b) (6)), but her ALC recovered and was $1.1 \times 10^9/L$ on (b) (6).

She was treated with acyclovir, paracetamol, ceftriaxone, enoxaparin, pantoprazole, dexamethasone, lactulose, probiotics, hydroxyzine, and prednisone. She was hospitalized from (b) (6) and was transferred to inpatient rehabilitation. She

improved and “was no longer bedridden” and was “mobile with the use of walker.” The treating physician considered concurrent viral meningitis and an MS relapse as a diagnosis. Ublituximab-xiiv was permanently discontinued.

Reviewer comment: This case of viral meningoencephalitis is somewhat unusual, particularly since the subject was apparently severely impaired (“bedridden”) and no infectious etiology was identified. A concurrent MS relapse is possible given the reported MRI findings, but would be unusual in this context. The subject’s JCV antibody titer was intermediate, and JCV PCR in CSF was not tested, so it is not possible to rule out PML based upon the information provided. However, the reported CSF profile (moderate lymphocytic pleocytosis, elevated glucose) is not typical for PML.

- Subject (b) (6) (a 32 year-old woman receiving ublituximab-xiiv) experienced the SAE central nervous system enteroviral infection (Grade 3, “meningoencephalitis of enterovirus etiology”) in (b) (6). She began treatment with ublituximab-xiiv on (b) (6), and received subsequent infusions on (b) (6). (b) (6) months after her most recent infusion, she developed fever and urinary urgency, and was diagnosed with a UTI for which she was treated with antibiotics. Following completion of her antibiotic course, her fever returned and she had dizziness and emesis.

She was hospitalized on (b) (6), then transferred to another hospital on (b) (6). Brain and cervical spine MRI showed “signs of demyelinating process with no MRI signs of activity and signs of posterior cranial fossa meningitis (granulomatous process could not be eliminated).” She was “conscious, but lethargic.” Chest CT showed “multiple small foci in both lungs (including subpleural and peribronchial foci), hyperdense focal node in sternum, which were suggestive of inflammatory changes in both lungs.” Retinal angiopathy was noted on ophthalmological examination. CSF obtained on (b) (6) showed elevated protein (1.15 g/L, reference 0.15 to 0.45), and potentially a pleocytosis (notation and units not clear in narrative). She was diagnosed with neurosarcoidosis presenting as meningoencephalitis.

Her condition deteriorated, and she became comatose. Brain MRI showed “cortical cerebellar sulci were diffusely flattened and hyperintense signal on T2-WI in the cerebral cortex of the cerebellum. With contrast enhancement, a pronounced vascular pattern in the meninges of the cerebellar hemispheres (hyperemia) and leptomeningeal contrast uptake were evident.” Repeat CSF showed elevated glucose (4.6 mmol/L, reference 0.15 to 0.45) and elevated protein (0.96 g/L, reference 0.15 to 0.45). One blood test was positive for enterovirus on PCR, but no other infectious evaluations were positive.

She was treated with IVIg, vinpocetine, “polypeptides of the cerebral cortex of cattle” (Cortixin), citicoline, ipidacrine, betahistine, choline alfoscerate, ursodeoxycholic acid,

mebicar, fosfomycin, maprotiline, mannitol, methylethylpyridinol, fluconazole, omeprazole, lactobacillus acidophilus, insulin, acetazolamide, betahistine, glucose, metoclopramide, paracetamol, glycine, levofloxacin, linezolid, meropenem, nadroparin, voriconazole, dexamethasone, and ofloxacin.

The event was reported as recovered/resolved on [REDACTED] (b) (6), and she was discharged from the hospital. Ublituximab-xiiy was permanently discontinued on [REDACTED] (b) (6).

Reviewer comment: The final diagnosis for this event is not clear based on the provided information. Her presentation, MRI findings, and CSF appear consistent with a meningoencephalitis. However, the basis for a neurosarcoidosis diagnosis is not provided, as the chest CT did not demonstrate hilar adenopathy and no biopsy was performed. Additionally, concurrent MS and neurosarcoidosis would be extremely uncommon. The report of a positive enterovirus PCR in blood is of unclear significance to her presentation, but given the other cases of enteroviral meningitis reported in this development program, this is a possible etiology.

- Subject [REDACTED] (b) (6) (a 32 year-old man receiving ublituximab-xiiy) experienced the SAE pulmonary tuberculosis (Grade 2, "infiltrative pulmonary tuberculosis in the phase of destruction") on [REDACTED] (b) (6). He began treatment with ublituximab-xiiy on [REDACTED] (b) (6), and received subsequent infusions on [REDACTED] (b) (6). He underwent Diaskintest, a tuberculosis screening method in Russia, which was negative on [REDACTED] (b) (6). He was hospitalized on [REDACTED] (b) (6) due to cough. Chest CT showed infiltrative pulmonary tuberculosis. He was diagnosed with tuberculosis on [REDACTED] (b) (6) and was treated with isoniazid, pyrazinamide, ethambutol, and rifampicin. The event was recovered/resolved with sequelae on [REDACTED] (b) (6) and the subject was discharged from the hospital. He was withdrawn from the study due to this SAE.

Reviewer comment: The serious infections reported in subjects receiving ublituximab-xiiy appear qualitatively more severe than those reported in subjects receiving teriflunomide, and also occurred at a higher frequency (5.5% versus 2.2%). The central nervous system viral infections (including one leading to death) are unusually severe and concerning, particularly in otherwise healthy, young RMS patients. Additionally, several SAEs are classified as Grade 2. Since these events were severe, medically significant, and/or required hospitalization, event should be considered at least Grade 3 based upon CTCAE definitions. See Section 8.3.1.

Cytopenias

- Subject [REDACTED] (b) (6) (a 26 year-old woman receiving ublituximab-xiiy) experienced the SAE neutropenia (Grade 4) on [REDACTED] (b) (6) after beginning treatment with ublituximab-xiiy on [REDACTED] (b) (6). The most recent infusion date prior to SAE onset was [REDACTED] (b) (6), which was her

Week 72 and last infusion. Associated AEs included stomatitis (treated with fluconazole and miramistin). At screening, her ANC was normal at $3.8 \times 10^9/L$, and was within normal limits until Week 96 labs (b) (6), at which time her absolute neutrophil count (ANC) was $0.1 \times 10^9/L$ (reference range 1.6 to $7.4 \times 10^9/L$). She had already completed study treatment as planned, so no action was taken with study treatments. The event was considered recovered on (b) (6), as her ANC improved to $1.9 \times 10^9/L$ on (b) (6) and $4.7 \times 10^9/L$ on (b) (6).

- Subject (b) (6) (a 43 year-old man receiving ublituximab-xiyy) experienced the SAE lymphocyte count decreased (Grade 4, "lymphocyte count decreased ($0.1 \times 10^9/L$) on (b) (6) treatment with ublituximab-xiyy on (b) (6). Subsequent infusions were received on (b) (6). ALC was $2.1 \times 10^9/L$ on (b) (6), $0.1 \times 10^9/L$ on (b) (6) (Study Day 2), $1.6 \times 10^9/L$ on (b) (6), and $1.0 \times 10^9/L$ on (b) (6). This was considered a medically important event, but the subject was not hospitalized and did not receive any specific treatment for this SAE. No concurrent TEAEs were reported. No action was taken with ublituximab-xiyy, and the subject completed study treatment as planned. His ALC remained within normal limits for the remainder of the study.

Reviewer comment: As presented in Section 8.4.6, subjects on ublituximab-xiyy appeared to have a sharp decrease in lymphocytes on Study Day 2, which is not unexpected given its mechanism of action. This subject appeared to recover spontaneously despite continued treatment, which is consistent with the median ALC trends noted for both Studies TG1101-RMS301 and TG1101-RMS302.

Hypersensitivity and Infusion-Related Reactions

- Subject (b) (6) (a 27 year-old woman receiving ublituximab-xiyy) experienced the SAE infusion related reaction (Grade 3, "delayed infusion reaction [hand pain, arm pain, jaw pain, bilateral leg pain]") on (b) (6) treatment with ublituximab-xiyy on (b) (6) (her fifth infusion). She also experienced nausea, feeling hot, flushing, hypokalemia, arm weakness, and drowsiness. She was hospitalized on (b) (6), and discharged (b) (6). An MS relapse was considered and she was treated with methylprednisolone; she returned to her baseline after 2 doses. She was also noted to have a "hazy and abnormal" urinalysis. The investigator indicated that this event was not an MS relapse, but was considered a "delayed infusion-related reaction." Prior to this event, on (b) (6) (one day after her second ublituximab-xiyy infusion), she experienced the AEs cough, tachycardia, facial flushing, nausea, vomiting, fever, and blood in urine, which were considered an infusion-related reaction. She also experienced the AE facial swelling on (b) (6) (one day after her second ublituximab-xiyy infusion), for which she was treated with diphenhydramine. Of note, her binding antidrug antibody testing results were

“presumptive positive” then negative at baseline, then “presumptive positive” and positive at Week 3 Day 15. She was withdrawn from the study on [REDACTED] (b) (6), due to “investigator or sponsor decision.”

Reviewer comment: This subject appears to have had recurrent infusion-related reactions to ublituximab-xiiy, which likely led to the “investigator or sponsor decision” for study discontinuation. Therefore, this case represents an adverse event leading to drug discontinuation.

- Subject [REDACTED] (b) (6) (a 31 year-old woman receiving ublituximab-xiiy) experienced the SAE anaphylactic reaction (Grade 4) on [REDACTED] (b) (6) in the setting of her second ublituximab-xiiy infusion, for which she was treated with dexamethasone but refused hospitalization. She experienced hypotension, dyspnea, abdominal pain, and cyanosis. She had her first infusion of ublituximab-xiiy on [REDACTED] (b) (6), after which she experienced the AE influenza-like syndrome and was treated with paracetamol. Ublituximab-xiiy was permanently withdrawn due to this SAE.
- Subject [REDACTED] (b) (6) (a 39 year-old woman receiving ublituximab-xiiy) experienced the SAE hypersensitivity (Grade 2) on [REDACTED] (b) (6) for which she was hospitalized, on the day of her first ublituximab-xiiy infusion.
- Subject [REDACTED] (b) (6) (a 31 year-old woman receiving ublituximab-xiiy) experienced the SAE myalgia (Grade 2) on [REDACTED] (b) (6) for which she was hospitalized, [REDACTED] (b) (6) her initial ublituximab-xiiy infusion on [REDACTED] (b) (6). She was treated with thioctic acid, diclofenac, diazepam, polymethylsiloxane polyhydrate, glycine, tizanidine, glucose, potassium chloride, insulin, and ranitidine. CPK was elevated at 1566 U/L with subsequent improvement to 33 U/L. The event was reported recovered/resolved and the subject was discharged on [REDACTED] (b) (6). The TEAE “hypersensitivity” (“edema of the face and edema and rashes in her extremities”) was also reported as ongoing at the time of this SAE. Study treatment was permanently discontinued.

Reviewer comment: It is not clear why this event would be classified as Grade 2, as it required hospitalization. Based upon CTCAE definitions, this event should be considered at least Grade 3. See Section 8.3.1. The etiology of her CPK elevation is not clear, but this event appears to be an IRR related to ublituximab-xiiy, and the coding of the event as myalgia is inappropriate upon review of the clinical scenario.

Reviewer comment: These hypersensitivity/infusion-related reaction (IRR)-related SAEs appear to be related to ublituximab-xiiy. Additionally, several SAEs are classified as Grade 2. Since these events were severe, medically significant, and/or required hospitalization, event should be considered at least Grade 3 based upon CTCAE definitions. See Section 8.3.1.

Other

- Subject (b) (6) (a 37 year-old man receiving ublituximab-xiyy) experienced the SAE pancreatitis chronic (Grade 2, "chronical pancreatitis exacerbation") on (b) (6), for which he was hospitalized and treated with platyphylline, omeprazole, and pancreatin. He began treatment with ublituximab-xiyy on (b) (6), and the most recent infusion prior to SAE onset was (b) (6). He had elevated AST, ALT, and GGT prior to the first dose of ublituximab-xiyy. The narrative indicates that no diagnostic test or laboratory test results were provided from the hospitalization, but his amylase and lipase levels collected as part of the study were within normal limits on (b) (6). He had mild lipase elevations up to 88 U/L prior to the event. The event was recovered/resolved on (b) (6). Pancreatitis was not mentioned in his relevant medical/surgical history provided in the applicant's narrative. He also experienced the AEs retinal vein thrombosis (b) (6) aspartate aminotransferase increased (b) (6) and non-alcoholic steatohepatitis without cholestasis (b) (6). He continued study treatment and received ublituximab-xiyy on (b) (6).
- Subject (b) (6) (a 29 year-old woman receiving ublituximab-xiyy) experienced the SAEs affective disorder ("mood disorder") and tubulointerstitial nephritis (Grade 2, "acute tubulointerstitial neuritis right") on (b) (6) respectively. She began treatment with ublituximab-xiyy on (b) (6), and underwent subsequent infusions on (b) (6). She had a non-serious TEAE of "neurosis disorders" on (b) (6), for which she was treated with trazodone, escitalopram, paroxetine, perazine, clorazepate, sertraline, pregabalin, and venlafaxine. For the SAE affective disorder (b) (6), reportedly "following a family argument...where the subject became intoxicated and could not calm down."), she was hospitalized and treated with paroxetine hydrochloride, propranolol, baclofen, and hydroxyzine. She recovered and was discharged on (b) (6).

For tubulointerstitial nephritis (b) (6) she was hospitalized and treated with IV fluids, amikacin, furazidin, hyoscine butylbromide, ciprofloxacin, and saccharomyces boulardii. At the time of this SAE (b) (6), her creatinine was elevated at 90 µmol/L (reference range 44 to 80 µmol/L), IgA was 0.47 g/L, and urinalysis was positive for leukocytes, hemoglobin, bacteria, and mucous threads. She was febrile and experienced abdominal pain. CT scan results were suggestive of acute right-sided pyelonephritis. The event was considered recovered/resolved on (b) (6), she was discharged from the hospital, and completed study treatment as planned.

Reviewer comment: It is not clear why the event tubulointerstitial nephritis would be classified as Grade 2, as it is severe, medically significant, and required hospitalization.

Based upon CTCAE definitions, this event should be considered at least Grade 3. See Section 8.3.1. This event likely should be classified as pyelonephritis given the urinalysis results, CT findings, and antibiotic treatment; however, pyelonephritis can cause tubulointerstitial nephritis. The laboratory data presented do not appear to be specific to a tubulointerstitial nephritis diagnosis.

Reviewer comment: This reviewer notes that the SAEs of neurological symptoms in both groups appear to represent suspected but not IRAP-confirmed MS relapses. In these cases, subjects were admitted to the hospital and most were treated with methylprednisolone. These events are captured as suspected relapses in the ADRL dataset.

Study TG1101-RMS302

Treatment-emergent SAEs in Study TG1101-RMS302 are summarized by SOC and PT in Table 50. Selected narratives are discussed below.

Table 50 (Reviewer). Study TG1101-RMS302, Serious Adverse Events by System Organ Class and Preferred Term

	Ublituximab-xiiy (N = 272) n (%)	Teriflunomide (N = 273) n (%)
Total Subjects with any SAE	28 (10.3)	21 (7.7)
Infections and infestations	12 (4.4)	10 (3.7)
Pneumonia	2 (0.7)	2 (0.7)
Acute sinusitis	3 (1.1)	0 (0.0)
COVID-19 pneumonia	2 (0.7)	1 (0.4)
Complicated appendicitis	1 (0.4)	1 (0.4)
Pyelonephritis acute	0 (0.0)	2 (0.7)
Appendicitis	1 (0.4)	0 (0.0)
Bronchitis	0 (0.0)	1 (0.4)
Chronic hepatitis B	1 (0.4)	0 (0.0)
Chronic tonsillitis	0 (0.0)	1 (0.4)
Epididymitis	1 (0.4)	0 (0.0)
Gastrointestinal infection	1 (0.4)	0 (0.0)
Periodontitis	0 (0.0)	1 (0.4)
Peritonitis	0 (0.0)	1 (0.4)
Pilonidal cyst	0 (0.0)	1 (0.4)
Pyelonephritis chronic	0 (0.0)	1 (0.4)
Septic shock	0 (0.0)	1 (0.4)
Tooth abscess	0 (0.0)	1 (0.4)
Nervous system disorders	2 (0.7)	4 (1.5)
Epilepsy	0 (0.0)	2 (0.7)
Cerebral infarction	0 (0.0)	1 (0.4)
Coordination abnormal	1 (0.4)	0 (0.0)
Dysaesthesia	1 (0.4)	0 (0.0)
Tremor	0 (0.0)	1 (0.4)
Eye disorders	1 (0.4)	1 (0.4)

	Ublituximab-xiyy (N = 272) n (%)	Teriflunomide (N = 273) n (%)
Astigmatism	0 (0.0)	1 (0.4)
Cataract	0 (0.0)	1 (0.4)
Glaucoma	1 (0.4)	0 (0.0)
Retinal degeneration	0 (0.0)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.5)	0 (0.0)
Desmoid tumour	1 (0.4)	0 (0.0)
Endometrial stromal sarcoma	1 (0.4)	0 (0.0)
Uterine cancer	1 (0.4)	0 (0.0)
Uterine leiomyoma	1 (0.4)	0 (0.0)
General disorders and administration site conditions	2 (0.7)	0 (0.0)
Decreased activity	1 (0.4)	0 (0.0)
Fatigue	1 (0.4)	0 (0.0)
Pyrexia	1 (0.4)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.4)	2 (0.7)
Concussion	0 (0.0)	1 (0.4)
Hand fracture	0 (0.0)	1 (0.4)
Tibia fracture	1 (0.4)	0 (0.0)
Blood and lymphatic system disorders	2 (0.7)	0 (0.0)
Bone marrow toxicity	1 (0.4)	0 (0.0)
Febrile neutropenia	1 (0.4)	0 (0.0)
Gastrointestinal disorders	1 (0.4)	1 (0.4)
Abdominal hernia	1 (0.4)	0 (0.0)
Pancreatitis acute	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	1 (0.4)	1 (0.4)
Muscular weakness	1 (0.4)	1 (0.4)
Surgical and medical procedures	2 (0.7)	0 (0.0)
Ovarian cystectomy	1 (0.4)	0 (0.0)
Pituitary gland operation	1 (0.4)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	1 (0.4)
Cholecystitis chronic	0 (0.0)	1 (0.4)
Metabolism and nutrition disorders	1 (0.4)	0 (0.0)
Hyperkalemia	1 (0.4)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (0.4)
Renal colic	0 (0.0)	1 (0.4)
Reproductive system and breast disorders	1 (0.4)	0 (0.0)
Ovarian cyst	1 (0.4)	0 (0.0)
Vascular disorders	1 (0.4)	0 (0.0)
Deep vein thrombosis	1 (0.4)	0 (0.0)

Source: ADAE where SAFFL=Y, TRTEMFL=Y, AESER=Y; AESOC and AEDECOD by TRT01A

Serious Infections

- One fatal infection-related SAE (pneumonia) is discussed in Section 8.4.1.
- Subject (b) (6) (a 46 year-old woman receiving ublituximab-xiyy) experienced the SAE chronic hepatitis B (Grade 3) on (b) (6). She had a reported history of hepatitis A in (b) (6). She received her first dose of ublituximab-xiyy on (b) (6), and most recently (b) (6).

She was hospitalized due to nausea, vomiting, dark urine, and jaundice on (b) (6). Laboratory evaluation was notable for ALT 512 U/L, AST 1341 U/L, direct bilirubin 93 mmol/L, and total bilirubin 148.7 mmol/L. Hepatitis B surface antigen and IgG tests were positive. Other hepatitis serologies were negative. Abdominal ultrasound showed diffuse changes, and elastography testing showed stage F4 fibrosis. She was treated with tenofovir starting on (b) (6). TEAEs of jaundice and iron deficiency anemia were also reported. The event was recovered/resolved with sequelae, and she was discharged on (b) (6). Study treatments were interrupted, and the subject discontinued study participation due to investigator/sponsor decision. At screening, this subject had a reactive hepatitis B surface antigen (b) (6) that was non-reactive on repeat testing (b) (6).

Reviewer comment: This case meets Hy's Law criteria, but is due to hepatitis B rather than ublituximab-xiiy directly. This subject should not likely have been included in this study due to hepatitis B surface antigen at screening, though confirmatory testing was negative. Screening laboratories did not include other hepatitis B testing. Hepatitis B reactivation is a known risk with other anti-CD20 treatments, so reactivation was likely the result of ublituximab-xiiy treatment.

Cytopenias

- Subject (b) (6) (a 35 year-old man receiving ublituximab-xiiy) experienced the SAE febrile neutropenia (Grade 3) on (b) (6). He received his first dose of ublituximab-xiiy on (b) (6) and a subsequent infusion on (b) (6). He was hospitalized on (b) (6) due to febrile neutropenia, worsening of hidradenitis suppurativa, and toothache. Blood cultures were negative. However, culture of a swab of an ulcer (unclear location, possibly related to hidradenitis suppurativa) grew "various bacterial colonies with a predominance of *E. Coli*" resistant to several antibiotics. He was treated with piperacillin/tazobactam, clindamycin, and filgrastim from (b) (6) laboratory evaluation was notable for leukopenia (WBCs $1.4 \times 10^9/L$) and an ANC of $0.2 \times 10^9/L$. The event was recovered/resolved, and he was discharged from the hospital on (b) (6). Study treatments were permanently discontinued. Concurrent TEAEs included toothache, which was considered as a possible source of infection in addition to a scrotal lesion. The study site reported that the subject was experiencing agranulocytosis due to methimazole. Per the Patient Profile, "nolotil (metamizol)" was initiated for toothache on (b) (6) and discontinued on (b) (6).

Reviewer comment: Metamizol is a pain medication with a known risk of agranulocytosis, and the timing of the TEAE febrile neutropenia is suggestive of a relationship with this drug rather than ublituximab-xiiy, as indicated by the investigator.

- Subject (b) (6) (a 39 year-old woman receiving ublituximab-xiiy) experienced the SAE

bone marrow toxicity (Grade 4, "possible toxic bone marrow damage") on (b) (6), which was documented as resolved on (b) (6). She received her first dose of ublituximab-xiiy on (b) (6), with subsequent infusions on (b) (6), and (b) (6). The narrative indicates that this subject experienced agranulocytosis in the setting of an upper respiratory tract infection with pharyngitis. She was hospitalized on (b) (6) and was treated with ceftazidime, fluconazole, and acyclovir. Pertinent laboratory values included absolute neutrophil count 0.81 g/L, hemoglobin 13.1 g/L, CRP 179 mg/L, fibrinogen 648 mg/dL (reference range 200-393 mg/dL). Peripheral smear showed a low percentage of segmented granulocytes (11%, reference range 34 to 71%), and myeloproliferative disease was excluded via cytomorphological examination. She was also found to have a "solid and fluid-filled lesion of 6x4mm on the right lobe of the thyroid." She was diagnosed with isolated neutropenia, "bone marrow damage," and pharyngitis. She was discharged on (b) (6). She had already completed blinded study treatment, as her last date of oral drug treatment was (b) (6). Concurrent TEAEs included gastroesophageal reflux disease and pharyngitis.

This event was assessed as doubtfully related to study treatment by the investigator. On the last double-blind period study visit (Week 104; (b) (6)), this subject had values within the reference range for hemoglobin, lymphocytes, neutrophils, platelets, erythrocytes, and leukocytes. She initiated participation in Study TG1101-RMS303, with the first ublituximab-xiiy infusion on (b) (6). The closest study visit during participation in Study TG1101-RMS303 was the screening visit, on (b) (6), at which time this subject had values within the reference range for hemoglobin, lymphocytes, neutrophils, platelets, erythrocytes, and leukocytes.

This event was assessed as doubtfully related to study treatment by the investigator. She consented to Study TG1101-RMS303 on (b) (6) and restarted ublituximab-xiiy (b) (6).

Reviewer comment: The narrative indicates that the subject's neutrophil count was 0 in the setting of a presumed respiratory tract infection, approximately 1 year after the most recent dose of ublituximab-xiiy and prior to enrollment in the extension study. However, the ANC documented in the narrative is $0.81 \times 10^9/L$, which is not consistent with agranulocytosis. It is not clear why this event was coded as bone marrow toxicity, as decreases in other cell lines were not noted. This event would likely have been more appropriately coded as neutropenia. Though neutropenia was reported in subjects receiving ublituximab-xiiy, this event appears to be potentially related to an acute infection rather than ublituximab-xiiy given the temporality. Of note, the neutrophil count mentioned in the narrative was not documented in the ADLB dataset for Study TG1101-RMS302 or TG1101-RMS303.

Hypersensitivity and Infusion-Related Reactions

No SAEs related to hypersensitivity or infusion-related reactions were reported.

Malignancy

- Subject (b) (6) (a 41 year-old woman receiving ublituximab-xiyy) experienced the SAE endometrial stromal sarcoma (Grade 2, "low grade endometrial stromal sarcoma) on (b) (6). She received her first dose of ublituximab-xiyy on (b) (6), and received subsequent infusions on (b) (6). She was hospitalized and underwent a hysterectomy on (b) (6) (following last planned study treatment administration), at which time the event was considered recovered /resolved. No concurrent TEAEs were reported.

Reviewer comment: Endometrial stromal sarcomas are rare malignant uterine tumors. This subject developed a low-grade tumor, which portends a better prognosis. It is not known whether this patient had prior exposure to tamoxifen or unopposed estrogen, which are known risk factors for this condition. Concomitant medications included an intrauterine contraceptive device. It is not clear why this SAE was rated as CTCAE Grade 2, as it is a severe, medically significant event that required hospitalization and surgical intervention. Based upon CTCAE definitions, this event should be considered at least Grade 3. See Section 8.3.1.

- Subject (b) (6) (a 48 year-old woman receiving ublituximab-xiyy) experienced the SAEs uterine leiomyoma ("planned uterine fibroid embolization procedure") and pituitary gland operation ("excision of pituitary adenoma") on (b) (6), respectively. Pertinent medical history included basal cell carcinoma (removal in (b) (6)) and asymptomatic pituitary adenoma (since (b) (6)). She received her first dose of ublituximab-xiyy on (b) (6), and received subsequent infusions on (b) (6). Concurrent TEAEs for uterine leiomyoma included menorrhagia (b) (6). She then underwent planned uterine fibroid embolization on (b) (6). She underwent pituitary adenoma removal after her last planned dose of ublituximab-xiyy. It is not clear based on the provided information what prompted removal of the previously diagnosed and asymptomatic pituitary adenoma, but concurrent TEAEs included procedural headache and insomnia. She was hospitalized (b) (6).
- Subject (b) (6) (a 35 year-old woman receiving ublituximab-xiyy) experienced the SAE desmoid tumor (Grade 2, "desmoid tumor in muscle," likely right lower extremity based on concurrent TEAE of "pain in the right lower limb") in (b) (6). He received his first dose of ublituximab-xiyy on (b) (6) and received subsequent infusions on (b) (6). He was not hospitalized, but underwent outpatient resection on (b) (6). The event was recovered/resolved with sequelae. No action was

taken with study medications, and he received his last infusion as planned on 12/16/2019.

Reviewer comment: It is not clear why this event would be classified as Grade 2, as it is severe, medically significant, and required surgical management and hospitalization. Based upon CTCAE definitions, this event should be considered at least Grade 3. See Section 8.3.1.

- Subject (b) (6) (a 37 year-old woman receiving ublituximab-xiyy) experienced the SAE uterine cancer (Grade 3, "uterus carcinoma") on (b) (6). She received her first dose of ublituximab-xiyy on (b) (6) with subsequent infusions on (b) (6). She was hospitalized on (b) (6) and underwent "surgical conization of cervix uteri," then was discharged on (b) (6). She was re-hospitalized on (b) (6) for hysterectomy, and the event was reported as recovered/resolved. Concurrent TEAEs included sinus polyp and cervical dysplasia. She continued study participation and received subsequent infusions on (b) (6).

Other

- Subject (b) (6) (a 43 year-old woman receiving ublituximab-xiyy) experienced the SAEs (all Grade 1) dysesthesia ("numbness of the left half of the face, left half of the body"), muscular weakness ("weakness in left leg"), fatigue ("general weakness"), and decreased activity ("decrease in efficiency") on (b) (6). She received her first dose of ublituximab-xiyy on (b) (6) and received a subsequent infusion on (b) (6). She was hospitalized on (b) (6) and was treated with methylprednisolone from (b) (6). She was discharged on (b) (6), and the event was considered recovered/resolved. Study treatments were permanently discontinued due to withdrawal of consent by the subject.

Reviewer comment: The treatment with methylprednisolone suggests that this event was a suspected relapse, but the provided narrative does not mention potential MS relapse, IRAP adjudication, or evaluation for causes of pseudorelapse. This event is captured as a suspected but unconfirmed relapse in the ADRL dataset. Additionally, it is not clear why these events would be classified as Grade 1, as she was hospitalized. Based upon CTCAE definitions, this event should be considered at least Grade 3. See Section 8.3.1.

- Subject (b) (6) (a 23 year-old woman receiving ublituximab-xiyy) experienced the SAE pyrexia (Grade 2, "fever") on (b) (6). She received her first dose of ublituximab-xiyy on (b) (6), with subsequent infusions on (b) (6). She was hospitalized for pyrexia on (b) (6) and was treated with paracetamol, then discharged on (b) (6). Concurrent TEAEs included back pain (since (b) (6)) and transaminases increased (b) (6). Neither the patient profile or narrative reported any details regarding an infectious workup or potential source of her fever. Her absolute lymphocyte and neutrophil counts were normal on (b) (6). No action was

taken with ublituximab-xiiy (oral study treatment interrupted then resumed), and she completed study treatment as planned.

Reviewer comment: It is not clear why this event would be classified as Grade 2, as it is required hospitalization. Based upon CTCAE definitions, this event should be considered at least Grade 3. See Section 8.3.1.

- Subject (b) (6) (a 34 year-old woman receiving ublituximab-xiiy) experienced the SAE coordination abnormal (Grade 2, "motor coordination syndrome") on (b) (6). She received her first dose of ublituximab-xiiy on (b) (6), and the last infusion prior to this event was (b) (6). She was hospitalized on (b) (6), treated with methylprednisolone, and discharged on (b) (6). Concurrent TEAEs included headache. No action was taken with study treatment, and she completed study treatment as planned.

Reviewer comment: Again, treatment with methylprednisolone suggests that this event was a suspected relapse, but the provided narrative does not mention potential MS relapse, IRAP adjudication, or evaluation for causes of pseudorelapse. This event is captured as a suspected but unconfirmed relapse in the ADRL dataset. It is not clear why this event would be classified as Grade 2, as it is required hospitalization. Based upon CTCAE definitions, this event should be considered at least Grade 3. See Section 8.3.1.

- Subject (b) (6) (a 35 year-old man receiving ublituximab-xiiy) experienced the SAE hyperkalemia (Grade 2) on (b) (6). He received his first dose of ublituximab-xiiy on (b) (6), and the last infusion prior to this SAE was on (b) (6). He had several non-serious TEAEs of hyperkalemia (Grade 3 on (b) (6), Grade 1 on (b) (6), and Grade 3 on (b) (6)). On (b) (6), his potassium was 5.8 mmol/L and on (b) (6) was 6.2 mmol/L, both highly elevated values. He was treated with furosemide (b) (6). He was discharged from the hospital on (b) (6). Concurrent TEAEs included renal cyst (since (b) (6)) and bundle branch block right. No action was taken with study treatment, and she completed study treatment as planned.

Reviewer comment: The etiology of this subject's recurrent hyperkalemia is not clear based on the information provided in the narrative. He did not appear to be taking any concomitant medications that are known to cause hyperkalemia (e.g., spironolactone), and his renal function (based on urea nitrogen and creatinine) was normal throughout the double-blind treatment period. Additionally, it is not clear why this event would be classified as Grade 2, as it is required hospitalization. Based upon CTCAE definitions, this event should be considered at least Grade 3. See Section 8.3.1.

Study TG1101-RMS303

Treatment-emergent SAEs in Study TG1101-RMS303, as of the BLA data cutoff (11/23/2020) are summarized by PT in Table 51. Fourteen subjects (2.2%) experienced an SAE in the extension period, 8 of whom previously received ublituximab-xiiy and 6 teriflunomide. Selected narratives are discussed below.

Table 51 (Reviewer). Study TG1101-RMS303, Serious Adverse Events by Preferred Term

	Ublituximab-xiiy/ Ublituximab-xiiy (N = 319)	Teriflunomide/ Ublituximab-xiiy (N = 323)	Overall (N = 642)
Total Subjects with any SAE	8 (2.5)	6 (1.9)	14 (2.2)
COVID-19 pneumonia	5 (1.6)	1 (0.3)	6 (0.9)
COVID-19	0 (0.0)	1 (0.3)	1 (0.2)
Febrile neutropenia	0 (0.0)	1 (0.3)	1 (0.2)
Fibula fracture	1 (0.3)	0 (0.0)	1 (0.2)
Immune reconstitution inflammatory syndrome	0 (0.0)	1 (0.3)	1 (0.2)
Infusion related reaction	0 (0.0)	1 (0.3)	1 (0.2)
Interstitial lung disease	0 (0.0)	1 (0.3)	1 (0.2)
Lumbosacral radiculopathy	0 (0.0)	1 (0.3)	1 (0.2)
Peritonitis	1 (0.3)	0 (0.0)	1 (0.2)
Salpingitis	1 (0.3)	0 (0.0)	1 (0.2)
Salpingo-oophoritis	1 (0.3)	0 (0.0)	1 (0.2)
Tibia fracture	1 (0.3)	0 (0.0)	1 (0.2)
Urticaria	0 (0.0)	1 (0.3)	1 (0.2)
Uterine leiomyoma	1 (0.3)	0 (0.0)	1 (0.2)
Vaginal haemorrhage	1 (0.3)	0 (0.0)	1 (0.2)

Source: ADAE for Phase 3 ISS (ISS-IDB1), where STUDYID = TG1101-RMS303, AESER=Y

Serious Infections

The serious infection-related TEAEs reported during Study TG1101-RMS303 included COVID-19-related events (n =7). See Section 8.5.7.

