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REPORT

2020

HEALTH TECHNOLOGY ASSESSMENT:

Disease modifying drugs for treatment of primary progressive multiple sclerosis

Title	Disease modifying drugs for treatment of primary progressive multiple sclerosis: A health technology assessment.
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Institution	Norwegian Institute of Public health, NIPH; (Folkehelseinstituttet, FHI) Camilla Stoltenberg, *Director*
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Key message

Objective

The objective for this health technology assessment was to evaluate clinical efficacy and cost effectiveness for disease-modifying drugs for the treatment of primary progressive multiple sclerosis (PPMS).

Key findings and conclusions

We have systematically collected and reviewed the evidence for clinical efficacy for disease modifying treatments for PPMS.

We included three randomised placebo-controlled trials that each compare the effect of one medication (either fingolimod, ocrelizumab or rituximab, respectively) with placebo. For each of the three drugs, we calculated the risk ratios for confirmed disease progression. We also report results in the form of hazard ratios.

Our results show that ocrelizumab and rituximab may reduce the risk of confirmed disease progression more than placebo. In total, the results do not give us good reason to assume that one drug is better than the other.

Fingolimod may also reduce the risk of confirmed disease progression, although to a lesser degree than for ocrelizumab and rituximab. We find these results to be less convincing than for ocrelizumab and rituximab.

We have not conducted a full health economic evaluation as we do not have strong reasons to believe that one specific drug is better or worse than the other, and because rituximab is substantially less costly than the two other treatments.

Title
Disease-modifying treatments for primary progressive multiple sclerosis (PPMS). A health technology assessment

Publication type
Health Technology Assessment

Does not answer everything
We have not investigated ethical, legal or organizational aspects of the use of disease modifying drugs in the treatment of primary progressive multiple sclerosis.

Publisher
National Institute of Public Health, 2019. On commission from Bestillerforum RHF.

Last literature search
February 2019

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Sammendrag

Mål

Målet for denne metodevurderingen var å vurdere klinisk effekt og kostnadseffektivitet av sykdomsbegrensende legemidler til behandling av primær progressiv multippel sklerose.

Hovedfunn og konklusjoner

Vi har systematisk vurdert effekt av sykdomsbegrensende legemidler for behandling av PPMS.

Vi inkluderte tre randomiserte placebokontrollerte studier, som hver sammenlikner effekten av ett legemiddel (henholdsvis okrelizumab, rituksimab eller fingolimod) med placebo. For hvert av legemidlene beregnet vi relativ risiko for vedvarende sykdomsprogresjon. Vi rapporterer også resultater i form av hasard ratio.

Våre resultater viser at okrelizumab og rituksimab muligens reduserer risiko for vedvarende sykdomsprogresjon mer enn placebo. Totalt sett gir ikke resultatene god grunn til å anta at det ene legemidlet er bedre enn det andre.

Fingolimod reduserer muligens også risikoen for vedvarende sykdomsprogresjon, om enn i noe mindre grad enn okrelizumab og rituximab. Vi finner disse resultatene mindre overbevisende enn resultatene for okrelizumab og rituksimab.

Vi har ikke gjennomført en fullstendig økonomisk evaluering ettersom resultatene ikke gir oss god grunn til å anta at det ene legemidlet er bedre eller dårligere enn de andre, samt at rituksimab er vesentlig rimeligere enn de to andre legemidlene.

Tittel
Sykdomsbegrensende legemidler for behandling av primær progressiv multippel sklerose (PPMS). En metodevurdering.

Publikasjonstype
Fullstendig metodevurdering

Svarer ikke på alt
Vi har ikke sett på etiske, juridiske eller organisatoriske aspekter ved bruk av sykdomsbegrensende legemidler i behandling av primær progressiv multippel sklerose

Hvem står bak denne publikasjonen
Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Bestillerforum RHF, Nye metoder, 2019

Når ble litteratursøket utført
Februar 2019

Forfattere
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Metode

Metodologi	Vi har utført en fullstendig metodevurdering i henhold til Folkehelseinstituttets metodehåndbok for systematiske oversikter (1).
Inklusjonskriterier	*Populasjon*: Menn og kvinner fra 18 år og oppover, diagnostisert med primær progressiv multippel sklerose, med eller uten foregående behandlinger. *Intervensjon*: 1) okrelizumab (har markedsføringstillatelse for PPMS i Norge), 2) alle legemidler med markedsføringstillatelse for RRMS i Norge (off-label bruk for PPMS), 3) rituksimab (off-label bruk for RRMS og PPMS) *Sammenligning*: Alle inkluderte intervensjoner, samt placebo. *Utfall:* Risiko for vedvarende sykdomsprogresjon (CDP), definert som 12 eller 24 ukers vedvarende økning i pasientens EDSS-score (Expanded Disability Status Scale). *Studiedesign:* Randomiserte, kontrollerte studier og registerstudier.
Dataanalyser	Resultatene presenteres som relativ risiko og hasard ratio for vedvarende sykdomsprogresjon.

Resultat

Bekreftet sykdomsprogresjon	Resultatene i form av relativ risiko (95% CI) for vedvarende sykdomsprogresjon var 0.93 (0.80 til 1.08), 0.84 (0.68 til 1.02) og 0.78 (0.59 til 1.02) for henholdsvis fingolimod, okrelizumab og rituksimab. Resultatene i form av hasard ratio (95% CI) for vedvarende sykdomsprogresjon var 0.88 (0.71 til 1.08), 0.76 (0.59til 0.98) og 0.77 (0.55 til 1.09) for henholdsvis fingolimod, okrelizumab og rituksimab. Våre resultater viser at okrelizumab og rituksimab muligens reduserer risiko for vedvarende sykdomsprogresjon mer enn placebo. Totalt sett gir ikke resultatene god grunn til å anta at det ene legemidlet er bedre enn det andre. Fingolimod reduserer muligens også risikoen for vedvarende sykdomsprogresjon, om enn i noe mindre grad enn okrelizumab og rituksimab. Vi finner disse resultatene mindre overbevisende enn resultatene for okrelizumab og rituksimab.
Helseøkonomisk aspekt	Vi har ikke gjennomført en fullstendig økonomisk evaluering ettersom resultatene ikke gir oss god grunn til å anta at det ene legemidlet er bedre eller dårligere enn de andre, samt at rituksimab er vesentlig rimeligere enn begge de to andre legemidlene.

