NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Ublituximab for treating relapsing multiple sclerosis [ID6350]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Neuraxpharm Pharmaceuticals:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Professional group submission** from:
   a. Association of British Neurologists
   b. UK Multiple Sclerosis SPECIALIST Nurses Association

4. **External Assessment Report** prepared by NHS Centre for Reviews and Dissemination and Centre for Health Economics, York

5. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost-comparison appraisal

Ublituximab for treating relapsing multiple sclerosis [ID6350]

Document B

Company evidence submission

August 2024

File name	Version	Contains confidential information	Date
ID6350 Ublituximab for treating relapsing multiple sclerosis	**V2**	**Yes**	**21st August 2024**

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Abbreviations

Abbreviation	Definition
AAN	American Academy of Neurology
ABN	Association of British Neurologists
ACTRIMS	Americas Committee for Treatment and Research in Multiple Sclerosis
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AHSCT	Autologous haematopoietic stem cell transplant
AIDS	Acquired immunodeficiency
ARR	Annualised relapse rate
BNF	British National Formulary
CCA	Cost-comparison analysis
CDC	Complement dependent cytotoxicity
CDI	Confirmed disability improvement
CDP	Confirmed disability progression
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CMSC	Consortium of Multiple Sclerosis Centers
CNS	Central nervous system
CRF	Case report form
CSF	Cerebro-spinal fluid
DMT	Disease-modifying therapies
DNA	Deoxyribonucleic acid
EAN	European Academy of Neurology
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDSS	Expanded disability status scale
ERG	Evidence Review Group
FcγR	Fc-gamma receptor
FIS	Fatigue impact scale
Gd	Gadolinium
GEE	Generalised estimating equation
H	Hour
HR	Hazard ratio
HRQoL	Health-related quality-of-life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IMSCOG	International Multiple Sclerosis Cognition Society
IRAP	Independent Relapse Adjudication Panel
IRR	Infusion-related reactions
IV	Intravenous
JCV	John Cunningham Virus
LLN	Lower limits of normal
mAb	Monoclonal antibody
MDT	Multi-disciplinary team
Mg	Milligrams
mITT	Modified intention-to-treat
MMRM	Mixed model repeated measures

MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MSQoL-54	Multiple sclerosis quality-of-life-54
MTC	Mixed treatment comparison
NA	Not applicable
NBR	Negative binomial regression
NEDA	No evidence of disease activity
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NK	Natural killer
NMA	Network meta-analysis
NMB	Net monetary benefit
PAS	Patient access scheme
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily
QoL	Quality-of-life
RCT	Randomised controlled trial
RES	Rapidly evolving severe
RMS	Relapsing multiple sclerosis
RoB	Risk of bias
RR	Rate ratio
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SDMT	Symbol digit modalities test
SE	Standard error
SF-36	Short Form-36
SLR	Systematic literature review
SMD	Standardised mean difference
SmPC	Summary of product characteristics
SPMS	Secondary progressive multiple sclerosis
SUCRA	Surface under the cumulative ranking
TA	Technology appraisal
TP	Transition probability
VAT	Value-added tax

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission focuses on part of the technology's full marketing authorisation. The full marketing authorisation for ublituximab is for the treatment of adults with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features, which covers both relapsing-remitting multiple sclerosis (RRMS) and relapsing forms of secondary progressive multiple sclerosis (SPMS), while this submission is focused only on adults with RRMS with active disease defined by clinical or imaging features (adult patients in the pivotal clinical trials were aged up to 55 years) (1). In clinical practice, the shift to SPMS is often identified retrospectively because the multiple sclerosis (MS) disease course is unpredictable for each patient. While the ULTIMATE I and II studies reported the proportion of the overall population that could be categorised in the respective subpopulations of RMS, baseline characteristics for the individual groups were not reported and these classifications were not monitored individually post-baseline (1). Consequently, there is no trial data specifically for the subgroup of adults with relapsing SPMS.

The proposed population for this technology appraisal (TA) is also narrower than the marketing authorisation because the evidence base for ublituximab with an active SPMS population is limited: only 20 patients [1.8%] across both treatment arms of the pivotal phase III trials for ublituximab, ULTIMATE I and II, were defined as having SPMS at baseline (1). Therefore, the trials lack sufficient subgroup data to conduct meaningful indirect comparisons or to perform robust cost-comparison analyses for an active SPMS population. Consequently, the company's submission varies slightly from the final NICE scope regarding the population considered. The decision problem addressed by this submission is summarised in Table 1.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active relapsing forms of MS.	This submission focuses on adults with RRMS.	The pivotal studies (ULTIMATE I and II) (1) included patients with RMS (RRMS and SPMS), but outcomes are not distinguished for the SPMS population separately (which was <2% of the overall, included population). Therefore, focus is placed on the RRMS population specifically.
Intervention	Ublituximab	Ublituximab	NA – In line with final NICE scope.
Comparator(s)	• ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ofatumumab	• ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ofatumumab	NA – In line with final NICE scope.
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example, expanded disability status scale [EDSS]) • disease progression	The outcome measures to be considered include: • relapse rate • disability (EDSS) (assessed at baseline and used as a basis for informing disability progression outcomes) • disease progression	Outcome measures included in this submission are based on those outcomes that have been included in the pivotal clinical trials of ublituximab (1).

	• symptoms of MS (such as fatigue, cognition or visual disturbance) • freedom from disease activity (for example lesions on magnetic resonance imaging (MRI) scans) • mortality • adverse effects of treatment • health-related quality-of-life (HRQoL).	• symptoms of MS (such as fatigue, cognition or visual disturbance) • freedom from disease activity (for example lesions on MRI scans) • mortality • adverse effects of treatment • HRQoL.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology guidance for the same indication, a cost-comparison may be carried out.	Cost-comparison analysis (CCA).	As ublituximab is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology guidance for the same indication, and as agreed by NICE, a cost-comparison is carried out for this submission.

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective.		
Subgroups to be considered	If the evidence allows, the following subgroups of people will be considered: • People with active and highly active RRMS • People with rapidly evolving severe (RES) RRMS	There are no subgroups considered in this submission.	The focus of this submission is on the RRMS population, rather than the RMS population that NICE defined in their final scope. Therefore, the population considered already includes the subgroup defined by NICE (i.e., people with active and highly active RRMS), making this subgroup analysis redundant. The RES subgroup was not assessed for the technology and is therefore not included in this submission.
Special considerations including issues related to equity or equality	NA	NA	NA

Abbreviations: CCA, cost-comparison analysis; EDSS, expanded disability status scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; QALY, quality-adjusted life year; RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

B.1.2 Description of the technology being evaluated

The technology being appraised is described in Table 2. Please see Appendix C for details of the summary of product characteristics (SmPC) and the UK Public Assessment Report. Both documents are included in the submission reference package.

Table 2 Technology being evaluated

UK approved name and brand name	UK approved name: Ublituximab Brand name: BRIUMVI®
Mechanism of action	B-cell dysregulation underlies the pathogenesis of MS (2–4). CD20 is an antigen expressed on pre-B-cells, immature/mature B-cells, memory B-cells, and a subpopulation of CD3-positive T cells (3). Anti-CD20 antibodies will therefore induce B-cell depletion through direct cell death, induction of complement pathways, and Fc-gamma receptor (FcγR)-mediated phagocytosis (antibody-dependent cellular cytotoxicity, ADCC) (5). Ublituximab is a type I chimeric IgG1 monoclonal antibody that binds to an epitope on CD20 that is distinct from the epitopes targeted by other anti-CD20 antibodies. Ublituximab is glycoengineered with a low fucose content in its fragment crystallizable region, which enhances its affinity for all variants of FcγRIIIa (or CD16A) and activates natural killer (NK)–cell function. In experimental studies, ublituximab showed predominant NK cell–mediated antibody-dependent cellular cytolysis while maintaining less complement-mediated lysis. In in vitro studies, ublituximab had 25 to 30 times the antibody-dependent cellular cytolysis potential of other anti-CD20 antibodies (1). Higher ADCC activity may allow lower doses and shorter infusion times, whereas weaker complement dependent cytotoxicity (CDC) activity may decrease infusion-related reactions (IRRs) (6). In the ULTIMATE I and II trials, participants who received ublituximab had a 96% decrease in the median number of CD19+ B cells 24 hours after the first dose (1).
Marketing authorisation/CE mark status	Ublituximab (BRIUMVI®, Neuraxpharm Pharmaceuticals) has a marketing authorisation in the UK for the treatment of adult patients with

	RMS with active disease defined by clinical or imaging features (7).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Ublituximab is indicated to treat adult RMS patients with active disease defined by clinical or imaging features (8). Contraindications are: • Hypersensitivity to the active substance or to particular excipients (Sodium chloride, Sodium citrate, Polysorbate 80, Hydrochloric acid (for pH adjustment), Water for injections). • Severe active infection. • Patients in a severely immunocompromised state. • Known active malignancies.
Method of administration and dosage	Ublituximab is administered as a concentrate for solution for infusion [sterile solution] and is administered as an intravenous (IV) infusion through a dedicated line. The following two pre-medications must be administered (orally, IV, intramuscular, or subcutaneously (SC)) prior to each infusion to reduce the frequency and severity of IRRs: • 100mg methylprednisolone or 10-20mg dexamethasone (or an equivalent) approximately 30-60 minutes prior to each infusion; • diphenhydramine approximately 30-60 minutes prior to each infusion; In addition, pre-medication with an antipyretic (e.g. paracetamol) may also be considered. The first dose of ublituximab is administered as a 150mg IV infusion (first infusion) over 4 hours, followed by a 450mg IV infusion (second infusion) over 1 hour, 2 weeks later. Subsequent doses are administered as a single 450mg IV infusion over 1 hour, every 24 weeks. The first subsequent dose of 450mg should be administered 24 weeks after the first infusion. A minimal interval of 5 months should be maintained between each dose of ublituximab. Patients need to be monitored for 1 hour after the first two infusions, however subsequent infusions do not require monitoring post infusion unless IRR and/or hypersensitivity has been observed.
Additional tests or investigations	The SmPC recommends verifying the patient's immune status before dosing since severely immunocompromised patients (e.g., significant

	neutropenia or lymphopenia) should not be treated (9). If progressive multifocal leukoencephalopathy (PML) is suspected, dosing with ublituximab must be withheld. Evaluation including MRI scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebro-spinal fluid (CSF) testing for John Cunningham Virus (JCV) Deoxyribonucleic acid (DNA) and repeat neurological assessments, should be considered.
List price and average cost of a course of treatment	List price is £2,947 per 150mg vial. At its list price, the annual drug acquisition costs for ublituximab are estimated to be [redacted] for the first year of treatment and [redacted] for subsequent years of treatment. At its discounted price, the annual drug acquisition costs for ublituximab are estimated to be [redacted] for the first year of treatment and [redacted] for subsequent years of treatment.
Patient access scheme/commercial arrangement (if applicable)	The list price of ublituximab is £2,947 per 150mg vial, while the patient access scheme (PAS) price is [redacted].

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CDC, complement dependent cytotoxicity; CSF, cerebro-spinal fluid; DNA, deoxyribonucleic acid; EU, European Union; FcγR, fc-gamma receptor; IRR, infusion-related reaction; JCV, John Cunningham Virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; NHS, National Health Service; NK, natural killer; PAS, patient access scheme; PML, progressive multifocal leukoencephalopathy; RMS, relapsing multiple sclerosis; SmPC, summary of product characteristics; UK, United Kingdom.

B.1.3 Health condition and position of the technology in the treatment pathway

Background

Multiple Sclerosis is a central nervous system (CNS) disorder that is chronic, inflammatory, demyelinating, and neurodegenerative. It frequently results in the development of clinical impairment that is permanent (10). Although MS can occur at any age, the majority of people are diagnosed between the ages of 20 and 50 (11). The manifestations of MS exhibit significant variability among individuals and can fluctuate daily. Common symptoms encompass pain, muscle weakness or spasticity, persistent fatigue, an unsteady gait or balance issues, visual disturbances, incontinence, and cognitive deficits (12–14). Multiple sclerosis represents the leading

cause of chronic neurological disability and affects two to three times more women than men (15,16). The life expectancy for individuals with MS is typically 5–10 years shorter than that of the general population (17,18), with approximately 50% of patients succumbing to complications associated with the advanced stages of MS (19).

The underlying causes of MS and the reasons behind its unpredictable course are still poorly understood (11). Multiple risk factors are implicated in the development of MS, including age, gender, race, heredity, geographic location, and infections such as herpes simplex, chlamydia, and rabies (20,21). Risk factors such as obesity, smoking, and the Epstein Barr virus are also associated with MS, while the relationship between low vitamin D levels and MS is well-established (22). Multiple sclerosis is, therefore, believed to arise from a complex interaction of genetic predisposition, dietary influences, and environmental factors (23,24). B-cells have been independently implicated in the pathophysiology of MS through their role in antigen presentation, cytokine production, autoantibody production and ectopic lymphoid follicle-like structures in the CNS (25). The underlying pathophysiological hallmarks of MS include inflammatory lesions that lead to neuronal demyelination, axonal damage, and subsequent neurological dysfunctions. These issues arise from the formation of multiple plaques in the grey and white matter of the brain and spinal cord (26). Consequently, MS is regarded as the most prevalent cause of neurological disability, as the inflammatory lesions associated with MS can impact a wide range of systems to varying degrees, resulting in numerous neurological symptoms and comorbidities (27).

The significant, detrimental impact that MS may have on patient quality-of-life (QoL) has been demonstrated in previous work (28). In a European study by Kobelt et al. 2017, it was found that among the 16,808 participants, work capacity declined from 82% to 8%, and utility declined from normal population values to less than zero with advancing disease. Fatigue and cognitive difficulties were reported by 95% and 71% of participants, respectively; with both having a significant independent effect on utility. Expanded disability status scale (EDSS) score has also been shown to be a very strong driver of utility; that is, QoL worsens with increasing EDSS score (28). Additionally, as a result of an inability to work and a subsequent over-reliance on

family-members and friends for support, the condition is known to impact the stress levels and QoL of individuals beyond just the affected patient (16,29,30). As reported by Hauser & Oksenberg 2006, fifteen years after diagnosis, fewer than 20% of patients with MS have no functional limitation, 50% to 60% require assistance when ambulating, 70% are limited or unable to perform major activities of daily living, and 75% are not employed (16). Disease state has been shown to have a marked effect on the proportion of patients below retirement age who are in employment. The previously cited European study also demonstrated the substantial economic burden that the condition can have on patients, healthcare systems, and broader society (28).

Types of MS

There are progressive and relapsing subtypes of MS, but disease rarely follows a predictable path. Relapsing multiple sclerosis includes people with RRMS and SPMS who continue to experience relapses. Meanwhile, primary progressive multiple sclerosis (PPMS) is characterised by a gradual disability progression from onset with minimal discernible clinical signs of neuroinflammation characterised by relapses and remissions (31).

RRMS

Relapsing-remitting MS is the most common form of the condition, affecting approximately 85% of patients with MS (32), and is characterised by clearly defined relapses of new or increasing neurologic symptoms (also called ‘attacks’ or ‘exacerbations’) followed by periods of partial or complete recovery (remissions) (33). During relapses, new symptoms emerge, or pre-existing symptoms worsen, leading to an acute deterioration in neurological function that persists for at least 24 hours. Typically, these relapses last for 4–6 weeks (32). When the condition is remitting, there may be no visible symptoms, or certain symptoms may continue, but there would be no progression of the disease during these periods. Over time, disability progressively worsens due to incomplete recovery from relapses. Relapsing-remitting MS can be characterised as either active (with relapses and/or evidence of new MRI activity over a specified period of time) or not active, as well as worsening (a confirmed increase in disability following a relapse) or not worsening

(33). A number of disease-modifying therapies (DMTs) have been approved to reduce the chance of relapses and disability progression in patients with RRMS (34). Early treatment initiation is advised so as to maximise the efficacy of currently available therapies, which are known to mainly act against the inflammatory components of MS (35).

SPMS

When the initial relapsing-remitting phase is followed by a transition to a progressive phase, the disease is known as SPMS (35), with an international panel of experts defining it as an "initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus" (35,36). Therefore, the underlying disease process shifts from the inflammatory course characteristic of RRMS, to a more steadily progressive phase characterised by permanent nerve damage or loss. McAlpine and Compston reported that "there is a fairly constant rate of change from a remitting to a progressive course, and that there is a gradual rise in the total percentage of progressive cases as the disease advances" (35,37). As estimated by survival analysis, the median time to secondary progression in MS patients with a relapsing-remitting onset in the Lyon series was 19·1 years, with a mean yearly rate of 2·5% of relapsing-remitting patients converting to SPMS (35,38). In a Canadian series, 30–40% of patients with an initial relapsing-remitting course developed SPMS within 10 years from disease onset, with a median time to conversion of between 10 and 15 years (35,39). A reasonable estimate of the median time from RRMS onset to secondary progression is believed to be about 19 years (35,40).

PPMS

Primary progressive MS affects approximately 10-15% of MS patients and involves the gradual worsening of neurologic symptoms and accumulation of disability, rather than the occurrence of relapses early in the disease course and remissions (41). This form of MS is unlike the relapsing forms in that it can take longer to diagnose (requires a minimum of 12 months of symptom progression), has far fewer treatment options, and has an average age of onset approximately 10 years older than in relapsing MS. As DMTs are medications that work primarily by reducing

inflammation in the CNS, they do not work as well in a disease course that is characterised by nerve degeneration rather than inflammation (41).

Epidemiology

According to recent statistics from the National MS Society, there are around 2.5 million patients with MS worldwide. In the UK, it is estimated that there are over 130,000 people with MS and approximately 7,000 people receive new diagnoses every year (42). This means around 1 in every 500 people in the UK lives with MS, and each week over 130 people are diagnosed with MS.

Clinical Pathway of Care

This section initially presents an overview of the diagnosis of MS; all currently available treatments for RRMS in the UK; followed by a description of the starting/stopping rules related to DMTs for RRMS; and a description of the subpopulations of interest that need to be considered when discussing the clinical care pathway. The existing treatment algorithm at the time of submission is then presented, followed by a detailed description of the intervention of interest (ublituximab) and its intended position in the treatment pathway.

Diagnosis

NICE guidelines for the management of MS in adults describe the process for diagnosing MS (43), which should be based on using a combination of history, examination, MRI, laboratory findings, and by following the 2017 McDonald criteria (44). Following referral to a consultant neurologist or specialist, diagnosis should involve the following steps:

- assessing that symptoms are consistent with an inflammatory demyelinating process; for example, headache is not suggestive of MS;
- excluding alternative diagnoses (targeted laboratory tests may be indicated if the history, examination or MRI findings are atypical);
- establishing that lesions on MRI scans have developed at different times and are in different anatomical locations for a diagnosis of RRMS;

- looking for CSF-specific oligoclonal bands if there is no clinical or radiological evidence of lesions developing at different times;
- establishing progressive neurological deterioration over 1 year or more for a diagnosis of PPMS (43).

Currently available DMTs

The following DMTs are currently available (at the time of submission) in the UK for the treatment of RRMS, including a description of the population for whom each treatment is intended (45):

- **alemtuzumab**: Recommended as an option, within its marketing authorisation, for treating highly active RRMS in adults with: highly active disease despite a full and adequate course of treatment with at least one DMT, or RES RRMS defined by two or more relapses in the previous year, and baseline MRI evidence of disease activity (46);

- **cladribine**: Recommended for the treatment of highly active RMS with: two or more disabling relapses in the past year and MRI scans show the patient has had more, or bigger, lesions (guidelines call this 'RES RRMS') or despite taking a DMT, the patient has had a relapse in the past year, and new or bigger lesions can be seen on MRI scans (47);

- **dimethyl fumarate**: Recommended as an option for treating adults with: active RRMS (normally defined as two clinically significant relapses in the previous 2 years), only if: they do not have highly active or RES RRMS, and the manufacturer provides dimethyl fumarate with the discount agreed in the PAS (48);
- **diroximel fumarate**: Recommended for patients with: active RMS defined by MRI scans that identify inflammation or new or enlarging lesions (and do not have highly active or RES RRMS), as long as the company provides diroximel fumarate according to the commercial arrangement (49);
- **fingolimod**: Recommended as an option for the treatment of highly active RRMS in adults, only if: they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment

with beta interferon, and the manufacturer provides fingolimod with the discount agreed as part of the PAS (50);

- **glatiramer acetate**: Recommended as an option for treating MS, only if: the person has RRMS, and the company provides it according to the commercial arrangement (51);
- **interferon beta-1a**: Recommended as an option for treating MS, only if: the person has RRMS, and the companies provide it according to commercial arrangements (51);
- **interferon beta-1b (Extavia)**: Recommended as an option for treating MS, only if: the person has RRMS, and has had two or more relapses within the last 2 years, or the person has SPMS with continuing relapses, and the company provides it according to the commercial arrangement (51);
- **natalizumab**: Recommended as an option for the treatment only of RES RRMS in adults (52);
- **ocrelizumab**: Recommended as an option for treating RRMS in adults with active disease defined by clinical or imaging features, only if: alemtuzumab is contraindicated or otherwise unsuitable, and the company provides ocrelizumab according to the commercial arrangement (53);
- **ofatumumab**: Recommended as an option for treating RRMS in adults with active disease defined by clinical or imaging features. This is only if the company provides ofatumumab according to the commercial arrangement (54);
- **peginterferon beta-1a**: Recommended, within its marketing authorisation, as an option for treating RRMS in adults (55);
- **ponesimod**: Recommended for treating RRMS with active disease defined by clinical or imaging features in adults, only if the company provides ponesimod according to the commercial arrangement (56);
- **teriflunomide**: Recommended as an option for treating adults with active RRMS (normally defined as two clinically significant relapses in the previous 2 years), only if they do not have highly active or RES RRMS, and the manufacturer provides teriflunomide with the discount agreed in the PAS (57).

Additional drugs such as **siponimod** are used for the treatment of active SPMS, meaning you're still having relapses or MRI scans show new or growing lesions, while **ozanimod** is available in Scotland if you have RMS and you've had a recent relapse and/or MRI scans show new signs that your MS is active, i.e., you have new lesions, but is not currently recommended in the rest of the UK (45,58).

The Association of British Neurologists (ABN) published updated guidelines for use of DMTs in MS in June, 2024 (59). These guidelines indicate that the current main treatment strategies are either an escalation approach (commencing on a moderate efficacy therapy to minimise potential risk and escalation to higher efficacy DMT if there is disease breakthrough) or an early intensive approach (using a higher efficacy DMT from outset to maximise early disease control with possible increased risk which may be minimised by later de-escalation).

Clinical expert opinion would suggest that early intervention with high efficacy DMTs is the optimal approach to improving clinical outcomes, and this is also reflective of current practices in the UK and across Europe (60). Such an approach has been associated with a significantly greater reduction of inflammatory activity (clinical relapses and new lesion formation at MRI) as well as disease progression, in terms of accumulation of irreversible clinical disability and neurodegeneration, compared to delayed DMT use or escalation strategy (60). Similarly, the ABN guidelines highlight that emerging evidence suggests improved long-term disability with high efficacy therapy initiation within two years of disease onset (59,61,62). The ABN classification of DMTs currently licensed within the UK is presented in Table 3 below (grouped by efficacy based on reduction in relapse rate).

Table 3 ABN classification of DMTs

ABN Classification of DMTs	**Therapies (in chronological order of commissioning)**
Moderate efficacy therapies for RRMS	Beta interferons Glatiramer acetate Fingolimod (may in some circumstances be used as an escalation therapy) Teriflunomide

	Dimethyl fumarate Ozanimod (Scotland only) Ponesimod (may in some circumstances be used as an escalation therapy) Diroximel fumarate
Higher efficacy therapies for RRMS**	Natalizumab* Alemtuzumab* Ocrelizumab* Cladribine* Ofatumumab*
Therapies for early PPMS	Ocrelizumab
Therapies for active SPMS	Interferon-beta 1b Siponimod

Abbreviations: ABN, Association of British Neurologists; DMT, disease-modifying therapy; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

* Also eligible for use in RES RRMS.

** Higher efficacy therapies are considered as those with >50% reduction (or otherwise significant reduction) in relapse rate compared to placebo/comparator. It must be noted that there is variation in whether DMTs were compared to active comparator or placebo and so studies are not directly comparable.

As highlighted, there are multiple different DMT treatment options for RRMS. However, choice of treatment is largely determined by extent of disease activity (63). The ABN have highlighted the complex treatment landscape in the area of RRMS, and have stressed the importance of patient involvement in decision making (59). To this point, the decision to prescribe a DMT for RRMS is primarily based on an informed discussion and mutual agreement between the prescribing clinician and the patient. This decision considers factors such as the level of disease activity, the patient's risk tolerance, preferences, and lifestyle factors such as family planning (64–66).

Starting and Stopping Treatment

As with choice of treatment, decisions to start or stop treatment, or to perform MRI for diagnosis and management, should recognise the importance of patient choice,

with patients being fully informed of relevant facts and uncertainties before making a decision with their MS specialist neurologist. Starting criteria that are common to all DMTs, as defined by the NHS England treatment algorithm, are presented below:

- Sustained disability due to MS is less than EDSS 7.0, i.e., at least ambulant with two crutches (patients experiencing a relapse may transiently have disability greater than EDSS 7.0; if they recover to a sustained EDSS less than 7.0, they are eligible for DMTs).
- It is important that, at the start of treatment, the patient understands that treatment may be stopped if it is ineffective, intolerable adverse events (AE) arise, the patient becomes pregnant or they develop progressive disease or fixed disability above EDSS 6.5.
- MS teams should proactively discuss the possibility of pregnancy as part of DMT selection. Where pregnancy is planned or desired, people with MS should usually be offered a DMT of at least similar efficacy which is compatible with pregnancy than if this were this not a consideration. The aim should be to allow people to make an informed choice about DMT use, taking into account safety around pregnancy alongside minimising the risk of relapse in the mother. DMTs in pregnancy must meet recognised commissioning criteria.
- Where generic or biosimilar options are available, treatment should be with the least expensive option (taking into account administration costs, dose needed and product price per dose) (58).

The following scenarios should lead to consideration of stopping treatment:

- No reduction in frequency or severity of relapses compared with pre-treatment phase following adequate exposure to the DMTs (which varies for each DMT, but should be a minimum of 6 months).
- Intolerable adverse effects of the drug.
- Development of inability to walk (EDSS 7.0), persistent for more than 6 months due to MS.
- Confirmed secondary progressive disease with an observable increase in disability for more than a 12-month period, in the absence of relapse activity.

Secondary progressive disease would usually only be diagnosed in patients with an EDSS of 6.0 or greater (58).

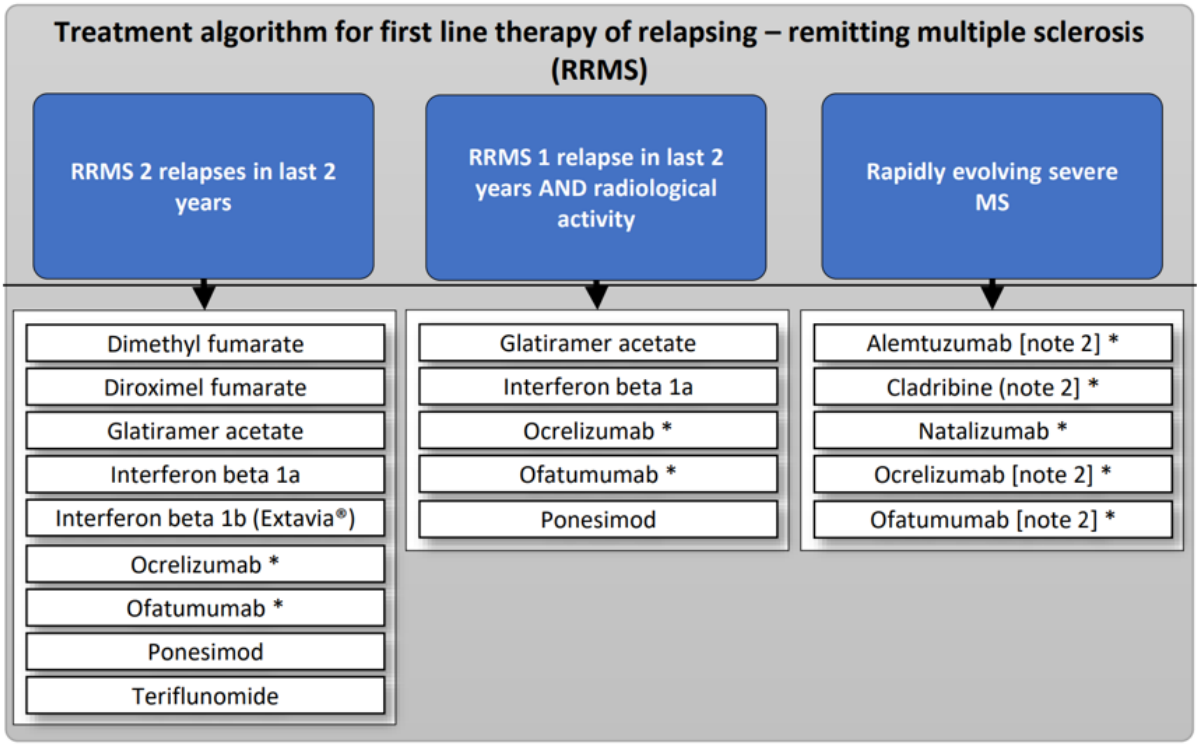
Treatment algorithm

As mentioned, the level of disease activity is one of the key factors which will inform choice of treatment, with the severity and frequency of relapses varying greatly between patients. Disease activity is defined as ‘active’ if at least two clinically significant relapses occur within the last 2 years. ‘Highly active’ disease is characterised by an unchanged/increased relapse rate or by ongoing severe relapses compared with the previous year, despite disease-modifying drug treatment. Rapidly evolving severe RRMS is defined by two or more disabling relapses in 1 year, and one or more gadolinium (Gd)-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI (67).

NICE provides guidelines for the management of MS in adults, which covers RRMS as well as other types of MS (43), while the NHS England treatment algorithm presents the recommended lines of therapy for RRMS patients (including relevant subpopulations), with recommended treatment switches also presented (58). It is highlighted that treatment switching can be done for reasons of intolerance (which includes burdensome modes of administration), disease activity or cumulative risk of PML with natalizumab, for example, and that none of the drugs promise 100% efficacy and some patients and physicians may choose to tolerate some disease activity without changing drugs (58).

It should be noted that the ABN guidelines indicate that the NHS England treatment algorithm adheres to NICE TA recommendations, which they claim may not necessarily reflect current perceptions of best clinical practice. They suggest that the algorithm does not always allow the needs of an individual to be met, for instance around pregnancy planning, and a further challenge is that the algorithm is hampered by inconsistent and outdated definitions of disease activity, which are largely based on pivotal study inclusion criteria used in historical NICE TAs (59). Nevertheless, details of the algorithm are presented below.

Figure 1 Treatment algorithm for first line therapy of RRMS

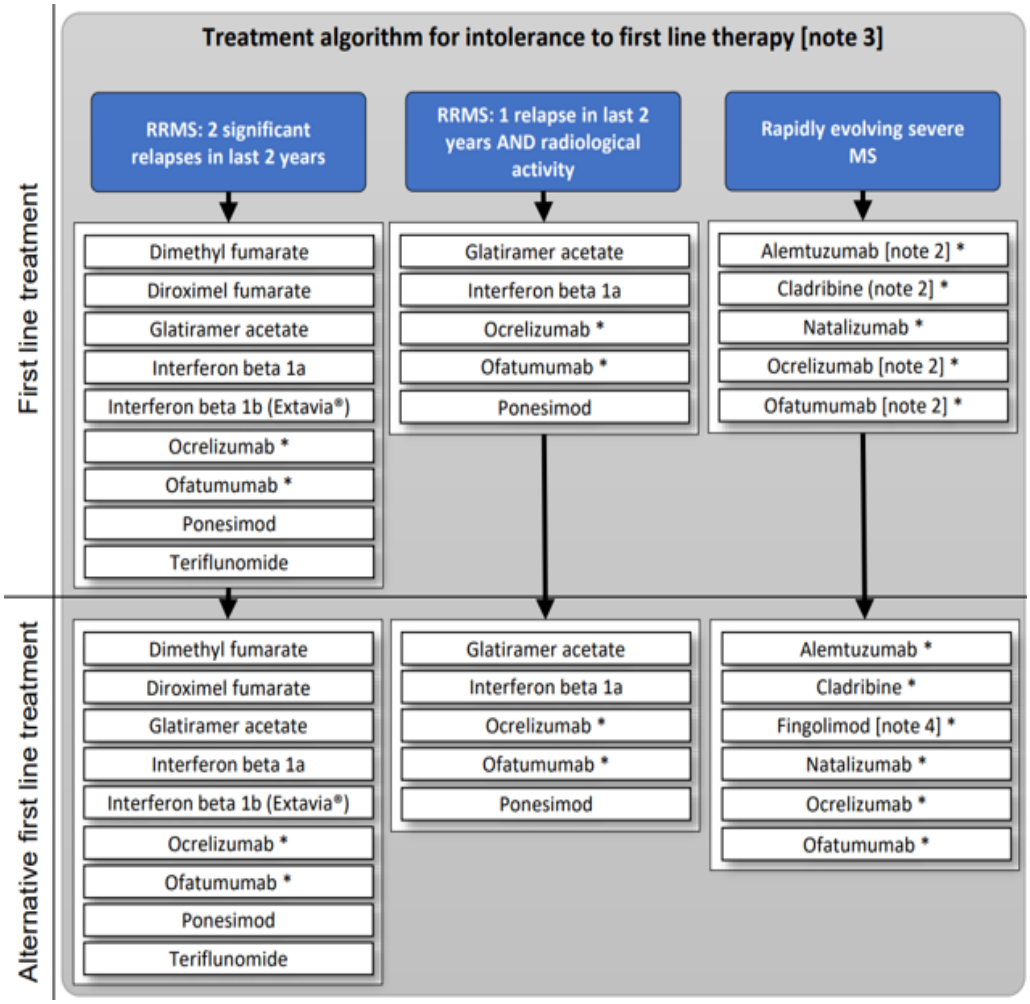


Abbreviations: MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Treatments with [*] suffix should be agreed at multi-disciplinary team (MDT) meeting.

[Note 2] alemtuzumab, ocrelizumab, ofatumumab and cladribine may be a safer option than natalizumab when JCV serology is high-index positive.

Figure 2 Treatment algorithm for intolerance to first line therapy



Abbreviations: MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Treatments with [*] suffix should be agreed at MDT.

[Note 2] alemtuzumab, ocrelizumab, ofatumumab and cladribine may be a safer option than natalizumab when JCV serology is high-index positive.

[Note 3] Intolerance to treatment; If a patient satisfies the eligibility criteria for a first line therapy, and then is relapse-free on a drug to which they become intolerant, they may be switched to another DMT even though their relapses may now fall outside the eligibility window.

[Note 4] NHS England 2014 clinical commissioning policy states that fingolimod can be used as an alternative to natalizumab for those patients receiving natalizumab who are at high risk of developing PML as defined by the following:

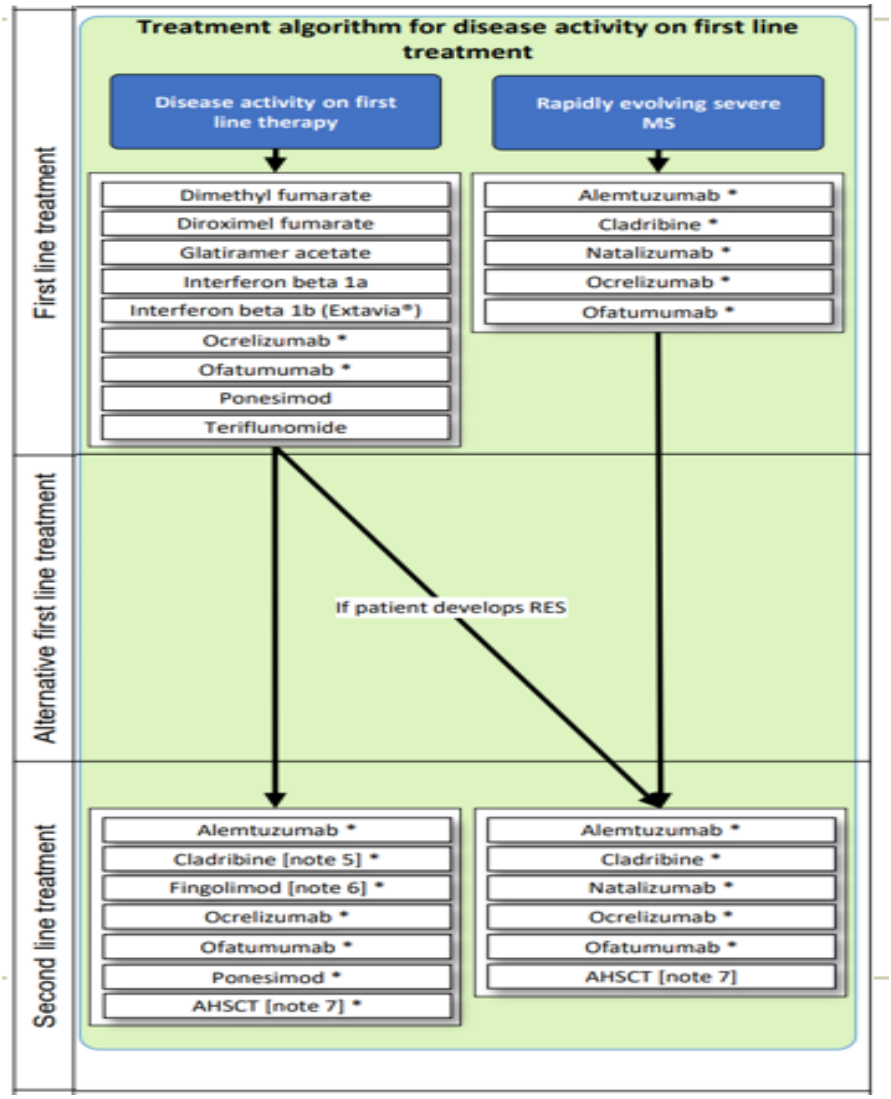
(i) JCV exposure indicated by anti-JCV antibody positive status,

(ii) Receiving an immunosuppressant prior to receiving natalizumab, or

(iii) natalizumab treatment duration of >2 years.

If patients develop a severe adverse effect to natalizumab (e.g., anaphylaxis), and they have not previously received fingolimod, then it may be appropriate to use fingolimod.

Figure 3 Treatment algorithm for disease activity on first line therapy



Abbreviations: MS, multiple sclerosis; RES, rapidly evolving severe.

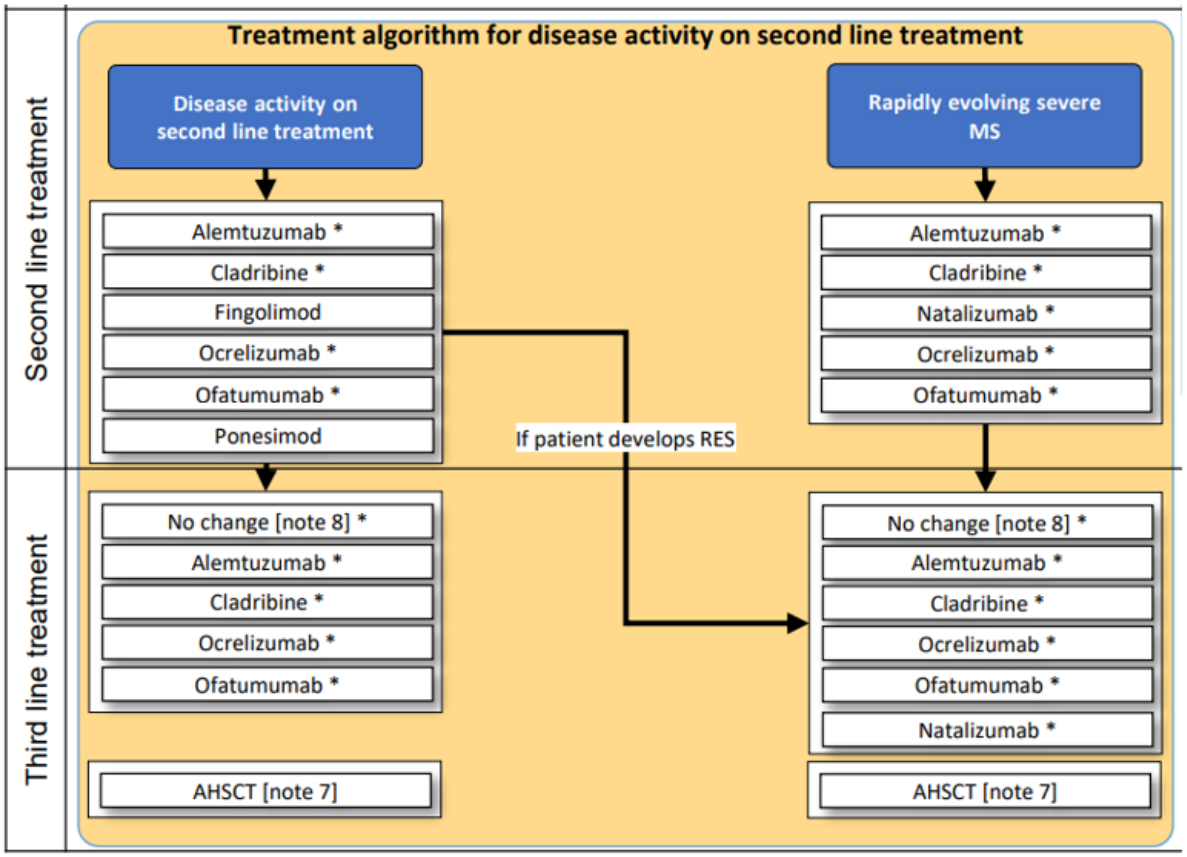
Treatments with [*] suffix should be agreed at MDT.

[Note 5] For cladribine to be given, NICE specifically defined treatment failure as “1 relapse in the previous year and MRI evidence of disease activity.”

[Note 6] For fingolimod: under previous guidance, fingolimod may be given if patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon or glatiramer acetate. This is now extended to include disease activity on dimethyl fumarate, diroximel fumarate, teriflunomide and ponesimod.

[Note 7] Autologous haematopoietic stem cell treatment (AHSCT) for autoimmunity is commissioned at specialised centres and should be discussed at a specialist MDT.

Figure 4 Treatment algorithm for disease activity on second line therapy



Abbreviations: MS, multiple sclerosis; RES, rapidly evolving severe.

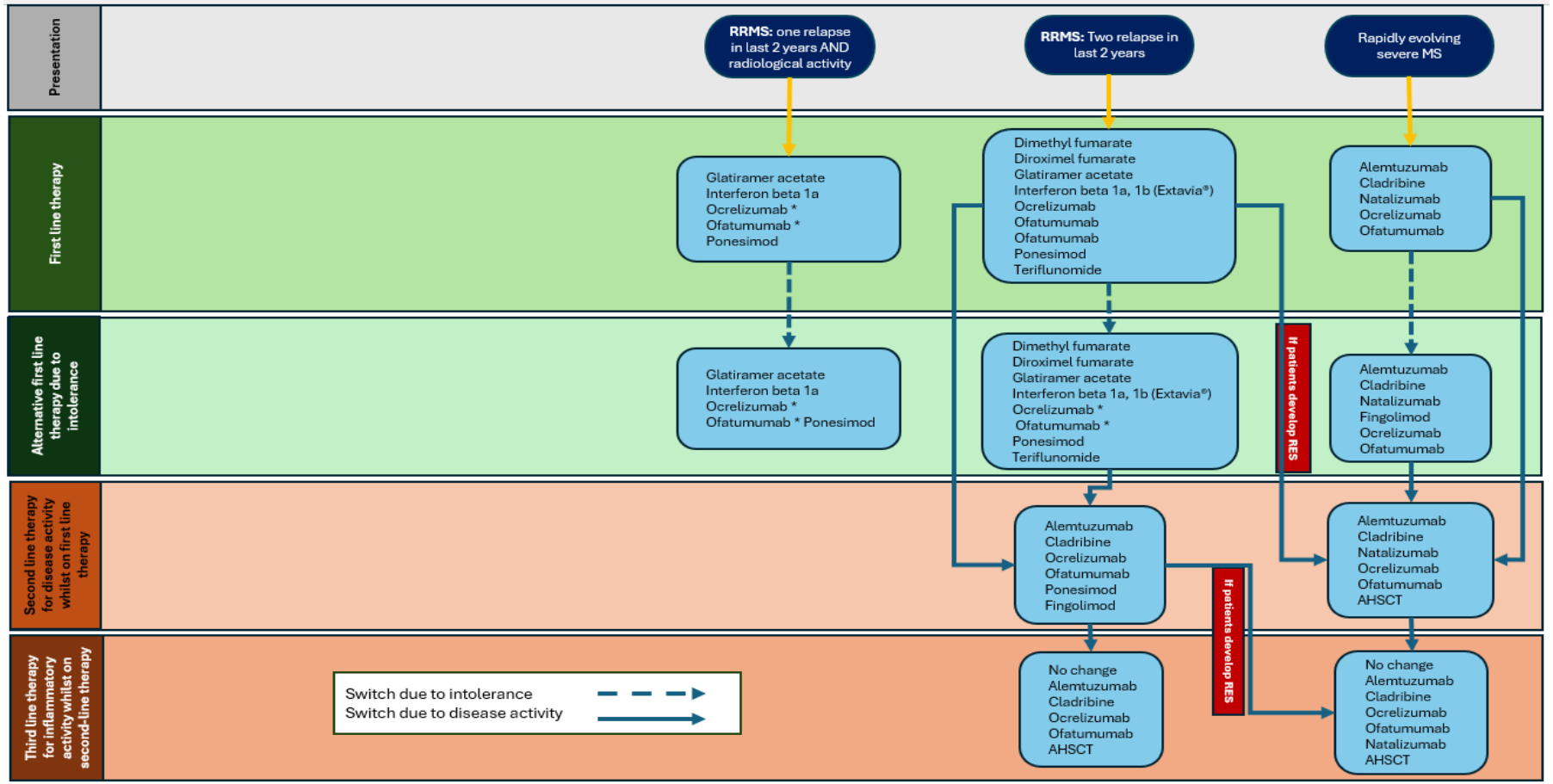
Treatments with [*] suffix should be agreed at MDT.

[Note 7] AHSCT for autoimmunity is commissioned at specialised centres and should be discussed at a specialist MDT.

[Note 8] After considering all these options, it may be appropriate to continue the second line therapy, despite evidence of disease activity. None of the drugs promise 100% efficacy and some patients and physicians may choose to tolerate some disease activity without changing drugs.

A comprehensive overview of the entire treatment algorithm is presented in Figure 5 below (58).

Figure 5 Treatment algorithm for RRMS



Abbreviations: AHSCT, autologous haematopoietic stem cell treatment; MS, multiple sclerosis; RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis.

Addition of ublituximab to the treatment algorithm

Ublituximab has been approved for the treatment of adult patients with RMS who have active disease defined by clinical or imaging features. However, as outlined in Section B.1.1 this submission is targeting RRMS only. Ublituximab offers an additional treatment option for adult patients with RRMS, including those patients with active, highly active, or RES RRMS. Like ocrelizumab and ofatumumab, ublituximab is intended for treating active, highly active, and RES RRMS patient populations for all lines of treatment. Shared decision-making between patients and physicians is key when deciding which treatment regimen to initiate in RMS. Evidence suggests that preference for SC or IV treatment options varies between individuals and this was validated by clinical experts in an advisory board (68). Ublituximab is anticipated to occupy a comparable position in the treatment algorithm as ocrelizumab and ofatumumab. However, ublituximab is likely to be considered as a treatment option, as part of shared decision-making, when an IV infusion is the preferred mode of administration. For this reason, ocrelizumab is the most relevant comparator for ublituximab in clinical practice as this is also administered by IV. Given the potential, based on existing clinical evidence, for ublituximab to provide similar or greater health benefits at similar or lower cost than these current NICE-recommended technologies for the same indication, a CCA has been carried out.

Ublituximab is a CD20-directed cytolytic monoclonal antibody (mAb). It is part of the anti-CD20 class of mAbs, which consists of treatments including ocrelizumab and ofatumumab, working by selectively depleting C20 expressing B-cell populations (69). Monoclonal antibodies have advantages over other DMTs, including long pharmacodynamic effects, which allow for relatively infrequent dosing (70,71). Their relative efficacy compared to alternative treatments for reduction in relapse rate and disability progression has previously been demonstrated in recent research assessing the comparative efficacy of treatments for RMS (72). CD20 expressing cells are eliminated by ublituximab mAbs through at least four distinct mechanisms, including (i) ADCC, (ii) complement-dependent cytotoxicity, (iii) antibody-dependent cellular phagocytosis, and (iv) induction of cell apoptosis (73). In previous in-vitro studies, ublituximab was shown to have 25 to 30 times the antibody-dependent cellular cytolysis potential of other anti-CD20 antibodies (74), and in phase II and III

trials, ublituximab was shown to induce B-cell depletion within 24 hours (1,5). Phase III, double-blind studies of ublituximab show lower annualised relapse rates (ARR) and fewer new T2 lesions on MRI than the comparator (teriflunomide) over a period of 96 weeks (1). The ARR results for ublituximab are particularly notable given that they are <0.10 over 96 weeks (0.08 in ULTIMATE I and 0.09 in ULTIMATE II) (1); reflecting a relapse rate of less than one relapse per decade. These results suggest that ublituximab may enhance the existing treatment paradigm in the area of RRMS through its improved associated clinical outcomes, while also reducing health service resource use and associated costs through its less intensive monitoring schedule.

Ublituximab has an advantage over other IV drugs due to its shorter infusion duration from the second infusion onwards, and no requirement for post-infusion monitoring from the third infusion onwards in the absence of infusion reactions. This feature can significantly improve patient management in hospitals by streamlining the treatment process and freeing up staff capacities for the NHS, which ultimately leads to better care for more MS patients. The shortened infusion process of ublituximab (per the SmPC, after first infusion, all subsequent infusions last 1 hour) not only helps improve efficiency in hospital workflows but also contributes to enhanced patient comfort and convenience. In addition, there is no need for monitoring post-infusion from the third infusion onwards with ublituximab, unless there are infusion reactions, which is not the case with ocrelizumab which requires patients to be monitored during the infusion and for at least one hour after the completion of each infusion (see section 4.4 of the SmPC, https://www.ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf) (75). By minimising the time spent on infusion, patients can experience reduced discomfort and may even be able to resume their daily activities sooner. Furthermore, the shorter infusion duration could help alleviate logistical challenges associated with scheduling and resource allocation within healthcare facilities, ultimately leading to improved overall patient care and management. This has been confirmed during a clinical advisory board meeting held on 8th February 2024 with leading MS consultants.

B.1.4 Equality considerations

No equality issues relating to ublituximab have been identified. Introduction of ublituximab is not likely to lead to recommendations which differentially impact patients protected by the equality legislation or disabled persons.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

Clinical outcomes and measures that were used in the cost-effectiveness analysis of ocrelizumab and ofatumumab (comparators specified in the final scope for this appraisal and relevant to the decision problem) are presented in Table 4. Key clinical drivers of the cost-effectiveness results are presented and the preferred assumptions from the committee that are relevant to the consideration of these outcomes are included. Additionally, any uncertainties in the assumptions and estimates used in the previous NICE appraisals are highlighted.