Subject (b) (6) (21 year-old woman who received ublituximab-xiiy during double-blind treatment) experienced the SAEs peritonitis, salpingitis, and salpingo-oophoritis. She received ublituximab-xiiy during double-blind treatment on (b) (6). She received her first infusion under Study TG1101-RMS303 on (b) (6) then second infusion on (b) (6). She experienced the SAE complicated appendicitis on (b) (6) (considered to be during double-blind treatment period). She experienced the TEAEs leukocyturia, pelvic pain, pyrexia, lymphadenitis, leukocytosis, salpingo-oophoritis, peritonitis, and salpingitis in (b) (6). She was reported to have sequelae of “bilateral pyosalpinx” and underwent bilateral tubectomy in (b) (6).

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Ublituximab-xiiy (Briumvi)

Cytopenias

Subject (b) (6) (21 year-old man who received teriflunomide during double-blind treatment) experienced the SAEs febrile neutropenia, immune reconstitution inflammatory syndrome (IRIS), and interstitial lung disease during the extension period while receiving ublituximab-xiiy. He received ublituximab-xiiy infusions on (b) (6). He experienced febrile neutropenia on (b) (6); he had a fever and underwent testing that demonstrated neutropenia (ANC 0.74 x10⁹/L on (b) (6), then 0.99 x10⁹/L on (b) (6), then 0.68 x 10⁹/L on (b) (6). Anti-streptolysin O was positive. He was diagnosed with IRIS and interstitial lung disease on (b) (6). He underwent chest CT which showed bilateral “interstitial inflammation in the lungs probably caused by COVID-19.” He was hospitalized, and COVID-19 testing was negative. Repeat chest CT on (b) (6) showed worsening of the bilateral polysegmental inflammation. He was diagnosed with suspected IRIS due to his chest CT findings. He was treated with plasmapheresis starting on (b) (6). He was discharged on (b) (6). Ublituximab-xiiy was discontinued due to these adverse events.

Reviewer comment: The basis for a diagnosis of IRIS is not clear in this case. The event occurred <1 month after initiating ublituximab-xiiy, after which immune reconstitution (i.e., B-cell repletion) would not be expected for at least 6 months. This reviewer suspects a viral pneumonia with associated neutropenia, which are likely related to ublituximab-xiiy.

Study TG1101-RMS201

Treatment-emergent SAEs in Study TG1101-RMS201 are summarized by PT in Table 52. The events cholelithiasis and diverticulum occurred in the same subject (b) (6).

Table 52 (Reviewer). Study TG1101-RMS201, Serious Adverse Events by Preferred Term

	Ublituximab-xiiy (N = 48)	Placebo (N = 13)
Total Subjects with any SAE	5 (10.4)	0 (0)
Appendicitis	1 (2.1)	0 (0)
Cholelithiasis	1 (2.1)	0 (0)
Diverticulum	1 (2.1)	0 (0)
Pregnancy	1 (2.1)	0 (0)
Pregnancy of partner	1 (2.1)	0 (0)
Seizure	1 (2.1)	0 (0)

Source: ADAE where TRTEMFL=Y, AESER=Y

Reviewer comment: Overall, the SAEs observed in Study TG1101-RMS201 appear consistent with that observed in the Phase 3 studies or are not unexpected.

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Study TG1101-RMS201E

Treatment-emergent SAEs in Study TG1101-RMS201E are summarized by PT in Table 53.

Table 53 (Reviewer). Study TG1101-RMS201E, Serious Adverse Events by Preferred Term

	Ublituximab-xiiy (N = 43)
Total Subjects with any SAE	7 (16.3)
COVID-19 pneumonia	2 (4.7)
Angina unstable	1 (2.3)
Cellulitis	1 (2.3)
Chest pain	1 (2.3)
Colitis	1 (2.3)
Coronary artery disease	1 (2.3)
Haemoperitoneum	1 (2.3)
Haemorrhagic ovarian cyst	1 (2.3)
Prostatitis	1 (2.3)
Vascular pseudoaneurysm	1 (2.3)

Source: ADAE where TRTEMFL=Y, AESER=Y

The SAE colitis was reported in Subject (b) (6), which is considered of interest due to recent updates to labeling for ocrelizumab, another anti-CD20 monoclonal antibody. This subject was a 38 year-old woman who received ublituximab-xiiy on (b) (6) (under Study TG1101-RMS201), then (b) (6)

She presented on (b) (6) with abdominal pain, nausea, vomiting, diarrhea, rectal bleeding, and bloody stools. CT scan showed "mild segmental wall thickening within the mid transverse colon possibly related to lack of distension." Laboratory evaluation was notable for positive fecal occult blood test, leukocytosis, and increased ANC. She was treated with antibiotics and symptomatic therapies (no steroids), and was discharged on (b) (6) with resolution of this event. No GI consult or colonoscopy were performed. No action was taken with ublituximab-xiiy during this event, and the subject continued study treatment as planned.

Reviewer comment: Though serious cases of colitis have been observed with ocrelizumab, this event does not appear to resemble such cases. Based on the nausea and vomiting observed with this case and resolution without immunotherapy (i.e., no steroids) or discontinuation of ublituximab-xiiy (i.e., negative rechallenge), this case is not likely to represent immune-mediated colitis due to ublituximab-xiiy. Given the spontaneous resolution, infectious colitis is thought to be more likely; however, no infectious studies were reported in the narrative.

120-Day Safety Update

Serious adverse events reported in the 120-Day Safety Update appeared consistent with those

reported in the BLA submission. However, the frequency of COVID-19 infection-related serious adverse events did increase, which is not unexpected given the time during which the extension studies are ongoing. See Section 8.5.7.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study TG1101-RMS301

Treatment-emergent adverse events (TEAEs) in Study TG1101-RMS301 leading to permanent discontinuation of study treatment are reported by PT in Table 54. Overall, subjects receiving ublituximab-xiyy were more likely to discontinue study treatment due to an adverse event than those receiving teriflunomide (6.6% vs. 0.7%, respectively). Additionally, the most common adverse events leading to discontinuation in the ublituximab-xiyy group were infections, hypersensitivity/infusion-related reactions, and cytopenias. Selected narratives for subjects receiving ublituximab-xiyy are discussed below, and several of these cases are discussed as SAEs in Section 8.4.2.

Table 54 (Reviewer). Study TG1101-RMS301, Adverse Events Leading to Permanent Discontinuation of Study Treatment, by Preferred Term

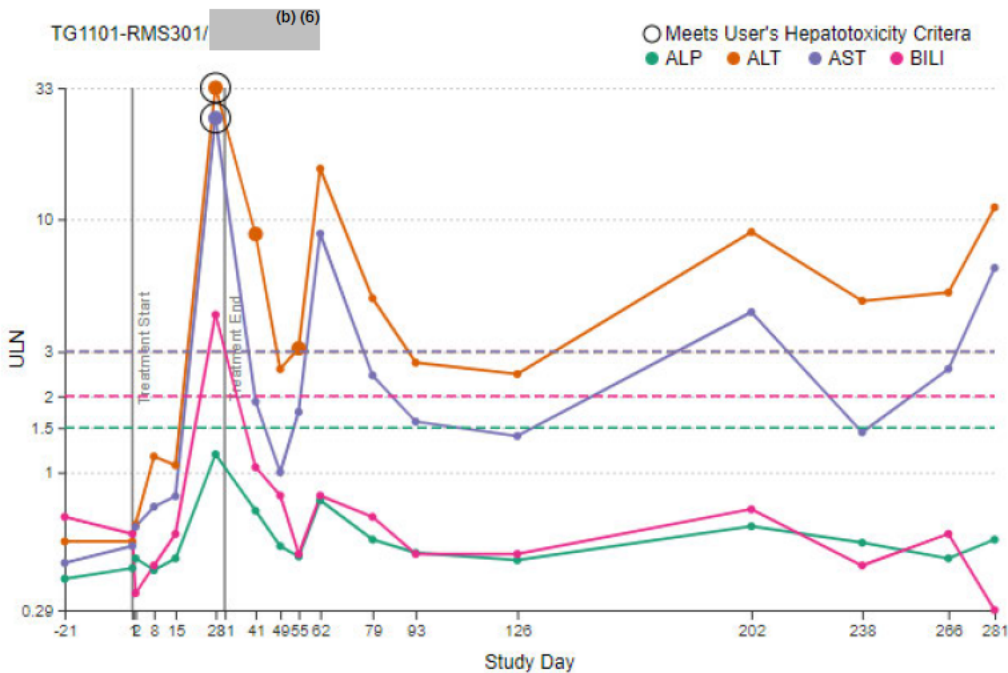
	Ublituximab-xiyy (N = 273) n (%)	Teriflunomide (N = 275) n (%)
Total Subjects with any TEAE leading to discontinuation	18 (6.6)	2 (0.7)
Central nervous system enteroviral infection	2 (0.7)	0 (0.0)
Hepatitis toxic	1 (0.4)	1 (0.4)
Anaphylactic reaction	1 (0.4)	0 (0.0)
Bronchospasm	1 (0.4)	0 (0.0)
Diarrhoea	1 (0.4)	0 (0.0)
Encephalitis	1 (0.4)	0 (0.0)
Femoral neck fracture	1 (0.4)	0 (0.0)
Hypersensitivity	1 (0.4)	0 (0.0)
Infusion related reaction	1 (0.4)	0 (0.0)
Lipase increased	0 (0.0)	1 (0.4)
Lymphopenia	1 (0.4)	0 (0.0)
Meningoencephalitis viral	1 (0.4)	0 (0.0)
Myalgia	1 (0.4)	0 (0.0)
Myocardial ischaemia	1 (0.4)	0 (0.0)
Neutropenia	1 (0.4)	0 (0.0)
Palpitations	1 (0.4)	0 (0.0)
Pulmonary tuberculosis	1 (0.4)	0 (0.0)
Rash maculo-papular	1 (0.4)	0 (0.0)
Toxic skin eruption	1 (0.4)	0 (0.0)

Source: ADAE where SAFFL=Y, TRTEMFL=Y, ADISAFL=Y, by TRT01A

- Subject (b) (6) (39 year-old man receiving ublituximab-xiiy) experienced the AE bronchospasm (Grade 2), which was reported verbatim as “bronchospastic syndrome (difficulty breathing, noisy breathing, prolonged inhalation, tachycardia, elevation of blood pressure to 168/101 mmHg)” on (b) (6), which was the date of her last ublituximab-xiiy infusion. This event was treated with dexamethasone and IV fluids. She also had a history of non-serious (Grade 2) infusion reaction (“pressing headache, pale skin, shortness of breath, lowering blood pressure to 70/50 mmHg, reducing heart rate to 55 beats per minute”) on (b) (6), which was also treated with dexamethasone. Treatment was discontinued due to this event.
- Subject (b) (6) (a 44 year-old man receiving ublituximab-xiiy) experienced the AE hepatitis toxic (Grade 2, “toxic hepatitis”) on (b) (6). He began treatment with ublituximab-xiiy on (b) (6), and received a subsequent infusion (b) (6). On (b) (6) laboratory values were notable for elevated AST 1027 U/L, ALT 1485 U/L, ALP 152 U/L, and bilirubin 88 µmol/L (reference range 0 to 21 µmol/L). Ublituximab-xiiy was discontinued, and lab values improved to AST 78 U/L and ALT 393 U/L on (b) (6), AST 71 U/L and ALT 139 U/L on (b) (6), but increased to AST 359 U/L and ALT 712 U/L on (b) (6), then improved AST 99 U/L and ALT 219 U/L on (b) (6), and AST 65 U/L and ALT 122 U/L on (b) (6). Dechallenge was positive. Pertinent laboratory values are depicted in Figure 5. He was treated with silicon dioxide, arginine citrate/betaine, thiotriazoline, and lactulose. Concurrent TEAEs included AST increased and ALT increased. The events AST and ALT increased were considered severe (Grade 3), but toxic hepatitis was considered moderate (Grade 2).

The Drug-Induced Liver Injury (DILI) Team was consulted for review of this case given its concerning, unexplained, and unexpected nature. Please refer to the Consultation Memorandum by Dr. Paul Hayashi, dated 9/20/2022. In consultation with the DILI Team, Information Requests were sent to the applicant on 7/28/2022 and 8/29/2022. The applicant submitted an updated narrative on 8/12/2022, which indicated that further evaluation of the etiology of this subject’s hepatitis was limited. The applicant was able to analyze stored serum samples at the DILI team’s request, and it was determined that the subject experienced acute hepatitis C infection based upon the positive hepatitis C antibody on Day 56 (with negative previous values) and hepatitis C RNA detected on Days 1 and 93.

Figure 5 (Reviewer). Study TG1101-RMS301 Subject (b) (6) Liver Laboratory Values



Source: FDA Analysis Studio, Hepatic Explorer using ADLB

Reviewer comment: This case was determined to be acute Hepatitis C infection, and is therefore unrelated to ublituximab-xiiy.

- Subject (b) (6) (a 38 year-old woman receiving ublituximab-xiiy) experienced the TEAE toxic skin eruption (Grade 2, "toxicodermatosis") on (b) (6), 2 days after her second ublituximab-xiiy infusion. She began treatment with ublituximab-xiiy on (b) (6) and received a subsequent infusion on (b) (6). She experienced fever on (b) (6) for which she was treated with paracetamol. She was treated with dexamethasone, quifenadine, paracetamol, activated charcoal, omeprazole, and methylprednisolone. On (b) (6), her laboratory values were notable for ALC of $0.8 \times 10^9/L$ and WBCs of $3.3 \times 10^9/L$. Study treatments were discontinued due to this SAE, which was recovered/resolved on (b) (6). No concurrent TEAEs were reported.
- Subject (b) (6) (a 28 year-old woman receiving ublituximab-xiiy) experienced the AE neutropenia (Grade 3, but not considered serious) on (b) (6) after beginning treatment with ublituximab-xiiy on (b) (6) and receiving subsequent infusions on (b) (6). On (b) (6), her ANC was $0.7 \times 10^9/L$, and WBC count was $2.3 \times 10^9/L$. On (b) (6), her ANC was $0.5 \times 10^9/L$, and WBC count was $2.1 \times 10^9/L$. Prior to this event, her on-treatment ANC nadir was $0.7 \times 10^9/L$ (b) (6). Of note, she had a low WBC count pre-dose ($3.0 \times 10^9/L$ on Week 1 Day 1, (b) (6); $2.4 \times 10^9/L$ on (b) (6)). Study

treatment was discontinued due to this event, which was reported as recovered/resolved on (b) (6). She did not receive any treatment for this SAE, and no concurrent TEAEs were reported with this event.

- Subject (b) (6) (a 42 year-old woman receiving ublituximab-xiiy) experienced the AE myocardial ischemia (Grade 2, "myocardial silent ischemia"). She had a history of dyslipidemia. She received her first dose of ublituximab-xiiy on (b) (6) and did not receive any subsequent doses. On (b) (6), she experienced Grade 2 myocardial ischemia, for which she was treated with metoprolol and rosuvastatin and the event resolved the same day. This event was considered an IRR by the investigator. Notably, her blood pressure was 90/60mmHg on the day of this event. Her heart rate was documented as 80 bpm. Pre-dose ECG was notable for incomplete right bundle branch block (RBBB, which was also observed at screening). Post-dose, she was noted to have ischemic changes (ST depression in II, III, AvF; T-wave inversion in V2-V5). Later that day, her ECG again demonstrated RBBB. ECGs on (b) (6) showed "ischemic type changes" and on (b) (6) showed incomplete RBBB. On (b) (6) her urinalysis was suggestive of infection, ALC was low at $0.4 \times 10^9/L$, and ANC was high at $8.6 \times 10^9/L$; a concurrent TEAE of lymphopenia was also reported. She discontinued study treatment due to the event of myocardial ischemia.

Reviewer comment: The etiology and characterization of this subject's "myocardial ischemia" is not clear from the information provided in the narrative. It is possible that the subject experienced hypotension (potentially due to a delayed infusion-related reaction), leading to demand ischemia and a positive troponin level, but this information is not provided. The role of her likely urinary tract infection in this event is also unclear.

- Subject (b) (6) is discussed in Section 8.4.2. She appeared to have recurrent IRRs which likely led to discontinuation, but the reason listed for discontinuation was "sponsor or investigator decision."

Study TG1101-RMS302

Treatment-emergent adverse events (TEAEs) in Study TG1101-RMS302 leading to permanent discontinuation of study treatment are reported by PT in Table 55. Again, subjects receiving ublituximab-xiiy were more likely to discontinue study treatment due to an adverse event than those receiving teriflunomide (1.8% vs. 0.7%, respectively). Additionally, the most common adverse events leading to discontinuation in the ublituximab-xiiy group were infections and cytopenias. Discontinuations due to AEs were less common in subjects receiving ublituximab-xiiy in Study TG1101-RMS302 compared to TG1101-RMS301. Selected narratives for subjects receiving ublituximab-xiiy are discussed below, and several of these cases are discussed as SAEs in Section 8.4.2.

Table 55 (Reviewer). Study TG1101-RMS302, Adverse Events Leading to Permanent Discontinuation of Study Treatment, by Preferred Term

	Ublituximab-xiyy (N = 272) n (%)	Teriflunomide (N = 273) n (%)
Total Subjects with any TEAE leading to discontinuation	5 (1.8)	2 (0.7)
Alanine aminotransferase increased	0 (0.0)	1 (0.4)
Chronic hepatitis B	1 (0.4)	0 (0.0)
Decreased activity	1 (0.4)	0 (0.0)
Dysaesthesia	1 (0.4)	0 (0.0)
Fatigue	1 (0.4)	0 (0.0)
Febrile neutropenia	1 (0.4)	0 (0.0)
Gastric ulcer	1 (0.4)	0 (0.0)
Hydrothorax	1 (0.4)	0 (0.0)
Left ventricular hypertrophy	1 (0.4)	0 (0.0)
Muscular weakness	1 (0.4)	0 (0.0)
Oedema peripheral	1 (0.4)	0 (0.0)
Pancreatitis haemorrhagic	1 (0.4)	0 (0.0)
Pneumonia	1 (0.4)	0 (0.0)
Pyelonephritis chronic	0 (0.0)	1 (0.4)
Tracheobronchitis	1 (0.4)	0 (0.0)

Source: ADAE where SAFFL=Y, TRTEMFL=Y, ADISAFL=Y, by TRT01A

- Subject (b) (6) (a 41 year-old woman receiving ublituximab-xiyy) experienced the SAE chronic hepatitis B (Grade 2, "chronic viral hepatitis B") on (b) (6). She received her first dose of ublituximab-xiyy on (b) (6), with subsequent infusions on (b) (6). Concurrent TEAEs included AST increased. She experienced AST 100 U/L and ALT 187 U/L on (b) (6), then AST 235 U/L and ALT 293 U/L on (b) (6). hepatitis B surface antigen was positive. She was treated with ademetonine and tenofovir (b) (6) and discontinued study participation due to this AE. Her last study labs on (b) (6) were notable for ALT 18 U/L and AST 21 U/L (normal). At screening (b) (6), hepatitis B surface antigen was negative.

Reviewer comment: Though hepatitis B surface antigen was negative at screening, this test alone is not adequate to determine whether a subject was previously infected with hepatitis B and therefore at risk for reactivation. Labeling for anti-CD20 therapies discusses hepatitis B reactivation risk and delineates the appropriate required screening; hepatitis B will be discussed in potential ublituximab-xiyy labeling as well.

Study TG1101-RMS303

Treatment-emergent adverse events (TEAEs) in Study TG1101-RMS303 leading to permanent

discontinuation of study treatment are reported by PT in Table 56. Selected narratives are discussed below, and several of these cases are discussed as SAEs in Section 8.4.2.

Table 56 (Reviewer). Study TG1101-RMS303, Adverse Events Leading to Permanent Discontinuation of Study Treatment, by Preferred Term

	Ublituximab-xiiy/ Ublituximab-xiiy (N = 319) n (%)	Teriflunomide/ Ublituximab-xiiy (N = 323) n (%)	Overall (N = 642) n (%)
Total Subjects with any TEAE leading to discontinuation	3 (0.9)	3 (0.9)	6 (0.9)
COVID-19 pneumonia	3 (0.9)	0 (0.0)	3 (0.5)
Infusion related reaction	0 (0.0)	2 (0.6)	2 (0.3)
Febrile neutropenia	0 (0.0)	1 (0.3)	1 (0.2)
Immune reconstitution inflammatory syndrome	0 (0.0)	1 (0.3)	1 (0.2)
Interstitial lung disease	0 (0.0)	1 (0.3)	1 (0.2)

Source: ADAE for Phase 3 ISS (ISS-IDB1), where STUDYID = TG1101-RMS303, ADISAFY=Y

Reviewer comment: Overall, the frequency of discontinuation due to adverse events was low (0.9%), but AEs leading to discontinuation included infections, cytopenias, infusion-related reactions, and interstitial lung disease. The subject who experienced febrile neutropenia, IRIS, and interstitial lung disease ((b) (6)) is discussed in Section 8.4.2.

Studies TG1101-RMS201/201E

One subject permanently discontinued study treatment (ublituximab-xiiy) during Study TG1101-RMS201 due to the TEAE of pregnancy.

120-Day Safety Update

Per the 120-day Safety Update, 8 additional subjects in Study TG1101-RMS303 discontinued ublituximab-xiiy due to an adverse event, mostly due to infection (specifically COVID-19 pneumonia).

8.4.4. Significant Adverse Events

Significant adverse events are discussed in other sections of this safety review. However, a case of hepatotoxicity in an ublituximab-xiiy-treated subject warrants discussion.

- Subject (b) (6) (a 38 year-old woman receiving ublituximab-xiiy) experienced the AE hepatotoxicity (Grade 3) on (b) (6) weeks after her second ublituximab-xiiy infusion. She began treatment with ublituximab-xiiy on (b) (6), and received subsequent infusions on (b) (6). Peak AST

was 229 U/L on (b) (6) normalized to 16 U/L on (b) (6), then was normal for the remainder of the study. Peak ALT was 388 U/L on (b) (6), normalized to 20 U/L on (b) (6), then was normal for the remainder of the study. Concurrent AEs included thrombocytopenia (platelet nadir $98 \times 10^9/L$, with recovery to baseline 1 week later), pyrexia, and GGT increased. Alkaline phosphatase was normal. Concomitant medications included propranolol and cholecalciferol. Additionally, per the Patient Profile document, this AE involved a protocol deviation, as the event occurred on the Day 28 visit but was not recognized until the Day 56 Visit by the investigators. Therefore, protocol procedures for this event were not followed and it does not appear that other evaluation was performed. The subject completed study participation as planned, and rechallenge was negative.

Reviewer comment: The etiology of this subject's AST/ALT elevation and thrombocytopenia is not clear, but the fact that the laboratory values resolved despite continued treatment suggests an etiology other than ublituximab-xiyy. However, a relationship to ublituximab-xiyy cannot be excluded based on the information provided.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study TG1101-RMS301

In Study TG1101-RMS301, 86.1% of subjects on ublituximab-xiyy and 89.1% of subjects on teriflunomide experienced at least 1 TEAE. Subjects receiving ublituximab-xiyy were more likely to experience CTCAE Grade 3 (25.6%), 4 (2.2%), and 5 (0.7%) events compared to those on teriflunomide (15.6%, 0.4%, and 0%, respectively) (Table 57).

Table 57 (Reviewer). Study TG1101-RMS301, TEAEs by CTCAE Severity

	Ublituximab-xiyy (N = 273) n (%)	Teriflunomide (N = 275) n (%)
Proportion of subjects experiencing any TEAE	235 (86.1)	245 (89.1)
Grade 1	206 (75.5)	205 (74.5)
Grade 2	154 (56.4)	154 (56.0)
Grade 3	70 (25.6)	43 (15.6)
Grade 4	6 (2.2)	1 (0.4)
Grade 5	2 (0.7)	0 (0)

Source: ADAE where SAFFL=Y, TRTEMFL=Y, Summary(USUBJID, TRT01A, ATOXGRN), tabulated by ATOXGRN and TRT01A

Reviewer comment: Please refer to Section 8.3.1 for discussion regarding the applicant's assignment of TEAE severity.

TEAEs in the SOC Infections and Infestations were most commonly reported, and occurred at a similar frequency in the ublituximab-xiyy and teriflunomide groups (49.5% vs. 48.4%,

respectively) (Table 58). TEAEs in the SOC General Disorders and Administration Site Conditions occurred more frequently in subjects on ublituximab-xiiy versus teriflunomide (39.2% versus 16.7%, respectively).

Table 58 (Reviewer). Study TG1101-RMS301, TEAEs by System Organ Class in Safety Population

	Ublituximab-xiiy (N = 273) n (%)	Teriflunomide (N = 275) n (%)
Total Subjects with any TEAE	235 (86.1)	245 (89.1)
Infections and infestations	135 (49.5)	133 (48.4)
Nervous system disorders	113 (41.4)	96 (34.9)
Investigations	95 (34.8)	80 (29.1)
Gastrointestinal disorders	81 (29.7)	84 (30.5)
General disorders and administration site conditions	107 (39.2)	46 (16.7)
Musculoskeletal and connective tissue disorders	55 (20.1)	62 (22.5)
Skin and subcutaneous tissue disorders	34 (12.5)	60 (21.8)
Blood and lymphatic system disorders	47 (17.2)	37 (13.5)
Respiratory, thoracic and mediastinal disorders	47 (17.2)	37 (13.5)
Psychiatric disorders	34 (12.5)	30 (10.9)
Injury, poisoning and procedural complications	30 (11.0)	30 (10.9)
Cardiac disorders	27 (9.9)	21 (7.6)
Vascular disorders	20 (7.3)	26 (9.5)
Reproductive system and breast disorders	18 (6.6)	21 (7.6)
Renal and urinary disorders	16 (5.9)	18 (6.5)
Eye disorders	14 (5.1)	16 (5.8)
Metabolism and nutrition disorders	6 (2.2)	12 (4.4)
Immune system disorders	10 (3.7)	6 (2.2)
Hepatobiliary disorders	7 (2.6)	7 (2.5)
Ear and labyrinth disorders	7 (2.6)	4 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.8)	4 (1.5)
Endocrine disorders	2 (0.7)	4 (1.5)
Surgical and medical procedures	3 (1.1)	3 (1.1)
Social circumstances	0 (0.0)	2 (0.7)
Congenital, familial and genetic disorders	0 (0.0)	1 (0.4)
Pregnancy, puerperium and perinatal conditions	1 (0.4)	0 (0.0)

Source: ADAE, SAFFL=Y, TRTEMFL=Y, AESOC by TRT01A

TEAEs occurring in >3% of subjects in either treatment group are listed by PT in Table 59. The most common TEAEs that were more frequent in the ublituximab-xiiy group included headache (30.8% ublituximab-xiiy versus 21.5% teriflunomide), pyrexia (15.0% vs 4.7%), lymphocyte count decreased (12.5% vs 2.9%), nausea (10.6% vs 5.5%), lymphopenia (9.9% vs 1.5%), respiratory tract infection viral (7.3% vs 2.9%), chills (7.0% vs 0.4%), rhinitis (6.2% vs 2.9%), aspartate aminotransferase increased (5.1% vs 1.5%), hyperthermia (4.8% vs 0.7%), body temperature increased (4.4% vs 1.1%), bronchitis (4.4% vs 1.8%), and influenza like illness (4.0% vs 1.5%).

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Table 59 (Reviewer). Study TG1101-RMS301, TEAEs Occurring in >3% of Either Treatment Group, by Preferred Term, in Safety Population

	Ublituximab-xiiy (N = 273) n (%)	Teriflunomide (N = 275) n (%)
Total Subjects with any TEAE	235 (86.1)	245 (89.1)
Headache	84 (30.8)	59 (21.5)
Pyrexia	41 (15.0)	13 (4.7)
Nasopharyngitis	34 (12.5)	44 (16.0)
Lymphocyte count decreased	34 (12.5)	8 (2.9)
Nausea	29 (10.6)	15 (5.5)
Lymphopenia	27 (9.9)	4 (1.5)
Respiratory tract infection viral	20 (7.3)	8 (2.9)
Chills	19 (7.0)	1 (0.4)
Diarrhoea	19 (7.0)	26 (9.5)
Rhinitis	17 (6.2)	8 (2.9)
Upper respiratory tract infection	17 (6.2)	15 (5.5)
Back pain	16 (5.9)	30 (10.9)
Abdominal pain	15 (5.5)	9 (3.3)
Pain in extremity	15 (5.5)	12 (4.4)
Aspartate aminotransferase increased	14 (5.1)	4 (1.5)
Hyperthermia	13 (4.8)	2 (0.7)
Oropharyngeal pain	13 (4.8)	10 (3.6)
Body temperature increased	12 (4.4)	3 (1.1)
Bronchitis	12 (4.4)	5 (1.8)
Cough	12 (4.4)	7 (2.5)
Fatigue	12 (4.4)	9 (3.3)
Influenza	12 (4.4)	11 (4.0)
Insomnia	12 (4.4)	8 (2.9)
Respiratory tract infection	12 (4.4)	10 (3.6)
Alanine aminotransferase increased	11 (4.0)	15 (5.5)
Hypertension	11 (4.0)	22 (8.0)
Influenza like illness	11 (4.0)	4 (1.5)
Neutropenia	11 (4.0)	12 (4.4)
Urinary tract infection	11 (4.0)	17 (6.2)
Asthenia	10 (3.7)	9 (3.3)
Neck pain	10 (3.7)	6 (2.2)
Tachycardia	10 (3.7)	6 (2.2)
Anxiety	8 (2.9)	11 (4.0)
Cystitis	8 (2.9)	9 (3.3)
Abdominal pain upper	7 (2.6)	14 (5.1)
Lipase increased	7 (2.6)	13 (4.7)
Alopecia	6 (2.2)	36 (13.1)
Leukopenia	5 (1.8)	13 (4.7)
Sinusitis	4 (1.5)	12 (4.4)
White blood cell count decreased	4 (1.5)	11 (4.0)

Source: ADAE, SAFFL=Y, TRTEMFL=Y, AEDECOD by TRT01A

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Study TG1101-RMS302

In Study TG1101-RMS302, 92.3% of subjects on ublituximab-xiiy and 93.8% of subjects on teriflunomide experienced at least 1 TEAE. Subjects receiving ublituximab-xiiy were more likely to experience CTCAE Grade 3 (14.7%), 4 (2.2%), and 5 (0.4%) events compared to those on teriflunomide (12.1%, 1.1%, and 0%, respectively) (Table 60).

Table 60 (Reviewer). Study TG1101-RMS302, TEAEs by CTCAE Severity

	Ublituximab-xiiy (N = 272) n (%)	Teriflunomide (N = 273) n (%)
Proportion of subjects experiencing any TEAE	251 (92.3)	256 (93.8)
Grade 1	226 (83.1)	232 (85.0)
Grade 2	171 (62.9)	151 (55.3)
Grade 3	40 (14.7)	33 (12.1)
Grade 4	6 (2.2)	3 (1.1)
Grade 5	1 (0.4)	0 (0)

Source: ADAE where SAFFL=Y, TRTEMFL=Y, Summary(USUBJID, TRT01A, ATOXGRN), tabulated by ATOXGRN and TRT01A

Reviewer comment: Please refer to Section 8.3.1 for discussion regarding the applicant's assignment of TEAE severity.

TEAEs in the SOC Infections and Infestations were most commonly reported, and occurred at a similar frequency in the ublituximab-xiiy and teriflunomide groups (62.1 vs 60.4%, respectively) (Table 61). Similar to Study TG1101-RMS301, TEAEs in the SOC General Disorders and Administration Site Conditions occurred more frequently in subjects on ublituximab-xiiy versus teriflunomide (46.3% versus 22.7%, respectively). Additionally, TEAEs in the SOC Respiratory, Thoracic and Mediastinal disorders occurred more frequently in subjects on ublituximab-xiiy versus teriflunomide (23.2% vs 11.7%).

Table 61 (Reviewer). Study TG1101-RMS302, TEAEs by System Organ Class in Safety Population

	Ublituximab-xiiy (N = 272) n (%)	Teriflunomide (N = 273) n (%)
Total Subjects with any TEAE	251 (92.3)	256 (93.8)
Infections and infestations	169 (62.1)	165 (60.4)
Nervous system disorders	126 (46.3)	113 (41.4)
Gastrointestinal disorders	110 (40.4)	118 (43.2)
General disorders and administration site conditions	126 (46.3)	62 (22.7)
Musculoskeletal and connective tissue disorders	74 (27.2)	57 (20.9)
Investigations	75 (27.6)	49 (17.9)
Skin and subcutaneous tissue disorders	50 (18.4)	74 (27.1)
Respiratory, thoracic and mediastinal disorders	63 (23.2)	32 (11.7)
Blood and lymphatic system disorders	47 (17.3)	45 (16.5)
Psychiatric disorders	49 (18.0)	37 (13.6)
Injury, poisoning and procedural complications	46 (16.9)	33 (12.1)
Cardiac disorders	41 (15.1)	29 (10.6)
Reproductive system and breast disorders	30 (11.0)	32 (11.7)
Vascular disorders	21 (7.7)	29 (10.6)
Renal and urinary disorders	21 (7.7)	18 (6.6)
Eye disorders	14 (5.1)	15 (5.5)
Ear and labyrinth disorders	16 (5.9)	10 (3.7)
Immune system disorders	15 (5.5)	11 (4.0)
Metabolism and nutrition disorders	12 (4.4)	10 (3.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (3.3)	6 (2.2)
Hepatobiliary disorders	6 (2.2)	5 (1.8)
Surgical and medical procedures	2 (0.7)	2 (0.7)
Congenital, familial and genetic disorders	2 (0.7)	0 (0.0)
Endocrine disorders	1 (0.4)	1 (0.4)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	1 (0.4)
Social circumstances	0 (0.0)	1 (0.4)

Source: ADAE, SAFFL=Y, TRTEMFL=Y, AESOC by TRT01A

TEAEs occurring in >3% of subjects in either treatment group are listed by PT in Table 62. The most common TEAEs that were more frequent in the ublituximab-xiiy group included headache (37.9% ublituximab-xiiy versus 31.9% teriflunomide), pyrexia (12.9% vs 5.1%), abdominal pain (10.3% vs 4.4%), influenza like illness (10.3% vs 2.6%), lymphopenia (9.6% vs 0.7%), chills (9.2% vs 1.1%), pharyngitis (8.8% vs 2.2%), insomnia (7.7% vs 2.9%), sinus tachycardia (7.4% vs 1.8%), infusion related reaction (7.0% vs 0.7%), hyperthermia (6.6% vs 1.5%), oropharyngeal pain (6.6% vs 3.3%), lymphocyte count decreased (5.5% vs 0.7%), throat irritation (5.1% vs 0.4%), body temperature increased (4.4% vs 1.1%), cough (4.4% vs 1.1%), acute sinusitis (3.7% vs 0.7%), aspartate aminotransferase increased (3.7% vs 2.2%), and erythema (3.3% vs 0.7%).