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Preface

This Health Technology Assessment (HTA) was commissioned by The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (Nye Metoder).

The following commission was given 28.01.2019: "*Legemidler til behandling av primær-progressiv MS (PPMS). Det opprinnelige oppdraget ble delt i to – en fullstendig metodevurdering for hver av indikasjonene RRMS og PPMS. Intervensjonen som skal undersøkes er: rituksimab og de legemidlene med markedsføringstillatelse for RRMS det er gjort studier på, det vil si cladribine, alemtuzumab, natalizumab, fingolimod, glatiramer acetate og ocrelizumab. (ID2019_018)"* (2). The National Institute of Public Health (NIPH) initiated the work in March 2019 (see *Appendix 1* for progress log).

This HTA includes assessment of clinical effect, as well as an assessment of health economic aspects with regards to disease-modifying drugs for the treatment of primary progressive multiple sclerosis. Assessment of safety was considered to be covered in the HTA for relapsing remitting multiple sclerosis (3).

The internal working group consisted of:

- Ingrid Kristine Ohm, researcher
- Torunn Elisabet Tjelle, senior researcher
- Christopher James Rose, statistician, researcher
- Vida Hamidi, health economist
- Gunhild Hagen, health economist
- Elisabet Vivianne Hafstad, information specialist
- Atle Fretheim, research director, NIPH

In addition to the authors, the following have contributed to the work:

Clinical experts:

- Lars Bø, MD, PhD, Senior consultant in Neurology and Professor, Haukeland universitetssykehus
- Elisabeth Gulowsen Celius, MD, Senior consultant in Neurology and Professor, Oslo universitetssykehus, Ullevål
- Trygve Holmøy, MD, PhD, Senior consultant in Neurology and Professor, Akershus universitetssykehus
- Rune Midgard, MD, former senior consultant in Neurology and associate Professor (now retired), Helse Møre and Romsdal Health Trust

Reviewers – internal (at NIPH):

- Doris Tove Kristoffersen, researcher
- Gunn Elisabeth Vist, senior researcher
- Ingrid Harboe, information specialist (reviewed the search strategy)

Reviewers – external:

- Kjell Morten Myhr, MD, PhD, Senior Consultant in Neurology and Professor, University of Bergen and Haukeland University Hospital
- Gro Owren Nygaard, MD, PhD, Senior Consultant in Neurology, Oslo University Hospital; Ullevål

Acknowledgements
We wish to thank researcher Julia Bidonde for providing valuable input to the project plan.

Conflict of interest
All authors and clinical experts have declared potential conflicts of interest.

We will emphasise that although the clinical experts and external reviewers have contributed with valuable input and comments, NIPH is solely responsible for the content of this report.

Kåre Birger Hagen	Atle Fretheim	Ingrid Kristine Ohm
Director reviews and health technology assessment	Research director	Project coordinator

Introduction

Definition of the disease

Multiple sclerosis (MS) (see *Appendix 2* for abbreviations) is a chronic, immune-mediated disease that causes demyelination in the central nervous system (CNS), i.e. brain and spinal cord (4;5). The disease consists of relapsing and progressive phenotypes that traditionally have been classified as relapsing-remitting (RRMS), and primary progressive (PPMS) or secondary progressive (SPMS) (6). Whereas RRMS is characterised by having periods of neurological deterioration (=relapses) followed by partial or complete recovery (=remission), with no progression between the attacks (relapses) (7), PPMS has been characterised by having gradual disease progression from onset, independent of relapses (5-7). The current view is that PPMS is part of the spectrum of progressive MS, and that differences between phenotypes are relative rather than absolute (8). To better determine the ongoing disease process, all phenotypes of MS can be characterised in respect to disease activity (active or not active, determined by clinical relapses and/or activity upon imaging), and progression of disability (8). Patients with active inflammatory disease could be potential candidates for treatment.

Epidemiology

Prevalence

The prevalence of MS in Norway increased steadily up to 2012-2013, to over 200 per 100,000 persons (9;10). However, the more recent estimates differ. A Lancet publication from 2019 reported the prevalence for MS in Norway in 2016 as 144 per 100 000 persons (11). In contrast, a poster presented at the 2019 ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis) conference showed the MS-prevalence in Norway to be 235 per 100 000 persons (based on numbers from two Norwegian counties) (12). Regardless, Norway is still considered a high-risk area for MS (9;10). The high prevalence could be explained by earlier diagnosis, as well as longer survival due to better treatment options (10). RRMS is the most common form of MS (85-90%), whereas PPMS is a less common type of MS, and is diagnosed in about 10 % of MS patients (ranging from less than 5% to over 15%, around the world) (13-18).

Age

The age of onset and diagnosis differs among the various types of MS. For example, whereas RRMS has an early onset and is often diagnosed in the mid- to late twenties, progressive MS (both PPMS and SPMS) is often diagnosed later, at around 40 years (13;19).

Gender ratio

Globally — and in Norway — about 66% to 75% of MS patients are female (10;13;20). The male-female distribution for PPMS however appears to be approximately equal (13).

Causes and risk factors

The cause of MS is unknown. So far, potential risk factors that have been identified are both genetic and environmental, including geography/latitude, vitamin D, viral infections, and smoking (5;6;19;21;22). Whether the risk factors are similar for the different types of MS is currently unknown.