Table 4 Clinical outcomes and measures for comparator technologies

	Outcomes	Measurement scale	Used in cost-effectiveness model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
NICE TA533 (ocrelizumab) (53)	• Relapses • Disability progression • Mortality • Conversion from RRMS to SPMS • AEs • Treatment discontinuation	• Relapses: Measured by relapse/exacerbation rate, as reported in relevant clinical trials and based on natural history data, in line with previous appraisals. • Disability progression: Measured by Kurtzke EDSS (76), with health states in the	All outcomes used in cost-effectiveness model.	The results were most sensitive to treatment effect on confirmed disability progression (CDP). All other parameters had only modest impact on the results, including excess mortality risk, and discontinuation.	• Committee believes that CDP-24 is a more robust measure than CDP-12 for inclusion in the base-case model as it is less likely to be confounded by longer-lasting temporary relapses. • No additional treatment effect related to conversion to SPMS is assumed.	Model assumptions which the Evidence Review Group (ERG) found reasonable were: • Stopping rules for DMTs: EDSS ≥7 or conversion to SPMS. • No impact of treatment on severity or duration of relapses. • Treatment reduces disability

		model defined by the EDSS. • Mortality: Measured by all-cause and condition-specific mortality rates. • Conversion from RRMS to SPMS: Measured by natural history data on progression rates. • AEs: Measured by event rates in relevant clinical trials. • Treatment discontinuation: Measured by all-cause discontinuation trial data.		Some exceptions were discontinuation rates for fingolimod, natalizumab, dimethyl fumarate, and teriflunomide.	• No increase in EDSS state following conversion to SPMS.	progression but not regression. • Rates of withdrawal from treatment and adverse effects are constant over time. • Disease-modifying therapy does not directly affect mortality. An indirect effect is modelled because treatment reduces EDSS progression and mortality rates are modelled to rise with EDSS. Model assumptions which the ERG found unreasonable were: • Confirmation of disability progression at 12 weeks. They believe that CDP-24 weeks is a more robust measure, less likely to be confounded by longer-lasting temporary relapses.

						• Effect on rate of conversion from RRMS to SPMS (assumed 50% of relative effect on CDP). • Conversion from RRMS to SPMS is accompanied by a one-point increase in EDSS. • Probability of EDSS improvement in SPMS disease. • No waning of treatment effects over time. • Rates of retreatment for alemtuzumab assumed 13% from year 6 onwards.
NICE TA699 (ofatumumab) (54)	• Relapses • Disability progression • Mortality • Conversion from RRMS to SPMS • AEs • Treatment discontinuation	• Relapses: Measured by relapse/exacerbation rate, as reported in relevant clinical trials and based on natural history data, in line with previous appraisals. • Disability progression: Measured by Kurtzke	All outcomes used in cost-effectiveness model.	It was seen that the estimates of effectiveness on disability worsening for each DMT had the greatest impact on the ICER and the net monetary benefit (NMB) results at	• Treatment waning was not included in the company submission. Due to little information available about the long-term treatment effect of ofatumumab, and to be in line with recent MS TAs, the	The ERG's amendments using alternative sources of information are provided: • Transition probabilities from RRMS to SPMS

		EDSS (76), with health states in the model defined by the EDSS. • Mortality: Measured by all-cause and condition-specific mortality rates. • Conversion from RRMS to SPMS: Measured by natural history data on progression rates. • AEs: Measured by event rates in relevant clinical trials. • Treatment discontinuation: Measured by all-cause discontinuation trial data.		a £30,000 threshold. Results from the one-way sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except the hazard ratio (HR) for disability worsening efficacy, which had the greatest impact.	ERG supports a precautionary approach to use a conservative assumption of waning of the treatment effect, where drug effectiveness wanes, with a 25% reduction after 5 years, then a 50% reduction after 8 years. • The availability of alternative transition probabilities (TPs) for progression from RRMS to SPMS, which had been used in recent MS TAs. The ERG suggests that TPs from RRMS to SPMS obtained from these previous appraisals should have been included in the economic analysis. • For ARR, the values used by the company for RRMS show that there is a steady decrease in the ARR.	obtained from TA624 (55). • Annualised relapse rates for a natural history cohort from TA527 (51). • Waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years). In general, the company's results were robust to individual changes made by the ERG, with the inclusion of waning of the treatment effect having the greatest impact on the ICER.

					Those used for SPMS show that at more severe EDSS levels, there is a greater frequency of relapses when compared to less severe EDSS levels. The gd is aware of other relapse frequency values reported in TA527 assessment (51), which is based on the British Columbia cohort. These values show that ARRs decrease as EDSS levels increase.	

Abbreviations: AE, adverse event; ARR, annualised relapse rate; CDP, confirmed disability progression; DMT, disease-modifying therapy; EDSS, expanded disability status scale; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; MS, multiple sclerosis; NMB, net monetary benefit; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TP, transition probability.

B.2.2 Resource use assumptions

Resource use and costs that were used in the cost-effectiveness analysis of ocrelizumab and ofatumumab (comparators specified in the final scope for this appraisal and relevant to the decision problem) are presented in Table 5. Key resource use/cost drivers of the cost-effectiveness results are presented and the preferred assumptions from the committee that are relevant to the consideration of these parameters are included. Additionally, any uncertainties in the assumptions and estimates used in the previous NICE appraisals are highlighted.

Table 5 Resource use and costs for comparator technologies

	Resource use/costs	Used in cost-effectiveness model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
NICE TA533 (ocrelizumab) (53)	• EDSS health state costs • Relapse costs • Drug acquisition costs • Costs associated with administration and patient monitoring • AE costs	All resource use and costs used in cost-effectiveness model.	Parameters including the administration costs of ocrelizumab, non-medical RRMS costs, direct costs of RRMS, and cost of relapses were found to be among the top 10 most important parameters in deterministic sensitivity analysis. However, their impact on the overall cost-effectiveness results was reported to be 'modest'.	• To make appropriate adjustments to account for list prices of treatments and PAS prices of treatments. • To exclude re-treatment with alemtuzumab from year 5 onwards (maximum of 4 courses of treatment) (77). • To utilise an alternative source of data for health state	Key uncertainties around resource use and costs included in the company submission that were addressed by the ERG, included assumptions related to retreatment rates with alemtuzumab and the source of data for health state costs.

			In a scenario analysis, the ICER for ocrelizumab compared with other DMTs was most sensitive to changing the source of social care costs.	costs (UK MS Survey data, as reported in TA320) (48).	
NICE TA699 (ofatumumab) (54)	• EDSS health state costs • Relapse costs • Drug acquisition costs • Costs associated with administration and patient monitoring • AE costs	All resource use and costs used in cost-effectiveness model.	Base-case results were robust to changes to resource use and cost-related input parameters.	Inclusion of disease management costs associated with treating people with SPMS: Tyas et al. (2007) (78) have collected resource use and costs for treating people with SPMS, which is based on a large UK MS study. For consistency with other recent MS TAs (55), the ERG suggest that these disease management costs associated with treating people with SPMS should have been included in the economic analysis.	Key uncertainty in the company-submitted model was related to the SPMS-specific disease management costs, which was addressed by the ERG in their revised model.

Abbreviations: AE, adverse event; DMT, disease-modifying therapy; EDSS, expanded disability status scale; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MS, multiple sclerosis; PAS, patient access scheme; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; UK, United Kingdom.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

In line with the decision problem (detailed in Table 1), a systematic literature review (SLR) was conducted on 18 September 2023 (updated on 3 June 2024) to identify all relevant clinical evidence regarding the efficacy and safety of ublituximab (BRIUMVI®) and other relevant comparators for the treatment of RMS. Studies that did not include ublituximab but did include a relevant comparator in the analysis, were included in the review. Comparators included in the review were other recommended mAb treatments for RMS: alemtuzumab, ocrelizumab, ofatumumab, and natalizumab, as well as additional DMTs which were included in order to ensure that a comprehensive network of treatments required to perform indirect comparisons was captured: interferon beta-1a [Rebif®], and teriflunomide. See Appendix D for full details of the NICE-advised process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.3.2 List of relevant clinical effectiveness evidence

All publications identified via the SLR which described an assessment of ublituximab were associated with the phase III, randomised, double-blind trials (ULTIMATE I and II; NCT03277261 and NCT03277248) (1) (see Appendix D). Details of the ULTIMATE trials are summarised in Table 6.

Table 6 Clinical effectiveness evidence - Ublituximab

Study	ULTIMATE I (NCT03277261)	ULTIMATE II (NCT03277248)
Study design	Phase III, multicentre, randomised, double-blind, double-dummy, active-controlled trials	
Population (key inclusion criteria)	- 18-55 years of age; - Diagnosis of RMS; - ≥two relapses in prior 2 years or one relapse in the year prior to screening and/or ≥1 Gd-enhancing lesion; - Documented MRI of brain with abnormalities consistent with MS; - Active disease; - EDSS 0-5.5 (inclusive) at screening; - B-cell counts ≥5% of total lymphocytes; - Neurologic stability ≥30 days prior to screening and baseline; - Willingness and ability to comply with trial and follow-up procedures, gave written consent.	

Study	ULTIMATE I (NCT03277261)	ULTIMATE II (NCT03277248)
Participant enrolment countries (sites)	10 countries (104 sites)	
	Belarus (4), Georgia (7), Poland (5), Russia (11), Serbia (4), Spain (3), Ukraine (10), United Kingdom (1), United States (12)	Belarus (3), Croatia (3), Poland (5), Russia (11), Spain (3), Ukraine (10), United Kingdom (2), United States (10)
Intervention(s)	Ublituximab 150mg (n = 274 assigned to receive treatment) Participants were administered ublituximab 150 milligrams (mg), IV infusion over 4 hours (h) on Day 1 followed by 450mg over 1 h on Days 15, 168, 336 and 504 (week 72) along with the oral placebo once daily (QD) from Day 1 up to the last day of week 95.	Ublituximab 150mg (n = 272 assigned to receive treatment) Participants were administered ublituximab 150 milligrams (mg), IV infusion over 4 hours (h) on Day 1 followed by 450mg over 1 h on Days 15, 168, 336 and 504 (week 72) along with the oral placebo once daily (QD) from Day 1 up to the last day of week 95.
Comparator(s)	Teriflunomide (n = 275 assigned to receive treatment) Participants were administered teriflunomide 14 mg tablet, orally, QD from Day 1 up to the last day of week 95 along with the placebo IV infusion on Days 1, 15, 168, 336 and 504 (week 72).	Teriflunomide (n = 273 assigned to receive treatment) Participants were administered teriflunomide 14 mg tablet, orally, QD from Day 1 up to the last day of week 95 along with the placebo IV infusion on Days 1, 15, 168, 336 and 504 (week 72).
Indicate if study supports application for marketing authorisation (yes/no)	Yes	Yes
Indicate if trial used in the economic model	Yes	Yes
Rationale for use/non-use in the model	Phase III, randomised controlled trial (RCT)	Phase III, RCT
Reported outcomes specified in the decision problem	• relapse rate • disability (EDSS) (assessed at baseline and used as a basis for informing disability progression outcomes) • disease progression (CDP) • symptoms of MS (such as fatigue, cognition or visual disturbance) • freedom from disease activity (for example lesions on MRI scans) • mortality • adverse effects of treatment • HRQoL	
All other reported outcomes	• Total no. of Gd-enhancing T1 lesions as detected by brain MRI at weeks 24, 48 and 96 • Total no. of new and/or enlarged T2 hyperintense lesions, detected by brain MRI at weeks 24, 48 and 96 • Total number of new T1 hypointense lesions at weeks 24, 48 and 96 • Volume of lesions • Change from baseline in MS Functional Composite (MSFC) score to week 96	

Study	ULTIMATE I (NCT03277261)	ULTIMATE II (NCT03277248)
	• % change in brain volume as detected by brain MRI from week 24 to week 96 • Proportion of patients who had no evidence of disease activity (NEDA) by week 24, 48 and 96 • Evidence of disease activity at 24 and 48 weeks • Participant who remained relapse free at 24 weeks • Time to first relapse • Disability improvement confirmed at 12 weeks, 24 weeks • Participants With impaired Symbol Digit Modalities Test (SDMT) at 24, 48 and 96 weeks • Proportion of patients with Ig levels at 48 and 96 weeks • Cell counts	
Summary of statistical analyses	• Based on the OPERA I and II studies' findings, the trial's sample size was determined by aiming for a 40% reduction in ARR with ocrelizumab (79). Based on data from the TENERE and TEMSO studies, which showed an ARR of roughly 29%, the ARR for teriflunomide was calculated (80,81). Thus, a reduction in ARR of roughly 40% in the ublituximab/oral placebo group compared to the teriflunomide/IV placebo group was anticipated as the hypothesised difference for this study. • With the exception of MRI-related analyses, the efficacy analyses were carried out in the pre-specified modified intention-to-treat (mITT) populations. These populations comprised all participants who had at least one baseline and one post-baseline efficacy assessment and had received at least one dose of a trial drug. • Every participant who took a trial medication at least once was included in the safety population. Data on safety was obtained throughout the course of the treatment and up until the final appointment with the participant. • MRI endpoints were assessed in the subgroup of participants in the mITT population. • A negative binomial regression (NBR) model was utilised to analyse the ARR, taking into account treatment differences between ublituximab and teriflunomide. The model included an offset for trial duration, clinic area, and EDSS score (baseline score of ≤3.5 or >3.5) as factors. • Every hypothesis test was carried out with a 0.05 two-sided significance threshold. Software from the SAS Institute, version 9.4, was used to perform the analyses.	
Critical appraisal of the study design	Low risk of bias, as assessed by Cochrane Collaboration risk of bias tool (82).	Low risk of bias, as assessed by Cochrane Collaboration risk of bias tool (82).

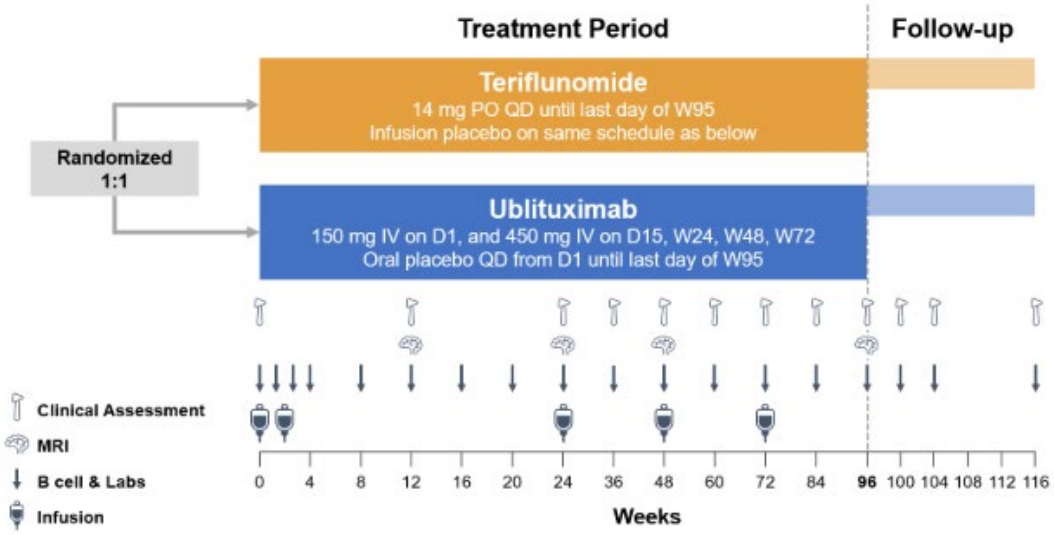
Abbreviations: ARR, annualised relapse rate; CDP, confirmed disability progression; EDSS, expanded disability status scale; Gd, gadolinium; h, hours; IV, intravenous; mITT, modified intention-to-treat; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, multiple sclerosis functional composite; NBR, negative binomial regression; NEDA, no evidence of disease activity; QD, once daily; RCT, randomised controlled trial; RMS, relapsing multiple sclerosis; SDMT, symbol digit modalities test.

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

The ULTIMATE trials were phase III, multicentre, double-blind, double-dummy, randomised, active-controlled trials conducted in parallel at non-overlapping sites. The trial was designed to evaluate the efficacy and safety of ublituximab infusions as

compared with oral teriflunomide, an inhibitor of pyrimidine synthesis, in patients with RMS. The trials were designed by the sponsor (TG Therapeutics), with guidance from an external steering committee. The sponsor analysed the data and provided both of the trial drugs and the placebos. An independent data and safety monitoring board regularly reviewed unblinded data and could advise the sponsor to stop the trial for efficacy, detrimental effects, or futility. The trial sponsor team, site investigators, and the steering committee were unaware of treatment assignments throughout the trials. A summary of the key study methodology for the ULTIMATE I and II trials is presented in Table 6, with the trial design presented in Figure 6.

Figure 6 Trial design for ULTIMATE I and II



Abbreviations: D, day; IV, intravenous; MRI, magnetic resonance imaging; PO, by mouth; QD, once daily; W, week.

The median follow-up was 95 weeks, with studies performed across 10 countries (Belarus, Georgia, Poland, Russia, Serbia, Spain, Ukraine, Spain, the UK, and the USA). Included patients were adults aged 18–55 years, with a diagnosis of RMS (meeting 2010 revised McDonald criteria) (83), at least two relapses in the previous 2 years, or one relapse or at least one Gd-enhancing lesion or both in the year before screening. Key inclusion and exclusion criteria are presented in Table 6. Patients were randomly assigned in a 1:1 ratio by means of an interactive Web-response system to receive IV ublituximab (at a dose of 150mg on day 1 for a duration of 4 hours, followed by 450mg for a duration of 1 hour on day 15 and at weeks 24, 48, and 72) in addition to oral placebo or to receive oral teriflunomide (at a

dose of 14mg QD starting on day 1 and continuing until the last day of week 95) in addition to IV placebo on the same schedule as that in the ublituximab group. On cessation of trial medication (after early termination or at week 96), participants could enter a 20-week follow-up period for monitoring of safety and relapses and to undergo teriflunomide-accelerated elimination.

The efficacy analyses, with the exception of MRI-related analyses, were performed in a pre-specified mITT population, which included all participants who received at least one dose of a trial drug and had one baseline and at least one post-baseline efficacy assessment. The safety population included all participants who received at least one dose of a trial drug. Safety data were collected during the treatment period and follow-up period until a participant's last visit. Magnetic resonance imaging endpoints were assessed in the subgroup of participants in the mITT population who had baseline and post-baseline MRI scans available.

ULTIMATE I and ULTIMATE II were identical in terms of endpoints, inclusion and exclusion criteria (Table 7), comparator, and statistical analysis plan. The primary efficacy endpoint was the ARR over a period of 96 weeks, defined as the number of confirmed relapses of MS per participant-year, according to pre-specified criteria. Each suspected relapse was adjudicated by an independent panel to confirm a protocol-defined relapse.

There were six hierarchically ordered secondary endpoints: the total number of Gd-enhancing lesions per T1-weighted MRI scan by week 96; the total number of new or enlarging hyperintense lesions per T2-weighted MRI scan by week 96; worsening of disability confirmed at 12 weeks (pooled across the two trials) (CDP-12); the number of participants with NEDA from week 24 to week 96; the number of participants who had impaired status according to the SDMT (a test for cognitive impairment that involves patients substituting a number for displayed geometric figures with the use of a key; impaired status was defined as a decrease from baseline of ≥4 points at any post-baseline assessment up to the week 96 visit); and the percentage change in brain volume from baseline to week 96.

Pre-specified tertiary endpoints, which were not included in the hierarchical analysis, were worsening of disability confirmed at 24 weeks (CDP-24) (defined as an

increase of ≥1.0 point from the baseline EDSS score if the baseline score was ≤5.5 or an increase of ≥0.5 points if the baseline score was >5.5, sustained for at least 24 weeks), pooled across trials; lessening of disability (defined as a reduction from the baseline EDSS score of ≥1.0 point, or ≥0.5 points if the baseline EDSS score was >5.5, sustained for at least 12 weeks or 24 weeks), pooled across the trials; and the change in the MSFC score (a three-part assessment of key clinical factors: leg function and ambulation, arm and hand function, and cognitive function; scores for each component are converted to standard scores [z scores], which are averaged to generate a single score). Participants also reported AEs at each visit; events were graded according to the Common Terminology Criteria for AEs, version 4.03 (84).

Table 7 Key inclusion and exclusion criteria for ULTIMATE I and ULTIMATE II

Inclusion criteria	Exclusion criteria
• 18-55 years of age. • Diagnosis of RMS. • ≥two relapses in prior 2 years or one relapse in the year prior to screening and/or ≥1 Gd-enhancing lesion. • Documented MRI of brain with abnormalities consistent with MS. • Active disease. • EDSS 0-5.5 (inclusive) at screening. • B-cell counts ≥5% of total lymphocytes; Neurologic stability ≥30 days prior to screening and baseline. • Female participants who were not of child-bearing potential, had documented surgical sterilisation, and female participants of child-bearing potential who had a negative serum pregnancy test at baseline. • Female participants of child-bearing potential and all male partners must have consented to use a medically/clinically acceptable method of contraception throughout the treatment period and for 20 weeks after the cessation of active treatment. Female participants of child-bearing potential must have agreed to undertake urine pregnancy tests every 4 weeks during active treatment and the follow-up period. • Fertile male participants participating in the study who were sexually active with women of child-bearing potential, must have agreed to use a condom during the treatment period and for an additional 20 weeks after cessation of active treatment. Agreed	• Exclusion related to medication • Treatment with anti-CD20 or other B-cell directed treatment. • Treatment with the following therapies at any time prior to randomisation: • Alemtuzumab • Natalizumab • Teriflunomide • Leflunomide • Stem cell transplantation • Contraindications to teriflunomide or incompatibility with use of teriflunomide. • Therapies that were disallowed (minimum of 4 weeks prior to randomisation): phenytoin, warfarin, tolbutamide, St John's Wort or cholestyramine. • Prior DMT exposure within months of screening. • Exclusion related to general health • Diagnosed with PPMS. • Pregnant or nursing. • ≥10 years disease duration from onset with participants EDSS ≤2.0. • Contraindication for MRI and/or Gd. • Known presence of other neurologic disorders that may mimic MS. • Evidence or known history of clinically significant infection. • History of clinically significant CNS trauma. • History of liver disease. • Previous diagnosis with a congenital or acquired immunodeficiency (AIDS). • Participants with significantly impaired bone marrow function or significant anaemia, leukopaenia, or thrombocytopaenia. • Past or history of medically significant AEs (including allergic reactions) at the time of randomisation from Corticosteroids,

to use an accelerated elimination procedure after the last dose of study medications or early termination from the study. • Willingness and ability to comply with trial and follow-up procedures, and gave written consent.	Diphenhydramine and Murine or mouse/human chimeric antibodies. • Absolute lymphocyte counts less than 1,000/microlitre. • Any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study. • Other significant concurrent, uncontrolled medical condition including, but not limited to, cardiac, renal, hepatic, haematological, gastrointestinal, endocrine, immunodeficiency syndrome, pulmonary, cerebral, psychiatric, or neurological disease which could have affected the participant's safety, impaired the participant's reliable participation in the trial, impaired the evaluation of endpoints, or necessitated the use of medication not allowed by the protocol, as determined by the principal investigator of the trial. • Participation in any other interventional clinical trial. Participation in non-interventional trial required approval by the Sponsor. • Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol. • Lack of immunity to varicella as determined by screening based on the level of VZV IgG. Participant could receive vaccine and be re-screened. • Vaccination with live virus within 2 months of randomisation. • 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.

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency; CNS, central nervous system; DMT, disease-modifying therapy; EDSS, expanded disability status scale; Gd, gadolinium; MRI, magnetic resonance imaging; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

In total, 549 and 545 patients underwent randomisation in the ULTIMATE I and ULTIMATE II trials, respectively. The baseline demographic and disease characteristics of the mITT population were similar between ULTIMATE I and ULTIMATE II (Table 8).

Table 8 Baseline characteristics and disease characteristics in ULTIMATE I and II

Characteristics	ULTIMATE I		ULTIMATE II	
	Ublituximab (n = 271)	**Teriflunomide (n = 274)**	**Ublituximab (n = 272)**	**Teriflunomide (n = 272)**
Mean age, years (SD)	36.2±8.2	37.0±9.6	34.5±8.8	36.2±9.0
Female, n (%)	166 (61.3)	179 (65.3)	178 (65.4)	176 (64.7)
Race, n (%)*				
Black	264 (97.4)	266 (97.1)	269 (98.9)	268 (98.5)
White	6 (2.2)	6 (2.2)	2 (0.7)	3 (1.1)

Others	1 (0.4)	2 (0.7)	1 (0.4)	1 (0.4)
Type of multiple sclerosis, no. (%):				
RRMS	264 (97.4)	270 (98.5)	268 (98.5)	267 (98.2)
SPMS	7 (2.6)	4 (1.5)	4 (1.5)	5 (1.8)
Time since symptom onset-year, mean ± SD	7.5±6.5	6.8±5.9	7.3±6.5	7.4±6.3
Time since diagnosis-year, mean ± SD	4.9±5.2	4.5±5.0	5.0±5.6	5.0±5.2
No previous disease-modifying therapy — no. (%)§	162 (59.8)	162 (59.1)	138 (50.7)	155 (57.0)
Previous disease-modifying therapy - no. (%)				
Interferon«	52 (19.2)	49 (17.9)	71 (26.1)	58 (21.3)
Glatiramer acetate	45 (16.6)	36 (13.1)	40 (14.7)	34 (12.5)
Laquinimod	19 (7.0)	22 (8.0)	29 (10.7)	30 (11.0)
Dimethyl fumarate	8 (3.0)	7 (2.6)	4 (1.5)	1 (0.4)
Fingolimod	5 (1.8)	2 (0.7)	2 (0.7)	3 (1.1)
Other	7 (2.6)	17 (6.2)	17 (6.2)	18 (6.6)
No. of relapses in previous 12 month, mean ± SD	1.3±0.6	1.4±0.7	1.3±0.6	1.2±0.6
No. of relapses in previous 24 month, mean ± SD	1.8±1.0	2.0±1.1	1.8±0.9	1.8±0.9
EDSS score at screening, mean ± SD¥	3.0±1.2	2.9±1.2	2.8±1.3	3.0±1.2
Volume of lesions on T2-weighted MRI — cm^3, mean ± SD¶	15.9±16.0	14.9±15.8	14.7±13.5	15.7±17.5
No. of T2 lesions, mean ± SD¶	64.1±38.6	60.4±37.0	65.3±41.2	64.0±41.2
Absence of Gd-enhancing lesions on T1-weighted MRI scan — no./total no. (%)¶	153/270 (56.7)	156/272 (57.4)	131/272 (48.2)	135/270 (50.0)
No. of Gd-enhancing lesions at baseline, mean ± SD¶	2.3±5.5	1.6±3.7	2.6±5.8	2.5±5.5

Abbreviations: EDSS, expanded disability status scale; Gd, gadolinium; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

* Race was reported by the participants.

§ No previous disease-modifying therapy was defined as no disease-modifying therapy in the 5 years before trial entry.

« Interferon therapies include interferon beta, interferon beta-1a, and interferon beta-1b.

¥ Scores on the EDSS range from 0 to 10.0, with higher scores indicating greater disability.

¶ Data were missing for 1 participant in the ublituximab group and 2 participants in the teriflunomide group in the ULTIMATE I trial and for 2 participants in the teriflunomide group in the ULTIMATE II trial.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The sample size for the trials was based on achieving a 40% reduction in ARR with ocrelizumab (another anti-CD20 mAb) based on the results of the OPERA I and II studies (79). The ARR for teriflunomide was based on the results from the TENERE and TEMSO trials, which reported an ARR of approximately 29% (80,81). Thus, the hypothesised difference for this trial was expected to be a reduction in ARR of approximately 40% in the ublituximab/oral placebo group as compared to teriflunomide/IV placebo. In the TEMSO study (80), the ARR was 0.319 and to allow for some drift to lower rates and some level of conservative estimates, it was hypothesised that the teriflunomide/oral placebo ARR would be approximately 0.29 yielding an ARR for ublituximab/placebo of 0.174 requiring 200 participants per group. Thus, using a two-sided test of the null hypothesis H0: rate ratio (RR) = 1.00 vs the alternative Ha: RR ≠ 1.00 using the Maximum Likelihood Estimate test statistic in a NBR model, samples of 220 participants in the teriflunomide/oral placebo group with an average exposure time of 1.75 years and 220 participants in the ublituximab/placebo group with an average exposure time of 1.75 years achieved 80% power to detect an event RR of 0.60 when the event rate in the teriflunomide/oral placebo Group (λ1) was 0.29 and the overall Type I error level (alpha) was 0.05 assuming a NBR distribution for the number of relapses in participants over the 100 weeks of follow-up. To allow for potential losses of up to 10%, this required sample size was increased to 220 per group or a total randomised of 440.

An independent committee, the Blinded Assessment Relapse Team, reassessed the sample size for the study when 210 of the 220 participants had been randomised. Assuming a uniform rate of recruitment over 8 to 10 months, the average duration of study drug exposure when 210 participants per group were recruited was estimated as 4.5 months, yielding approximately 4.5 x 210 = 945 person months or approximately 43 person years of observation (the denominator to compute the ARR). The sample sizes needed per group per study, based on the ARR findings at the interim assessment, were calculated assuming a 40% lower ARR for ublituximab versus teriflunomide.

The safety population included all participants who received at least one dose of study drug (ublituximab or teriflunomide, with corresponding placebos). All safety assessments including toxicity were performed on the safety population by treatment actually received. The ITT population consisted of all randomised participants. Participants were analysed by randomised treatment group. Analyses of key efficacy endpoints based on ITT population served as sensitivity analyses. The mITT population consisted of all participants 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 performed based on the mITT population. The MRI analyses were based on the subset of participants in the mITT population who had one baseline and post-baseline MRI efficacy assessment (mITT-MRI). Participants were analysed by randomised treatment group.

Efficacy Analyses

The primary efficacy endpoint was tested at a two-sided Type I error of 5%. If the null hypothesis on the primary efficacy endpoint was rejected, the null hypotheses on the secondary efficacy endpoints were tested. The key secondary outcomes were tested using a hierarchical approach with the order specified using a step-down procedure where each test was a Type1 error 0.05.

Primary Endpoint – Analysis of Annualised Relapse Rate

The primary efficacy variable was ARR, defined as the number of relapses (protocol-defined and confirmed by Independent Relapse Adjudication Panel (IRAP)) per participant-year (a year is equal to 365.25 days). The ARR (primary endpoint) data were analysed using the mITT with a NBR model to accommodate the potential over-dispersed data appropriately. The model included the total number of confirmed relapses with onset between randomisation date and the day of last study treatment as response variable, treatment group, EDSS strata (baseline EDSS score ≤3.5 versus >3.5) and clinic region as covariates. Relapses that occurred after study drugs were withdrawn were assessed over the remainder of the study period and these data were utilised as part of additional sensitivity analysis as long as the participant did not withdraw their consent to be in the trial.

The treatment group had two levels (teriflunomide/IV placebo or ublituximab/oral placebo). In order to account for different treatment durations among participants, the log-transformed standardised treatment duration (randomisation to date last treatment before early withdrawal or completion of week 96 assessment) were included in the model as an "offset" variable for appropriate computation of the ARR. SAS PROC GENMOD was used to assess the overall model with participants in a repeated statement using a Generalised Estimating Equation (GEE) approach. Two-sided 95% confidence intervals (CIs) of the RR were provided for the comparisons of ublituximab/oral placebo versus teriflunomide/IV placebo. The estimated relapse rate and its two-sided 95% CIs were provided for each treatment group.

Secondary Endpoints

The key secondary outcomes were tested using a hierarchical approach with the order specified below using a step-down procedure where each test was at a Type I error 0.05. If any endpoints failed to reach significance, then formal testing of significance of the subsequent secondary outcomes were not performed.

1. Total number of Gd-enhancing T1-lesions per MRI scan by week 96.
2. Total number of new and enlarging T2 hyperintense lesions per MRI scan by week 96.
3. Time to CDP for at least 12 weeks occurring during the 96-week, double-blind treatment period.*
4. Proportion of participants with NEDA from week 24 to week 96.
5. Proportion of participants reaching impaired SDMT from baseline to week 96.
6. Percentage change in Brain Volume from baseline to week 96.

*CDP for at least 12 weeks during the 96-week treatment period was analysed using pooled data from the two identical ULTIMATE studies.

The total number of Gd-enhancing T1-lesions was calculated as the sum of the individual number of lesions at weeks 12, 24, 48, and 96, divided by the total number of MRI scans of the brain. The total number of new and enlarging T2 hyperintense lesions was calculated as the sum of the individual number of lesions at weeks 24, 48, and 96, divided by the total number of MRI scans of the brain. The MRI count variables were assessed for differences between the treatment groups using NBR with an offset based on time on study and covariates, region, baseline EDSS strata,

and baseline MRI counts. Percent brain volume change was assessed between the two groups using linear mixed effects models (PROC MIXED in SAS) with covariates of region, baseline EDSS strata, and baseline brain volume.

Disability progression was defined as an increase of ≥1.0 point from the baseline EDSS score that was not attributable to another aetiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score was 5.5 or less, and ≥0.5 when the baseline score was above 5.5. Disability progression was considered confirmed when the increase in the EDSS score was confirmed at regularly scheduled visits at least 12 or 24 weeks after the initial documentation of neurological worsening. Note that CDP for at least 12 weeks during the 96-week treatment period was analysed using pooled data from the two identical ULTIMATE studies. With the exception of this endpoint (CDP), which was analysed at the pooled level, all other secondary efficacy endpoints were tested if and only if the individual study secondary endpoint listed ahead of it reached the significance level at 0.05.

All pre-specified pooled analyses are listed below. However, only CDP for at least 12 weeks was part of the secondary analysis and the remainder were included in the tertiary analysis.

1. Time to CDP for at least 12 weeks (secondary analysis).
2. Time to CDP for at least 24 weeks (tertiary analysis).
3. Time to Confirmed Disability Improvement (CDI) for at least 12 weeks (tertiary analysis).
4. Time to CDI for at least 24 weeks (tertiary analysis).

Progression to CDP results present the proportion who achieved CDP at week 96 and associated 95% CIs for each treatment group. The median time-to-event with two-sided 95% CIs as well as the proportion of participants remaining event-free at times of interest were estimated using Kaplan-Meier methods implemented with PROC LIFETEST in SAS. All time to CDP (and CDI) endpoints were analysed similarly.

The proportion of participants with NEDA was calculated at week 96. A participant with NEDA was defined as a participant without relapses confirmed by the IRAP, without MRI activities (no T1 Gd+ lesions and no new/enlarging T2 lesions), and no

12-week CDP. Any evidence of disease activity including week 24 to week 96 was counted as not reaching NEDA. Any evidence of disease activity before week 24 did not count. No Evidence of Disease Activity rates were compared using logistic regression (Proc GENMOD in SAS) with baseline adjustments the same as used in the primary analysis plus baseline MRI counts and without an offset to take into account time on study.

Change in cognition (SDMT) was assessed using the total score at each SDMT visit which was defined as the total number of correct answers reported in the case report form (CRF). Impaired SDMT was defined as a decrease from baseline of at least 4 points at any post-baseline assessment up to the week 96 visit. The proportion of impaired SDMT was analysed in all participants in the mITT population. Symbol Digit Modalities Test rates were compared using logistic regression (Proc GENMOD in SAS) with baseline adjustments the same as used in the primary endpoint analysis, without treatment duration offset, but including log-transformed baseline MRI counts (T1 unenhancing, T2, Gd-enhancing). To avoid zero values for the log transformation of MRI counts, 1 was added to each observation before transforming.

Tertiary Endpoints and Other Variables

All tertiary analyses were assessed at a Type I error of 0.05 with no adjustment for multiplicity.

1. Change in MSFC score from baseline to Week 96.
2. Time to CDP for at least 24 weeks.
3. Time to CDI for at least 12 weeks.
4. Time to CDI for at least 24 weeks.
5. Health outcomes (Multiple Sclerosis Quality-of-Life-54 (MSQoL-54) (inclusive of Short Form-36 (SF-36)); Fatigue Impact Scale (FIS), hospitalisation, steroid use, time out of work).
6. Total volume of Gd-enhancing T1 lesions per MRI scan over the treatment period.
7. Volume of T2 lesions.
8. Volume of hypointense T1 lesion component (black holes).
9. Proportion of participants free of disability progression at weeks 24, 48 and 96.
10. Proportion of participants with a relapse.

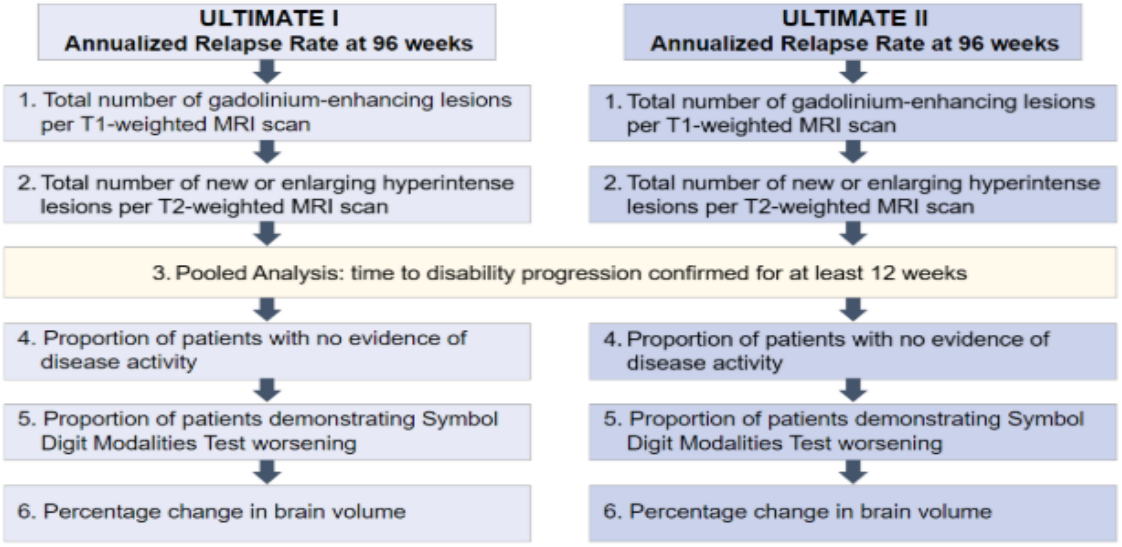
11. Time to first confirmed relapse.
Change in MSFC and Health Outcomes (MSQoL-54 (inclusive of SF36), FIS), were analysed using linear Mixed Models, including results with baseline as a covariate along with region and other covariates if used in the primary analyses.

The analysis of CDI at 12 and 24 weeks utilised the same approach as that used for CDP. 12-week CDI was defined as a reduction from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained and confirmed at the next scheduled visit at least 12 weeks after the initial documentation of neurological improvement. Similarly, 24-week CDI required an initial reduction from baseline EDSS score and a subsequent confirmation of the reduction at all regular scheduled visits for at least 24 weeks after the initial documentation of neurological worsening. Hospitalisation, Steroid Use, and Time Out of Work were summarised by descriptive statistics as well as frequency and percentage. For Time Out of Work, percentages of missed work hours were compared between arms using Wilcoxon rank sum tests. For Steroid Use, the number of IRAP-confirmed relapses treated with steroid were analysed the same way as the primary endpoint.

For analysis of lesion volume-related variables (Total volume of Gd-enhancing T1 lesions per MRI scan over the treatment period, Volume of T2 lesions, Volume of hypointense T1 lesion component (black holes)), Mixed Model Repeated Measures (MMRM) analyses were implemented via PROC MIXED in SAS. Time to first confirmed relapse was defined as (date of relapse onset – date of randomisation + 1) and was regarded as censored at the end of treatment. The analysis was similar to the one of time to CDP. The proportions of participants with a relapse and participants free of disability progression at different time points were estimated using the Kaplan-Meier method. Finally, safety assessments were based on the incidence, intensity, and type of AEs, as well as on clinical laboratory results, physical examination, and vital sign measures.

The statistical testing sequence is illustrated in Figure 7 below.

Figure 7 Statistical testing sequence for ULTIMATE I and II



Abbreviations: MRI, magnetic resonance imaging.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

Critical appraisal of the included RCTs was performed using established risk of bias (RoB) tools recommended for health technology assessment (HTA) submissions (82). The primary publications of clinical studies meeting the criteria for inclusion were assessed by reviewers using an appropriate, and validated, quality assessment instrument, with any disagreements resolved by discussion or following the input of a third reviewer. The complete quality assessment is presented in Appendix D.

B.3.6 Clinical effectiveness results of the relevant studies

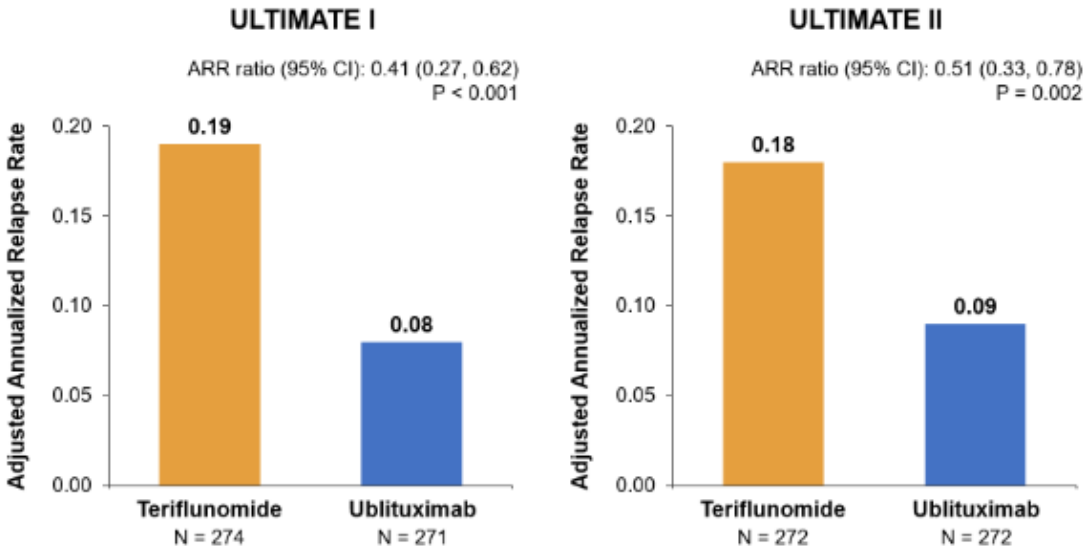
The data discussed in this section have been taken from the primary analysis for ULTIMATE I and ULTIMATE II (1), in which a total of 549 and 545 patients were randomised, respectively. Further details on all outcomes are presented in Appendix D.

Primary endpoint: ARR at 96 weeks in ULTIMATE I and II

Over a 96-week period in the ULTIMATE I trial, the adjusted ARR was 0.08 in the ublituximab group and 0.19 in the teriflunomide group (RR: 0.41; 95% CI: 0.27 to

0.62; p<0.001). In the ULTIMATE II trial, the corresponding rates were 0.09 and 0.18 (RR: 0.51; 95% CI: 0.33 to 0.78; p = 0.002). Results are presented in Figure 8.

Figure 8 ARR over 96 weeks results in ULTIMATE I and II



Abbreviations: ARR, annualised relapse rate; CI, confidence interval.

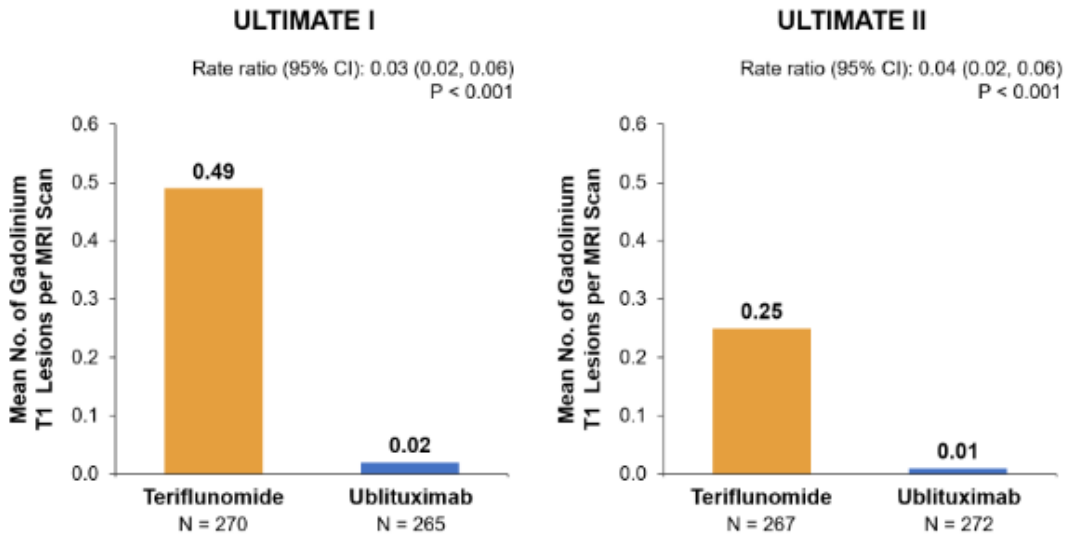
Secondary endpoints: MRI-related endpoints in ULTIMATE I and II

In the ULTIMATE I trial, 265 participants in the ublituximab group and 270 participants in the teriflunomide group underwent imaging assessments; in the ULTIMATE II trial, 272 participants and 267 participants, respectively, underwent imaging assessments. In the ULTIMATE I trial, the mean total number of Gd-enhancing lesions per T1-weighted MRI scan was 0.02 in the ublituximab group and 0.49 in the teriflunomide group (RR, 0.03; 95% CI, 0.02 to 0.06; p<0.001); in the ULTIMATE II trial, the corresponding numbers were 0.01 and 0.25 (RR, 0.04; 95% CI, 0.02 to 0.06; p<0.001).

In the ULTIMATE I trial, the mean total number of new or enlarging hyperintense lesions per T2-weighted MRI scan was 0.21 in the ublituximab group and 2.79 in the teriflunomide group (RR, 0.08; 95% CI, 0.06 to 0.10; p<0.001); in the ULTIMATE II trial, the corresponding numbers were 0.28 and 2.83 (RR, 0.10; 95% CI, 0.07 to 0.14; p<0.001). The percent change in brain volume was not considered to be significantly different between groups because of the failure of the preceding clinical endpoint in the hierarchical analysis (worsening of disability at 12 weeks), and because the 95% CIs for the between-group differences included zero in the

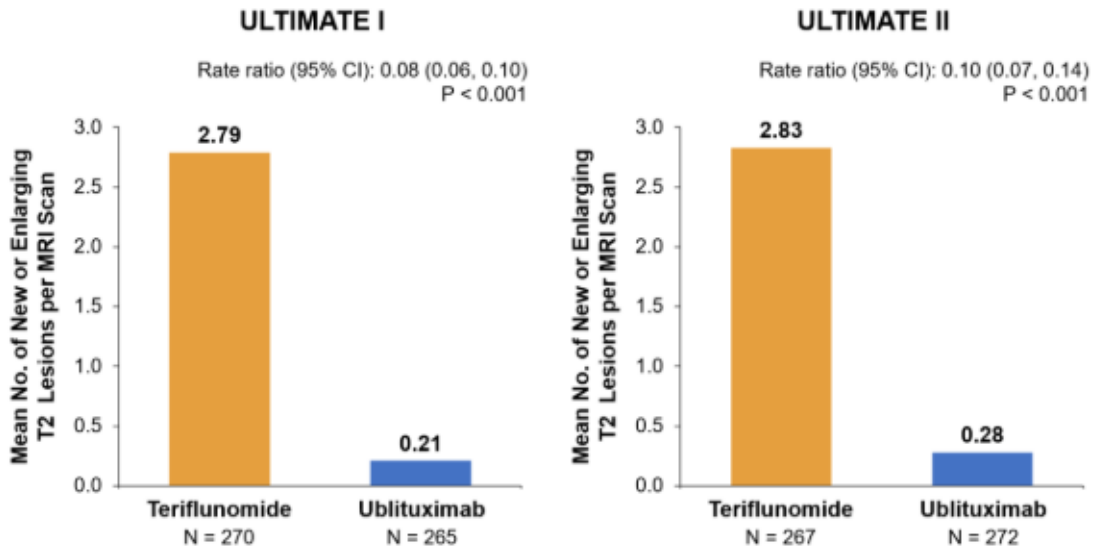
ULTIMATE II trial (but not in the ULTIMATE I trial). Results for the MRI-related endpoints are presented in Figure 9 and Figure 10.

Figure 9 Gd-enhancing lesion per T1-weighted MRI scan by week 96 results in ULTIMATE I and II



Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging.

Figure 10 New or enlarging hyperintense lesions per T2-weighted MRI scan by week 96 results in ULTIMATE I and II

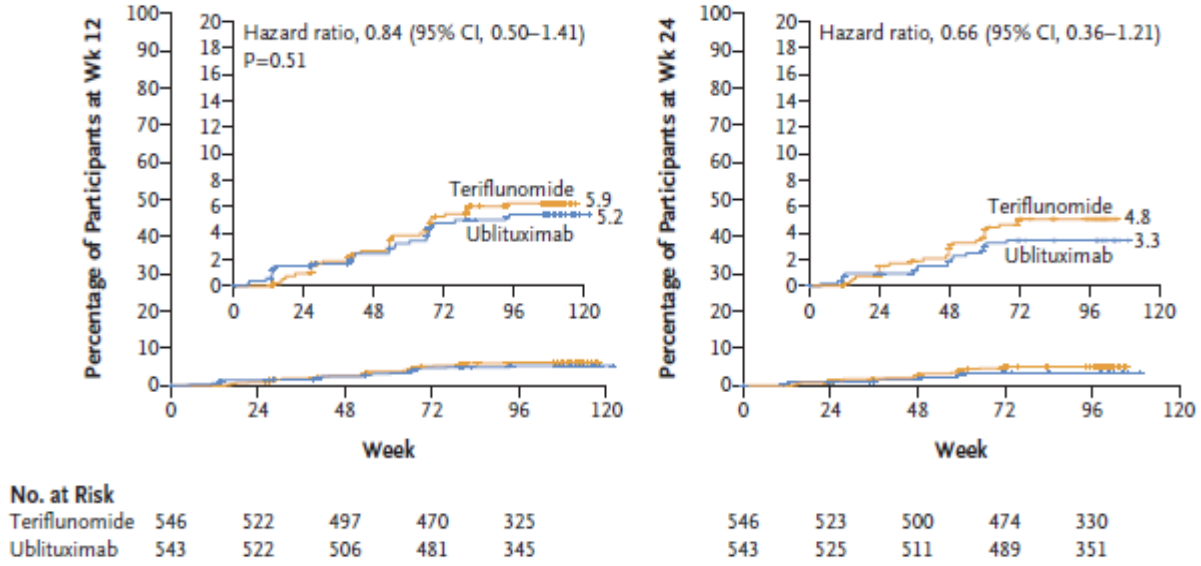


Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging.

Secondary and tertiary endpoints: Pooled analysis CDP-12 and CDP-24

In the pre-specified pooled analysis, 5.2% of the participants in the ublituximab group had worsening of disability confirmed at 12 weeks (defined as an increase of 1.0 or more points in the EDSS score if the baseline score was 5.5 or lower, or an increase of 0.5 or more points if the baseline score was greater than 5.5, sustained for at least 12 weeks), as compared with 5.9% of the participants in the teriflunomide group (HR, 0.84; 95% CI, 0.50 to 1.41; p = 0.51); 3.3% of the participants in the ublituximab group had worsening of disability confirmed at 24 weeks (defined as an increase of 1.0 or more points in the EDSS score if the baseline score was 5.5 or lower, or an increase of 0.5 or more points if the baseline score was greater than 5.5, sustained for at least 24 weeks), as compared with 4.8% of the participants in the teriflunomide group (HR, 0.66; 95% CI, 0.36 to 1.21). These results were not considered to be significantly different between trial groups because of the failure of the hierarchical analysis. Results of these analyses are presented in Figure 11.

Figure 11 CDP-12 and CDP-24 results in ULTIMATE I and II



Abbreviations: CDP-12, confirmed disability progression at 12 weeks; CDP-24, confirmed disability progression at 24 weeks; CI, confidence interval.

Multiple Sclerosis Quality of Life 54 (MSQOL-54) results from ULTIMATE I and II

The RCTs gathered QoL data using the MSQOL-54 (including the SF-36) questionnaire at several points: day 1 (before dosing), week 24 (pre-dose), week 48 (pre-dose), and week 96 or upon treatment discontinuation. The MSQOL-54 and the SF-36 are widely recognised instruments for assessing HRQoL. The MSQOL-54 comprises 54 items covering 12 scales such as physical health, emotional well-being, pain, and social function, alongside two single-item measures for satisfaction with sexual function and overall QoL. Conversely, the SF-36 is a generic tool applicable to the general population, featuring 36 items that evaluate eight health domains, including physical functioning, pain, and general health perceptions. These instruments provide a comprehensive view of how a new treatment can improve the QoL of patients with MS. The table below (Table 9) compares the efficacy of ublituximab vs teriflunomide across various MSQOL-54 components, based on data from ULTIMATE I and II. For the MSQOL-54 analysis, key findings are as follows:

Cognitive Function: Ublituximab showed a minor increase in cognitive function compared to teriflunomide, with a difference of 1.402 (p = 0 .152), although this was not statistically significant.