Table 62 (Reviewer). Study TG1101-RMS302, TEAEs Occurring in >3% of Either Treatment Group in Safety Population, by Preferred Term

	Ublituximab-xiiy (N = 272) n (%)	Teriflunomide (N = 273) n (%)
Total Subjects with any TEAE	251 (92.3)	256 (93.8)
Headache	103 (37.9)	87 (31.9)
Nasopharyngitis	66 (24.3)	54 (19.8)
Back pain	35 (12.9)	23 (8.4)
Pyrexia	35 (12.9)	14 (5.1)
Respiratory tract infection	30 (11.0)	28 (10.3)
Nausea	29 (10.7)	28 (10.3)
Abdominal pain	28 (10.3)	12 (4.4)
Influenza like illness	28 (10.3)	7 (2.6)
Lymphopenia	26 (9.6)	2 (0.7)
Diarrhoea	25 (9.2)	32 (11.7)
Chills	25 (9.2)	3 (1.1)
Upper respiratory tract infection	24 (8.8)	23 (8.4)
Alopecia	13 (4.8)	48 (17.6)
Pharyngitis	24 (8.8)	6 (2.2)
Respiratory tract infection viral	22 (8.1)	23 (8.4)
Insomnia	21 (7.7)	8 (2.9)
Sinus tachycardia	20 (7.4)	5 (1.8)
Infusion related reaction	19 (7.0)	2 (0.7)
Hyperthermia	18 (6.6)	4 (1.5)
Oropharyngeal pain	18 (6.6)	9 (3.3)
Arthralgia	17 (6.3)	13 (4.8)
Cystitis	17 (6.3)	11 (4.0)
Sinusitis	17 (6.3)	12 (4.4)
Anxiety	16 (5.9)	12 (4.4)
Asthenia	16 (5.9)	20 (7.3)
Constipation	16 (5.9)	17 (6.2)
Dizziness	16 (5.9)	12 (4.4)
Dyspepsia	16 (5.9)	15 (5.5)
Fatigue	16 (5.9)	11 (4.0)
Pain in extremity	16 (5.9)	12 (4.4)
Toothache	16 (5.9)	15 (5.5)
Lymphocyte count decreased	15 (5.5)	2 (0.7)
Oral herpes	14 (5.1)	16 (5.9)
Throat irritation	14 (5.1)	1 (0.4)
Abdominal pain upper	13 (4.8)	9 (3.3)
Body temperature increased	12 (4.4)	3 (1.1)
Bronchitis	12 (4.4)	13 (4.8)
Cough	12 (4.4)	3 (1.1)
Dysmenorrhoea	12 (4.4)	15 (5.5)
Urinary tract infection	11 (4.0)	12 (4.4)
Acute sinusitis	10 (3.7)	2 (0.7)
Alanine aminotransferase increased	10 (3.7)	11 (4.0)
Aspartate aminotransferase increased	10 (3.7)	6 (2.2)
Hypertension	10 (3.7)	15 (5.5)
Tachycardia	10 (3.7)	10 (3.7)

	Ublituximab-xiiy (N = 272) n (%)	Teriflunomide (N = 273) n (%)
Anaemia	9 (3.3)	14 (5.1)
Erythema	9 (3.3)	2 (0.7)
Vaginal infection	9 (3.3)	6 (2.2)
Myalgia	8 (2.9)	9 (3.3)
Neutropenia	7 (2.6)	11 (4.0)
Rhinitis	7 (2.6)	13 (4.8)
Neutrophilia	6 (2.2)	13 (4.8)
Leukocytosis	5 (1.8)	12 (4.4)
Vomiting	5 (1.8)	12 (4.4)
Hypoaesthesia	4 (1.5)	10 (3.7)
Gastroenteritis	3 (1.1)	10 (3.7)
Rash	3 (1.1)	10 (3.7)

Source: ADAE, SAFFL=Y, TRTEMFL=Y, AEDECOD by TRT01A

Study TG1101-RMS303

TEAEs occurring in >1% of the safety population in Study TG1101-RMS303 as of the BLA data cutoff date (11/23/2020) are summarized by PT in Table 63. Overall, 36.0% of subjects experienced at least 1 TEAE. The frequency of TEAEs was higher in those who had previously received teriflunomide (41.2%) compared to ublituximab-xiiy (30.7%). Common TEAEs include infections (COVID-19, COVID-19 pneumonia, and nasopharyngitis), chills, pyrexia, infusion-related reaction, and headache.

Table 63 (Reviewer). Study TG1101-RMS303, TEAEs Occurring in >1% of Safety Population, by Preferred Term

	Ublituximab-xiiy/ Ublituximab-xiiy (N = 319)	Teriflunomide/ Ublituximab-xiiy (N = 323)	Overall (N = 642)
Total Subjects with any TEAE	98 (30.7)	133 (41.2)	231 (36.0)
Chills	7 (2.2)	27 (8.4)	34 (5.3)
Pyrexia	14 (4.4)	20 (6.2)	34 (5.3)
COVID-19	13 (4.1)	10 (3.1)	23 (3.6)
Headache	8 (2.5)	14 (4.3)	22 (3.4)
Infusion related reaction	1 (0.3)	11 (3.4)	12 (1.9)
COVID-19 pneumonia	7 (2.2)	2 (0.6)	9 (1.4)
Nausea	1 (0.3)	8 (2.5)	9 (1.4)
Neutropenia	7 (2.2)	2 (0.6)	9 (1.4)
Tachycardia	4 (1.3)	5 (1.5)	9 (1.4)
Nasopharyngitis	3 (0.9)	5 (1.5)	8 (1.2)
Arthralgia	4 (1.3)	3 (0.9)	7 (1.1)
Throat irritation	3 (0.9)	4 (1.2)	7 (1.1)

Source: ADAE for Phase 3 ISS (ISS-IDB1), where STUDYID = TG1101-RMS303, TRTEMFL=Y, AEDECOD by TRT01A

Reviewer comment: These findings are consistent with those observed in the double-blind treatment periods of Studies TG1101-RMS301 and TG1101-RMS302. However, the

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frequency of COVID-19 infection was higher in the extension study, presumably related to period effects. Refer to Section 8.5.7 for discussion of COVID-19.

Study TG1101-RMS201

In Study TG1101-RMS201, 100% of subjects experienced at least 1 TEAE while on ublituximab-xiiy, compared to 61.5% of subjects while receiving placebo. TEAEs in the SOC Nervous System Disorders were most commonly reported (70.8% ublituximab-xiiy, 0% placebo). TEAEs in the SOC Infections and Infestations occurred in 58.3% of subjects on ublituximab-xiiy (compared to 30.8% when on placebo), and TEAEs under the SOC Gastrointestinal Disorders occurred in 58.3% of subjects on ublituximab-xiiy (compared to 7.7% when on placebo). TEAEs in all other SOCs occurred more frequently in subjects on ublituximab-xiiy versus placebo.

TEAEs occurring in >5% of subjects are listed by PT in Table 64. The most common TEAEs that were more frequent while subjects were receiving ublituximab-xiiy were fatigue (29.2%), headache (25.0%), nausea (18.8%), arthralgia (14.6%), dizziness (14.6%), hypoaesthesia (14.6%), infusion related reaction (14.6%), and upper respiratory tract infection (14.6%).

Reviewer comment: The safety data from Study TG1101-RMS201 are not considered placebo-controlled due to the delayed start design.

Table 64 (Reviewer). Study TG1101-RMS201, TEAEs Occurring in >5% of Safety Population, by Preferred Term

	Ublituximab-xiiy (N = 48) n (%)	Placebo (N = 13) n (%)
Total Subjects with any TEAE	48 (100.0)	8 (61.5)
Fatigue	14 (29.2)	1 (7.7)
Headache	12 (25.0)	0 (0)
Nausea	9 (18.8)	0 (0)
Nasopharyngitis	5 (10.4)	3 (23.1)
Arthralgia	7 (14.6)	0 (0)
Dizziness	7 (14.6)	0 (0)
Hypoaesthesia	7 (14.6)	0 (0)
Infusion related reaction	7 (14.6)	0 (0)
Upper respiratory tract infection	7 (14.6)	0 (0)
Back pain	6 (12.5)	0 (0)
Influenza	6 (12.5)	0 (0)
Rash	5 (10.4)	1 (7.7)
Sinusitis	5 (10.4)	1 (7.7)
Cough	5 (10.4)	0 (0)
Diarrhoea	5 (10.4)	0 (0)
Throat irritation	5 (10.4)	0 (0)
Constipation	4 (8.3)	0 (0)
Depression	4 (8.3)	0 (0)
Dysphagia	4 (8.3)	0 (0)
Muscle spasms	4 (8.3)	0 (0)
Pyrexia	4 (8.3)	0 (0)
Vomiting	4 (8.3)	0 (0)
Abdominal discomfort	2 (4.2)	1 (7.7)
Abdominal pain upper	3 (6.3)	0 (0)
Contusion	3 (6.3)	0 (0)
Flushing	3 (6.3)	0 (0)
Fungal infection	3 (6.3)	0 (0)
Insomnia	3 (6.3)	0 (0)
Migraine	3 (6.3)	0 (0)
Musculoskeletal pain	3 (6.3)	0 (0)
Oropharyngeal pain	3 (6.3)	0 (0)
Pain	2 (4.2)	1 (7.7)
Pruritis	3 (6.3)	0 (0)
Vision blurred	3 (6.3)	0 (0)

Source: ADAE for TG1101-RMS201 where SAFFL=Y, TRTEMFL=Y for ublituximab-xiiy, PTRTEMFL=Y for placebo

Study TG1101-RMS201E

In Study TG1101-RMS201E, 76.7% of subjects experienced at least 1 TEAE. TEAEs in the SOC Infections and Infestations were most commonly reported (41.9%), followed by Respiratory Thoracic and Mediastinal Disorders (30.2%) and General Disorders and Administration Site Conditions (27.9%). The most common (>5%) TEAEs included fatigue (11.6%), throat irritation

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(11.6%), urinary tract infection (11.6%), rash (9.3%), bronchitis (7.0%), dyspnea (7.0%), gait disturbance (7.0%), and sinusitis (7.0%).

120-Day Safety Update

Per the 120-day Safety Update, reported TEAEs appeared consistent with those reported at the time of BLA submission.

8.4.6. Laboratory Findings

Laboratory data from ADLB were analyzed for Studies TG1101-RMS301 and TG1101-RMS302. This analysis will focus on laboratory parameters of interest that were identified based on prior knowledge of the safety profile of anti-CD20 therapies, as well as the adverse events from the ublituximab-xiiy development program.

Laboratory values were evaluated at each scheduled timepoint (designated by applicant's ANL01FL=Y in ADLB dataset), and descriptive analyses (including analyses of change from baseline) are presented for Baseline, Week 4, Week 24, Week 48, and Week 96 of the DBT period for Studies TG1101-RMS301 and TG1101-RMS302. OLE data from Study TG1101-RMS303 were also reviewed for overall consistency with DBT period findings. Laboratory data collected via local laboratories or outside of scheduled study visits are discussed in the context of adverse events.

Study TG1101-RMS301

Hematology

Leukocytes

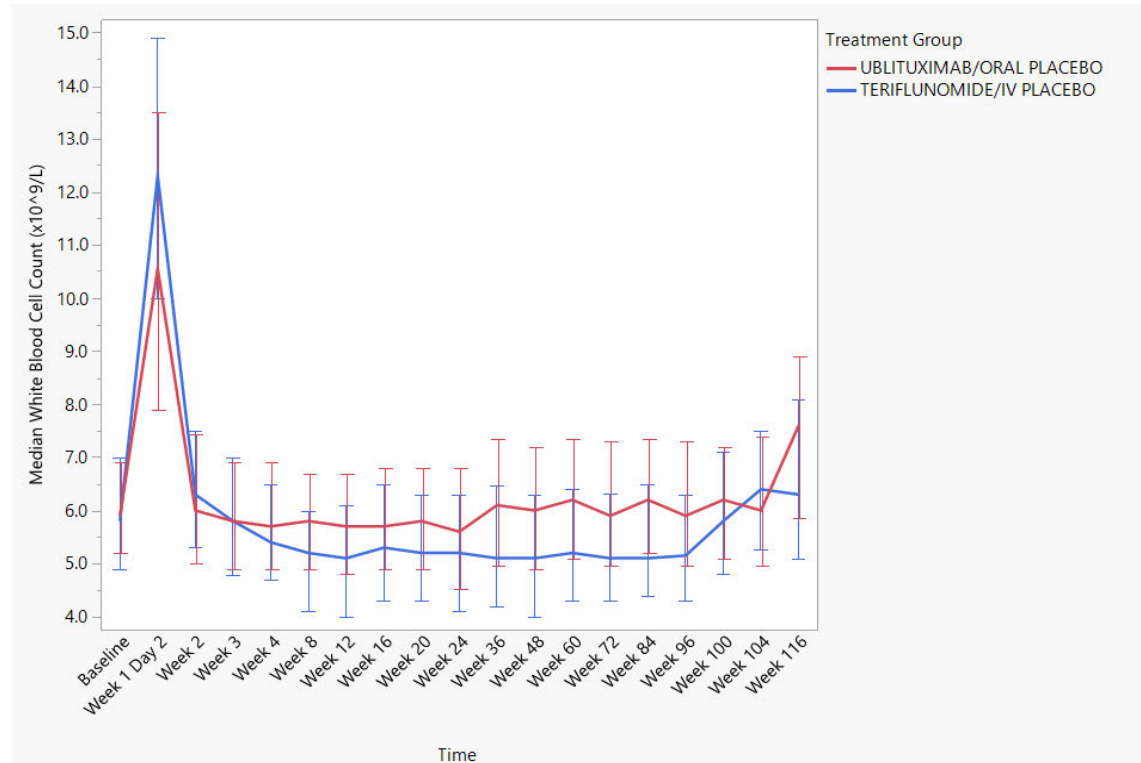
Overall leukocyte count (white blood cell count [WBC], # cells $\times 10^9/L$) were evaluated at each visit during DBT, with representative timepoints shown in Table 65 and median WBCs over time in Figure 6.

Table 65 (Reviewer). Study TG1101-RMS301, WBCs (x10⁹/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiy (n = 273)	Teriflunomide (n = 275)
Baseline	Mean (SD)	6.2 (1.8)	6.1 (1.6)
	Median	5.9	5.8
	Min, Max	2.3, 15.5	2.3, 11.3
Week 4	N	268	271
	Mean (SD)	6.0 (1.7)	5.7 (1.7)
	Median	5.7	5.4
	Min, Max	2.5, 14.8	13.6
	Mean (SD) change from baseline	-0.2 (1.7)	-0.3 (1.5)
	Median change from baseline	-0.2	-0.4
	Min, Max change from baseline	-8.4, 6.7	-4.4, 9.2
Week 24	N	260	263
	Mean (SD)	5.9 (1.7)	5.5 (2.0)
	Median	5.6	5.2
	Min, Max	2.4, 13.6	2.4, 23.6
	Mean (SD) change from baseline	-0.4 (1.9)	-0.6 (1.9)
	Median change from baseline	-0.4	-0.6
Week 48	N	255	260
	Mean (SD)	6.1 (1.7)	5.4 (1.8)
	Median	6.0	5.1
	Min, Max	2.3, 14.3	2.4, 13.5
	Mean (SD) change from baseline	-0.1 (2.0)	-0.6 (1.8)
	Median change from baseline	-0.1	-0.7
Week 96	N	233	248
	Mean (SD)	6.4 (1.9)	5.4 (1.7)
	Median	5.9	5.2
	Min, Max	3.5, 15.4	2.6, 12.7
	Mean (SD) change from baseline	0.1 (1.9)	-0.6 (1.7)
	Median change from baseline	0	-0.7
	Min, Max change from baseline	-9.6, 6.6	-7.5, 9.2

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=WBCB, by TRT01A

Figure 6 (Reviewer). Study TG1101-RMS301, WBC ($\times 10^9/L$) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=WBCH, by TRT01A

Additionally, 20.5% of subjects on ublituximab-xiiy ($n = 56$) and 29.8% of subjects on teriflunomide ($n = 82$) experienced WBCs between 2.0 to $3.5 \times 10^9/L$, and 0.7% of subjects on ublituximab-xiiy ($n = 2$) and 0.7% of subjects on teriflunomide ($n = 2$) experienced WBCs $\leq 2.0 \times 10^9/L$.

Reviewer comment: The peak in WBCs at Week 1 Day 2 (Figure 6) likely reflects reactive leukocytosis in response to corticosteroid administration in the setting of infusion pre-medication. Overall, there appears to be a trend towards lower WBC count in the teriflunomide group compared to ublituximab-xiiy, as mean and median WBC values appeared to be lower in teriflunomide-treated subjects, and the mean/median changes from baseline tended to be more negative in teriflunomide-treated subjects. This finding is not necessarily unexpected due to the broader lymphocyte targeting of teriflunomide compared to ublituximab-xiiy. Additionally, after Week 96 (when teriflunomide was stopped), WBC counts appeared to recover in this group. Week 116 values are difficult to interpret due to low sample size at that time point ($n = 9$ ublituximab-xiiy, $n = 15$ teriflunomide).

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Please refer to Section 8.5.4 for discussion of TEAEs related to leukocyte count (e.g., leukopenia).

Neutrophils

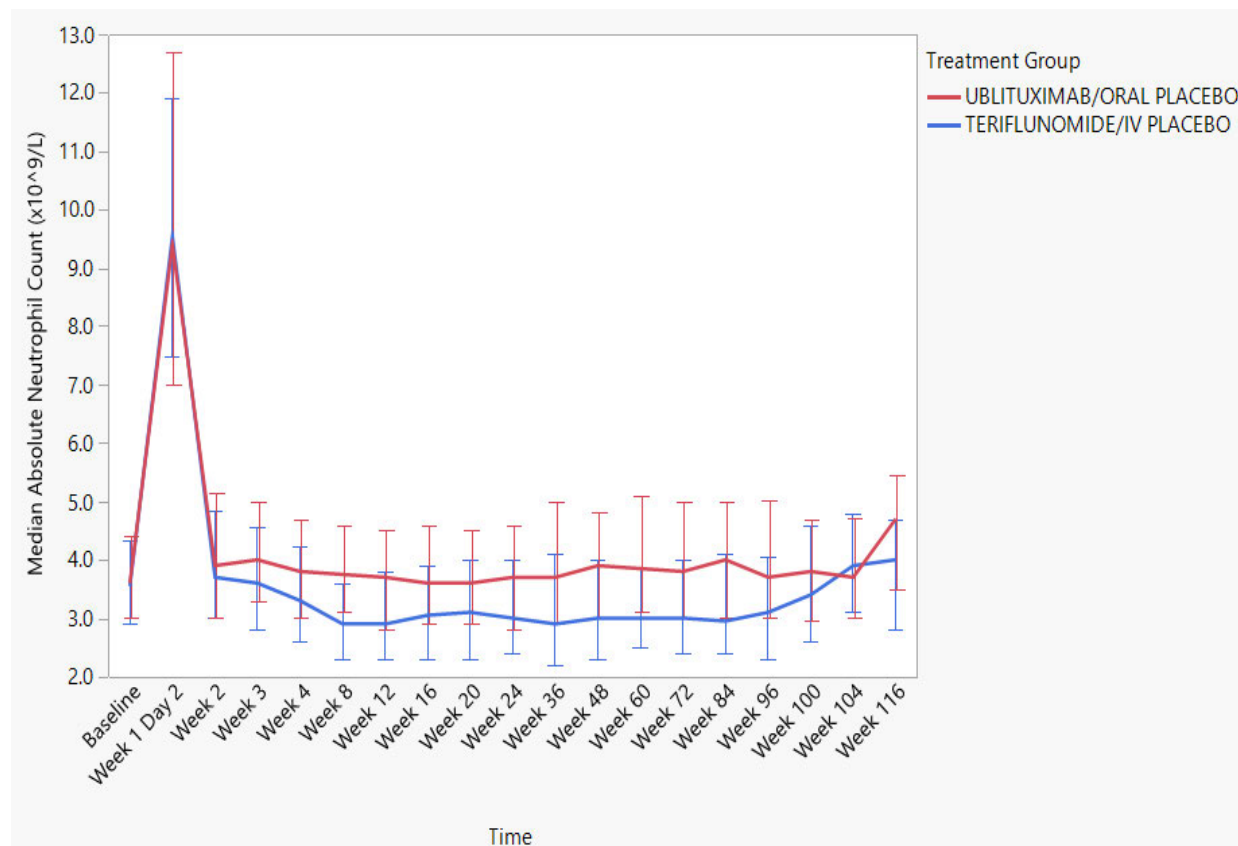
Absolute neutrophil count (ANC, # cells x10⁹/L) was evaluated at each visit during DBT, with representative timepoints shown in Table 66 and median ANC over time in Figure 7.

Table 66 (Reviewer). Study TG1101-RMS301, Absolute Neutrophil Count (x10⁹/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiyy (n = 273)	Teriflunomide (n = 275)
Baseline	Mean (SD)	3.9 (1.5)	3.8 (1.4)
	Median	3.6	3.6
	Min, Max	0.7, 12.9	0.8, 9.1
Week 4	N	267	266
	Mean (SD)	4.0 (1.5)	3.5 (1.4)
	Median	3.8	3.3
	Min, Max	0.9, 12.2	0.8, 11.0
	Mean (SD) change from baseline	0.1 (1.5)	-0.3 (1.3)
	Median change from baseline	0.2	-0.3
	Min, Max change from baseline	-8.6, 6.0	-4.2, 8.4
Week 24	N	255	261
	Mean (SD)	3.9 (1.5)	3.3 (1.7)
	Median	3.7	3.0
	Min, Max	0.7, 11.1	1.2, 20.6
	Mean (SD) change from baseline	-0.03 (1.8)	-0.4 (1.7)
	Median change from baseline	-0.1	-0.5
Week 48	N	254	260
	Mean (SD)	4.1 (1.5)	3.3 (1.5)
	Median	3.9	3.0
	Min, Max	1.2, 12.0	1.0, 10.0
	Mean (SD) change from baseline	0.2 (1.7)	-0.5 (1.6)
Week 96	N	230	245
	Mean (SD)	4.1 (1.7)	3.3 (1.4)
	Median	3.7	3.1
	Min, Max	0.1, 13.2	1.2, 10.3
	Mean (SD) change from baseline	0.2 (1.7)	-0.4 (1.4)
	Median change from baseline	0.2	-0.5
	Min, Max change from baseline	-8.3, 6.0	-6.9, 5.4

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=NEUT, by TRT01A

Figure 7 (Reviewer). Study TG1101-RMS301, Absolute Neutrophil Count ($\times 10^9/L$) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=NEUT, by TRT01A

Additionally, 7.7% of subjects on ublituximab-xiiy ($n = 21$) and 17.8% of subjects on teriflunomide ($n = 49$) experienced ANC between 1.0 to $1.5 \times 10^9/L$, 1.1% of subjects on ublituximab-xiiy ($n = 3$) and 0.7% of subjects on teriflunomide ($n = 2$) experienced ANC between 0.5 to $1.0 \times 10^9/L$, and 1.1% of subjects on ublituximab-xiiy ($n = 3$) and 0% of subjects on teriflunomide ($n = 0$) experienced ANC $\leq 0.5 \times 10^9/L$.

Reviewer comment: The peak in ANC at Week 1 Day 2 (Figure 7) likely reflects reactive leukocytosis in response to corticosteroid administration in the setting of infusion pre-medication. Again, there appears to be a trend towards lower ANC in the teriflunomide group compared to ublituximab-xiiy, as mean and median ANC values appeared to be lower in teriflunomide-treated subjects, and the mean/median changes from baseline tended to be more negative in teriflunomide-treated subjects. Additionally, after Week 96 (when teriflunomide was stopped), ANC appeared to recover in this group. Week 116 values are difficult to interpret due to low sample size at that time point ($n = 9$)

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ublituximab-xiiy, n = 15 teriflunomide). Neutropenia is a known safety issue with teriflunomide. However, subjects who received ublituximab-xiiy were more likely to experience ANC $\leq 0.5 \times 10^9/L$ (1.1% ublituximab-xiiy versus 0% teriflunomide).

Please refer to Section 8.5.4 for discussion of TEAEs related to neutrophil count (e.g., neutropenia).

Lymphocytes

Absolute lymphocyte count (ALC, # cells $\times 10^9/L$) was evaluated at each visit during DBT, with representative timepoints shown in Table 67Table 66 and median ALC over time in Figure 8.

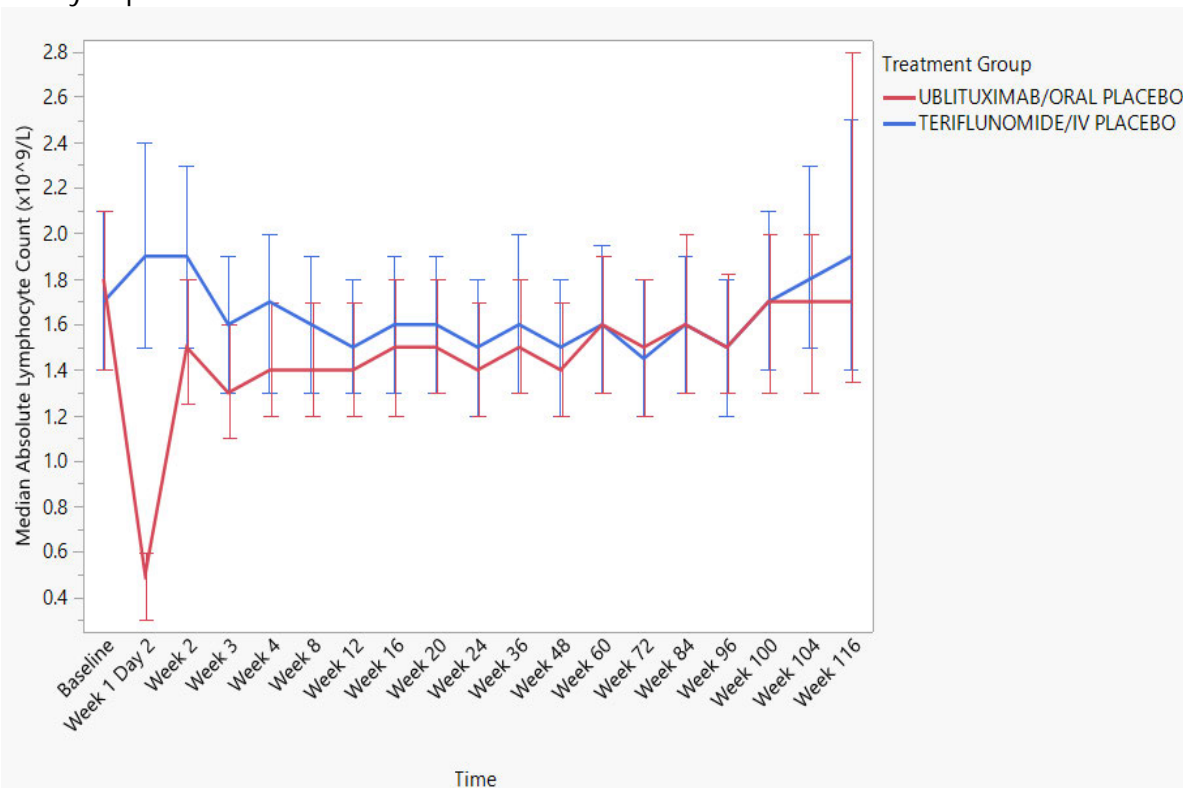
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 Ublituximab-xiiv (Briumvi)

Table 67 (Reviewer). Study TG1101-RMS301, Absolute Lymphocyte Count (x10⁹/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiv (n = 273)	Teriflunomide (n = 275)
Baseline	Mean (SD)	1.8 (0.5)	1.8 (0.5)
	Median	1.8	1.7
	Min, Max	0.8, 4.1	0.3, 3.8
Week 4	N	267	266
	Mean (SD)	1.5 (0.4)	1.7 (0.5)
	Median	1.4	1.7
	Min, Max	0.5, 2.8	0.5, 3.4
	Mean (SD) change from baseline	-0.4 (0.4)	-0.1 (0.4)
	Median change from baseline	-0.3	-0.1
Week 24	N	255	261
	Mean (SD)	1.5 (0.4)	1.6 (0.5)
	Median	1.4	1.5
	Min, Max	0.5, 3.2	0.3, 4.3
	Mean (SD) change from baseline	-0.4 (0.4)	-0.2 (0.4)
	Median change from baseline	-0.3	-0.2
Week 48	N	254	260
	Mean (SD)	1.5 (0.4)	1.6 (0.5)
	Median	1.4	1.5
	Min, Max	0.5, 2.8	0.3, 3.3
	Mean (SD) change from baseline	-0.3 (0.4)	-0.2 (0.4)
	Median change from baseline	-0.3	-0.2
Week 96	N	230	245
	Mean (SD)	1.6 (0.4)	1.6 (0.5)
	Median	1.5	1.5
	Min, Max	0.6, 3.7	0.6, 3.0
	Mean (SD) change from baseline	-0.2 (0.5)	-0.2 (0.4)
	Median change from baseline	-0.2	-0.2
	Min, Max change from baseline	-2.1, 0.9	-2.0, 1.4

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=L YM, by TRT01A

Figure 8 (Reviewer). Study TG1101-RMS301, Absolute Lymphocyte Count ($\times 10^9/L$) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=L YM, by TRT01A

Additionally, 29.7% of subjects on ublituximab-xiiy ($n = 81$) and 26.5% of subjects on teriflunomide ($n = 73$) experienced ALC between 0.5 to $1.0 \times 10^9/L$, and 61.2% of subjects on ublituximab-xiiy ($n = 167$) and 3.6% of subjects on teriflunomide ($n = 10$) experienced $ALC \leq 0.5 \times 10^9/L$.

Reviewer comment: Subjects who received ublituximab-xiiy were much more likely to experience $ALC \leq 0.5 \times 10^9/L$ (61.2% ublituximab-xiiy versus 3.6% teriflunomide). Though low ALC is not unexpected given the mechanism of action of ublituximab-xiiy, this frequency of severe lymphopenia is concerning. This observation is likely driven by ALC at Week 1 Day 2, where the median ALC in subjects on ublituximab-xiiy decreased sharply then recovered, but remained lower than that of teriflunomide for most of the treatment period.

Please refer to Section 8.5.4 for discussion of TEAEs related to lymphocyte count (e.g., lymphopenia).

Hemoglobin, Hematocrit, and Erythrocytes

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Ublituximab-xiiy (Briumvi)

There did not appear to be a clinically significant difference or trend in hemoglobin, hematocrit, or erythrocyte count values or change between the treatment groups. The frequency of subjects experiencing abnormal hemoglobin (either <120 g/L or >160 g/L) or hematocrit (either <0.35 L/L or >0.5 L/L) was similar between the treatment groups. However, subjects on teriflunomide were more likely to experience erythrocytes <4.0 x10¹²/L compared to those on ublituximab-xiiy (20.0% versus 12.5%, respectively).

Platelets

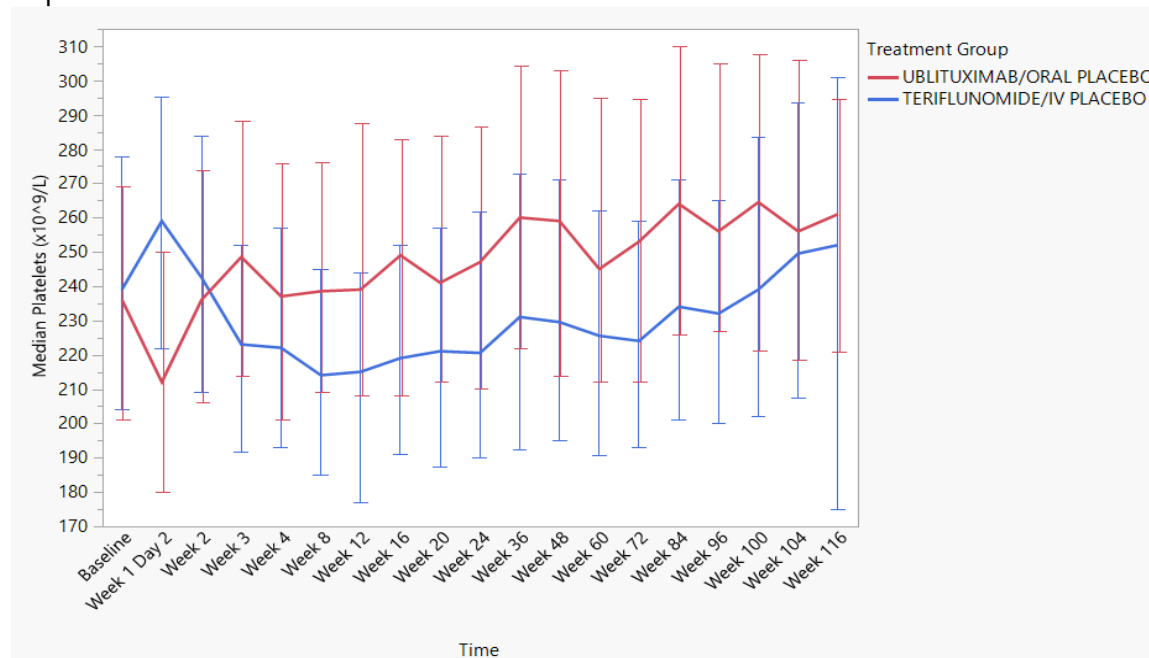
Platelet count (x10⁹/L) was evaluated at each visit during DBT, with representative timepoints shown in Table 68 and median platelet count over time in Figure 9.