Pathophysiology

MS is a chronic, immune-mediated, demyelinating disease in which the immune system attacks and damages the protective myelin sheaths that surround axons within the CNS (5;19;23). The inflammatory process causes areas of demyelination: lesions or plaques, which can be seen using Magnetic Resonance Imaging (MRI) (5). In addition, MRI can also show atrophy in the brain resulting from axonal degeneration and loss (19;23). Although the exact pathogenesis for MS is unknown, the process is likely caused by overlapping phases of inflammation and neurodegeneration, and seems to involve activated immune cells such as B- and T-cells (19;23;24). Traditionally, PPMS has been thought of as a predominantly degenerative process, with little or no inflammation involved (19;23). The exact mechanism of PPMS is still largely unknown, but there is emerging evidence of inflammatory processes in PPMS as well (24;25).

Clinical presentation and diagnosis

While RRMS is characterised by rapidly evolving relapses (attacks) where symptoms develop within hours/days and slowly recede over days or weeks, PPMS develops slowly but steadily from onset, without remissions (13). Compared with RRMS, PPMS symptoms may only become evident at a later stage of disease (13). Patients with PPMS often present with spinal cord syndrome, such as asymmetric spastic paraparesis (80%) (26). Symptoms are often associated with loss of motor control and include impaired mobility, stiffness, clumsiness, imbalance and dragging of legs (13;26). In addition to sensory symptoms, such as numbness and dysesthesia (abnormal sense of touch), other common symptoms include fatigue, erectile dysfunction, and micturition (urination) disorders (13). Cognitive function, including working and verbal memory, spatial reasoning, attention and verbal fluency are also commonly be affected in PPMS (13).

For MS to be diagnosed, the patient needs to be closely evaluated with respect to neurologic history, physical examination, and MRI (4;6;23). Although not required for a general MS diagnosis, lumbar puncture with examination of cerebrospinal fluid (CSF) may be of value to increase the diagnostic certainty (4;23). According to the McDonald criteria (last updated in 2017) (27), a diagnosis of PPMS requires evidence of at least one year of disease progression, in addition to at

least two of the following criteria: a) one or more lesions (hyperintense T2) characteristic of MS in one or more specified areas of the brain, b) two or more lesions (hyperintense T2) in the spinal cord, or c) presence of CSF-specific oligoclonal bands (4;27). These criteria are also included in the Norwegian national guidelines on MS (28).

As the disease develops and progresses, patients experience increasing disability. Disability can be defined as loss of abilities caused by non-traumatic damage to the CNS, resulting in impaired body function (29). Progression of disease can be assessed/measured by using the Expanded Disability Status Scale (EDSS). EDSS is an ordinal scale ranging from 0-10 (in half-step increments), in which higher scores indicate increasing disability (4;30).

Treatment

There is no cure for MS. The available treatment is meant to manage symptoms and delay progression. For RRMS there are several disease modifying treatments available (3), whereas only one drug, ocrelizumab (Ocrevus), has marketing authorisation for PPMS. Based on a review of key trials in PPMS, Narayan *et al* (31) suggest a strategy where a combination of immune-modulatory, myelin-restorative, and neuro-generative therapies could be provided in the early stages of the disease.

Objective

The objective of this report was to assess clinical efficacy and cost effectiveness of disease modifying treatments of patients with PPMS.

Methods

Literature search

An information specialist performed the literature search in accordance with the project plan (*Appendix 3*). The search used index terms (Medical Subject Headings and EMTREE terms where appropriate), and free text terms related to the population, generic drug names and study designs of interest (the "PICOS" is described in *Table 1*). No restrictions with regards to publication year or language were applied to the search. The bibliographies of selected publications were screened for potentially relevant studies missed by the electronic searches. The search strategies are detailed in *Appendix 4*.

Selection of studies

The studies included in this HTA were selected in a two-step process. In both steps, two persons worked independently, assessing articles against the inclusion criteria (*Table 1*). In the first step, two persons read all titles and abstracts retrieved by the literature search and selected potentially relevant full-texts. In the second step, the two persons read all the selected full text articles to decide which articles should be included in the HTA. Any disagreements throughout this work were resolved either through discussion or by consulting a third researcher.

Eligibility criteria

We based the selection of studies on the criteria in *Table 1*:

Table 1: *Inclusion and exclusion criteria*

PICOS	Inclusion	Exclusion
Population	- Men and women - Age: 18+ years - Diagnosis: PPMS, treatment naïve or not	Pregnant women
Intervention	- Ocrelizumab (only drug with MA for PPMS in Norway) - All drugs* with MA for RRMS in Norway (off-label use for PPMS) - Rituximab (used off-label for RRMS and PPMS)	Rituximab for subcutaneous administration was excluded since this has not been used for the present indication
Comparison	- All included interventions - Placebo	
Outcome	- Risk of confirmed disability progression (CDP), defined as increase in EDSS (expanded disability status scale) score, sustained over 12 or 24 weeks	Reports on the cellular and molecular mechanisms of the medicines
Study design	- Randomised controlled trials - Non-randomised controlled studies using registry data	

MA: marketing authorisation, *alemtuzumab, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, teriflunomide, cladribine, interferon β-1a (Avonex, Rebif), peg-interferon β-1a, interferon β-1b (Betaferon, Extavia)

We did not include additional outcomes as confirmed disability progression (CDP) is the clinically most important one, and safety outcomes were assumed to be sufficiently addressed in the previous HTA report on RRMS (3).