Change in Health: Ublituximab significantly improved the perception of health change (mean change: 17.170) compared to teriflunomide (mean change: 12.353), with a difference of 4.817 (p = 0.001).

Energy: Patients on ublituximab reported a significant increase in energy levels (mean change: 2.149) compared to those on teriflunomide (mean change: 0.109), with a difference of 2.040 (p = 0.043).

Emotional Well-being: Improvement in emotional well-being was slightly higher in the ublituximab group (mean change: 3.455) compared to teriflunomide (mean change: 2.251), although not statistically significant (p = 0.220).

Health Distress: Ublituximab showed a trend towards reducing health distress more than teriflunomide, with a mean difference of 2.236 (p = 0.070).

Mental Health Composite Score: Ublituximab significantly improved the mental health composite score (mean change: 2.814) compared to teriflunomide (mean change: 0.529), with a difference of 2.285 (p = 0.020).

Physical Health Composite Score: Ublituximab also significantly improved the physical health composite score (mean change: 1.928) compared to teriflunomide (mean change: -0.687), with a difference of 2.614 (p = 0.002).

Overall Quality of Life: There was a slight improvement in overall quality of life with ublituximab (mean change: 1.668) compared to teriflunomide (-0.103), with a difference of 1.771 (p = 0.050).

Pain: Both treatments resulted in a reduction of pain, but the difference between them was not significant (p = 0.513).

Physical Health: Ublituximab showed a significant improvement in physical health (mean change: 2.019) compared to teriflunomide (-1.469), with a difference of 3.487 (p = 0.001).

Role Limitations Due to Emotional Problems: There was no significant difference between the treatments (p = 0.120).

Role Limitations Due to Physical Problems: Ublituximab showed significant improvement (mean change: 3.687) compared to teriflunomide (-1.691), with a difference of 5.379 (p = 0.014).

Satisfaction with Sexual Function: Both treatments showed a decrease in satisfaction with sexual function, with no significant difference between them (p = 0.847).
Social Function: There was a slight improvement in social function with ublituximab (mean change: 0.268) compared to teriflunomide (-1.065), although not statistically significant (p = 0.205).
Sexual Function: Both treatments resulted in a reduction of sexual function, with no significant difference between them (p = 0.504).

Overall, ublituximab demonstrated significant improvements in several MSQOL-54 endpoints, particularly in change in health, energy, mental health composite score, physical health composite score, and physical health, compared to teriflunomide.

Table 9 Multiple Sclerosis Quality of Life 54 [MSQOL-54] results from ULTIMATE I and II

Endpoints	UBLITUXIMAB				TERIFLUNOMIDE				UBLITUXIMAB vs. TERIFLUNOMIDE		
	N	N valid	Baseline mean (SD)	Change from Baseline [95 % CI]	N	N valid	Baseline mean (SD)	Change from Baseline [95 % CI]	Diff-in-Diff [95% CI]	p-value	SMD [95% CI]
MSQOL-54 Cognitive function	543	539	72.532 (21.009)	0.451 [-1.380 ; 2.281]	546	541	74.362 (21.844)	-0.952 [-2.770 ; 0.867]	1.402 [-0.519 ; 3.323]	0.152	0.044 [-0.076 ; 0.163]
MSQOL-54 Change in health	543	539	39.007 (25.295)	17.170 [14.319 ; 20.021]	546	541	39.695 (24.511)	12.353 [9.522 ; 15.184]	4.817 [1.913 ; 7.722]	0.001	0.099 [-0.020 ; 0.219]
MSQOL-54 Energy	543	539	50.111 (19.629)	2.149 [0.271 ; 4.026]	546	542	52.496 (21.230)	0.109 [-1.745 ; 1.964]	2.040 [0.066 ; 4.013]	0.043	0.062 [-0.058 ; 0.181]
MSQOL-54 Emotional well-being	543	539	61.978 (18.644)	3.455 [1.661 ; 5.249]	546	542	64.052 (19.246)	2.251 [0.461 ; 4.041]	1.204 [-0.719 ; 3.127]	0.22	0.037 [-0.082 ; 0.157]
MSQOL-54 Health distress	543	539	59.341 (24.143)	4.393 [2.149 ; 6.637]	546	541	61.645 (25.234)	2.158 [-0.073 ; 4.388]	2.236 [-0.181 ; 4.652]	0.07	0.055 [-0.064 ; 0.175]
MSQOL-54 Health Perceptions	543	540	50.000 (18.173)	0.694 [-1.125 ; 2.514]	546	542	51.236 (19.279)	-0.420 [-2.232 ; 1.391]	1.115 [-0.818 ; 3.048]	0.258	0.034 [-0.085 ; 0.154]
MSQOL-54 Mental Health Composite Score	543	539	63.168 (19.421)	2.814 [0.987 ; 4.641]	546	541	65.311 (19.944)	0.529 [-1.292 ; 2.349]	2.285 [0.354 ; 4.217]	0.02	0.071 [-0.049 ; 0.190]
MSQOL-54 Physical Health Composite Score	543	525	61.585 (18.035)	1.928 [0.353 ; 3.502]	546	525	63.563 (18.663)	-0.687 [-2.247 ; 0.874]	2.614 [0.939 ; 4.289]	0.002	0.095 [-0.026 ; 0.216]
MSQOL-54 Overall quality of life	543	539	62.684 (17.346)	1.668 [-0.004 ; 3.340]	546	542	64.924 (17.758)	-0.103 [-1.765 ; 1.560]	1.771 [0.002 ; 3.540]	0.05	0.060 [-0.059 ; 0.179]
MSQOL-54 Pain	543	539	74.242 (22.396)	-2.597 [-4.740 ; -0.454]	546	542	76.571 (23.953)	-3.347 [-5.467 ; -1.227]	0.749 [-1.497 ; 2.996]	0.513	0.020 [-0.099 ; 0.139]
MSQOL-54 Physical Health	543	539	68.066 (26.045)	2.019 [-0.032 ; 4.069]	546	542	70.231 (25.919)	-1.469 [-3.498 ; 0.561]	3.487 [1.358 ; 5.617]	0.001	0.098 [-0.021 ; 0.217]

MSQOL-54 Role limitations due to emotional problems	543	539	61.348 (41.260)	2.380 [-1.756 ; 6.516]	546	542	63.715 (40.831)	-1.099 [-5.213 ; 3.016]	3.478 [-0.907 ; 7.863]	0.12	0.047 [-0.072 ; 0.167]
MSQOL-54 Role limitations due to physical problems	543	539	48.748 (41.432)	3.687 [-0.297 ; 7.672]	546	542	52.214 (41.150)	-1.691 [-5.646 ; 2.263]	5.379 [1.114 ; 9.644]	0.014	0.075 [-0.044 ; 0.195]
MSQOL-54 Satisfaction with sexual function	543	523	66.348 (29.773)	-3.491 [-6.646 ; -0.335]	546	526	66.540 (30.740)	-3.161 [-6.300 ; -0.022]	-0.330 [-3.689 ; 3.029]	0.847	-0.006 [-0.127 ; 0.115]
MSQOL-54 Social function	543	539	72.658 (20.825)	0.268 [-1.685 ; 2.222]	546	542	74.485 (21.084)	-1.065 [-3.004 ; 0.873]	1.334 [-0.727 ; 3.395]	0.205	0.039 [-0.081 ; 0.158]
MSQOL-54 Sexual function	543	525	79.592 (24.018)	-4.055 [-6.469 ; -1.641]	546	526	79.640 (25.363)	-4.930 [-7.335 ; -2.525]	0.875 [-1.691 ; 3.441]	0.504	0.021 [-0.100 ; 0.142]

Abbreviations: CI, confidence interval; N, randomised patients; N valid, number of patients; SD, standard deviation; SMD, standardised mean difference; NA, not available/not reached/not estimable; p-value, t-test.

Model: MMRM (Mixed Model Repeated Measures) of the change from baseline at all post-baseline time points. The model includes treatment, region, baseline EDSS strata, visit, treatment-by-visit interaction, and baseline value as covariates and uses an unstructured covariance matrix, restricted maximum likelihood estimation and the Satterthwaite method for degrees of freedom.

SF-36 results from ULTIMATE I and II

Change from baseline in SF-36 for all post-baseline timepoints is shown in Table 10. Statistically significant improvements favouring ublituximab vs teriflunomide were seen in physical component summary, physical functioning, and role-physical. When evaluating the change from baseline in SF-36 at week 96 only, improvements were seen for ublituximab vs teriflunomide for all components.

Table 10 SF-36 results from ULTIMATE I and II

Component	Teriflunomide (n = 546)	Ublituximab (n = 543)	p-value
Physical Component Summary	-1.0	0.1	0.01
Mental Component Summary	1.0	1.6	0.28
Bodily Pain	-1.5	-1.1	0.43
General Health	-0.1	0.4	0.23
Mental Health	1.3	2.0	0.22
Physical Functioning	-0.6	0.8	0.001
Role-Emotional	-0.3	0.8	0.12
Role-Physical	-0.5	1.0	0.01
Social Functioning	0.2	0.6	0.42
Vitality	0.3	1.2	0.06

Summary of primary, secondary, and tertiary efficacy endpoints at week 96 in ULTIMATE I and ULTIMATE II

Table 11 Clinical Results from ULTIMATE I, ULTIMATE II, and the Pooled Analysis

Endpoint at 96 weeks (mITT population and pre-specified pooled analyses)#	ULTIMATE I			ULTIMATE II			ULTIMATE I and II		
	Ublituximab (n = 271)	Teriflunomide (n = 274)	p-value	Ublituximab (n = 272)	Teriflunomide (n = 272)	p-value	Ublituximab (n = 543)	Teriflunomide (n = 546)	p-value
Primary endpoint: Relapse rate									
Adjusted ARR (95% CI)	0.08 (0.04 to 0.14)	0.19 (0.12 to 0.28)		0.09 (0.05 to 0.17)	0.18 (0.11 to 0.29)		-	-	
Rate ratio (95% CI)	0.41 (0.27 to 0.62)		<0.001	0.51 (0.33 to 0.78)		0.002	-		-
Secondary endpoints: MRI-related endpoints¶									
Gd-enhancing lesions per T1-weighted MRI scan, per scan per participant*									
Mean (95% CI)	0.02 (0.01 to 0.03)	0.49 (0.35 to 0.68)		0.01 (0.00 to 0.02)	0.25 (0.16 to 0.39)		-	-	
Rate ratio (95% CI)	0.03 (0.02 to 0.06)		<0.001	0.04 (0.02 to 0.06)		<0.001	-		-
New or enlarging hyperintense lesions per T2-weighted MRI scan by week 96§									
Mean (95% CI)	0.21 (0.14 to 0.32)	2.79 (2.14 to 3.64)		0.28 (0.20 to 0.40)	2.83 (2.13 to 3.77)		-	-	
Rate ratio (95% CI)	0.08 (0.06 to 0.10)		<0.001	0.10 (0.07 to 0.14)		<0.001	-		-
Percent change in brain volume from baseline to week 96¥									
Least-squares mean (95% CI)	−0.20 (−0.23 to −0.17)	−0.13 (−0.16 to −0.10)		−0.19 (−0.23 to −0.16)	−0.18 (−0.21 to −0.15)		-	-	
Difference	−0.07 (−0.11 to −0.04)		-	−0.02 (−0.05 to 0.02)		-	-		-
Secondary endpoints: Disability-related endpoints									
NEDA, week 24 to week 96**									
No. of participants (%)	121 (44.6)	41 (15.0)		117 (43.0)	31 (11.4)		-	-	
Odds ratio (95% CI)	5.44 (3.54 to 8.38)		-	7.95 (4.92 to 12.84)		-	-		-
Worsening on SDMT from baseline to week 96									
No. of participants (%)	79 (29.2)	87 (31.8)		79 (29.0)	86 (31.6)		-	-	
Odds ratio (95% CI)	0.87 (0.60 to 1.26)		-	0.86 (0.60 to 1.25)		-	-		-
Secondary endpoints: Pooled Analysis results									

Worsening of disability confirmed at 12 weeks¦									
No. of participants (%)	-	-		-	-		28 (5.2)	32 (5.9)	
Hazard ratio (95% CI)	-		-	-		-	0.84 (0.50 to 1.41)		0.51
Tertiary endpoint: Pooled Analysis results									
Worsening of disability confirmed at 24 weeks									
No. of participants (%)	-	-		-	-		18 (3.3)	26 (4.8)	
Hazard ratio (95% CI)	-		-	-		-	0.66 (0.36 to 1.21)		-
Other Endpoints									
Time to first confirmed relapse (number of patients with at least one IRAP-confirmed relapse during treatment)									
No. of participants with at least one IRAP-confirmed relapse during treatment (%)	36 (13.3)	68 (24.8)		34 (12.5)	72 (26.5)		-	-	
Hazard ratio (95% CI)	0.50 (0.33 to 0.75)		0.0009	0.43 (0.28 to 0.65)		<0.0001	-		-

Abbreviations: ARR, annualised relapse rate; CI, confidence interval; Gd, gadolinium; IRAP, Independent Relapse Adjudication Panel; mITT, modified intention-to-treat; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity; SDMT, symbol digit modalities test.

All rate ratios, hazard ratios, odds ratios, and difference values are for the ublituximab group as compared with the teriflunomide group. The order of the secondary endpoints according to the hierarchical analysis plan is provided in the Statistical Analysis section. The hierarchy failed at the third secondary endpoint (worsening of disability confirmed at 12 weeks). Where p-values are not provided, it is because of the failure of hierarchical testing results.

¶ Secondary MRI-related endpoints were assessed in 265 participants in the ublituximab group and 270 participants in the teriflunomide group in the ULTIMATE I trial, and in 272 participants in the ublituximab group and 267 participants in the teriflunomide group in the ULTIMATE II trial.

* The total number of Gd-enhancing T1-lesions was calculated as the sum of the individual number of lesions at weeks 12, 24, 48, and 96, divided by the total number of MRI scans of the brain.

§ The total number of new or enlarging lesions was calculated as the sum of the individual number of lesions at weeks 24, 48, and 96, divided by the total number of MRI scans of the brain.

¥ The change in brain volume was assessed with the use of a MMRM of the percent changes from baseline in the cube root–transformed volume.

¦ Worsening of disability that was confirmed at 12 weeks was defined as an increase of 1.0 or more points in the EDSS score if the baseline score was 5.5 or lower, or an increase of 0.5 or more points if the baseline score was greater than 5.5, sustained for at least 12 weeks.

** No evidence of disease activity was defined as no confirmed relapses, no MRI activity, and no worsening of disability at 12 weeks from week 24 to week 96, including week 24.

Further graphs of results from the ULTIMATE I and II trials are presented in Appendix D.

B.3.7 Subgroup analysis

There were no subgroup analyses performed as part of this submission. As outlined in Table 1, the overall population assessed as part of this submission are the active and highly active RRMS population, which NICE had originally defined as a subgroup. Therefore, reporting of results related to the individual active or highly active subgroups from the ULTIMATE trials is not relevant to the submission. Similarly, there were no data for the RES RRMS subgroup (also defined as a subgroup by NICE) available from the ULTIMATE trials. These subgroups were not assessed as part of the clinical effectiveness evidence synthesis or in the economic analysis. Results of additional subgroup analyses that were performed utilising ULTIMATE trial data, i.e., based on various baseline patient demographics and disease characteristics, are not presented in this submission.

B.3.8 Meta-analysis

Two phase III studies evaluated ublituximab in adult patients with RMS (Table 6). The two phase III ULTIMATE studies were identical in terms of design, endpoints, inclusion and exclusion criteria, active comparator and statistical analysis plan. Both phase III studies, and studies associated with the comparators of interest, i.e., ocrelizumab and ofatumumab (as well as additional comparators that were required to create the network of evidence), were included in the network meta-analysis (NMA). Trials included in the NMA were based on a systematic identification of relevant evidence. Comparator treatments included in the SLR to create the required network were: alemtuzumab, natalizumab, ocrelizumab, ofatumumab, interferon beta-1a [Rebif®], and teriflunomide. A full description of the SLR methodology and results is outlined in Appendix D 1.1.

B.3.9 Indirect and mixed treatment comparisons

Mixed treatment comparisons (MTCs) were conducted for the outcomes of ARR, CDP-12, CDP-24, and all-cause discontinuation in the ITT population. The feasibility of performing NMA for each outcome of interest was assessed by checking network connectivity and ensuring the availability of more trials than number of intervention nodes. For all outcomes, we first calculated direct effect estimates by pooling RRs for ARR and discontinuation, and HRs for CDP using DerSimonian-Laird random-

effects model. We then performed NMA using a contrast-based random-effects model with a common heterogeneity estimate using the methodology of multivariate meta-analysis using ‘network’ suite in Stata (85–87). The 'design-by-treatment' model was used to examine the consistency assumption at network level (global test of consistency). If there was evidence of inconsistency in the network, we used the side-splitting approach to identify if there was a specific modality of interventions that contributed to inconsistency in the network and to run an inconsistency model if we were not able to explain the observed inconsistency. The side-splitting method used to assess local (loop-specific) inconsistency in each closed network loop as the difference between direct and indirect evidence (86,88).

We visualised the network of interventions using network plots in which the size of the node (circle) corresponds to the number of patients randomised to that intervention and the thickness of the lines corresponds to the number of studies available for each comparison. Comparative effects of interventions for all pairwise comparisons are presented in league tables with placebo as reference intervention. For the ARR outcome, when studies didn’t report an annualised rate, we used relapse rate reported for the duration of study and calculated the rate per year for inclusion in the analysis. We performed sensitivity analysis excluding these studies to assess robustness of the results, and also performed a sensitivity analysis based on exclusion of studies where relapse rate had to be imputed based on number of relapse-free patients. For the treatment discontinuation outcome, we performed a sensitivity analysis excluding the CARE-MS I and II trials due to the unique dosing schedule associated with alemtuzumab. We also performed network meta-regressions for these outcomes, adjusting for trial follow-up duration. The meta-regression on study duration was conducted to explore whether the time at which the outcome was observed (follow-up time) influenced the relative treatment effects.

We ranked interventions using the surface under the cumulative ranking curve (SUCRA) values. Surface under the cumulative ranking curve values are calculated using probability rankings to determine which intervention is most likely to be the most effective – an intervention with a SUCRA value of 100 is considered the most effective, whereas a value of 0 indicates that the intervention is the least effective. Stata (StataCorp., Release 18.0 College Station, TX) was used for all data analyses

(89). All comparisons were two-tailed using a threshold p-value ≤0.05. Results of the NMA are presented below, with further details related to the methodology presented in Appendix D 1.1.

Included studies

An SLR was conducted to identify RCTs of treatments for RMS. The scope of the SLR was broader than the NICE decision problem in terms of the range of comparators included, as well as the outcomes of interest. A broader list of comparators was required in order to ensure that a comprehensive network with robust estimates of effect could be created. Therefore, for evidence included in the NMA that were outside of the NICE decision problem scope, results are not presented unless required by the nature of the information presented, i.e., network diagrams, etc. The SLR identified a total of 15 RCTs (based on 239 individual records) providing data for the NMA based on ITT populations. Full details on the methodology and results of the SLR are presented in Appendix D 1.1. An overview of the trials, and associated treatments, included in the NMA is presented in Table 12.

Excluded studies

None of the 15 RCTs identified via the SLR were excluded from the NMA, i.e., all identified trials reported data relevant to at least one outcome included in the analysis.

Table 12 Summary of trials included in NMA

Study reference/ID								
	Alemtuzumab	**Interferon beta-1a (Rebif®)**	**Natalizumab**	**Ocrelizumab**	**Ofatumumab**	**Teriflunomide**	**Ublituximab**	**Placebo**
AFFIRM (90)			✓					✓
ASCLEPIOS I and II (91)					✓	✓		
CARE-MS I and II (92,93)	✓	✓						
IMPROVE (94,95)		✓						✓
OPERA I and II (79)		✓		✓				
OWIMS (96)		✓						✓

PRISMS (97)		✓						✓
TEMSO (80)						✓		✓
TENERE (81)		✓				✓		
TOWER (98)						✓		✓
ULTIMATE I and II (1)						✓	✓	

B.3.9.1 ARR

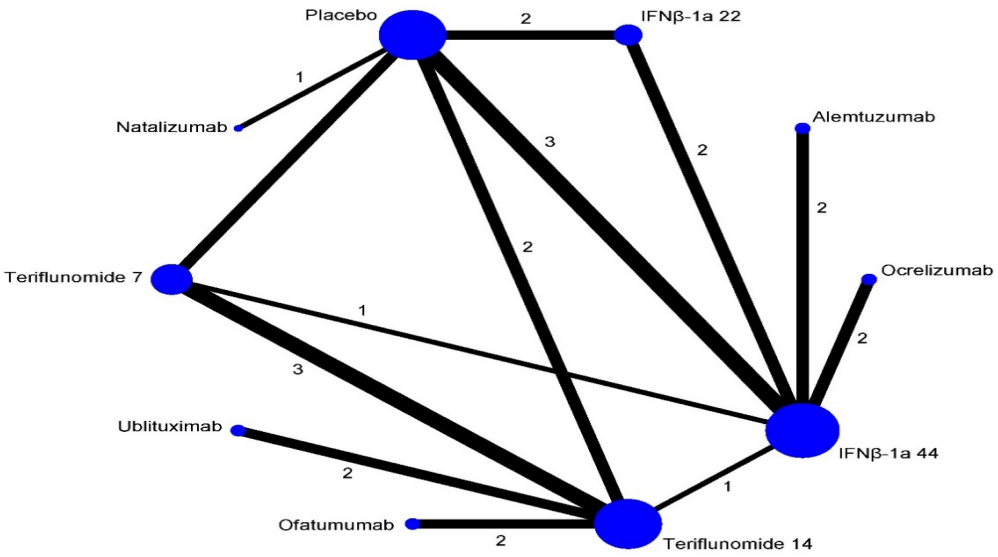
The primary analysis for the ARR outcome included data from 15 RCTs. The network of treatments and number of trials for each direct comparison is shown in Figure 12. The analysis showed ublituximab was superior to placebo (RR 0.31 [95% CI: 0.20, 0.47]), and that there was no statistically significant difference between ublituximab and ocrelizumab or ofatumumab, but the results for the comparison of ublituximab versus ocrelizumab showed a direction in favour of ublituximab. In the comparison with ofatumumab, the results showed a direction in favour of the comparator. Treatment effect estimates from the NMA are presented in Table 13. Rankings and SUCRA values are presented in Table 14.

For the ARR outcome analysis, there was evidence of global inconsistency (p-value from design-by-treatment model = 0.002) with 5 of 8 pairwise comparisons showing statistically significant inconsistency from the side-splitting model. The following sensitivity analyses were performed: (1) an inconsistency model to assess the robustness of the results and account for the observed inconsistency; (2) excluding data from the OWIMS and IMPROVE trials which reported relapse rate results, rather than ARR specifically, due to their shorter trial durations; (3) excluding data from the OWIMS and PRISMS trials, where relapse rate had to be imputed based on number of relapse-free patients; (4) a network meta-regression analysis to adjust for varying follow-up durations across included trials.

The results from sensitivity analysis using the inconsistency model were broadly similar to the consistency model, with no statistically significant difference between ublituximab and ocrelizumab or ofatumumab and a statistically significant result in favour of ublituximab in the comparison with placebo (RR 0.66 [95% CI: 0.58, 0.75]). Similarly, the results for sensitivity analysis excluding the OWIMS and IMPROVE trials showed ublituximab was superior to placebo (RR 0.31 [95% CI: 0.21, 0.46]). As

in the base-case analysis, there was no statistically significant difference between ublituximab and the other mAbs, but the results for the comparison of ublituximab versus ocrelizumab showed a direction in favour of ublituximab. The results of sensitivity analysis excluding the OWIMS and PRISMS trials were also broadly similar to the base-case analysis. Finally, no effect modification was observed in the network meta-regression analysis adjusting for follow-up duration of included trials. Figures associated with the results of all sensitivity analyses for this outcome are presented in the section 'Uncertainties in the indirect and MTCs'.

Figure 12 Network of treatment for ARR outcome analysis (n = 15 RCTs)



The size of the node (circle) corresponds to the number of patients randomised to that intervention. The thickness of the lines corresponds to the number of studies for each comparison.

Table 13 NMA results for ARR outcome (n = 15 RCTs)

ublituximab			
0.75 (0.44,1.28)	**ocrelizumab**		
1.02 (0.64,1.62)	1.35 (0.84,2.18)	**ofatumumab**	
0.31 (0.20,0.47)	**0.41 (0.30,0.58)**	**0.30 (0.22,0.43)**	**placebo**

Results are RR and their 95% CIs. For column compared to row, RR <1 means the top-left treatment is better [RR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the comparison of all active drugs versus placebo.

Table 14 SUCRA for treatments for ARR outcome (n = 15 RCTs)

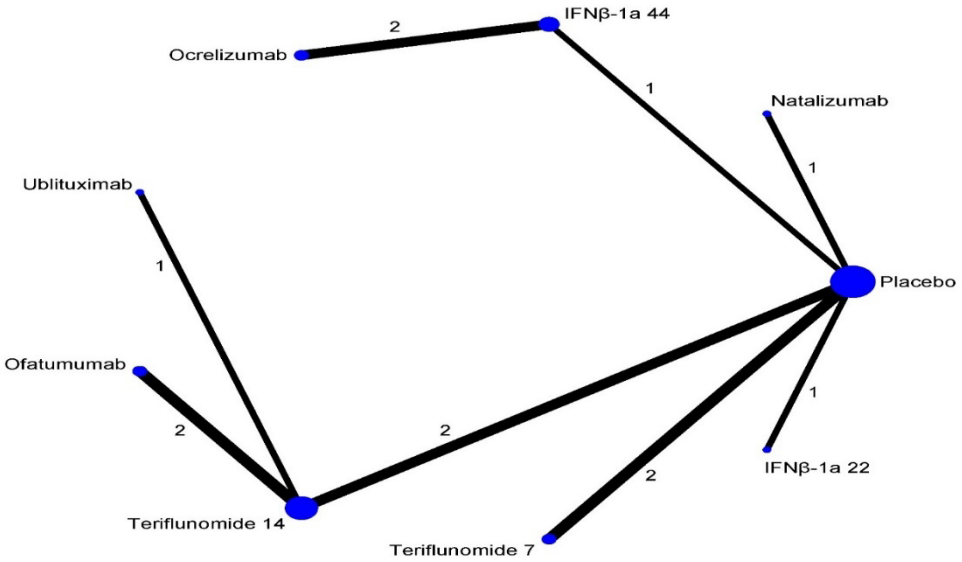
Treatment	SUCRA
ofatumumab	85.4
ublituximab	83.9
ocrelizumab	62.5

Abbreviations: SUCRA, surface under the cumulative ranking.

B.3.9.2 CDP-12

The network of treatments for CDP-12 included data from 10 RCTs. The network of treatments and number of trials for each direct comparison is provided in Figure 13. For this analysis, there was no closed loop of evidence, and the model was assumed consistent by definition. The analysis showed no evidence of a statistically significant difference between ublituximab and ocrelizumab or ofatumumab, but the results for the comparison of ublituximab versus placebo showed a direction in favour of ublituximab (RR 0.58 [95% CI: 0.33, 1.03]). Treatment effect estimates from the NMA are presented in Table 15. Rankings and SUCRA values are presented in Table 16.

Figure 13 Network of treatments for CDP-12 outcome analysis (n = 10 RCTs)



The size of the node (circle) corresponds to the number of patients randomised to that intervention. The thickness of the lines corresponds to the number of studies for each comparison.

Table 15 NMA results for CDP-12 outcome (n = 10 RCTs)

ublituximab			
1.55 (0.74,3.27)	**ocrelizumab**		
1.28 (0.72,2.30)	0.83 (0.45,1.50)	**ofatumumab**	
0.58 (0.33,1.03)	**0.37 (0.23,0.60)**	**0.45 (0.31,0.65)**	**placebo**

Results are HR and their 95% CIs. For column compared to row, HR <1 means the top-left treatment is better [HR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the comparison of all active drugs versus placebo.

Table 16 SUCRA for treatments for CDP-12 outcome (n = 10 RCTs)

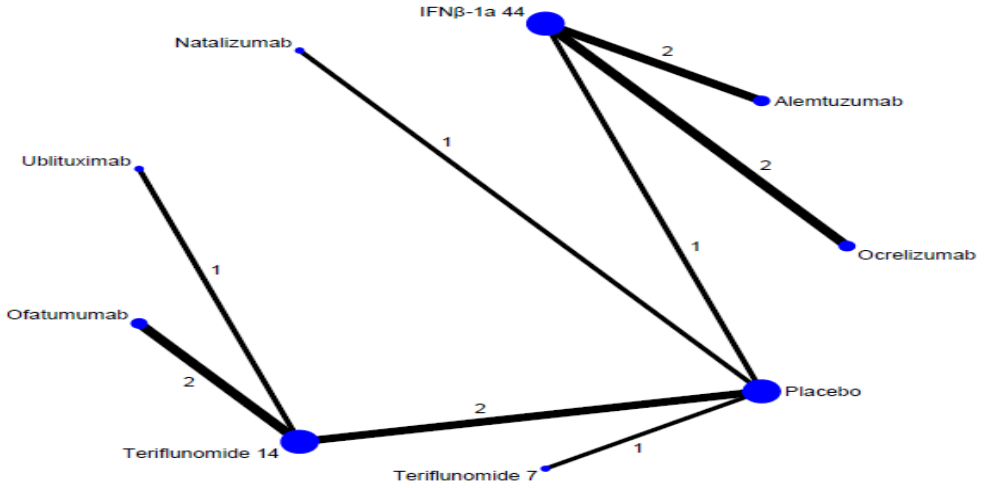
Treatment	SUCRA
ocrelizumab	93.9
ofatumumab	84.2
ublituximab	58.0

Abbreviations: SUCRA, surface under the cumulative ranking.

B.3.9.3 CDP-24

The network of treatments for CDP-24 included data from 12 RCTs. The network of treatments and number of trials for each direct comparison is provided in Figure 14. There was no closed loop of evidence, and the model was assumed consistent by definition. The analysis showed that there was no statistically significant difference between ublituximab and ocrelizumab or ofatumumab, but the results for the comparison of ublituximab versus ofatumumab showed a direction in favour of ublituximab (Table 17). Rankings and SUCRA values are presented in Table 18. It should be mentioned that from a clinical effectiveness assessment perspective, prioritising a 24-week timeframe over a 12-week timeframe when evaluating CDP is more advantageous. The 24-week period provides a more reliable and comprehensive view of long-term disability progression, minimising the influence of short-term fluctuations and transient changes that may not accurately reflect true disease progression. This longer timeframe allows for the observation of sustained and meaningful changes in patient condition, which is critical for assessing the true efficacy of a treatment.

Figure 14 Network of treatments for CDP-24 outcome analysis (n = 12 RCTs)



The size of the node (circle) corresponds to the number of patients randomised to that intervention. The thickness of the lines corresponds to the number of studies for each comparison.

Table 17 NMA results for CDP-24 outcome (n = 12 RCTs)

ublituximab			
1.29 (0.57,2.90)	**ocrelizumab**		
0.97 (0.49,1.92)	0.75 (0.41,1.40)	**ofatumumab**	
0.52 (0.27,1.02)	**0.40 (0.26,0.63)**	**0.54 (0.35,0.82)**	**placebo**

Results are HR and their 95% CIs. For column compared to row, HR <1 means the top-left treatment is better [HR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the comparison of all active drugs versus placebo.

Table 18 SUCRA for treatments for CDP-24 outcome (n = 12 RCTs)

Treatment	SUCRA
ocrelizumab	**84.4**
ublituximab	**63.6**
ofatumumab	**61.8**

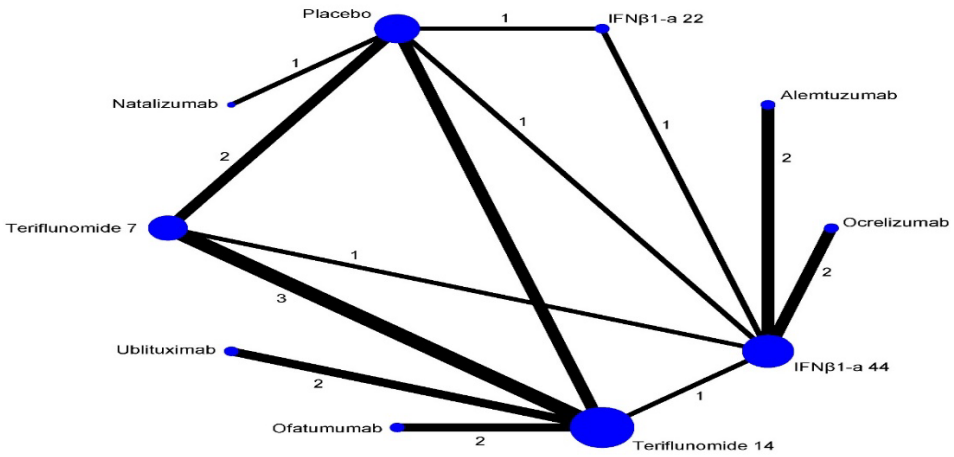
Abbreviations: SUCRA, surface under the cumulative ranking.

B.3.9.4 Treatment discontinuation

All-cause treatment discontinuation was reported in 13 RCTs. The network of treatments and number of trials for each direct comparison is provided in Figure 15. Treatment effect estimates from the NMA are presented in Table 19. The analysis showed that there was no statistically significant difference between ublituximab and ocrelizumab or ofatumumab. Rankings and SUCRA values are presented in Table 20.

There was no evidence of global inconsistency (p-value from design-by-treatment model = 0.787) or comparison-specific inconsistency from the side-splitting model. A sensitivity analysis was also performed for this outcome, excluding the CARE-MS I and II trials due to the unique dosing schedule associated with alemtuzumab. This analysis showed no statistically significant difference between ublituximab and ocrelizumab or ofatumumab. Additionally, no effect modification was observed in the network meta-regression analysis adjusting for follow-up duration of included trials. Figures associated with the results of all sensitivity analyses for this outcome are presented in the section 'Uncertainties in the indirect and MTCs.

Figure 15 Network of treatments for treatment discontinuation (n = 13 RCTs)



The size of the node (circle) corresponds to the number of patients randomised to that intervention. The thickness of the lines corresponds to the number of studies for each comparison.

Table 19 NMA results for treatment discontinuation outcome (n = 13 RCTs)

ublituximab			
1.11 (0.61,2.01)	**ocrelizumab**		
1.16 (0.74,1.82)	1.05 (0.63,1.73)	**ofatumumab**	
0.91 (0.59,1.40)	0.82 (0.52,1.29)	0.78 (0.58,1.05)	**placebo**

Results are RR and their 95% CIs. For column compared to row, RR <1 means the top-left treatment is better [RR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the com-parison of all active drugs versus placebo.

Table 20 SUCRA for treatments for treatment discontinuation outcome (n = 13 RCTs)

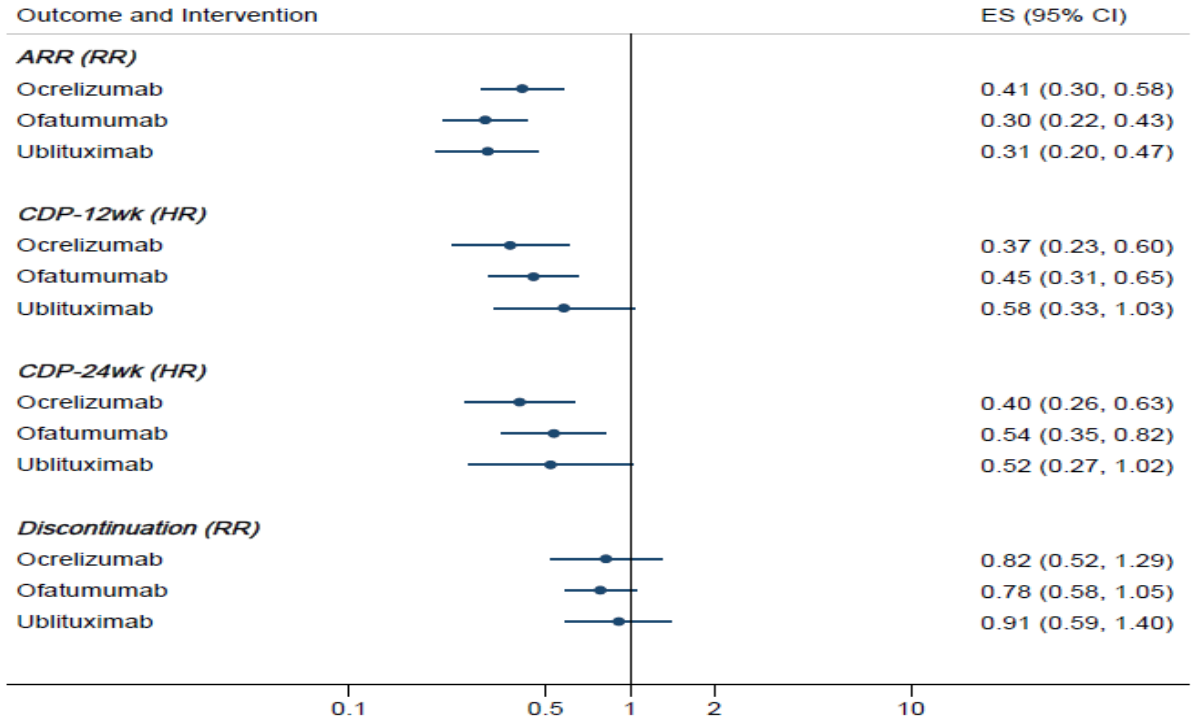
Treatment	SUCRA
ofatumumab	73.7

ocrelizumab	65.1
ublituximab	52.2

Abbreviations: SUCRA, surface under the cumulative ranking.

Forest plots for all outcomes presented above are presented in Figure 16 below.

Figure 16 Forest plots for all outcomes



Abbreviations: CDP, confirmed disability progression; HR, hazard ratio; RR, rate ratio.

Uncertainties in the indirect and mixed treatment comparisons

Sensitivity analyses were performed to consider uncertainty associated with inputs and assumptions in the base-case analyses.

Sensitivity analyses for the ARR outcome

Table 21 Direct and indirect estimates of effect for the network of ARR outcome for pairwise inconsistency

Comparison	Direct RR (95% CI)	Indirect RR (95% CI)	Inconsistency factor (IF)	Standard error of IF	Inconsistency p-value
placebo vs interferon beta-1a 44*	1.22 (1.09, 1.37)	2.25 (1.46, 3.46)	0.608	0.224	**0.007**
placebo vs interferon beta-1a 22*	1.09 (0.97, 1.23)	4.06 (2.00, 8.21)	1.303	0.369	**0.000**
placebo vs teriflunomide 14 mg	1.52 (1.23, 1.89)	1.16 (0.66, 2.05)	-0.276	0.306	0.368

placebo vs teriflunomide 7 mg	1.36 (1.21, 1.53)	0.66 (0.43, 1.01)	-0.728	0.223	**0.001**
interferon beta-1a 44 vs interferon beta-1a 22*	0.92 (0.82, 1.04)	0.25 (0.12, 0.51)	-1.303	0.369	**0.000**
interferon beta-1a 44 vs teriflunomide 14 mg	0.89 (0.52, 1.51)	1.16 (0.87, 1.56)	0.276	0.306	0.368
interferon beta-1a 44 vs teriflunomide 7 mg	0.54 (0.36, 0.81)	1.12 (0.95, 1.31)	0.728	0.223	**0.001**
teriflunomide 14 mg vs teriflunomide 7 mg*	0.84 (0.69, 1.02)	3.46 (0.10, 115.39)	1.417	979.019	0.999

Abbreviations: CI, confidence interval; IF, inconsistency factor; RR, rate ratio.

* All the evidence about these contrasts comes from the trials which directly compare them. This is to indicate these comparisons are coherent (i.e., consistent) by definition, because they are informed by multi-arm trials. Significant inconsistency p-value means estimates from direct and indirect comparison are statistically different. p-value for global test of inconsistency = **0.002**.

N.B. Statistical tests of inconsistency have low power and thus typically, p-value <0.1 is considered as important inconsistency; important inconsistency p-values are bolded and highlighted.

Table 22 Sensitivity analysis using inconsistency model for ARR outcome analysis (n = 15 RCTs)

ublituximab			
1.29 (0.64,2.58)	**ocrelizumab**		
1.02 (0.68,1.52)	0.79 (0.41,1.53)	**ofatumumab**	
0.66 (0.58,0.75)	**0.31 (0.27,0.37)**	**0.24 (0.13,0.43)**	**placebo**

Results are RR and their 95% CIs. For column compared to row, RR <1 means the top-left treatment is better [RR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the comparison of all active drugs versus placebo.

Table 23 Sensitivity analysis excluding OWIMS and IMPROVE trials for ARR outcome analysis (n = 13 RCTs)

ublituximab			
0.78 (0.46,1.32)	**ocrelizumab**		
1.02 (0.65,1.60)	1.31 (0.82,2.11)	**ofatumumab**	
0.31 (0.21,0.46)	**0.40 (0.28,0.57)**	**0.30 (0.22,0.42)**	**placebo**

Results are RR and their 95% CIs. For column compared to row, RR <1 means the top-left treatment is better [RR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the comparison of all active drugs versus placebo.

Table 24 Sensitivity analysis excluding OWIMS and PRISMS trials for ARR outcome analysis (n = 13 RCTs)

ublituximab			
1.22 (0.73,2.03)	**ocrelizumab**		

1.02 (0.69,1.52)	0.84 (0.53,1.31)	**ofatumumab**	
0.30 (0.21,0.42)	**0.24 (0.17,0.36)**	**0.29 (0.23,0.37)**	**placebo**

Results are RR and their 95% CIs. For column compared to row, RR <1 means the top-left treatment is better [RR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the comparison of all active drugs versus placebo.

Table 25 Meta-regression analysis adjusting for follow-up duration for ARR outcome

ublituximab			
1.15 (0.56,2.37)	**ofatumumab**		
0.84 (0.40,1.77)	0.73 (0.38,1.43)	**ocrelizumab**	
0.35 (0.18,0.67)	**0.31 (0.19,0.50)**	**0.42 (0.25,0.68)**	**placebo**

p-value for effect modification: 0.672 (duration of follow-up did not reduce between-study heterogeneity).

Sensitivity analyses for the treatment discontinuation outcome

Table 26 Direct and indirect estimates of effect for the network of all-cause treatment discontinuation outcome for pairwise inconsistency

Comparison	Direct RR (95% CI)	Indirect RR (95% CI)	Inconsistency factor (IF)	Standard error of IF	Inconsistency p-value
placebo vs interferon beta-1a 44*	0.88 (0.46, 1.68)	0.66 (0.41, 1.06)	-0.287	0.406	0.479
placebo vs interferon beta-1a 22*	0.78 (0.42, 1.46)	0.44 (0.11, 1.84)	-0.575	0.812	0.479
placebo vs teriflunomide 14 mg	1.01 (0.83, 1.23)	1.21 (0.56, 2.60)	0.189	0.408	0.643
placebo vs teriflunomide 7 mg	1.05 (0.86, 1.28)	1.35 (0.62, 2.96)	0.245	0.413	0.553
interferon beta-1a 44 vs interferon beta-1a 22*	0.89 (0.48, 1.63)	1.57 (0.37, 6.69)	0.575	0.812	0.479
interferon beta-1a 44 vs teriflunomide 14 mg	1.52 (0.91, 2.53)	1.26 (0.70, 2.27)	-0.189	0.408	0.643
interferon beta-1a 44 vs teriflunomide 7 mg	1.63 (0.96, 2.77)	1.28 (0.71, 2.31)	-0.245	0.413	0.553
teriflunomide 14 mg vs teriflunomide 7 mg*	1.05 (0.88, 1.25)	1.32 (0.03, 59.05)	0.231	938.046	0.999

Abbreviations: CI, confidence interval; IF, inconsistency factor; RR, rate ratio.

* All the evidence about these contrasts comes from the trials which directly compare them. This is to indicate these comparisons are coherent (i.e., consistent) by definition, because they are informed by multi-arm trials.
Significant inconsistency p-value means estimates from direct and indirect comparison are statistically different.
p-value for global test of inconsistency = 0.787.
N.B. Statistical tests of inconsistency have low power and thus typically, p-value <0.1 is considered as important inconsistency; important inconsistency p-values are bolded and highlighted.

Table 27 NMA results for treatment discontinuation outcome (excluding CARE-MS I and II) (n = 11 RCTs)

ublituximab			
1.11 (0.60,2.04)	**ocrelizumab**		
1.16 (0.74,1.84)	1.05 (0.62,1.76)	**ofatumumab**	
0.91 (0.58,1.42)	0.82 (0.51,1.31)	0.78 (0.57,1.06)	**placebo**

Results are RR and their 95% CIs. For column compared to row, RR <1 means the top-left treatment is better [RR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the comparison of all active drugs versus placebo.

Table 28 Meta-regression analysis adjusting for follow-up duration for treatment discontinuation outcome

ublituximab			
0.97 (0.33,2.79)	**ofatumumab**		
1.41 (0.26,7.62)	1.46 (0.32,6.59)	**ocrelizumab**	
0.80 (0.34,1.85)	0.82 (0.49,1.39)	0.57 (0.14,2.27)	**placebo**

p-value for effect modification: 0.597 (duration of follow-up did not reduce between-study heterogeneity).

While these analyses synthesised results from different timepoints, sensitivity analyses using network meta-regression were performed for the ARR and treatment discontinuation outcome analyses to adjust for timepoint, with no effect modification observed. Sensitivity analyses were performed, as described above, to test the robustness of the base-case analyses, with little deviation from the base-case findings. Results of this NMA are broadly in line with the findings presented in a recently-conducted comparative analysis of a larger list of DMTs (72).

B.3.10 Adverse reactions

Adverse events from ULTIMATE I and ULTIMATE II are presented in this section. The safety population included all participants who received at least one dose of the trial drug. Safety data were collected during the treatment period and follow-up period until a participant's last visit (1).

In a pooled analysis of the two trials, 486 of 545 patients (89.2%) in the ublituximab group and 501 of 548 (91.4%) in the teriflunomide group had at least one AE. A total of 116 patients (21.3%) in the ublituximab group reported grade 3 or higher AEs, compared with 77 (14.1%) in the teriflunomide group. The most common AEs occurring in at least 10% of patients treated with ublituximab were infusion-reated

reactions (IRRs) (47.7%), nasopharyngitis (18.3%), pyrexia (13.9%), headache (34.3%), and nausea (10.6%). Adverse events that occurred in at least 10% of teriflunomide recipients included headache (26.6%), nasopharyngitis (17.9%), alopecia (15.3%), IRRs (12.2%), and diarrhoea (10.6%). Serious AEs (SAEs) occurred in 59 ublituximab recipients (10.8%) and in 40 teriflunomide patients (7.3%). Three deaths occurred among ublituximab patients: one from pneumonia, one from encephalitis following measles, and one from salpingitis following an ectopic pregnancy.

Table 29 Adverse events (Safety population)*

Events	ULTIMATE I		ULTIMATE II	
	Ublituximab (n = 273)	Teriflunomide (n = 275)	Ublituximab (n = 272)	Teriflunomide (n = 273)
Any adverse event, n (%)	235 (86.1)	245 (89.1)	251 (92.3)	256 (93.8)
Adverse event leading to treatment discontinuation, n (%)	18 (6.6)	2 (0.7)	5 (1.8)	2 (0.7)
Infection, n (%)	135 (49.5)	133 (48.4)	169 (62.1)	165 (60.4)
Infusion-related reaction, n (%)	120 (44.0)	19 (6.9)	140 (51.5)	48 (17.6)
Neoplasm, n (%)ł	0	0	2 (0.7)	1 (0.4)
Serious adverse events, n (%)	31 (11.4)	19 (6.9)	28 (10.3)	21 (7.7)
Serious infection, n (%)‡	15 (5.5)	6 (2.2)	12 (4.4)	10 (3.7)
Death, n (%)§	2 (0.7)	0	1 (0.4)	0

* The safety population included all participants who received at least one dose of a trial drug. Shown are the data collected during the double-blind, controlled treatment period.
† In both trials, neoplasms that occurred in the ublituximab group were endometrial (time to onset, 558 days) and uterine (time to onset, 210 days). A tongue neoplasm (time to onset, 494 days) occurred in the teriflunomide group.
‡ In both trials, the most frequently reported serious infections were pneumonia in the ublituximab group and urinary tract infections in the teriflunomide group.
§ The deaths that occurred in the ublituximab group were due to pneumonia (deemed to be possibly related to treatment), encephalitis (after measles), and salpingitis (after ectopic pregnancy).

Infection

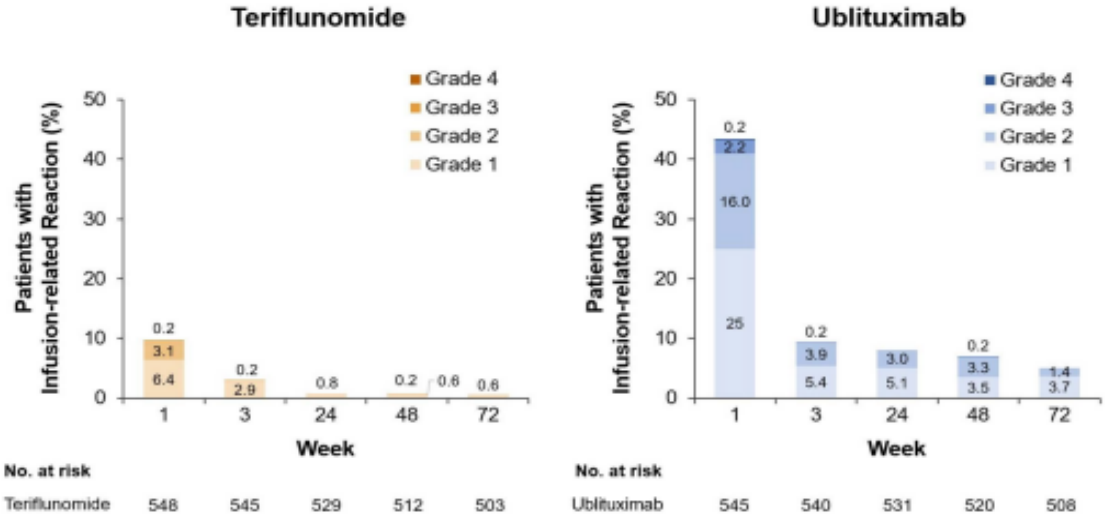
Infections occurred in 304 participants (55.8%) who received ublituximab and in 298 participants (54.4%) who received teriflunomide. Most infections were respiratory tract–related and were grade 1 or 2 in severity. Nasopharyngitis occurred in 18.3% of ublituximab recipients and in 17.9% of teriflunomide recipients; respiratory tract infections occurred in 7.7% and 6.9%, respectively; pharyngitis occurred in 5.9% and 2.2%, respectively; and urinary tract infections occurred in 4.0% and 5.3%,

respectively. Serious infections occurred in 5.0% of ublituximab recipients and in 2.9% of teriflunomide recipients. Seven participants (1.3%) who received ublituximab and 1 participant (0.2%) who received teriflunomide discontinued one of the trials because of an infection. No opportunistic infections were reported. Herpes virus–associated infections occurred in 5.7% of ublituximab recipients and in 4.6% of teriflunomide recipients. All were grade 1 or 2 in severity and resolved. There were no cases of PML in either group over a period of 96 weeks.