Table 68 (Reviewer). Study TG1101-RMS301, Platelet Count ($\times 10^9/L$) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiy (n = 273)	Teriflunomide (n = 275)
Baseline	Mean (SD)	239.0 (52.6)	241.7 (51.5)
	Median	236.0	239.0
	Min, Max	128.0, 475.0	110.0, 369.0
Week 4	N	238	271
	Mean (SD)	240.0 (53.5)	227.5 (51.6)
	Median	237.0	222.0
	Min, Max	129.0, 467.0	114.0, 409.0
	Mean (SD) change from baseline	0.6 (46.5)	-13.9 (39.8)
	Median change from baseline	0.0	-14.0
	Min, Max change from baseline	-229, 233.0	-161, 139.0
Week 24	N	260	264
	Mean (SD)	251.8 (57.7)	227.3 (52.2)
	Median	247.0	220.5
	Min, Max	119.0, 450.0	113.0, 377.0
	Mean (SD) change from baseline	12.6 (45.0)	-13.3 (41.0)
	Median change from baseline	13.0	-13.0
	Min, Max change from baseline	-156, 223.0	-169.0, 127.0
Week 48	N	254	260
	Mean (SD)	262.6 (62.8)	235.2 (62.7)
	Median	259.0	229.5
	Min, Max	102.0, 585.0	116.0, 724.0
	Mean (SD) change from baseline	24.1 (44.5)	-5.5 (52.3)
	Median change from baseline	22.0	-9.0
	Min, Max change from baseline	-128.0, 169.0	-183.0, 455.0
Week 96	N	235	248
	Mean (SD)	268.3 (63.6)	234.6 (52.8)
	Median	256.0	232.0
	Min, Max	146.0, 560.0	95.0, 423.0
	Mean (SD) change from baseline	29.8 (45.5)	-7.0 (44.0)
	Median change from baseline	31.0	-8.0
	Min, Max change from baseline	-104.0, 216.0	-186.0, 132.0

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=PLAT, by TRT01A

Figure 9 (Reviewer). Study TG1101-RMS301, Platelet Count ($\times 10^9/L$) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=PLAT, by TRT01A

Low platelet counts were more frequent in teriflunomide-treated subjects. Specifically, 14.3% of subjects on ublituximab-xiyy ($n = 39$) and 19.3% of subjects on teriflunomide ($n = 53$) experienced a platelet count between 100 and 150 $\times 10^9/L$, and 0.7% of subjects on ublituximab-xiyy ($n = 2$) and 1.5% of subjects on teriflunomide ($n = 4$) experienced a platelet count between 50 and 100 $\times 10^9/L$. No subjects experienced a platelet count $<50 \times 10^9/L$.

Reviewer comment: Teriflunomide-treated subjects tended to have a lower platelet count than those on ublituximab-xiyy post-baseline. A 10% reduction in platelet count was observed in subjects on teriflunomide compared to placebo in pivotal trials supporting approval of teriflunomide, and reduced platelets are described as a labeled adverse event for teriflunomide, so this is not unexpected. However, a few patients on ublituximab-xiyy experienced a platelet count $<100 \times 10^9/L$. The etiology of these cases is not clear; we will continue postmarketing surveillance for additional cases of thrombocytopenia. Thrombocytopenia is not an established risk of anti-CD20 therapies. Moreover, anti-CD20 therapies are sometimes used for treatment of immune-mediated thrombocytopenia.

Please refer to Section 8.5.4 for discussion of TEAEs related to platelet count (e.g., thrombocytopenia).

Chemistry

AST

Aspartate aminotransferase (AST) was evaluated at each visit during the double blind treatment period, with representative timepoints shown in Table 69 and median AST over time in Figure 10.

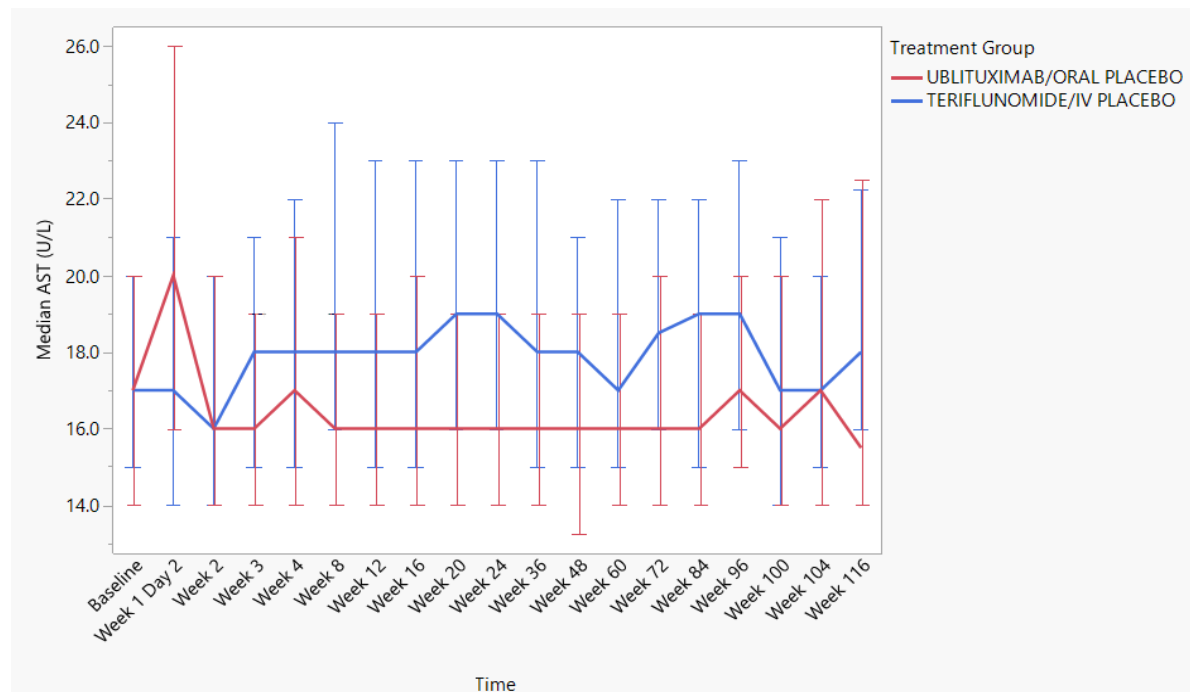
Table 69 (Reviewer). Study TG1101-RMS301, AST (IU/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiy (n = 273)	Teriflunomide (n = 275)
Baseline	Mean (SD)	18.5 (7.6)	19.9 (18.2)
	Median	17.0	17.0
	Min, Max	8.0, 88.0	9.0, 284.0
Week 4	N	264	273
	Mean (SD)	26.6 (67.4)	21.1 (18.2)
	Median	17.0	18.0
	Min, Max	7.0, 1027.0	8.0, 280.0
	Mean (SD) change from baseline	8.0 (66.6)	1.2 (21.2)
	Median change from baseline	0.0	1.0
Week 24	Min, Max change from baseline	-14.0, 1006.0	-239.0, 223.0
	N	255	263
	Mean (SD)	17.8 (7.6)	20.3 (7.4)
	Median	16.0	19.0
	Min, Max	8.0, 85.0	10.0, 63.0
	Mean (SD) change from baseline	-0.7 (8.0)	0.4 (19.3)
Week 48	Median change from baseline	0.0	1.0
	Min, Max change from baseline	-68.0, 67.0	-267.0, 50.0
	N	252	255
	Mean (SD)	18.3 (12.7)	20.0 (9.9)
	Median	16.0	18.0
	Min, Max	9.0, 143.0	9.0, 117.0
Week 96	Mean (SD) change from baseline	-0.3 (11.6)	0.9 (11.4)
	Median change from baseline	-1.0	1.0
	Min, Max change from baseline	-68.0, 108.0	-65.0, 102.0
	N	238	247
	Mean (SD)	20.1 (16.8)	21.9 (21.8)
	Median	17.0	19.0
Week 96	Min, Max	9.0, 157.0	10.0, 317.0
	Mean (SD) change from baseline	1.4 (15.6)	2.6 (20.6)
	Median change from baseline	0.0	2.0
	Min, Max change from baseline	-70.0, 141.0	-79.0, 275.0

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=AST, by TRT01A

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Figure 10 (Reviewer). Study TG1101-RMS301, Median AST (IU/L) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=AST, by TRT01A

Subjects with significant elevations in AST are discussed in Section 8.5.5.

Shift analyses indicated that 5.5% of patients on ublituximab-xiiy (n = 15) and 1.8% of patients on teriflunomide (n = 5) experienced increased AST to >3x ULN from baseline values of <3x ULN.

Reviewer comment: Comparison of summary statistics (e.g., mean/median AST values and change from baseline) did not indicate a clinically meaningful difference in AST over time between the groups. However, elevations in AST were more common in subjects on ublituximab-xiiy compared to teriflunomide. It is important to note that hepatotoxicity is a known safety issue with teriflunomide so subjects experiencing an increase in AST in the ublituximab-xiiy group twice the rate for a comparator with a boxed warning for hepatotoxicity is an unanticipated finding. Refer to Section 8.5.5 for discussion regarding the DILI team consultation obtained for this application.

Please refer to Section 8.5.5 for discussion of TEAEs related to hepatotoxicity and further shift analyses across Studies TG1101-RMS301 and TG1101-RMS302.

ALT

Alanine aminotransferase (ALT) was evaluated at each visit during the double blind treatment

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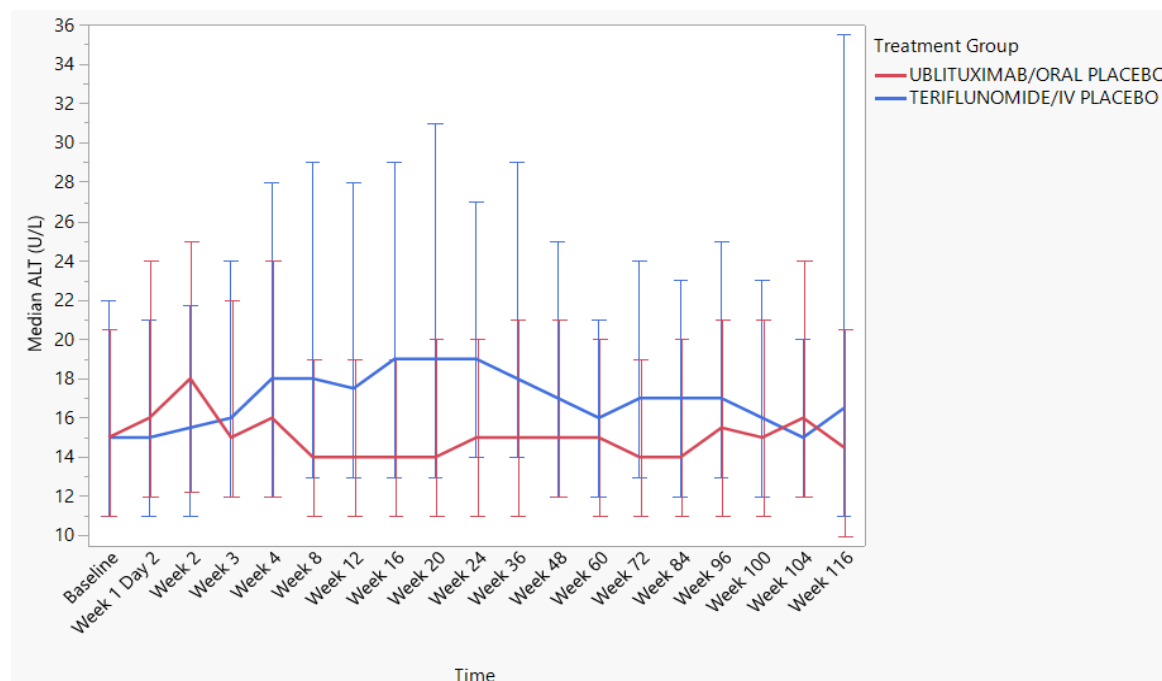
period, with descriptive analyses at representative timepoints shown in Table 70 and median ALT over time in Figure 11.

Table 70 (Reviewer). Study TG1101-RMS301, ALT (IU/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiy (n = 273)	Teriflunomide (n = 275)
Baseline	Mean (SD)	18.6 (15.4)	21.5 (27.8)
	Median	15.0	15.0
	Min, Max	5.0, 174.0	5.0, 321.0
Week 4	N	267	273
	Mean (SD)	32.6 (104.4)	25.5 (38.1)
	Median	16.0	18.0
	Min, Max	5.0, 1485.0	5.0, 555.0
	Mean (SD) change from baseline	13.9 (104.0)	4.1 (32.2)
	Median change from baseline	0	3.0
Week 24	Min, Max change from baseline	-69.0, 1461.0	-220.0, 400.0
	N	259	270
	Mean (SD)	17.7 (11.2)	23.4 (15.6)
	Median	15.0	19.0
	Min, Max	5.0, 93.0	6.0, 117.0
	Mean (SD) change from baseline	-1.0 (13.0)	1.9 (28.4)
Week 48	Median change from baseline	0.0	3.0
	Min, Max change from baseline	-154.0, 53.0	-290.0, 106.0
	N	255	260
	Mean (SD)	18.6 (12.7)	21.8 (17.0)
	Median	15.0	17.0
	Min, Max	5.0, 117.0	5.0, 184.0
Week 96	Mean (SD) change from baseline	-0.4 (13.8)	1.1 (22.8)
	Median change from baseline	0	2.0
	Min, Max change from baseline	-158.0, 77.0	-137.0, 175.0
	N	240	251
	Mean (SD)	19.5 (15.7)	24.7 (45.9)
	Median	15.5	17.0
Week 96	Min, Max	7.0, 133.0	6.0, 663.0
	Mean (SD) change from baseline	0.5 (15.6)	3.8 (43.9)
	Median change from baseline	1.0	2.0
	Min, Max change from baseline	-160.0, 80.0	-174.0, 604.0

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=ALT, by TRT01A

Figure 11 (Reviewer). Study TG1101-RMS301, Median ALT Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=ALT, by TRT01A

Subjects with significant elevations in ALT are discussed in Section 8.5.5.

Shift analyses indicated that 3.3% of patients on ublituximab-xiiy (n = 9) and 3.3% of patients on teriflunomide (n = 9) experienced increased ALT to >3x ULN from baseline values of <3x ULN. Elevations in ALT above the ULN occurred at a similar frequency in the ublituximab-xiiy (4.0%) and teriflunomide groups (3.3%).

Reviewer comment: Comparison of summary statistics (e.g., mean/median ALT and change in ALT from baseline) did not indicate a clinically meaningful difference in ALT over time between the groups. However, it is important to note that hepatotoxicity is a known safety issue with teriflunomide. Refer to Section 8.5.5 for discussion regarding the DILI team consultation obtained for this application.

Please refer to Section 8.5.5 for discussion of TEAEs related to hepatotoxicity and further shift analyses across Studies TG1101-RMS301 and TG1101-RMS302.

Bilirubin

Total, direct, and indirect bilirubin concentrations (in $\mu\text{mol/L}$) were reviewed, and there were no apparent clinically significant differences between the treatment groups in terms of mean/median values, peak values, or changes from baseline.

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Elevations in total bilirubin above the ULN were more commonly observed in subjects receiving ublituximab-xiiy (1.5%) compared to those on teriflunomide (0.4%). However, a similar percentage of subjects on ublituximab-xiiy (2.6%) and teriflunomide (2.5%) experienced a shift from a normal baseline total bilirubin (<1.5x ULN) to a high total bilirubin (>1.5x ULN).

Reviewer comment: The frequency of bilirubin elevations appears higher in subjects receiving ublituximab-xiiy compared to those on teriflunomide.

Please refer to Section 8.5.5 for discussion of TEAEs related to hepatotoxicity and further shift analyses across Studies TG1101-RMS301 and TG1101-RMS302.

Hy's Law Cases

One potential Hy's Law case (AST or ALT >3x ULN, total bilirubin >2x ULN, and ALP <2x ULN) was reported in a subject receiving ublituximab-xiiy. This subject (ID # [REDACTED]^{(b) (6)}) experienced a TEAE with the PT hepatitis toxic (Grade 2) that led to treatment discontinuation, and is discussed in Section 8.4.3.

No potential Hy's Law cases were noted in the teriflunomide group.

Please refer to Section 8.5.5 for discussion of TEAEs related to hepatotoxicity and further shift analyses across Studies TG1101-RMS301 and TG1101-RMS302.

Alkaline Phosphatase

Alkaline phosphatase (IU/L) values over time were reviewed, and there were no apparent clinically significant differences between the treatment groups in terms of mean/median values, peak values, or changes from baseline.

Elevations in ALP >1.5x ULN from a normal baseline (<1.5x ULN) occurred in 0.4% of subjects on ublituximab-xiiy and 1.1% on teriflunomide. Additionally, 2 subjects on teriflunomide (0.7%) experienced peak ALP between 2 and 3x ULN, compared to 0 subjects on ublituximab-xiiy.

Renal Function

There were no apparent clinically significant trends for blood urea nitrogen (BUN) or creatinine in either treatment group over time, as mean/median values and changes from baseline were similar between the treatment groups. Additionally, creatinine values ≥ 130 $\mu\text{mol/L}$ and BUN values >9 mmol/L occurred at similar frequencies in both treatment groups.

Pancreatic Enzymes

Amylase elevations 2 to 3x ULN were reported in 0.7% of subjects on ublituximab-xiiy, and 0.4% on teriflunomide; elevations 5 to 10x ULN were reported in 0.7% of subjects on ublituximab-xiiy and 0% on teriflunomide. Lipase elevations 3 to 5x ULN were reported in 1.8% of subjects on ublituximab-xiiy and 2.2% on teriflunomide; elevations 5 to 10x ULN were reported in 0.4% of subjects on ublituximab-xiiy and 1.8% on teriflunomide.

Amylase >400 U/L occurred in 2 subjects receiving ublituximab-xiiy, both of whom were reported as having TEAEs. One of these subjects (# [REDACTED]^{(b) (6)}) was the 32 year-old woman who experienced measles and encephalitis leading to death (Section 8.4.1).

Lipase >400 U/L occurred in 1 subject receiving ublituximab-xiiy ([REDACTED]^{(b) (6)}) at Week 8, and was reported as a TEAE.

TEAEs of amylase increased were reported in 2.2% (n = 6) of subjects on ublituximab-xiiy versus 0.4% (n = 1) on teriflunomide. TEAEs of lipase increased were reported in 2.6% (n = 7) of subjects on ublituximab-xiiy versus 4.7% (n = 13) on teriflunomide. Pancreatitis chronic was reported in 0.4% (n = 1) subject on ublituximab-xiiy versus 1.1% (n = 3) on teriflunomide. TEAEs of pancreatic toxicity was reported in 0.7% (n = 2) of subjects on teriflunomide, but none in ublituximab-xiiy. The TEAE pancreatic steatosis was reported in 0.4% (n = 1) of subjects on ublituximab-xiiy, but none in teriflunomide.

Reviewer comment: Of note, teriflunomide labeling contains a warning for pancreatitis in pediatric patients and a separate mention of pancreatitis as an adverse reaction identified in postmarketing experience. Though there is no obvious signal for pancreatic toxicity at this time, a concern was raised during the review of ocrelizumab and enhanced pharmacovigilance was recommended. Enhanced pharmacovigilance with ublituximab-xiiy also appears to be warranted based on these data as well.

Other Chemistry

There were no apparent clinically significant trends for urate, albumin, sodium, calcium, phosphate, and chloride in either treatment group over time, as mean/median values and changes from baseline were similar between the treatment groups.

Immunoglobulins

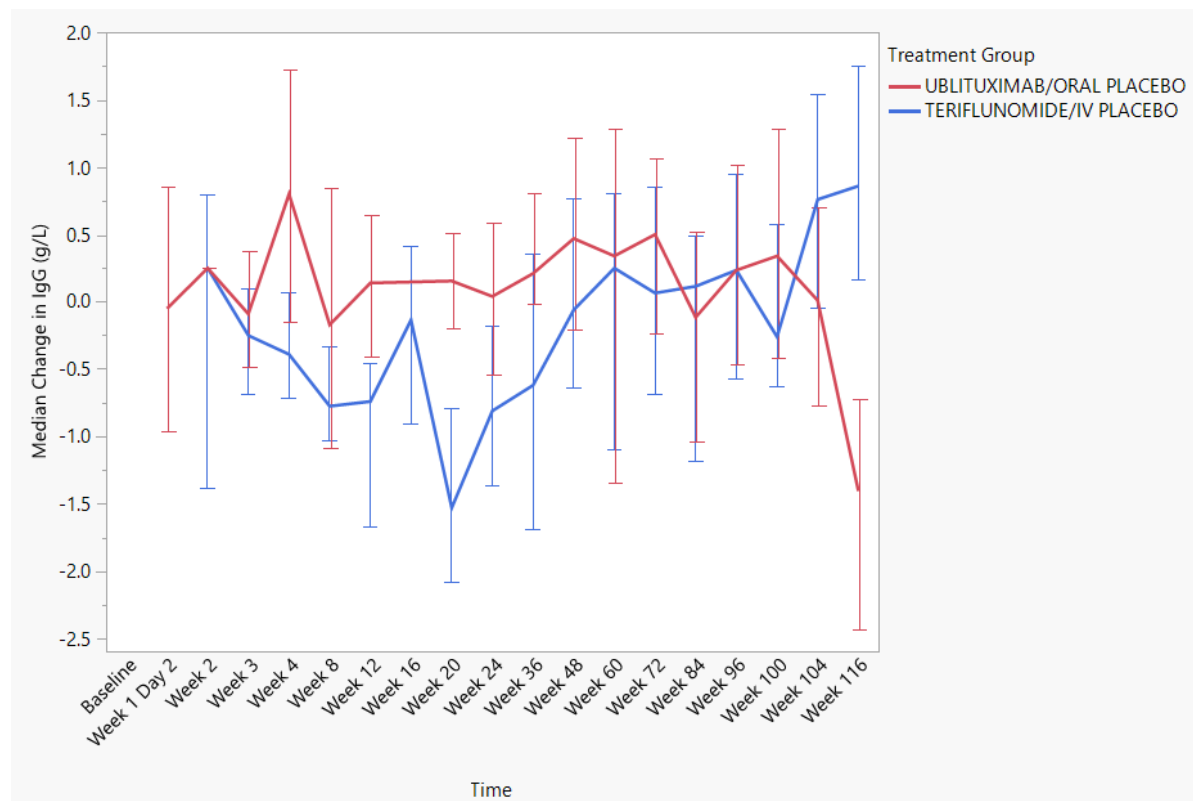
IgG

Median IgG for the ublituximab-xiiy group was 9.7 g/L at baseline, 9.8 g/L at week 24, then 10.0

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g/L at week 96, compared to 9.5 g/L, 8.7 g/L, and 9.9 g/L for teriflunomide, respectively. Across the DBT period, 1.8% of subjects on ublituximab-xiiy (n = 5) and 3.3% on teriflunomide (n = 9) experienced IgG <5.5 g/L. Median change in IgG from baseline over the DBT period is presented in Figure 12.

Figure 12 (Reviewer). Study TG1101-RMS301, Median Change in IgG (g/L) from Baseline Over Time, Safety Population



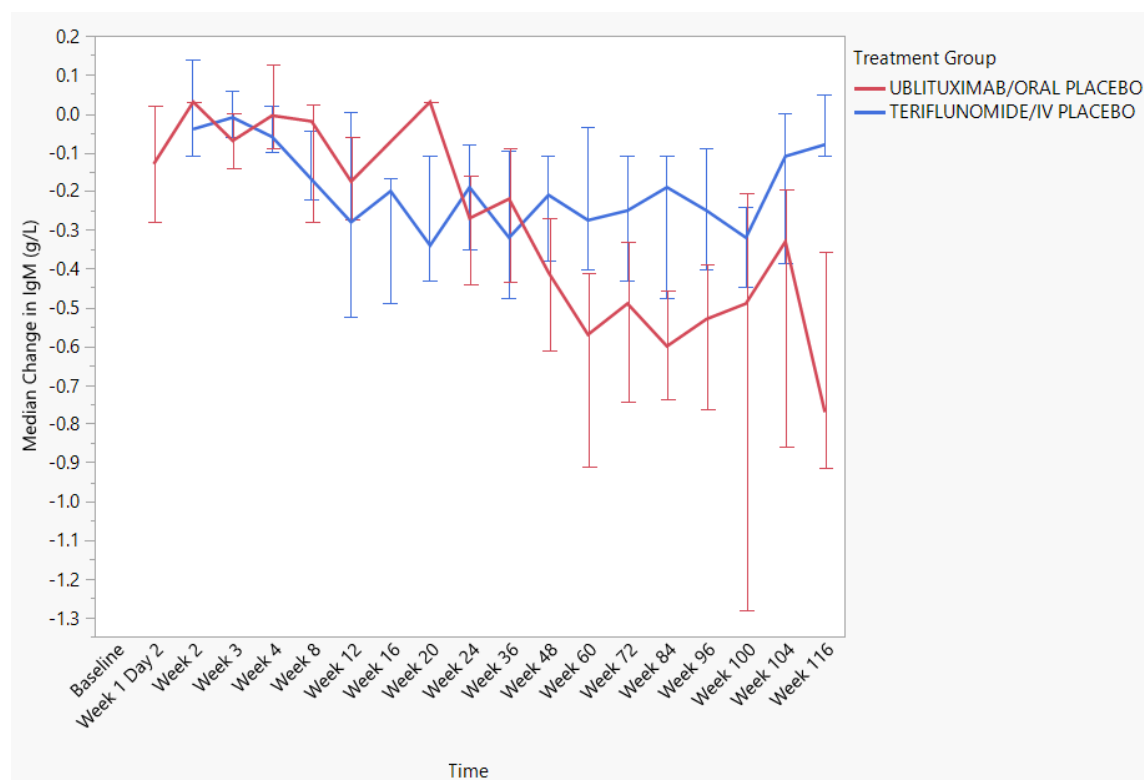
Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=IGG, by TRT01A

Reviewer comment: Though expected long-term given the mechanism of action of ublituximab-xiiy, there was not a clear trend for reduction in IgG associated with ublituximab-xiiy during the DBT period. Median values at Week 116 should be interpreted with caution due to the small number of subjects at that time (n = 9 on ublituximab-xiiy, 15 on teriflunomide). Changes in IgG noted for ocrelizumab required years of exposure to identify, so the lack of a finding in the DBT period was expected and does not preclude labeling for what appears to be an effect that requires prolonged exposure to any anti-CD20 therapy.

IgM

Median IgM for the ublituximab-xiyy group was 1.4 g/L at baseline, 1.0 g/L at week 24, then 0.9 g/L at week 96, compared to 1.4 g/L, 1.1 g/L, and 1.2 g/L for teriflunomide, respectively. Across the DBT period, 20.5% of subjects on ublituximab-xiyy (n = 56) and 5.5% on teriflunomide (n = 15) experienced IgM <0.4 g/L. Median change in IgM from baseline over the DBT period is presented in Figure 13.

Figure 13 (Reviewer). Study TG1101-RMS301, Median Change in IgM (g/L) from Baseline Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=IGM, by TRT01A

Reviewer comment: Reduction in immunoglobulins is expected long-term given the mechanism of action of ublituximab-xiyy, and there was a clear trend for declining IgM levels over time in the ublituximab-xiyy group.

CD19+ B-cells

The primary pharmacodynamic effect of ublituximab-xiyy is depletion of CD19+ B-cells. Absolute CD19+ B-cell count was evaluated at each visit during DBT, with representative timepoints shown in Table 71 and median absolute CD19+ B-cell count over time in Figure 14.

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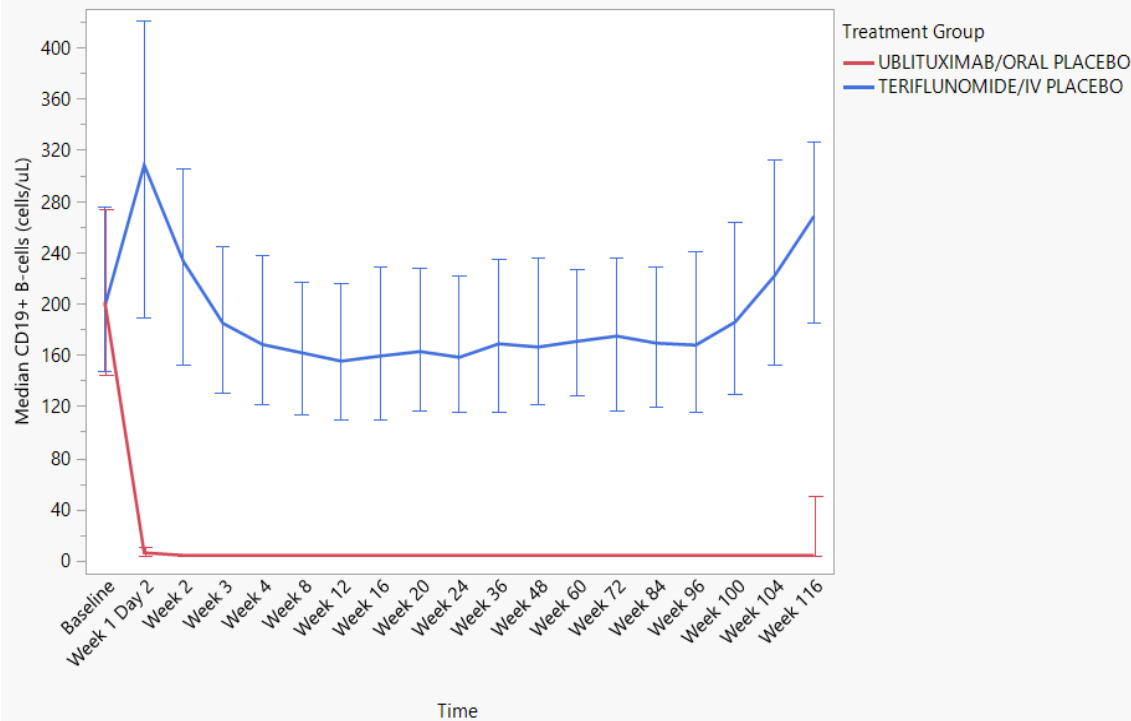
Table 71 (Reviewer). Study TG1101-RMS301, Absolute CD19+ B-cell Count (cells/ μ L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiy (n = 273)	Teriflunomide (n = 275)
Baseline	Mean (SD)	224.4 (121.3)	223.8 (121.3)
	Median	202.0	198.0
	Min, Max	16.0, 882.0	66.0, 943.0
Week 4	N	260	268
	Mean (SD)	4.4 (4.6)	183.8 (91.6)
	Median	4.0	168.5
	Min, Max	1.0, 71.0	1.0, 621.0
	Mean (SD) change from baseline	-223.0 (122.6)	-40.6 (78.8)
	Median change from baseline	-201.0	-29.0
	Min, Max change from baseline	-878, -12.0	-501, 276.0
Week 24	N	257	268
	Mean (SD)	10.7 (19.2)	176.0 (98.9)
	Median	4.0	158.5
	Min, Max	1.0, 128.0	1.0, 734.0
	Mean (SD) change from baseline	-218.0 (122.5)	-45.2 (75.8)
	Median change from baseline	-198.0	-40.0
	Min, Max change from baseline	-878.0, -12.0	-386.0, 244.0
Week 48	N	252	256
	Mean (SD)	12.7 (32.6)	187.8 (99.1)
	Median	4.0	166.5
	Min, Max	1.0, 269.0	1.0, 719.0
	Mean (SD) change from baseline	-215.0 (122.0)	-35.8 (90.1)
	Median change from baseline	-193.0	-32.5
	Min, Max change from baseline	-878.0	-509.0
Week 96	N	234	249
	Mean (SD)	7.5 (21.1)	188.9 (112.6)
	Median	4.0	168.0
	Min, Max	1.0, 183.0	4.0, 952.0
	Mean (SD) change from baseline	-219.0 (124.9)	-33.5 (97.8)
	Median change from baseline	-198.0	-32.0
	Min, Max change from baseline	-877.0, 4.0	-516.0, 557.0

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=CD19BCLA, by TRT01A

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Figure 14 (Reviewer). Study TG1101-RMS301, Absolute CD19+ B-cell Count (cells/ μ L) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD= CD19BCLA, by TRT01A

In Study TG1101-RMS301, there were 41 subjects who received ublituximab-xiyy who had post-baseline CD19+ B-cell counts > 100 cells/ μ L. These values were most common at Weeks 100 (n = 9) and Week 103 (n = 13). Of these 41 subjects, 3 experienced 1 IRAP-confirmed relapse, and 1 experienced 2 IRAP-confirmed relapses.

Reviewer comment: It appears that ublituximab-xiyy depleted CD19+ B-cells in a majority of subjects. Several subjects did not have complete B-cell depletion, but this did not appear to substantially impact efficacy.