Data extraction

One researcher extracted the data from the selected publications and a second researcher verified the findings. The following data were extracted:

Study characteristics

- Information about the publication (author names, year of publication).
- Description of study (design and setting, clinical trial identification)
- Participant characteristics (number of participants in the trial, age, gender, MS diagnosis, disease duration, and status of disease, e.g. by EDSS)
- Description of intervention and comparator (i.e. drug, dose, frequency)
- Outcome (number of events, methods used to ascertain outcome data, estimates of risk, length of follow-up).

In addition to study characteristics (detailed above), we obtained estimates of relative treatment effect reported by the included studies. To compare risk (i.e., probability) of CDP among PPMS patients treated with each of the interventions compared to a placebo, we extracted reported numbers or proportions of patients with CDP at end of follow-up and used Review Manager 5.3 (32) to impute risk ratios and 95% confidence intervals. To compare time-to-CDP among patients treated with each of the interventions compared to placebo, we extracted reported hazard ratios for CDP and 95% confidence intervals. We followed the intention-to-treat (ITT) principle and included all patients recruited, and analysed patients in the groups to which they were randomized.

Lower risk of CDP is favourable. Risk ratio equal to 1 (RR=1) indicates that, on average, there is no difference in risk of CDP between patients treated with one of the interventions compared to placebo, while risk ratio less than one (RR<1) favours the intervention over placebo. Longer time-to-CDP (and hence lower instantaneous rate of CDP) is favourable. Hazard ratio equal to one (HR=1) indicates that, on average, there is no difference in instantaneous rate of CDP between patients treated with one of the interventions compared to placebo, while hazard ratio less than one (HR<1) favours the intervention over placebo.

Risk of bias of included studies

Two researchers independently assessed the included studies using the Cochrane risk of bias tool (33), rating each study as being at low, unclear, or high risk of bias on seven domains: selection bias (random sequence generation and allocation bias), performance bias, detection bias, attrition bias, reporting bias, and other. Based on this, each study was summarised as being at low, unclear,

or high overall risk of bias (*Appendix 7*. Risk of bias of included studies). Any disagreements were resolved through discussion or by consulting a third researcher.

Deviation from project plan

The project plan (*Appendix 3*. Project plan) specifies that "if available, we will analyse and present CDP as a relative risk (= risk ratio) or odds ratio, or as a mean difference in EDSS score from baseline". However, risk ratio only addresses the question of whether CDP is likely to occur, rather than how long (after some index time, such as starting treatment for example) patients will be free of CDP. This latter question is addressed by time-to-CDP analyses and is conventionally quantified as a hazard ratio. After publishing the protocol, we judged that information about *if* (i.e., risk ratio) and *when* (i.e., hazard ratio) would be relevant to stakeholders, and chose to additionally analyse hazard ratios, which are reported by all included studies.

We did not plan to present anticipated absolute estimates of effect for each treatment, but because readers generally find both relative and absolute estimates of treatment effect informative, we used GRADEpro (34) to calculate risk of disability progression for each outcome. While risk ratio and hazard ratio quantify different things (see above), they can both be re-expressed as risk with placebo, and risk difference (compared to placebo) with treatment. We present risks in units of patients per 1000 patients. We would expect these estimates to differ between the outcomes (risk ratio versus hazard ratio) because hazard ratios are used in time-to-CDP analyses, while risk ratios are used to quantify the relative probabilities of an event occurring. Anticipated "absolute" effect estimates based on hazard ratios should therefore be interpreted with caution.

Data analyses

As mentioned above, we analysed CDP as risk ratio with 95% confidence interval (95% CI). We estimated risk ratios using the numbers of patients who experienced CDP and the number of patients enrolled in each arm of the trials. The data were analysed according to the intention-to-treat (ITT) principle: patients were analysed in the arms to which they were allocated, and all patients were included in the analysis. In addition, we extracted published point estimates of hazard ratios and measures of precision (95% confidence intervals). Two studies analysed the data according to the ITT-principle (7;35), whereas one used a modified ITT-population for their data analysis, i.e. the patients had to have taken at least one dose of study drug (36). However, from what the authors report, it seems unlikely that there is large differences between the total number of randomised patients and the number of patients included in the efficacy analysis (36). Because each comparison was supported by only one study, we did not conduct a meta-analysis.

We present our results in summary of findings tables and forest plots. We performed statistical analyses and made forest plots using Review Manager 5.3 (32). GRADEpro (34) was used to prepare summary of findings tables (34;37;38), where risk ratio data was set as dichotomous outcomes and hazard ratio data was set as time-to-event outcomes.

Minimal clinically important difference

A statistically significant result of an intervention in a clinical trial does not necessarily mean that it is a clinically important effect (39). Thus, setting a relevant threshold of what could be considered as an important effect for patients (a minimal clinically important difference) would help us assess the results of clinical trials (40). To set a relevant threshold for our outcome and population, we performed a simple literature search for any references of minimal clinically important difference for disease progression in patients with PPMS. As we found no data for our specific outcome (CDP), we consulted with our clinical experts. They pointed out that although any delay in disease progression would be meaningful for the individual patient, a clinical effect of 10% could be considered reasonable. We acknowledge that these are opinions, and that others may disagree.

To assess our results in light of a threshold of minimal clinically important difference, we made a forest plot with all treatments, showing both the risk ratios and hazard ratios, and inserted the threshold level at 0.9, i.e. 10% effect of the intervention. Values below this threshold could be considered to represent an important effect, whereas values above this threshold, but still below 1 could be considered to represent a less important effect.

Grading the certainty of evidence

The certainty of evidence for the chosen outcome was assessed by using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach in accordance with the GRADE handbook (41). Certainty of evidence is classified as in *Table 2* (42). Two researchers assessed certainty of evidence, and any disagreements were resolved through discussion and by consulting other team members and colleagues.