Infusion-Related Reactions

Infusion-related reactions occurred in 47.7% of the participants who received ublituximab. Pyrexia, headache, chills, and influenza-like illness were the most frequently reported events. Most were mild to moderate in severity (as graded by the investigator), were reported at the time of the first infusion (43.3%) and decreased in frequency with subsequent doses. Grade 3 or higher IRRs were observed in 2.8% of the participants who received ublituximab. Two participants had a grade 4 IRR. One participant had anaphylaxis during the second infusion; the participant recovered, and no further doses of ublituximab were administered. The other participant had a decrease in lymphocytes at the first infusion; treatment was not needed, and the dosage was not changed. Six participants (1.1%) discontinued ublituximab because of an IRR, including three participants during the first infusion and three after the first infusion.

Figure 17 Treatment-Emergent Adverse Events of Infusion-Related Reaction Based on Investigator Reported Data (Safety Population)



Adverse events that led to discontinuation of study treatment

During the controlled treatment period, the proportion of patients discontinuing study treatment due to an AE was low overall. However, the incidence was higher in the ublituximab group (4.2%; 23 patients) compared with the teriflunomide group (0.72%; 4 patients).

Safety profile summary

Overall, the ULTIMATE I and II trials demonstrated ublituximab to be well-tolerated with a safety profile similar to teriflunomide. The number of patients who experienced any AE was well balanced between the two treatment groups. The total number of patients reporting SAEs was similarly well balanced between groups and low relative to the overall number of patients reporting AEs. Infusion-related reactions were more common with ublituximab and occurred in almost half the participants; IRRs associated with ublituximab were mostly mild to moderate in severity and decreased in frequency with subsequent doses, despite increases in infusion flow rates after the first infusion. Six participants discontinued ublituximab because of IRRs, including five grade 2 IRRs and one grade 4 event of anaphylaxis. Although no opportunistic infections occurred in either group in either of the trials, a higher frequency of

infections, including serious infections, was observed with ublituximab than with teriflunomide.

B.3.11 Conclusions about comparable health benefits and safety

ULTIMATE I and ULTIMATE II were double-blind, randomised, active-controlled phase III trials, evaluating the efficacy and safety of ublituximab infusions as compared with oral teriflunomide, an inhibitor of pyrimidine synthesis, in patients with RMS (1). The two studies were identical in terms of design, endpoints, inclusion and exclusion criteria, and active comparator. The duration of treatment was 96 weeks. In both trials, randomisation was carried out appropriately, with participants randomly assigned in a 1:1 ratio by means of an interactive Web-response system. The trial population in ULTIMATE I and ULTIMATE II is reflective of UK clinical practice, with relevant endpoints investigated for patients with RMS. The baseline characteristics of the participants were generally consistent with previous anti-CD20 trials in RMS, with the exception that participants from Eastern Europe were over-represented.

Robust oversight of the trial enhances the validity of the reported results. The trials were designed by the sponsor, but with guidance from an external steering committee. An independent data and safety monitoring board regularly reviewed unblinded data and could advise the sponsor to stop the trial for efficacy, detrimental effects, or futility. The protocols were approved by the institutional review boards or independent ethics committees at each trial centre, and the trials were conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki.

The primary endpoint was reached in both ULTIMATE I and ULTIMATE II, where ARR was significantly lower with ublituximab than teriflunomide. In the ULTIMATE I trial, the adjusted ARR over a period of 96 weeks was 0.08 in the ublituximab group and 0.19 in the teriflunomide group (RR, 0.41; 95% CI, 0.27 to 0.62; p<0.001). The corresponding rates in the ULTIMATE II trial were 0.09 and 0.18 (RR, 0.51; 95% CI, 0.33 to 0.78; p = 0.002). In addition, MRI-related endpoints showed positive results for ublituximab. In the ULTIMATE I trial, the mean total number of Gd-enhancing lesions per T1-weighted MRI scan was 0.02 in the ublituximab group and 0.49 in the teriflunomide group (RR, 0.03; 95% CI, 0.02 to 0.06; p<0.001); in the ULTIMATE II

trial, the corresponding numbers were 0.01 and 0.25 (RR, 0.04; 95% CI, 0.02 to 0.06; p<0.001). In the ULTIMATE I trial, the mean total number of new or enlarging hyperintense lesions per T2-weighted MRI scan was 0.21 in the ublituximab group and 2.79 in the teriflunomide group (RR, 0.08; 95% CI, 0.06 to 0.10; p<0.001); in the ULTIMATE II trial, the corresponding numbers were 0.28 and 2.83 (RR, 0.10; 95% CI, 0.07 to 0.14; p<0.001).

The percentage of participants with worsening of disability was similar in the two treatment groups. In the pre-specified pooled analysis, 5.2% of the participants in the ublituximab group had worsening of disability confirmed at 12 weeks, as compared with 5.9% of the participants in the teriflunomide group (HR, 0.84; 95% CI, 0.50 to 1.41; p = 0.51); 3.3% of the participants in the ublituximab group had worsening of disability confirmed at 24 weeks, as compared with 4.8% of the participants in the teriflunomide group (HR, 0.66; 95% CI, 0.36 to 1.21). No robust conclusions can be drawn from the disability progression outcome analyses. However, on the basis of all results presented above, the ULTIMATE I and II trials demonstrated that ublituximab may lead to a reduction in patient and health care burden associated with relapses and lesions.

In ULTIMATE I and ULTIMATE II, safety outcomes were comparable between the treatment groups. In a pooled analysis of the two trials, 486 of 545 participants (89.2%) who received ublituximab and 501 of 548 participants (91.4%) who received teriflunomide had at least one AE. Grade 3 or higher AEs occurred in 116 participants (21.3%) who received ublituximab and in 77 (14.1%) who received teriflunomide.

Despite the availability of other DMTs for the treatment of RMS, many patients continue to experience disease activity. The ULTIMATE I and II studies demonstrate that ublituximab is an efficacious treatment, with lower ARR associated with IV ublituximab than with oral teriflunomide. Indeed, the ARR results for ublituximab are particularly notable given that they are <0.10 over 96 weeks (0.08 in ULTIMATE I and 0.09 in ULTIMATE II); reflecting a relapse rate of less than one relapse per decade. Comparable results have not been achieved by any comparator DMTs currently available. Additional results estimated via the NMA indicate that there is no statistically significant difference between ublituximab and either of the NICE-defined

comparators to ublituximab (ocrelizumab and ofatumumab) for the additional outcomes of CDP-12, CDP-24, or treatment discontinuation.

B.3.12 Ongoing studies

There are no ongoing studies that will provide additional evidence over the next 12 months for the indication being appraised.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Multiple sclerosis is a chronic, neurological condition which affects the brain, optic nerves, and spinal cord. It often results in progressive neurological impairment and severe disability. Multiple sclerosis has an unpredictable course which varies in severity and rate of progression. Relapsing-remitting multiple sclerosis is the most common clinical form of MS. It is characterised by periods of remission (where people may have no symptoms, or they may be relatively stable) followed by relapses (which may or may not result in residual disability). Relapsing-remitting multiple sclerosis can progress to SPMS, characterised by more persistent or gradually increasing disability (99).

Ublituximab has been approved for the treatment of adult patients with RMS who have active disease defined by clinical or imaging features. However, as outlined in Section B.1 this submission is targeting RRMS only. Ublituximab offers an additional treatment option for adult patients with RRMS, including those patients with active, highly active, or RES RRMS. Ublituximab is intended as an alternative treatment option to ocrelizumab and ofatumumab, which are currently recommended for the active, highly active, and RES RRMS patient populations for all lines of treatment. Therefore, ublituximab is anticipated to occupy a comparable position in the treatment algorithm to these two comparators. Given the potential, based on existing clinical evidence, for ublituximab to provide similar or greater health benefits at similar or lower cost than these current NICE-recommended technologies for the same indication, a CCA has been carried out.

All therapies included in this CCA are provided by specialist MS neurologists and nurses in secondary care, supported by multidisciplinary teams. Treatment with ublituximab and ocrelizumab are delivered in their entirety through MS-specialist clinics, due to their formulations as IV infusions. Treatment with ofatumumab is prescribed and initiated in the secondary care setting, as with other therapies, but it can be subsequently provided in the home-setting via SC injections. This difference in service provision is considered in the drug administration cost calculations of the CCA.

B.4.2 Cost-comparison analysis inputs and assumptions

Features of the cost-comparison analysis

A CCA was conducted to evaluate the costs associated with ublituximab, as compared to ofatumumab and ocrelizumab in the context of NHS England. The CCA assumes equivalent treatment effectiveness, disease progression and disease-related mortality between the intervention and the comparators; therefore, they were cancelled out from the CCA. The population characteristics in the model are based on the ULTIMATE I and II clinical trials (1).

The model was developed using a Markov model structure consisting of two discrete states that simulate living patients who receive treatment, and those who die during each model cycle. Patients transitioning to the death state are determined by general mortality rates from the UK, and are assumed to incur no costs.

The model consists of an annual cycle length and the base-case time horizon was set to five years. This time horizon was selected to account for higher treatment initiation costs and to allow the costs to stabilise over time. In this way, we can adequately demonstrate any differences in the costs associated with each of the included therapies.

Following the NICE user guide for CCA, discounting was not applied in the base-case analysis. However, a scenario with costs discounted at a rate of 3.5% is presented.

Intervention and comparators' acquisition costs

The treatment acquisition costs considered in this cost-comparison are described in Table 30.

Drug acquisition costs were estimated separately for treatment initiation and subsequent treatment doses to derive the drug acquisition costs in the first model cycle (i.e., year 1) and subsequent model cycles (i.e., years 2+). Dosing regimens were used to calculate the total drug use and were based on the relevant SmPC for the included treatments: Ublituximab is initially administered as a 150mg IV infusion, followed by a 450mg IV infusion 2 weeks later. Subsequent doses are administered as a single 450mg IV infusion every 24 weeks (9). Ofatumumab is administered as a

20mg SC injection at weeks 0, 1 and 2, followed by subsequent monthly dosing (100). Ocrelizumab is initiated at a dose of 600mg dose, administered as two separate IV infusions; first as a 300mg infusion, followed 2 weeks later by a second 300mg infusion. Subsequent doses of ocrelizumab thereafter are administered as a single 600mg IV infusion every 6 months (100).

The drug costs presented are based on publicly available list prices, sourced from the British National Formulary (BNF) (102). Any discounts from commercial PAS for ofatumumab and ocrelizumab were excluded from the analyses, as these values are not available to the public.

Table 30 Acquisition costs of the intervention and comparator technologies

	Ublituximab	Ofatumumab	Ocrelizumab
Pharmaceutical formulation	150mg concentrate for solution for infusion	20mg solution for injection in pre-filled syringe	300mg concentrate for solution for infusion
(Anticipated) care setting	Secondary care	Secondary care for treatment initiation	Secondary care
Acquisition cost (excluding VAT)	List price per 150mg vial: £2,947.00 PAS price per 150mg vial: [redacted]	List price per 20mg solution: £1,492.50	List price per 300mg vial: £4,790.00
Method of administration	IV infusion	SC injection	IV infusion
Doses	• **Initiation:** 150mg followed by 450mg IV infusions • **Subsequent doses:** 450mg IV infusion	• **Initiation:** 20mg • **Subsequent doses:** 20mg	• **Initiation:** 600mg as two separate 300mg IV infusions • **Subsequent doses:** 600mg IV infusion
Dosing frequency	• **Initiation:** week 0 and week 2 • **Subsequent doses:** Every 24 weeks	• **Initiation:** weeks 0, 1 and 2 • **Subsequent doses:** Monthly	• **Initiation:** week 0 and week 2 • **Subsequent doses:** Every 6 months
Dose adjustments	No dose reductions are recommended. In case of dose interruption or infusion rate reduction due to IRR, the total duration of the infusion would be increased, but not the total dose.	No dose adjustment is recommended.	No dose reductions are recommended. Dose interruption and slowing due to IRRs will result in a change in the infusion rate and increase the total duration of the infusion, but not the total dose.

	Ublituximab	Ofatumumab	Ocrelizumab
Average length of a course of treatment	Continuous treatment	Continuous treatment	Continuous treatment
Average cost of a course of treatment (acquisition costs only)	List price: • **Initiation:** [redacted] in year 1 • **Subsequent doses:** [redacted] per subsequent year PAS price: • **Initiation:** [redacted] in year 1 • **Subsequent doses:** [redacted] per subsequent year	• **Initiation:** £20,895 in year 1 • **Subsequent doses:** £17,910 per subsequent year	• **Initiation:** £19,160 in year 1 • **Subsequent doses:** £19,160 per subsequent year
(Anticipated) average interval between courses of treatment	NA – continuous treatment	NA – continuous treatment	NA – continuous treatment
(Anticipated) number of repeat courses of treatment	NA	NA	NA

Abbreviations: IRR, infusion-related reaction; IV, intravenous; mg, milligram; NA, not applicable; SC, subcutaneous; VAT, value-added tax.

Intervention and comparators' healthcare resource use and associated costs

Drug administration costs

The drug administration methods for ublituximab and ocrelizumab involve IV infusions that differ in the duration of the infusion and the monitoring time after the infusion at each session. This difference is considered in the cost calculations per drug administration by accounting for the proportion of bed-day costs and nursing costs per infusion. All other potential costs that may influence the drug administration were assumed identical between the two. Drug administration costs associated with IV infusions are presented in Table 31.

The bed-day costs for delivering the IV infusion therapy were sourced from the literature (103) and were inflation-adjusted. The nurse cost per hour were sourced from the PSSRU Unit Costs of Health and Social Care 2023 (hospital-based nurse band 6) (104). The total time required for the preparation, infusion and monitoring of patients receiving the infusions were sourced from the respective SmPC of the therapies.

Additionally, for those treatments delivered via IV infusions, the analysis also considered the pre-medication required to reduce and prevent IRRs, administered 30 minutes prior to each infusion. These included 100mg IV methylprednisolone, an antihistamine (chlorphenamine maleate, 4mg) and an antipyretic (paracetamol, 500mg). The unit costs for the pre-medication were sourced from the BNF and were applied to each treatment administration.

The drug administration method for ofatumumab involves a SC injection for which a cost is only attributed at treatment initiation, while subsequent administrations incur no costs. This approach is undertaken under the assumption that patients follow a two-hour training on self-administration from a MS-specialist nurse, in line with TA699 (54). Drug administration costs associated with SC injections for ofatumumab are presented in Table 32.

Table 31 Drug administration cost calculations for intravenous infusions

	First infusion		Subsequent infusions	
	Ublituximab	**Ocrelizumab**	**Ublituximab**	**Ocrelizumab**
Cost inputs				
Cost input 1: Bed day cost	£426.08			
Cost input 1: Source	Barker et al., 2020 (103)			
Cost input 2: Nurse cost per hour	£58.00			
Cost input 2: Source	PSSRU Unit Costs of Health and Social Care 2023. (Hospital-based nurse band 6) (104)			
Drug administration calculations				
Infusion preparation time (h)	1	1	1	1
Infusion time (h)	4	5	1	2.75
Time interval between patients (h)	0.25	0.25	0.25	0.25
Total infusion time per patient (h)	4.25	5.25	1.25	3.00
Monitoring after infusion (h)	1.00	1.00	0.00	1.00
Total preparation, infusion and monitoring time per patient per session(h)	6.25	7.25	2.25	5.00
Patients per bed per day	1.00	1.00	3.00	1.00
Nurse costs for infusion per patient	£362.50	£420.50	£130.50	£290.00
Cost per bed-day	£332.87	£386.13	£119.83	£266.30
Total	**£695.37**	**£806.63**	**£250.33**	**£556.30**

Abbreviations: h, hours; PSSRU, Personal Social Services Research Unit.

Table 32 Drug administration cost for subcutaneous injections

	Ofatumumab	
	First administration	**Subsequent administrations**
Cost input: MS nurse for 2 hours of training to teach self-administration	£116.00	£0
Cost input: Source	PSSRU Unit Costs of Health and Social Care 2023. (Hospital-based nurse band 6) (104)	

Abbreviations: h, hours; MS, multiple sclerosis; PSSRU, Personal Social Services Research Unit.

Resource use costs

Due to the comparable health outcomes of ublituximab, ofatumumab and ocrelizumab, it has been assumed that the resource utilisation for monitoring patients would be the same for all therapies in the CCA. This assumption is supported by the previous appraisal for ofatumumab, which assumes equal resource utilisation as ocrelizumab (54). The costs for resource use were extracted from TA699 and were inflation-adjusted, totalling £457.32 in the first year for treatment initiation and £377.88 for subsequent years of treatment. Estimated in TA699, these values encompass visits to the neurologist, MS nurse visits, ophthalmology visits, and undergoing regular testing such as full blood count, liver function test, urinalysis, renal function test, thyroid function test, Varicella zoster virus test, herpes papillomavirus test, Tuberculin skin test, Hepatitis B virus test and MRI. The costs of resource utilisation for patient monitoring are applied in each model cycle and are presented in Table 33.

Table 33 Resource costs of the intervention and comparator technologies

	Ublituximab	Ofatumumab	Ocrelizumab
Resource use costs in year 1	£457.32	£457.32	£457.32
Resource use costs in years 2+	£377.88	£377.88	£377.88

Adverse reaction unit costs and resource use

The costs of treating AEs were considered in the CCA separately for non-serious and SAEs. Unit costs for treating each non-serious and SAE were obtained from TA699 (54) and were inflation-adjusted. Unit cost inputs were then weighted by the proportion of patients experiencing SAEs from the relevant clinical trials of ublituximab, ofatumumab and ocrelizumab (10.8% for patients receiving ublituximab; 9.1% for patients receiving ofatumumab; and 7.0% for patients receiving ocrelizumab) (1,79,91). The list of AE costs included in the CCA has been aligned with previous TAs of ofatumumab and ocrelizumab (53,54) as this approach has been deemed appropriate by the ERG given that AEs are not key drivers of economic models of DMTs in MS. The list of costs inputs for AE management is presented in Table 34.

Table 34 AE management cost inputs and estimated costs per treatment

	Costs		Ublituximab n = 545	Ofatumumab n = 946	Ocrelizumab n = 825
	Non-serious AE	SAE			
Proportion of SAEs	-	-	10.8%	9.1%	7.0%
Arthralgia	£4.58	£556.06	3.9%	5.2%	5.6%
Back pain	£0.00	£849.41	9.4%	7.6%	6.4%
Bronchitis	£97.24	£98.47	4.4%	2.5%	5.1%
Depression	£1,046.91	£3,821.54	0.7%	4.8%	7.8%
Fatigue	£0.00	£67.02	5.1%	7.5%	7.8%
Headache	£0.00	£271.40	34.3%	13.3%	11.3%
Influenza-like illness	£0.00	£0.00	7.2%	2.2%	4.6%
IRR	£0.00	£0.00	5.0%	10.9%	34.3%
Injection site pain	£0.00	£48.34	0.0%	0.2%	0.2%
Insomnia	£0.00	£0.00	6.1%	4.1%	5.6%
Nasopharyngitis	£0.00	£48.34	18.3%	18.0%	14.8%
PML	£16,338.11	£16,338.11	0.0%	0.0%	0.0%
Sinusitis	£0.00	£0.00	3.9%	3.2%	5.6%
Upper respiratory tract infection	£48.34	£48.34	7.5%	10.3%	15.2%
Urinary tract infection	£2.60	£909.69	4.0%	10.3%	11.6%
One time cost	**-**	**-**	**£44.38**	**£91.20**	**£125.63**

Abbreviations: AE, adverse event; IRR, infusion-related reaction; PML, progressive multifocal leukoencephalopathy; SAE, serious adverse event.

Miscellaneous unit costs and resource use

There are no anticipated differences in any other cost category between the treatments included in this CCA.

Clinical expert validation

An external consultation with three health economic experts was held to validate the methodology used for calculating the annual treatment costs, drug administration costs, resource use costs and adverse event costs implemented in the model. Further, the cost-comparison model was subject to review and quality control before finalisation.

Unit costs were sourced from the BNF, the PSSRU Unit Costs of Health and Social Care report and prior NICE technology appraisals to ensure that the results of the analysis are appropriate for decision making in the UK.

Clinical expert validation was not sought for any costs or healthcare resource use value elicitation.

Uncertainties in the inputs and assumptions

The CCA is aligned with the approved product labels for the intervention and the comparators. Modelling choices and assumptions made in the CCA are presented in Table 35.

Table 35 Key model assumptions

Model assumptions	Rationale
Modelled costs were not discounted.	As per the NICE guidance, discounting of costs is not normally required in a CCA. However, a scenario analysis has been carried out to estimate the impact of discounting costs at a rate of 3.5%.
All modelled treatments have the same efficacy.	Given the results of the NMA, ublituximab is associated with a similar relative efficacy as ofatumumab and ocrelizumab.
Patients do not discontinue treatment.	This is a simplifying assumption, given that the cost-comparison model is based on the premise of similar efficacy across treatments. The impact of treatment discontinuation is explored in a scenario analysis.
Administration costs for subcutaneous injections (ofatumumab) are only applied in the first cycle.	Patients will receive their first administration of ofatumumab in the secondary care setting, while subsequent administrations are provided in the home setting. A two-hour training on self-administration from an MS-specialist nurse was assumed. Self-administrations are assumed to incur no costs.

IV administration cost estimations exclude detailed overhead costs in the absence of reliable data.	The cost of IV infusion therapy is based on the hospital bed-day costs as a proxy for hospital overhead costs, and the nurse cost per hour as a proxy for labour costs. The total administration costs for IV therapies were calculated using these costs and the infusion time required for each therapy, per the SmPC of the respective therapies. All other overhead costs that may be attributed to IV administrations in the clinical setting were assumed the same between treatments and were excluded from the calculations. These may include, but are not limited to, maintenance and other facility costs, cost of equipment and information technology, pharmacy costs, administrative costs, supportive staff costs, miscellaneous costs, etc.
Healthcare resource use costs are assumed the same for all therapy.	Due to similar expected health outcomes, healthcare resource use costs are not expected to differ between treatments. The input cost was derived from a previous TA in RRMS and it is assumed to encompass visits to the neurologist, MS nurse visits, ophthalmology visits, and undergoing regular testing.

Abbreviations: IV, intravenous; MS, multiple sclerosis; NMA, network meta-analysis; RRMS, relapsing-remitting multiple sclerosis; SmPC, summary of product characteristics; TA, technology appraisal; UK, United Kingdom.

B.4.3 Base-case results

Base-case results for a 5-year time horizon with ublituximab (at list price and with-PAS price) are presented in Table 36. Confidential PAS discounts for comparators are not included in the CCA because these values are not publicly known.

The results indicate that the total costs associated with treating RRMS patients with ublituximab are comparable to ofatumumab and ocrelizumab at their list prices. At its PAS price, ublituximab proves to be a cost-saving option, compared to ofatumumab and ocrelizumab. Additionally, as an IV infusion, ublituximab incurs less costs for drug administration and AE management than ocrelizumab.

Table 36 Total costs for the intervention and comparator technologies over a 5-year time horizon

	Drug acquisition costs	Drug administration costs	Resource use costs	Adverse event costs	TOTAL COSTS
Ublituximab, list price	[redacted]	£3,649	£1,966	£44	[redacted]
Ublituximab, PAS price	[redacted]	£3,649	£1,966	£44	[redacted]
Ofatumumab	£92,402	£116	£1,966	£91	£94,575
Ocrelizumab	£95,658	£5,526	£1,966	£126	£103,276

B.4.4 Sensitivity and scenario analyses

One-way sensitivity analysis

The one-way sensitivity analysis involved analysing the impact on the incremental costs when changing a single parameter at a time to reflect the uncertainty/variability in the estimation of that parameter. Except for the treatment package costs, the lower and upper bounds were set based on the 95% CIs of input values, where available, or were estimated to be within ±30% of the base-case value, where CIs were not available. The package costs for ublituximab, ofatumumab and ocrelizumab were assumed to be fixed in the sensitivity analysis

The results of the one-way sensitivity analysis are presented as separate tornado diagrams for the comparisons versus ofatumumab and ocrelizumab in Figure 18 and Figure 19, respectively. For each comparison, the ten most influential parameters are shown in descending order of cost difference sensitivity. In both comparisons, the two parameters with the greatest influence on the results were the nurse cost per hour and the bed-day costs, used for the estimation of administration costs of treatments. The CCA results are less sensitive to most other input parameters.

Figure 18 One-way sensitivity analysis; ublituximab vs ofatumumab

Abbreviations: AE, adverse event.

Figure 19 One-way sensitivity analysis; ublituximab vs ocrelizumab

Abbreviations: AE, adverse event.

Scenario analyses

Two scenario analyses were conducted to test alternative assumptions:

1. Costs are discounted at a rate of 3.5%;
2. Treatments are discontinued, based on rates derived from the NMA described in Section 3.2.4.

The second scenario explores the potential impact in the likelihood of treatment discontinuation. For this analysis, the model structure was modified to include an additional health state for patients who discontinued treatment. Patient transitioning to off-treatment was determined by treatment-specific discontinuation probabilities, using the RRs from the NMA, which were converted to annual probabilities. Specifically, an annual discontinuation probability of 6.8% was implemented for ublituximab, 5.9% for ofatumumab and 6.1% for ocrelizumab. Patients who discontinued treatment were assumed to incur no costs.

The results of the scenario analyses are presented in Table 37 below.

Table 37 Total costs derived from scenario analyses

	Base case	3.5% discounting	Treatment discontinuation
Ublituximab, list price	[redacted]	[redacted]	[redacted]
Ublituximab, PAS price	[redacted]	[redacted]	[redacted]
Ofatumumab	£94,575	£88,610	£86,454

Ocrelizumab	£103,276	£96,539	£93,672

Abbreviations: PAS, patient access scheme.

B.4.5 Subgroup analysis

There is no difference in the dosing schedules between the overall population and the highly active or RES subpopulations. Therefore, changes in the costs associated with the intervention or cost-comparison results are not expected from subgroup analyses.

B.4.6 Interpretation and conclusions of economic evidence

The clinical evidence presented demonstrated the use of ublituximab to be comparable to both ofatumumab and ocrelizumab as a treatment for RRMS. Similarly, the CCA has demonstrated that at its discounted PAS price, ublituximab represents a cost-saving alternative for the NHS in England, of up to [redacted] in savings compared to ofatumumab and up to [redacted] in savings compared to ocrelizumab, supporting its reimbursement as a valuable treatment option for patients with RRMS.

A further advantage demonstrated in this CCA is the potential cost-savings to the NHS from lower drug administration costs for IV infusions, compared to ocrelizumab. The shortened infusion process of ublituximab contributes to enhanced patient comfort and convenience and helps improve efficiency in hospital workflows by streamlining the treatment process and freeing up staff capacities for the NHS, which ultimately leads to better care for more MS patients. These results are generalisable to adults with active relapsing forms of MS in England and Wales.

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B.6 Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Price details of treatments included in the submission

Appendix I: Checklist of confidential information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ublituximab for treating relapsing multiple sclerosis [ID6350]

Summary of Information for Patients (SIP)

August 2024

File name	Version	Contains confidential information	Date
ID6350 Ublituximab for treating relapsing multiple sclerosis - SIP	**2**	**No**	**21st August 2024**

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Ublituximab **Brand name:** Briumvi®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The full marketing authorisation for ublituximab is for the treatment of adults with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features, which covers both relapsing-remitting multiple sclerosis (RRMS) and relapsing forms of secondary progressive multiple sclerosis (SPMS). However, the submission of evidence which is being appraised by NICE focusses on use of the treatment only amongst adults with RRMS.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Ublituximab (Brimuvi®, Neuraxpharm Pharmaceuticals) has a marketing authorisation in the UK for the treatment of adult patients with RMS with active disease defined by clinical or imaging features (https://assets.publishing.service.gov.uk/media/654514ff49ec56000d4767d3/Marketing_authorisations_granted_15_October_to_31_October_2023.pdf) (1).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The company (Neuraxpharm Pharmaceuticals) has met with the MS Society, ShiftMS and the MS Trust at various meetings in order to make them aware of the new treatment.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is MS?

Multiple Sclerosis (MS) is a central nervous system disorder that is chronic, inflammatory, demyelinating, and neurodegenerative. It frequently results in the development of clinical impairment that is permanent (2). Although MS can occur at any age, the majority of people are diagnosed between the ages of 20 and 50 (3). The manifestations of MS exhibit significant variability among individuals and can fluctuate daily.

Symptoms:

Common symptoms include pain, muscle weakness or spasticity, persistent fatigue, an unsteady gait or balance issues, visual disturbances, incontinence, and cognitive deficits. Multiple sclerosis represents the leading cause of chronic neurological disability and affects two to three times more women than men (4,5).

What causes MS?

Multiple sclerosis is an autoimmune condition. The underlying causes of MS and the reasons behind its unpredictable course are still poorly understood (3). Multiple risk factors are implicated in the development of MS, including age, gender, race, heredity, geographic location, and infections such as herpes simplex, chlamydia, and rabies (6,7). Risk factors such as obesity, smoking, and the Epstein Barr virus are also associated with MS, while the relationship between low vitamin D levels and MS is well-established (8). Multiple sclerosis is, therefore, believed to arise from a complex interaction of genetic predisposition, dietary influences, and environmental factors (9,10). Consequently, MS is regarded as the most prevalent cause of neurological disability, as the inflammatory lesions associated with MS can impact a wide range of systems to varying degrees, resulting in numerous neurological symptoms and comorbidities (11).

How many people get MS?

- Prevalence and incidence rates vary in different parts of the UK, in general, becoming progressively higher in more northerly populations. Multiple sclerosis is more than twice as common in females as in males. Females in the 50–59-year age group are three times more likely than males of a similar age to have MS (12).
- The MS Trust estimates the prevalence rates of MS to be:

  - 190 per 100,000 in England (around 105,450 people).
  - 179 per 100,000 in Wales (about 5,600 people) (13).

What is a relapse?
The emergence of new symptoms or the return of previous ones for a duration of 24 hours or longer, without the presence of an infection or a shift in body temperature, is referred to as a relapse (14)**.**

Disease Burden

Relapse episodes, a common symptom of RRMS, can include a variety of sensory symptoms (such as tingling, burning, or numbness), motor symptoms (such as weakness, stiffness, clumsiness, difficulty walking, speech, and swallowing impairments), visual disturbances, physical or mental fatigue interfering with daily activities, mood disorders (such as anxiety and depression), genitourinary and bowel dysfunction, tremor, and stiffness, among other symptoms. This disability (especially the inability to walk) worsens over time regardless of relapse activity if RRMS develops into SPMS. Within 15 to 20 years of stopping treatment, 50–60% of people with RRMS develop secondary progressive illness and after 14 years, the average patient can no longer walk 100 metres without assistance (15).

Impact on quality-of-life (QoL)

Multiple sclerosis has a negative effect on QoL because of the emotional and mental impact of the disease. Previous research has indicated that patients with MS reported significantly worse QoL compared to both epilepsy and diabetes groups on the Physical Functioning, Role Limitations-Physical, Energy, and Social Function scales (16). In MS patients, worse QoL is linked to increased disability, symptoms of anxiety and sadness, exhaustion, and physical comorbidities. As a result, interventions that reduce disability are expected to yield the most substantial improvement in QoL (17).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

NICE guidelines for the management of MS in adults describe the process for diagnosing MS (18), which should be based on using a combination of history, examination, magnetic resonance imaging (MRI), laboratory findings, and by following the 2017 McDonald criteria (19). Following referral to a consultant neurologist or specialist, diagnosis should involve the following steps:

- assessing that symptoms are consistent with an inflammatory demyelinating process; for example, headache is not suggestive of MS,
- excluding alternative diagnoses (targeted laboratory tests may be indicated if the history, examination or MRI findings are atypical),
- establishing that lesions on MRI scans have developed at different times and are in different anatomical locations for a diagnosis of RRMS,
- looking for cerebrospinal fluid-specific oligoclonal bands if there is no clinical or radiological evidence of lesions developing at different times,
- establishing progressive neurological deterioration over 1 year or more for a diagnosis of primary progressive multiple sclerosis (PPMS) (18).

2c) Current treatment options:

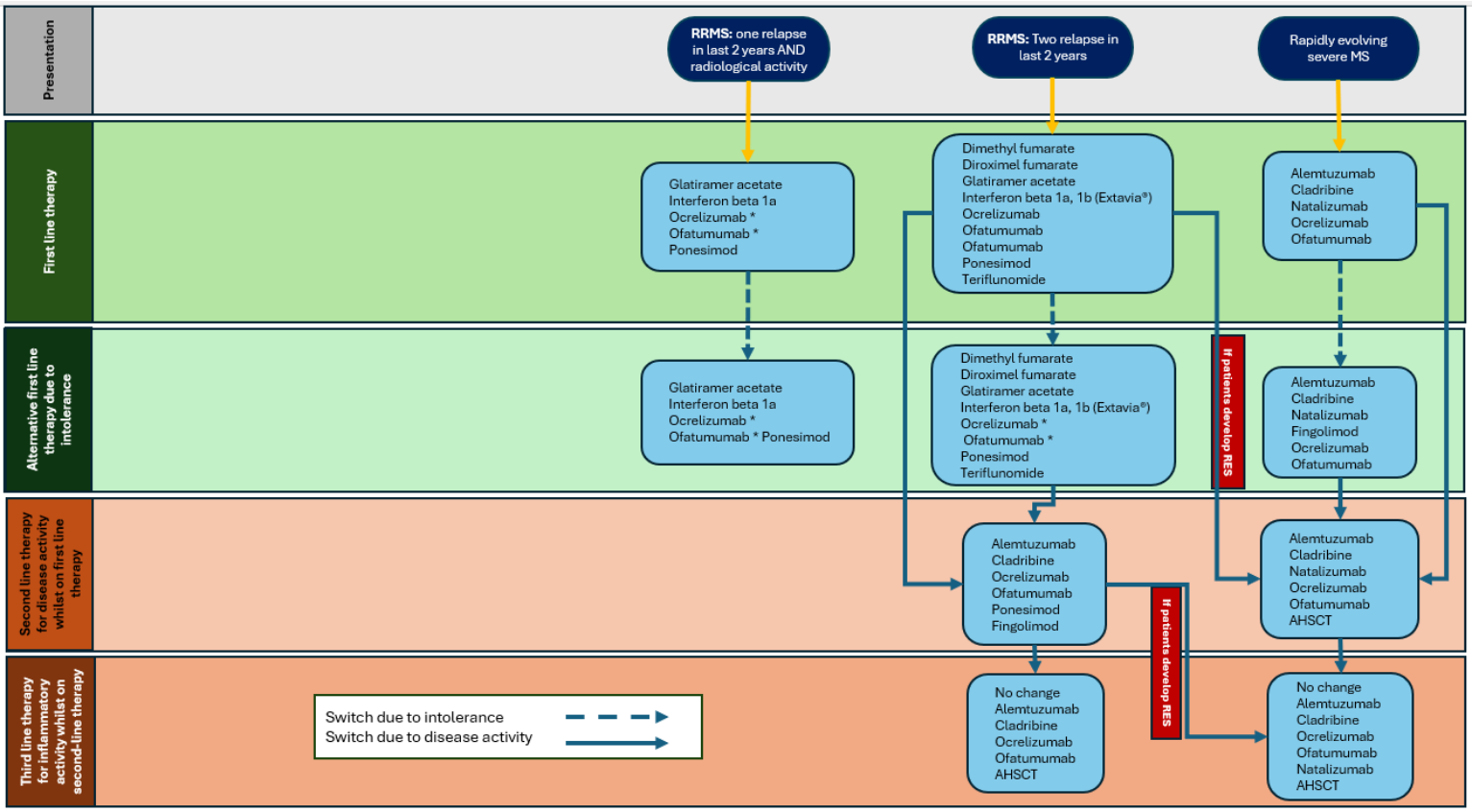
The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Treatment pathway and implementation of ublituximab

NICE provides guidelines for the management of MS in adults (18), while the NHS England treatment pathway presents the recommended lines of therapy for RRMS patients, with recommended treatment switches also presented (20) (Figure 1). The Association of British Neurologists have highlighted the complex treatment landscape in the area of RRMS, and have stressed the importance of patient involvement in decision making (21). To this point, the decision to prescribe a medication for RRMS is primarily based on an informed discussion and mutual agreement between the prescribing clinician and the patient. This decision considers factors such as the level of disease activity, the patient's risk tolerance, preferences, and lifestyle factors such as family planning (22–24).

Figure 1 ***Treatment algorithm for RRMS***



Ublituximab has been approved for the treatment of adult patients with RMS who have active disease defined by clinical or imaging features. Ublituximab offers an additional treatment option for adult patients with RRMS, including those patients with active, highly active, or rapidly evolving severe (RES) RRMS. Ublituximab is intended as an alternative treatment option to ocrelizumab and ofatumumab, which are currently recommended for the active, highly active, and RES RRMS patient populations for all lines of treatment. Therefore, ublituximab is anticipated to occupy a comparable position in the treatment pathway to these two comparators.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The clinical study by Martinez et al. 2016 has assessed preferences for treatments like ublituximab in a population of patients with MS, using a discrete choice experiment (25). The discrete choice experiment uses a survey-based experimental design, where participants are presented with a series of hypothetical scenarios. This enables the quantification of the relative importance of each attribute/level during the decision-making process.

In their research, Martinez et al. 2016 included a total of 125 patients in the final analysis (62.9% female, mean age 44.5 years, 71.5% with RRMS diagnosis). They found that the most important factor for patients was the possibility of suffering from the side effects of the treatment (relative importance [RI] = 50%), followed by a delay in disease progression (RI = 19.4%), and route and frequency of administration (RI = 14.3%). Therefore, on the basis of the findings from this study, the most important attribute for MS patients was side effects of treatments, followed by delay in disability progression. Experience with treatments and time since MS diagnosis changed patients' preferences (25).

Research published by Kremer et al. 2015, which also involved an assessment of preferences of patients with MS for attributes of treatments in decision-making through a series of focus groups, indicated that patients value effectiveness and unwanted effects most (26).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Ublituximab is designed to treat MS by targeting specific cells in the immune system. It belongs to a group of treatments called monoclonal antibodies (mAbs), which work by removing certain B-cells that play a role in MS (27). Monoclonal antibodies like ublituximab have benefits over other treatments, including long-lasting effects so patients don't need to take them as often (28,29). Studies have shown that ublituximab can reduce the rate of MS relapses and slow down disability progression better than some other treatments (30).

Ublituximab works by removing B-cells in the body through a special process:

- In regular treatments, certain sugars in the body can block its effectiveness (31).
- Ublituximab is engineered to aovid this problem, making it more effective at its job (31).

In laboratory studies, ublituximab was shown to be 25 to 30 times more powerful than other similar treatments (32). Clinical trials also showed that it could start working within 24 hours

(33,34). Over a period of 96 weeks, patients taking ublituximab had fewer relapses and fewer new lesions on MRI scans compared to those taking another medication called teriflunomide (33). This suggests that ublituximab could provide better outcomes for patients with RRMS while also reducing less frequent monitoring and potentially reducing healthcare costs.

Further information on how ublituximab works is provided in the Patient Information Leaflet (Package leaflet: Information for the patient | Briumvi. (35)) and in the associated Summary of Product Characteristics (36).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Ublituximab is not intended to be used in combination with any other medicine.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is ublituximab taken?

Patients take ublituximab as an intravenous (IV) infusion (drip directly into veins). Treatment is initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions (35).

How much and how often ublituximab will be given?

First and second doses

The first dose is administered as a 150mg IV infusion (first infusion), followed by a 450mg IV infusion (second infusion) 2 weeks later.

Subsequent doses

Subsequent doses are administered as a single 450mg IV infusion every 24 weeks. The first subsequent dose of 450mg should be administered 24 weeks after the first infusion. A minimal interval of 5 months should be maintained between each dose of ublituximab.

Ublituximab has an advantage over other IV drugs due to its shorter infusion duration from the second infusion onwards, and no requirement for post-infusion monitoring from the third infusion onwards in the absence of infusion reactions. This feature can significantly improve patient management in hospitals by streamlining the treatment process and freeing up staff capacities for the NHS, which ultimately leads to better care for more MS patients. The shortened infusion process of ublituximab (after first infusion, all subsequent infusions last 1 hour) not only helps improve efficiency in hospital workflows but also contributes to enhanced patient comfort and convenience. In addition, there is no need for monitoring post-infusion from the third infusion onwards with ublituximab, unless there are infusion reactions, which is not the case with ocrelizumab which requires patients to be monitored during the infusion and for at least one hour after the completion of each infusion (https://www.ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf). By minimising the time spent on infusion, patients can experience reduced discomfort and may even be able to resume their daily activities sooner. Furthermore, the shorter infusion duration could help alleviate logistical challenges associated with scheduling and resource allocation within healthcare facilities, ultimately leading to improved overall patient care and management. Additionally, premedication for ublituximab infusions can be administered through various routes, including oral, subcutaneous, intramuscular, and intravenous, offering greater convenience for patients compared to ocrelizumab.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of ublituximab in RMS

The ULTIMATE trials were phase III, multicentre, double-blind, double-dummy, randomised, active-controlled trials conducted in parallel at non-overlapping sites. The trials were designed to evaluate the efficacy and safety of ublituximab infusions as compared with oral teriflunomide in patients with RMS. In brief, the patient inclusion criteria consisted of (33):

- at least two relapses in the previous 2 years, or one relapse or at least one gadolinium-enhancing lesion or both in the year before screening;
- brain MRI with abnormalities consistent with MS;
- a score on the Expanded Disability Status Scale (EDSS) of 0 to 5.5 at screening;
- neurologic stability for at least 30 days before screening and the baseline assessment.

Key Exclusion Criteria:

- Treatment with anti-CD20 or other B cell directed treatment;
- Treatment with alemtuzumab, natalizumab, teriflunomide and stem cell transplantation at any time prior to randomisation;
- Therapies that were disallowed (minimum of 4 weeks prior to randomisation): phenytoin, warfarin, tolbutamide, St John's Wort or cholestyramine;

- Prior diease-modifying therapy exposure within months of screening;
- Diagnosed with PPMS;
- Pregnant or nursing;
- ≥10 years disease duration from onset with participants EDSS ≤2.0.

1,094 patients were randomised across 104 sites in 10 countries (33). Both studies were completed by November 2020 (37,38).

Table 1 Study location and site details (39)

Country, n (%)	**ULTIMATE I (n = 549)**	**ULTIMATE II (n = 545)**
Belarus	64 (11.7)	64 (11.7)
Croatia	-	49 (9.0)
Georgia	83 (15.1)	-
Poland	41 (7.5)	77 (14.1)
Russia	133 (24.2)	163 (29.9)
Serbia	64 (11.7)	-
Spain	5 (0.9)	8 (1.5)
UK	4 (0.7)	5 (0.9)
Ukraine	107 (19.5)	143 (26.2)
USA	48 (8.7)	36 (6.6)

Further information about ULTIMATE I and ULTIMATE II can be found in the following sources:
• Steinman. L, 2022. (Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis - PubMed (nih.gov))
• ULTIMATE I and II ClinicalTrials.gov numbers, NCT03277261 and NCT03277248).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In the ULTIMATE I and II studies, the efficacy of ublituximab was measured according to how well it improved outcomes after 96 weeks of treatment:

- Annualised relapse rate at 96 weeks (number of confirmed MS relapses in a year);

- Total number of gadolinium-enhancing T1 lesions by week 96;
- Total number of new or enlarging T2 hyperintense lesions by week 96;
- The number of participants with no evidence of disease activity from week 24 to week 96;
- Time to confirmed disability progression (CDP) for at least 12 weeks;
- Time to CDP for at least 24 weeks.

The key efficacy results of the ULTIMATE I and II studies after 96 weeks of treatment with ublituximab were as follows (39):

- When compared to teriflunomide, ublituximab showed a significant 60% and 49% relative reduction in annualised relapse rate in ULTIMATE I and ULTIMATE II, respectively;
- Total number of gadolinium-enhancing T1 lesions and new or enlarging T2 hyperintense lesions reduced significantly in both trials;
- A significantly greater proportion of patients receiving ublituximab therapy attained no evidence of disease activity (44.6% in ULTIMATE I and 43% in ULTIMATE II);
- As compared with teriflunomide, ublituximab was associated with a very low rate of disability progression, with >94% of patients not showing a 12-week CDP and >96% of patients not showing a 24-week CDP;
- Ublituximab exhibited a favourable safety and tolerability profile with no unexpected safety signals.

Further information related to an indirect treatment comparison performed is available in Sections 3.8 and 3.9 of the main submission; comparable effectiveness of ublituximab with the comparator treatments of ocrelizumab and ofatumumab has been demonstrated for the outcomes of annualised relapse rate, CDP, and treatment discontinuation.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the ULTIMATE I and ULTIMATE II trials, QoL assessments of patients were conducted using the Multiple components of Multiple Sclerosis Quality of Life-54 and Short Form-36 measures (40).

At the 96-week timepoint, there were statistically significant improvements favouring ublituximab over teriflunomide in a number of Multiple Sclerosis Quality of Life-54 components, including overall QoL, physical and mental health composites, physical role limitations, physical health, changes in health, and energy. Compared to teriflunomide, ubituximab significantly improved the Short Form-36 in the areas of physical functioning, role-physical, and physical component summary (40).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In the ULTIMATE I and II trials, ubltuximab was generally a well-tolerated treatment option (33).

The most common side effects experienced by patients receiving ublituximab were infection (respiratory tract–related, nasopharyngitis, pharyngitis, urinary tract infections) in ULTIMATE I and ULTIMATE II. The most common side effects, which affected all participants who received at least one dose of a trial drug in ULTIMATE I and ULTIMATE II, are summarised in Table 2 below (33):

Table 2 Adverse events (Safety population)

Event	**ULTIMATE I**		**ULTIMATE II**	
	Ublituximab (n = 273)	Teriflunomide (n = 275)	Ublituximab (n = 272)	Teriflunomide (n = 273)
Any adverse event, n (%)	235 (86.1)	245 (89.1)	251 (92.3)	256 (93.8)
Adverse event leading to treatment discontinuation, n (%)	18 (6.6)	2 (0.7)	5 (1.8)	2 (0.7)
Infection, n (%)	135 (49.5)	133 (48.4)	169 (62.1)	165 (60.4)
Infusion-related reaction, n (%)	120 (44.0)	19 (6.9)	140 (51.5)	48 (17.6)
Neoplasm, n (%)	0	0	2 (0.7)	1 (0.4)
Serious adverse event, n (%)	31 (11.4)	19 (6.9)	28 (10.3)	21 (7.7)
Serious infection, n (%)	15 (5.5)	6 (2.2)	12 (4.4)	10 (3.7)
Death, n (%)§	2 (0.7)	0	1 (0.4)	0

§ The deaths that occurred in the ublituximab group were due to pneumonia (deemed to be possibly related to treatment), encephalitis (after measles), and salpingitis (after ectopic pregnancy).

More than 1 in 10 patients may experience infusion-related responses, which are the most frequent side effect of ublituximab treatment. These are mostly mild reactions, but they can occasionally become serious (35). If a patient experiences any side effects while they are taking ublituximab, they should talk to their doctor, pharmacist or nurse as soon as possible.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration .

Effectiveness

The annualised relapse rate results for ublituximab from the ULTIMATE I and II studies are particularly notable given that they are <0.10 over 96 weeks (0.08 in ULTIMATE I and 0.09 in ULTIMATE II); reflecting a relapse rate of less than one relapse per decade. This is a level of clinical efficacy for this outcome that has not been achieved by comparator treatments (33).

Benefits related to mode of administration

As detailed previously, ublituximab has a shorter infusion duration from the second infusion onwards, and there is no requirement for post-infusion monitoring from the third infusion onwards in the absence of infusion reactions. This feature can significantly improve patient management in hospitals, and also lead to a less invasive experience for patients.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Ublituximab is administered by IV in the hospital setting, and therefore the disadvantages will mirror the disadvantages associated with existing, comparable IV treatments.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

This submission presents a cost-comparison analysis, which is based on evidence that ublituximab is equally or more effective than treatments currently recommended by NICE for RRMS.

A cost-comparison tool was created to compare the costs associated with ublituximab against the costs of treatment with ofatumumab and ocrelizumab. Both ofatumumab and ocrelizumab were considered relevant comparators for the model as they are recommended for use in the same patient population for which ublituximab is being positioned.

The cost-comparison model considers different cost components associated with treatments. These include:

- The cost of the drug;
- The cost of administering the drug – this is estimated differently for drugs administered via an IV infusion or a subcutaneous injection;
- The cost of other healthcare resource use, such as visits to the specialists and regular testing required throughout the year; and
- The cost for treating an adverse event or side effect that emerges from the modelled treatments.

The model compares the different cost components over five years to account for higher initiation costs (i.e., starting treatment costs) and to allow the costs to stabilise over time so an accurate overall cost could be considered.

The results of the cost-comparison analysis indicate that ublituximab represents a valuable alternative to the NHS in England and Wales. The introduction of ublituximab as an alternative IV infusion therapy also provides a notable benefit in the reduced frequency of infusions needed compared to ocrelizumab, which can decrease the overall burden to the NHS and to patients. A reduction in infusion frequency can lead to shorter hospital visits and an enhanced patient experience, with the same or better efficacy.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Ublituximab achieves high levels of clinical effectiveness in relation to the annualised relapse rate outcome, and also frees up staff capacities for the NHS due to the shortened infusion process of ublituximab as well as the fact that there is no requirement for post-infusion monitoring from the third infusion onwards in the absence of infusion reactions (see further details on these points in previous sections, as well as in the main submission of evidence).

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality issues relating to ublituximab have been identified. Introduction of ublituximab is not likely to lead to recommendations which differentially impact patients protected by the equality legislation or disabled persons.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf Further information on the relevant clinical trial data for ublituximab: • Steinman. L, 2022. (Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis - PubMed (nih.gov)) • ULTIMATE I and II ClinicalTrials.gov numbers, NCT03277261 and NCT03277248).

Further information on MS:

- https://www.mssociety.org.uk/about-ms/types-of-ms?gad_source=1&gclid=CjwKCAjwqMO0BhA8EiwAFTLgIDgTUyUBg4qQ7PcHK4e3b4_KDA_94sTpNoOLMYS7-qF1fzdHFdarWRoC9UMQAvD_BwE

4b) Glossary of terms

CDP: Confirmed disability progression
EDSS: Expanded disability status scale
IV: Intravenous
mAb: Monoclonal antibody
MRI: Magnetic resonance imaging
MS: Multiple sclerosis
NHS: National Health Service
NICE: National Institue for Health and Care Excellence
PPMS: Primary progressive multiple sclerosis
QoL: Quality-of-life
RES: Rapidly evolving severe
RI: Relative importance
RMS: Relapsing multiple sclerosis
RRMS: Relapsing-remitting multiple sclerosis
SPMS: Secondary progressive multiple sclerosis
UK: United Kingdom

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND

CARE EXCELLENCE

Cost Comparison Appraisal

Ublituximab for treating relapsing multiple sclerosis [ID6350]

Clarification questions

August 2024

File name	Version	Contains confidential information	Date
ID6350 Ublituximab for treating relapsing multiple sclerosis – Clarification questions	**1**	**Yes**	**23rd August 2024**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Clinical trial data

A1. Priority question: Please provide the full clinical study reports for both ULTIMATE trials.

Company Response: Full clinical study reports have now been provided for the ULTIMATE I and II trials.

A2. Table 8 in Document B presents baseline characteristics (p 48).

i) For number of relapses in previous 12 months and 24 months, please provide the proportion of patients with 0, 1, 2, 3, etc, relapses.

ii) Please provide p-values of differences between study arms for age, % female, % SPMS, time since symptom onset, time since diagnosis, % no previous disease modifying treatment, % previous disease modifying treatment, no. of T2 lesions, and no. of Gd-enhancing lesions.

Company Response: (i) Please see details related to the proportion of patients with 0, 1, 2, 3, ≥4 relapses in ULTIMATE I and II (1,2), in Table 1 below.