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Hematology

Leukocytes

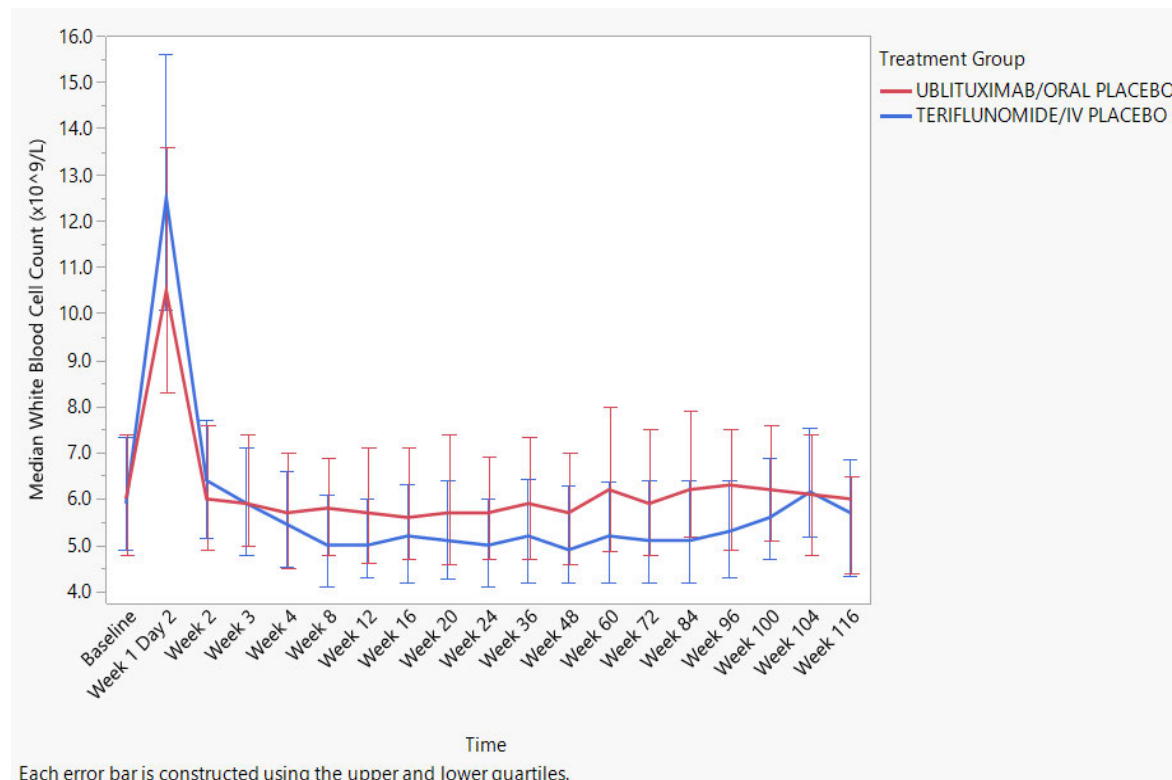
Overall leukocyte count (WBCs, # cells $\times 10^9$ /L) were evaluated at each visit during DBT, with representative timepoints shown in Table 72 and median WBCs over time in Figure 15.

Table 72 (Reviewer). Study TG1101-RMS302, WBCs (x10⁹/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiy (n = 272)	Teriflunomide (n = 273)
Baseline	Mean (SD)	6.3 (1.8)	6.3 (2.4)
	Median	6.0	5.9
	Min, Max	3.3, 13.6	2.8, 31.1
Week 4	N	271	272
	Mean (SD)	6.1 (2.2)	5.8 (1.7)
	Median	5.7	5.5
	Min, Max	2.5, 17.4	2.0, 12.4
	Mean (SD) change from baseline	-0.2 (1.8)	-0.5 (2.2)
	Median change from baseline	-0.3	-0.4
	Min, Max change from baseline	-6.4, 7.5	-23.8, 7.5
Week 24	N	270	259
	Mean (SD)	6.1 (2.2)	5.3 (1.8)
	Median	5.7	5.0
	Min, Max	2.0, 15.5	2.6, 16.8
	Mean (SD) change from baseline	-0.2 (1.9)	-1.0 (2.3)
	Median change from baseline	-0.1	-0.8
	Min, Max change from baseline	-6.0, 7.1	-23.5, 8.9
Week 48	N	266	255
	Mean (SD)	6.2 (2.2)	5.3 (1.5)
	Median	5.7	4.9
	Min, Max	3.1, 17.9	2.2, 11.5
	Mean (SD) change from baseline	-0.2 (1.8)	-1.0 (2.0)
	Median change from baseline	-0.2	-0.8
	Min, Max change from baseline	-5.6, 10.2	-22.7, 2.6
Week 96	N	249	240
	Mean (SD)	6.6 (2.2)	5.4 (1.6)
	Median	6.3	5.3
	Min, Max	3.1, 17.5	2.1, 12.3
	Mean (SD) change from baseline	0.3 (2.0)	-0.9 (2.2)
	Median change from baseline	0.3	-0.7
	Min, Max change from baseline	-5.8, 9.8	-24.4, 5.4

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=WBCB, by TRT01A

Figure 15 (Reviewer). Study TG1101-RMS302, WBC ($\times 10^9/L$) Over Time, Safety Population



Each error bar is constructed using the upper and lower quartiles.
Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=WBC, by TRT01A

Additionally, 22.4% of subjects on ublituximab-xiiy ($n = 61$) and 28.2% of subjects on teriflunomide ($n = 77$) experienced WBCs between 2.0 to $3.5 \times 10^9/L$, and 1.8% of subjects on ublituximab-xiiy ($n = 5$) and 0.7% of subjects on teriflunomide ($n = 2$) experienced WBCs $\leq 2.0 \times 10^9/L$.

Reviewer comment: The peak in WBCs at Week 1 Day 2 (Figure 15) likely reflects reactive leukocytosis in response to corticosteroid administration in the setting of infusion pre-medication. Overall, there appears to be a trend towards lower WBC count in the teriflunomide group compared to ublituximab-xiiy, as mean and median WBC values appeared to be lower in teriflunomide-treated subjects, and the mean/median changes from baseline tended to be more negative in teriflunomide-treated subjects. Additionally, after Week 96 (when teriflunomide was stopped), WBC counts appeared to recover in this group; week 116 values are difficult to interpret due to low sample size at that time point ($n = 3$ ublituximab-xiiy, $n = 8$ teriflunomide). However, in contrast to Study TG1101-RMS301 results, subjects on ublituximab-xiiy were more likely to have WBCs $\leq 2.0 \times 10^9/L$ compared to those on teriflunomide.

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Please refer to Section 8.5.4 for discussion of TEAEs related to leukocyte count (e.g., leukopenia).

Neutrophils

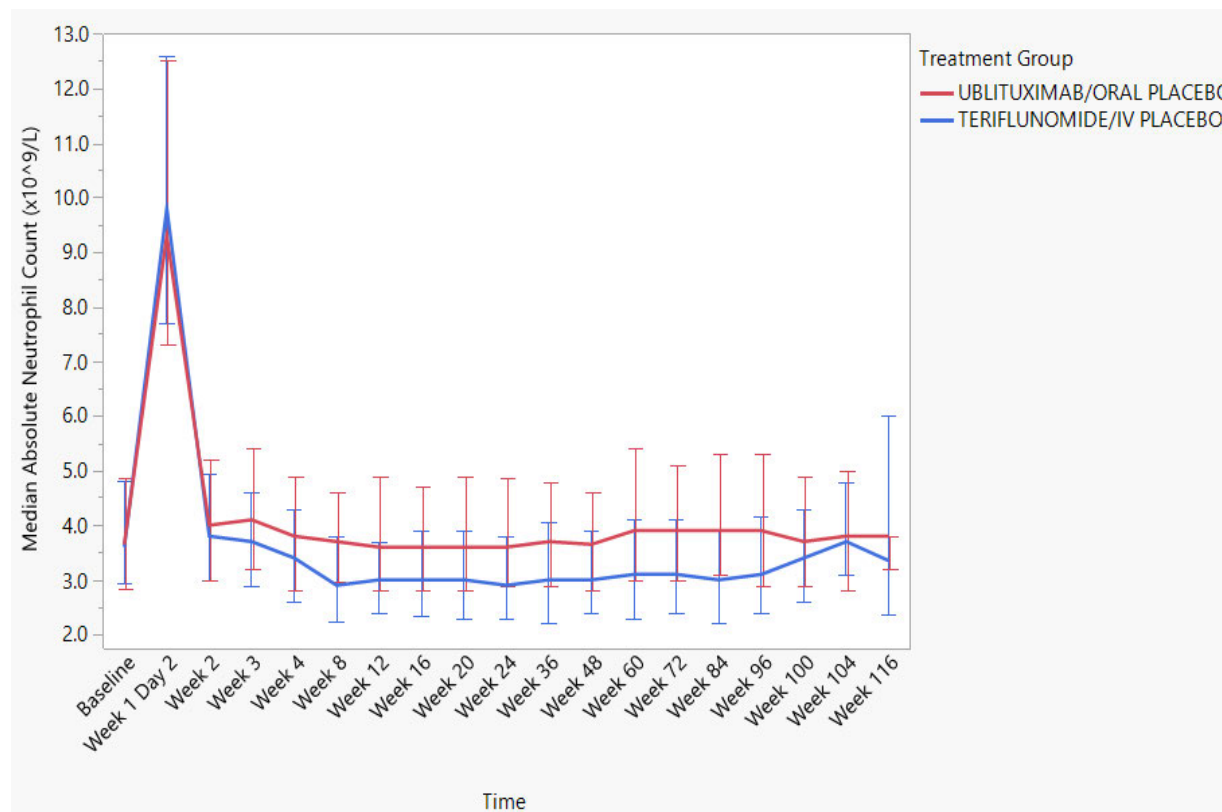
Absolute neutrophil count (ANC, # cells x10⁹/L) was evaluated at each visit during DBT, with representative timepoints shown in Table 73 and median ANC over time in Figure 16.

Table 73 (Reviewer). Study TG1101-RMS302, Absolute Neutrophil Count (x10⁹/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiyy (n = 272)	Teriflunomide (n = 273)
Baseline	Mean (SD)	4.0 (1.4)	4.0 (2.0)
	Median	3.7	3.6
	Min, Max	1.5, 8.9	1.3, 25.9
Week 4	N	271	271
	Mean (SD)	4.1 (1.9)	3.6 (1.4)
	Median	3.8	3.4
	Min, Max	1.0, 15.9	1.1, 9.7
	Mean (SD) change from baseline	0.1 (1.6)	-0.4 (1.9)
	Median change from baseline	0.1	-0.3
	Min, Max change from baseline	-5.0, 8.3	-21.4, 6.6
Week 24	N	268	255
	Mean (SD)	4.0 (1.9)	3.2 (1.5)
	Median	3.6	2.9
	Min, Max	0.8, 12.2	1.0, 14.9
	Mean (SD) change from baseline	0.1 (1.7)	-0.8 (2.0)
	Median change from baseline	-0.1	-0.7
Week 48	N	264	254
	Mean (SD)	4.0 (1.8)	3.2 (1.3)
	Median	3.7	3.0
	Min, Max	1.1, 16.2	0.9, 8.2
	Mean (SD) change from baseline	0 (1.6)	-0.8 (1.7)
Week 96	N	249	237
	Mean (SD)	4.3 (1.9)	3.3 (1.2)
	Median	3.9	3.1
	Min, Max	1.3, 14.7	0.8, 9.1
Week 96	Mean (SD) change from baseline	0.3 (1.7)	-0.7 (2.0)
	Median change from baseline	0.2	-0.6
	Min, Max change from baseline	-4.6, 9.3	-22.1, 3.4

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=NEUT, by TRT01A

Figure 16 (Reviewer). Study TG1101-RMS302, Absolute Neutrophil Count ($\times 10^9/L$) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=NEUT, by TRT01A

Additionally, 12.1% of subjects on ublituximab-xiiy ($n = 33$) and 12.1% of subjects on teriflunomide ($n = 33$) experienced ANC between 1.0 to $1.5 \times 10^9/L$, 2.2% of subjects on ublituximab-xiiy ($n = 6$) and 2.6% of subjects on teriflunomide ($n = 7$) experienced nadir ANC between 0.5 to $1.0 \times 10^9/L$, and 0.7% of subjects on ublituximab-xiiy ($n = 2$) and 0% of subjects on teriflunomide ($n = 0$) experienced ANC $\leq 0.5 \times 10^9/L$.

Reviewer comment: The peak in ANC at Week 1 Day 2 (Figure 16) likely reflects reactive leukocytosis in response to corticosteroid administration in the setting of infusion pre-medication. Again, there appears to be a trend towards lower ANC in the teriflunomide group compared to ublituximab-xiiy, as mean and median ANC values appeared to be lower in teriflunomide-treated subjects, and the mean/median changes from baseline tended to be more negative in teriflunomide-treated subjects. Additionally, after Week 96 (when teriflunomide was stopped), ANC appeared to recover in this group. Week 116 values are difficult to interpret due to low sample size at that time point ($n = 3$ ublituximab-xiiy, $n = 8$ teriflunomide). Neutropenia is a known safety issue with

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teriflunomide. However, subjects who received ublituximab-xiiy were more likely to experience ANC $\leq 0.5 \times 10^9/L$ (0.7% ublituximab-xiiy versus 0% teriflunomide). Neutropenia will be discussed in labeling.

Please refer to Section 8.5.4 for discussion of TEAEs related to neutrophil count (e.g., neutropenia).

Lymphocytes

Absolute lymphocyte count (ALC, # cells $\times 10^9/L$) was evaluated at each visit during DBT, with representative timepoints shown in Table 74 and median ALC over time in Figure 17.

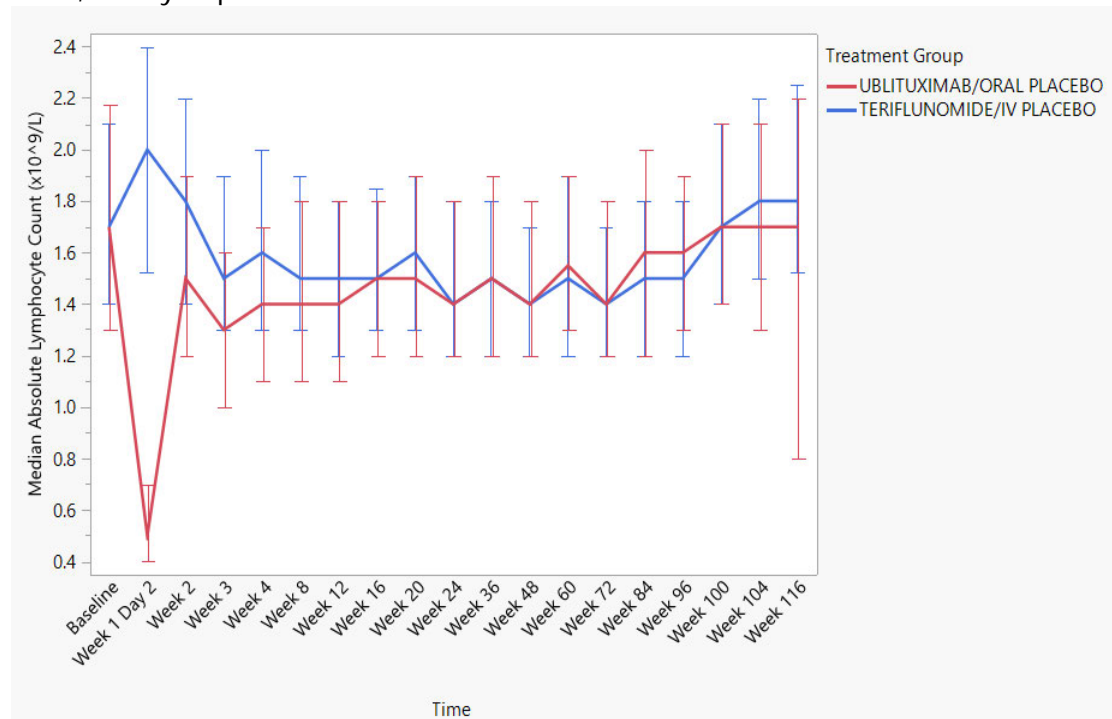
Table 74 (Reviewer). Study TG1101-RMS302, Absolute Lymphocyte Count (x10⁹/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiy (n = 272)	Teriflunomide (n = 273)
Baseline	Mean (SD)	1.8 (0.6)	1.8 (0.6)
	Median	1.7	1.7
	Min, Max	0.7, 4.0	0.7, 4.9
Week 4	N	271	271
	Mean (SD)	1.5 (0.5)	1.7 (0.5)
	Median	1.4	1.6
	Min, Max	0.4, 4.2	0.7, 4.8
	Mean (SD) change from baseline	-0.4 (0.5)	-0.1 (0.5)
	Median change from baseline	-0.3	-0.1
Week 24	Min, Max change from baseline	-2.6, 1.5	-3.4, 2.4
	N	268	255
	Mean (SD)	1.5 (0.5)	1.5 (0.5)
	Median	1.4	1.4
	Min, Max	0.5, 3.8	0.4, 3.3
	Mean (SD) change from baseline	-0.3 (0.5)	-0.3 (0.4)
Week 48	Median change from baseline	-0.2	-0.2
	Min, Max change from baseline	-2.7, 0.8	-2.4, 0.8
	N	264	254
	Mean (SD)	1.5 (0.5)	1.5 (0.5)
	Median	1.4	1.4
	Min, Max	0.5, 3.7	0.5, 3.1
Week 96	Mean (SD) change from baseline	-0.3 (0.5)	-0.3 (0.5)
	Median change from baseline	-0.2	-0.2
	Min, Max change from baseline	-2.7, 2.4	-3.0, 1.3
	N	249	237
	Mean (SD)	1.7 (0.5)	1.6 (0.5)
	Median	1.6	1.5
Week 96	Min, Max	0.6, 3.5	0.7, 3.1
	Mean (SD) change from baseline	-0.2 (0.6)	-0.2 (0.4)
	Median change from baseline	-0.1	-0.2
	Min, Max change from baseline	-2.7, 1.6	-1.8, 1.6

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=L YM, by TRT01A

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Figure 17 (Reviewer). Study TG1101-RMS302, Absolute Lymphocyte Count ($\times 10^9/L$) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=L YM, by TRT01A

Additionally, 34.2% of subjects on ublituximab-xiiy ($n = 93$) and 22.7% of subjects on teriflunomide ($n = 62$) experienced ALC between 0.5 and $1.0 \times 10^9/L$, and 55.1% of subjects on ublituximab-xiiy ($n = 150$) and 3.3% of subjects on teriflunomide ($n = 9$) experienced $ALC \leq 0.5 \times 10^9/L$.

Reviewer comment: Similar to the results of Study TG1101-RMS301, subjects who received ublituximab-xiiy were much more likely to experience $ALC \leq 0.5 \times 10^9/L$ (55.1% ublituximab-xiiy versus 3.3% teriflunomide). Though low ALC is not unexpected given the mechanism of action of ublituximab-xiiy, this frequency of severe lymphopenia is concerning. This observation is likely driven by ALC at Week 1 Day 2, where the median ALC in subjects on ublituximab-xiiy decreased sharply then recovered, but remained lower than that of teriflunomide through Week 12.

Please refer to Section 8.5.4 for discussion of TEAEs related to lymphocyte count (e.g., lymphopenia).

Hemoglobin, Hematocrit, and Erythrocytes

There did not appear to be a clinically significant difference or trend in hemoglobin, hematocrit,

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or erythrocyte count values or change between the treatment groups. The frequency of subjects experiencing abnormal hemoglobin (either <120 g/L or >160 g/L) or hematocrit (either <0.35 L/L or >0.5 L/L) was similar between the treatment groups. However, subjects on teriflunomide were more likely to experience erythrocyte count <4.0 x10¹²/L compared to those on ublituximab-xiiy (18.7% versus 12.9%, respectively).

Platelets

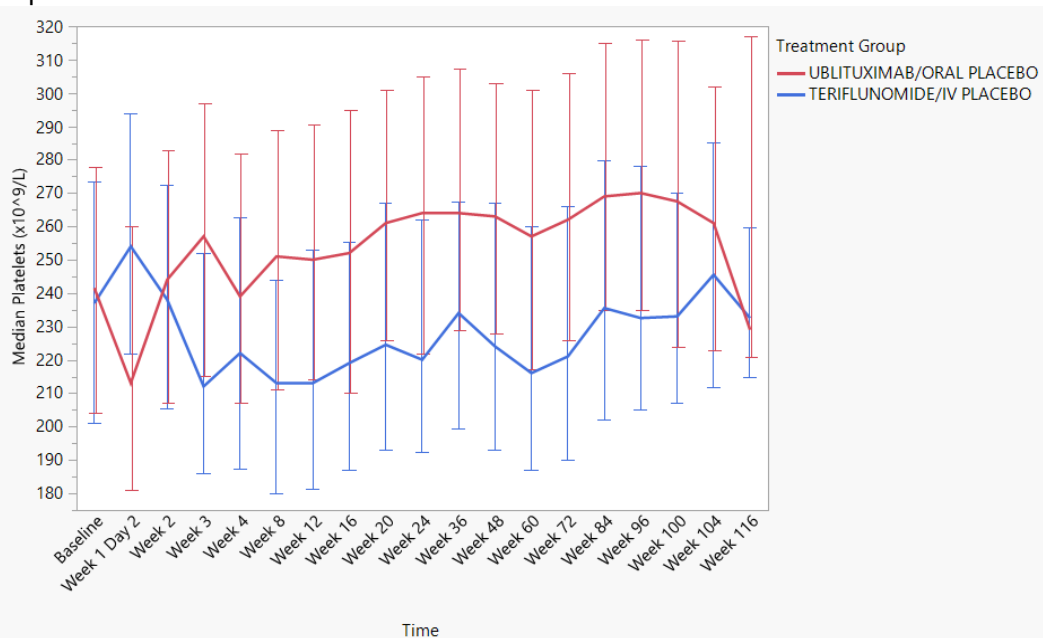
Platelet count (x10⁹/L) was evaluated at each visit during DBT, with representative timepoints shown in Table 75 and median platelet count over time in Figure 18.

Table 75 (Reviewer). Study TG1101-RMS302, Platelet Count (x10⁹/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiy (n = 272)	Teriflunomide (n = 273)
Baseline	Mean (SD)	244.4 (57.1)	239.9 (50.0)
	Median	241.5	237.0
	Min, Max	98.0, 529.0	129.0, 383.0
Week 4	N	271	272
	Mean (SD)	245.3 (58.7)	225.7 (52.3)
	Median	239.0	222.0
	Min, Max	89.0, 439.0	20.0, 365.0
	Mean (SD) change from baseline	0.9 (41.7)	-14.0 (42.3)
	Median change from baseline	3.0	-11.5
	Min, Max change from baseline	-248.0, 180.0	-363.0, 143.0
Week 24	N	270	261
	Mean (SD)	265.4 (62.9)	228.0 (50.8)
	Median	264.0	220.0
	Min, Max	107.0, 534.0	127.0, 393.0
	Mean (SD) change from baseline	21.1 (42.3)	-10.4 (41.7)
	Median change from baseline	20.0	-10.0
	Min, Max change from baseline	-98.0, 208.0	-155.0, 150.0
Week 48	N	267	255
	Mean (SD)	270.6 (65.8)	233.4 (57.0)
	Median	263.0	224.0
	Min, Max	102.0, 557.0	121.0, 420.0
	Mean (SD) change from baseline	25.9 (43.5)	-4.6 (42.5)
	Median change from baseline	22.0	-1.0
	Min, Max change from baseline	-99.0, 281.0	-140.0, 137.0
Week 96	N	250	240
	Mean (SD)	282.1 (69.7)	240.8 (56.2)
	Median	270.0	232.5
	Min, Max	127.0, 563.0	111.0, 405.0
	Mean (SD) change from baseline	36.7 (45.0)	2.1 (43.0)
	Median change from baseline	34.0	3.5
	Min, Max change from baseline	-91.0, 232.0	-155.0, 150.0

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=PLAT, by TRT01A

Figure 18 (Reviewer). Study TG1101-RMS302, Platelet Count ($\times 10^9/L$) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=PLAT, by TRT01A

Low platelet counts were more frequent in teriflunomide-treated subjects. Specifically, 13.6% of subjects on ublituximab-xiiy ($n = 37$) and 20.9% of subjects on teriflunomide ($n = 57$) experienced a platelet count between 100 and 150 $\times 10^9/L$, 0.7% of subjects on ublituximab-xiiy ($n = 2$) and 0% of subjects on teriflunomide ($n = 0$) experienced a platelet count between 50 and 100 $\times 10^9/L$, and 0% of subjects on ublituximab-xiiy ($n = 0$) and 0.4% of subjects on teriflunomide ($n = 1$) experienced a platelet count $\leq 50 \times 10^9/L$.

Reviewer comment: Similar to Study TG1101-RMS301, teriflunomide-treated subjects tended to have a lower platelet count than those on ublituximab-xiiy post-baseline. A 10% reduction in platelet count was observed in subjects on teriflunomide compared to placebo in pivotal trials, so this is not unexpected. However, a few patients on ublituximab-xiiy experienced a platelet count $< 100 \times 10^9/L$. See reviewer comment regarding this finding in Study TG1101-RMS301.

Please refer to Section 8.5.4 for discussion of TEAEs related to platelet count (e.g., thrombocytopenia).

Chemistry

AST

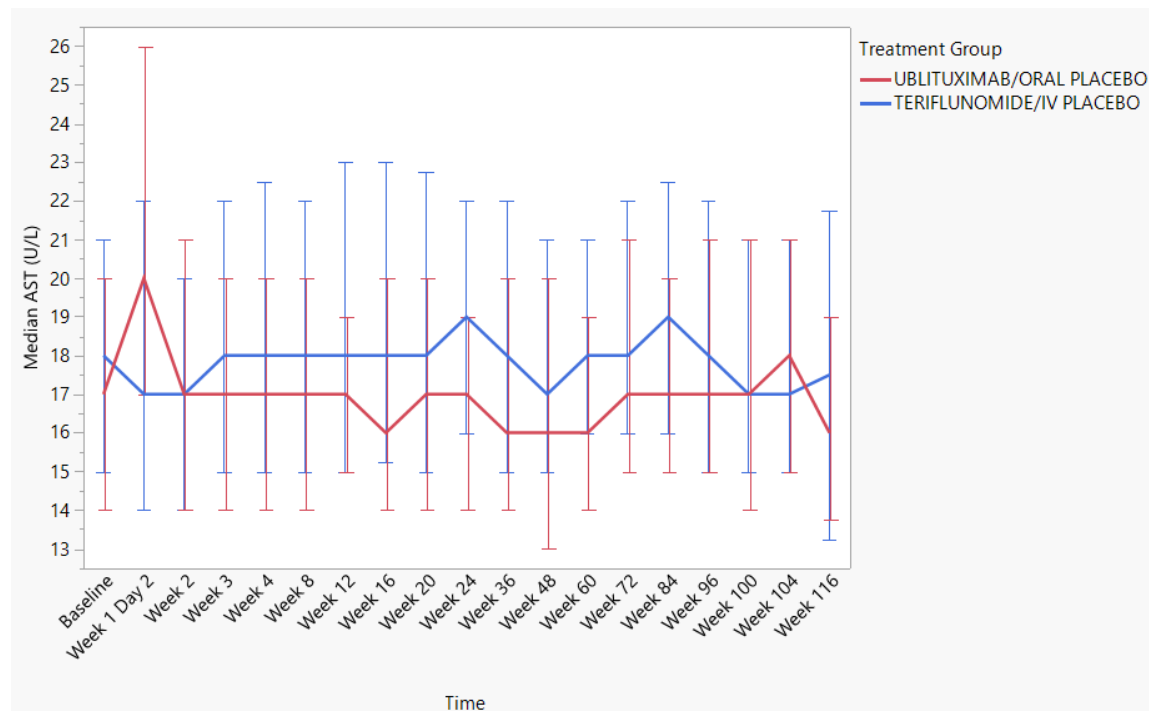
Aspartate aminotransferase (AST) was evaluated at each visit during the double blind treatment period, with representative timepoints shown in Table 76, and median AST over time in Figure 19.

Table 76 (Reviewer). Study TG1101-RMS302, AST (IU/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiy (n = 272)	Teriflunomide (n = 273)
Baseline	Mean (SD)	17.8 (5.3)	23.0 (41.3)
	Median	17.0	18.0
	Min, Max	7.0, 45.0	9.0, 570.0
Week 4	N	271	273
	Mean (SD)	20.5 (14.2)	21.7 (20.3)
	Median	17.0	18.0
	Min, Max	6.0, 129.0	9.0, 291.0
	Mean (SD) change from baseline	2.6 (13.7)	-1.3 (39.7)
	Median change from baseline	0	0
Week 24	Min, Max change from baseline	-23.0, 115.0	-474.0, 246.0
	N	262	258
	Mean (SD)	17.5 (6.2)	20.2 (7.5)
	Median	17.0	19.0
	Min, Max	7.0, 81.0	10.0, 72.0
	Mean (SD) change from baseline	-0.3 (6.2)	-2.2 (41.5)
Week 48	Median change from baseline	0	1.0
	Min, Max change from baseline	-23.0, 66.0	-548.0, 49.0
	N	268	249
	Mean (SD)	18.0 (11.0)	19.4 (7.2)
	Median	16.0	17.0
	Min, Max	5.0, 167.0	11.0, 67.0
Week 96	Mean (SD) change from baseline	0.2 (10.9)	-3.0 (42.0)
	Median change from baseline	-1.0	1.0
	Min, Max change from baseline	-28.0, 148.0	-551, 44.0
	N	245	239
	Mean (SD)	19.0 (9.2)	20.0 (6.9)
	Median	17.0	18.0
Week 96	Min, Max	7.0, 129.0	10.0, 72.0
	Mean (SD) change from baseline	1.2 (9.1)	-2.7 (42.9)
	Median change from baseline	1.0	1.0
	Min, Max change from baseline	-28.0, 111.0	-548.0, 51.0

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=AST, by TRT01A

Figure 19 (Reviewer). Study TG1101-RMS302, Median AST (IU/L) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=AST, by TRT01A

Subjects with significant elevations in AST are discussed in Section 8.5.5.

Shift analyses indicated that 2.9% of patients on ublituximab-xiiy (n = 8) and 1.5% of patients on teriflunomide (n = 4) experienced increased AST to >3x ULN from baseline values of <3x ULN. Elevations in AST occurred at a similar frequency in the ublituximab-xiiy (2.9%) and teriflunomide groups (2.2%).

Reviewer comment: With the exception of a few outliers, the frequency and magnitude of elevated AST values appears similar between the treatment groups. Comparison of summary statistics (e.g., mean and median) did not indicate a clinically meaningful difference in AST over time between the groups. However, it is important to note that hepatotoxicity is a known safety issue with teriflunomide. Refer to Section 8.5.5 for discussion regarding the DILI team consultation obtained for this application.

Please refer to Section 8.5.5 for discussion of TEAEs related to hepatotoxicity.

ALT

Alanine aminotransferase (ALT) was evaluated at each visit during the double blind treatment

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 Laura Baldassari, MD, MHS
 BLA 761238
 Ublituximab-xiiy (Briumvi)

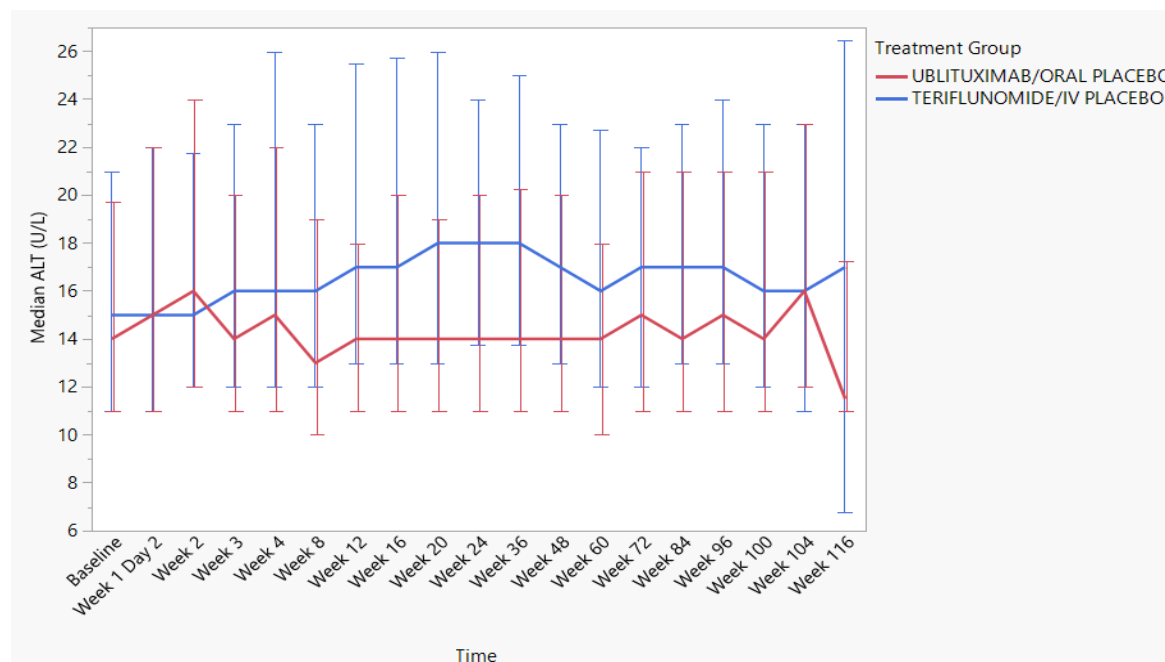
period, with descriptive analyses at representative timepoints shown in Table 77 and median ALT over time in Figure 20.