Table 2: *Certainty of evidence classification according to GRADEpro (34)*

Grade	Definition
High certainty ⊕⊕⊕⊕	Further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty ⊕⊕⊕◯	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty ⊕⊕◯◯	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty ⊕◯◯◯	Any estimate of effect is very uncertain

Standardised statements for the reporting of effects

We also present textual descriptions of effect estimates using standardised statements for the reporting of effects (43), in the summary of findings tables. Given a judgement about whether an effect estimate corresponds to an important, less important, or no benefit or harm (the columns

of *Table 3*), and a GRADE assessment of the certainty of evidence (the rows of *Table 3*), a standardized statement can be chosen and adapted to communicate the magnitude, direction, and the certainty of evidence supporting an effect estimate in "plain language".

Table 3: *Standardised sentences for reporting effects (43).*

GRADE	Important benefit/harm	Less important benefit/harm	No important benefit/harm
High	[Intervention] improves/reduces [outcome] (high certainty evidence)	[Intervention] slightly improves/reduces [outcome] (high certainty evidence)	[Intervention] makes little or no difference to [outcome] (high certainty evidence) Or [Intervention] does not have an important effect on [outcome] Or [Intervention] has little or no effect on [outcome]
Moderate	[Intervention] probably improves/reduces [outcome] (moderate certainty evidence)	[Intervention] probably slightly improves/reduces [outcome] (moderate certainty evidence) Or [Intervention] probably leads to slightly better/worse/less/more [outcome] (moderate certainty evidence)	Intervention] probably makes little or no difference to [outcome] (moderate certainty evidence)
Low	[Intervention] may improve/reduce [outcome] (low certainty evidence)	[Intervention] may slightly improve/reduce [outcome] (low certainty evidence	[Intervention] may make little or no difference to [outcome] (low certainty evidence
Very low	We don't know if/It is uncertain whether [intervention] improves/reduces [outcome] because the certainty of this evidence is very low		

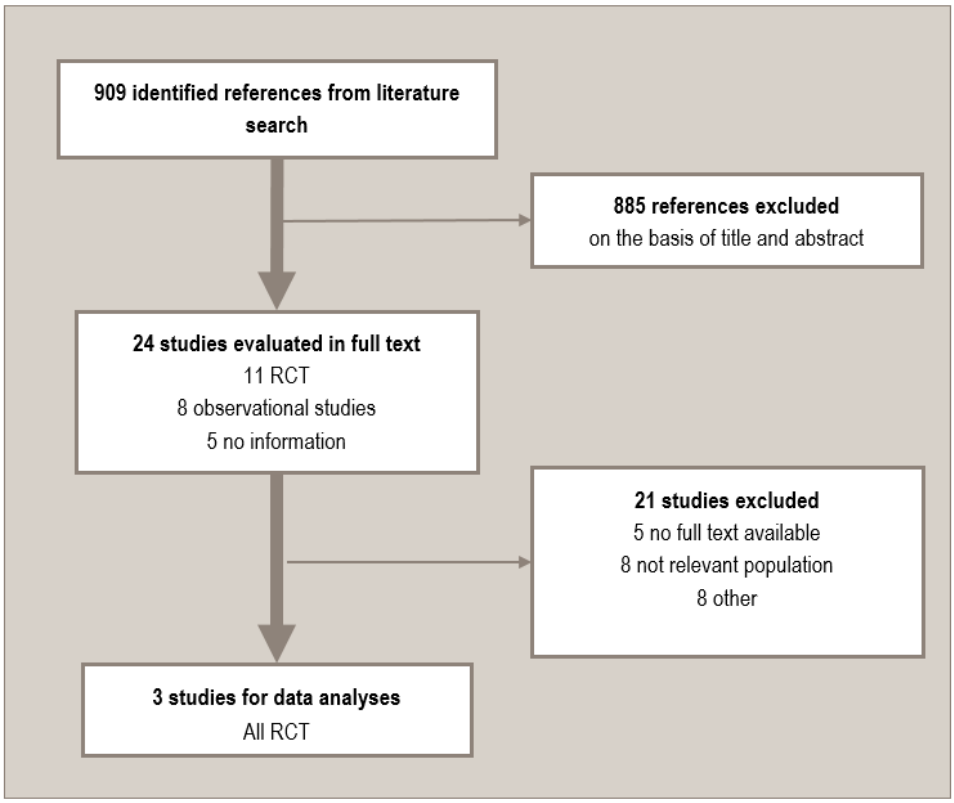
Results

Description of studies

Results of the literature search

The search identified 909 references, of which 885 were excluded on the basis of title and abstract. Of the remaining 24 studies, 21 were excluded after full text evaluation (see *Appendix 5* for reasons for exclusion) and 3 studies (RCTs) were ultimately included in our HTA (7;35;36). The selection process is presented in *Figure 1*.

Figure 1. *Flow chart of article selection*



Excluded studies

The full list of excluded studies, with reasons for why they were excluded, is presented in *Appendix 5*. Excluded studies with reasons. In brief, the main reasons for exclusion were due to full text publications not being available, and that the study population was not relevant for our HTA, i.e. the study population was a mix of patients with various subtypes of MS, and/or the PPMS populations were too small to be of much use.

Included studies

Features of the three studies included in this HTA are presented in *Table 4*, and in more detail in *Appendix 6*. In brief, all three RCTs study different interventions compared with placebo: fingolimod (36), ocrelizumab (35), and rituximab (7). In total, 1 993 participants were recruited in the three studies, and the follow-up time varied from 2 to 3 years. In the ocrelizumab-study (35), the included study population was slightly younger than that of the other trials (*Table 4*). In the rituximab-study (7), the population had had MS symptoms and MS diagnoses for longer than that of the participants in the other studies (*Table 4*). We assessed all studies to have low risk of bias (details are presented in *Appendix 7*).