Table 1. ***Number of relapses in ULTIMATE I and II (baseline characteristics)***

Number of relapses in the year prior to screening, n (%)	ULTIMATE I		ULTIMATE II	
	Ublituximab (n = 271)	Teriflunomide (n = 274)	Ublituximab (n = 272)	Teriflunomide (n = 272)
0	11 (4.1)	8 (2.9)	16 (5.9)	15 (5.5%)
1	178 (65.7)	173 (63.1)	182 (66.9%)	192 (70.6%)
2	68 (25.1)	79 (28.8)	66 (24.3%)	51 (18.8%)
3	13 (4.8)	10 (3.6)	4 (1.5%)	12 (4.4%)
≥4	1 (0.4)	4 (1.5)	4 (1.5%)	2 (0.7%)
Number of relapses in the 2 years prior to screening, n (%)				
0	2 (0.7)	2 (0.7)	5 (1.8%)	6 (2.2%)
1	105 (38.7)	89 (32.5)	112 (41.2%)	104 (38.2%)
2	122 (45.0)	125 (45.6)	113 (41.5%)	122 (44.9%)
3	24 (8.9)	38 (13.9)	30 (11.0%)	29 (10.7%)
≥4	18 (6.6)	20 (7.3)	12 (4.4%)	11 (4.0%)

Company Response: (ii) Please see details related to P-values of differences between study arms for specific baseline characteristics in the ULTIMATE studies (1,2), in Table 2 below.

Table 2. ***Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population)****

	ULTIMATE I and II		
	Ublitixumab (n = 543)	**Teriflunomide (n = 546)**	**P-value**
Age (years) **Mean** **SD**	 35.343 8.6281	 36.586 9.3035	0.0224
Gender, n (%) **Male** **Female**	 199 (36.6%) 344 (63.4%)	 191 (35.0%) 355 (65.0%)	0.5663
Type of MS at Screening, n (%) **Relapsing-remitting** **Secondary progressive**	 532 (98.0%) 11 (2.0%)	 537 (98.4%) 9 (1.6%)	0.6599
Time since first MS Symptoms (years) **Mean** **SD**	 7.415 6.4909	 7.102 6.0803	0.4115
Time since diagnosis (years) **Mean** **SD**	 4.965 5.4283	 4.734 5.0699	0.4686
Received approved DMT, n (%) **Yes** **No**	 198 (36.5%) 345 (63.5%)	 169 (31.0%) 377 (69.0%)	0.0544
Number of Gd-enhancing lesions** **Mean** **SD**	 2.4 5.62	 2.0 4.67	0.2286
No. of T2 lesions** **Mean** **SD**	 64.7 39.90	 62.2 39.17	0.2953

Abbreviations: DMT, disease modifying therapy; Gd, gadolinium; MS, multiple sclerosis; SD, standard deviation.

* The modified intention-to-treat population included all participants who received at least one dose of a trial drug and had one baseline and at least one post-baseline efficacy assessment.

** Data were missing for 1 participant in the ublituximab group and 2 participants in the teriflunomide group in the ULTIMATE I trial and for 2 participants in the teriflunomide group in the ULTIMATE II trial.
P-values were based on t-test for continuous variables, and chi-square test or exact test for categorical variables.

A3. Priority question: Please provide a summary of AEs and SAEs for ocrelizumab, and ofatumumab from their respective trials. If feasible, please provide an indirect comparison (such as an NMA) of AEs and SAEs for ublituximab, ocrelizumab, and ofatumumab.

Company Response: A summary of adverse events (AEs) and serious adverse events (SAEs) for ocrelizumab and ofatumumab from their respective trials, has been presented in Tables 3-7 below.

As part of an advisory board meeting with methodological experts (statistical and health economic), the topic of performing network meta-analysis (NMA) for AEs was

discussed. This process is extremely complex and, more importantly, prone to issues due to the fact that there are often minor differences in how AEs are defined across clinical trials. One also needs to consider the impact of varying duration of follow-up when interpreting results. Because certain AEs are more likely to occur at the start of treatment, i.e., infusion-related reactions, there tends to be a related survivorship bias when it comes to interpreting the results of an NMA of AEs. For the above reasons, we were strongly advised not to perform such an analysis due to the inherent issues.

The approach of not performing NMA for AEs, and focussing only on the outcomes of annualised relapse rate (ARR), confirmed disability progression (CDP), and treatment discontinuation, is consistent with previous NICE technology appraisals including NICE TA533 (3) and NICE TA699 (4), which also did not perform indirect treatment comparison related to AEs for the different monoclonal antibodies (mAbs). Indeed, this topic was discussed in the clarification questions that were raised by the External Assessment Group (EAG) following the company submission as part of NICE TA533 (3).

In this case, the EAG requested clarification from the company regarding AE data that the company had utilised that they had derived from a previous submission of evidence for daclizumab (NICE TA441 (5)). Following clarification questions, the submitting company in NICE TA533 (3) subsequently determined that the data they had initially believed to have been estimated from an NMA as part of NICE TA441 (5) had actually not been estimated via NMA due to heterogeneity in AE reporting that did not allow for the pooling of data (see issues with such analyses, described previously). Therefore, the approach to not performing NMA for this outcome is consistent across previous submissions to NICE in this clinical area.

Ocrelizumab – Adverse events

AE data for ocrelizumab are based on data extracted from the primary publication of the OPERA I and II trials (6).

Table 3. ***Adverse events – Safety population****

Events	OPERA I		OPERA II	
	Ocrelizumab (n = 408)	Interferon beta-1a (n = 409)	Ocrelizumab (n = 417)	Interferon beta-1a (n = 417)
Any adverse event, n (%)	327 (80.1)	331 (80.9)	360 (86.3)	357 (85.6)
Adverse event leading to treatment discontinuation, n (%)	13 (3.2)	26 (6.4)	16 (3.8)	25 (6.0)
At least 1 infusion-related reaction, n (%)	126 (30.9)	30 (7.3)	157 (37.6)	50 (12.0)
Infection, n (%)†	232 (56.9)	222 (54.3)	251 (60.2)	219 (52.5)
System organ class infection or infestation, n (%)	231 (56.6)	216 (52.8)	251 (60.2)	217 (52.0)
Herpes infection				
Herpes zoster	9 (2.2)	4 (1.0)	8 (1.9)	4 (1.0)
Oral herpes	9 (2.2)	8 (2.0)	15 (3.6)	9 (2.2)
Neoplasm, n (%)‡	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)
Death, n (%)§	0	1 (0.2)	1 (0.2)	1 (0.2)
Any serious adverse events, n (%)	28 (6.9)	32 (7.8)	29 (7.0)	40 (9.6)
Serious infection or infestation, n (%)¶	5 (1.2)	12 (2.9)	6 (1.4)	12 (2.9)

* Shown are data collected during the double-blind, controlled treatment period. The safety population included all the patients who received any study drug. Data for patients who underwent randomisation and received a therapy that was different from that intended are summarised according to the therapy actually received. Patients who did not undergo randomisation but who received a study drug were included in the safety population, and their data are summarised according to the therapy actually received.

† Infections were identified either as adverse events as defined in the *Medical Dictionary for Regulatory Activities* infections system organ class "infections and infestations" or as an adverse event with pathogen information provided.

‡ The neoplasms reported in the OPERA I trial were ductal breast carcinoma (in two patients) and renal cancer (in one) in the ocrelizumab group and mantle-cell lymphoma (in one) in the interferon beta-1a group. The neoplasms reported in the OPERA II trial were malignant melanoma (in one patient) in the ocrelizumab group and squamous-cell carcinoma (in one) in the interferon beta-1a group.

§ Deaths occurring during the trials were due to suicide (one in the ocrelizumab group in the OPERA II trial and one in the interferon beta-1a group in the OPERA I trial) and mechanical ileus (one in the interferon beta-1a group in the OPERA II trial).

¶ Serious infections and infestations reported in the ocrelizumab group were appendicitis (in three patients), cellulitis (in two), pyelonephritis (in two), and biliary sepsis, device-related infection, herpes simplex infection, pneumonia, and upper respiratory tract infection (in one patient each). Serious infections and infestations reported in the interferon beta-1a group were appendicitis (in three patients), limb abscess (in two), injection-site cellulitis (in two), pneumonia (in two), urinary tract infection (in two), and acute tonsillitis, anal abscess, infective cholecystitis, cystitis, infectious enterocolitis, viral gastritis, gastroenteritis, perirectal abscess, staphylococcal septic arthritis, staphylococcal sepsis, tooth infection, viral infection, and viral pericarditis (in one patient each).

All analyses presented in this updated table below are based on information available as of January 20, 2016, encompassing all AEs observed up until the study clinical cut-off date prior to patients transitioning to the open-label extension.

Table 4. ***Updated list of adverse events* (Safety population, pooled OPERA I and OPERA II)***

Event, n (%)	Interferon beta-1a (n = 826)	Ocrelizumab (n = 825)
Any adverse event	689 (83.4)	688 (83.4)
Most frequently reported adverse events†		
Infusion-related reaction	82 (9.9)	283 (34.3)
Nasopharyngitis	84 (10.2)	123 (14.9)
Upper respiratory tract infection	88 (10.7)	125 (15.2)
Headache	125 (15.1)	93 (11.3)
Urinary tract infection	100 (12.1)	96 (11.6)
Fatigue	64 (7.7)	65 (7.9)
Influenza-like illness	177 (21.4)	38 (4.6)
Injection site erythema	129 (15.6)	1 (<1)
Infusion-related reactions		
Patients with at least one infusion-related reaction	82 (9.9)	283 (34.3)
Total no.	112	505
Grade‡		
1	56 (6.8)	179 (21.7)
2	24 (2.9)	83 (10.1)
3	2 (<1)	20 (2.4)
4	0	1 (<1)§
5	0	0
System organ class infection or infestation	434 (52.5)	483 (58.5)
Herpes infection		
Herpes zoster	8 (1.0)	17 (2.1)
Oral herpes	18 (2.2)	25 (3.0)
Death††	2 (<1)	1 (<1)
Any serious adverse events	73 (8.8)	58 (7.0)
Serious infection or infestation§§	24 (2.9)	11 (1.3)

* The safety population included all patients who received any study drug. Randomised patients who received incorrect therapy different from that intended were summarised in the group according to the therapy actually received. Patients who were not randomised, but who received study drug, were included in the safety population and summarised according to the therapy actually received.

† These events were reported by at least 10% of patients in any group. The events are listed by decreasing incidence among ocrelizumab-treated patients.

‡ Grading in severity: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, 5 = death.

§ One patient had a serious infusion-related reaction at the first infusion, with the symptom of Grade 4 bronchospasm.

†† Deaths occurring during the study were due to mechanical ileus (one in the interferon beta-1a arm in the OPERA II study) and suicide (one in the interferon beta-1a arm in the OPERA I study and one in the ocrelizumab arm in the OPERA II study).

§§ Serious infections and infestations reported were: appendicitis (n=3), abscess limb (n=2), injectionsite cellulitis (n=2), pneumonia (n=2), urinary tract infection (n=2), acute tonsillitis, anal abscess, cholecystitis infective, cystitis, enterocolitis infectious, gastritis viral, gastroenteritis, perirectal abscess, septic arthritis staphylococcal, staphylococcal sepsis, tooth infection, viral infection, and viral pericarditis (all n=1) with IFNβ-1a, and appendicitis (n=3), cellulitis (n=2), pyelonephritis (n=2), biliary sepsis, device-related infection, herpes simplex, pneumonia, and upper respiratory tract infection (all n=1) with ocrelizumab.

Table 5. ***Most frequently reported adverse events* (Safety population†)***

Event, n (%)	**OPERA I**		**OPERA II**	
	Ocrelizumab (n = 408)	**Interferon beta-1a (n = 409)**	**Ocrelizumab (n = 417)**	**Interferon beta-1a (n = 417)**
Infusion-related reaction	126 (30.9)	30 (7.3)	157 (37.6)	50 (12.0)
Nasopharyngitis	43 (10.5)	43 (10.5)	79 (18.9)	41 (9.8)
Upper respiratory tract infection	59 (14.5)	35 (8.6)	66 (15.8)	52 (12.5)
Headache	33 (8.1)	54 (13.2)	60 (14.4)	70 (16.8)
Urinary tract infection	52 (12.7)	57 (13.9)	44 (10.6)	43 (10.3)
Fatigue	21 (5.1)	28 (6.8)	43 (10.3)	36 (8.6)
Influenza-like illness	15 (3.7)	85 (20.8)	23 (5.5)	92 (22.1)
Injection site erythema	0	74 (18.1)	1 (0.2)	53 (12.7)

* These events were reported by at least 10% of patients in any group. The events are listed by decreasing incidence among ocrelizumab-treated patients.

† Randomised patients who received incorrect therapy different from that intended were summarised in the group according to the therapy actually received. Patients who were not randomised, but who received study drug, were included in the safety population and summarised according to the therapy actually received.

Table 6. ***Infusion-related reactions by grade* (Safety population†)***

Grade, n (%)	**OPERA I**		**OPERA II**	
	Ocrelizumab (n = 408)	**Interferon beta-1a (n = 409)**	**Ocrelizumab (n = 417)**	**Interferon beta-1a (n = 417)**
Total number	235	46	270	64
1	73 (17.9)	22 (5.4)	106 (25.4)	35 (8.4)
2	38 (9.3)	8 (2.)	45 (10.8)	14 (3.4)
3	14 (3.4)	0	6 (1.4)	1 (0.2)
4	1 (0.2)§	0	0	0
5	0	0	0	0

* Grading in severity: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, 5 = death.

† The safety population included all patients who received any study drug. Randomised patients who received incorrect therapy different from that intended were summarised in the group according to the therapy actually received. Patients who were not

randomised, but who received study drug, were included in the safety population and summarised according to the therapy actually received.

§ One patient had a serious infusion-related reaction at the first infusion, with the symptom of Grade 4 bronchospasm.

Ofatumumab – Adverse events

AE data for ofatumumab are based on data extracted from the primary publication of the ASCLEPIOS I and II trials (7).

Table 7. ***Adverse events – Safety population****

Events	ASCLEPIOS I		ASCLEPIOS II	
	Ofatumumab (n = 465)	Teriflunomide (n = 462)	Ofatumumab (n = 481)	Teriflunomide (n = 474)
Any adverse event, n (%)	382 (82.2)	380 (82.3)	409 (85.0)	408 (86.1)
Adverse event leading to treatment discontinuation, n (%)	27 (5.8)	24 (5.2)	27 (5.6)	25 (5.3)
Infection, n (%)	229 (49.2)	238 (51.5)	259 (53.8)	255 (53.8)
Injection-related systemic reaction, n (%)†	75 (16.1)	76 (16.5)	116 (24.1)	64 (13.5)
Serious adverse event	48 (10.3)	38 (8.2)	38 (7.9)	36 (7.6)
Serious infection, n (%)‡	12 (2.6)	7 (1.5)	12 (2.5)	10 (2.1)
Serious injection-related reaction, n (%)	2 (0.4)	0	0	0
Neoplasm, n (%)§	3 (0.6)	3 (0.6)	2 (0.4)	1 (0.2)
Death, n (%)	0	0	0	1 (0.2)¶

* Shown is the number of patients with at least one event and the percentage of all patients in each group. Adverse events were coded according to the preferred terms in the Medical Dictionary for Regulatory Activities, version 20.0. Relapses of multiple sclerosis that were reported as adverse events were excluded.

† Only reactions or symptoms that occurred within 24 hours after injection are included (i.e., time to onset of reaction, ≤24 hours).

‡ Serious infections and infestations that were reported in the ofatumumab group were appendicitis (in 8 patients), gastroenteritis (in 3), urinary tract infection (in 3), influenza (in 2), and cystitis, escherichia urinary tract infection, kidney infection, lower respiratory tract infection, neutropenic sepsis, osteomyelitis, pneumonia, upper respiratory tract infection, urosepsis, and viral respiratory tract infection (in 1 patient each). Serious infections and infestations that were reported in the teriflunomide group were appendicitis (in 2 patients), urinary tract infection (in 2), and abscess of the sweat glands, campylobacter infection, cystitis, influenza pneumonia, osteomyelitis, paronychia, peritonitis, pneumonia, postoperative abscess, salpingo-oophoritis, sepsis, tickborne viral encephalitis, and viral infection (in 1 patient each).

§ Neoplasms that were reported in patients receiving ofatumumab were one case of malignant melanoma in situ (time to onset, 39 days), one case of invasive breast carcinoma (time to onset, 149 days), one case of recurrent non-Hodgkin's lymphoma (time to onset, 31 days), and two cases of basal-cell carcinoma (time to onset, 120 and 258 days). Neoplasms that were reported in patients receiving teriflunomide were one case of fibrosarcoma (time to onset, 652 days), one case of cervix carcinoma (time to onset, 341 days), and two cases of basal-cell carcinoma (time to onset, 8 and 401 days). None of the malignant events were considered by the investigator to be related to trial treatment, and no cluster of neoplasms was identified.

¶ The cause of death was aortic dissection.

An extensive list of treatment-emergent AEs from the pooled ASCLEPIOS I and II trials are presented for the safety dataset, regardless of trial treatment relationship, in Table S7 of the supplementary material (https://www.nejm.org/doi/suppl/10.1056/NEJMoa1917246/suppl_file/nejmoa1917246_appendix.pdf).

Network meta-analyses

A4. Please discuss whether the transitivity assumption of the similarity of trials is valid for the NMAs. Please describe the possible effect modifiers and discuss whether they are similar enough across trials.

Company Response: As indicated, a valid NMA relies on the assumption that the different sets of studies included in the analysis are similar, on average, in all important factors that may affect the relative effects.

Firstly, we only considered interventions that were jointly randomised to our patient population of interest. In addition, we have presented the distribution of important effect modifiers across comparisons via descriptive tables of common baseline characteristics (Tables 8-10).

The characteristics indicate a homogeneity (similarity) in distribution of effect modifiers across available direct comparisons. The tables show very little variability across trials and available direct comparisons. While we explored the possibility of performing network meta-regression analyses for these covariates, a lack of variability across studies indicated that we would be underpowered to see any important effect modifications. We would, therefore, suggest that the transitivity assumption holds.

Table 8. ***Potential effect modifiers across clinical studies***

	AFFIRM		**ASCLEPIOS I**		**ASCLEPIOS II**		**CARE-MS I**		**CARE-MS II**		
	Natalizumab (n = 627)	**Placebo (n = 315)**	**Ofatumumab (n = 465)**	**Teriflunomide (n = 462)**	**Ofatumumab (n = 481)**	**Teriflunomide (n = 474)**	**Alemtuzumab (n = 376)**	**Interferon beta-1a (n = 187)**	**Alemtuzumab 24mg (n = 170)**	**Alemtuzumab 12mg (n = 426)**	**Interferon beta-1a (n = 202)**
Mean age (SD)	35.6±8.5	36.7±7.8	38.9±8.8	37.8±9.0	38.0±9.3	38.2±9.5	33·0±8·0	33·2±8·5	35·1 (8·40)	34·8 (8·36)	35·8 (8·77)
% female	72	67	68	69	66	67	65	65	71	66	65
Race – white (%)	96	94	88	89	87	88	94	96	84	90	93
Time since diagnosis – years (mean, SD)	5.0 (median)	6.0 (median)	5.77±6.05	5.64±6.20	5.59±6.38	5.48±6.00	NR	NR	NR	NR	NR
RRMS %	100	100	94.2	93.9	94.0	94.9	100	100	100	100	100
No. relapses in past year (mean, SD)	1.53±0.91	1.50±0.77	1.2±0.6	1.3±0.7	1.3±0.7	1.3±0.7	1.8±0.8	1.8±0.8	1·6 (0·86)	1·7 (0·86)	1·5 (0·75)
EDSS score (mean, SD)	2.3±1.2	2.3±1.2	2.97±1.36	2.94±1.36	2.90±1.34	2.86±1.37	2.0±0.8	2.0±0.8	2·7 (1·17)	2·7 (1·26)	2·7 (1·21)

Abbreviations: EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

Table 9. ***Potential effect modifiers across clinical studies***

	IMPROVE		**OPERA I**		**OPERA II**		**OWIMS**			**PRISMS**		
	Interferon beta-1a (n = 120)	**Placebo (n = 60)**	**Ocrelizumab (n = 410)**	**Interferon beta-1a (n = 411)**	**Ocrelizumab (n = 417)**	**Interferon beta-1a (n = 418)**	**Interferon beta-1a 44 mg (n = 98)**	**Interferon beta-1a 22 mg (n = 95)**	**Placebo (n = 100)**	**Interferon beta-1a 44 mg (n = 184)**	**Interferon beta-1a 22 mg (n = 189)**	**Placebo (n = 187)**
Mean age (SD)	34.0±7.8	35.2±10.5	37.1±9.3	36.9±9.3	37.2±9.1	37.4±9.0	35.5±7.4	35.4±7.3	34.9±7.8	35·6 (range = 28·4–41·0)	34·8 (range = 29·3–39·8)	34·6 (range = 28·8–40·4)
% female	73	70	66	66	65	67	71	73	74	66	67	75
Race – white (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Time since diagnosis – years (mean, SD)	NR	NR	3.82±4.80	3.71±4.63	4.15±4.95	4.13±5.07	NR	NR	NR	6·4 (range = 2·9–10·3)	5·4 (range = 3·0–11·2)	4·3 (range = 2·4–8·4)
RRMS %	100	100	NR	NR	NR	NR	100	100	100	100	100	100
No. relapses in past year (mean, SD)	NR	NR	1.31±0.65	1.33±0.64	1.32±0.69	1.34±0.73	NR	NR	NR	NR	NR	NR
EDSS score (mean, SD)	2.5 (median)	2.25 (median)	2.86±1.24	2.75±1.29	2.78±1.30	2.84±1.38	2.6±1.4	2.7±1.2	2.6±1.3	2·5 (1·3)	2·5 (1·2)	2·4 (1·2)

Abbreviations: EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

Table 10. ***Potential effect modifiers across clinical studies***

	TEMSO			**TENERE**			**TOWER**			**ULTIMATE I**		**ULTIMATE II**	
	Teriflunomide 14 mg (n = 359)	**Teriflunomide 7 mg (n = 366)**	**Placebo (n = 363)**	**Teriflunomide 14 mg (n = 111)**	**Teriflunomide 7 mg (n = 109)**	**Interferon beta-1a (n = 104)**	**Teriflunomide 14 mg (n = 372)**	**Teriflunomide 7 mg (n = 408)**	**Placebo (n = 389)**	**Ublituximab (n = 271)**	**Teriflunomide (n = 274)**	**Ublituximab (n = 272)**	**Teriflunomide (n = 272)**
Mean age (SD)	37.8±8.2	37.4±9.0	38.4±9.0	36.8±10.3	35.2±9.2	37.0±10.6	38.2±9.4	37.4±9.4	38.1±9.1	36.2±8.2	37.0±9.6	34.5±8.8	36.2±9.0
% female	71	70	76	70	64	68	69	74	70	61	65	65	65
Race – white (%)	97	97	98	100	100	100	84	81	82	97	97	99	99
Time since diagnosis – years (mean, SD)	5.59±5.44	5.29±5.36	5.13±5.59	NR	NR	NR	5.27±5.9	5.3±5.45	4.92±5.66	4.9±5.2	4.5±5.0	5.0±5.6	5.0±5.2
RRMS %	92.8	91.0	90.6	97.3	100	100	99	96	97	97.4	98.5	98.5	98.2
No. relapses in past year (mean, SD)	1.3±0.7	1.4±0.7	1.4±0.7	1.4±0.8	1.3±0.8	1.2±1.0	1.4±0.7	1.4±0.7	1.4±0.8	1.3±0.6	1.4±0.7	1.3±0.6	1.2±0.6
EDSS score (mean, SD)	2.67±1.24	2.68±1.34	2.68±1.34	2.3±1.4	2.0±1.2	2.0±1.2	2.71±1.35	2.71±1.39	2.69±1.36	3.0±1.2	2.9±1.2	2.8±1.3	3.0±1.2

Abbreviations: EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

A5. The NMAs include several treatments that make no contribution to the comparison between ublituximab, ocrelizumab and ofatumumab (e.g. natalizumab, alemtuzumab and INFβ1a-22). Can the company please justify why these treatments were included in the submitted NMAs, and if possible, supply NMAs with those treatments removed.

Company Response: The comparators included in our systematic literature review (SLR) and NMA consisted of recommended monoclonal antibodies (mAbs): alemtuzumab, natalizumab, ocrelizumab, and ofatumumab. Additional studies which focussed on treatment with either interferon beta-1a (Rebif®) or teriflunomide were also included in the SLR and NMA as these studies were identified as relevant to creating the network of evidence required to perform indirect treatment comparisons between mAbs. Included treatments were, therefore, selected on the basis of currently licenced mAbs, with additional disease modifying therapies (DMTs) also included in the analyses in order to ensure that all evidence required to perform indirect comparisons between the target mAbs was identified.

We acknowledge that this list of comparators is broader than the final two comparators that have been defined by NICE, i.e., ocrelizumab and ofatumumab. However, this extended comparator list was defined at a point in the evidence generation process at which the comparators ultimately defined by NICE was unknown. While all treatments included in each analysis are visible in the network diagrams, focus of the results of the NMA is placed specifically on the comparisons between ublituximab, ocrelizumab, and ofatumumab.

To address the query from the EAG, we have now prepared contribution matrices which show the % weight for all direct comparisons included in the analyses (Figure 1-4). When performing an NMA, each direct comparison contributes to the estimation of each network meta-analytic summary effect by a different weight. The contribution matrix (plot) presents the percentage of weight that each direct comparison contributes to any network effect estimate. The graph shows the percentage contribution of the column-defining direct comparison to the row-defining network estimate. The last two rows provide the number of available trials for column-defining direct comparisons and their percent contribution in the entire network. As indicated by these matrices, including these additional interventions in the network impacts the

precision of effect estimates (i.e., more power by including more trials) and it impacts the precision and robustness of heterogeneity estimate for the network (both important factors in NMA). Looking at the percentage of weight from these additional comparisons; they all contribute to comparisons of interest and the entire network.

In addition, we have also performed further sensitivity analyses, with natalizumab, alemtuzumab, and interferon beta-1a 22, removed from individual outcome analyses, as requested by the EAG. Results of these analyses are presented in Tables 11-14, and they are, to a great degree, similar to the primary analyses.

Figure 1. ***Contribution matrix – ARR***

		Direct comparisons in the network												
		PLC-IFNβ44	PLC-IFNβ22	PLC-NTLZMB	PLC-TRFL14	PLC-TRFL7	ALTZMB-IFNβ44	IFNβ44-IFNβ22	IFNβ44-OCRLMB	IFNβ44-TRFL14	IFNβ44-TRFL7	OFTUMB-TRFL14	TRFL14-TRFL7	TRFL14-UBLXMB
Network meta-analysis estimates	**Mixed estimates**													
	PLC-IFNβ 44	31.7	24.0		4.7	5.3		24.0		4.5	5.5		0.2	
	PLC-IFNβ 22	11.5	62.1		2.3	2.6		16.4		2.2	2.7		0.1	
	PLC-NTLZMB			100.0										
	PLC-TRFL 14	1.0	1.0		77.5	[illegible]		1.0		1.8	0.2		8.8	
	PLC-TRFL 7	1.3	1.2		9.7	74.2		1.2		0.1	2.4		9.8	
	ALTZMB-IFNβ 44						100.0							
	IFNβ 44-IFNβ 22	4.3	6.1		0.9	1.0		85.9		0.8	1.0			
	IFNβ 44-OCRLMB								100.0					
	IFNβ 44-TRFL 14	14.8	14.4		27.5	1.7		14.4		13.4	6.0		7.7	
	IFNβ 44-TRFL 7	14.6	13.9		2.4	26.1		13.9		4.8	17.1		7.2	
	OFTUMB-TRFL 14											100.0		
	TRFL 14-TRFL 7	0.2	0.2		28.8	28.5		0.2		2.0	2.3		38.0	
	TRFL 14-UBLXMB													100.0
	Indirect estimates													
	PLC-ALTZMB	15.9	16.0		3.2	3.5	38.6	16.0		3.0	3.7		0.2	
	PLC-OCRLMB	15.9	16.0		3.2	3.5		16.0	38.6	3.0	3.7		0.2	
	PLC-OFTUMB	0.7	0.7		38.8	5.8		0.7		1.3	0.2	46.0	5.9	
	PLC-UBLXMB	0.7	0.7		38.8	5.8		0.7		1.3	0.2		5.9	46.0
	ALTZMB-IFNβ 22	2.9	4.2		0.7	0.7	47.2	42.9		0.6	0.8			
	ALTZMB-NTLZMB	10.6	12.0	27.6	2.4	2.6	27.6	12.0		2.3	2.8		0.1	
	ALTZMB-OCRLMB						50.0		50.0					
	ALTZMB-OFTUMB	7.4	8.7		15.0	1.1	23.7	8.7		4.5	3.0	23.7	4.1	
	ALTZMB-TRFL 14	9.9	10.9		19.4	1.3	31.5	10.9		6.7	4.0		5.4	
	ALTZMB-TRFL 7	9.7	10.6		1.9	18.3	32.0	10.6		3.2	8.6		5.1	
	ALTZMB-UBLXMB	7.4	8.7		15.0	1.1	23.7	8.7		4.5	3.0		4.1	23.7
	IFNβ 44-NTLZMB	15.9	16.0	38.6	3.2	3.5		16.0		3.0	3.7		0.2	
	IFNβ 44-OFTUMB	9.9	10.9		19.4	1.3		10.9		6.7	4.0	31.5	5.4	
	IFNβ 44-UBLXMB	9.9	10.9		19.4	1.3		10.9		6.7	4.0		5.4	31.5
	IFNβ 22-NTLZMB	7.7	31.1	42.4	1.7	1.9		11.4		1.6	2.0		0.1	
	IFNβ 22-OCRLMB	2.9	4.2		0.7	0.7		42.9	47.2	0.6	0.8			
	IFNβ 22-OFTUMB	4.8	19.7		22.5	1.9		10.7		3.7	2.2	30.4	4.2	
	IFNβ 22-TRFL 14	6.2	29.5		33.3	2.4		14.7		5.5	3.0		5.4	
	IFNβ 22-TRFL 7	5.8	29.2		3.1	31.9		15.2		2.4	7.0		5.4	
	IFNβ 22-UBLXMB	4.8	19.7		22.5	1.9		10.7		3.7	2.2		4.2	30.4
	NTLZMB-OCRLMB	10.6	12.0	27.6	2.4	2.6		12.0	27.6	2.3	2.8		0.1	
	NTLZMB-OFTUMB	0.5	0.6	31.3	25.8	4.3		0.6		1.0	0.1	31.3	4.5	
	NTLZMB-TRFL 14	0.7	0.7	46.0	38.8	5.8		0.7		1.3	0.2		5.9	
	NTLZMB-TRFL 7	0.8	0.9	45.4	6.5	37.1		0.9		0.1	1.7		6.6	
	NTLZMB-UBLXMB	0.5	0.6	31.3	25.8	4.3		0.6		1.0	0.1		4.5	31.3
	OCRLMB-OFTUMB	7.4	8.7		15.0	1.1		8.7	23.7	4.5	3.0	23.7	4.1	
	OCRLMB-TRFL 14	9.9	10.9		19.4	1.3		10.9	31.5	6.7	4.0		5.4	
	OCRLMB-TRFL 7	9.7	10.6		1.9	18.3		10.6	32.0	3.2	8.6		5.1	
	OCRLMB-UBLXMB	7.4	8.7		15.0	1.1		8.7	23.7	4.5	3.0		4.1	23.7
	OFTUMB-TRFL 7	0.1	0.1		19.2	19.0		0.1		1.3	1.6	39.5	19.0	
	OFTUMB-UBLXMB											50.0		50.0
	TRFL 7-UBLXMB	0.1	0.1		19.2	19.0		0.1		1.3	1.6		19.0	39.5
Entire network		0.0	6.1	9.7	8.7	13.5	7.8	8.3	10.7	8.3	2.7	2.7	8.4	4.7
Included studies		3	2	1	2	2	2	2	2	1	1	2	3	2

Figure 2. ***Contribution matrix – CDP-12***

Network meta-analysis estimates	Direct comparisons in the network							
	PLC-IFNβ44	PLC-IFNβ22	PLC-NTLZMB	PLC-TRFL14	PLC-TRFL7	IFNβ44-OCRLMB	OFTUMB-TRFL14	TRFL14-UBLXMB
Mixed estimates								
PLC-IFNβ 44	100.0							
PLC-IFNβ 22		100.0						
PLC-NTLZMB			100.0					
PLC-TRFL 14				100.0				
PLC-TRFL 7					100.0			
IFNβ 44-OCRLMB						100.0		
OFTUMB-TRFL 14							100.0	
TRFL 14-UBLXMB								100.0
Indirect estimates								
PLC-OCRLMB	50.0					50.0		
PLC-OFTUMB				50.0			50.0	
PLC-UBLXMB				50.0				50.0
IFNβ 44-IFNβ 22	50.0	50.0						
IFNβ 44-NTLZMB	50.0		50.0					
IFNβ 44-OFTUMB	33.3			33.3			33.3	
IFNβ 44-TRFL 14	50.0			50.0				
IFNβ 44-TRFL 7	50.0				50.0			
IFNβ 44-UBLXMB	33.3			33.3				33.3
IFNβ 22-NTLZMB		50.0	50.0					
IFNβ 22-OCRLMB	33.3	33.3				33.3		
IFNβ 22-OFTUMB		33.3		33.3			33.3	
IFNβ 22-TRFL 14		50.0		50.0				
IFNβ 22-TRFL 7		50.0			50.0			
IFNβ 22-UBLXMB		33.3		33.3				33.3
NTLZMB-OCRLMB	33.3		33.3			33.3		
NTLZMB-OFTUMB			33.3	33.3			33.3	
NTLZMB-TRFL 14			50.0	50.0				
NTLZMB-TRFL 7			50.0		50.0			
NTLZMB-UBLXMB			33.3	33.3				33.3
OCRLMB-OFTUMB	25.0			25.0		25.0	25.0	
OCRLMB-TRFL 14	33.3			33.3		33.3		
OCRLMB-TRFL 7	33.3				33.3	33.3		
OCRLMB-UBLXMB	25.0			25.0		25.0		25.0
OFTUMB-TRFL 7				33.3	33.3		33.3	
OFTUMB-UBLXMB							50.0	50.0
TRFL 14-TRFL 7				50.0	50.0			
TRFL 7-UBLXMB				33.3	33.3			33.3
Entire network	16.7	11.1	11.1	20.8	11.1	9.3	10.0	10.0
Included studies	1	1	1	2	2	2	2	1

Figure 3. ***Contribution matrix – CDP-24***

		Direct comparisons in the network							
		PLC-IFNβ44	PLC-NTLZMB	PLC-TRFL14	PLC-TRFL7	ALTZMB-IFNβ44	IFNβ44-OCRLMB	OFTUMB-TRFL14	TRFL14-UBLXMB
Network meta-analysis estimates	**Mixed estimates**								
	PLC-IFNβ 44	100.0							
	PLC-NTLZMB		100.0						
	PLC-TRFL 14			100.0					
	PLC-TRFL 7				100.0				
	ALTZMB-IFNβ 44					100.0			
	IFNβ 44-OCRLMB						100.0		
	OFTUMB-TRFL 14							100.0	
	TRFL 14-UBLXMB								100.0
	Indirect estimates								
	PLC-ALTZMB	50.0				50.0			
	PLC-OCRLMB	50.0					50.0		
	PLC-OFTUMB			50.0				50.0	
	PLC-UBLXMB			50.0					50.0
	ALTZMB-NTLZMB	33.3	33.3			33.3			
	ALTZMB-OCRLMB					50.0	50.0		
	ALTZMB-OFTUMB	25.0		25.0		25.0		25.0	
	ALTZMB-TRFL 14	33.3		33.3		33.3			
	ALTZMB-TRFL 7	33.3			33.3	33.3			
	ALTZMB-UBLXMB	25.0		25.0		25.0			25.0
	IFNβ 44-NTLZMB	50.0	50.0						
	IFNβ 44-OFTUMB	33.3		33.3				33.3	
	IFNβ 44-TRFL 14	50.0		50.0					
	IFNβ 44-TRFL 7	50.0			50.0				
	IFNβ 44-UBLXMB	33.3		33.3					33.3
	NTLZMB-OCRLMB	33.3	33.3				33.3		
	NTLZMB-OFTUMB		33.3	33.3				33.3	
	NTLZMB-TRFL 14		50.0	50.0					
	NTLZMB-TRFL 7		50.0		50.0				
	NTLZMB-UBLXMB		33.3	33.3					33.3
	OCRLMB-OFTUMB	25.0		25.0			25.0	25.0	
	OCRLMB-TRFL 14	33.3		33.3			33.3		
	OCRLMB-TRFL 7	33.3			33.3		33.3		
	OCRLMB-UBLXMB	25.0		25.0			25.0		25.0
	OFTUMB-TRFL 7			33.3	33.3			33.3	
	OFTUMB-UBLXMB							50.0	50.0
	TRFL 14-TRFL 7			50.0	50.0				
	TRFL 7-UBLXMB			33.3	33.3				33.3
Entire network		19.9	10.6	19.9	10.6	9.7	9.7	9.7	9.7
Included studies		1	1	2	1	2	2	2	1

Figure 4. ***Contribution matrix – All-cause treatment discontinuation***

		Direct comparisons in the network												
		PLC-IFNβ44	PLC-IFNβ22	PLC-NTLZMB	PLC-TRFL14	PLC-TRFL7	ALTZMB-IFNβ44	IFNβ44-IFNβ22	IFNβ44-OCRLMB	IFNβ44-TRFL14	IFNβ44-TRFL7	OFTUMB-TRFL14	TRFL14-TRFL7	TRFL14-UBLXMB
Network meta-analysis estimates	**Mixed estimates**													
	PLC-IFNβ 44	22.2	6.2		16.6	16.0		6.2		16.8	15.8		0.2	
	PLC-IFNβ 22	5.8	54.7		5.7	5.5		17.0		5.8	5.4		0.1	
	PLC-NTLZMB			100.0										
	PLC-TRFL 14	1.0	0.4		64.0	16.4		0.4		1.4			16.4	
	PLC-TRFL 7	1.0	0.4		16.6	63.6		0.4			1.3		16.7	
	ALTZMB-IFNβ 44						100.0							
	IFNβ 44-IFNβ 22	5.4	15.9		5.3	5.2		57.7		5.4	5.1		0.1	
	IFNβ 44-OCRLMB								100.0					
	IFNβ 44-TRFL 22	10.1	3.7		13.6	0.2		3.7		37.0	15.8		15.9	
	IFNβ 44-TRFL 7	10.1	3.7			13.9		3.7		16.9	34.6		17.0	
	OFTUMB-TRFL 14											100.0		
	TRFL 14-TRFL 7				15.4	15.4				1.5	1.5		66.1	
	TRFL 14-UBLXMB													100.0
	Indirect estimates													
	PLC-ALTZMB	11.1	4.1		11.1	10.7	37.0	4.1		11.2	10.5		0.2	
	PLC-OCRLMB	11.1	4.1		11.1	10.7		4.1	37.0	11.2	10.5		0.2	
	PLC-OFTUMB	0.7	0.3		32.0	10.9		0.3		1.0		43.9	10.9	
	PLC-UBLXMB	0.7	0.3		32.0	10.9		0.3		1.0			10.9	43.9
	ALTZMB-IFNβ 22	3.6	11.5		4.0	3.9	40.3	28.9		4.1	3.8		0.1	
	ALTZMB-NTLZMB	7.4	3.1	26.8	8.3	8.0	26.8	3.1		8.4	7.9		0.1	
	ALTZMB-OCRLMB						50.0		50.0					
	ALTZMB-OFTUMB	5.1	2.2		7.2	0.1	27.5	2.2		12.3	7.9	27.5	8.0	
	ALTZMB-TRFL 14	6.7	2.8		9.4	0.1	38.5	2.8		18.5	10.5		10.7	
	ALTZMB-TRFL 7	6.7	2.8			9.5	38.2	2.8		11.3	17.3		11.3	
	ALTZMB-UBLXMB	5.1	2.2		7.2	0.1	27.5	2.2		12.3	7.9		8.0	27.5
	IFNβ 44-NTLZMB	11.1	4.1	37.0	11.1	10.7		4.1		11.2	10.5		0.2	
	IFNβ 44-OFTUMB	6.7	2.8		9.4	0.1		2.8		18.5	10.5	38.5	10.7	
	IFNβ 44-UBLXMB	6.7	2.8		9.4	0.1		2.8		18.5	10.5		10.6	38.5
	IFNβ 22-NTLZMB	3.8	27.3	39.6	4.3	4.1		12.3		4.4	4.1		0.1	
	IFNβ 22-OCRLMB	3.6	11.5		4.0	3.9		28.9	40.3	4.1	3.8		0.1	
	IFNB 22-OFTUMB	1.9	17.3		15.6	3.6		12.9		6.9	4.1	30.2	7.6	
	IFNβ 22-TRFL 14	2.4	25.7		23.4	4.6		18.1		10.3	5.4		10.0	
	IFNβ 22-TRFL 7	2.4	25.7		4.6	23.5		17.9		5.9	9.7		10.4	
	IFNβ 22-UBLXMB	1.9	17.3		15.6	3.6		12.9		6.9	4.1		7.6	30.1
	NTLZMB-OCRLMB	7.4	3.1	26.8	8.3	8.0		3.1	26.8	8.4	7.9		0.1	
	NTLZMB-OFTUMB	0.5	0.2	30.3	21.3	8.2		0.2		0.7		30.3	8.2	
	NTLZMB-TRFL 14	0.7	0.3	43.9	32.0	10.9		0.3		1.0			10.9	
	NTLZMB-TRFL 7	0.7	0.3	43.8	11.1	31.8		0.3			0.9		11.1	
	NTLZMB-UBLXMB	0.5	0.2	30.3	21.3	8.2		0.2		0.7			8.2	30.3
	OCRLMB-OFTUMB	5.1	2.2		7.2	0.1		2.2	27.5	12.3	7.9	27.5	8.0	
	OCRLMB-TRFL 14	6.7	2.8		9.4	0.1		2.8	38.5	18.5	10.5		10.7	
	OCRLMB-TRFL 7	6.7	2.8			9.5		2.8	38.2	11.3	17.3		11.3	
	OCRLMB-UBLXMB	5.1	2.2		7.2	0.1		2.2	27.5	12.3	7.9		8.0	27.5
	OFTUMB-TRFL 7				10.3	10.3				1.0	1.0	44.4	33.1	
	OFTUMB-UBLXMB											50.0		50.0
	TRFL 7-UBLXMB				10.3	10.3				1.0	1.0		33.1	44.3
Entire network		0.0	4.2	5.9	8.4	11.0	7.8	8.6	5.9	8.6	7.3	6.1	8.7	8.7
Included studies		1	1	1	2	2	2	1	2	1	1	2	3	2

Table 11. ***New sensitivity analysis excluding data for alemtuzumab, natalizumab, and interferon beta-1a 22 for ARR outcome***

ublituximab			
0.70 (0.45,1.07)	**ocrelizumab**		
1.02 (0.68,1.53)	**1.47 (1.02,2.10)**	**ofatumumab**	
0.31 (0.22,0.45)	**0.45 (0.35,0.57)**	**0.31 (0.23,0.40)**	**placebo**

Results are RR and their 95% CIs. For column compared to row, RR <1 means the top-left treatment is better [RR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the comparison of all active drugs versus placebo.

Table 12. ***New sensitivity analysis excluding data for alemtuzumab, natalizumab, and interferon beta-1a 22 for CDP-12 outcome***

ublituximab			
1.55 (0.74,3.27)	**ocrelizumab**		
1.28 (0.72,2.30)	0.83 (0.45,1.50)	**ofatumumab**	
0.58 (0.33,1.03)	**0.37 (0.23,0.60)**	**0.45 (0.31,0.65)**	**placebo**

Results are HR and their 95% CIs. For column compared to row, HR <1 means the top-left treatment is better [HR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the comparison of all active drugs versus placebo.

Table 13. ***New sensitivity analysis excluding data for alemtuzumab, natalizumab, and interferon beta-1a 22 for CDP-24 outcome***

ublituximab			
1.40 (0.62,3.15)	**ocrelizumab**		
0.97 (0.49,1.92)	0.69 (0.37,1.29)	**ofatumumab**	
0.57 (0.29,1.11)	**0.40 (0.26,0.63)**	**0.58 (0.38,0.89)**	**placebo**

Results are HR and their 95% CIs. For column compared to row, HR <1 means the top-left treatment is better [HR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the comparison of all active drugs versus placebo.

Table 14. ***New sensitivity analysis excluding data for alemtuzumab, natalizumab, and interferon beta-1a 22 for all-cause treatment discontinuation outcome***

ublituximab			
1.11 (0.60,2.04)	**ocrelizumab**		
1.16 (0.74,1.84)	1.05 (0.62,1.76)	**ofatumumab**	
0.91 (0.58,1.42)	0.82 (0.51,1.31)	0.78 (0.57,1.06)	**placebo**

Results are RR and their 95% CIs. For column compared to row, RR <1 means the top-left treatment is better [RR >1 favours the treatment in the row]. Bolded comparisons are statistically significant. Blue highlighted cells are effect estimates for the com-parison of all active drugs versus placebo.

A6. The submission notes that there was evidence of inconsistency in the NMAs. Given this, can the company please comment in more detail on how reliable the comparisons of ublituximab, ocrelizumab and ofatumumab are in the NMAs?

Company Response: To address this point, we have performed a loop specific consistency assessment to indicate which closed loops have inconsistency problems based on the ARR outcome analysis. Results presented in Table 15 indicate that there is important inconsistency in only one loop (P-value bolded in red). Robustness of results for the ARR outcome analysis was also demonstrated via the sensitivity analysis using the inconsistency model included in the initial submission, with results broadly similar to the primary (base-case) analysis, with no statistically significant difference between ublituximab and ocrelizumab or ofatumumab and a statistically significant result in favour of ublituximab in the comparison with placebo (see B.3.9 of Document B of the original submission).

As highlighted in response to Q.A4, there is minimal variability across effect modifiers in included trials, i.e., strong homogeneity in distribution of effect modifiers across available direct comparisons. Therefore, it is unlikely that the observed inconsistency has any important impact on the results.

Table 15. ***Loop-specific incoherence (inconsistency) assessment***

Loop			ROR	RoR 95% CI	P-value	Loop Heterogeneity (tau2)
Placebo	Interferon beta-1a 44	Teriflunomide 7	2.07	(1.00,4.44)	0.062	0.011
Placebo	Interferon beta-1a 44	Interferon beta-1a 22	2.00	(1.09,3.67)	**0.025**	0.003
Placebo	Interferon beta-1a 44	Teriflunomide 14	1.47	(1.00,3.25)	0.342	0.000

* Interferon beta-1a 44	Teriflunomide 14	Teriflunomide 7	1.32	(1.00,3.07)	0.513	0.023
*Placebo	Teriflunomide 14	Teriflunomide 7	1.05	(1.00,1.40)	0.744	0.004

Abbreviations: CI, confidence interval; ROR, ratio of odds ratio.

* These loops are formed only by multi-arm trial(s).

A7. Priority question: Given the concerns about the robustness of the NMAs, has the company considered comparing ublituximab, ocrelizumab and ofatumumab using anchored or unanchored matching-adjusted indirect comparisons (MAICs)? If not, can the company justify why MAICs were not considered?

Company Response: Matching-adjusted indirect comparison (MAIC) was considered prior to performing the NMA. While we acknowledge that NMAs are limited by cross-trial differences, and that by combining individual patient data with published aggregate data MAIC may reduce the observed cross-trial differences, NMA was considered to be the most appropriate methodology for this submission for the reasons presented below.

Firstly, in order to determine that population adjustment was likely to produce less biased estimates than would be available through standard indirect comparisons, we would have needed to (i) show there were grounds for believing one or more of the available covariates was an effect modifier, and (ii) show that there was sufficient imbalance in those effect modifiers to result in a material bias, in relation to the observed relative treatment effect. Neither of these conditions could be met based on the available data. Indeed, as per the response provided to Q.A4 and the comparability of potential effect modifiers across included clinical studies, and as highlighted in Table 16 below, there is little reason to suggest that results of an NMA would be biased by cross-trial differences.

If assumptions about the relationship between covariates and outcomes and about the distribution of these covariates in different study populations are incorrect or untestable, the results of a MAIC could be biased or misleading. Network meta-analysis, however, typically requires fewer and less stringent assumptions about the underlying data because it operates on a broader set of studies and uses a more generalised framework for evidence synthesis.

Secondly, as specified in the NICE Decision Support Unit (DSU) Technical Support Document (9), there is a risk associated with assumptions being applied in a submission that are fundamentally different from, or incompatible with, the assumptions being made in another submission on the same condition. Therefore, to ensure consistency with prior analyses, we aimed to follow the methodology for evidence synthesis as has been applied in previous submissions including NICE TA533 (3) and NICE TA699 (4), neither of which performed a MAIC. In these submissions, as well as in submissions of related therapies such as NICE TA127 (10), the EAG have found the NMA methodology applied to be methodologically suitable.

Table 16. ***Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population)****

	ASCLEPIOS I	ASCLEPIOS II	OPERA I	OPERA II	ULTIMATE I	ULTIMATE II
	Ofatumumab (n = 465)	Ofatumumab (n = 481)	Ocrelizumab (n = 410)	Ocrelizumab (n = 417)	Ublituximab (n = 271)	Ublituximab (n = 272)
Mean age (SD)	38.9±8.8	38.0±9.3	37.1±9.3	37.2±9.1	36.2±8.2	34.5±8.8
% female	68	66	66	65	61	65
Race – white (%)	88	87	NR	NR	97	99
Time since diagnosis – years (mean, SD)	5.77±6.05	5.59±6.38	3.82±4.80	4.15±4.95	4.9±5.2	5.0±5.6
RRMS %	94.2	94.0	NR	NR	97.4	98.5
No. relapses in past year (mean, SD)	1.2±0.6	1.3±0.7	1.31±0.65	1.32±0.69	1.3±0.6	1.3±0.6
EDSS score (mean, SD)	2.97±1.36	2.90±1.34	2.86±1.24	2.78±1.30	3.0±1.2	2.8±1.3

Abbreviations: EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

A8. If possible, please supply the statistical code and data sets used to conduct the NMAs, for checking by the EAG.

Company Response: Firstly, we would like to note that a generic set of code used across the outcome analyses included in the NMA were provided in Appendix D of the submission under the heading of '*Programming language for the indirect or mixed treatment comparison*'. In addition to this, we have now provided the complete code below, as well as Stata data files and do-files for all outcomes.