Table 77 (Reviewer). Study TG1101-RMS302, ALT (IU/L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiiy (n = 272)	Teriflunomide (n = 273)
Baseline	Mean (SD)	17.3 (12.0)	22.6 (52.5)
	Median	14.0	15.0
	Min, Max	5.0, 119.0	836.0
Week 4	N	272	273
	Mean (SD)	21.2 (21.7)	24.6 (45.0)
	Median	15.0	16.0
	Min, Max	5.0, 153.0	5.0, 693.0
	Mean (SD) change from baseline	3.9 (20.5)	2.0 (55.7)
	Median change from baseline	0	2.0
Week 24	Min, Max change from baseline	-69.0, 142.0	-638.0, 606.0
	N	268	262
	Mean (SD)	17.0 (11.4)	20.9 (12.2)
	Median	14.0	18.0
	Min, Max	5.0, 114.0	6.0, 104.0
	Mean (SD) change from baseline	-0.4 (11.1)	-1.2 (53.4)
Week 48	Median change from baseline	0	2.0
	Min, Max change from baseline	-89.0, 69.0	-820.0, 99.0
	N	269	256
	Mean (SD)	18.4 (20.0)	20.5 (12.8)
	Median	14.0	17.0
	Min, Max	5.0, 279.0	6.0, 117.0
Week 96	Mean (SD) change from baseline	1.0 (20.5)	-1.8 (54.5)
	Median change from baseline	0	2.0
	Min, Max change from baseline	-90.0, 267.0	-823.0, 105.0
	N	250	240
	Mean (SD)	18.7 (12.3)	20.6 (13.5)
	Median	15.0	17.0
Week 96	Min, Max	5.0, 93.0	6.0, 137.0
	Mean (SD) change from baseline	1.1 (12.4)	-1.9 (56.4)
	Median change from baseline	1.0	1.5
	Min, Max change from baseline	-91.0, 64.0	-826.0, 125.0

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=ALT, by TRT01A

Figure 20 (Reviewer). Study TG1101-RMS302, Median ALT Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=ALT, by TRT01A

Subjects with significant elevations in ALT are discussed in Section 8.5.5.

Shift analyses indicated that 3.3% of patients on ublituximab-xiiy (n = 9) and 3.3% of patients on teriflunomide (n = 9) experienced increased ALT to >3x ULN from baseline values of <3x ULN. Elevations in ALT occurred at a similar frequency in the ublituximab-xiiy (3.3%) and teriflunomide groups (3.7%).

Reviewer comment: Again, with the exception of a few outliers, the frequency and magnitude of elevated ALT values appears similar between the treatment groups. Comparison of summary statistics (e.g., mean and median) did not indicate a clinically meaningful difference in ALT over time between the groups. However, it is important to note that hepatotoxicity is a known safety issue with teriflunomide. Refer to Section 8.5.5 for discussion regarding the DILI team consultation obtained for this application.

Please refer to Section 8.5.5 for discussion of TEAEs related to hepatotoxicity.

Bilirubin

Total, direct, and indirect bilirubin concentrations (in $\mu\text{mol/L}$) were reviewed, and there were no apparent clinically significant differences between the treatment groups in terms of mean/median values, peak values, or changes from baseline.

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BLA 761238
Ublituximab-xiiy (Briumvi)

Elevations in total bilirubin above the ULN occurred at a similar frequency in subjects receiving ublituximab-xiiy (1.1%) and teriflunomide (1.1%). A similar percentage of subjects on ublituximab-xiiy (2.2%) and teriflunomide (2.6%) experienced a shift from a normal baseline total bilirubin (<1.5x ULN) to a high total bilirubin (>1.5x ULN).

Reviewer comment: The frequency of bilirubin elevations appears similar in subjects receiving ublituximab-xiiy and teriflunomide in Study TG1101-RMS302. However, one subject on ublituximab-xiiy experienced total bilirubin 5 to 10x ULN, compared to none on teriflunomide.

Please refer to Section 8.5.5 for discussion of TEAEs related to hepatotoxicity.

Hy's Law Cases

One subject on ublituximab-xiiy (0.4%) and 2 on teriflunomide (0.7%) were considered as potential Hy's Law cases (AST or ALT >3x ULN, total bilirubin >2x ULN, and ALP <2x ULN). The subject on ublituximab-xiiy is ID # [REDACTED]^{(b) (6)}, who was a 46 year-old woman who experienced the SAE chronic hepatitis B. This case is discussed in Section 8.4.2.

Reviewer comment: The subject on ublituximab-xiiy who met Hy's Law Criteria did so in the setting of Hepatitis B, and is therefore not representative of drug-induced liver injury. The 2 cases reported in teriflunomide-treated subjects are not unexpected given the safety profile of teriflunomide. See Section 8.5.5.

Alkaline phosphatase

Alkaline phosphatase (IU/L) values over time were reviewed, and there were no apparent clinically significant differences between the treatment groups in terms of mean/median values, peak values, or changes from baseline.

Elevations in ALP >1.5x ULN from a normal baseline (<1.5x ULN) occurred in 0.4% of subjects on ublituximab-xiiy and 0.7% on teriflunomide. Additionally, 1 subject on teriflunomide (0.4%) experienced peak ALP between 2 and 3x ULN, compared to 0 subjects on ublituximab-xiiy.

Renal function

There were no apparent clinically significant trends for BUN or creatinine in either treatment group over time, as mean/median values and changes from baseline were similar between the treatment groups. Creatinine values ≥ 130 $\mu\text{mol/L}$ were slightly more frequent in ublituximab-xiiy-treated subjects (0.7% ublituximab-xiiy versus 0.4% teriflunomide), but BUN values >9 mmol/L were more common in teriflunomide-treated subjects (5.9% teriflunomide versus 1.5%

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Laura Baldassari, MD, MHS
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Ublituximab-xiiy (Briumvi)

ublituximab-xiiy). However, maximum BUN and creatinine values were similar between the groups.

Pancreatic Enzymes

Amylase elevations 2 to 3x ULN were reported in 0.4% of subjects on ublituximab-xiiy, and 0% on teriflunomide; elevations 3 to 5x ULN were reported in 0% of subjects on ublituximab-xiiy and 0.4% on teriflunomide. Lipase elevations 3 to 5x ULN were reported in 0.4% of subjects on ublituximab-xiiy and 2.6% on teriflunomide; elevations 5 to 10x ULN were reported in 0.7% of subjects on ublituximab-xiiy and 0.7% on teriflunomide.

No subjects in either treatment group experienced amylase >400 U/L. Lipase >400 U/L occurred in 2 subjects receiving ublituximab-xiiy (# (b) (6)). The elevation in subject (b) (6) occurred on Day 2 of the study. Both subjects had these values documented as TEAEs.

TEAEs of amylase increased were reported in 1.8% (n = 5) of subjects on ublituximab-xiiy versus 0% on teriflunomide. TEAEs of lipase increased were reported in 2.9% (n = 8) of subjects on ublituximab-xiiy versus 2.2% (n = 6) on teriflunomide. TEAEs of pancreatic enzymes increased were reported in 0.7% (n = 2) of subjects on ublituximab-xiiy versus 0% on teriflunomide. Pancreatic disorder was reported in 0.4% (n = 1) subject on ublituximab-xiiy versus 0% on teriflunomide. Pancreatitis haemorrhagic was reported in 0.4% (n = 1) subject on ublituximab-xiiy versus 0% on teriflunomide. The TEAEs pancreatic toxicity and pancreatitis acute were reported in 0.4% (n = 1) of subjects on teriflunomide, but none in ublituximab-xiiy. The TEAE pancreatic steatosis was reported in 0% of subjects on ublituximab-xiiy, and 0.4% (n = 1) of subjects on teriflunomide.

Reviewer comment: Of note, teriflunomide labeling contains a warning for pancreatitis in pediatric patients and a separate mention of pancreatitis as an adverse reaction identified in postmarketing experience. Though there is no obvious signal for pancreatic toxicity at this time, a concern was raised during the review of ocrelizumab and enhanced pharmacovigilance was recommended. Enhanced pharmacovigilance also appears to be warranted based on these data as well.

Other Chemistry

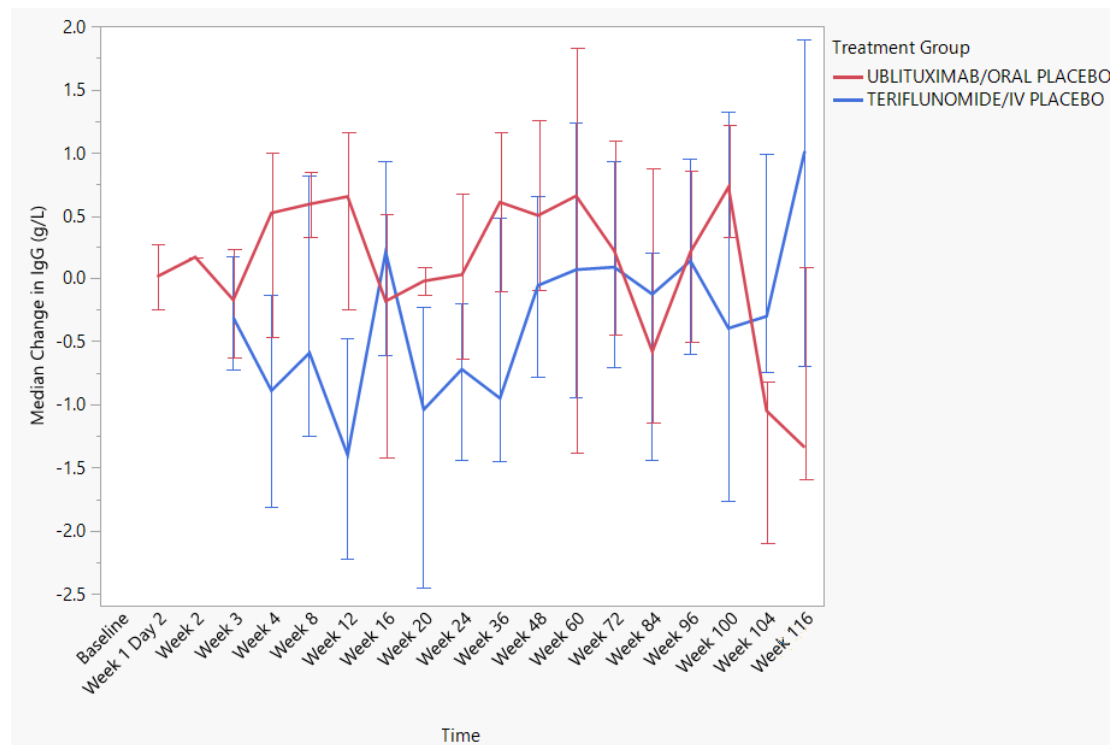
There were no apparent clinically significant trends for urate, albumin, sodium, calcium, phosphate, and chloride in either treatment group over time, as mean/median values and changes from baseline were similar between the treatment groups.

Immunoglobulins

IgG

Median IgG for the ublituximab-xiiy group was 9.9 g/L at baseline, 9.9 g/L at week 24, then 10.0 g/L at week 96, compared to 9.5 g/L, 8.9 g/L, and 9.9 g/L for teriflunomide, respectively. Across the DBT period, 2.6% of subjects on ublituximab-xiiy (n = 7) and 1.8% on teriflunomide (n = 5) experienced IgG <5.5 g/L. Median change in IgG from baseline over the DBT period is presented in Figure 21.

Figure 21 (Reviewer). Study TG1101-RMS302, Median Change in IgG (g/L) from Baseline Over Time, Safety Population



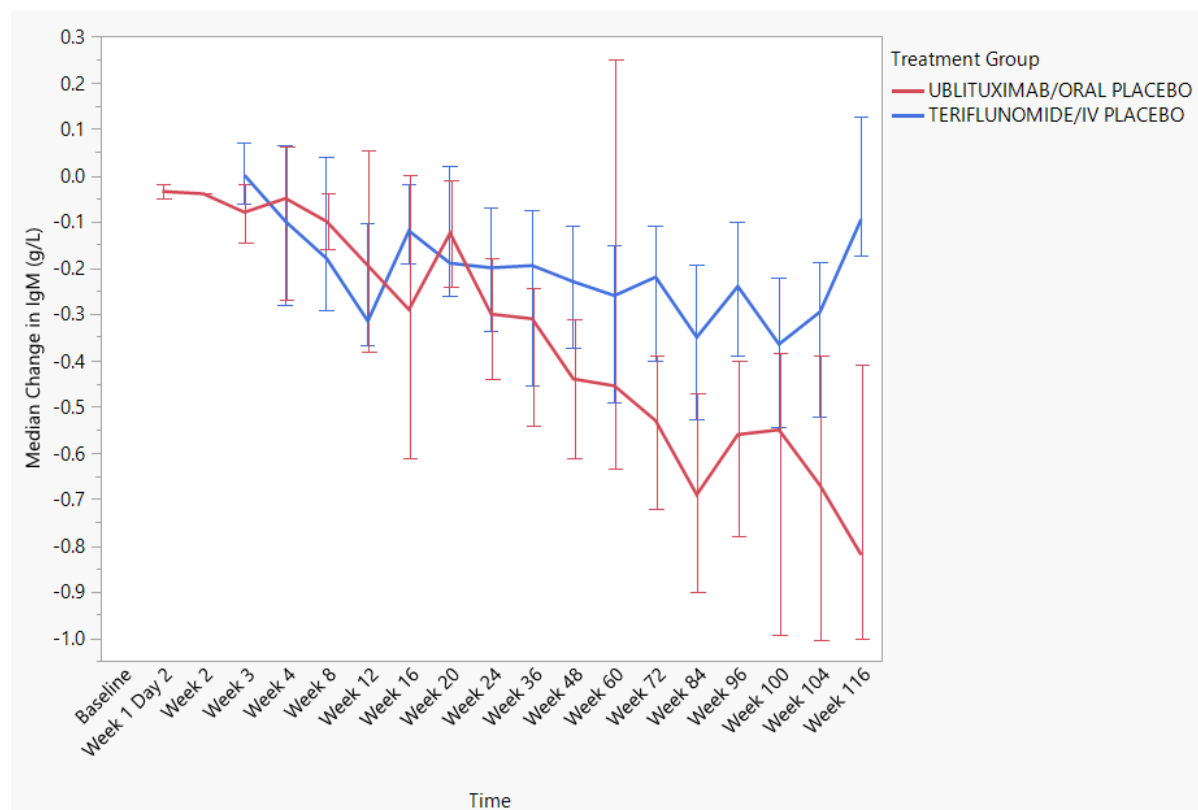
Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=IGG, by TRT01A

Reviewer comment: Though expected long-term given the mechanism of action of ublituximab-xiiy, there was not a clear trend for reduction in IgG associated with ublituximab-xiiy during the DBT period. Median values after Week 96 should be interpreted with caution due to the small number of subjects with recorded values at those time points.

IgM

Median IgM for the ublituximab-xiyy group was 1.3 g/L at baseline, 1.0 g/L at week 24, then 0.7 g/L at week 96, compared to 1.4 g/L, 1.1 g/L, and 1.2 g/L for teriflunomide, respectively. Across the DBT period, 23.9% of subjects on ublituximab-xiyy (n = 65) and 6.6% on teriflunomide (n = 18) experienced IgM <0.4 g/L. Median change in IgM from baseline over the DBT period is presented in Figure 22.

Figure 22 (Reviewer). Study TG1101-RMS302, Median Change in IgM (g/L) from Baseline Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=IGM, by TRT01A

Reviewer comment: Reduction in immunoglobulins is expected long-term given the mechanism of action of ublituximab-xiyy, and there was a clear trend for declining IgM levels over time in the ublituximab-xiyy group compared to teriflunomide over at least 96 weeks of DBT. Sample size at Weeks 100, 104, and 116 was small and therefore these values should be interpreted with caution.

CD19+ B-cells

Clinical Review
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 BLA 761238
 Ublituximab-xiyy (Briumvi)

The primary pharmacodynamic effect of ublituximab-xiyy is depletion of CD19+ B-cells. Absolute CD19+ B-cell count was evaluated at each visit during DBT, with representative timepoints shown in Table 78 and median absolute CD19+ B-cell count over time in Figure 23.

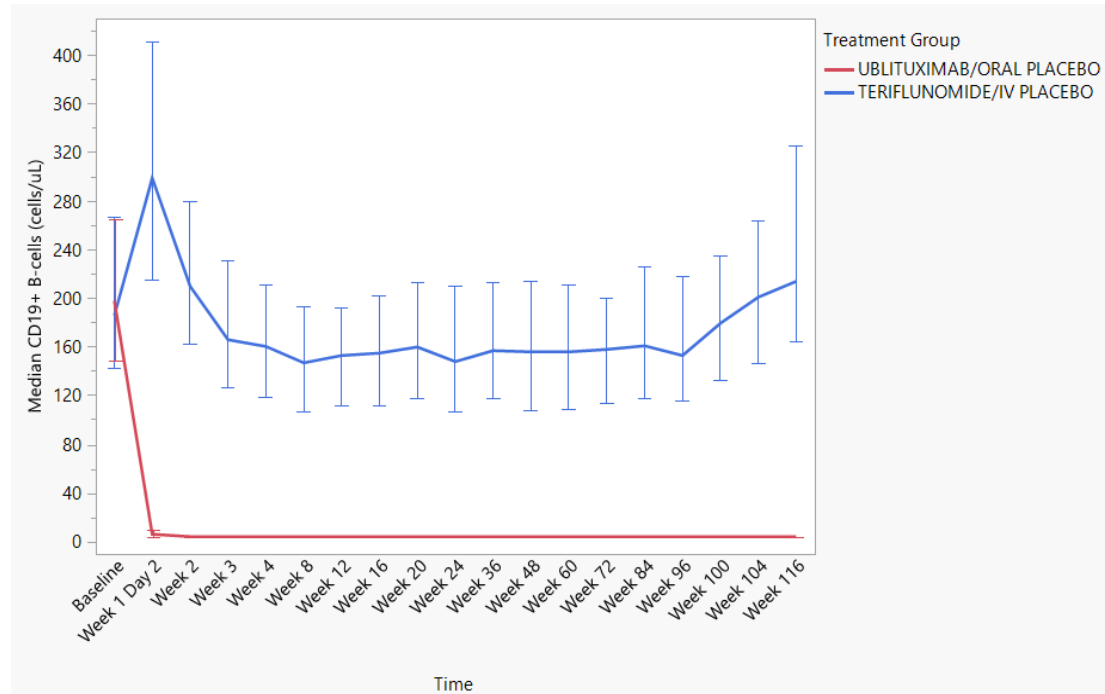
Table 78 (Reviewer). Study TG1101-RMS302, Absolute CD19+ B-cell Count (cells/ μ L) Over Time, Safety Population

Time	Parameter	Ublituximab-xiyy (n = 272)	Teriflunomide (n = 273)
Baseline	Mean (SD)	225.0 (116.5)	221.4 (130.4)
	Median	198.0	186.0
	Min, Max	17.0, 713.0	20.0, 1073.0
Week 4	N	268	272
	Mean (SD)	4.9 (13.0)	179.8 (109.6)
	Median	4.0	160.5
	Min, Max	1.0, 213.0	4.0, 1119.0
	Mean (SD) change from baseline	-221.0 (116.4)	-42.1 (108.2)
	Median change from baseline	-193.0	-25.5
	Min, Max change from baseline	-709.0, -13.0	-830.0, 676.0
Week 24	N	267	262
	Mean (SD)	9.6 (18.4)	170.6 (92.9)
	Median	4.0	148.0
	Min, Max	1.0, 159.0	4.0, 610.0
	Mean (SD) change from baseline	-215.0 (115.0)	-48.4 (104.3)
	Median change from baseline	-185.0	-35.0
	Min, Max change from baseline	-709.0, -13.0	-852.0, 270.0
Week 48	N	262	249
	Mean (SD)	7.7 (17.1)	176.4 (96.7)
	Median	4.0	156.0
	Min, Max	1.0, 179.0	4.0, 546.0
	Mean (SD) change from baseline	-219.0 (116.6)	-43.1 (98.6)
	Median change from baseline	-188.0	-37.0
	Min, Max change from baseline	-709, -1.0	-765.0, 256.0
Week 96	N	251	239
	Mean (SD)	9.2 (42.5)	175.0 (87.6)
	Median	4.0	153.0
	Min, Max	1.0, 571.0	4.0, 541.0
	Mean (SD) change from baseline	-220.0 (122.5)	-43.6 (110.6)
	Median change from baseline	-193.0	-30.0
	Min, Max change from baseline	-709.0, 245.0	-943.0, 148.0

Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD=CD19BCLA, by TRT01A

Clinical Review
Laura Baldassari, MD, MHS
BLA 761238
Ublituximab-xiiy (Briumvi)

Figure 23 (Reviewer). Study TG1101-RMS302, Absolute CD19+ B-cell Count (cells/ μ L) Over Time, Safety Population



Error bars represent interquartile range; Source: ADLB, SAFFL=Y, ANL01FL=Y, PARAMCD= CD19BCLA, by TRT01A

In Study TG1101-RMS302, there were 23 subjects who received ublituximab-xiiy who had post-baseline CD19+ B-cell counts > 100 cells/ μ L. These values were most common at Weeks 100 (n = 5) and Week 104 (n = 7). Of these 23 subjects, 3 experienced 1 IRAP-confirmed relapse, 1 experienced 2 IRAP-confirmed relapses, and 1 experienced 3 IRAP-confirmed relapses.

Reviewer comment: It appears that ublituximab-xiiy depleted CD19+ B-cells in a majority of subjects. Several subjects did not have complete B-cell depletion, and one subject who had 3 relapses also had incomplete B-cell depletion.

Study TG1101-RMS303

Of note, only tabulation datasets (i.e., SDTM) were submitted for Study TG1101-RMS303; no analysis datasets (ADAM) were submitted. The SDTM laboratory dataset submitted only contained screening and Week 1 Day 1 laboratory values for IgG and IgM. Therefore, analysis of immunoglobulins in the setting of longer-term exposure was planned but not conducted.

Study TG1101-RMS201

Given the size, duration, and supportive nature of Study TG1101-RMS201, only B-cell counts

will be reviewed. As discussed in Section 6.4, the primary endpoint for Study TG1101-RMS201 was the percentage of subjects who experienced a >95% reduction in CD19+ B-cells. However, the applicant conducted this analysis using the percentage of CD19+ B-cells, rather than the absolute count, which is not interpretable. Additionally, the absolute CD19+ B-cell count was not collected after screening, so it is not possible to conduct such analyses in this trial population.

8.4.7. Vital Signs

Vital signs, specifically blood pressure (systolic and diastolic), heart rate, temperature, and weight, were reviewed at each scheduled study visit (i.e., ANL01FL = Y) for the safety population. Vital sign-related TEAEs are also discussed in this section.

Study TG1101-RMS301

Blood Pressure

Systolic blood pressure (SBP) below 90 mmHg or above 160 mmHg was infrequent in both treatment groups. SBP <90 mmHg occurred in 1.8% of subjects on ublituximab-xiiy compared to 0.7% on teriflunomide. SBP >160 mmHg occurred in 0.7% of subjects on ublituximab-xiiy compared to 1.5% on teriflunomide.

Diastolic blood pressure (DBP) below 60 mmHg occurred in 5.1% of subjects on ublituximab-xiiy compared to 5.1% on teriflunomide, indicating similar frequencies. DBP >90 mmHg occurred in 16.8% of subjects on ublituximab-xiiy compared to 22.9% on teriflunomide.

The TEAE hypertension occurred in 4.0% of subjects on ublituximab-xiiy and 8.0% on teriflunomide. The TEAE blood pressure increased occurred in 1.5% of subjects on ublituximab-xiiy and 1.8% on teriflunomide. Hypertensive crisis occurred in 1 subject on teriflunomide (0.4%). Hypotension occurred in 1.1% of subjects on ublituximab-xiiy compared to 0% on teriflunomide.

Reviewer comment: Teriflunomide labeling currently contains a warning regarding increased blood pressure. TEAEs related to increased blood pressure occurred at a higher frequency in the teriflunomide group.

Heart Rate

Heart rate (HR) below 50 beats per minute (bpm) or above 120 bpm was infrequent in both treatment groups. HR <50 bpm occurred in 0.7% of subjects on ublituximab-xiiy compared to 1.5% on teriflunomide. No subjects experienced HR >120bpm at a scheduled study visit.

Clinical Review
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BLA 761238
Ublituximab-xiiy (Briumvi)

The TEAE tachycardia was reported in 3.7% of subjects on ublituximab-xiiy, compared to 2.2% on teriflunomide. The TEAE sinus tachycardia was reported in 1.8% of subjects in each group. Heart rate increased was reported in 0.4% of subjects on ublituximab-xiiy versus 0% on teriflunomide.

The TEAEs bradycardia and sinus bradycardia each were reported in 0.7% of subjects on ublituximab-xiiy compared to 0.4% on teriflunomide. Heart rate-related TEAEs are also summarized in Table 79.

Weight

Similar proportions of subjects in each treatment group experienced a >10% weight loss compared to baseline (13.9% ublituximab-xiiy versus 14.9% teriflunomide). However, subjects in the ublituximab-xiiy group were more likely to experience a >10% weight gain compared to baseline (14.7% ublituximab-xiiy versus 9.8% teriflunomide).

The TEAE weight increased occurred in 1.1% of subjects on ublituximab-xiiy compared to 0.7% on teriflunomide. The TEAE weight decreased occurred in 1.1% of subjects on ublituximab-xiiy compared to 3.3% on teriflunomide.

Temperature

No subjects in either group experienced temperature >38.1°C at a scheduled study visit. Similar proportions of subjects in each group experienced temperature <36.0°C at a scheduled study visit (14.3% ublituximab-xiiy versus 14.5% teriflunomide).

The TEAE pyrexia occurred in 15.0% of subjects on ublituximab-xiiy compared to 4.7% on teriflunomide. The TEAE body temperature increased occurred in 4.4% of subjects on ublituximab-xiiy compared to 1.1% on teriflunomide. The TEAE hyperthermia occurred in 4.8% of subjects on ublituximab-xiiy compared to 0.7% on teriflunomide.

Reviewer comment: Though the frequency of abnormal temperature at scheduled study visits was similar between the groups, subjects on ublituximab-xiiy were more likely to experience TEAEs of pyrexia, body temperature increased, or hyperthermia. This is not unexpected given reports of these events as IRRs.

Study TG1101-RMS302

Blood Pressure

Systolic blood pressure (SBP) below 90 mmHg or above 160 mmHg was infrequent in both

treatment groups. SBP <90 mmHg was more frequent in ublituximab-xiiy-treated subjects (1.5% ublituximab-xiiy versus 0.4% teriflunomide). SBP >160 mmHg occurred in 1.8% of subjects on ublituximab-xiiy compared to 1.8% on teriflunomide.

Diastolic blood pressure (DBP) below 60 mmHg occurred in 5.9% of subjects on ublituximab-xiiy compared to 2.6% on teriflunomide. DBP >90 mmHg occurred in 16.5% of subjects on ublituximab-xiiy compared to 21.2% on teriflunomide.

The TEAE hypertension occurred in 3.7% of subjects on ublituximab-xiiy and 5.5% on teriflunomide. The TEAE blood pressure increased occurred in 0.7% of subjects on ublituximab-xiiy and 0.7% on teriflunomide. Blood pressure systolic increased occurred in 0% of subjects on ublituximab-xiiy compared to 0.4% on teriflunomide, and essential hypertension was reported in 0% of subjects on ublituximab-xiiy compared to 0.4% on teriflunomide.

Hypotension occurred in 0% of subjects on ublituximab-xiiy compared to 1.1% on teriflunomide, and blood pressure decreased occurred in 0% of subjects on ublituximab-xiiy compared to 0.4% on teriflunomide.

Reviewer comment: Teriflunomide labeling currently contains a warning regarding increased blood pressure. DBP elevation >90 mmHg was more frequent in teriflunomide-treated subjects, but SBP >160 mmHg occurred at a similar frequency in each group. TEAEs related to increased blood pressure appeared to be more frequent in the teriflunomide group as well.

Heart Rate

HR below 50 beats per minute (bpm) or above 120 bpm was infrequent in both treatment groups. HR <50 bpm occurred in 0.7% of subjects on ublituximab-xiiy compared to 1.8% on teriflunomide. One subject in the ublituximab-xiiy group (0.4%) experienced HR >120bpm, compared to 0 in the teriflunomide group.

The TEAE sinus tachycardia was reported in 7.4% of subjects on ublituximab-xiiy, compared to 1.8% on teriflunomide. The TEAE tachycardia was reported in 3.7% of subjects in each group. Heart rate increased was reported in 1.5% of subjects on ublituximab-xiiy versus 0.7% on teriflunomide.

The TEAE sinus bradycardia was reported in 1.1% of subjects on ublituximab-xiiy compared to 0.4% on teriflunomide. Sinus bradycardia was reported in 0.4% of subjects in each group.

Heart rate-related TEAEs are also summarized in Table 79.

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Weight

Subjects on teriflunomide were slightly more likely to experience a >10% weight loss compared to baseline compared to those on ublituximab-xiiy (12.8% teriflunomide versus 7.0% ublituximab-xiiy). Subjects in the ublituximab-xiiy group were more likely to experience a >10% weight gain compared to baseline (17.3% ublituximab-xiiy versus 8.8% teriflunomide).

The TEAE weight increased occurred in 0.7% of subjects in both groups. The TEAE weight decreased occurred in 0.7% of subjects on ublituximab-xiiy compared to 0.4% on teriflunomide.

Reviewer comment: The occurrence of weight-related TEAEs was not as frequent in Study TG1101-RMS302, and was similar between the treatment groups (for both weight loss and gain). However, subjects on ublituximab-xiiy were more likely to experience a >10% weight gain.

Temperature

Body temperature >38.1°C at a scheduled study visit was infrequent in both groups, but occurred in 1.1% of subjects on ublituximab-xiiy compared to 0.4% on teriflunomide. Similar proportions of subjects in each group experienced temperature <36.0°C at a scheduled study visit (17.3% ublituximab-xiiy versus 21.6% teriflunomide).

The TEAE pyrexia occurred in 12.9% of subjects on ublituximab-xiiy compared to 5.1% on teriflunomide. The TEAE hyperthermia occurred in 6.6% of subjects on ublituximab-xiiy compared to 1.5% on teriflunomide. The TEAE body temperature increased occurred in 4.4% of subjects on ublituximab-xiiy compared to 1.1% on teriflunomide.

Reviewer comment: Though the frequency of abnormal temperature at scheduled study visits was similar between the groups, subjects on ublituximab-xiiy were more likely to experience TEAEs of pyrexia, body temperature increased, or hyperthermia. This observation is not surprising given the association of these PTs with IRRs.

Study TG1101-RMS303

Given the open-label nature of Study TG1101-RMS303, detailed review of vital signs will not be presented.

Study TG1101-RMS201

Given the size, duration, and supportive nature of Study TG1101-RMS201, detailed review of vital signs will not be presented.

8.4.8. Electrocardiograms (ECGs)

Studies TG1101-RMS301 and TG1101-RMS302

Though relatively infrequent, potential ECG-related TEAEs were reported in both treatment groups. These TEAEs are summarized for Studies TG1101-RMS301 and TG1101-RMS302 in Table 79.

Table 79 (Reviewer). ECG-Related TEAEs in Studies TG1101-RMS301 and TG1101-RMS302

Preferred Term	Study TG1101-RMS301		Study TG1101-RMS302	
	Ublituximab-xiiy (n = 273) n (%)	Teriflunomide (n = 275) n (%)	Ublituximab-xiiy (n = 272) n (%)	Teriflunomide (n = 273) n (%)
Sinus tachycardia	5 (1.8)	5 (1.8)	20 (7.4)	5 (1.8)
Tachycardia	10 (3.7)	6 (2.2)	10 (3.7)	10 (3.7)
Electrocardiogram QT prolonged	3 (1.1)	3 (1.1)	3 (1.1)	2 (0.7)
Atrial conduction time prolongation	0 (0)	0 (0)	3 (1.1)	2 (0.7)
Sinus bradycardia	2 (0.7)	1 (0.4)	3 (1.1)	1 (0.4)
Bradycardia	2 (0.7)	1 (0.4)	1 (0.4)	1 (0.4)
Heart rate increased	1 (0.4)	0 (0)	4 (1.5)	2 (0.7)
Bundle branch block right	1 (0.4)	0 (0)	2 (0.7)	0 (0)
Extrasystoles	1 (0.4)	0 (0)	0 (0)	1 (0.4)
Supraventricular extrasystoles	1 (0.4)	1 (0.4)	1 (0.4)	0 (0)
Atrial fibrillation	0 (0)	0 (0)	1 (0.4)	0 (0)
Atrial tachycardia	0 (0)	0 (0)	1 (0.4)	0 (0)
Left ventricular hypertrophy	0 (0)	0 (0)	1 (0.4)	0 (0)
Ventricular arrhythmia	1 (0.4)	0 (0)	0 (0)	0 (0)
Ventricular extrasystoles	1 (0.4)	0 (0)	0 (0)	0 (0)
Arrhythmia	0 (0)	0 (0)	0 (0)	1 (0.4)
Cardiac flutter	0 (0)	0 (0)	0 (0)	1 (0.4)
Electrocardiogram repolarisation abnormality	0 (0)	0 (0)	0 (0)	1 (0.4)
Electrocardiogram ST segment depression	0 (0)	1 (0.4)	0 (0)	0 (0)
Electrocardiogram T wave amplitude decreased	0 (0)	0 (0)	0 (0)	1 (0.4)
Nodal rhythm	0 (0)	1 (0.4)	0 (0)	0 (0)
Sinus arrhythmia	0 (0)	0 (0)	0 (0)	1 (0.4)

Reviewer comment: Most TEAEs were related to heart rate (e.g., sinus tachycardia, tachycardia, bradycardia, sinus bradycardia). TEAEs related to increased heart rate appeared to be more frequent in the ublituximab-xiiy group. The frequency of the TEAE QTc prolongation appeared similar between the treatment groups.

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8.4.9. QT

Study TG1101-RMS301

Per the Summary of Clinical Safety, the applicant only performed normality interpretations for ECGs in Study TG1101-RMS301. QT values were not collected. The TEAE electrocardiogram QT prolonged was reported in 1.1% of subjects in each treatment group.