Table 4: *Included RCTs for effect analyses*

	Hawker 2009 (7) Rituximab vs placebo		**Lublin 2016* (36) Fingolimod vs placebo**		**Montalban 2017 (35) Ocrelizumab vs placebo**	
Study name	OLYMPUS		INFORMS		ORATORIO	
Study number	NCT00087529		NCT00731692		NCT01194570	
Follow-up in regards to CDP	24 months = 2 years		36 months = 3 years**		At least 30 months = 2.5 years†	
Risk of bias	Low		Low		Low	
Intervention vs comparator	Rituximab	Placebo	Fingolimod	Placebo	Ocrelizumab	Placebo
Number of patients	n=292	n=147	n=336	N=487	n=487	n=244
Age of participants: mean ± SD	49.6 ± 8.7	50.1 ± 9.0	48.5 ± 8.6	48.5 ± 8.3	44.7 ± 7.9	44.4 ± 8.3
Years since MS diagnosis: mean ± SD	3.8 ± 4.2	4.1 ± 4.2	2.8 ± 2.6	2.9 ± 2.3	2.9 ± 3.2	2.8 ± 3.3
Years since first symptoms of MS: mean ± SD	9.0 ± 6.8	9.2 ± 6.4	5.8 ± 2.5	5.9 ± 2.4	6.7 ± 4.0	6.1 ± 3.6

CDP: confirmed disability progression, n: total number of participants in the study, MS: multiple sclerosis, SD: standard deviation

** Lublin et al had two cohorts in their study with two different doses of fingolimod. They presented the results from the arm that was given 0.5 mg fingolimod compared to the placebo group from both cohorts.*

***Patients were treated for 36 months or up to a maximum treatment duration of 5 years. Clinical assessments (such as EDSS) were done at regular intervals, until month 36.*

† At least 120 weeks or until a pre-specified number of confirmed disability progression events had occurred.

Ongoing studies

The list detailing relevant ongoing clinical trials is found in *Appendix 8*. In brief, we found 25 ongoing trials that represent 7,925 planned participants. The largest study is a one-year observational cohort study of biotin without comparator (n=3000), planned to finish in 2019. Ocrelizumab is the main intervention in seven ongoing studies (likely to include a total of 2 688 participants), while only one study is planned for rituximab (n=10).

Results – confirmed disability progression

Risk of CDP (confirmed disease progression) at 12 weeks was reported in all three studies. CDP is here defined as an increase in EDSS score that is sustained over 12 weeks (7;35;36).

Risk ratio – confirmed disability progression

Risk ratio is the ratio of the probability of an outcome (e.g., CDP) for the intervention versus the comparator during a defined time-period (approximately two years in the included studies). In

this report, risk ratios less than one (RR<1) favour the intervention, while risk ratios greater than one (RR>1) favour the comparator.

Figure 2: *Forest plot of risk ratios - confirmed disease progression 12 weeks*

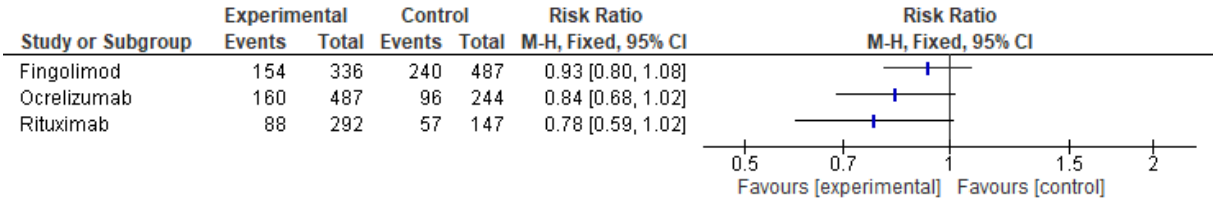


Table 5: *Summary of findings: risk ratio of confirmed disease progression 12 weeks*

Treatment, study type, participants	Risk ratio (95% CI)	Anticipated absolute risk of CDP		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with placebo*	Risk difference with treatment		
Fingolimod *1 RCT* *n=823* *3 years*	**RR 0.93** (0.80 to 1.08)	425 per 1 000	**30 fewer per 1,000** (85 fewer to 34 more)	⨁⨁◯◯ LOW [a,b]	Fingolimod may slightly reduce the risk of CDP more than placebo
Ocrelizumab *1 RCT* *n=731* *2.5 years*	**RR 0.84** (0.68 to 1.02)	425 per 1 000	**68 fewer per 1,000** (136 fewer to 8 more)	⨁⨁◯◯ LOW [a,c]	Ocrelizumab may reduce the risk of CDP more than placebo
Rituximab *1 RCT* *n=439* *2 years*	**RR 0.78** (0.59 to 1.02)	425 per 1 000	**93 fewer per 1,000** (174 fewer to 9 more)	⨁⨁◯◯ LOW [a,c]	Rituximab may reduce the risk of CDP more than placebo

Computed as dichotomous data, using RevMan and GRADEpro. CDP: confirmed disability progression 12 weeks, RR: risk ratio, CI: confidence interval, n: total number of participants in the study, RCT: randomised controlled trial.
**Calculated from the risk with placebo for all three studies (fingolimod: 493/1000, ocrelizumab: 393/1000, rituximab: 388/1000), and set as moderate risk.*
Reasons for downgrading in GRADE: [a] Inconsistency: rated one down because the outcome is based on only one relatively small study, [b] Imprecision: rated one down because the 95% CI crosses 1 substantially (=no difference). See Discussion section for deliberation on our GRADE-assessments. [c] Imprecision: rated one down because the 95% CI is very wide. See Discussion section for deliberation on our GRADE-assessments.

Fingolimod

For fingolimod, the risk ratio (95% CI) for CDP at 12 weeks was found to be 0.93 (0.80, 1.08), i.e. patients who receive fingolimod may be expected to have a 7% reduction in risk of CPD compared to patients who receive placebo (over time periods similar to the included study; *Figure 2*, *Table 5*). However, the confidence interval includes values above 1, so it is plausible that patients who receive fingolimod are actually at equal or greater risk of CDP compared to those who receive placebo.