For augmented data formats

ARR

```
* to draw network diagram
twoway || pci .9510565162951536 -.3090169943749473 -.5877852522924734 .8090169943749473,
lcolor(black) lpattern(solid) lwidth(2.55)|||| pci .9510565162951536 -.3090169943749473
.9510565162951535 .3090169943749475, lcolor(black) lpattern(solid) lwidth(1.7)|||| pci
.9510565162951536 -.3090169943749473 .5877852522924732 -.8090169943749473, lcolor(black)
lpattern(solid) lwidth(.85)|||| || || pci .9510565162951536 -.3090169943749473 -.9510565162951536
.3090169943749472, lcolor(black) lpattern(solid) lwidth(1.7)|||| pci .9510565162951536 -
.3090169943749473 0 -1, lcolor(black) lpattern(solid) lwidth(1.7)|||| ||pci .5877852522924731
.8090169943749475 -.5877852522924734 .8090169943749473, lcolor(black) lpattern(solid)
lwidth(1.7)|||| || || || || || || ||pci -.5877852522924734 .8090169943749473 .9510565162951535
.3090169943749475, lcolor(black) lpattern(solid) lwidth(1.7)|||| || pci -.5877852522924734
.8090169943749473 0 1, lcolor(black) lpattern(solid) lwidth(1.7)|||| || pci -.5877852522924734
.8090169943749473 -.9510565162951536 .3090169943749472, lcolor(black) lpattern(solid)
lwidth(.85)|||| pci -.5877852522924734 .8090169943749473 0 -1, lcolor(black) lpattern(solid)
lwidth(.85)|||| |||| || || || || |||| || || || |||| || || ||pci -.9510565162951535 -.3090169943749476 -
.9510565162951536 .3090169943749472, lcolor(black) lpattern(solid) lwidth(1.7)|||| || ||pci -
.9510565162951536 .3090169943749472 0 -1, lcolor(black) lpattern(solid) lwidth(2.55)|||| pci -
.9510565162951536 .3090169943749472 -.587785252292473 -.8090169943749475, lcolor(black)
lpattern(solid) lwidth(1.7)|||||| ||||scatteri .9510565162951536 -.3090169943749473
"PLCB",mlabpos(11) mcolor(blue) mlabcolor(black) mlabsize() msize(9)||scatteri .5877852522924731
.8090169943749475 "ALTZMB",mlabpos(2) mcolor(blue) mlabcolor(black) mlabsize()
msize(1.8)||scatteri -.5877852522924734 .8090169943749473 "IFNBHI",mlabpos(4) mcolor(blue)
mlabcolor(black) mlabsize() msize(9.9)||scatteri .9510565162951535 .3090169943749475
"IFNBLO",mlabpos(1) mcolor(blue) mlabcolor(black) mlabsize() msize(3.6)||scatteri
.5877852522924732 -.8090169943749473 "NTLZMB",mlabpos(10) mcolor(blue) mlabcolor(black)
mlabsize() msize(.9)||scatteri 0 1 "OCRLMB",mlabpos(3) mcolor(blue) mlabcolor(black) mlabsize()
msize(1.8)||scatteri -.9510565162951535 -.3090169943749476 "OFTUMB",mlabpos(7) mcolor(blue)
mlabcolor(black) mlabsize() msize(1.8)||scatteri -.9510565162951536 .3090169943749472
"TRFLHI",mlabpos(5) mcolor(blue) mlabcolor(black) mlabsize() msize(9)||scatteri 0 -1
"TRFLLO",mlabpos(9) mcolor(blue) mlabcolor(black) mlabsize() msize(5.4)||scatteri -
.587785252292473 -.8090169943749475 "UBLXMB", mcolor(blue) mlabcolor(black) mlabsize()
aspect(1) legend(off) xscale(off) yscale(off) msize(1.8) mlabpos(8) ylabels(, nogrid)
plotregion(margin(15 15 10 10)) graphregion(style(plotregion)) scale(0.8)

* for side-splitting (a.k.a. node-splitting)
mvmeta _y _S  , bscovariance(exch 0.5)  eq(_y_ALTZMB: _trtdiffALTZMB _trtdiffIFNBHI
_trtdiffIFNBLO _trtdiffNTLZMB _trtdiffOCRLMB _trtdiffOFTUMB _trtdiffTRFLHI _trtdiffTRFLLO
_trtdiffUBLXMB _trtdiffincoALTZMB, _y_IFNBHI: _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero
_trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoIFNBHI, _y_IFNBLO: _trtdiffzero
_trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero
_trtdiffincoIFNBLO, _y_NTLZMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero
```

_trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoNTLZMB, _y_OCRLMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoOCRLMB, _y_OFTUMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoOFTUMB, _y_TRFLHI: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffincoTRFLHI, _y_TRFLLO: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffincoTRFLLO, _y_UBLXMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffincoUBLXMB) commonparm noconst network(sidesplit) suppress(uv mm)

* for consistency model
mvmeta _y _S , eform bscovariance(exch 0.5) longparm suppress(uv mm) vars(_y_ALTZMB _y_IFNBHI _y_IFNBLO _y_NTLZMB _y_OCRLMB _y_OFTUMB _y_TRFLHI _y_TRFLLO _y_UBLXMB)

* for inconsistency model and global test of inconsistency
mvmeta _y _S , eform bscovariance(exch 0.5) longparm suppress(uv mm) eq(_y_IFNBHI: des_PLCBIFNBHIIFNBLO, _y_TRFLHI: des_IFNBHITRFLHITRFLLO, _y_TRFLLO: des_IFNBHITRFLHITRFLLO) vars(_y_ALTZMB _y_IFNBHI _y_IFNBLO _y_NTLZMB _y_OCRLMB _y_OFTUMB _y_TRFLHI _y_TRFLLO _y_UBLXMB)

* to generate league table of comparative effectiveness
netleague, eform lab(Placebo Alemtuzumab "IFNB-1a 44" Natalizumab Ocrelizumab Ofatumumab "Teriflunomide 14" "Teriflunomide 7" Ublituximab) sort(Ublituximab Alemtuzumab "IFNB-1a 44" Natalizumab Ocrelizumab Ofatumumab "Teriflunomide 14" "Teriflunomide 7" Placebo)

* for network probability ranking and SUCRA values
mvmeta, noest pbest(min in 1, zero id(refid) all reps(5000) gen(prob) stripprefix(_y_) zeroname(PLCB) rename(PLCB = PLCB, ALTZMB = ALTZMB, IFNBHI = IFNBHI, IFNBLO = IFNBLO, NTLZMB = NTLZMB, OCRLMB = OCRLMB, OFTUMB = OFTUMB, TRFLHI = TRFLHI, TRFLLO = TRFLLO, UBLXMB = UBLXMB))
>
sucra prob*, labels(Placebo Alemtuzumab "IFNB-1a 44" Natalizumab Ocrelizumab Ofatumumab "Teriflunomide 14" "Teriflunomide 7" Ublituximab)

All-cause treatment discontinuation

* to draw network diagram
twoway || pci .9510565162951536 -.3090169943749473 -.5877852522924734 .8090169943749473, lcolor(black) lpattern(solid) lwidth(.8)|||| pci .9510565162951536 -.3090169943749473 .9510565162951535 .3090169943749475, lcolor(black) lpattern(solid) lwidth(.8)|||| pci .9510565162951536 -.3090169943749473 .5877852522924732 -.8090169943749473, lcolor(black) lpattern(solid) lwidth(.8)|||| || || pci .9510565162951536 -.3090169943749473 -.9510565162951536 .3090169943749472, lcolor(black) lpattern(solid) lwidth(1.6)|||| pci .9510565162951536 -.3090169943749473 0 -1, lcolor(black) lpattern(solid) lwidth(1.6)|||| ||pci .5877852522924731 .8090169943749475 -.5877852522924734 .8090169943749473, lcolor(black) lpattern(solid) lwidth(1.6)|||| || || || || || || ||pci -.5877852522924734 .8090169943749473 .9510565162951535 .3090169943749475, lcolor(black) lpattern(solid) lwidth(.8)|||| || pci -.5877852522924734 .8090169943749473 0 1, lcolor(black) lpattern(solid) lwidth(1.6)|||| || pci -.5877852522924734 .8090169943749473 -.9510565162951536 .3090169943749472, lcolor(black) lpattern(solid) lwidth(.8)|||| pci -.5877852522924734 .8090169943749473 0 -1, lcolor(black) lpattern(solid) lwidth(.8)|||| |||| || || || || |||| || || || |||| || || ||pci -.9510565162951535 -.3090169943749476 -.9510565162951536 .3090169943749472, lcolor(black) lpattern(solid) lwidth(1.6)|||| || ||pci -.9510565162951536 .3090169943749472 0 -1, lcolor(black) lpattern(solid) lwidth(2.4)|||| pci -.9510565162951536 .3090169943749472 -.587785252292473 -.8090169943749475, lcolor(black) lpattern(solid) lwidth(1.6)|||||| ||||scatteri .9510565162951536 -.3090169943749473 "PLCB",mlabpos(11) mcolor(blue) mlabcolor(black) mlabsize() msize(6.3)||scatteri .5877852522924731 .8090169943749475 "ALTZMB",mlabpos(2) mcolor(blue) mlabcolor(black) mlabsize() msize(1.8)||scatteri -.5877852522924734 .8090169943749473 "IFNBHI",mlabpos(4)

```
mcolor(blue) mlabcolor(black) mlabsize() msize(7.2)||scatteri .9510565162951535
.3090169943749475 "IFNBLO",mlabpos(1) mcolor(blue) mlabcolor(black) mlabsize()
msize(1.8)||scatteri .5877852522924732 -.8090169943749473 "NTLZMB",mlabpos(10) mcolor(blue)
mlabcolor(black) mlabsize() msize(.9)||scatteri 0 1 "OCRLMB",mlabpos(3) mcolor(blue)
mlabcolor(black) mlabsize() msize(1.8)||scatteri -.9510565162951535 -.3090169943749476
"OFTUMB",mlabpos(7) mcolor(blue) mlabcolor(black) mlabsize() msize(1.8)||scatteri -
.9510565162951536 .3090169943749472 "TRFLHI",mlabpos(5) mcolor(blue) mlabcolor(black)
mlabsize() msize(9)||scatteri 0 -1 "TRFLLO",mlabpos(9) mcolor(blue) mlabcolor(black) mlabsize()
msize(5.4)||scatteri -.587785252292473 -.8090169943749475 "UBLXMB", mcolor(blue)
mlabcolor(black) mlabsize() aspect(1) legend(off) xscale(off) yscale(off) msize(1.8) mlabpos(8)
ylabels(, nogrid) plotregion(margin(15 15 10 10)) graphregion(style(plotregion)) scale(0.8)

* for side-splitting (a.k.a. node-splitting)
mvmeta _y _S  , bscovariance(exch 0.5)  eq(_y_ALTZMB: _trtdiffALTZMB _trtdiffIFNBHI
_trtdiffIFNBLO _trtdiffNTLZMB _trtdiffOCRLMB _trtdiffOFTUMB _trtdiffTRFLHI _trtdiffTRFLLO
_trtdiffUBLXMB _trtdiffincoALTZMB, _y_IFNBHI: _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero
_trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoIFNBHI, _y_IFNBLO: _trtdiffzero
_trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero
_trtdiffincoIFNBLO, _y_NTLZMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero
_trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoNTLZMB, _y_OCRLMB: _trtdiffzero _trtdiffzero
_trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoOCRLMB,
_y_OFTUMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero
_trtdiffzero _trtdiffzero _trtdiffincoOFTUMB, _y_TRFLHI: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero
_trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffincoTRFLHI, _y_TRFLLO: _trtdiffzero
_trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero
_trtdiffincoTRFLLO, _y_UBLXMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero
_trtdiffzero _trtdiffzero _trtdiffone _trtdiffincoUBLXMB) commonparm noconst network(sidesplit)
suppress(uv mm)

* for consistency model
mvmeta _y _S  , eform  bscovariance(exch 0.5) longparm suppress(uv mm)  vars(_y_ALTZMB
_y_IFNBHI _y_IFNBLO _y_NTLZMB _y_OCRLMB _y_OFTUMB _y_TRFLHI _y_TRFLLO
_y_UBLXMB)

* for inconsistency model and global test of inconsistency
mvmeta _y _S  , eform  bscovariance(exch 0.5) longparm suppress(uv mm) eq(_y_TRFLHI:
des_IFNBHITRFLHITRFLLO, _y_TRFLLO: des_IFNBHITRFLHITRFLLO) vars(_y_ALTZMB
_y_IFNBHI _y_IFNBLO _y_NTLZMB _y_OCRLMB _y_OFTUMB _y_TRFLHI _y_TRFLLO
_y_UBLXMB)

* to generate league table of comparative effectiveness
netleague, eform lab(Placebo Alemtuzumab "IFNB-1a 44" "IFNB-1a 22" Natalizumab Ocrelizumab
Ofatumumab "Teriflunomide 14" "Teriflunomide 7" Ublituximab) sort(Ublituximab Alemtuzumab "IFNB-
1a 44" "IFNB-1a 22" Natalizumab Ocrelizumab Ofatumumab "Teriflunomide 14" "Teriflunomide 7"
Placebo)

* for network probability ranking and SUCRA values
mvmeta, noest pbest(min  in 1, zero id(refid) all reps(5000) gen(prob) stripprefix(_y_)
zeroname(PLCB) rename(PLCB = PLCB, ALTZMB = ALTZMB, IFNBHI = IFNBHI, IFNBLO = IFNBLO,
NTLZMB = NTLZMB, OCRLMB = OCRLMB, OFTUMB = OFTUMB, TRFLHI = TRFLHI, TRFLLO =
TRFLLO, UBLXMB = UBLXMB))
>
sucra prob*, labels(Placebo Alemtuzumab "IFNB-1a 44" "IFNB-1a 22" Natalizumab Ocrelizumab
Ofatumumab "Teriflunomide 14" "Teriflunomide 7" Ublituximab)
```

CDP-12

* to draw network diagram
twoway pci 0 1 .984807753012208 .1736481776669304, lcolor(black) lpattern(solid) lwidth(.8)|||| pci 0 1 -.6427876096865396 .7660444431189778, lcolor(black) lpattern(solid) lwidth(.8)|||| pci 0 1 .6427876096865393 .766044443118978, lcolor(black) lpattern(solid) lwidth(.8)|||| || || pci 0 1 -.8660254037844385 -.5000000000000004, lcolor(black) lpattern(solid) lwidth(1.6)|||| pci 0 1 -.9848077530122081 .17364817766693, lcolor(black) lpattern(solid) lwidth(1.6)|||| |||| || pci .984807753012208 .1736481776669304 .8660254037844387 -.4999999999999998, lcolor(black) lpattern(solid) lwidth(1.6)|||| || || || |||| || || || || |||| || || || |||| || || ||pci -.3420201433256687 -.9396926207859084 -.8660254037844385 -.5000000000000004, lcolor(black) lpattern(solid) lwidth(1.6)|||| || |||| pci -.8660254037844385 -.5000000000000004 .3420201433256689 -.9396926207859083, lcolor(black) lpattern(solid) lwidth(.8)|||||| ||||scatteri 0 1 "PLCB",mlabpos(3) mcolor(blue) mlabcolor(black) mlabsize() msize(6.3)||scatteri .984807753012208 .1736481776669304 "IFNBHI",mlabpos(12) mcolor(blue) mlabcolor(black) mlabsize() msize(2.7)||scatteri -.6427876096865396 .7660444431189778 "IFNBLO",mlabpos(4) mcolor(blue) mlabcolor(black) mlabsize() msize(.9)||scatteri .6427876096865393 .766044443118978 "NTLZMB",mlabpos(2) mcolor(blue) mlabcolor(black) mlabsize() msize(.9)||scatteri .8660254037844387 -.4999999999999998 "OCRLMB",mlabpos(11) mcolor(blue) mlabcolor(black) mlabsize() msize(1.8)||scatteri -.3420201433256687 -.9396926207859084 "OFTUMB",mlabpos(8) mcolor(blue) mlabcolor(black) mlabsize() msize(1.8)||scatteri -.8660254037844385 -.5000000000000004 "TRFLHI",mlabpos(7) mcolor(blue) mlabcolor(black) mlabsize() msize(4.5)||scatteri -.9848077530122081 .17364817766693 "TRFLLO",mlabpos(6) mcolor(blue) mlabcolor(black) mlabsize() msize(1.8)||scatteri .3420201433256689 -.9396926207859083 "UBLXMB", mcolor(blue) mlabcolor(black) mlabsize() aspect(1) legend(off) xscale(off) yscale(off) msize(.9) mlabpos(10) ylabels(, nogrid) plotregion(margin(15 15 10 10)) graphregion(style(plotregion)) scale(0.8)

* for side-splitting (a.k.a. node-splitting)
mvmeta loghr _S , bscovariance(exch 0.5) eq(loghr_IFNBHI: _trtdiffIFNBHI _trtdiffIFNBLO _trtdiffNTLZMB _trtdiffOCRLMB _trtdiffOFTUMB _trtdiffTRFLHI _trtdiffTRFLLO _trtdiffUBLXMB _trtdiffincoIFNBHI, loghr_IFNBLO: _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoIFNBLO, loghr_NTLZMB: _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoNTLZMB, loghr_OCRLMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoOCRLMB, loghr_OFTUMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoOFTUMB, loghr_TRFLHI: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffincoTRFLHI, loghr_TRFLLO: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffincoTRFLLO, loghr_UBLXMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffincoUBLXMB) commonparm noconst network(sidesplit) suppress(uv mm)
* for consistency model
mvmeta loghr _S , eform bscovariance(exch 0.5) longparm suppress(uv mm) vars(loghr_IFNBHI loghr_IFNBLO loghr_NTLZMB loghr_OCRLMB loghr_OFTUMB loghr_TRFLHI loghr_TRFLLO loghr_UBLXMB)

* for inconsistency model and global test of inconsistency
**N.B. no closed loop of evidence.
mvmeta loghr _S , eform bscovariance(exch 0.5) longparm suppress(uv mm) vars(loghr_IFNBHI loghr_IFNBLO loghr_NTLZMB loghr_OCRLMB loghr_OFTUMB loghr_TRFLHI loghr_TRFLLO loghr_UBLXMB)

* to generate league table of comparative effectiveness
netleague, eform lab(Placebo "IFNB-1a 44" "IFNB-1a 22" Natalizumab Ocrelizumab Ofatumumab "Teriflunomide 14" "Teriflunomide 7" Ublituximab) sort(Ublituximab "IFNB-1a 44" "IFNB-1a 22" Natalizumab Ocrelizumab Ofatumumab "Teriflunomide 14" "Teriflunomide 7" Placebo)

* for network probability ranking and SUCRA values

mvmeta, noest pbest(max in 1, zero id(refid) all reps(5000) gen(prob) stripprefix(loghr_) zeroname(PLCB) rename(PLCB =, IFNBHI =, IFNBLO =, NTLZMB =, OCRLMB =, OFTUMB =, TRFLHI =, TRFLLO =, UBLXMB =))
>
sucra prob*, labels(Placebo "IFNB-1a 44" "IFNB-1a 22" Natalizumab Ocrelizumab Ofatumumab "Teriflunomide 14" "Teriflunomide 7" Ublituximab)

CDP-24

* to draw network diagram
twoway || pci -.6427876096865396 .7660444431189778 .984807753012208 .1736481776669304, lcolor(black) lpattern(solid) lwidth(.8)|||| pci -.6427876096865396 .7660444431189778 .8660254037844387 -.4999999999999998, lcolor(black) lpattern(solid) lwidth(.8)|||| || || pci -.6427876096865396 .7660444431189778 -.8660254037844385 -.5000000000000004, lcolor(black) lpattern(solid) lwidth(1.6)|||| pci -.6427876096865396 .7660444431189778 -.9848077530122081 .17364817766693, lcolor(black) lpattern(solid) lwidth(.8)|||| ||pci .6427876096865393 .766044443118978 .984807753012208 .1736481776669304, lcolor(black) lpattern(solid) lwidth(1.6)|||| || || || || || |||| pci .984807753012208 .1736481776669304 0 1, lcolor(black) lpattern(solid) lwidth(1.6)|||| || || || |||| || || || |||| || || ||pci -.3420201433256687 -.9396926207859084 -.8660254037844385 -.5000000000000004, lcolor(black) lpattern(solid) lwidth(1.6)|||| || |||| pci -.8660254037844385 -.5000000000000004 .3420201433256689 -.9396926207859083, lcolor(black) lpattern(solid) lwidth(.8)|||||| ||||scatteri -.6427876096865396 .7660444431189778 "PLCB",mlabpos(4) mcolor(blue) mlabcolor(black) mlabsize() msize(4.75)||scatteri .6427876096865393 .766044443118978 "ALTZMB",mlabpos(2) mcolor(blue) mlabcolor(black) mlabsize() msize(1.9)||scatteri .984807753012208 .1736481776669304 "IFNBHI",mlabpos(12) mcolor(blue) mlabcolor(black) mlabsize() msize(4.75)||scatteri .8660254037844387 -.4999999999999998 "NTLZMB",mlabpos(11) mcolor(blue) mlabcolor(black) mlabsize() msize(.95)||scatteri 0 1 "OCRLMB",mlabpos(3) mcolor(blue) mlabcolor(black) mlabsize() msize(1.9)||scatteri -.3420201433256687 -.9396926207859084 "OFTUMB",mlabpos(8) mcolor(blue) mlabcolor(black) mlabsize() msize(1.9)||scatteri -.8660254037844385 -.5000000000000004 "TRFLHI",mlabpos(7) mcolor(blue) mlabcolor(black) mlabsize() msize(4.75)||scatteri -.9848077530122081 .17364817766693 "TRFLLO",mlabpos(6) mcolor(blue) mlabcolor(black) mlabsize() msize(.95)||scatteri .3420201433256689 -.9396926207859083 "UBLXMB", mcolor(blue) mlabcolor(black) mlabsize() aspect(1) legend(off) xscale(off) yscale(off) msize(.95) mlabpos(10) ylabels(, nogrid) plotregion(margin(15 15 10 10)) graphregion(style(plotregion)) scale(0.8)

* for side-splitting (a.k.a. node-splitting)
mvmeta loghr _S , bscovariance(exch 0.5) eq(loghr_ALTZMB: _trtdiffALTZMB _trtdiffIFNBHI _trtdiffNTLZMB _trtdiffOCRLMB _trtdiffOFTUMB _trtdiffTRFLHI _trtdiffTRFLLO _trtdiffUBLXMB _trtdiffincoALTZMB, loghr_IFNBHI: _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoIFNBHI, loghr_NTLZMB: _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoNTLZMB, loghr_OCRLMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoOCRLMB, loghr_OFTUMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffincoOFTUMB, loghr_TRFLHI: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffzero _trtdiffincoTRFLHI, loghr_TRFLLO: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffzero _trtdiffincoTRFLLO, loghr_UBLXMB: _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffzero _trtdiffone _trtdiffincoUBLXMB) commonparm noconst network(sidesplit) suppress(uv mm)

* for consistency model
mvmeta loghr _S , eform bscovariance(exch 0.5) longparm suppress(uv mm) vars(loghr_ALTZMB loghr_IFNBHI loghr_NTLZMB loghr_OCRLMB loghr_OFTUMB loghr_TRFLHI loghr_TRFLLO loghr_UBLXMB)

* for inconsistency model and global test of inconsistency
**N.B. no closed loop of evidence.

```
mvmeta loghr _S  , eform  bscovariance(exch 0.5) longparm suppress(uv mm)  vars(loghr_ALTZMB
loghr_IFNBHI loghr_NTLZMB loghr_OCRLMB loghr_OFTUMB loghr_TRFLHI loghr_TRFLLO
loghr_UBLXMB)

* to generate league table of comparative effectiveness
netleague, eform lab(Placebo Alemtuzumab "IFNB-1a 44" Natalizumab Ocrelizumab Ofatumumab
"Teriflunomide 14" "Teriflunomide 7" Ublituximab) sort(Ublituximab Alemtuzumab "IFNB-1a 44"
Natalizumab Ocrelizumab Ofatumumab "Teriflunomide 14" "Teriflunomide 7" Placebo)

* for network probability ranking
mvmeta, noest pbest(max  , zero id(refid) all reps(5000) gen(prob) stripprefix(loghr_)
zeroname(PLCB) rename(PLCB =, ALTZMB =, IFNBHI =, NTLZMB =, OCRLMB =, OFTUMB =,
TRFLHI =, TRFLLO =, UBLXMB =))
>
sucra prob*, labels(Placebo Alemtuzumab "IFNB-1a 44" Natalizumab Ocrelizumab Ofatumumab
"Teriflunomide 14" "Teriflunomide 7" Ublituximab)
```

Other questions

A9. Priority question: On page 31 of Document B, it is stated that ocrelizumab is the most relevant comparator because it is also administered intravenously. However, NHS England recently reported that it will be offering ocrelizumab via injection, based on evidence from the OCARINA II RCT (of ocrelizumab given twice a year as 10-minute subcutaneous injection versus usual intravenous infusion of ocrelizumab). Please comment on how this might affect:

i) What the most relevant comparator is

ii) The importance of ublituximab to patients, relative to ocrelizumab and ofatumumab, given that it will be the only anti-CD20 therapy for MS to be given intravenously.

iii) The submission claims (p 32) that ublituximab reduces IV time and monitoring burden.

Company Response:

i) The introduction of a subcutaneous (SC) formulation of ocrelizumab does not diminish its role as a key comparator for ublituximab in clinical practice. Ublituximab, administered intravenously (IV), remains an important treatment option for adult patients with relapsing-remitting multiple sclerosis (RRMS), especially for those who prefer or require IV

administration. Clinical experts in an advisory board have validated that patient preference for SC or IV options varies, making shared decision-making between patients and physicians essential. Therefore, ocrelizumab, despite the availability of an SC option, remains the most relevant comparator due to its similar dosing schedule and previously established IV administration route, which aligns closely with ublituximab.

ii) The introduction of an SC injection option for ocrelizumab does not impact the significance of ublituximab for patients with RRMS. Ocrelizumab will continue to be available as an IV therapy, meaning that ublituximab will not be the only anti-CD20 therapy administered as an IV. As illustrated in the graph below, derived from the IQVIA database, the UK market share of the IV form of ocrelizumab has been increasing over the past 12 months (up to July 2024), even with the availability of the SC form of ofatumumab. Therefore, it is expected that ocrelizumab as an IV formulation will remain a relevant comparator to ublituximab.

Figure 5. ***Market share for ocrelizumab IV new initiations***

As per the summary of product characteristics for the new ocrelizumab formulation, patients may start treatment with ocrelizumab in its SC or IV form, and patients currently receiving IV ocrelizumab may continue treatment with IV ocrelizumab or transition to SC ocrelizumab (11). The introduction of ublituximab, as an alternative IV therapy to ocrelizumab,

offers more personalised care options that cater to individual patient needs and goals. By expanding the range of available treatment choices, it allows physicians and patients to collaboratively choose the best suitable regimen.

iii) The submission's claim that ublituximab reduces IV time and monitoring burden remains valid when compared to ocrelizumab in its IV form. Ublituximab's shorter infusion duration and decreased monitoring needs as an IV alternative treatment for RRMS, contribute to more efficient patient management in hospital settings. With the introduction of ocrelizumab in its SC form, resource use in the secondary setting is still required for post-injection monitoring and healthcare supervision, albeit to a lesser extent. Although the preparation, administration, and monitoring time—and associated costs—are significantly lower with SC ocrelizumab at treatment initiation, the difference narrows in subsequent cycles, highlighting the continued relevance of ublituximab as an important IV option. In addition to this, any productivity gains in the secondary care setting from the introduction of ocrelizumab SC formulation, could lead to an increased workload for healthcare practitioners due to greater patient throughput.

A10. Please provide a rationale and justification for the use of lower rates of depression and UTI for ublituximab in the cost-comparison analysis when compared with ocrelizumab and ofatumumab? Please provide tabulated comparative data on these specific adverse events for all treatment arms of all the trials included in the NMA of ublituximab, ocrelizumab and ofatumumab.

Company Response: The use of lower rates of depression and urinary tract infection (UTI) for ublituximab in the cost-comparison analysis, relative to ocrelizumab and ofatumumab, is justified by the lower incidence of these AEs observed in the ULTIMATE I and II trials. In these trials, a smaller proportion of patients experienced depression and UTI compared to those in the comparator trials.

The AE frequencies were sourced directly from the published results of the ULTIMATE I and II trials for ublituximab (12), the ASCLEPIOS I and II trials for ofatumumab (7), and the OPERA I and II trials for ocrelizumab (6). The number and proportion of patients who experienced each AE in these trials, including depression and UTI, are detailed in Table 17 below, as well as the cost calculations for the intervention and comparators. Details of the depression and UTI rates across all clinical studies included in the NMA are presented in Table 18.

Table 17. ***Adverse event management inputs and cost estimates***

Adverse event	Trial-based AE rates						Cost inputs		Average (inflated) cost		
	Ublituximab (N = 545)		Ofatumumab (N = 946)		Ocrelizumab (N = 825)		Non-serious AE	Serious AE	Ublituximab	Ofatumumab	Ocrelizumab
	n	%	n	%	n	%					
Arthralgia	21	3.9%	49	5.2%	46	5.6%	£3.72	£451.24	£64.29	£54.72	£43.35
Back pain	51	9.4%	72	7.6%	53	6.4%	£0.00	£689.29	£91.95	£77.22	£59.72
Bronchitis	24	4.4%	24	2.5%	42	5.1%	£78.91	£79.91	£97.37	£97.35	£97.33
Depression	4	0.7%	45	4.8%	64	7.8%	£849.56	£3,101.16	£1,347.28	£1,299.15	£1,241.97
Fatigue	28	5.1%	71	7.5%	64	7.8%	£0.00	£54.39	£7.26	£6.09	£4.71
Headache	187	34.3%	126	13.3%	93	11.3%	£0.00	£220.24	£29.38	£24.67	£19.08
Influenza-like illness	39	7.2%	21	2.2%	38	4.6%	£0.00	£0.00	£0.00	£0.00	£0.00
Infusion related reaction	27	5.0%	103	10.9%	283	34.3%	£0.00	£0.00	£0.00	£0.00	£0.00
Injection site pain	N/A	0.0%	2	0.2%	2	0.2%	£0.00	£39.23	£5.23	£4.39	£3.40
Insomnia	33	6.1%	39	4.1%	46	5.6%	£0.00	£0.00	£0.00	£0.00	£0.00
Nasopharyngitis	100	18.3%	170	18.0%	122	14.8%	£0.00	£39.23	£5.23	£4.39	£3.40
PML	N/A	0.0%	N/A	0.0%	0.00	0.0%	£13,258.28	£13,258.28	£16,338.11	£16,338.11	£16,338.11
Sinusitis	21	3.9%	30	3.2%	46	5.6%	£0.00	£0.00	£0.00	£0.00	£0.00
Upper respiratory tract infection	41	7.5%	97	10.3%	125	15.2%	£39.23	£39.23	£48.34	£48.34	£48.34
Urinary tract infection	22	4.0%	97	10.3%	96	11.6%	£2.11	£738.21	£100.80	£85.06	£66.37
Proportion of serious AEs	**59**	**10.8%**	**86**	**9.1%**	**58**	**7.0%**	-	-	-	-	-
One-time AE cost used in the model	-	-	-	-	-	-	-	-	**£44.38**	**£91.20**	**£125.63**

Abbreviations: AE, adverse event; PML, progressive multifocal leukoencephalopathy.

Table 18. ***Adverse events (Depression and UTI) across clinical studies***

Clinical trial	Adverse event	
	Depression, n (%)	Urinary tract infection, n (%)
AFFIRM:		
Natalizumab (n = 627)	(19)	(20)
Placebo (n = 312)	(16)	(17)
ASCLEPIOS I and II:		
Ofatumumab (n = 946)	45 (4.8)	97 (10.3)
Teriflunomide (n = 936)	48 (5.1)	78 (8.3)
CARE-MS I:		
Alemtuzumab (n = 376)	NR	64 (17)
Interferon beta-1a (n = 187)	NR	8 (4)
CARE-MS II:		
Alemtuzumab 24mg (n = 161)	NR	37 (23)
Alemtuzumab 12mg (n = 435)	NR	93 (21)
Interferon beta-1a (n = 202)	NR	23 (11)
IMPROVE:		
Interferon beta-1a (n = 120)	1 (0.8)	NR
Placebo (n = 60)	2 (3.3)	NR
OWIMS:		
Interferon beta-1a 44mg (n = 98)	(8)	NR
Interferon beta-1a 22mg (n = 95)	(4)	NR
Placebo (n = 100)	(8)	NR
OPERA I and II:		
Ocrelizumab (n = 825)	64 (7.8)	96 (11.6)
Interferon beta-1a (n = 826)	54 (6.5)	100 (12.1)
PRISMS:		
Interferon beta-1a 44mg (n = 184)	44 (24)	NR
Interferon beta-1a 22mg (n = 189)	39 (21)	NR
Placebo (n = 187)	52 (28)	NR
TEMSO:		
Teriflunomide 14mg (n = 358)	0	1 (0.3)
Teriflunomide 7mg (n = 368)	0	0
Placebo (n = 360)	1 (0.3)	1 (0.3)
TENERE:		
Teriflunomide 14mg (n = 110)	0	NR
Teriflunomide 7mg (n = 110)	1 (0.9)	NR
Interferon beta-1a (n = 101)	0	NR
TOWER:		
Teriflunomide 14mg (n = 371)	NR	2 (1)
Teriflunomide 7mg (n = 409)	NR	2 (< 1)
Placebo (n = 385)	NR	2 (1)
ULTIMATE I:		
Ublituximab (n = 273)	0	11 (4.0)
Teriflunomide (n = 275)	0	17 (6.2)
ULTIMATE II:		
Ublituximab (n = 272)	4 (1.5)	11 (4.0)
Teriflunomide (n = 273)	7 (2.6)	12 (4.4)

Abbreviations: NR, not reported.

A11. How many UK patients would be potentially eligible to receive ublituximab, out of the 130,000 patients in the UK in total?

Company Response: Per the budget impact analysis performed for the submission, we have estimated that [redacted] patients will be eligible to receive treatment with ublituximab in the first year of market entry, to up to [redacted] patients by the fifth year, in the UK. The introduction of ublituximab in the treatment pathway is expected to reduce the utilisation of other treatments and displace the use of other treatment options. Therefore, based on the projected uptake of ublituximab, we estimate that [redacted] patients will be expected to receive ublituximab in the first year, to up to [redacted] patients by the fifth year. These values were estimated using data from a market forecast study on the number of MS patients who are diagnosed with RRMS, and who are treated with a mAb injectable therapy per year (13).

Section B: Clarification on cost-effectiveness data

B1. Priority question: Impact of the new 'under-the-skin' injection for ocrelizumab on its acquisition and administration costs.

a) **Please comment on the effects of the recent 10-minute 'under-the-skin' twice-yearly injection on the acquisition and administration costs of ocrelizumab.**

Company Response: Using the available information from the NHS Dictionary of Medicines + Devices and the British National Formulary to retrieve the drug acquisition costs of ocrelizumab in its SC and IV forms respectively, the estimated annual cost of treatment remains unchanged regardless of the route of administration. However, the shorter administration time and reduced need for post-injection monitoring compared to the IV form will decrease the overall resource use costs for treatment administration with SC ocrelizumab.

Table 19 compares the annual costs for drug acquisition and Table 20 compares the resource use costs for drug administration with ocrelizumab in IV and SC forms. Note that the drug administration estimates assume the same monitoring time after injection in first and subsequent doses of SC, as this is determined by the physician.

Table 19. ***Drug acquisition costs for ocrelizumab in IV and SC forms***

	Ocrelizumab (IV)	Ocrelizumab (SC)
Cost per pack	£4,790.00	£9,580.00
Vial size/unit strength (mg)	300mg	920mg
Dose per administration	• Initiation: 600mg as two separate 300mg IV infusions • Subsequent doses: 600mg	920 mg
Dosing frequency	• Initiation: week 0 and week 2 • Subsequent doses: Every 6 months	Every 6 months
Annual cost in year 1	£19,160.00	£19,160.00
Annual cost in subsequent years	£19,160.00	£19,160.00

Abbreviations: IV, intravenous; SC, subcutaneous.

Table 20. ***Drug administration cost calculations for ocrelizumab in IV and SC forms***

Resource use per administration	Ocrelizumab IV First infusion	Ocrelizumab IV Subsequent infusions	Ocrelizumab SC injections
Preparation time (h)	1.00	1.00	0.50
Infusion/injection time (h)	5.00	2.75	0.17
Time interval between patients (h)	0.25	0.25	0.25

Total infusion/injection time per patient (h)	5.25	3.00	0.42
Monitoring after infusion/injection (h)	1.00	1.00	1.00
Total time per patient per session(h)	7.25	5.00	1.92
Patients per bed per day	1.00	1.00	4.00
Nurse costs for infusion per patient	£420.50	£290.00	£111.17
Cost per bed-day	£386.13	£266.30	£102.08
Total cost per administration	**£806.63**	**£556.30**	**£213.25**
Annual drug administration costs	**£1,056.97**	**£1,112.60**	**£426.50**

Abbreviations: IV, intravenous; SC, subcutaneous.

To estimate the cost per administration, a nurse cost of £58.00 per hour and a bed day cost of £426.08 was used.

b) Please update the acquisition and administration costs of ocrelizumab to reflect the 'under-the-skin' injection and provide a revised version of the model reflecting the changes. This may include a separate comparator treatment for ocrelizumab subcutaneous, in addition to ocrelizumab IV, if relevant. Please sign-post the changes made to the model.

Company Response: A revised version of the model has been submitted to reflect the changes requested. In the updated version, the drug acquisition and administration costs of ocrelizumab 'under-the-skin' injection have been included and are reflected in the new comparator 'Ocrelizumab (SC)'. The rows or cells highlighted in green in represent the changes implemented in the model.

During the model update, the Company has identified the exclusion of two parameters from the deterministic sensitivity analysis. We apologise for the oversight and highlight that these have been added in the new model version, and the corresponding tornado charts have been updated in the submission forms.

B2. Please comment on why the costs of treating adverse events are included in the company's base case cost-comparison analysis, when the health-related quality of life impact of the adverse events is not considered and no difference in discontinuation rates between ublituximab and its comparators is considered.

Company Response: In a cost-comparison analysis, the inclusion of health-related quality of life measures is not typically required. The impact of AEs is implicitly reflected in the patient outcomes' through the discontinuation rates, as patients who experience AEs are more likely to discontinue treatment. In the submitted cost-

comparison analysis, AE management costs were included in the base-case to ensure that cost comparisons were made fairly, taking into account similar cost components across the modelled treatments. This approach indicated that the costs of treating AEs are minimal in relation to the overall costs of the intervention and its comparators. AE management costs have also been included, following the NICE user guide for a cost-comparison submission. Section 4.2.10 of the user guide states that the cost of AEs for the intervention and comparators need to be calculated in a cost-comparison analysis (14).

B3. Please clarify whether the cost of subsequent treatment use should be included in the model after treatment discontinuation in the company's scenario analysis and, if so, please clarify which costs should be considered. Please provide a revised version of the model accordingly and clearly signpost any changes made to the model.

Company Response: The model does not include the costs of subsequent treatments after treatment discontinuation, and assumes that patients follow the natural progression of the disease, without any residual benefit from the discontinued therapy. Modelling subsequent treatments is challenging due to the absence of clinical evidence to determine the most appropriate choice of subsequent therapy. The wide range of available treatment options and the lack of sequential efficacy data present challenges for the modelling process. In addition to this, subsequent treatment costs are likely to be similar regardless of the initial treatment received. Therefore, we do not consider the costs associated with subsequent treatments to be necessary in the cost-comparison model. This approach also aligns with previous submissions of therapies in RRMS (3,4,15).

B4. Please comment on why discounting of costs is not included in the company's base case cost-comparison analysis, when a model time horizon of five years is considered.

Company Response: In the NICE user guide for a single technology cost-comparison submission, section 4.2.2 states that discounting of costs is not normally required for a cost comparison analysis (14). Accordingly, the discount rate was set to zero in the base-case analysis and a discounting rate was applied in a scenario

analysis to estimate the effect of discounting costs over the time horizon of five years.

Section C: Textual clarification and additional points

Textual clarifications

C1. The submission uses academic-in-confidence markings (AIC, yellow highlight) in various places, but particularly for the NMA results. It is the EAG's understanding that such AIC marking should no longer be used. Nor can we see any reason why this material should be confidential, as it is mostly based on published data. Could the company please either:

a. Justify why AIC marked information should be confidential, based on current NICE guidelines for confidentiality marking,

b. Or confirm that the AIC confidentiality marking can be disregarded.

Company Response: Thank you for highlighting this point. As per (b) above, and based on current NICE guidelines for confidentiality marking, we confirm that the confidentiality marking can be disregarded. These confidentiality markings have been removed in updated versions of the submitted documents.

C2. There are some places in the submission where there are cross-referencing errors (e.g. Section B.3.7) Could the company please confirm what these should refer to, or if they are typos?

Company Response: We cannot identify the cross-referencing errors that are being referred to in this question. In Section B.3.7 (Subgroup analysis), there is one cross-reference/cross-link to Table 1 – The decision problem, and this is an appropriate reference given the context of what is being described, i.e., inclusion of subgroups in the evidence submission. The link also appears to work correctly (and appears correctly) in our version of the submitted document. We are unable to identify any errors related to cross-referencing, but would be happy to clarify/address these if they are specified.

C3. Please clarify whether there is an error in Table 8, which reports that over 97% of trial participants were black.

Company Response: Yes, thank you for highlighting. The data are correct but the order of categories in the 'Characteristics' row should be 'White, Black, Other' rather than 'Black, White, Other', as currently presented.

Database searches

C4. The clinical evidence searches in Appendix D aimed to find clinical effectiveness and safety data associated with ublituximab and other relevant comparators for the treatment of RMS. As the company did not use an adverse effects filter or include any search terms for adverse effects, could any relevant safety data have been missed?

Company Response: It is very unlikely that any relevant safety data have been missed, due to the detailed and comprehensive nature of the searches. While a separate search for safety evidence was not performed, and an adverse effects filter was not included in the search strategies, a very large volume of clinical studies was screened during the review process (>11k studies following de-duplication of database searches). We are confident that all studies meeting the criteria for inclusion were appropriately screened and included.

While certain study types were excluded as they did not meet the criteria for inclusion in the SLR, i.e., observational and phase II studies etc., we are confident that the most high-quality safety data reported in phase III clinical trials has been captured in this review. The relevance of safety data from alternative study types for this review is questionable given that the data from phase III RCTs would have taken precedence. For instance, although we are aware of the availability of safety data from an earlier phase II study of ublituximab, the study included only 48 patients receiving ublituximab on-study. These types of studies did not fall within the criteria for inclusion, and the subsequently-captured phase III safety data would take precedence over such phase II data.

As seen in NICE TA533 (3), the company submission also did not include a separate, systematic search for safety evidence associated with ocrelizumab. Instead, the company obtained safety data primarily from the OPERA I and OPERA

II trials (6) and also from previous NICE technology appraisals for daclizumab (5) and alemtuzumab (16). In this case, the review group acknowledged that although a more systematic and transparent process for sourcing data on the safety of ocrelizumab would have been preferable, clinical experts advising the EAG did not identify any key issues pertaining to ocrelizumab safety that were not covered in the company submission.

As stated by the EAG in the NICE TA533 submission also in relation to the exclusion of the phase II trial for ocrelizumab, 'phase II trial relapse rate and disability progression outcomes are likely to be underpowered, hindering any comparisons with those in the phase III OPERA trials' (3).

The safety data that have been utilised in subsequent analyses performed as part of this submission of evidence were, therefore, sourced from the pivotal phase III trials associated with the treatments of interest, i.e., ULTIMATE I and II (ublituximab) (12), OPERA I and II (ocrelizumab) (6), and ASCLEPIOS I and II (ofatumumab) (7). We are confident that these are the most appropriate safety data associated with each of these treatments.

C5. In the clinical evidence searches in Appendix D, Table 11 provides the links of resources that were hand-searched for conference abstracts but not the actual strategies. Please could the company provide the strategies?

Company Response: Search strategies and number of hits per line for conference searches has now been provided in Tables 21-24 below. It should be noted that formal search strategies were not conducted for searches performed for the American Academy of Neurology Conferences or for the Consortium of Multiple Sclerosis Centers Conferences. Therefore, while the available online information for these conferences was searched for relevant abstracts, formal search strategies are unavailable for these conferences.

Table 21. ***Search strategies in Americas Committee for Treatment and Research in Multiple Sclerosis Conferences***

ACTRIMS 2019	Search Term	Results
#1	Ublituximab	4
#2	Ocrelizumab	33

#3	Ofatumumab	12
#4	Alemtuzumab	63
#5	Natalizumab	67
#6	RMS	267
#7	Relapse	219
ACTRIMS 2020	**Search Term**	**Results**
#1	Ublituximab	6
#2	Ocrelizumab	75
#3	Ofatumumab	11
#4	Alemtuzumab	65
#5	Natalizumab	42
#6	Teriflunomide	6
#7	RMS	233
#8	Relapse	236
ACTRIMS 2021	**Search Term**	**Results**
#1	Ublituximab	0
#2	Ocrelizumab	53
#3	Ofatumumab	7
#4	Alemtuzumab	5
#5	Natalizumab	51
#6	Teriflunomide	28
#7	RMS	261
#8	Relapse	137
ACTRIMS 2022	**Search Term**	**Results**
#1	Ublituximab	3
#2	Ocrelizumab	28
#3	Ofatumumab	10
#4	Alemtuzumab	8
#5	Natalizumab	21
#6	Teriflunomide	23
#7	RMS	79
#8	Relapse	98
ACTRIMS 2023	**Search Term**	**Results**
#1	Ublituximab	23

#2	Ocrelizumab	181
#3	Ofatumumab	27
#4	Alemtuzumab	26
#5	Natalizumab	90
#6	Teriflunomide	40
#7	RMS	378
#8	Relapse	347
ACTRIMS 2024	**Search Term**	**Results**
#1	Ublituximab	3
#2	Ocrelizumab	44
#3	Ofatumumab	28
#4	Alemtuzumab	7
#5	Natalizumab	29
#6	Teriflunomide	20
#7	RMS	162
#8	Relapse	203

Table 22. ***Search strategies in European Committee for Treatment and Research in Multiple Sclerosis Conferences***

ECTRIMS 2019	**Search Term**	**Results**
#1	Ublituximab	7
#2	Ocrelizumab	76
#3	Ofatumumab	9
#4	Alemtuzumab	248
#5	Natalizumab	263
#6	Teriflunomide	173
#7	RMS	839
#8	Relapse	759
ECTRIMS 2020	**Search Term**	**Results**
#1	Ublituximab	1
#2	Ocrelizumab	421
#3	Ofatumumab	94
#4	Alemtuzumab	221
#5	Natalizumab	35

#6	Teriflunomide	41
#7	RMS	1,388
#8	Relapse	1,211
ECTRIMS 2021	**Search Term**	**Results**
#1	Ublituximab	20
#2	Ocrelizumab	337
#3	Ofatumumab	139
#4	Alemtuzumab	150
#5	Natalizumab	288
#6	Teriflunomide	209
#7	Randomised	117
#8	Relapse	217
ECTRIMS 2022	**Search Term**	**Results**
#1	Ublituximab	0
#2	Ocrelizumab	294
#3	Ofatumumab	34
#4	Alemtuzumab	60
#5	Natalizumab	213
#6	Teriflunomide	127
#7	Interferon beta-1a	104
#8	Randomised	165
#9	Relapse	797
ECTRIMS 2023	**Search Term**	**Results**
#1	Ublituximab	7
#2	Ocrelizumab	282
#3	Ofatumumab	69
#4	Alemtuzumab	170
#5	Natalizumab	200
#6	Teriflunomide	138
#7	Interferon beta-1a	98
#8	RMS	750
#9	Relapse	746

Table 23. ***Search strategies in European Academy of Neurology Conferences***

EAN 2019	Search Term	Results
#1	Ublituximab	3
#2	Ocrelizumab	74
#3	Ofatumumab	0
#4	Alemtuzumab	101
#5	Natalizumab	77
#6	Teriflunomide	27
#7	Interferon beta-1a	34
#8	Randomised	194
#9	Relapse	208
EAN 2020	**Search Term**	**Results**
#1	Ublituximab	0
#2	Ocrelizumab	78
#3	Ofatumumab	44
#4	Alemtuzumab	58
#5	Natalizumab	62
#6	Teriflunomide	50
#7	Interferon beta-1a	82
#8	Randomised	229
#9	Relapse	244
EAN 2021	**Search Term**	**Results**
#1	Ublituximab	3
#2	Ocrelizumab	37
#3	Ofatumumab	16
#4	Alemtuzumab	10
#5	Natalizumab	57
#6	Teriflunomide	19
#7	Interferon beta-1a	10
#8	Randomised	147
#9	Relapse	106
EAN 2022	**Search Term**	**Results**
#1	Ublituximab	24
#2	Ocrelizumab	112
#3	Ofatumumab	45

#4	Alemtuzumab	26
#5	Natalizumab	60
#6	Teriflunomide	81
#7	Interferon beta-1a	18
#8	Randomised	124
#9	Relapse	210
EAN 2023	**Search Term**	**Results**
#1	Ublituximab	0
#2	Ocrelizumab	36
#3	Ofatumumab	46
#4	Alemtuzumab	4
#5	Natalizumab	59
#6	Teriflunomide	11
#7	Interferon beta-1a	15
#8	Randomised	122
#9	Relapse	226

Table 24. ***Search strategies in International Multiple Sclerosis Cognition Society Conferences***

IMSCOGS 2016 & 2017	**Search Term**	**Results**
#1	Ublituximab	0
#2	Ocrelizumab	0
#3	Ofatumumab	0
#4	Alemtuzumab	0
#5	Natalizumab	6
#6	Teriflunomide	0
#7	Interferon beta-1a	0
#8	Randomised	536
#9	Relapse	1
#10	Multiple sclerosis	86
IMSCOGS 2018	**Search Term**	**Results**
#1	Ublituximab	0
#2	Ocrelizumab	0
#3	Ofatumumab	0

#4	Alemtuzumab	0
#5	Natalizumab	0
#6	Teriflunomide	0
#7	Interferon beta-1a	0
#8	Randomised	1
#9	Relapse	2
#10	Multiple sclerosis	102
IMSCOGS 2019	**Search Term**	**Results**
#1	Ublituximab	0
#2	Ocrelizumab	0
#3	Ofatumumab	0
#4	Alemtuzumab	0
#5	Natalizumab	7
#6	Teriflunomide	0
#7	Interferon beta-1a	2
#8	Randomised	9
#9	Relapse	2
#10	Multiple sclerosis	122
IMSCOGS 2020	**Search Term**	**Results**
#1	Ublituximab	0
#2	Ocrelizumab	9
#3	Ofatumumab	0
#4	Alemtuzumab	0
#5	Natalizumab	0
#6	Teriflunomide	0
#7	Interferon beta-1a	8
#8	Randomised	7
#9	Relapse	1
#10	Multiple sclerosis	65
IMSCOGS 2022	**Search Term**	**Results**
#1	Ublituximab	0
#2	Ocrelizumab	2
#3	Ofatumumab	0
#4	Alemtuzumab	0

#5	Natalizumab	3
#6	Teriflunomide	0
#7	Interferon beta-1a	3
#8	Randomised	138
#9	Relapse	2
#10	Multiple sclerosis	94

C6. In the clinical evidence searches in Appendix D, Table 3 doesn't show the fully documented update search with hits per line for Embase. Please can the company submit this evidence so we can appraise it?

Company Response: An updated version of this search strategy is presented below. As highlighted in response to Q.C7, searches were actually performed in Embase and MEDLINE together. Any search strategy tables in the Appendices which are titled with 'Embase' therefore consist of searches performed in Embase AND MEDLINE. The search updates performed in these databases, as referenced in this question, are presented for the respective databases in Table 25 and Table 26 below (331 hits across databases).