Study TG1101-RMS302

Per the Summary of Clinical Safety, the applicant only performed normality interpretations for ECGs in Study TG1101-RMS302. QT values were not collected. The TEAE electrocardiogram QT prolonged was reported in 1.1% of subjects on ublituximab-xiiy and 0.7% on teriflunomide.

Study TG1101-RMS201

The applicant provided a tabulation of subjects with post-treatment QTcF >450, >480, and >500 msec. All subjects had QTcF ≤ 450 msec at baseline. Post-baseline, 97.9% of subjects had QTcF ≤ 450 msec, and one subject (2.1%) had QTcF between 450 and 480 msec. Per the applicant's analysis, no subjects had a change from baseline > 60msec. Change from baseline was ≤30 msec in 91.7% of subjects and 30 to 60 msec in 8.3%.

Reviewer comment: Overall, there does not appear to be a clinically significant effect of ublituximab-xiiy on QTc, as expected for a monoclonal antibody.

8.4.10. Immunogenicity

According to the applicant's Bioanalytical Report referenced in the CSR, 234 out of 271 (86.3%) of subjects receiving ublituximab-xiiy in Study TG1101-RMS301 and 239 out of 272 (87.9%) subjects receiving ublituximab-xiiy in Study TG1101-RMS302 developed anti-drug antibodies. Please refer to the Clinical Pharmacology Review.

One subject in Study TG1101-RMS301 (Subject (b) (6)) experienced IRRs with several ublituximab-xiiy infusions, and was found to have binding anti-drug antibodies (See Section 8.4.2, SAE of infusion related reaction). Screening confirmation testing for binding anti-drug antibodies was negative (after a presumptive positive screening), then on Weeks 3 and 24, confirmation testing was positive. Additionally, neutralizing antibody testing was positive at Week 24, after being negative at Weeks 1 and 3. She discontinued study treatment due to "investigator or sponsor decision," but it appears that recurrent IRRs in the setting of antidrug binding antibodies were the reason for discontinuation.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Mortality

Please refer to Section 8.4.1 for discussion of deaths that have occurred in the ublituximab-xiiy development program, all due to serious infections. These cases, and other known deaths in the development program, with a data cut-off date of 8/13/2022, are presented in Table 80. No deaths were reported in teriflunomide-treated subjects.

Table 80 (Reviewer). Mortality in Ublituximab-xiiy RMS Development Program

	TG1101-RMS301/302		TG1101-RMS303	TG1101-RMS201/201E
	Ublituximab-xiiy (N = 545) N (%)	Teriflunomide (N = 548) N (%)	Ublituximab-xiiy (n = 642) N (%)	Ublituximab-xiiy (n = 45) N (%)
Deaths	3 (0.6)	0 (0)	20 (3.1)	4 (8.9)
COVID-19 and COVID-19 pneumonia	0 (0)	0 (0)	20 (3.1)	4 (8.9)
Encephalitis	1 (0.2)	0 (0)	0 (0)	0 (0)
Salpingitis	1 (0.2)	0 (0)	0 (0)	0 (0)
Pneumonia	1 (0.2)	0 (0)	0 (0)	0 (0)

Source: Applicant's Response to Information Request dated 8/18/2022, data cutoff: 8/13/2022

An Information Request requesting updated mortality data was sent to the applicant on 7/28/2022. The applicant responded on 8/18/2022, indicating that as of 8/13/2022, 24 total deaths occurred since the BLA cutoff date. All deaths were due to COVID-19-related events, and occurred in 4 subjects in Study TG1101-RMS201E and 20 subjects in Study TG1101-RMS303.

Data from the development programs of other anti-CD20 therapies was also reviewed to further evaluate this mortality signal. In pooled trials of ocrelizumab in subjects with RMS, 1 death occurred in 825 subjects treated with ocrelizumab (0.1%). In pooled controlled trials of ofatumumab in subjects with RMS, 0 deaths occurred in subjects treated with ofatumumab. These data are summarized in Table 81.

Table 81 (Reviewer). Mortality in Anti-CD20 Therapy Development Programs in Relapsing MS

	Ublituximab-xiiy				Ocrelizumab		Ofatumumab	
	TG1101-RMS301/302		TG1101-RMS303	TG1101-RMS201/201E	Pooled controlled phase RMS trials		Pooled controlled phase RMS trials	
	Ublituximab-xiiy (N = 545)	TFN* (N = 548)	Ublituximab-xiiy (n = 642)	Ublituximab-xiiy (n = 45)	Ocrelizumab (n = 825)	IFN (n = 826)	Ofatumumab (n = 946)	TFN (n = 936)
Deaths	3 (0.6)	0 (0)	10 (1.6)	1 (2.2)	1 (0.1)	2 (0.2)	0 (0)	1 (0.1)

*TFN: teriflunomide; values reported as n (%)

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The death reported in an ocrelizumab-treated subject with RMS was due to suicide and therefore not drug-related. The deaths in interferon beta-1a-treated subjects in the ocrelizumab development program were due to suicide and ileus and were not considered to be drug-related.

Per the Clinical BLA Review for ocrelizumab by Dr. Gerard Boehm, in Study WA25046 for primary progressive MS, the mortality risk for ocrelizumab was 0.8% (4/486) compared to 0.4% (1/239) for placebo. The causes of death for ocrelizumab-treated subjects were pneumonia, pulmonary embolism, aspiration pneumonia, and metastatic pancreatic cancer.

Reviewer comment: Though data from the PPMS population can be considered useful for comparison purposes, their generalizability to an RMS population is limited due to important differences in these populations, mainly older age and increased disability in the PPMS population and therefore increased susceptibility to infection and sequelae.

Per the Clinical sBLA Review for ofatumumab by Dr. Lawrence Rodichok, in Study COMB157G2302 for RMS, one death occurred in a subject treated with teriflunomide. This subject experienced aortic and vertebral artery dissection 152 days after the last dose of teriflunomide, for which he or she underwent cardiothoracic surgery that was complicated by aortic rupture leading to death.

Reviewer comment: The risk of mortality associated with serious infections in subjects treated with ublituximab-xiiy appears higher than that observed in the ofatumumab and ocrelizumab development programs. It is difficult to compare deaths attributed to COVID-19 in subjects on ublituximab-xiiy due to the fact that controlled trials for other anti-CD20 therapies were not occurring during the COVID-19 pandemic. Emerging literature during the COVID-19 pandemic has suggested a higher risk of severe COVID-19 disease and mortality associated with anti-CD20 therapies.

8.5.2. Serious Infections

Infections, including serious and fatal infections, are a known risk with ublituximab-xiiy. Serious infections were included as an adverse event of special interest (AESI), and are summarized in Table 82.

Table 82 (Reviewer). Serious Infections in Ublituximab-xiiy RMS Development Program

Category		TG1101-RMS301/302		TG1101-RMS303	TG1101-RMS201
		Ublituximab-xiiy (N = 545) N (%)	Teriflunomide (N = 548) N (%)	Ublituximab-xiiy (n = 642) N (%)	Ublituximab-xiiy (n = 48) N (%)
Serious infections	Any (AESI per applicant)	27 (5.0)	16 (2.9)	8 (1.2)	1 (2.1)
Infections and Infestations (SOC)	Any	304 (55.8)	298 (54.4)	69 (10.7)	28 (58.3)
Infection-related SAE	Any	27 (5.0)	16 (2.9)	8 (1.2)	1 (2.1)
CNS infections (SAEs)	CNS enteroviral infection	2 (3.7)	0 (0)	0 (0)	0 (0)
	Encephalitis	1 (0.2)	0 (0)	0 (0)	0 (0)
	Meningoencephalitis viral	1 (0.2)	0 (0)	0 (0)	0 (0)
	Meningitis	0 (0)	0 (0)	2 (3.1)	0 (0)
	Meningitis viral	0 (0)	0 (0)	1 (0.2)	0 (0)
COVID-19 (SAEs)	COVID-19	0 (0)	0 (0)	1 (0.2)	0 (0)
	COVID-19 pneumonia	4 (0.7)	2 (0.4)	6 (0.9)	0 (0)
Other selected infection-related SAEs	Pneumonia	5 (0.9)	2 (0.4)	0 (0)	0 (0)
	Acute sinusitis	3 (0.6)	0 (0)	0 (0)	0 (0)
	Appendicitis/complicated appendicitis	3 (0.6)	1 (0.2)	0 (0)	1 (2.1)
	Bullous erysipelas	1 (0.2)	0 (0.0)	0 (0)	0 (0)
	Measles	1 (0.2)	0 (0.0)	0 (0)	0 (0)
	Peritonsillar abscess	1 (0.2)	0 (0.0)	0 (0)	0 (0)
	Pulmonary tuberculosis	1 (0.2)	0 (0.0)	0 (0)	0 (0)
	Salpingitis/Salpingo-oophoritis	1 (0.2)	0 (0.0)	2 (0.3)	0 (0)
	Upper respiratory tract infection	1 (0.2)	0 (0.0)	0 (0)	0 (0)
	Bacterial infection	0 (0.0)	1 (0.2)	0 (0)	0 (0)
	Lyme disease	1 (0.2)	0 (0.0)	0 (0)	0 (0)
	Pyelonephritis acute	0 (0.0)	3 (0.5)	0 (0)	0 (0)
	Urinary tract infection	1 (0.2)	0 (0.0)	0 (0)	0 (0)
	Chronic hepatitis B	1 (0.2)	0 (0.0)	0 (0)	0 (0)
	Epididymitis	1 (0.2)	0 (0.0)	0 (0)	0 (0)
	Gastrointestinal infection	1 (0.2)	0 (0.0)	0 (0)	0 (0)
	Peritonitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0)

Source: ADAE for respective studies, TRTEMFL=Y and SAFFL=Y; data cutoff 11/23/2020

The applicant provided an updated tabulation of serious infections following an Information Request sent on 7/28/2022, with response received on 8/18/2022. Across all RMS studies (including extension studies) as of 7/5/2022, the applicant indicated that 150 subjects (14.7%) exposed to ublituximab-xiiy experienced a serious infection (n = 102 COVID-19; n = 63 non-COVID-19). See Section 8.5.7 for discussion related to COVID-19.

Serious infections that occurred in the development programs for ocrelizumab and ofatumumab for RMS were also reviewed (Table 83). The pivotal trials for ofatumumab also utilized teriflunomide as a comparator, so are more appropriate for comparison with the ublituximab-xiyy development program. Though the frequency of infection-related SAEs is higher in both treatment groups in the ublituximab-xiyy development program compared to ofatumumab, the relative risk for an infection-related SAE for ublituximab-xiyy compared with teriflunomide is 1.7 (5.0%/2.9%), and for ofatumumab compared with teriflunomide is 1.4 (2.5%/1.8%). Infection-related SAEs were more frequent in interferon beta-1a-treated subjects compared to those on ocrelizumab in the pooled controlled phase 3 RMS trials; therefore, this comparison was not considered to be appropriate.

Table 83 (Reviewer). Comparison of Infection-Related SAEs and TEAEs Across Anti-CD20 Therapy Development Programs

	Ublituximab-xiyy				Ofatumumab	
	TG1101-RMS301/302		TG1101-RMS303	TG1101-RMS201	Pooled controlled phase 3 RMS trials	
	Ublituximab-xiyy (N = 545)	TFN (N = 548)	Ublituximab-xiyy (n = 642)	Ublituximab-xiyy (n = 45)	Ofatumumab (n = 946)	TFN (n = 936)
SAEs under Infections & Infestations SOC (N (%))	27 (5.0)	16 (2.9)	8 (1.2)	1 (2.1)	24 (2.5)	17 (1.8)
Relative risk for anti-CD20 vs comparator	1.7	NA	NA	NA	1.4	NA
TEAEs under Infections & Infestations SOC (N (%))	304 (55.8)	298 (54.4)	69 (10.7)	28 (58.3)	507 (53.6)	505 (54.0)
Relative risk for anti-CD20 vs comparator	1.03	NA	NA	NA	0.99	NA

Source: For ublituximab, ADAE for respective studies, TRTEMFL=Y and SAFFL=Y, data cutoff 11/23/2020; for ofatumumab, sBLA Clinical Review by Dr. Lawrence Rodichok.

Four cases of central nervous system infections were reported in subjects receiving ublituximab-xiyy during the double-blind period of Studies TG1101-RMS301 and TG1101-RMS302, and additional 3 cases have been reported in subjects during Study TG1101-RMS303 as of 7/5/2022. These events have included CNS enteroviral infection, encephalitis, meningoencephalitis viral, meningitis, meningitis enteroviral, and meningitis viral. Of note, a case of West Nile Virus meningoencephalitis in a 34 year-old woman in Study TG1101-RMS303 occurred on 8/27/2022 and was submitted to IND 127265 (Report #TGT002657).

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PML was considered in 2 cases during the double-blind period, but in one case CSF JCV PCR was negative (Subject (b) (6)). In the other case, CSF JCV PCR was not reportedly available (Subject (b) (6)) so it is not possible to rule out PML, but the reported CSF profile appeared atypical for PML. An Information Request was sent on 7/28/2022, and a response was received on 8/12/2022, regarding cases with a potential diagnosis of PML. The applicant indicated that the MRI for Subject (b) (6) was reviewed by an independent radiologist and was considered inconsistent with PML. For Subject (b) (6), the MRI findings were considered consistent with MS; PML was excluded based on high CSF pleocytosis, MRI findings, clinical features, and positive response to acyclovir. The applicant identified a teriflunomide-treated subject where the diagnosis of PML was considered (Subject (b) (6)); this subject was determined not to have PML based upon MRI findings.

The cases of viral meningitis, specifically enterovirus, were only observed in the ublituximab-xiiy group. A signal for viral meningitis has not been noted in clinical trials for other anti-CD20 therapies. Specifically, no cases of viral meningitis, encephalitis, or enteroviral infections were reported in ofatumumab or ocrelizumab controlled trials for RMS. In trials of ocrelizumab for other indications, one case of cryptococcal meningoencephalitis (subject with systemic lupus erythematosus/lupus nephritis) and one case of viral meningoencephalitis (subject with rheumatoid arthritis) were reported in subjects on ocrelizumab.

Of note, no serious herpes virus infections were reported in the ublituximab-xiiy development program. As of 7/5/22, per the applicant's analysis, herpes virus related infections were reported in 4.0% of ublituximab-xiiy-treated subjects across all RMS studies.

COVID-19 infections are discussed in Section 8.5.7.

Reviewer Comment: Though the relative risk of serious infections appear to be similar to that of ofatumumab compared to teriflunomide, the reports of viral meningitis and encephalitis in the ublituximab-xiiy development program are concerning and appear to be unique to ublituximab-xiiy.

8.5.3. Infusion-Related Reactions

Infusion-related reactions are a known risk associated with monoclonal antibodies, and were included as an AESI for Studies TG1101-RMS301 and TG1101-RMS302. TEAEs designated as IRRs by the investigators were reviewed. The applicant flagged IRRs in the ADAE dataset via 2 different variables: one indicating events that were considered by investigator to be an IRR (variable *IRR*) and the other using an algorithm-generated AESI flag using a custom query (variable *CQ02NAM*). *CQ02NAM* defined an IRR as an adverse event of a preferred term of

interest that occurred within 24 hours of an infusion, and was listed as recovered/resolved. The summary tabulations evaluating IRR below are based upon the investigator determination.

Reviewer Comment: The Investigator-determined IRR flag was thought to be more appropriate and clinically relevant given the input of clinical judgment and lack of assumptions regarding occurrence and resolution within 24 hours.

The Phase 3 study protocols for ublituximab-xiiy required premedication 30-60 minutes prior to each infusion with an oral antihistamine (diphenhydramine 50mg) and an oral corticosteroid (dexamethasone 10-20mg). Additionally, the protocol specified management guidelines for IRRs.

The applicant tabulated the number of infusions completed with and without interruption, as well as the number of incomplete infusions for Studies TG1101-RMS301 and TG1101-RMS302. These results, along with other pertinent data discussed in the applicant's CSR, are presented in Table 84. Infusion interruption was more common in subjects receiving ublituximab-xiiy versus teriflunomide (13.2% and 11.0% versus 2.2% and 1.8%, respectively).

Table 84 (Reviewer). Studies TG1101-RMS301 and TG1101-RMS302 Exposure to IV Study Treatment, Safety Population

	TG1101-RMS301		TG1101-RMS302	
	Ublituximab-xiiy (n = 273)	Teriflunomide (n = 275)	Ublituximab-xiiy (n = 272)	Teriflunomide (n = 273)
Total started infusions	1304 (100) ¹	1334 (100)	1340 (100)	1303 (100)
Infusions completed without interruption	1254 (96.2)	1325 (99.3)	1300 (97.0)	1298 (99.6)
Infusions completed with interruption	38 (2.9)	2 (0.1)	37 (2.8)	4 (0.3)
Incomplete infusions	12 (0.9)	7 (0.5)	3 (0.2)	1 (0.1)
# subjects with ≥1 started infusion	273 (100)	275 (100)	272 (100)	273 (100)
# subjects without infusion interruption	237 (86.8)	269 (97.8)	242 (89.0)	268 (98.2)
# subjects with any infusion interruption	36 (13.2)	6 (2.2)	30 (11.0)	5 (1.8)

¹n(%); Source: Applicant's CSRs for Studies TG1101-RMS301 (Table 42) and TG1101-RMS302 (Table 42)

SAEs considered to be infusion-related reactions are discussed in Section 8.4.2. These 4 events in ublituximab-xiiy-treated subjects (0.7%) included anaphylactic reaction (n = 1), infusion related reaction (n = 1; described as hand, arm, jaw, and leg pain), hypersensitivity (n = 1), and lymphocyte count decreased (n = 1). The events of hypersensitivity and lymphocyte count decreased occurred after the first infusion, anaphylactic reaction after the second infusion, and infusion related reaction after the fourth infusion of ublituximab-xiiy.

The overall frequency of TEAEs considered as IRRs by the investigator occurring in >5 subjects receiving ublituximab-xiiy in the pooled Study TG1101-RMS301 or TG1101-RMS302 population are reported in Table 85. IRRs occurred in 47.7% of subjects receiving ublituximab-xiiy compared to 12.2% on teriflunomide. CTCAE Grade 3 or higher IRRs occurred in 2.8% of subjects on ublituximab-xiiy compared to 0.2% on teriflunomide. The most common preferred terms for IRRs among ublituximab-xiiy-treated subjects included pyrexia (9.5%), chills (7.9%), headache (7.5%), influenza-like illness (5.9%), infusion related reaction (5.0%), and hyperthermia (4.6%).

Table 85 also summarizes the frequency of IRRs by infusion number. Among subjects on ublituximab-xiiy, IRRs were most common with the first infusion (43.3% of subjects on ublituximab-xiiy) and decreased with subsequent infusions to 9.4% (Week 2), 7.9% (Week 24), 6.6% (Week 48) and 4.8% (Week 96).

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Table 85 (Reviewer). Infusion-Related Reactions in Ublituximab-xiiy RMS Development Program

	Ublituximab-xiiy (N = 545) N (%)	Teriflunomide (N = 548) N (%)
Any infusion-related reaction (IRR)	260 (47.7)	67 (12.2)
≥ Grade 3 IRR	15 (2.8)	1 (0.2)
IRR-related SAE	4 (0.7)	0 (0)
IRR TEAE Preferred Terms		
Pyrexia	52 (9.5)	4 (0.7)
Chills	43 (7.9)	3 (0.5)
Headache	41 (7.5)	12 (2.2)
Influenza like illness	32 (5.9)	5 (0.9)
Infusion related reaction	27 (5.0)	3 (0.5)
Hyperthermia	25 (4.6)	2 (0.4)
Nausea	18 (3.3)	2 (0.4)
Sinus tachycardia	17 (3.1)	3 (0.5)
Body temperature increased	15 (2.8)	2 (0.4)
Lymphocyte count decreased/Lymphopenia	16 (2.9)	1 (0.2)
Throat irritation	14 (2.6)	0 (0)
Tachycardia	13 (2.4)	4 (0.7)
Pain in extremity	8 (1.5)	0 (0)
Tremor	8 (1.5)	0 (0)
Erythema	7 (1.3)	0 (0)
Dizziness	6 (1.1)	2 (0.4)
Oropharyngeal pain	6 (1.1)	2 (0.4)
Hypersensitivity	6 (1.1)	1 (0.2)
Pruritis	6 (1.1)	0 (0)
% Subjects with an IRR by Infusion #		
1 st infusion (Week 0)	236 (43.3)	53 (9.7)
2 nd infusion (Week 2)	51 (9.4)	16 (2.9)
3 rd infusion (Week 24)	43 (7.9)	5 (0.9)
4 th infusion (Week 48)	36 (6.6)	4 (0.7)
5 th infusion (Week 96)	26 (4.8)	3 (0.5)

Source: ISS ADAE where TRTEMFL=Y, SAFFL=Y, and IRR=Y. IRRs based on investigator determination.

Reviewer comment: Infusion-related reactions were frequent in ublituximab-xiiy-treated subjects, particularly with the first infusion, despite required pre-medication. These reactions were more likely to occur with the first infusion, with decreasing frequency over subsequent infusions. The case of anaphylaxis occurred with the second infusion. Pre-medication for prevention of infusion-related reactions will be included in labeling. The reported rates of IRR do not indicate a clear reduction over time to no risk, and therefore labeling should describe a need for monitoring for IRR after every infusion.

8.5.4. Cytopenias

Cytopenias were also listed as an AESI for Studies TG1101-RMS301 and TG1101-RMS302. TEAEs designated as cytopenia-related AESIs by the applicant, as well as other TEAEs considered to be cytopenia-related were reviewed. Laboratory results are reviewed in Section 8.4.6.

Labeling for teriflunomide, the active comparator for these studies, contains a warning regarding Bone Marrow Effects, which mentions decreased leukocytes, neutrophils, lymphocytes, and platelets associated with teriflunomide use.

The frequency of cytopenia-related TEAEs, including AESIs, are reported in Table 86. Subjects receiving ublituximab-xiiy were more likely to experience cytopenia-related TEAEs, particularly lymphopenia and lymphocyte count decreased, which is not unexpected given the mechanism of action of ublituximab-xiiy.

Table 86 (Reviewer). Cytopenia-Related Treatment-Emergent Adverse Events in Ublituximab-xiiy RMS Development Program

	TG1101-RMS301/302		TG1101-RMS303
	Ublituximab-xiiy (N = 545) N (%)	Teriflunomide (N = 548) N (%)	Ublituximab-xiiy (n = 642) N (%)
Any Cytopenia AESI per applicant	140 (25.7)	89 (16.2)	22 (3.4)
<i>Lymphocytes</i>			
Lymphopenia	53 (9.7)	6 (1.1)	6 (0.9)
Lymphocyte count decreased	49 (9.0)	10 (1.8)	1 (0.2)
<i>Neutrophils</i>			
Neutropenia	18 (3.3)	23 (4.2)	9 (1.4)
Neutrophil count decreased	9 (1.7)	6 (1.1)	2 (0.3)
Febrile neutropenia	1 (0.2)	0 (0.0)	1 (0.2)
<i>White blood cells</i>			
Leukopenia	11 (2.0)	19 (3.5)	3 (0.5)
WBC count decreased	7 (1.3)	15 (2.7)	1 (0.2)
<i>Platelets</i>			
Thrombocytopenia	4 (0.7)	8 (1.5)	3 (0.5)
Platelet count decreased	1 (0.2)	7 (1.3)	1 (0.2)
<i>Hemoglobin</i>			
Anemia	16 (2.9)	21 (3.8)	3 (0.5)
Iron deficiency anemia	8 (1.5)	3 (0.5)	0 (0)
Hypochromic anemia	1 (0.2)	3 (0.5)	0 (0)
Hemoglobin decreased	0 (0)	2 (0.4)	0 (0)
Microcytic anemia	0 (0)	1 (0.2)	0 (0)

Source: ISS (Studies 301 and 302 only) ADAE where TRTEMFL=Y, SAFFL=Y

Reviewer comment: Subjects receiving ublituximab-xiiy were more likely to experience lymphopenia and lymphocyte count decreased, which is not unexpected given the mechanism of action of ublituximab-xiiy. Neutropenia and thrombocytopenia were more common among teriflunomide-treated subjects, which is described in current teriflunomide labeling. However, ublituximab-xiiy-treated subjects were more likely to have $ANC \leq 0.5 \times 10^9/L$ compared to teriflunomide-treated subjects.

8.5.5. Hepatic Disorders

Hepatic dysfunction was listed as an AESI for Studies TG1101-RMS301 and TG1101-RMS302. TEAEs designated as liver-related AESIs by the applicant, as well as liver-related events under the SOCs Hepatobiliary Disorders and Investigations were reviewed. Laboratory results are reviewed in Section 8.4.6.

Labeling for teriflunomide, the active comparator for these studies, currently contains a boxed warning for hepatotoxicity. Specifically, the boxed warning states that “clinically significant and potentially life-threatening liver injury, including acute liver failure requiring transplant, has been reported in patients treated with AUBAGIO in the postmarketing setting. Concomitant use of AUBAGIO with other hepatotoxic drugs may increase the risk of severe liver injury. Obtain transaminase and bilirubin levels within 6 months prior to initiation of AUBAGIO and monitoring ALT levels at least monthly for 6 months. If drug induced liver injury is suspected, discontinue AUBAGIO and start accelerated elimination procedure.”

The Drug-Induced Liver Injury (DILI) Team was consulted for review of a reported case of toxic hepatitis and the overall frequency of liver function testing abnormalities observed in subjects on ublituximab-xiiy. Please refer to the Consultation Memorandum by Dr. Paul Hayashi, dated 9/20/2022.

Four cases meeting Hy’s Law laboratory criteria for drug-induced liver injury occurred across Studies TG1101-RMS301 and TG1101-RMS302, 2 of which were in subjects receiving ublituximab-xiiy:

- Subject (b) (6) (Study TG1101-RMS301) receiving ublituximab-xiiy experienced the TEAE hepatitis toxic leading to discontinuation (See Section 8.4.3). This event was determined to be related to acute hepatitis C.
- Subject (b) (6) (Study TG1101-RMS302) receiving ublituximab-xiiy experienced the SAE chronic hepatitis B (See Section 8.4.2)

Reviewer comment: The event experienced by Subject (b) (6) was determined to be acute hepatitis C (refer to section 8.4.3). This case of hepatitis B is discussed in Section 8.4.2. The hepatic injury is related to hepatitis B in this case, which was likely reactivated due to ublituximab-xiiy, as this is a known safety risk with anti-CD20 therapies.

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Two additional cases of hepatitis B occurred in Study TG1101-RMS302 (subjects [REDACTED] (b) (6) and [REDACTED] (b) (6), which are discussed in Section 8.4.2 and 8.4.3, respectively).

Other cases involving significant AST (>5x ULN), ALT (>5x ULN), and bilirubin (>2x ULN) elevations in ublituximab-xiiy-treated subjects are summarized in Table 87.

Table 87 (Reviewer). Notable Cases of Hepatic Enzyme Elevations in Ublituximab-xiiv-Treated Subjects, Studies TG1101-RMS301 and TG1101-RMS302

Subject ID Demographics	Study Day of Onset	Peak AST (U/L)	Peak ALT (U/L)	Peak Total Bilirubin (µmol/L)	TEAE Reported (Grade)	Reviewer Comments
(b) (6) 30yo man	2	278	396	21	Transaminases increased (Grade 3)	GGT elevated at 246 U/L. Improved on Study Day 8 then resolved by Study Day 15. Concomitant viral respiratory tract infection, then dyspnea and fatigue. UTX continued.
(b) (6) 45yo woman	28	83	226	6	ALT increased (Grade 3), AST increased (Grade 2)	Resolved on Study Day 35. UTX dosing continued. Etiology unknown.
(b) (6) 27yo woman	1	13	14	45 (Day 420)	Blood bilirubin increased	Gilbert's syndrome, recurrent increased bilirubin.
(b) (6) 27yo man	420	15	12	55	Blood bilirubin increased (Grade 2)	Bilirubin elevated (22 µmol/L) at screening, peak was 55 µmol/L on Day 420. Possible Gilbert's syndrome.
(b) (6) 24yo man	738	252	77	7	AST increased (Grade 3)	Recovered as of Day 843 (last infusion 9 months earlier). Etiology unknown.
(b) (6) 44yo woman	Multiple	WNL	WNL	66	Hyperbilirubinemia (Recurrent, Grades 1-3)	Bilirubin elevated (25 µmol/L) at screening, peak was 66 µmol/L on Day 702. Indirect > direct elevation, potentially undiagnosed Gilbert's syndrome.
(b) (6) 38yo woman	28	229	388	5	Hepatotoxicity (Grade 3)	See Section 8.4.4. Etiology not presented UTX dosing continued, labs normalized in <1 month.
(b) (6) 44yo man	28	334	731	3	Transaminases increased (Grade 3)	Improved on Day 35 then resolved on Day 56. UTX continued, AST/ALT remained WNL. Etiology unknown.
(b) (6) 24yo woman	15	211	63	6	Not reported as AE	Improved on Day 19 then resolved on Day 28. Etiology unknown.
(b) (6) 26yo man	Screening	WNL	WNL	54	Blood bilirubin increased (Recurrent, Grade 1)	Bilirubin elevated (54 µmol/L) at screening, which was also peak value. Indirect > direct elevation, potentially undiagnosed Gilbert's syndrome.
(b) (6) 39yo woman	2	238	240	7	AST increased (Grade 3) ALT increased (Grade 3)	Resolved by Study Day 9. UTX continued, AST/ALT remained WNL. Etiology unknown.
(b) (6) 26yo man	141	WNL	WNL	5	Blood bilirubin increased (Grade 1)	Bilirubin elevated (34 µmol/L) at screening, and peak value of 50 µmol/L on Day 141. Possible Gilbert's syndrome
(b) (6) 27yo man	425	227	144	7	Hepatic enzyme increased (Grade 3)	Resolved by Study Day 454, UTX continued. Etiology unknown.

The frequency of liver-related TEAEs, including AESIs, are reported in Table 88.

Table 88 (Reviewer). Liver-related Treatment-Emergent Adverse Events in Ublituximab-xiiy RMS Development Program

	TG1101-RMS301/302		TG1101-RMS303
	Ublituximab-xiiy (N = 545) N (%)	Teriflunomide (N = 548) N (%)	Ublituximab-xiiy (N = 642) N (%)
Hepatobiliary Disorders (SOC)	13 (2.4)	12 (2.2)	0 (0)
Any Hepatic Dysfunction AESI per applicant	47 (8.6)	45 (8.2)	6 (0.9)
Any Liver-related TEAE			
Alanine aminotransferase increased	21 (3.9)	26 (4.7)	2 (0.3)
Aspartate aminotransferase increased	24 (4.4)	10 (1.8)	0 (0)
Gamma-glutamyltransferase increased	5 (0.9)	6 (1.1)	3 (0.5)
Transaminases increased	7 (1.3)	3 (0.5)	0 (0)
Hepatotoxicity	3 (0.6)	2 (0.4)	0 (0)
Hepatic enzyme increased	1 (0.2)	2 (0.4)	0 (0)
Hepatic steatosis	2 (0.4)	1 (0.2)	0 (0)
Hyperbilirubinemia	1 (0.2)	2 (0.4)	0 (0)
Blood alkaline phosphatase increased	1 (0.2)	1 (0.2)	1 (0.2)
Chronic hepatitis B	2 (0.4)	0 (0)	0 (0)
Hepatitis toxic	1 (0.2)	1 (0.2)	0 (0)
Liver function test increased	0 (0.0)	2 (0.4)	0 (0)
Blood bilirubin increased	0 (0)	1 (0.2)	1 (0.2)
Drug-induced liver injury	0 (0.0)	1 (0.2)	0 (0)
Hepatitis	1 (0.2)	0 (0)	0 (0)
Hepatomegaly	0 (0)	1 (0.2)	0 (0)
Non-alcoholic steatohepatitis	1 (0.2)	0 (0)	0 (0)

A summary of worst post-baseline liver function test elevations are summarized in Table 89. Notably, per the applicant's analysis presented in the Summary of Clinical Safety (Table 40), 1 subject in each treatment group across Studies TG1101-RMS301 and TG1101-RMS302 experienced ALT $\geq$ 20x ULN, and 2 subjects on ublituximab-xiiy and 1 on teriflunomide experienced AST $\geq$ 20x ULN.

Table 89 (Reviewer). Summary of Post-Baseline Worst Liver Function Test Elevations in Studies TG1101-RMS301 and TG1101-RMS302

	Criteria	Study TG1101-RMS301		Study TG1101-RMS302	
		Ublituximab-xiyy (N = 273)	Teriflunomide (N = 275)	Ublituximab-xiyy (N = 272)	Teriflunomide (N = 273)
Alanine Aminotransferase	2-<3x ULN	14 (5.2)	20 (7.3)	12 (4.4)	18 (6.6)
	3-<5x ULN	5 (1.8)	5 (1.8)	6 (2.2)	7 (2.6)
	5-<10x ULN	3 (1.1)	4 (1.5)	2 (0.7)	1 (0.4)
	>=10x ULN	2 (0.7)	3 (1.1)	1 (0.4)	3 (1.1)
Aspartate Aminotransferase	2-<3x ULN	5 (1.8)	7 (2.6)	7 (2.6)	4 (1.5)
	3-<5x ULN	9 (3.3)	3 (1.1)	4 (1.5)	1 (0.4)
	5-<10x ULN	5 (1.8)	3 (1.1)	3 (1.1)	5 (1.8)
	>=10x ULN	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)
Total Bilirubin	2-<3x ULN	2 (0.7)	1 (0.4)	2 (0.7)	4 (1.5)
	3-<5x ULN	2 (0.7)	0 (0)	0 (0)	1 (0.4)
	5-<10x ULN	0 (0)	0 (0)	1 (0.4)	0 (0)

Values reported as n (%)

Reviewer comment: Given the known risk of hepatotoxicity risk with teriflunomide, the similar frequency of liver-related adverse events and liver function test elevations observed in the teriflunomide and ublituximab-xiyy groups was concerning. Additionally, the magnitude of LFT elevations appears similar between the treatment groups. However, an underlying mechanism of this potential safety signal is unclear, as monoclonal antibodies are generally not considered to have directly hepatotoxic potential. Please refer to the Consultation Memorandum by Dr. Paul Hayashi, dated 9/20/2022. The DILI team concluded that there did not appear to be a signal for a direct hepatotoxicity (i.e., non-hepatitis B reactivation) risk associated with ublituximab-xiyy.