Based on the number of patients who experienced CDP, we calculated anticipated absolute risk of CDP and the risk difference of fingolimod versus placebo: among 1000 patients receiving placebo,

425 would be anticipated to experience CDP, but with fingolimod, 30 fewer patients (i.e. 395 patients) would be anticipated to experience CDP. Due to sampling variance (i.e., "the play of chance") and the relatively small sample sizes of the studies, there is considerable uncertainty. The 95% CI shows that it is plausible that between 85 *fewer* patients (i.e. 340 patients) and 34 *more* patients (i.e. 459 patients) would be anticipated to experience CDP when receiving fingolimod than when receiving placebo (*Table 5*).

Ocrelizumab

For ocrelizumab, the risk ratio (95% CI) for CDP at 12 weeks was found to be 0.84 (0.68, 1.02), i.e. patients who receive ocrelizumab may be expected to have a 16% reduction in risk of CPD compared to patients who receive placebo (over time periods similar to the included study; *Figure 2*, *Table 5*). However, the confidence interval includes values above 1, so it is plausible that patients who receive ocrelizumab are actually at equal or greater risk of CDP compared to those who receive placebo.

Based on the number of patients who experienced CDP, we calculated anticipated absolute risk of CDP and the risk difference of ocrelizumab versus placebo: among 1000 patients receiving placebo, 425 would be anticipated to experience CDP, but with ocrelizumab, 68 fewer patients (i.e. 357 patients) would be anticipated to experience CDP. The 95% CI shows that it is plausible that between 136 *fewer* patients (i.e. 289 patients) and 8 *more* patients (i.e. 433 patients) would be expected to experience CDP when receiving ocrelizumab than when receiving placebo (*Table 5*).

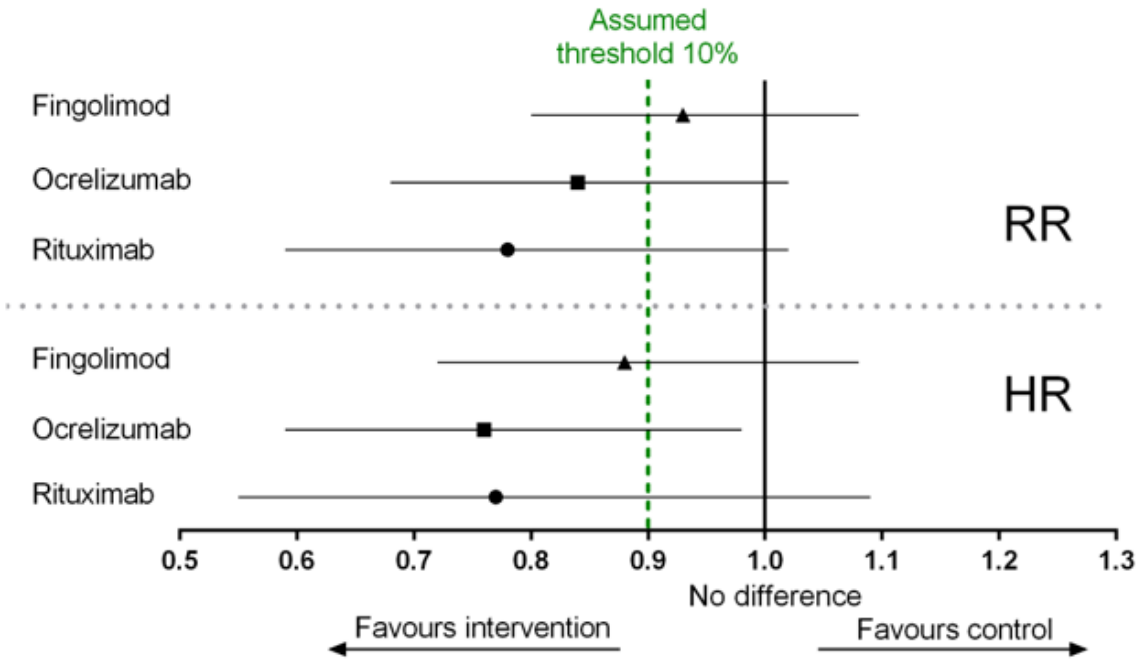
Rituximab

For rituximab, the risk ratio (95% CI) for CDP at 12 weeks was found to be 0.78 (0.59, 1.02), i.e. patients who receive rituximab may be expected to have a 22% reduction in risk of CPD compared to patients who receive placebo (over time periods similar to the included study; *Figure 2*, *Table 5*). However, the confidence interval includes values above 1, so it is plausible that patients who receive rituximab are actually at equal or greater risk of CDP compared to those who receive placebo.

Based on the number of patients who experienced CDP, we calculated anticipated absolute risk of CDP and the risk difference of rituximab versus placebo. Among 1000 patients receiving placebo, 425 patients would be anticipated to experience CDP, but with rituximab, 93 fewer patients (i.e. 332 patients) would be anticipated to experience CDP. The 95% CI shows that it is plausible that between 174 *fewer* patients (i.e. 251 patients) and 9 *more* patients (i.e. 434 patients) would be anticipated to experience CDP when receiving rituximab than when receiving placebo (*Table 5*).

Based on the assumed threshold of minimal clinically important difference (green line in *Figure 3*) and our GRADE assessment, we summarised the results of risk ratio using standardised sentences (43) as follows: ocrelizumab and rituximab may reduce the risk of CDP more than placebo (low certainty evidence). Fingolimod may also slightly reduce the risk of CDP more than placebo (low certainty evidence).