Table 25. ***Search strategy in EMBASE – Update (18th September 2023 to 3rd June 2024)***

	Database: ***EMBASE and Medline combined – Update (18th September 2023 to 3rd June 2024)***	**Results**
#1	Exp multiple sclerosis/ OR exp myelitis, transverse/ OR exp neuromyelitis optica/ OR exp demyelinating diseases/ OR exp postvaccinal encephalitis/	3961
#2	(multiple sclerosis or encephalomyelitis or demyelinating disease or neuromyelitis optica or devic or transverse myelitis or optic neuritis).mp	3413
#3	(relapsing or relaps* or remit* or relapsing remitting*).mp.	12725
#4	(RRMS or RMS).mp	872
#5	#1 OR #2 OR #3 OR #4	16226
#6	exp Ofatumumab/ OR exp alemtuzumab/ OR exp ocrelizumab/ OR exp Ublituximab/ OR exp natalizumab/ OR exp teriflunomide/	615
#7	(Teriflunomide or A 771726 or A77 1726 or A77-1726 or A771726 or aubagio or hmr 1726 or hmr1726).mp	71
#8	(Ublituximab or Anti-CD20 Monoclonal Antibody or TG-1101).mp.	115

#9	(Ofatumumab or OMB157 or HYMAX-CD20 2F2 or HUMAXCD20-2F2 or Arzerra or GSK1841157 or GSK-1841157).mp	91
#10	(alemtuzumab or campath 1h or anti-CD52 or anti CD52).mp	244
#11	(natalizumab or antegren or tysabri or ocrelizumab or ocrevus or humani#se anti CD20 antibody).mp	318
#12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	715
#13	#5 AND #12	476
#14	exp clinical trial/	41891
#15	exp randomization/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/	20657
#16	exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/	21105
#17	exp clinical trials as topic/	1593
#18	exp placebo/ or exp placebo effect/	5582
#19	clinical trial*.mp.	30694
#20	control?ed clinical trial.mp.	961
#21	randomi#ed controlled trial.mp.	20601
#22	randomi#ation.mp.	2617
#23	((random* adj2 allocat*) or (random* adj2 assign*)).tw.	3089
#24	placebo*.mp.	5752
#25	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	11364
#26	Animal experiment/ not (human experiment/ or human/)	21387
#27	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	52766
#28	25 or 26	24297
#29	27 not 28	51736
#30	13 and 29	241

Table 26. ***Search strategy in Medline – Update (18th September 2023 to 3rd June 2024)***

	Database: *EMBASE and Medline combined – Update (18th September 2023 to 3rd June 2024)*	**Results**
#1	Exp multiple sclerosis/ OR exp myelitis, transverse/ OR exp neuromyelitis optica/ OR exp demyelinating diseases/ OR exp postvaccinal encephalitis/	2710

#2	(multiple sclerosis or encephalomyelitis or demyelinating disease or neuromyelitis optica or devic or transverse myelitis or optic neuritis).mp	4605
#3	(relapsing or relaps* or remit* or relapsing remitting*).mp.	9418
#4	(RRMS or RMS).mp	959
#5	#1 OR #2 OR #3 OR #4	14136
#6	exp Ofatumumab/ OR exp alemtuzumab/ OR exp ocrelizumab/ OR exp Ublituximab/ OR exp natalizumab/ OR exp teriflunomide/	97
#7	(Teriflunomide or A 771726 or A77 1726 or A77-1726 or A771726 or aubagio or hmr 1726 or hmr1726).mp	79
#8	(Ublituximab or Anti-CD20 Monoclonal Antibody or TG-1101).mp.	75
#9	(Ofatumumab or OMB157 or HYMAX-CD20 2F2 or HUMAXCD20-2F2 or Arzerra or GSK1841157 or GSK-1841157).mp	54
#10	(alemtuzumab or campath 1h or anti-CD52 or anti CD52).mp	92
#11	(natalizumab or antegren or tysabri or ocrelizumab or ocrevus or humani#se anti CD20 antibody).mp	220
#12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	412
#13	#5 AND #12	308
#14	exp clinical trial/	16730
#15	exp randomization/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/	14522
#16	exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/	14371
#17	exp clinical trials as topic/	7354
#18	exp placebo/ or exp placebo effect/	81
#19	clinical trial*.mp.	33132
#20	controled clinical trial.mp.	1194
#21	randomi#ed controlled trial.mp.	20331
#22	randomi#ation.mp.	5741
#23	((random* adj2 allocat*) or (random* adj2 assign*)).tw.	8631
#24	placebo*.mp.	7591
#25	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti.	36748
#26	exp animals/ not humans.sh	68619

#27	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	58351
#28	25 or 26	87946
#29	27 not 28	55643
#30	13 and 29	90

C7. Why does the PubMed strategy remove some MEDLINE records? Could any relevant evidence have been missed as a result?

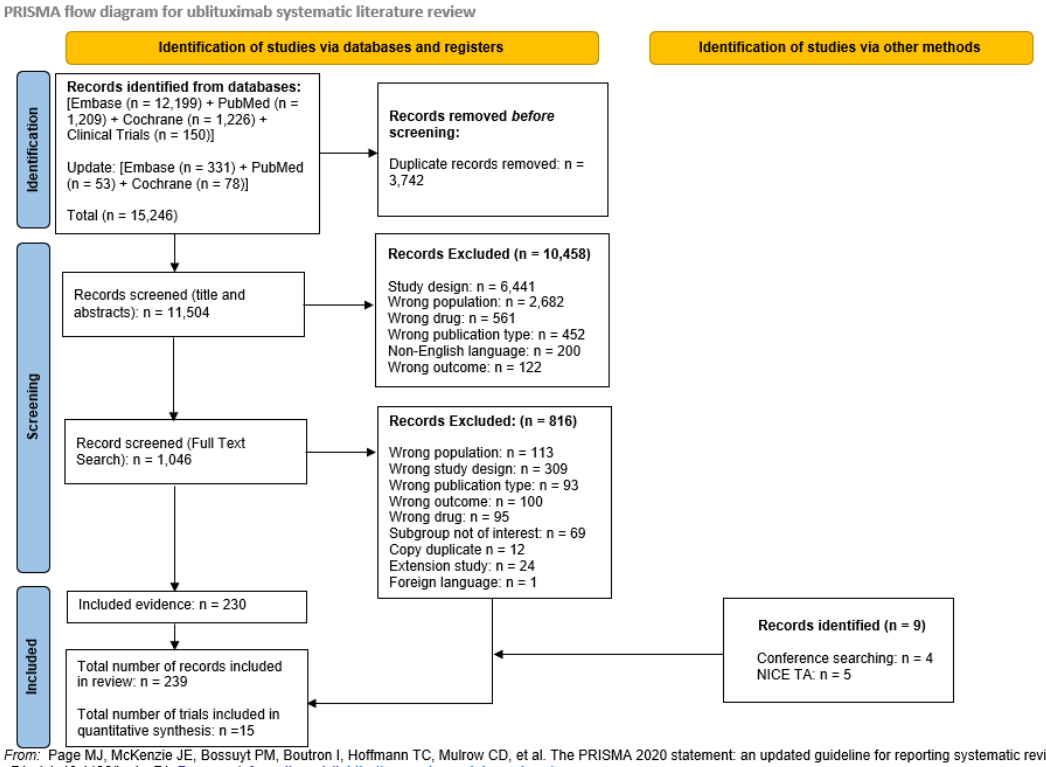
Company Response: MEDLINE records were removed from the PubMed search strategy because Embase and MEDLINE searches were run together, and the number of hits in the Embase search strategy is reflective of this. Therefore, the titles of Tables 1-3 in the Appendices should be amended to read:

- **Table 1 Search strategy in EMBASE and Medline (to 18th September 2023)**
- **Table 2 Search strategy in EMBASE and Medline – additional searches for interferon beta-1a (to 28th December 2023)**
- **Table 3 Search strategy in EMBASE and Medline – Update (18th September 2023 to 3rd June 2024)**

C8. The PRISMA flow diagram lists ‘databases and registers’ but doesn’t show the hits from clinicaltrials.gov in with the databases, instead it shows the number or relevant hits from this source later. Please could the company provide a more detailed PRISMA diagram?

Company Response: Yes, please see an updated PRISMA diagram presented in Figure 6 below. The number of hits identified via clinicaltrials.gov and impact on subsequent numbers has now been presented.

Figure 6. ***PRISMA flow diagram for SLR***



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. doi: 10.1136/bmj. n71. For more information, visit: http://www.prisma-statement.org/

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Cost Comparison Appraisal

Ublituximab for treating relapsing multiple sclerosis [ID6350]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists
3. Job title or position	Consultant Neurologist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists' is a professional membership organisation, and its mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. The ABN receives funding mainly from its member subscriptions and annual conference income. Additional funding from external charity organisations is received to solely fund fellowships. Additionally, the ABN receives sponsorship from pharmaceutical companies. Sponsoring companies have no input, control nor opportunity to influence the ABN.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	In the past 12 months, the ABN has received sponsorship from the following companies to support the ABN Annual Conference. Sponsorship companies have no editorial input, control over the agenda, speaker selection, content development nor opportunity to influence the conference. Sponsorship is £18,020 per company. - Roche - Novartis
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is reduction in relapse rates in patients with active relapsing remitting MS including patients with highly active and rapidly evolving MS, to a similar extent as other already licenced similar MS treatments. In addition, it should have a positive impact on disability progression, fewer side effects or be more convenient for patients or cost-effective for healthcare systems than currently available licensed therapies.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response would be suppression of clinical relapses and inflammatory MRI activity. Whilst the goal of treatment is to reduce these as much as possible, a clinically significant response would be reduction of relapse rate to less than baseline (pre-treatment or on first line treatment), or a relapse rate similar to other similar currently available licensed therapies.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There are NICE approved disease modifying treatments for relapsing remitting MS including treatments licenced for highly active and rapidly evolving MS. These are all detailed in the NHS England treatment algorithm.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, there is the NHS England treatment algorithm which details commissioning guidance, and the ABN guidelines which detail clinical approaches. https://www.england.nhs.uk/wp-content/uploads/2024/03/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies-july-23.pdf

9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The NHSE DMT commissioning treatment algorithm and ABN guidelines for MS care aim to remove variability of care and prescribing. These mandate that all patients receiving highly effective MS DMT are discussed at a dedicated MS multidisciplinary meeting in order to further reduce variability across professionals.
9c. What impact would the technology have on the current pathway of care?	It would provide further choice for patients with relapsing MS, in particular patients who have chosen a B cell therapy, but who have infusion reactions to the alternative 6-monthly infusion, ocrelizumab. By offering an alternative treatment it would further allow early highly effective treatment for MS which has been shown to reduce long term disability and disease progression. In addition the shorter infusion time of ublituximab could be more acceptable for patients who have time constraints or fatigue from long infusion times.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	The duration of infusion is 1 hour compared to 2-3.5 hours for a current comparator intravenous drug. This will positively impact healthcare resources by freeing up time in infusion units. Quicker infusion times will allow more patients to be treated in a shorter time frame, allowing earlier access to treatment, thereby preventing accrual of disability due to waiting times.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology will be used in specialist secondary care clinics in line with other disease modifying treatments for MS.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No significant additional investment is required as the use of ublituximab will likely be used as an alternative to other infusible monoclonal antibodies already in use. Delivery of the drug will be comparable to similar used drugs, and no significant additional training is anticipated.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Evidence suggests that highly effective disease modifying treatments are most effective when given as early as possible in the disease course. Current pressures on resources required to deliver infusions mean that in some services there can be long delays in starting treatment. By providing a 6 monthly infusible treatment that can be delivered over 1 hour will relieve pressures on infusion units and this is likely to allow more timely access to treatments. Some patients have developed reactions to other similar medications, and an alternative option may lessen infusion reactions, increasing tolerability and compliance. There is some evidence from the ublituximab trials that the B cell depletion rates are quicker after the first infusion, suggesting that this drug may be quicker acting than similar treatments, and therefore may be a better alternative for patients with rapidly evolving MS who need urgent treatment (Steinman L, et al. Ublituximab versus teriflunomide in relapsing multiple sclerosis. N Engl J Med. 2022;387(8):704–1 ; Hauser SL et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017;376(3):221–34)
11a. Do you expect the technology to increase length of life more than current care?	In natural history cohorts, MS has a small effect on reducing life expectancy. However, current unpublished evidence suggests that in more contemporaneous populations, more likely to be on treatment, MS does not affect life expectancy. This additional access to treatment would not be expected to change this.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, as stated above, early access to high efficacy treatment can prevent MS related disability in the long term improving quality of life. Treatment delivered in a 1 hour infusion, will reduce patients time receiving treatment, allowing them to continue with their normal daily activities due to the shorter treatment time window.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None currently identified within the population (RRMS) that is currently being appraised.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As described above, the shorter infusion time compared to the other similar intravenous treatments will potentially make more time available in infusion units and free up capacity to see more patients and therefore widen access and shorten time to starting treatment.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	These will run in line with current NHSE guidance. This requires no additional testing to that used in current practice.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be	No

innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	No
16b. Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse effects include infusion reactions, which are normally mild and self-limiting and generally don't affect patient management or quality of life significantly. Also, infections, which are mild for most patients. The reported SE's are not significantly different or unexpected in comparison to similar treatments already in use.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	N/A

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Annualised relapse rate, new or enlarging T2 lesions on MRI, confirmed disability progression, as reported
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There is likely to be a long term small risk of hypogammaglobulinaemia, in similar drugs estimated at a rate of approximately 8% in 10 years. There is also a theoretical long term small increased risk of PML and malignancies.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatments?	Ocrelizumab, one of the main alternative medications, has recently been released as a subcutaneous infusion which can be delivered over 10 minutes. This may offer a significant advantage over ublituximab; however, a quick intravenous infusion will still be a useful option for some patients. Real world long term follow up studies on treatments with similar mechanisms have been reassuring in terms of prolonged efficacy and safety data.
21. How do data on real-world experience compare with the trial data?	None available as yet

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	MS disproportionately affects women in a 3:1 ratio, particularly women of child bearing age.
22b. Consider whether these issues are different from issues with current care and why.	no

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Quicker infusion, allowing increased infusion capacity due to shorter time on unit • More choice for patients who have side effects from current licensed medications • Well-established mechanism of action which has previously shown excellent benefits for patients with MS • This is an additional high efficacy disease modifying treatment for RRMS, shown to be more effective than a currently-licensed treatment in 2 large multi-centre randomised controlled trials

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Cost Comparison Appraisal

Ublituximab for treating relapsing multiple sclerosis [ID6350]

Professional organisation submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK Multiple Sclerosis SPECIALIST Nurses Association UKMSSNA
3. Job title or position	[redacted] UKMSSNA
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKMSSNA is a professional organisation that supports MS nurses, through education, networking, peer support and advice. The organisation is funded by grants and membership fees.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Biogen £8000 for meeting and to allow committee to get together to do work on MS nurse competency document. Janssen (Ponesimod) 10,000 to fund the MS nurse competency document
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce the relapses and decrease lesion load although in Ultimate trials I and II there was not a statistically relevant decline in disease progression.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduce in relapse rate, reduction in lesion load (NEDA) no evidence of disease activity
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are a number of disease modifying therapies some first line in which this medication would be based which aim to reduce relapse rate, reduce lesion load and reduce progression of the disease pathway. MS is a spectrum disease and all patients that have this will have different symptoms most accumulate more damage to the central nervous system over time leading to disease progression and further disability and increase in symptoms. There is not one treatment that fits all, some patients respond to the treatments that are currently available well others don't. The range of treatments available means that patients have a choice and can choose treatments that fit in to their lifestyle. Treatment range means that if a patient is not responding to a medication, we can try a different disease modifying therapy. All of the treatments available currently do not cure the patient/disease they just increase the time frame over wellness by preventing relapses which then reduces the impact of MS, on the central nervous system preventing as much accumulation of damage to the central nervous system. This allows a patient to live well with the condition longer.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	With disease modifying therapies
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	New guidelines by the Academy of British neurologist have just been brought out which has a treatment pathway and at what point which Disease modifying therapies should be used.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are variations depending on patient choice, patients circumstances ie pregnancy, trying for a baby or breast feeding.
9c. What impact would the technology have on the current pathway of care?	The medication would allow patients a further choice and health care professionals another option.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	There are currently other Disease modifying therapies that are infusion based.
10a. How does healthcare resource use differ between the technology and current care?	It does not differ as it would be administered in hospital like some of the other therapies
10b. In what clinical setting should the technology be used? (For example,	Secondary care setting ideally infusion suite

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training for health care professionals on how the medication works how to administer it side effect, wash out period ect
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	It may benefit some patients and as it can be used first line it could mean using a treatment that has higher efficacy at the beginning of the pathway.
11a. Do you expect the technology to increase length of life more than current care?	no
11b. Do you expect the technology to increase health-related quality of life more than current care?	no
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This would not be approprete for women considering a family or pregnant yet as there is no data to allow for this use

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	For patients it will mean coming in to a hospital environment to get treatment some patients like this so don't. For the hospital and staff it means finding space, training staff and taking the requirements to ensure it is safe for the patient ie bloods. This is no different to a lot of the MS disease modifying therapies.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Due to the reduction in B cell antibodies blood tests will need to be done prior to starting medication pregnancy test and possibly checks for antibodies for things like measles chicken pox
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It would not be found until real world data was in place or other trials were done on alternative outcomes such as cognition fatigue. other disease modifying therapies have shown reduction on fatigue

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It provides another treatment, and its mode of action is different to some other disease modifying therapies. It showed 50% reduction in relapses so on this basis it would come midway between therapies although Tysabri which has higher efficacy is not used first line.
16a. Is the technology a 'step-change' in the management of the condition?	yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Another option for treatment if other treatment has been ineffective
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is a concern about the number of people who died in the trials (3 deaths) and high-risk adverse events occurred in 21.3% of the treatment group. The lack of evidence of reducing disease progression this could have been to the trial design as it would not make sense for a medication to reduce relapses and lesion load and not impact on the long-term disability.

Sources of evidence

18. Do the clinical trials on the technology reflect	Yes except designated trial area might not be as easy to get bed/seats for patients in an infusion suite

current UK clinical practice?	
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes to a point relapse rate, lesion load, disease progression are all used as outcome measure for trials
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that we are aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No except patient experience
20. Are you aware of any new evidence for the comparator treatments?	Ocrevus pregnancy data, Ocrevus 10 year findings, Ocrevus v Tysabri
21. How do data on real-world experience	Not aware of any real world data on this product as it has recently finished trail process

compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• A choice for MS patients • A choice for clinicians to use either after another disease modifying therapy has failed or to start treating people with MS • concerns about space, staff to monitor infusions. • concerns about safety data • amount of infusion rate reactions

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External Assessment Group Report

Cost comparison evaluation process

Ublituximab for treating relapsing multiple sclerosis

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Date completed	13/09/2024

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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors
A Zhou critiqued the cost-comparison analyses and wrote Sections 5 and 6 of this report.
E Uphoff and M Corbett critiqued the clinical evidence and wrote Sections 2, 3 and 4 of this report.
H Fulbright provided information science support.
C Rothery critiqued the cost-comparison analyses, contributed to writing Sections 5 and 6 of the report and had overall responsibility for the cost-comparison.
M Simmonds had overall responsibility for the clinical sections of the report and contributed to the writing of the report.

Note on the text
All commercial-in-confidence (CIC) data have been [redacted].

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List of abbreviations

AE	adverse event	MRI	magnetic resonance imaging
ARR	annualised relapse rate	MS	multiple sclerosis
BNF	British National Formulary	MSQOL-54	Multiple Sclerosis Quality of Life-54
CDI	confirmed disease improvement	NEDA	no evidence of disease activity
CDP	confirmed disease progression	NHS	National Health Service
CI	confidence Interval	NICE	National Institute for Health and Care Excellence
CS	company submission	NMA	network meta-analysis
CSR	Clinical Study Report	OR	odds ratio
DMT	disease-modifying therapy	PAS	patient access scheme
EAG	Evidence Assessment Group	PfC	points for clarification
EDSS	expanded disability status scale	QALY	quality-adjusted life year
Gd	Gadolinium	RCT	randomised controlled trial
h	hour	RMS	relapsing multiple sclerosis
HR	hazard ratio	RRMS	relapsing-remitting multiple sclerosis
HRQoL	health-related quality of life	RR	risk ratio
HTA	health technology assessment	SAE	serious adverse event
ICER	incremental cost-effectiveness ratio	SC	subcutaneous
IRR	infusion-related reactions	SD	standard deviation
IV	intravenous	SF-36	Short Form-36
mAb	monoclonal antibody	SLR	systematic literature review
MAIC	matching-adjusted indirect comparison	SPMS	secondary progressive multiple sclerosis
MHRA	Medicines and Healthcare products Regulatory Agency	SUCRA	surface under the cumulative ranking curve

EXTERNAL ASSESSMENT REPORT: COST COMPARISON EVALUATION PROCESS

1 EXECUTIVE SUMMARY

1.1 Summary of clinical evidence

The clinical evidence supplied by the company included the two ULTIMATE trials of ublituximab and a network meta-analysis of treatments for RRMS. The ULTIMATE trials showed that ublituximab appears to be an effective treatment for RRMS, being superior to teriflunomide in reducing relapse rates. However, the trials did not show a benefit of ublituximab compared to teriflunomide for worsening disability outcomes at 12 and 24 weeks. It is unclear whether this result is driven by the low proportion of patients experiencing a worsening of disability over the trial periods.

The network meta-analyses suggested that ublituximab may have similar efficacy to ocrelizumab and ofatumumab for reduction of relapse rates and slowing of disease progression. There was, however, considerable uncertainty in the results, and some evidence of network inconsistency. Results for disease progression at 12 months and treatment discontinuation were in the direction of favouring ocrelizumab and ofatumumab over ublituximab, although any differences were not statistically significant.

1.2 Summary of cost-effectiveness evidence

The costs considered in the company's cost comparison analysis comprised of drug acquisition costs; drug administration costs, monitoring costs, and adverse event costs, which were estimated per patient per year. Monitoring costs did not differ by treatment. Therefore, the only difference in costs between ublituximab and its comparators are: (i) the acquisition costs in the first and subsequent years; (ii) the administration method (SC or IV) and the duration of infusion and monitoring time; and (iii) resource use associated with adverse events. Patients do not discontinue treatment in the company's base case analysis, while the impact of treatment discontinuation was explored in a scenario analysis. The total costs of ublituximab, ofatumumab, and ocrelizumab (IV or SC) are compared over a 5-year time horizon (without discounting).

1.3 EAG critique of cost-comparison approach to this technology assessment

1.3.1 Clinical evidence

The EAG notes several areas of concern with the clinical evidence presented that raise doubts as to whether ublituximab can be considered equivalent in efficacy to ocrelizumab and ofatumumab.

The EAG reanalysed some components of the ULTIMATE trials, to investigate whether the effectiveness of ublituximab varied across subgroups of patients. Of particular concern is that [redacted]

There was no direct evidence to compare ublituximab with ocrelizumab and ofatumumab, and comparisons were performed indirectly via network meta-analysis (NMA). The comparison between ublituximab and ocrelizumab was very indirect, going via IFNβ-1a, placebo and teriflunomide. This was of concern as there was evidence of network inconsistency, so the comparison may not be robust. Sensitivity analyses varying the network structure found that, for annualised relapse rate (ARR), the comparison between ublituximab and ocrelizumab was not robust. Some sensitivity analyses favoured ublituximab and others favoured ocrelizumab. All confidence intervals were wide, and no results were statistically significant, suggesting substantial overall uncertainty.

For ARR the NMAs found ublituximab to be almost identical in effect to ofatumumab, and possibly slightly superior to ocrelizumab, but confidence intervals are wide and the possibility that ublituximab is slightly inferior to the other treatments cannot be ruled out. For both disease progression at 12 months (CDP-12) and treatment discontinuation the results were in the direction of favouring ofatumumab and ocrelizumab, so it is possible that ublituximab is inferior to the other treatments on these outcomes. However, confidence intervals were wide and no result was statistically significant.

Differences across trials in healthcare settings and in how events were defined precluded comparisons of adverse event rates using NMA. Although the EAG considered that currently there is little robust evidence to suggest that ublituximab has a different safety profile to ofatumumab and ocrelizumab, the exception to this could be infusion or injection related reactions. Given the differences in how the anti-CD20s are administered, patient preferences regarding the setting, frequency and duration of administration, together with the risk of infusion or injection related reactions, may play an important role when deciding which treatment may be best to use.

1.3.2 Cost-comparison

The EAG considers the company's cost-comparison analysis to be appropriate under the assumption of near equivalence in efficacy, in terms of treatment effectiveness, disease progression and disease-related mortality, and similar safety profile (including discontinuation rates) for ublituximab and its comparators of ofatumumab and ocrelizumab. However, the EAG notes that the existing clinical evidence from the NMA for the outcomes of ARR, CDP-12 and CDP-24 suggests that there is a non-zero probability that ublituximab is less (or more) effective than ofatumumab and ocrelizumab (IV).

Therefore, we can only conclude that there is not sufficient evidence to distinguish between the treatments.

The company's inclusion of differential adverse event costs in the first year of treatment appears unnecessary given the underlying assumption that the safety profile is comparable between the treatments and the company's assumption that there is no difference in the discontinuation rate between treatments (to switch to next subsequent treatment). The EAG concludes that the inclusion of separate AE costs, whilst not considering their HRQoL impact, is unnecessary in the company's cost comparison analysis. Furthermore, the EAG's clinical advisor did not consider there to be any reason for differential rates of the more-costly adverse event of depression between the treatments (0.7% for ublituximab, 4.8% for ofatumumab and 7.8% for ocrelizumab (IV)).

The CS did not consider the impact of the quick 'under-the-skin' injection for ocrelizumab on its acquisition and administration costs. The EAG requested at points for clarification to update the revised version of the model to reflect the changes to the acquisition and administration costs of ocrelizumab 'under-the-skin' injection. The company included the ocrelizumab 'under-the-skin' injection as a new comparator, ocrelizumab (SC), in the cost comparison analysis. Uncertainty remains about the percentage of patients to use different forms of ocrelizumab (IV or SC).

1.4 Overall summary

The EAG generally agrees with the rationale for a cost comparison approach, given that ublituximab is assumed to have a similar mechanism of action to the other anti-CD20 monoclonal antibodies (ocrelizumab and ofatumumab), which have been approved by NICE for relapsing-remitting multiple sclerosis.

The EAG, informed by clinical advice, considers it plausible that ublituximab could provide similar health benefits (and have a similar safety profile) as ocrelizumab and ofatumumab. The EAG considers that the evidence presented broadly supports this position, and ublituximab could reasonably be used as an alternative therapy to ocrelizumab and ofatumumab.

However, the EAG has some concerns as to whether the evidence presented by the company is sufficiently robust to be confident that ublituximab is equivalent in efficacy to ocrelizumab and ofatumumab, for the purposes of a cost-comparison analysis. This is particularly because of the indirect nature of the comparison between ublituximab and the other treatments, with network meta-analysis results having considerably uncertainty as to the exact effectiveness of any of the treatments.

2 BACKGROUND

In this report the EAG has reviewed the company submission (CS) from Neuraxpharm UK to NICE on the cost comparison of ublituximab (Briumvi) within its marketing authorisation for treating relapsing multiple sclerosis (RMS) in adult patients who have active disease defined by clinical or imaging features.

2.1 Rationale for using a cost comparison approach in the appraisal

The EAG agrees with the rationale for a cost comparison approach, given that ublituximab is assumed to have a similar mechanism of action to the other anti-CD20 monoclonal antibodies (mAb) (ocrelizumab and ofatumumab), which have been approved by NICE for relapsing-remitting multiple sclerosis (RRMS) in 2018[1] and 2021[2], respectively.

Evidence cited by the company ahead of the decision problem meeting to support a cost comparison approach included the two ULTIMATE trials of ublituximab, a published network meta-analysis (NMA) of treatments for RMS[3], and a report on oral and monoclonal antibody treatments for RMS by the Institute for Clinical and Economic Review (ICER).[4]

The EAG, informed by clinical advice, considers it plausible that ublituximab could provide similar health benefits (and have a similar safety profile) as ocrelizumab and ofatumumab but this is subject to uncertainty. Our appraisal of the evidence is discussed in section 4, and a critique of the cost comparison in section 5.2.

2.2 Description of relapsing multiple sclerosis and the treatment pathway

The company provided an acceptable description of multiple sclerosis (MS). In response to clarification question A11, the company estimated that 14,958 patients in the UK are living with RRMS with active disease and may be eligible to receive treatment with ublituximab in the first year of market entry.

Disease-modifying therapies (DMTs) relevant to the population in scope include moderate efficacy therapies and higher efficacy therapies. Ublituximab, along with the two relevant comparators ofatumumab and ocrelizumab, are classed as higher efficacy therapies. The EAG's clinical advisor agrees with the company that early intervention with a higher efficacy DMT appears to be associated with better long-term outcomes; moderate efficacy treatments are the preferred option for a minority of patients, for example because of comorbidities, patient preference for oral medication, or for older patients with very mild symptoms who would prefer a gentler treatment option.

2.3 Differences and similarities between ublituximab and relevant comparators

2.3.1 Indication

Ublituximab is indicated for treating RRMS in adults with active disease defined by clinical or imaging features. This differs from the final scope issued by NICE (see section 3) but is in line with the indications for ofatumumab and ocrelizumab. Ocrelizumab is only recommended for adults with RRMS and active disease if alemtuzumab is contraindicated or unsuitable. However, the EAG's clinical advisor explained that alemtuzumab is now rarely used because of toxicity concerns.

Clinical advice to the EAG indicates that ublituximab may be considered as an alternative to ofatumumab or ocrelizumab in all suitable positions in the clinical pathway. However, clinicians would usually not opt for a second anti-CD20 mAb if one in an earlier line of treatment showed a lack, or loss, of efficacy.

2.3.2 Mechanism of action

The company described the mechanism of action of ublituximab in Table 2 (p. 13) and on p. 31 of the CS. Ublituximab induces death of CD20 expressing B-cells, which play a role in the autoimmune reaction targeting the central nervous system. The company mention four distinct mechanisms which lead to the death of CD20 expressing B-cells. By counteracting the autoimmune reaction damaging the central nervous system, the frequency of relapses and the occurrence and severity of neurological disability are reduced.

The EAG's clinical advisor explained that the anti-CD20 mAb treatments ocrelizumab and ofatumumab have similar working mechanisms, and that all three treatments cause profound B-cell suppression. There are differences in the extent to which each treatment relies on different biological pathways to achieve cell death of CD20 expressing B-cells. However, in practice this is unlikely to lead to differences in the efficacy of the three treatments, since CD20 cell death is the important outcome (rather than mechanism of cell death).

3 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

3.1 Population

NICE's final scope encompasses adults with relapsing multiple sclerosis with active disease; this covers both RRMS and relapsing forms of secondary progressive MS (SPMS) and reflects ublituximab's full marketing authorisation. The company's submission addressed a narrower population, focussing on adults with RRMS with active disease (defined by clinical or imaging features). Although this is narrower than the population in NICE's scope, it is nevertheless the same as the populations defined in NICE's recommendations for both the comparators in this appraisal, i.e. ofatumumab (TA 699) and ocrelizumab (TA 533). The company's submission also notes that the ublituximab evidence base for the active SPMS population is limited, since less than 2% of participants in the ULTIMATE I and II trials had SPMS at baseline.

3.2 Intervention

This is in line with NICE's scope. Ublituximab is administered during an outpatient appointment through intravenous (IV) infusion in week 0, week 2, and subsequently every 24 weeks.

3.3 Comparators

The EAG's clinical adviser considered that the comparators (ofatumumab and ocrelizumab) considered in the decision problem in both the company's submission and in NICE's scope were appropriate and reflected current NHS practice. Both ofatumumab and ocrelizumab are anti-CD20 therapies (like ublituximab) and both have a significant market share, being higher efficacy therapies.

Ofatumumab differs notably from ublituximab in its mode, setting and frequency of administration, being given as a subcutaneous injection by the patient at home, using a pre-filled injection pen, at weeks 0, 1, 2, 4, and monthly thereafter. Until recently, and as described in the CS, ocrelizumab was administered using the same mode and (very similar) frequency of delivery as ublituximab i.e., as an IV infusion at weeks 0, 2, and every six months thereafter. However, in July 2024, following the publication of results of the OCARINA II randomised trial, the Medicines and Healthcare products Regulatory Agency (MHRA) approved ocrelizumab for subcutaneous administration. Ocrelizumab can therefore now be administered subcutaneously in NHS outpatient settings. The EAG's clinical adviser stated that this will shorten ocrelizumab's administration time, which will be good for patients and for NHS capacity.

As the subcutaneous ocrelizumab issue was not covered in the company's submission, the EAG asked the company (in clarification question A9) to comment on how it might affect: i) what the most

relevant comparator is, ii) the importance of ublituximab to patients, given that it will be the only anti-CD20 therapy for MS to be given intravenously and iii) the submission claims that ublituximab reduces IV time and monitoring burden. The company response stated that patient preference for subcutaneous or IV options varies and that ocrelizumab remains the most relevant comparator (despite the availability of a subcutaneous ofatumumab), due to its similar dosing schedule to ublituximab and because the option to deliver it intravenously will remain. The company acknowledged though that less resource use would be required with subcutaneous ocrelizumab when compared with its IV delivery.

Given the anticipated similarities in efficacy and safety profiles across the three anti-CD20 therapies considered in the submission, patient preferences regarding mode, setting, frequency and duration of administration may play an important role when deciding which treatment to use. Section 5.2.4 describes the cost implications of these differences in administration.

3.4 Outcomes

The outcomes covered in the company's submission were in line with those specified in the NICE scope, except for severity of relapse; this outcome was not evaluated in the ublituximab trials. The EAG's clinical adviser indicated that severity of relapse is not usually reported in MS trials, with relapse typically being viewed in terms of being present or absent, rather than by severity.

4 SUMMARY OF THE EAG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

4.1 Critique of the methods of the review

The original company submission included searches to identify clinical evidence for adult patients with relapsing forms of multiple sclerosis (RMS). A description of the searches and most of the search strategies were included in Appendix D (pp. 2-15). In response to the EAG's points for clarification, the company provided additional information, search strategies, and corrections to errors. Overall, the searches were conducted appropriately using a small range of relevant databases, conference proceedings, and a single trials registry. See appendix 1for the full report of the search strategies.

The systematic review included randomised studies published in English of adult patients with RMS receiving ublituximab, alemtuzumab, natalizumab, ocrelizumab, ofatumumab, interferon beta-1a [Rebif®], or teriflunomide. Fifteen RCTs were included, of which two were trials of ublituximab (ULTIMATE I and ULTIMATE II). Appendix D of the CS lists excluded trials; there is no record of individual papers or records that were excluded.

An extension study to the ULTIMATE trials is currently ongoing (TG1101-RMS303). In this single-arm study, participants who have completed the treatment phase of either trial are treated with ublituximab up to 312 weeks.[5]

4.2 Critique of the direct evidence

4.2.1 Trial designs and critical appraisal

Protocols of the ULTIMATE trials were previously published alongside study results.[6] The EAG received the Clinical Study Reports (CSRs) ahead of the clarification response.

In the ULTIMATE RCTs, patients received ublituximab or teriflunomide for 96 weeks, followed by a 20-week follow-up period. The trials were double-blind, with patients in the ublituximab arm receiving a placebo tablet and patients in the teriflunomide arm receiving placebo injections (CS section B.3.3). The EAG judges the trial designs to be appropriate.

A host of previous treatments were listed as exclusion criteria, including alemtuzumab, natalizumab, teriflunomide, stem cell transplantation, and anti-CD20 or other B-cell directed treatments. The EAG's clinical adviser notes that this is not reflective of clinical practice in the NHS. Excluding patients who would be eligible to receive ublituximab in practice may be a risk to the generalisability of trial results. A single-arm trial is ongoing to assess the efficacy of ublituximab after switching from ocrelizumab, rituximab, or ofatumumab.[7]

The EAG's clinical adviser considered baseline characteristics of study samples (CS Table 8, p. 48) to be generally representative of UK clinical practice, and similar to trials of ocrelizumab and ofatumumab.[8, 9] Most participants were recruited from centres

[redacted]

Information provided by the company as part of the clarification response (Q A2) shows that participants in the combined teriflunomide study arms were slightly older than participants in the combined ublituximab arms ([redacted]).

The company presents risk of bias assessments of ULTIMATE I and II using Cochrane's Risk of Bias 2 tool (CS Appendix D). The EAG agrees with the company's judgements of low risk of bias in all risk of bias domains. However, it is unclear which outcome was used to assess the outcome-specific domains of the Risk of Bias 2 tool. The company has identified the double-blinded, dummy-controlled nature of the trials as a strength. The EAG agrees, with the caveat that the common occurrence of infusion-related reactions in the ublituximab study arms may have made it possible for treating clinicians to identify the medication received (see section 4.4.1).

4.2.2 Efficacy of ublituximab versus teriflunomide – main analyses

The CS reports on the primary analysis of data from the modified intention-to-treat (mITT) analyses of 545 patients in ULTIMATE I and 544 patients in ULTIMATE II. Outcomes include annualised relapse rate (ARR), number of Gadolinium (Gd) enhancing lesions per T1 and T2-weighted MRI scans, disability measured with the Expanded Disability Status Scale (EDSS), confirmed disease progression at 12 weeks (CDP-12) and 24 weeks (CDP-24), and health-related quality of life (HRQoL) measured with the Multiple Sclerosis Quality of Life 54 scale (MSQOL-54), which includes Short Form-36 (SF-36).

The importance of the results of the ULTIMATE trials for this appraisal is limited because teriflunomide, being a moderate efficacy therapy, is not a relevant comparator. Key results at 96-week follow-up are presented in table 11 of the CS (pp. 66-67). Results were broadly consistent ULTIMATE I and ULTIMATE II.

The absolute number of confirmed relapses was very low (Table 1). ARR was adjusted for region and baseline EDSS score. The ARR was lower in the ublituximab study arms than the teriflunomide arms in ULTIMATE I (rate ratio 0.41, 95% CI 0.27; 0.62) and ULTIMATE II (rate ratio 0.51, 95% CI 0.33; 0.78).

Table 1 Summary of ARR results (mITT population)

	ULTIMATE I		ULTIMATE II	
	Ublituximab (N=271)	Teriflunomide (N=274)	Ublituximab (N=272)	Teriflunomide (N=272)
Mean duration of treatment (years)	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses during treatment	[redacted]	[redacted]	[redacted]	[redacted]
Mean number of relapses per participant[a]	[redacted]	[redacted]	[redacted]	[redacted]
Median number of relapses per participant[a]	[redacted]	[redacted]	[redacted]	[redacted]
Minimum number of relapses per participant[a]	[redacted]	[redacted]	[redacted]	[redacted]
Maximum number of relapses per participant[a]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted ARR	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted ARR	0.08	0.19	0.09	0.18

Source: CSRs ULTIMATE trials.

a. During treatment period.

Data on worsening of disability were pooled and showed no conclusive difference between study arms at 12 weeks (HR 0.84, 95% CI 0.50; 1.41) and 24 weeks (HR 0.66, 95% CI 0.36; 1.21) (Table 2). The EAG's clinical adviser explained that this finding is disappointing and may be explained by a relatively low percentage of participants showing worsening of disability (5.5% at 12 weeks and 4.0% at 24 weeks). In addition, the clinical adviser indicated that teriflunomide is more effective at reducing disability than it is at preventing relapse.

Table 2 Results for worsening of disability ULTIMATE trials

	POOLED DATA ULTIMATE TRIALS	
	Ublituximab (N=543)	Teriflunomide (N=546)
Worsening of disability at 12 weeks		
No. of patients (%)	28 (5.2)	32 (5.9)
HR	0.84 (0.50; 1.41)	
Worsening of disability at 24 weeks		
No. of patients (%)	18 (3.3)	26 (4.8)
HR	0.66 (0.36; 1.21)	

Abbreviations: HR; Hazard Ratio

Table 3 summarises results for secondary and tertiary outcomes. Measures of disease activity and time to confirmed relapse indicated a benefit of ublituximab compared to teriflunomide.

Table 3 Results for other secondary and tertiary outcomes ULTIMATE I and II

	ULTIMATE I		ULTIMATE II	
	Ublituximab (N=271)	Teriflunomide (N=274)	Ublituximab (N=272)	Teriflunomide (N=272)
DISEASE ACTIVITY				
Gd-enhancing lesions per T1-weighted MRI scan				
Mean	0.02	0.49	0.01	0.25
RR (95% CI)	0.03 (0.02; 0.06), p<0.001		0.04 (0.02; 0.06), p<0.001	
New or enlarging hyperintense lesions per T2-weighted MRI scan				
Mean	0.21	2.79	0.28	2.83
RR (95% CI)	0.08 (0.06; 0.10), p<0.001		0.10 (0.07; 0.14), p<0.001	
Percentage change in brain volume baseline to week 96				
Least-squares mean (95% CI)	-0.20 (-0.23; -0.17)	-0.13 (-0.16; -0.10)	-0.19 (-0.23; -0.16)	-0.18 (-0.21; -0.15)
Difference (95% CI)	-0.07 (-0.11; -0.04)		-0.02 (-0.05; 0.02)	
DISABILITY-RELATED OUTCOMES				
Time to first confirmed relapse				
No. of participants with at least one confirmed relapse during treatment (%)	36 (13.3)	68 (24.8)	34 (12.5)	72 (26.5)
HR	0.50 (0.33; 0.75), p<0.001		0.43 (0.28; 0.65), p<0.001	
NEDA[a]				
No. of participants (%)	121 (44.6)	41 (15.0)	117 (43.0)	31 (11.4)
OR (95% CI)	5.44 (3.54; 8.38)		7.95 (4.92; 12.84)	

a. Including no confirmed relapses, no MRI activity, and no worsening of disability.
Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; NEDA, no evidence of disease activity; OR, odds ratio.

The company summarise results for HRQoL data in Table 9 and Table 10 of the CS (pp. 63-65). There was a benefit for ublituximab compared to teriflunomide for some but not all domains of the Multiple Sclerosis Quality of Life 54 (MSQOL-54), including change in health, energy, mental health, physical health, and role limitations due to physical problems. HRQoL measured with the SF-36 showed a statistically significant improvement for ublituximab when compared to the teriflunomide study arm for physical functioning, the role-physical component, and vitality.

4.2.3 Subgroup analyses

No subgroup analyses are presented in the CS, though a published abstract reports on results from pooled analyses of the ULTIMATE trials in a subgroup of participants with highly active disease.[10] The unadjusted ARR in patients with highly active disease was higher for ublituximab (0.145, N=88)

than teriflunomide (0.496, N=80). Confirmed disability progression at 12 weeks was 8% for ublituximab versus 5% for teriflunomide.

4.2.2.1 Subgroup analyses performed by the EAG

The CSRs report additional subgroup analyses for ARR. The EAG notes that the trials were not powered for these analyses and the absolute number of annual relapses is very low, limiting the statistical power to detect differences.

[redacted]

The EAG performed additional subgroup analyses by combining data reported in the CSRs for both trials. These analyses are based on reported ARR values and their confidence intervals as the original trial data was not available to the EAG. Standard deviations were calculated from confidence intervals assuming normally distributed data. ARRs and their variances were pooled across the two trials for each subgroup and each trial arm using a simple weighted average with sample size as the weights. Standard t-tests were then used to test for differences between arms within subgroups, and for difference between subgroups.

The EAG notes that these summary analyses are simplistic and may not reflect exactly what would be found using a proper analysis of the original trial data, particularly due the assumption of normality. Results are presented here to summarise potential concerns with the trial data. Table 4 presents the results of the EAG subgroup analyses. It shows the estimated ARR and its 95% confidence interval for each subgroup, and the p-value for the t-test comparing the subgroups.

[redacted]

[redacted]

Table 4 Subgroup analyses for ARR in the pooled ULTIMATE trials performed by the EAG

Factor	Subgroup	ARR	95% CI		P - value
Gender	Female	[redacted]	[redacted]	[redacted]	
	Male	[redacted]	[redacted]	[redacted]	[redacted]
Age	<38	[redacted]	[redacted]	[redacted]	
	≥38	[redacted]	[redacted]	[redacted]	[redacted]
Region	USA or Western Europe	[redacted]	[redacted]	[redacted]	
	Eastern Europe	[redacted]	[redacted]	[redacted]	[redacted]
EDSS	≤3.5	[redacted]	[redacted]	[redacted]	
	>3.5	[redacted]	[redacted]	[redacted]	[redacted]
Relapses	0 or 1	[redacted]	[redacted]	[redacted]	
	2	[redacted]	[redacted]	[redacted]	
	3 or more	[redacted]	[redacted]	[redacted]	[redacted]
Prior drug use	Yes	[redacted]	[redacted]	[redacted]	
	No	[redacted]	[redacted]	[redacted]	[redacted]
Gd-enhancing lesions	0	[redacted]	[redacted]	[redacted]	
	1 or more	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; EDSS, expanded disability status scale; Gd, Gadolinium

4.3 Critique of the indirect treatment comparisons

No trial has directly compared ublituximab to the comparator treatments, ocrelizumab and ofatumumab. The company therefore performed a series of network meta-analyses to compare the three treatments.

4.3.1 Summary of the trials included in the indirect treatment comparisons

Risk of bias assessment results were reported in Table 26 of the CS appendices document. This reported that all six trials of ublituximab, ocrelizumab and ofatumumab were judged to be at low risk of bias. However, the reporting of these results was limited, since no clarifying text was provided to justify how judgements were derived.

Table 21 in the appendices document of the CS compared trial baseline characteristics of the trials included in the NMAs, although there was no accompanying text discussing the data. In clarification question A4, the EAG therefore asked the company to describe possible effect modifiers and discuss whether they were similar enough across trials to justify whether the transitivity assumption had been met (for the NMAs). In clarification question A7, the EAG also asked about the robustness of the NMAs and to justify adopting an NMA approach (rather than a matching-adjusted indirect comparisons (MAIC) approach). Data tables comparing trials for possible effect modifiers were

included in the company responses to both clarification questions. A modified version of Table 16 (time since symptom onset has been added) from the company's clarification response is presented here as Table 5.

Table 5 Comparison of baseline characteristics across trials (adapted from Table 16 of company's clarification response)

Characteristic	ASCLEPIOS I	ASCLEPIOS II	OPERA I	OPERA II	ULTIMATE I	ULTIMATE II
	Ofatumumab (n = 465)	**Ofatumumab (n = 481)**	**Ocrelizumab (n = 410)**	**Ocrelizumab (n = 417)**	**Ublituximab (n = 271)**	**Ublituximab (n = 272)**
Age*	38.9±8.8	38.0±9.3	37.1±9.3	37.2±9.1	36.2±8.2	34.5±8.8
% Female	68	66	66	65	61	65
Race – white (%)	88	87	NR	NR	97	99
Time since diagnosis, years*	5.77±6.05	5.59±6.38	3.82±4.80	4.15±4.95	4.9±5.2	5.0±5.6
Time since symptom onset, years*	8.4±6.8	8.2±7.4	6.7±6.4	6.7±6.1	7.5±6.5	7.3±6.5
RRMS %	94.2	94.0	NR	NR	97.4	98.5
No. relapses in past year (mean, SD)	1.2±0.6	1.3±0.7	1.31±0.65	1.32±0.69	1.3±0.6	1.3±0.6
EDSS score*	2.97±1.36	2.90±1.34	2.86±1.24	2.78±1.30	3.0±1.2	2.8±1.3

*Mean, SD

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; EDSS, expanded disability disease scale; SD, standard deviation

The company stated that the baseline characteristics indicate very little variability in effect modifiers across trials and that the transitivity assumption holds. The EAG identified a systematic review and NMA which compared anti-CD20 monoclonal antibodies for relapsing-remitting multiple sclerosis.[11] The possible effect modifiers listed in that paper were: age, time since symptom onset, time since diagnosis, EDSS score, and the number of relapses in the past year. These characteristics were covered in the company's submission and responses to clarification. Although the EAG agrees that the trials were similar enough to warrant using NMAs to compare trial outcomes, the EAG also notes (and agrees with) the company's assertion that NMAs were not appropriate for adverse event outcomes due to heterogeneity across trials in event definitions and follow up durations (see also Section 4.4).

4.3.2 Summary and critique of the network meta-analysis methods

The company included a range of relevant treatments for MS in the NMAs, and not just the key treatments specified in the NICE scope. NMAs were performed for four outcomes as specified in the scope, namely:

- Annualised relapse rate (ARR),
- CDP-12 and CDP-24,
- Treatment discontinuation

NMAs were not performed for number of Gd-enhancing T1-lesions, confirmed disease improvement (CDI), adverse events or quality-of-life outcomes.

The EAG have examined the methods used for the NMAs and the Stata code used to perform them, and judge that all analyses were performed correctly, with appropriate consideration given to potential problems with the analyses, such as inconsistency between direct and indirect evidence.

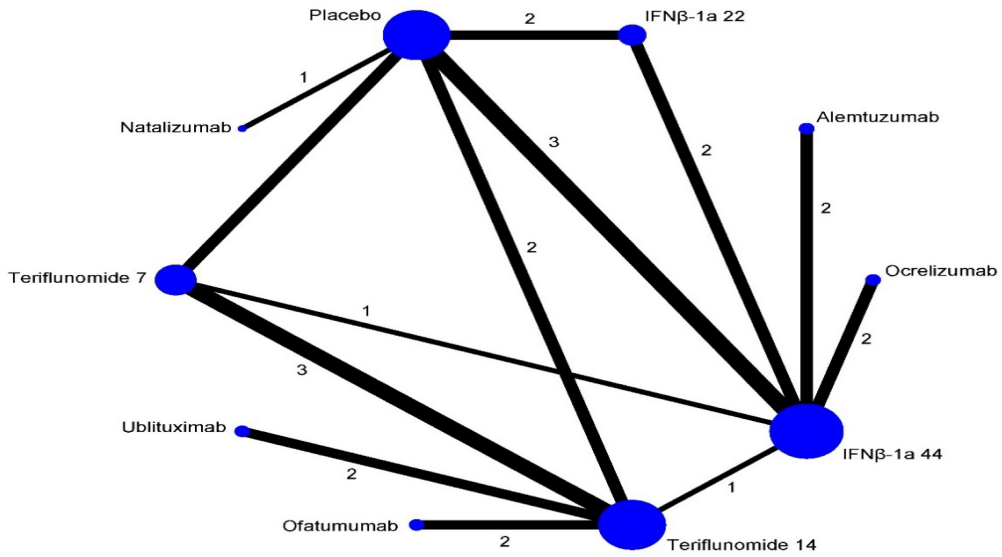
Figure 1 shows the network diagram for the analysis of ARR (taken from CS Figure 12). The EAG notes that ublituximab and ofatumumab are both "leaf nodes" connected to the network only via teriflunomide. Consequently, the comparison between ublituximab and ofatumumab essentially reduces to a simple Bucher indirect comparison of their respective trials (ULTIMATE and ASCLEPIOS). This means that the comparison between ublituximab and ofatumumab should be robust to any variations or inconsistences in the wider network, but does rely on the assumption that the trials are sufficiently similar in their conduct and recruited populations to be directly comparable.

Conversely, the comparison between ublituximab and ocrelizumab is very indirect, going via IFNβ-1a, placebo and teriflunomide. This makes the comparison much less robust and subject to bias due to inconsistency in the network or any differences in conduct or population across all the included trials.

The network also includes several treatments (alemtuzumab, natalizumab and IFNβ-1a 22), which contribute little or no information to the comparison between ublituximab, ocrelizumab and ofatumumab. The EAG requested NMAs that excluded these treatments, which were supplied by the company. The company also performed sensitivity analyses accounting for potential inconsistency in the network, accounting for different follow-up times in the trials, and removing trials where ARR or other outcomes had to be imputed.

Network diagrams for other outcomes were reported in the CS. These generally included fewer trials, and did not have any loops in the network, so it was not possible to test for inconsistency for outcomes other than ARR.

Figure 1 Network diagram for the ARR NMA (CS Figure 12)

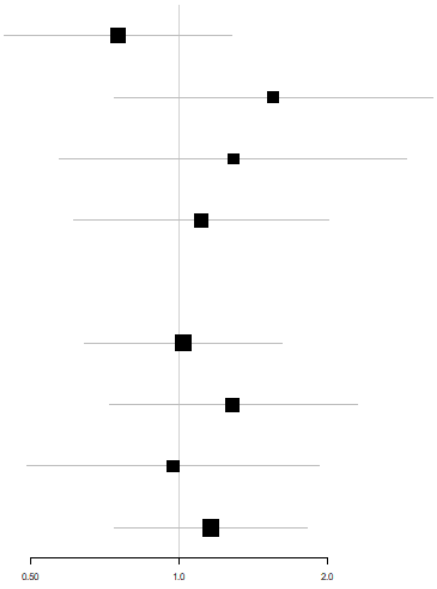


4.3.3 Summary of the network meta-analysis results

Figure 2 presents the results of the main NMAs for the four outcomes considered. This restricts presentation to the comparison between ublituximab and ocrelizumab, and between ublituximab and ofatumumab, excluding all other treatments not of relevance in this assessment. Squares to the left of a relative risk or hazard ratio of one indicate results favouring ublituximab; to the right favours the comparator.

Figure 2 Summarised results of the company NMAs

Comparator	Outcome	RR/HR	95% CI	
Ocrelizumab	ARR	0.75	0.44	1.28
	CDP-12	1.55	0.74	3.27
	CDP-24	1.29	0.57	2.9
	Discontinuation	1.11	0.61	2.01
Ofatumumab	ARR	1.02	0.64	1.62
	CDP-12	1.28	0.72	2.3
	CDP-24	0.97	0.49	1.92
	Discontinuation	1.16	0.74	1.82



Abbreviations: ARR, annualised relapse rate; CDP, confirmed disease progression; CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; RR, relative risk.

For ARR the NMAs found ublituximab to be almost identical in mean effect to ofatumumab, and possibly slightly superior to ocrelizumab. This suggests that ublituximab is plausibly similar in effect to both the other treatments. However, in both cases confidence intervals are wide and the possibility that ublituximab is inferior to the other treatments cannot be ruled out. Likewise, it is also possible that ublituximab is superior to both ofatumumab and ocrelizumab.