8.5.6. Reduction in Immunoglobulins

Reduction in immunoglobulins (specifically IgG and IgM) is a known potential safety risk with anti-CD20 therapies, especially with long-term use. The applicant designated hypogammaglobulinemia as an AESI for Studies TG1101-RMS301 and TG1101-RMS302, and pertinent TEAEs are summarized in Table 90. No cases of hypogammaglobulinemia occurred in these studies, but 3 cases of decreased IgM occurred in the pooled double-blind period of Studies TG1101-RMS301 and TG1101-RMS302. As discussed in Section 8.4.6, subjects treated with ublituximab-xiyy had a clear decline in IgM levels during the double-blind treatment period for both studies compared to teriflunomide (Figure 13; Figure 22).

Table 90 (Reviewer). Immunoglobulin-Related Treatment-Emergent Adverse Events in Ublituximab-xiiy RMS Development Program

	TG1101-RMS301/302		TG1101-RMS303
	Ublituximab-xiiy (N = 545)	Teriflunomide (N = 548)	Ublituximab-xiiy (n = 642)
Hypogammaglobulinemia (AESIs)	4 (0.7)	0 (0.0)	0 (0)
Blood IgG decreased/ hypogammaglobulinemia	0 (0)	0 (0)	0 (0)
Blood IgM decreased	3 (0.6)	0 (0)	0 (0)
Blood IgA decreased	1 (0.2)	0 (0)	0 (0)

Values reported as n (%)

The frequency of immunoglobulin laboratory values below clinically relevant thresholds is presented in Table 91. There was not a clear differential risk in IgA and IgG reduction between ublituximab-xiiy and teriflunomide, but subjects treated with ublituximab-xiiy were more likely to experience IgM < 0.4g/L compared to those on teriflunomide (20.5% vs 5.5%, respectively, for Study TG1101-RMS301 and 23.9% vs 6.6% for Study TG1101-RMS302). This finding is consistent with the observation of IgM decline in ublituximab-xiiy-treated subjects during double-blind treatment (Section 8.4.6; Figure 13; Figure 22).

Table 91 (Reviewer). Frequency of Decreased Immunoglobulin Laboratory Values, Studies TG1101-RMS301 and TG1101-RMS302

	Criteria	Study TG1101-RMS301		Study TG1101-RMS302	
		Ublituximab-xiiy (N = 273)	Teriflunomide (N = 275)	Ublituximab-xiiy (N = 272)	Teriflunomide (N = 273)
Immunoglobulin A	<0.7 g/L	8 (2.9)	10 (3.6)	8 (2.9)	6 (2.2)
Immunoglobulin G	<5.5 g/L	5 (1.8)	9 (3.3)	7 (2.6)	5 (1.8)
Immunoglobulin M	<0.4 g/L	56 (20.5)	15 (5.5)	65 (23.9)	18 (6.6)

Values reported as n (%)

Reviewer comment: Based upon regulatory experience with other anti-CD20 therapies, the likelihood of observing consistent hypogammaglobulinemia and other immunoglobulin reductions in a 2-year study period is low. However, a trend for declining IgM in ublituximab-xiiy-treated subjects was observed during the double-blind treatment period. A postmarketing requirement regarding characterization of the long-term risk of decreased IgG and IgM was issued for ocrelizumab and ofatumumab, and will be issued for ublituximab-xiiy, if approved.

8.5.7. COVID-19

The COVID-19 pandemic began in early 2020, with vaccine availability beginning in late 2020 in the United States. Patients receiving immunosuppressive treatments are more likely to

experience severe disease (e.g., pneumonia) requiring hospitalization. In particular, patients with MS receiving anti-CD20 therapies are thought to be at higher risk of severe COVID-19 disease manifestations, but it is difficult to quantify or compare this risk since no controlled studies of anti-CD20 therapies are ongoing (other than ublituximab-xiiy) over the past few years.

COVID-19-related TEAEs in the ublituximab-xiiy development program are summarized in Table 92. As indicated in Section 8.5.1, as of 8/13/2022, 24 COVID-19-related deaths have occurred in ublituximab-xiiy-treated subjects in Studies TG1101-RMS303 and TG1101-RMS201E since the BLA cutoff date. The applicant indicated that 7/24 subjects who died (29%) had received at least one dose of a COVID-19 vaccine while on ublituximab-xiiy, which likely resulted in impaired response to vaccination.

Table 92 (Reviewer). COVID-19-Related Treatment-Emergent Adverse Events in Ublituximab-xiiy RMS Development Program

	TG1101-RMS301/302		TG1101-RMS303	TG1101-RMS201/201E
	Ublituximab-xiiy (N = 545)	Teriflunomide (N = 548)	Ublituximab-xiiy (n = 642)	Ublituximab-xiiy (n = 43)
COVID-19 related SAEs ¹	4 (0.7)	3 (0.5)	90 (10.6)	9 (20.9)
Death due to COVID-19 ²	0 (0)	0 (0)	20 (3.1)	4 (9.3)
COVID-19-related TEAEs ³				
COVID-19	4 (0.7)	2 (0.4)	23 (3.6)	1 (2.3)
Suspected COVID-19	2 (0.4)	0 (0)	1 (0.2)	0 (0)
COVID-19 pneumonia	4 (0.7)	2 (0.4)	9 (1.4)	2 (4.7)
Coronavirus infection	0 (0)	1 (0.2)	3 (0.5)	0 (0)

¹ As of 7/5/2022, per Information Request response received 8/18/2022; ²Deaths as of 8/13/2022, per Information Request response received 8/18/2022; ³Source: ADAE where TRTEMFL=Y, SAFFL=Y (as of BLA cutoff date); Values reported as n (%)

The applicant provided an updated tabulation of COVID-19 SAEs/TEAEs and deaths following an Information Request sent on 7/28/2022, with response received on 8/18/2022. As of 7/5/2022, in Study TG1101-RMS303, 275 subjects (32.3%) had experienced a COVID-19 infection-related TEAE, including 90 (10.6%) serious infections. In Study TG1101-RMS201E, 9 subjects (20.9%) have experienced a COVID-19 infection-related TEAE, all of which were serious.

In the Information Request response received 8/18/2022, the applicant provided a review of available information related to COVID-19 epidemiology and severity in patients with RMS, including those on other anti-CD20 therapies. The applicant indicated that the deaths due to COVID-19 in Study TG1101-RMS303 occurred primarily during regional surges in Eastern European countries. The applicant provided data suggesting that patients with RMS who developed COVID-19 were at higher risk for death. The applicant presented results of an analysis suggesting similar rates of COVID-19 mortality among patients on ublituximab-xiiy and

ocrelizumab. Additionally, the applicant indicated that newer treatment strategies for COVID-19 in the setting of anti-CD20 therapies have helped to mitigate the mortality risk.

Reviewer comment: The COVID-19 pandemic began in March of 2020, shortly before the BLA data cutoff. Experience regarding COVID-19 in the ublituximab-xiiy development program has been primarily from the open-label extension studies, and it is therefore difficult to fully address a potentially differential risk of severe disease with ublituximab-xiiy in the absence of controlled data. However, literature suggests an increased risk of severe COVID-19 disease in the setting of other anti-CD20 therapies, which is further complicated by attenuation of vaccine response observed with these therapies. Given the risks of serious infection discussed in Section 8.5.2, serious viral infection, which includes COVID-19, will be discussed in labeling if ublituximab-xiiy is approved.

8.5.8. Malignancy

Malignancy is a known potential safety risk with immunosuppressant treatments, including anti-CD20 therapies, especially with long-term use. The applicant designated malignancy as an AESI for Studies TG1101-RMS301 and TG1101-RMS302, and pertinent TEAEs are summarized in Table 93.

Table 93 (Reviewer). Malignancy-Related Treatment-Emergent Adverse Events in Ublituximab-xiiy RMS Development Program

	TG1101-RMS301/302		TG1101-RMS303	TG1101-RMS201	TG1101-RMS201E
	Ublituximab-xiiy (N = 545)	Teriflunomide (N = 548)	Ublituximab-xiiy (n = 642)	Ublituximab-xiiy (n = 43)	Ublituximab-xiiy (n = 43)
Any Malignancy (AESI)	2 (0.4)	1 (0.2)	1 (0.2)	0 (0)	1 (2.3)
Endometrial stromal sarcoma	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)
Uterine cancer	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)
Tongue neoplasm	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Oophorectomy	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)
Basal cell carcinoma	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.3)

Source: ADAE for respective study, as of BLA cutoff date

Per the 120-Day Safety Update, additional malignancies reported included leukemia (n = 1) and uterine cancer (n = 1), which occurred in subjects who received teriflunomide in the parent study. A case of pseudomyxoma peritonei (verbatim term: "myxoma left sartorius muscle") on (b) (6) was reported in Subject # (b) (6), which occurred during Study TG1101-RMS303. Per the submitted narrative, no treatment was reported and the event was not recovered/not resolved. No action was taken with ublituximab-xiiy for this event.

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Reviewer comment: Pseudomyxoma peritonei is a rare malignant tumor of the peritoneum. However, the verbatim term "Myxoma left [sartorius] muscle" indicates a benign tumor that is also rare. Given the lack of reported treatment, it is likely that this event was miscoded as pseudomyxoma peritonei.

Reviewer comment: The incidence of malignant neoplasms was low for both treatment groups. No single type of malignancy appears prominent. Additionally the duration of exposure was relatively short and may limit the interpretation of these data.

8.6. Safety Analyses by Demographic Subgroups

Safety analyses by sex and age group were conducted. Meaningful subpopulation analysis by race was precluded by the small number of non-Caucasian participants enrolled in the clinical studies.

Review of TEAEs by sex demonstrated that women on ublituximab-xiiy were somewhat more likely to experience upper respiratory tract infections, urinary tract infections/cystitis, and symptoms typically associated with IRRs (e.g., headache, pyrexia, nausea) compared to men (Table 94). Men receiving ublituximab-xiiy were more likely to experience chills. Otherwise, there did not appear to be any clear differences between men and women, among subjects receiving ublituximab-xiiy.

Review of TEAEs by age (<38 years versus ≥38 years) demonstrated that certain preferred terms associated with respiratory tract infections (e.g., nasopharyngitis, rhinitis, bronchitis, and respiratory tract infection) were somewhat more common in the younger subpopulation receiving ublituximab-xiiy (Table 95). Otherwise, there did not appear to be any clear differences between the age subgroups among subjects receiving ublituximab-xiiy.

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Table 94 (Reviewer). Treatment Emergent Adverse Events by Sex, Pooled Studies TG1101-RMS301 and TG1101-RMS302

Preferred Term	Ublituximab-xiiy		Teriflunomide	
	Female (n = 345)	Male (n = 200)	Female (n = 356)	Male (n = 192)
Headache	40.0 (138)	24.5 (49)	30.6 (109)	19.3 (37)
Nasopharyngitis	21.4 (74)	13.0 (26)	18.3 (65)	17.2 (33)
Pyrexia	16.5 (57)	9.5 (19)	5.6 (20)	3.6 (7)
Nausea	14.2 (49)	4.5 (9)	9.6 (34)	4.7 (9)
Back pain	11.6 (40)	5.5 (11)	9.8 (35)	9.4 (18)
Diarrhea	9.3 (32)	6.0 (12)	11.2 (40)	9.4 (18)
Abdominal pain	9.3 (32)	5.5 (11)	4.5 (16)	2.6 (5)
Lymphopenia	9.3 (32)	10.5 (21)	1.1 (4)	1.0 (2)
Respiratory tract infection	9.0 (31)	5.5 (11)	7.0 (25)	6.8 (13)
Lymphocyte count decreased	9.0 (31)	9.0 (18)	1.4 (5)	2.6 (5)
Upper respiratory tract infection	8.4 (29)	6.0 (12)	7.0 (25)	6.8 (13)
Influenza like illness	7.8 (27)	6.0 (12)	3.1 (5)	0 (0)
Respiratory tract infection viral	7.5 (26)	8.0 (16)	5.9 (21)	5.2 (10)
Pharyngitis	7.5 (26)	3.0 (6)	3.1 (5)	0.5 (1)
Oropharyngeal pain	7.0 (24)	3.5 (7)	4.8 (17)	1.0 (2)
Cystitis	6.7 (23)	1.0 (2)	5.6 (20)	0 (0)
Bronchitis	6.4 (22)	1.0 (2)	3.7 (13)	2.6 (5)
Hyperthermia	6.4 (22)	4.5 (9)	1.4 (5)	0.5 (1)
Pain in extremity	6.4 (22)	4.5 (9)	5.6 (20)	2.1 (4)
Insomnia	6.4 (22)	5.5 (11)	2.0 (7)	4.7 (9)
Urinary tract infection	5.8 (20)	1.0 (2)	6.7 (24)	2.6 (5)
Cough	5.8 (20)	2.0 (4)	2.2 (8)	1.0 (2)
Infusion related reaction	5.5 (19)	4.0 (8)	0.6 (2)	0.5 (1)
Abdominal pain upper	5.2 (18)	1.0 (2)	5.6 (20)	1.6 (3)
Dizziness	5.2 (18)	3.0 (6)	2.8 (10)	3.6 (7)
Chills	5.2 (18)	13.0 (26)	0.8 (3)	0.5 (1)
Fatigue	5.2 (18)	5.0 (10)	3.4 (12)	4.2 (8)
Anxiety	5.2 (18)	3.0 (6)	5.6 (20)	1.6 (3)
Sinus tachycardia	5.2 (18)	3.5 (7)	1.1 (4)	3.1 (6)
Toothache	3.5 (12)	5.5 (11)	4.8 (17)	2.1 (4)
Rhinitis	2.9 (10)	7.0 (14)	4.5 (16)	2.6 (5)
Dyspepsia	2.6 (9)	7.0 (14)	3.4 (12)	4.2 (8)
Tachycardia	2.6 (9)	5.5 (11)	3.4 (12)	2.1 (4)

Source: ISS (Studies 301 and 302 only) ADAE where TRTEMFL=Y, SAFFL=Y, by TRT01A and SEX; Values reported as n (%)

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Table 95 (Reviewer). Treatment Emergent Adverse Events by Age, Pooled Studies TG1101-RMS301 and TG1101-RMS302

Preferred Term	Ublituximab-xiiy		Teriflunomide	
	Age <38 (n = 326)	Age ≥38 (n = 219)	Age <38 (n = 302)	Age ≥38 (n = 246)
Headache	39.6 (129)	26.5 (58)	29.8 (90)	22.8 (56)
Nasopharyngitis	21.8 (71)	13.2 (29)	20.5 (62)	14.6 (36)
Pyrexia	16.0 (52)	11.0 (24)	4.3 (13)	5.7 (14)
Lymphopenia	11.0 (36)	7.8 (17)	1.0 (3)	1.2 (3)
Nausea	10.7 (35)	10.5 (23)	8.6 (26)	6.9 (17)
Respiratory tract infection viral	10.1 (33)	4.1 (9)	7.0 (21)	4.1 (10)
Chills	10.1 (33)	5.0 (11)	0.3 (1)	1.2 (3)
Lymphocyte count decreased	9.8 (32)	7.8 (17)	2.0 (6)	1.6 (4)
Abdominal pain	9.5 (31)	5.5 (12)	4.3 (13)	3.3 (8)
Respiratory tract infection	8.6 (28)	6.4 (14)	7.9 (2)	5.7 (14)
Influenza like illness	8.6 (28)	5.0 (11)	1.7 (5)	2.4 (6)
Back pain	8.3 (27)	11.0 (24)	8.3 (25)	11.4 (28)
Diarrhea	8.0 (26)	8.2 (18)	10.6 (32)	10.6 (26)
Hyperthermia	7.7 (25)	2.7 (6)	0.7 (2)	1.6 (4)
Upper respiratory tract infection	7.4 (24)	7.8 (17)	7.0 (21)	6.9 (17)
Pharyngitis	6.7 (22)	4.6 (10)	3.0 (9)	1.2 (3)
Oropharyngeal pain	6.4 (21)	4.6 (10)	4.0 (12)	2.8 (7)
Rhinitis	6.1 (20)	1.8 (4)	4.6 (14)	2.8 (7)
Toothache	6.1 (20)	1.4 (3)	4.6 (14)	2.8 (7)
Pain in extremity	6.1 (20)	5.0 (11)	2.6 (8)	6.5 (16)
Insomnia	6.1 (20)	5.9 (13)	3.6 (11)	2.0 (5)
Cystitis	5.8 (19)	2.7 (6)	4.6 (14)	2.4 (6)
Dizziness	5.8 (19)	2.3 (5)	2.3 (7)	4.1 (10)
Fatigue	5.8 (19)	4.1 (9)	2.3 (7)	5.3 (13)
Infusion related reaction	5.8 (19)	3.7 (8)	0.7 (2)	0.4 (1)
Anxiety	5.8 (19)	2.3 (5)	3.6 (11)	4.9 (12)
Asthenia	5.5 (18)	3.7 (8)	6.0 (18)	4.5 (11)
Dyspepsia	5.2 (17)	2.7 (6)	3.3 (10)	4.1 (10)
Cough	4.0 (13)	5.0 (11)	2.6 (8)	0.8 (2)
Sinus tachycardia	4.0 (13)	5.5 (12)	2.6 (8)	0.8 (2)
Urinary tract infection	3.1 (10)	5.5 (12)	3.3 (10)	7.7 (19)

Source: ISS (Studies 301 and 302 only) ADAE where TRTEMFL=Y, SAFFL=Y, by TRT01A and AGEGR1; Values reported as n (%)

Reviewer comment: Overall, there did not appear to be clinically meaningful differences in adverse events among age and sex subgroups.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Please refer to Section 8.5.8.

8.8.2. Human Reproduction and Pregnancy

The ublituximab-xiiy development program included a small number of pregnancies, with few adverse outcomes. The clinical data are insufficient to support conclusions about effects of ublituximab-xiiy on human reproduction and pregnancy. Please refer to the nonclinical review regarding the reproductive toxicity observed in monkeys.

In Studies TG1101-RMS301 and TG1101-RMS302, contraception was required throughout the treatment period and for 20 weeks after cessation of active treatment. Pregnancy tests were required every 4 weeks during the double-blind treatment and follow-up periods. See Section 13.2 (Inclusion Criteria).

In Study TG1101-RMS301, pregnancy was reported in 4 subjects receiving ublituximab-xiiy and 1 receiving teriflunomide. In Study TG1101-RMS302, pregnancy was reported in 4 subjects receiving ublituximab-xiiy and 1 subject receiving teriflunomide. Two partner pregnancies were reported among subjects receiving ublituximab-xiiy. In Study TG1101-RMS201, one subject receiving ublituximab-xiiy became pregnant and 1 pregnancy of a partner was reported.

Among the 9 subjects who became pregnant while on ublituximab-xiiy, 4 resulted in healthy, full-term infants, 3 resulted in elective abortions, and 2 had unknown outcomes due to withdrawal of consent (one with conception following treatment completion). One subject who underwent elective abortion did so due to ectopic pregnancy, which required surgical intervention that was complicated by salpingitis and death (See Section 8.4.1).

Among the 3 partner pregnancies in subjects on ublituximab-xiiy, 1 resulted in a healthy, full-term infant, 1 resulted in elective abortion, and 1 had an unknown outcome due to withdrawal of consent.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable, as subjects in the pediatric age group were not studied.

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8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose, Drug Abuse Potential, and Withdrawal

There were no cases of overdose. The potential for drug abuse is minimal. No subjects were identified that may have had drug withdrawal symptoms.

Rebound

Rebound of disease activity is a concern following discontinuation of MS treatments, particularly natalizumab and fingolimod. There was no indication of an increase in relapses after discontinuation of ublituximab-xiiy, although this was not specifically studied.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.9.2. Expectations on Safety in the Postmarket Setting

In the postmarketing setting, expected adverse reactions include infections due to the immunosuppressant effects of ublituximab-xiiy, specifically related to reduction in CD19+ B-cells and immunoglobulins. Given the clinical trial data and regulatory experience with other anti-CD20 therapies, infections could be serious or fatal, and specific infections to note include hepatitis B reactivation, PML, other CNS viral infections, COVID-19, and pneumonia. Hepatitis B reactivation and PML are discussed in labeling for other approved anti-CD20 therapies.

Infusion-related reactions are also anticipated, but should be at least partially mitigated with required use of premedication and required post-infusion observation.

Potential safety signals that warrant further evaluation in the postmarketing setting include abnormal liver function testing independent of hepatitis B, reduction in immunoglobulins, immune-mediated colitis, thrombocytopenia, and malignancy.

8.9.3. Additional Safety Issues From Other Disciplines

Please refer to discussion of Hepatic Disorders (Section 8.5.5) for interaction with the Drug Induced Liver Injury Team, who were consulted for this review. Please refer to the Consultation Memorandum by Dr. Paul Hayashi, dated 9/20/2022.

Please refer to the discussion of Human Reproduction and Pregnancy (Section 8.8.2) for interaction with the Division of Maternal and Pediatric Health (DPMH) and Nonclinical

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regarding embryofetal toxicity.

8.10. Integrated Assessment of Safety

The primary population for the ISS includes subjects from Studies TG1101-RMS301 and TG1101-RMS302, comprising a pooled double-blind treatment period population. Adverse events are attributed to the actual treatment (TRT01A).

Adverse Events by Preferred Term

The most common TEAEs by PT that occurred in >5% of the pooled double-blind treatment periods of Studies TG1101-RMS301 and TG1101-RMS302 are presented in Table 96.

Table 96 (Reviewer). TEAEs Occurring in $\geq 5\%$ of Ublituximab-xiiy-Treated Subjects, Pooled Analysis of Phase 3 Double-Blind Data

	Ublituximab-xiiy (N = 545)	Teriflunomide (N = 548)
Total Subjects with any Adverse Events	486 (89.2)	501 (91.4)
Headache	187 (34.3)	146 (26.6)
Nasopharyngitis	100 (18.3)	98 (17.9)
Pyrexia	76 (13.9)	27 (4.9)
Nausea	58 (10.6)	43 (7.8)
Lymphopenia	53 (9.7)	6 (1.1)
Back pain	51 (9.4)	53 (9.7)
Lymphocyte count decreased	49 (9.0)	10 (1.8)
Chills	44 (8.1)	4 (0.7)
Diarrhoea	44 (8.1)	58 (10.6)
Abdominal pain	43 (7.9)	21 (3.8)
Respiratory tract infection	42 (7.7)	38 (6.9)
Respiratory tract infection viral	42 (7.7)	31 (5.7)
Upper respiratory tract infection	41 (7.5)	38 (6.9)
Influenza like illness	39 (7.2)	11 (2.0)
Insomnia	33 (6.1)	16 (2.9)
Pharyngitis	32 (5.9)	12 (2.2)
Pain in extremity	31 (5.7)	24 (4.4)
Oropharyngeal pain	31 (5.7)	19 (3.5)
Hyperthermia	31 (5.7)	6 (1.1)
Fatigue	28 (5.1)	20 (3.6)
Infusion related reaction	27 (5.0)	3 (0.5)

Source: ISS (Studies 301 and 302 only) ADAE where TRTEMFL=Y, SAFFL=Y, by TRT01A; Values reported as n (%)

Summary of Safety Issues

The risks identified with ublituximab-xiiy are discussed in previous sections of this review, but are summarized below.

A major risk observed with ublituximab-xiiy is that of infection. Serious and fatal infections occurred in ublituximab-xiiy-treated patients during the controlled trials, and are discussed in Section 8.5.1 and 8.5.2. Additionally, the COVID-19 pandemic that occurred during the Phase 3 trials for ublituximab-xiiy led to observation of several serious and fatal cases of COVID-19 associated with ublituximab-xiiy treatment (Section 8.5.7). However, serious infections also have been reported with other anti-CD20 therapies approved for RMS, and the relative risk compared to teriflunomide appears similar to that observed in controlled trials for ublituximab-xiiy. Ongoing clinical surveillance and monitoring of immunoglobulins may be able to mitigate the risk of more serious infections. In the postmarketing setting, prescribers should also encourage patients to receive all vaccinations, including for COVID-19, prior to initiating treatment with ublituximab-xiiy if possible, given the known interference with vaccine response. These concerns will be discussed in labeling. Additionally, the observed clinical benefit associated with ublituximab-xiiy is thought to outweigh this risk. If ublituximab-xiiy is approved, enhanced pharmacovigilance should be performed for serious and opportunistic infections, including hepatitis B reactivation, PML, and other central nervous system viral infections.

Infusion-related reactions, including some serious reactions, were observed during ublituximab-xiiy infusion, and are discussed in Section 8.5.3. Subjects enrolled in the clinical trials received premedication for IRR prevention, and in the postmarketing setting, patients will be required to receive premedication with corticosteroids and an antihistamine, and remain under observation post-infusion. Though the risk of IRRs appeared to decrease with subsequent infusions, the applicant provided data indicating that this risk was not negligible. Therefore, post-infusion monitoring will be a requirement for all infusions. The observed clinical benefit associated with ublituximab-xiiy is thought to outweigh this risk.

Decreased immunoglobulins are a known risk associated with anti-CD20 therapies, particularly with long-term use. Please refer to Section 8.5.6. A decrease in IgM was observed in ublituximab-xiiy-treated subjects during the controlled clinical trials, but in other anti-CD20 therapy development programs, reduction in IgG did not occur until after years of treatment. Therefore, we do not expect to observe decreased IgG in the clinical trial setting. A postmarketing requirement is necessary to better characterize this risk with ublituximab-xiiy and how it translates to risk of infection over time. Additionally, labeling will instruct prescribers to monitor immunoglobulins during treatment with ublituximab-xiiy.

Cytopenias were considered an AESI by the applicant, and are discussed in Section 8.5.4. Lymphopenia is not unexpected given the mechanism of action of ublituximab-xiiy, but neutropenia was observed at a rate similar to that of teriflunomide, which is labeled for neutropenia. Additionally, subjects receiving ublituximab-xiiy were more likely to experience ANC $<0.5 \times 10^9/L$ compared to those on teriflunomide. However, there was no obvious association of neutropenia with infection.

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Embryofetal toxicity is discussed in the nonclinical and DPMH reviews, and will be addressed in labeling. The nonclinical embryofetal safety results are concerning for a risk in addition to that associated with B-cell depletion. The clinical data obtained during the RMS development program are insufficient to support conclusions about effects of ublituximab-xiiy on human reproduction and pregnancy.

Other potential signals that warrant ongoing and potentially enhanced pharmacovigilance in the postmarketing setting include pancreatitis (given the observation of elevated pancreatic enzymes), hepatic disorders (independent of Hepatitis B reactivation), thrombocytopenia, immune-mediated colitis (given recent identification of this risk with ocrelizumab) and malignancy.

Overall, both the benefit and risk of treatment of RMS with ublituximab-xiiy appears consistent with that of other anti-CD20 therapies approved for RMS.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not convened.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

See the final negotiated Prescribing Information.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not recommended at this time. See the DRM review for rationale.

12. Postmarketing Requirements and Commitments

See the approval letter for the post-marketing requirements and commitments.

A postmarketing requirement related to monitoring of IgG and IgM with long-term use of ublituximab-xiiy is appropriate.

13. Appendices

13.1. References

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13.2. Study TG1101-RMS301 and TG1101-RMS302 Eligibility Criteria

Inclusion Criteria:

Subjects must meet the following inclusion criteria to be eligible for participation in this study:

1. 18-55 age
2. Diagnosis of RMS (McDonald criteria 2010; Appendix C)
3. ≥ 2 relapses in prior 2 years or 1 relapse in the year prior to screening and/or ≥ 1 Gd enhancing lesion
4. Documented MRI of brain with abnormalities consistent with MS
5. Active disease
6. EDSS 0-5.5 (inclusive) at screening

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7. B cell counts $\geq 5\%$ of total lymphocytes
8. Neurologic stability ≥ 30 days prior to screening and baseline
9. Female subjects who are not of child-bearing potential, have documented surgical sterilization (see Appendix A), and female subjects of child-bearing potential who have a negative serum pregnancy test at baseline. Female subjects of child-bearing potential (see Appendix A), and all male partners must consent to use a medically/clinically acceptable method of contraception throughout the treatment period and for 20 weeks after the cessation of active treatment. Female subjects of child-bearing potential (see Appendix A) must agree to undertake urine pregnancy tests every 4 weeks during active treatment and the follow up period.
10. Fertile male subjects participating in the study who are sexually active with women of childbearing potential, must agree to use a condom during the treatment period and for an additional 20 weeks after cessation of active treatment. Agree to use an accelerated elimination procedure after the last dose of study medications or early termination from the study (see Section 6.10.1)
11. Willingness and ability to comply with trial and follow-up procedures, give written consent

Exclusion Criteria:

Subjects who meet any of the following exclusion criteria are not to be enrolled to this study:

1. Treatment with Anti-CD20 or other B cell directed treatment
2. Treatment with the following therapies at any time prior to randomization:
 - a. Alemtuzumab
 - b. Natalizumab,
 - c. Teriflunomide,
 - d. Leflunomide, and
 - e. Stem cell transplantation
3. Contraindications to teriflunomide or incompatibility with use of teriflunomide.
4. Therapies that are disallowed (minimum of 4 weeks prior to randomization): phenytoin, warfarin, tolbutamide, St John's Wort or cholestyramine
5. Prior DMT exposure within months of screening:
 - a. 24 months with cladribine
 - b. 6 months with daclizumab, azathioprine, methotrexate, or cyclophosphamide
 - c. 90 days with fingolimod, or experimental S1P modulators, IV immunoglobulin, and plasmapheresis
 - d. 30 days with glatiramer acetate, interferons, dimethyl fumarate, laquinimod or glucocorticoids
6. Diagnosed with Primary Progressive MS (PPMS)
7. Pregnant or nursing
8. ≥ 10 years disease duration from onset with subjects EDSS ≤ 2.0

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9. Contraindication for MRI and/or gadolinium
10. Known presence of other neurologic disorders that may mimic MS
11. Current evidence or known history of clinically significant infection including:
 - a. Chronic or ongoing active viral, bacterial, or fungal infectious disease requiring long term systemic treatment such as, but not limited to: PML, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis (TB), or active hepatitis C
 - b. Previous serious opportunistic or atypical infections
 - c. History of positive serology for hepatitis B or hepatitis C or HIV
12. History of clinically significant CNS trauma (e.g., traumatic brain injury, cerebral contusion, spinal cord compression)
13. History of liver disease, including but not limited to:
 - a. Known history of active hepatitis B or C any time prior to randomization or known history of active hepatitis A within 3 years prior to randomization
 - b. Presence of clinically significant chronic liver or biliary disease
 - c. Moderate or severe hepatic impairment defined as Child Pugh Score B or C, respectively, based on measurement of total bilirubin, serum albumin, International Normalized Ratio (INR) and as well as on presence /absence and severity of ascites and hepatic encephalopathy
 - d. Any of the following abnormal laboratory values at screening or first infusion:
 - i. ALT/SGPT >2X the Upper Limit of Normal (ULN)
 - ii. AST/SGOT >2X ULN
14. Previous diagnosis with a congenital or acquired immunodeficiency (AIDS)
15. History of renal impairment, including, but not limited to:
 - a. Hypoproteinemia (e.g., in case of severe renal disease or nephrotic syndrome) with serum albumin <3.0 g/dL
 - b. Severe renal insufficiency requiring renal dialysis
16. Past or current history of medically significant adverse effects (including allergic reactions) from:
 - a. Corticosteroids
 - b. Diphenhydramine
 - c. Murine or mouse/human chimeric antibodies
17. Subjects with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia
 - a. Hematocrit <24% and/or
 - b. Absolute white blood cell count <4,000 cells/mm³ and/or
 - c. Platelet count <150,000 cells/mm³ and/or
 - d. Absolute neutrophil $\leq$ 1,500 cells/mm³
18. Absolute lymphocyte counts less than 1000/microliter
19. Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

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- a. Symptomatic, or history of documented congestive heart failure (New York Heart Association functional classification III-IV [see Appendix B])
 - b. QTcF: Female >450 msec; male > 430 msec Angina not well-controlled by medication
 - c. Poorly controlled or clinically significant atherosclerotic vascular disease including cerebrovascular accident (CVA), transient ischemic attack (TIA), angioplasty, cardiac or vascular stenting in the past 6 months prior to screening
20. Other significant concurrent, uncontrolled medical condition including, but not limited to, cardiac, renal, hepatic, hematological, gastrointestinal, endocrine, immunodeficiency syndrome, pulmonary, cerebral, psychiatric, or neurological disease which could affect the subject's safety, impair the subject's reliable participation in the trial, impair the evaluation of endpoints, or necessitate the use of medication not allowed by the protocol, as determined by the PI of the trial
21. Current participation in any other interventional clinical trial. Participation in non-interventional trial requires approval by the Sponsor
22. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol
23. Lack of immunity to varicella as determined by screening based on the level of VZV IgG. Subject may receive vaccine and be rescreened
24. Vaccination with live virus within 2 months of randomization
25. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation or bone marrow transplantation

13.3. Financial Disclosure

Covered Clinical Study (Name and/or Number): TG1101-RMS301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>388</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

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influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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Covered Clinical Study (Name and/or Number): TG1101-RMS302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>343</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): TG1101-RMS201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>57</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		

Clinical Review
 Laura Baldassari, MD, MHS
 BLA 761238
 Ublituximab-xiiy (Briumvi)

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURA E BALDASSARI
12/28/2022 10:41:46 AM

PAUL R LEE
12/28/2022 10:42:21 AM