For both CDP-12 and treatment discontinuation the results were in the direction of favouring ofatumumab and ocrelizumab, so it is possible that ublituximab is inferior to the other treatments on these outcomes. However, confidence intervals were wide and no result was statistically significant. The estimated effect sizes were also small, so any advantage ofatumumab and ocrelizumab might have over ublituximab is likely to be modest. For CDP-24, ublituximab appeared very similar in mean effect to ofatumumab, but may be slightly inferior to ocrelizumab. Again, however, all confidence intervals were wide, and no result was statistically significant.

The company calculated Surface Under the Cumulative Ranking (SUCRA) scores in each NMA. These are summarised in Table 6. For none of the four outcomes did ublituximab have the highest SUCRA score, suggesting it would not be the preferred treatment of the three for any outcome. However, for ARR the SUCRAs for ublituximab and ofatumumab were only marginally different.

Table 6 SUCRA scores from the NMAs

	Ublituximab	Ocrelizumab	Ofatumumab
ARR	83.9	62.5	85.4
CDP-12	58.0	93.9	84.2
CDP-24	63.6	84.4	61.8
Treatment discontinuation	52.2	65.1	73.7

Abbreviations: ARR, annualised relapse rate; CDP, confirmed disease progression

The company tested for inconsistency between direct and indirect evidence for the ARR NMA (the only analysis where this was possible). The analysis found some evidence of inconsistency in the network. This appeared to be mainly due to inconsistency in the network loops involving placebo, IFNβ-1a and teriflunomide 7. This inconsistency is unlikely to adversely impact the comparison between ublituximab and ofatumumab, but could affect the comparison with ocrelizumab. This means the comparison between ublituximab and ocrelizumab may not be robust.

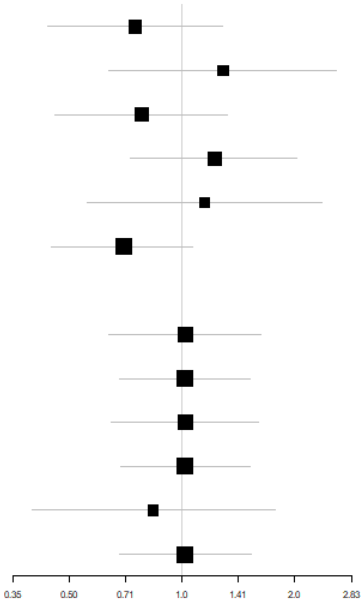
The company performed several sensitivity analyses for the NMAs. Figure 3 summarises their results for the ARR NMA. These were:

- The original analysis ("Main" in the figure)
- Accounting for network inconsistency
- Removing the OWIMS, IMPROVE or PRISM trials from the network (as ARR results were imputed for these trials rather than directly reported)
- Adjusting for variation in follow-up duration
- The EAG requested analysis removing alemtuzumab, natalizumab and IFNβ-1a 22 ("EAG reduced network")

Squares to the left of a relative risk of one indicate results favouring ublituximab; to the right favours the comparator.

Figure 3 Summary of company sensitivity analyses for the ARR NMA

Comparator	Analysis	RR	95% CI	
Ocrelizumab	Main	0.75	0.44	1.28
	Inconsistency	1.29	0.64	2.58
	No OWIMS or IMPROVE	0.78	0.46	1.32
	No OWIMS or PRISM	1.22	0.73	2.03
	Adjusted for follow-up duration	1.15	0.56	2.37
	EAG reduced network	0.7	0.45	1.07
Ofatumumab	Main	1.02	0.64	1.62
	Inconsistency	1.02	0.68	1.52
	No OWIMS or IMPROVE	1.02	0.65	1.6
	No OWIMS or PRISM	1.02	0.69	1.52
	Adjusted for follow-up duration	0.84	0.4	1.77
	EAG reduced network	1.02	0.68	1.53



Abbreviations: ARR, annualised relapse rate; CI, confidence interval; EAG, Evidence Assessment Group; NMA, network meta-analysis; RR, relative risk

Comparison between ublituximab and ofatumumab is largely robust to all sensitivity analyses. This is because the comparison is largely independent of the rest of the wider network of treatments. Adjusting for follow-up duration might lead to slightly favouring ublituximab, but confidence intervals were wide.

In contrast, the comparison between ublituximab and ocrelizumab is not robust to the sensitivity analyses. While the original analysis and the reduced network requested by the EAG both show results in the direction of favouring ublituximab, analyses adjusted for consistency and follow-up duration are in the direction of favouring ocrelizumab. All confidence intervals are wide suggesting

substantial overall uncertainty. This demonstrates that the very indirect nature of the comparison between ublituximab and ocrelizumab (via IFNβ-1a, placebo and teriflunomide) does lead to substantial uncertainty when comparing the two treatments, and no comparison based on an NMA can be considered robust.

A smaller number of sensitivity analyses were also performed for CDP-12, CDP-24 and treatment discontinuation. Results from these were generally consistent with the main NMAs, so they are not reported in detail here.

4.4 Safety and adverse events

4.4.1 Safety of ublituximab versus teriflunomide

The comparison of safety outcomes for ublituximab and teriflunomide has limited relevance to this submission, as teriflunomide is not a relevant comparator and is known to cause fewer side effects than higher efficacy therapies such as anti-CD 20 mAbs.

Adverse reactions which occurred in the safety population of the ULTIMATE trials are described in section B.3.10 of the CS (pp. 80-84). Table 7 summarises adverse events from Table 29 of the CS (p. 82) and the CSRs. Adverse events leading to treatment discontinuation were not common, but more prevalent in the ublituximab study arms. In ULTIMATE I,

[redacted]

[redacted] Infusion-related reactions commonly occurred in the ublituximab study arms, and more frequently than for participants who received teriflunomide (with a placebo injection).

Table 7 Adverse event results for the ULTIMATE I and II trials (safety population)

Outcome	ULTIMATE I		ULTIMATE II	
	Ublituximab, n (%)	**Teriflunomide, n (%)**	**Ublituximab, n (%)**	**Teriflunomide, n (%)**
Any adverse event	235 (86.1%)	245 (89.1%)	251 (92.3%)	256 (93.8%)
AE ≥ grade 3	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to temporary interruption	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to treatment discontinuation	18 (6.6%)	2 (0.7%)	5 (1.8%)	2 (0.7%)
Infusion-related reactions	120 (44.0%)	19 (6.9%)	140 (51.5%)	48 (17.6%)

Abbreviations: AE, adverse event

4.4.2 Safety of ublituximab compared with ocrelizumab and ofatumumab

In clarification question A3, the EAG requested a summary of AEs and SAEs for ocrelizumab and ofatumumab from their respective trials and an indirect comparison, if feasible. The company stated that, following an advisory board meeting with methodological experts, they were strongly advised not to perform an NMA, primarily due to the likelihood of differences across trials in how AEs are defined and variation in trial follow-up durations. The company added that this approach was consistent with previous appraisals. The company provided tables of AEs for ocrelizumab and ofatumumab in their response the clarification question A3. The EAG notes that heterogeneity in how adverse events were defined could arise from the differences in trial settings, with the ublituximab trials being primarily set in Eastern European locations and the ocrelizumab and ofatumumab trials being mainly set in Western European and North American locations.

In clarification question A10, the EAG requested the company to provide a rationale and justification for the use of lower rates of depression and urinary tract infection for ublituximab in the cost-comparison analysis when compared with ocrelizumab and ofatumumab. The company said this was justified by the lower incidence of these AEs observed in the ULTIMATE I and II trials.

The EAG therefore extracted depression and urinary tract infection adverse event data for all the anti-CD20 therapy trial arms, which are summarised in Table 8. This indicates that the underlying rates of these adverse events in the ublituximab trial populations were notably lower than in the ocrelizumab and ofatumumab trial populations. In light of this, the EAG considers that it is not appropriate for the company to compare absolute adverse event rates for the anti-CD20 trial arms (which were used in the model) without also considering the variation in rates across all arms of the trials, and without considering the relative difference in rates within each trial. The EAG therefore concludes that the evidence for assuming a clear difference in anti-CD20 adverse effect profiles is inadequate, and notes the relevance here of the company's aforementioned assertion regarding adverse event heterogeneity across trials (in definitions and follow up durations), which precluded a comparison using network meta-analysis.

Table 8 Adverse event data for depression and urinary tract infections in the anti-CD20 trials

Outcome (% incidence)	Trial and arm					
	ULTIMATE I & II pooled		ASCLEPIOS I & II pooled		OPERA 1 & 2* pooled	
	Ubli	Terif	Ofa	Terif	Ocre	Inter
Urinary tract infections	4.0	5.3	10.3	8.3	11.6	12.1
Depression	1.5	2.4	4.8	5.1	6.8	6.9

Abbreviations: Inter, Interferon beta-1a; Ocre, Ocrelizumab; Ofa, Ofatumumab; Terif, Teriflunomide; Ubli, Ublituximab
*OPERA I &II depression data were calculated using data from the clinicaltrials.gov records NCT01247324 and NCT01412333.

4.5 Summary

Results from the two ULTIMATE trials provide conclusive evidence that ublituximab reduces the rate of relapse when compared to teriflunomide. However, the EAG notes that ublituximab was not conclusively superior to teriflunomide in terms of disease progression.

Ublituximab was compared to ofatumumab and ocrelizumab indirectly through network meta-analysis. The EAG notes some concerns with the very indirect nature of the comparison between ublituximab and ocrelizumab, potential inconsistencies in the network and a lack of robustness of analyses to changes in the network.

Ublituximab appeared to be similar in effectiveness to ofatumumab in terms of mean relapse rate (ARR). The comparison with ocrelizumab was very uncertain, with ocrelizumab having slightly higher, or slightly lower relapse rates depending on the analysis performed. The EAG notes that ublituximab was possibly marginally inferior to both ofatumumab and ocrelizumab for CDP-12 and treatment discontinuation, although results were not statistically significant.

Differences across trials in healthcare settings and in how events were defined precluded comparisons of adverse event rates using network meta-analysis. However, the EAG considered that currently there is little robust evidence to suggest that ublituximab has a different safety profile to ofatumumab and ocrelizumab. The exception to this could be infusion or injection related reactions, although these events rarely appear to be serious. Nevertheless, given the differences in how the anti-CD20s are administered, patient preferences regarding the setting, frequency and duration of administration, together with the risk of infusion or injection related reactions, may play an important role when deciding which treatment may be best to use.

Overall, the EAG considers that the evidence suggests that ublituximab is plausibly similar in efficacy and safety to other anti-CD20 monoclonal antibodies. However, the evidence is not particularly robust, and it is possible that ublituximab may be marginally inferior to both ofatumumab and ocrelizumab, particularly in terms of disease progression and treatment discontinuation. This raises

concerns as to whether ublituximab would be clinically preferable to the other treatments, and to whether assuming treatment equivalence in the cost-comparison analyses is robust and appropriate.

5 SUMMARY OF THE EAG'S CRITIQUE OF COST COMPARISON EVIDENCE SUBMITTED

The appropriateness of assessing the cost-effectiveness of ublituximab in the context of a cost comparison analysis relies on the validity of the assumption of equivalent efficacy, in terms of treatment effectiveness, disease progression and disease-related mortality, and similar safety profile (including discontinuation rates) for ublituximab and its comparators of ofatumumab and ocrelizumab. The EAG critique of the cost comparison evidence assumes that it is appropriate for the assessment to proceed as a cost comparison analysis, and seeks to answer under what circumstances ublituximab is likely to be cost saving or equivalent in cost to the selected comparators.

The EAG highlights throughout the subsequent subsections, features of the cost comparison that may be affected by uncertainty surrounding the validity of assuming equivalent efficacy and safety of ublituximab to ofatumumab and ocrelizumab.

5.1 Summary of company's cost comparison and assumptions

5.1.1 Summary of cost comparison

The company presents a cost comparison of ublituximab, as compared to ofatumumab and ocrelizumab (IV and SC), over a 5-year time horizon (without discounting), using a Markov model with three discrete states of 'on-treatment', 'off-treatment', and 'death' in order to simulate the proportion of living patients who receive treatment each year. The costs included in the company's cost comparison are: (i) drug acquisition costs; (ii) drug administration costs; (iii) monitoring costs; and (iv) adverse event costs. Unit costs were informed by national public sources[12-14] and previous NICE guidance[1] with inflation adjustment. Table 9 summarises the costs used in the company's cost comparison analysis.

Table 9 Summary of costs used in the company's cost comparison analysis

Item	Cost comparison analysis input	Source
Drug acquisition costs per year		
Ublituximab	List Price first year: [redacted] subsequent years: [redacted] PAS Price first year: [redacted] subsequent years: [redacted]	Ublituximab is initially administered as a 150mg IV infusion, followed by a 450mg IV infusion 2 weeks later. Subsequent doses are administered as a single 450mg IV infusion every 24 weeks. Ublituximab list price per 150mg vial is [redacted] and PAS price per 150mg vial is [redacted]
Ofatumumab	List Price first year: £20,895 subsequent years: £17,910	Ofatumumab is administered as a 20mg SC injection at weeks 0, 1 and 2, followed by subsequent monthly dosing. Ofatumumab list price per 20mg solution is £1,493.50.
Ocrelizumab (IV)	List Price first year: £19,160 subsequent years: £19,160	Ocrelizumab (IV) is initiated at a dose of 600mg, administered as two separate IV infusions; first as a 300mg infusion, followed 2 weeks later by a second 300mg infusion. Subsequent doses of ocrelizumab (IV) thereafter are administered as a single 600mg IV infusion every 6 months. Ocrelizumab (IV) list price per 300mg vial is £4,790.00.
Ocrelizumab (SC)	List Price first year: £19,160 subsequent years: £19,160	Ocrelizumab (SC) is administrated as a 920mg SC injection every 6 months. Ocrelizumab (SC) list price per 920mg solution is £9,580.00.
Administration costs per year		
Ublituximab	First year: £1,445 Subsequent years: £544	Ublituximab involves IV infusions by accounting for the proportion of bed-day costs and nursing costs per infusion. The total time per patient for the first infusion is 6.25 hours, and 2.25 hours for the subsequent infusions, which includes preparation, infusion and monitoring time. The model uses £58.00 nurse cost per hour[14] and £426.08 bed-day cost[13] multiplied by the total time to calculate the administration cost for each infusion (the first infusion: £695.37 and the subsequent infusion: £250.33). Detailed drug administration costs associated with IV infusions are shown in company submission Table 31. Pre-medication required before IV infusions to reduce and prevent IRRs. These include 100mg IV methylprednisolone, an antihistamine (chlorphenamine maleate, 4mg) and an antipyretic (paracetamol, 500mg). The unit costs for the pre-medication were sourced from the BNF and were applied to each treatment administration.[12]
Ofatumumab	First year: £116 Subsequent years: £0	The drug administration method for ofatumumab involves a SC injection for which a cost is only attributed at treatment initiation, while subsequent administrations incur no costs. This approach is undertaken under the assumption that patients follow a two-hour training on self-administration from a MS-specialist nurse, in line with TA699.[2] Detailed drug administration cost for SC injections are shown in company submission Table 32.
Ocrelizumab (IV)	First year: £1,057 Subsequent years: £1,113	Ocrelizumab also involves IV infusion and only differs by the duration of the infusion and the monitoring time

		after the infusion at each session, compared to ublituximab. The total time per patient for the first infusion is 7.25 hours and 5.00 hours for the subsequent infusions, which includes preparation, infusion and monitoring time. And the total cost for the first infusion is £806.63 and for subsequent infusions is £ £556.30. Detailed drug administration costs associated with IV infusions are shown in company submission Table 31.
Ocrelizumab (SC)	First year: £426.50 Subsequent years: £426.50	Ocrelizumab (SC) is administered by a doctor or nurse as a subcutaneous injection. Compared to ocrelizumab (IV), it has shorter preparation time (0.5 hours) and injection time (0.17 hours). Pre-medication is also required before each injection. These include dexamethasone, 20mg, an antihistamine (chlorphenamine maleate, 4mg) and an antipyretic (paracetamol, 500mg). The unit costs for the pre-medications were sourced from the BNF and were applied to each treatment administration.[12]
Monitoring costs per year		
Ublituximab	First year: £457.32 Subsequent years: £377.88	Due to the comparable health outcomes of ublituximab, ofatumumab and ocrelizumab, it has been assumed that the resource utilisation for monitoring patients would be the same for all therapies. The costs for resource use were extracted from TA699 and were inflation-adjusted.[2]
Ofatumumab	First year: £457.32 Subsequent years: £377.88	
Ocrelizumab (IV)	First year: £457.32 Subsequent years: £377.88	
Ocrelizumab (SC)	First year: £457.32 Subsequent years: £377.88	
Adverse event costs (one-time cost)		
Ublituximab	£44.38	The costs of treating AEs were considered separately for non-serious and serious AEs (SAEs). Unit costs for treating each non-serious and SAE were obtained from TA699 and were inflation-adjusted. [2] Unit cost inputs were then weighted by the proportion of patients experiencing SAEs from the relevant clinical trials of ublituximab, ofatumumab and ocrelizumab (IV) (10.8% for patients receiving ublituximab; 9.1% for patients receiving ofatumumab; and 7.0% for patients receiving ocrelizumab (IV)). The detailed cost inputs for AE management are shown in company submission Table 34.
Ofatumumab	£91.20	
Ocrelizumab (IV)	£125.63	
Ocrelizumab (SC)	£125.63	In the company's response to EAG points for clarification, where ocrelizumab (SC) is added as an additional comparator, the company assumes that ocrelizumab (SC) has the same AE profile as ocrelizumab (IV).

Abbreviations: AE, adverse event; BNF, British National Formulary; IRR, infusion-related reactions; IV, intravenous; MS, multiple sclerosis; PAS, patient access scheme; SC, subcutaneous.

5.1.2 Assumptions

The key assumptions underlying the company's cost comparison analysis are as follows:

- Ofatumumab and ocrelizumab are the most relevant comparators for the population of adults with RRMS with active disease.
- Equivalent (or very similar) effectiveness, disease progression and disease-related mortality between ublituximab and its comparators means that it is appropriate to evaluate ublituximab in the context of a cost-comparison analysis.
- Equivalent (or very similar) safety profile between ublituximab and its comparators, although the company has included differences in the resource use and costs associated with both serious and non-serious adverse events in the cost comparison analysis.
- There are differences in the cost of IV infusion therapy for ublituximab and ocrelizumab (IV) based on hospital bed day costs, as a proxy for hospital overhead costs, and nurse cost per hour, as a proxy for labour costs. All other overhead costs attributed to IV administration are assumed the same.
- Patients receive their first administration of ofatumumab in the secondary care setting, while subsequent administrations are provided in the home setting. A two-hour training on self-administration from an MS-specialist nurse was assumed, while self-administrations are assumed to incur no costs.
- Equivalent monitoring costs between ublituximab and its comparators.
- Patients do not discontinue treatment in the company's base case analysis. The impact of treatment discontinuation is explored in a scenario analysis. In the scenario analysis, the company assumes that there is no difference in subsequent treatment costs post-discontinuation.
- A time horizon of 5 years is used to compare the costs of ublituximab and its comparators.
- Discounting of costs is not included in the company's base case analysis. The impact of discounting costs at 3.5% per annum is explored in a scenario analysis.
- No subgroup analyses presented. No differences in the dosing schedules between the overall population and the highly active or RMS subpopulation.

5.2 EAG critique of the company's cost comparison

The EAG conducted a technical validation of the executable model by cross-checking values against the company submission and auditing formulae. The EAG detected no errors in the executable model.

The EAG critique focuses on the following aspects of the cost comparison analysis:

- Uncertainty in the existing clinical evidence for equivalence of treatment effect;
- Adverse events;
- Acquisition costs
- Administration costs;

- Treatment discontinuation and subsequent treatment use;
- Time horizon and discounting.

5.2.1 Uncertainty in the existing clinical evidence

The existing clinical evidence from the NMA for the outcomes of ARR, CDP-12 and CDP-24 suggests that there is a non-zero probability that ublituximab is less (or more) effective than ofatumumab and ocrelizumab (IV) (see Section 4.3.3 . The consequences of uncertainty for patient outcomes have not been assessed, which would require a full cost-effectiveness analysis with probabilistic sensitivity analysis. The EAG notes that when the difference in effectiveness between two treatments is not statistically significant, the only valid conclusion is that there is not sufficient evidence to distinguish between the treatments, i.e., it is not sufficient to conclude that the treatments are equivalent. Therefore, there remains uncertainty about the assumption of equivalent (or very similar) effectiveness, disease progression and disease-related mortality between ublituximab and its comparators, ofatumumab and ocrelizumab (IV or SC).

Uncertainty in health outcomes will also affect uncertainty in total costs. The treatment duration of the interventions is assumed to be 5 years in the absence of other information, but if this duration differs by treatment then the length of time spent in health states and time to next treatment received will also differ. Therefore, the corresponding resource use and costs for the interventions will be different.

5.2.2 Adverse events

A key assumption in a cost comparison analysis is the equivalence (or very similar) safety profile between the interventions under comparison. Only substantial differences between interventions in costs directly relating to health outcomes that indicate that the intervention and comparator(s) may not provide similar overall health benefits should be considered in a cost comparison. The company's inclusion of differential adverse events in the first year of treatment appears unnecessary given the underlying assumption that the safety profile is comparable between the treatments and the company's assumption that there is no difference in the discontinuation rate between treatments (and switching to subsequent treatments).

The health-related quality of life (HRQoL) impact of the AEs is not included in the cost comparison. The EAG notes that if the difference in AEs is considered sufficiently important for inclusion in the company's cost comparison, then the HRQoL impact (utility decrement) for the AEs should also be considered. However, a full cost-effectiveness analysis would be required to capture the impact on HRQoL due to AEs and the consequences of discontinuing treatment.

The EAG concludes that the inclusion of separate AE costs, whilst not considering their HRQoL impact, is unnecessary in the company's cost comparison analysis. Furthermore, the EAG's clinical

advisor did not consider there to be any reason for the differential rates of the more costly AE of depression (0.7% for ublituximab, 4.8% for ofatumumab and 7.8% for ocrelizumab (IV), see Table 34 of CS), which has a unit cost of £3,822 as a serious AE and £1,046 as a non-serious AE (see also Section 4.4). The lower percentage of patients experiencing treatment-related depression (a more costly event) for ublituximab compared to the comparators is the main driver of the lower one-off AE cost included in the company's cost comparison for ublituximab (£44.34) compared to comparators (£91.20 for ofatumumab and £125.63 for ocrelizumab (IV or SC)).

5.2.3 Acquisition costs

The cost comparison model estimates acquisition costs in the first and subsequent years for ublituximab and comparators. The list price for ublituximab in the first year is [redacted] and [redacted] per subsequent year, which is higher than the list price of ofatumumab (first year: £20,895, subsequent years: £17,910) and ocrelizumab (IV or SC) (£19,160 per year). The PAS price for ublituximab is [redacted] in the first year and [redacted] per subsequent year, which is [redacted] than the comparator list price.

The EAG notes that there are confidential commercial arrangements in place for the comparator treatments. The drug acquisition costs used in the CS and in this report include only the confidential pricing agreement for ublituximab. Table 10 presents details of the treatments with confidential price which differs from the publicly available list price used to generate the results in this report. These prices were made available to the EAG and were used to replicate all analyses presented in the EAR. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices are correct as of 13th August 2024.

Table 10 Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Ublituximab	Simple PAS
Ofatumumab	Simple PAS
Ocrelizumab (IV & SC)	Simple PAS

Abbreviations: IV, intravenous; PAS, patient access scheme; SC, subcutaneous.

5.2.4 Administration costs

The cost comparison analysis includes differences in the administration method and duration of infusion and monitoring time for the treatments. Ublituximab and ocrelizumab (IV) involve IV infusions that differ in the duration of the infusion and the monitoring time after the infusion at each session, which is approximated by the proportion of bed-day costs and nursing costs per infusion. Ublituximab's infusion time is assumed to be 1 hour shorter for the first infusion and 1.75 hours

shorter for subsequent infusions compared to ocrelizumab (IV). In addition, no monitoring time for subsequent infusions is required with ublituximab. Consequently, the administration costs for ublituximab are lower than ocrelizumab (IV) (see Table 31 of CS).

Ofatumumab involves a SC injection, for which an administration cost is only attributed at treatment initiation and subsequent administrations occur no costs. This method assumes that patients follow a two-hour training on self-administration from a MS-specialist nurse, in line with the approach used in TA699.[2] Consequently, the administration costs for ofatumumab are much lower than ublituximab and ocrelizumab (see Table 32 of CS).

The EAG cross-checked the administration cost assumptions with previous NICE TAs 699 and 533 and validated them with the EAG's clinical advisor.[1, 2] The approach used by the company is in line with previous TAs and is considered reasonable in the context of the cost comparison.

However, the EAG notes that the CS did not consider the impact of the new 'under-the-skin' injection for ocrelizumab on its acquisition and administration costs.[1] Ocrelizumab can now be administered via a quick 'under-the-skin' twice-yearly injection, which reduces the infusion time. Therefore, the benefits of ublituximab's shorter infusion time compared to ocrelizumab (SC) is no longer expected to hold. The EAG requested at points for clarification to update the revised version of the model to reflect the changes to the acquisition and administration costs of ocrelizumab 'under-the-skin' injection. The company included ocrelizumab 'under-the-skin' injection as a new comparator, ocrelizumab (SC), in the cost comparison analysis. Table 11 compares the resource use costs for drug administration with ocrelizumab in IV and SC forms. Compared to ocrelizumab (IV), ocrelizumab (SC) has shorter preparation time (0.5 hours) and injection time (0.17 hours). Uncertainty remains about the percentage of patients to use different forms of ocrelizumab (IV or SC). The EAG's clinical advisor considered that current patients who already use ocrelizumab (IV) are more likely to continue with IV infusions, but newly treated ocrelizumab patients are more likely to use SC injection because of the time and cost-savings. Therefore, in the long-term, it is expected that most patients treated with ocrelizumab will be administrated SC injection. The percentage of patients treated with ocrelizumab IV and SC will impact the cost comparison results.

Table 11 Drug administration cost calculations for ocrelizumab in IV and SC forms (from company response to EAG clarifications, Table 20)

Resource use per administration	Ocrelizumab IV First infusion	Ocrelizumab IV Subsequent infusions	Ocrelizumab SC injections
Preparation time (h)	1.00	1.00	0.50
Infusion/injection time (h)	5.00	2.75	0.17
Time interval between patients (h)	0.25	0.25	0.25
Total infusion/injection time per patient (h)	5.25	3.00	0.42
Monitoring after infusion/injection (h)	1.00	1.00	1.00

Total time per patient per session(h)	7.25	5.00	1.92
Patients per bed per day	1.00	1.00	4.00
Nurse costs for infusion per patient	£420.50	£290.00	£111.17
Cost per bed-day	£386.13	£266.30	£102.08
Total cost per administration	**£806.63**	**£556.30**	**£213.25**
Annual drug administration costs	**£1,056.97**	**£1,112.60**	**£426.50**

Abbreviations: h, hour; IV, intravenous; SC, subcutaneous.

5.2.5 Treatment discontinuation and subsequent treatment use

The company assumes no treatment discontinuation in its base case analysis, but a separate scenario analysis is provided where differential discontinuation rates between the three treatments are considered ([redacted] for ublituximab, [redacted] for ofatumumab, and [redacted] for ocrelizumab). The differential discontinuation rates in the scenario analysis have minimal impact on the results of the cost comparison because the costs of subsequent treatments post-discontinuation are not included in the model.

The EAG's clinical advisor considered it reasonable to assume that ublituximab, ofatumumab and ocrelizumab have very similar discontinuation rates, and that the subsequent treatments used post-discontinuation would be expected to be similar across the three interventions. Therefore, the EAG considers no treatment discontinuation to be a reasonable approximation in the context of the cost comparison, under the assumption of equivalence (or very similar) safety profile between the interventions under comparison.

5.2.6 Time horizon and discounting

The time horizon used in the company's base case is set to five years, which the company states was selected to account for higher treatment initiation costs and to allow the costs to stabilise over time. The EAG considers a 5-year time horizon to be a reasonable choice, but notes that because treatment discontinuation is not considered in the model the costs accrued annually do not change after the first year; the annual costs only change insofar as general population mortality rates are incorporated into the analysis to determine the number of patients alive each year to receive treatment (and the company's model incorporates a half-cycle correction to account for timing of death during an annual cycle). Therefore, the EAG considers it important to present the differences in annual costs between the interventions, rather than only presenting the total cost difference over a 5-year time horizon (see Table 15 in Section 6.2). The effect of increasing the annual costs over a longer time horizon provides an illustration of the budget impact per patient remaining on treatment.

The company did not include discounting in their results over a 5-year time horizon, on the basis that NICE methods guidance indicates that discounting may not be required for cost comparisons. The EAG considers it appropriate to use discounting when the differences in costs between treatments are

extended over a longer time period of five years. However, as noted above, the EAG considers it important to present the differences in annual costs between the treatments, which do not need to be discounted.

6 COMPANY AND EAG COST COMPARISON RESULTS

The following section details the results of the company's base case and scenario analyses, followed by the EAG's preferred base case. All results include the PAS price for ublituximab and list price for comparators. A separate confidential appendix presents the results of the company and EAG preferred base case when confidential PAS prices for comparators are included.

6.1 Company cost comparison results

Table 12 presents the company's base case results for ublituximab, ofatumumab and ocrelizumab (IV or SC) over a 5-year horizon. The total costs (with PAS price) for ublituximab are [redacted] than its comparators.

Table 12 Total costs for the intervention and comparator technologies over a 5-year time horizon (from CS, Table 36)

	Drug acquisition costs	Drug administration costs	Resource use costs	Adverse event costs	TOTAL COSTS
Ublituximab, list price	[redacted]	£3,649	£1,966	£44	[redacted]
Ublituximab, PAS price	[redacted]	£3,649	£1,966	£44	[redacted]
Ofatumumab	£92,402	£116	£1,966	£91	£94,575
Ocrelizumab (IV)	£95,658	£5,526	£1,966	£126	£103,276
Ocrelizumab (SC)	£95,658	£2,150	£1,966	£126	£99,899

Abbreviations: IV, intravenous; PAS, patient access scheme; SC, subcutaneous.

The company provided two scenario analyses: (i) costs are discounted at a rate of 3.5% per annum; and (ii) treatments are discontinued, with an annual discontinuation probability of [redacted] for ublituximab, [redacted] for ofatumumab and [redacted] for ocrelizumab based on the NMA (rates converted to annual probabilities). Table 13 below shows the results of the company's scenario analyses. The total costs (with PAS price) for ublituximab are [redacted] than its comparators for both scenarios.

Table 13 Total costs derived from scenario analyses (from CS, Table 37)

	Base case	3.5% discounting	Treatment discontinuation
Ublituximab, list price	[redacted]	[redacted]	[redacted]
Ublituximab, PAS price	[redacted]	[redacted]	[redacted]
Ofatumumab	£94,575	£88,610	£86,454
Ocrelizumab (IV)	£103,276	£96,539	£93,672
Ocrelizumab (SC)	£99,899	£93,386	£90,615

Abbreviations: IV, intravenous; PAS, patient access scheme; SC, subcutaneous.

6.2 Results of EAG preferred base case

The EAG preferred base case reflects the assumptions included in the company's base case with the (i) exclusion of differential adverse event costs; and (ii) inclusion of discounting of costs over a 5-year time horizon (Table 14).

Table 14 Accumulated EAG base case results over a 5-year time horizon

Company base case					
	Drug acquisition costs	Drug administration costs	Resource use costs	Adverse event costs	TOTAL COSTS
Ublituximab, PAS price	[redacted]	£3,649	£1,966	£44	[redacted]
Ofatumumab	£92,402	£116	£1,966	£91	£94,575
Ocrelizumab (IV)	£95,658	£5,526	£1,966	£126	£103,276
Ocrelizumab (SC)	£95,658	£2,150	£1,966	£126	£99,899
Company base case + exclusion of adverse events costs					
	Drug acquisition costs	Drug administration costs	Resource use costs	Adverse event costs	TOTAL COSTS
Ublituximab, PAS price	[redacted]	£3,649	£1,966	£0	[redacted]
Ofatumumab	£92,402	£116	£1,966	£0	£94,484
Ocrelizumab (IV)	£95,658	£5,526	£1,966	£0	£103,150
Ocrelizumab (SC)	£95,658	£2,150	£1,966	£0	£99,774
Company base case + exclusion of adverse events costs + 3.5% annual discount rate (EAG base case)					
	Drug acquisition costs	Drug administration costs	Resource use costs	Adverse event costs	TOTAL COSTS
Ublituximab, PAS price	[redacted]	£3,470	£1,843	0	[redacted]
Ofatumumab	£86,560	£116	£1,843	0	£88,519
Ocrelizumab (IV)	£89,409	£5,162	£1,843	0	£96,413
Ocrelizumab (SC)	£89,409	£2,010	£1,843	0	£93,261

Abbreviations: IV, intravenous; PAS, patient access scheme; SC, subcutaneous.

The exclusion of adverse events costs and inclusion of a 3.5% annual discount rate has only a small impact on the cost comparison results, with the total cost for ublituximab (with PAS price) [redacted] than its comparators.

The EAG also considers it important to present the results separately for the first year and subsequent years, rather than over a 5-year time period, so that the annual difference in costs between the treatments can be assessed. Table 15 shows that the differences in costs over the 5-year time horizon in the company's base case and EAG base case (without discounting) is largely from subsequent years costs.

Table 15 Company base case and EAG base case with results reported separately for the first year and subsequent years

	Ublituximab	Ofatumumab	Ocrelizumab (IV)	Ocrelizumab (SC)	Incremental Δ Ublituximab vs Ofatumumab	Incremental Δ Ublituximab vs Ocrelizumab (IV)	Incremental Δ Ublituximab vs Ocrelizumab (SC)
Company base case							
First year costs	[redacted]	£21,560	£20,807	£20,174	[redacted]	[redacted]	[redacted]
Subsequent year costs (each year)	[redacted]	£18,288	£20,655	£19,969	[redacted]	[redacted]	[redacted]
Company base case: Over 5 years (undiscounted)	[redacted]	£94,575	£103,276	£99,899	[redacted]	[redacted]	[redacted]
EAG base case							
First year costs (same as company but excluding one-time AE costs)	[redacted]	£21,468	£20,682	£20,048	[redacted]	[redacted]	[redacted]
Subsequent year costs (each year)	[redacted]	£18,288	£20,655	£19,969	[redacted]	[redacted]	[redacted]
EAG base case: Over 5 years (discounted at rate of 3.5% per year)	[redacted]	£88,519	£96,413	£93,261	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event ; EAG, evidence assessment group; IV, intravenous; SC, subcutaneous.

7 EQUALITIES AND INNOVATION

The EAG agrees with the company that introducing ublituximab to NHS practice is not likely to impact differentially on groups of patients with protected characteristics or disabled persons. As with all treatments administered in hospital, equitable access across English regions depends on the local availability of technology and personnel.

Ublituximab is an anti-CD20 monoclonal antibody, and similar in terms of mechanisms of action to comparators ocrelizumab and ofatumumab. The company does not argue that ublituximab is a novel, innovative therapy in terms of working mechanisms, safety profile, or treatment effects. In the CS, the company argued that the shorter infusion time of ublituximab compared to ocrelizumab (from the second infusion) is an improvement, though this argument is less relevant with the recent introduction of ocrelizumab subcutaneous injections (see Section 3.3).

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

8.1 Conclusions on clinical evidence

The evidence for ublituximab is drawn from the ULTIMATE trials, which are large, high-quality RCTs. There is good evidence from the trials that ublituximab is superior to teriflunomide at reducing relapse rate. However, the trials did not show a benefit of ublituximab compared to teriflunomide for worsening disability outcomes at 12 and 24 weeks. Subgroup analyses of the ULTIMATE trials performed by the EAG [redacted].

The introduction of ocrelizumab by subcutaneous injection raises some doubts as to whether ublituximab, which requires IV infusion, will be preferred by patients.

Ublituximab was compared to ocrelizumab and ofatumumab using appropriate and properly conducted network meta-analyses. The results suggested that ublituximab is plausibly similar in efficacy to ocrelizumab and ofatumumab for response rate and disease progression. However, the NMAs comparing ublituximab to ocrelizumab were highly indirect, subject to network inconsistency and not robust to sensitivity analyses. This raises concerns to whether the two treatments can be considered equally effective. The NMAs also suggested that ublituximab might be marginally inferior to ocrelizumab and ofatumumab in terms of disease progression at 12 months and treatment discontinuation, although these findings were not statistically significant.

The EAG considers that currently there is little robust evidence to suggest that ublituximab has a different safety profile to ofatumumab and ocrelizumab, but the exception to this could be infusion or injection related reactions. Given the differences in how the anti-CD20s are administered, patient preferences may play an important role when deciding which treatment may be best to use.

8.2 Conclusions on cost-effectiveness

The EAG is largely satisfied with the company's approach to the cost-comparison analysis based on differential drug acquisition and administration costs. However, the EAG considers it unnecessary to include separate adverse event costs, whilst not considering their health-related quality of life impact because a key underlying assumption is that the safety profile is comparable between the treatments and there is no difference in the discontinuation rate between treatments. The lower percentage of patients experiencing treatment-related depression (a more-costly adverse event) for ublituximab compared to the comparators is the main driver of the lower one-off AE cost included in the

company's cost comparison. In the company's base case, ublituximab has [redacted] acquisition costs than the comparator list price (confidential commercial arrangements are in place for the comparator treatments). The cost comparison analysis includes differences in the administration method and duration of infusion and monitoring time for the treatments. The EAG is satisfied with the approach used by the company but noted that the CS did not consider the impact of the 'under-the-skin' injection for ocrelizumab (SC), which has shorter preparation and injection time compared to ocrelizumab (IV). Uncertainty remains about the percentage of patients to use different forms of ocrelizumab (IV or SC), which will impact the cost comparison results.

8.3 Areas of uncertainty

Table 16 lists the EAG's areas of concern, where the evidence presented may impact on the robustness and suitability of using a cost-comparison approach.

Table 16 Outstanding areas of uncertainty

Issue	Description	Report sections
Subgroup analyses of ULTIMATE trials	[redacted]	4.2.2.1
Indirect nature of comparison of ublituximab and ocrelizumab	NMAs comparing ublituximab and ocrelizumab were subject to inconsistency and were not robust to some of the sensitivity analyses. This led to uncertainty as to whether they can be considered as equivalent.	4.3.2; 4.3.3
NMAs of disease progression and treatment discontinuation	Ublituximab might be marginally inferior to ocrelizumab and ofatumumab in terms of disease progression at 12 months and treatment discontinuation.	4.3.3
Availability of ocrelizumab by subcutaneous injection	The CS does not consider the new treatment option of ocrelizumab by subcutaneous injection, which may impact on costs and patient preferences.	3.3; 5.2.4

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10 APPENDICES

Appendix 1: Clinical Evidence Searches

The original company submission included searches to identify clinical evidence for adult patients with relapsing forms of multiple sclerosis (RMS). A description of the searches and some of the search strategies were included in CS Appendix D (pp. 2-15).

In response to the EAG's points for clarification (PfC), the company provided additional information and corrections to errors.

Table 17 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	In the original company submission: • no strategies were listed for the searches of conference abstracts. This was raised as a PfC. The company responded with all further strategies that were documented. • the update search for Ovid Embase was not documented with hits per line. This was raised as a PfC. The company responded with the fully documented strategy. • it was unclear why the PubMed strategy removed some MEDLINE records. This was raised as a PfC. The company explained that this was because this database had also been searched on another platform (concurrently with Embase). The company updated the names of some of the Tables to make this clearer. • the PRISMA listed 'databases and registers' but did not show the hits from clinicaltrials.gov in with the databases and registers. Instead, the PRISMA presented the number or relevant this from this source elsewhere in the diagram. This was raised as a PfC. The company responded with an updated PRISMA.
Were appropriate sources searched?	PARTLY	A small range of relevant databases, conference proceedings, and a single trials registry were searched. No dedicated HTA databases were searched (e.g. INAHTA), only one dedicated trials registry was searched, and there were no searches of websites of bodies such as NICE, etc.
Was the timespan of the searches appropriate?	YES	The time span of the searches was appropriate.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with interventions and the study type. Data on adverse effects was not sought directly, even though this was part of the inclusion criteria. The EAG queried this as a PfC and the company responded that they were confident that no data on adverse effects was missed and that safety data from relevant trials had been used.
Were appropriate search terms used?	YES	Although the PubMed terms for interferon beta-1a were not as comprehensive compared with the terms used on other databases, this was acceptable since the same database had also been searched on another platform (concurrently with Embase) with more detailed search terms.
Were any search restrictions applied appropriate?	YES	Animal studies were removed appropriately
Were any search filters used, validated and referenced?	PARTLY	A randomised controlled trials filter was used but not referenced.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Single Technology Appraisal

Ublituximab for treating relapsing multiple sclerosis [ID6350]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **on 24 September 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 7 of the EAG report, the EAG state that 'The ULTIMATE trials showed that ublituximab appears to be an effective treatment for RRMS, being superior to teriflunomide in reducing relapse rates'. The above statement is accurate, however it does not present the full picture as ublituximab was also superior to teriflunomide in reducing T1Gd+ and T2 lesions. We suggest that this statement is amended to reflect the full extent of the superiority of ublituximab compared to teriflunomide.	Sentence should read: 'The ULTIMATE trials showed that ublituximab appears to be an effective treatment for RRMS, being superior to teriflunomide in reducing relapse rates and radiological outcomes (reducing T1Gd+ and T2 lesions)'.	The current statement does not reflect the full extent of the superiority of ublituximab.	Not a factual inaccuracy. This is intended as a short summary of the evidence for the primary outcome.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 8 of the EAG report, when referring to the subgroup analyses, the EAG state [redacted]. [redacted] Use of the term 'inferior' in this context would, therefore, not appear to be appropriate. Although 'inferior' itself does not automatically confirm statistical significance unless explicitly stated, if you say a product is 'inferior', it should ideally be backed by statistically significant evidence. If there is no significant difference, the product should be described as 'not superior' or 'comparable' rather than 'inferior'. Alternatively, text should read that [redacted] We note that the term 'inferior' is used on 11 occasions in the report, always in the context of ublituximab 'possibly being inferior' or being 'marginally inferior' to the comparator. However, on none of these occasions is the report referring to results where ublituximab is actually statistically significantly inferior to teriflunomide. Results should not be over-stated in this way	On all occasions where the term 'inferior' is used throughout the report (not just at the highlighted point on Page 8), we request that more statistically appropriate terminology is used in light of the presented results. Please see suggestions for appropriate terminology in the 'Description of problem' column.	In the context of statistical analysis, especially when the results are not statistically significant, it is important to be careful with the terminology used. The term 'inferior' can imply a more definitive conclusion than the data supports, particularly if the differences are not statistically significant.	Not a factual inaccuracy. In all places in the main body of the report where "inferior" is used this is clearly caveated with phrasing such as "possibly" or "potentially" and lack of statistical significance, and/or small sample sizes are discussed. We have amended the text for those cases in the summary sections (e.g. page 8) where

and appropriate terminology should be used in the context of the actual results presented.			this was not the case.

Issue 3

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
On Page 16 of the EAG report in Table 1, the mean number of relapses per participant in the teriflunomide arm of the ULTIMATE I trial is reported to be [redacted].	Adjust value from [redacted] to [redacted] for mean number of relapses per participant in the teriflunomide arm of the ULTIMATE I trial.	Incorrect value reported.	Amended as suggested in Table 1.

However, as reported in the CSR this number is [redacted] and therefore, if presented to two decimal places, this value needs to be changed to [redacted].			

Issue 4

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
On Page 16 of the EAG report in Table 1, the mean number of relapses per participant in the ublituximab and teriflunomide arms of the ULTIMATE II trial is reported to be [redacted] and [redacted], respectively. However, as reported in the CSR, the mean number of IRAP-confirmed relapses during treatment was [redacted] in the ublituximab group and [redacted] in the teriflunomide	Adjust ublituximab value from [redacted] to [redacted] and teriflunomide value from [redacted] to [redacted] for mean number of relapses per participant in the ULTIMATE II trial.	Incorrect values reported.	Amended as suggested in Table 1.

group. If presented to two decimal places, these values therefore need to be changed to [redacted] and [redacted], respectively.			

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 17 of the EAG report, the EAG state that 'HRQoL measured with the SF-36 was better in the ublituximab than the teriflunomide study arm for physical functioning, the role-physical component, and vitality'. While this is true, it is not the full picture as these are only the components for which ublituximab was superior to teriflunomide (by nature of statistical significance). Ublituximab was in fact better than teriflunomide for all components of the SF-36, but	This statement should be more appropriately aligned with the results as presented in the original submission of evidence, i.e., 'Statistically significant improvements favouring ublituximab vs teriflunomide were seen in physical component summary, physical functioning, and role-physical. When evaluating the change from baseline in SF-36 at week 96 only, improvements were seen for ublituximab vs teriflunomide for all components'.	The currently presented statement does not accurately depict the true SF-36 HRQoL results.	Reworded as follows: "HRQoL measured with the SF-36 showed a statistically significant improvement for ublituximab compared to the teriflunomide study arm for physical functioning, the role-physical component, and vitality."

the results were not statistically significant for the components other than the three aforementioned.			

Issue 6

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
On Page 18 of the EAG report, the EAG state that '[redacted]'. This is a confusing statement as it does not tell us anything about the results for the female cohort, only [redacted] The same point can be made about the [redacted]' statement. Again, in ULTIMATE I, results [redacted]	This statement should be more appropriately aligned with actual results of these analyses. If focussing on these subgroups specifically, the statement should more appropriately read along the lines of: 'In ULTIMATE I, [redacted] The beneficial effects of ublituximab on outcomes including reduction in Gd+ T1 lesions and new/enlarging T2 lesions, and NEDA at Week 96, have been demonstrated across all patient subgroups assessed'.	The currently presented statement(s) do not accurately depict the true results.	We have amended Section 4.2.2.1 (page 18) to clarify these subgroup comparisons and their statistical significance

All of the above comments should be considered not only in relation to the specific text that has been highlighted by the company as part of Issue 6 but also in statements that have been made by the EAG regarding their concerns with results of subgroup analyses in the Executive Summary, Conclusions, and Areas of Uncertainty. It is our view that the tone of these statements and areas for concern that have been highlighted by the EAG are not consistent with the true results of these analyses. In addition to the above points, we would like to highlight that this statement is referring to one specific outcome, i.e., relapse rate. However, if the EAG view results as presented in the poster linked (https://www.tgtherapeutics.com/wp-content/uploads/2022/06/Hartung-1054-TG-EAN-2022-Subpopulations-poster-15Jun22b.pdf), it is evident that ublituximab provided a statistically significant reduction in Gd+ T1 lesions and new/enlarging T2 lesions vs teriflunomide at Week 96 for all evaluable participant subgroups (P<0.0001), and that a significantly higher proportion of ublituximab-treated vs teriflunomide-treated participants achieved NEDA by Week 96 (re-baselined at Week 24) across all subgroups. The impact of			

ublituximab on B-cell depletion has also shown to be strong across age categories, as demonstrated in the following poster: https://www.tgtherapeutics.com/wp-content/uploads/2022/10/1055-TGTX-ECTRIMS-2022-B-Cell-Depletion-13Oct22a.pdf.			

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 26 of the EAG report, the EAG state that 'The EAG requested tabulated comparative data on those specific adverse	The company provided the originally-requested data and therefore, the statement that we did not should be removed/redacted.	The currently presented statement is not correct.	The text on p26 has been amended to reflect this.

events for all treatment arms of all the trials of ublituximab, ocrelizumab and ofatumumab which were included in the NMA. The table provided in the company's response (Table 17, question A10) only reported data for the anti-CD20 arms (i.e. trial comparator arm data were not presented)'. The data requested by the EAG were in fact provided in Table 18 of the Clarification Questions Responses document, and therefore the statement from the EAG is not correct.			

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 42 of the EAG report in Table 16, the EAG state that 'NMAs comparing ublituximab and ocrelizumab were subject to inconsistency and were not robust to sensitivity analyses'. Indeed, this comparison was robust to certain sensitivity analyses and this should be acknowledged in any related statements.	Suggested text: 'NMAs comparing ublituximab and ocrelizumab were subject to inconsistency and were not robust to certain sensitivity analyses. In some cases, results were in favour of ocrelizumab and in others were in favour of ublituximab'.	The currently presented statement does not accurately depict the true results.	We have amended text to read "were not robust to some of the sensitivity analyses" in Table 16.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 18 of the EAG report, we see that subgroup analyses were performed using aggregated results from the CSR. However, the details provided for these analyses raise concerns regarding the accuracy and robustness of the findings. Given the limitations associated with using aggregate data, as well as the potential for	We recommend the complete removal of Section 4.2.3 and its associated conclusions throughout the report. This is due to insufficient detail provided on the statistical methods used for the analyses. Unless the EAG can present a more thorough explanation of their statistical approach, as outlined in the justification for amendment column, these	1- **Subgroup Analyses Not Powered:** [redacted] This is a common limitation in clinical trials where the original design may not include sufficient sample sizes for subgroups, which undermines the reliability of statistical results derived from these analyses. As a result, conclusions based on [redacted] should be treated with caution, as they increase the risk of both type I and type II errors. 2- **Pooling Aggregate-Level Data:** The EAG pooled data across the trials using aggregate-level data, such as reported ARR values and confidence intervals, instead of using individual patient-level data. This method introduces the potential for inaccuracies in the estimates and restricts the ability to perform more nuanced and reliable analyses, such as interaction testing between subgroups. Aggregating data at this level may obscure meaningful heterogeneity within the trials. Moreover, the EAG did not provide details on whether these analyses were	Not a factual inaccuracy. We note that our subgroup analyses results concur with the limited results presented in the clinical study reports, and the company has not suggested that the general conclusions of our analyses are incorrect. If the company think our results are incorrect, we suggest they supply the committee with the correct subgroup analyses based on pooling the patient-level data from the BE HEARD trials. The EAG acknowledges that there are limitations with performing subgroup analyses by pooling reported data, and that the results may not exactly

errors in interpretation, the conclusions drawn from these subgroup analyses should be viewed with considerable caution.	conclusions should not be considered valid.	conducted within a meta-analytical framework, such as using a random-effects model (e.g., DerSimonian & Laird method) or a fixed-effects model. Such an omission raises concerns about the robustness of the findings. 3- **Lack of Clarity on Pooling Methodology:** There is no explicit explanation of the statistical method used for pooling the studies (e.g., inverse variance weighting). Furthermore, when performing subgroup comparisons, the interaction p-value is typically derived from Cochran's Q statistic to assess heterogeneity between subgroups. The absence of such details undermines the transparency and interpretability of the results. 4- **Potential Misinterpretation of ARR and P-Value Limitations:** Based on the reported results, it appears that the ARR may have been treated as a mean value, with the standard error extracted from the confidence interval, followed by the calculation of a t-test. Relying solely on p-values for subgroup comparisons, without presenting effect sizes or discussing clinical relevance, is problematic. Additionally, the thresholds for statistical significance are not clearly defined. The lack of clarity regarding how confidence intervals were calculated and how p-values were derived further raises questions about the validity of the statistical methods employed in the subgroup analyses.	match analyses performed on the original trial data. We also acknowledge (as stated in the report, but now clarified on page 18) that the subgroups were often small and events few, which limits the power of analyses to detect genuine differences. We note that we originally included more detail on these subgroup analyses but removed it from the report on grounds of length. We have added some additional detail back into the revised report in Section 4.2.2.1 (page 18). However, we do not think a detailed description of methods used is required as we acknowledge that an analysis of summary data is innately limited, and using original trial data would be preferable. We note that effect estimates and their confidence intervals are presented in Table 4.

		5- **Confidence Intervals Crossing Zero:** The confidence interval for the USA or Western Europe subgroup [redacted] Despite this, conclusions are still drawn about the efficacy of ublituximab in this subgroup. This inconsistency between the data and the interpretation further highlights the need for a more cautious and rigorous approach to subgroup analysis.	We note that the report already states that the USA/Western Europe subgroup is small [redacted]