Figure 3: Forest plot summary



RR: risk ratio; HR: hazard ratio. The Assumed threshold is the assumed effect size for a minimally clinically important difference, i.e. we consider effect sizes larger than 10% to represent an important effect, and effect sizes below 10% as less important effects.

Hazard ratio – confirmed disability progression

A hazard ratio is the ratio of the hazard rates for the intervention and comparator (under the assumption of proportional hazards). A hazard rate quantifies how many CDPs would be expected to occur at a given moment for patients receiving a specific treatment. In this report, a hazard ratio less than one (HR<1) favours the intervention, while greater than one (HR>1) favours the comparator.

Figure 4: *Forest plot of hazard ratio - confirmed disease progression 12 weeks*

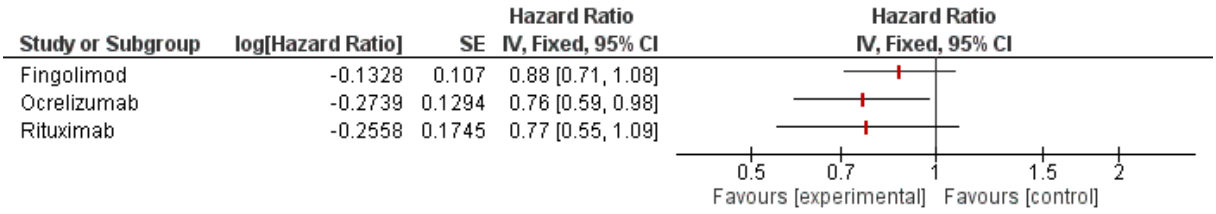


Table 6: *Summary of findings: hazard ratio of confirmed disease progression 12 weeks*

Treatment, study type, participants	Hazard ratio (95% CI)	Anticipated absolute risk of CDP		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with placebo*	Risk difference with treatment		
Fingolimod *1 RCT* *n=823* *3 years*	**HR 0.88** (0.72 to 1.08)	425 per 1 000	**39 fewer per 1,000** (96 fewer to 25 more)	⨁◯◯◯ VERY LOW [a,b]	It is uncertain whether fingolimod reduces the risk of CDP more than placebo
Ocrelizumab *1 RCT* *n=731* *2.5 years*	**HR 0.76** (0.59 to 0.98)	425 per 1 000	**82 fewer per 1,000** (146 fewer to 6 fewer)	⨁⨁◯◯ LOW [a,c]	Ocrelizumab may reduce the risk of CDP more than placebo
Rituximab *1 RCT* *n=439* *2 years*	**HR 0.77** (0.55 to 1.09)	425 per 1 000	**78 fewer per 1,000** (163 fewer to 28 more)	⨁◯◯◯ VERY LOW [a,b]	It is uncertain whether rituximab reduces the risk of CDP more than placebo

Computed as time-to-event data using GRADEpro. CDP: confirmed disability progression 12 weeks, HR: hazard ratio, CI: confidence interval, n: total number of participants in the study, RCT: randomised controlled trial.
**Calculated from the risk with placebo for all three studies (fingolimod: 493/1000, ocrelizumab: 393/1000, rituximab: 388/1000), and set as moderate risk.*
Reasons for downgrading in GRADE: [a] Inconsistency: rated one down because the outcome is based on only one relatively small study, [b] Imprecision: rated two down because the 95% CI is very wide and crosses 1 substantially (= no difference), [c] Imprecision: rated one down because the 95% CI is very wide. See Discussion section for deliberation on our GRADE-assessments.

Fingolimod

For fingolimod, the published hazard ratio (95% CI) for CDP at 12 weeks was 0.88 (0.71, 1.08) (36), i.e. disease progression may be expected to occur for patients who received fingolimod at 88% of the rate that it occurs for patients who received placebo (*Figure 4*, *Table 6*). However, the confidence interval includes values above 1, so it is plausible that patients who receive fingolimod actually experience CDP at the same rate or sooner than those who receive placebo.

Based on the number of patients who experienced CDP, we calculated anticipated absolute risk of CDP and the risk difference of fingolimod versus placebo. Of 1000 patients receiving placebo, 425 would be anticipated to experience CDP. When receiving fingolimod, 39 fewer patients (i.e. 389 patients) would be anticipated to experience CDP. The 95% CI shows that it is plausible that between 96 *fewer* patients (i.e. 329 patients) and 25 *more* patients (i.e. 450 patients) would be anticipated to experience CDP when receiving fingolimod than when receiving placebo (*Table 6*).

Ocrelizumab

For ocrelizumab, the hazard ratio (95% CI) for CDP at 12 weeks was published as 0.76 (0.59, 0.98) (35), i.e. disease progression may be expected to occur for patients who received ocrelizumab at 76% of the rate that it occurs for patients who received placebo (*Figure 4*, *Table 6*). Because the confidence interval is entirely below 1, it is unlikely that ocrelizumab is not beneficial, although we posit that a hazard ratio of 0.98 would likely not correspond to a clinically important benefit if judged against an assumed minimal clinically important difference of 10% (*Figure 3*).

Based on the number of patients who experienced CDP, we calculated anticipated absolute risk of CDP and the risk difference of ocrelizumab versus placebo. Of 1000 patients receiving placebo, 425 would be anticipated to experience CDP. When receiving ocrelizumab, 82 fewer patients (i.e. 343 patients) would be anticipated to CDP. Based on the 95% CI however, this may span from 146 *fewer* patients (i.e. 279 patients) to 6 *fewer* patients (i.e. 431 patients) would be anticipated to experience CDP when receiving ocrelizumab than when receiving placebo (*Table 6*).

Rituximab

For rituximab, the hazard ratio (95% CI) for CDP at 12 weeks was published as 0.77 (0.59, 1.09) (7), i.e. disease progression may be expected to occur for patients who received rituximab at 77% of the rate that it occurs for patients who received placebo (*Figure 4*, *Table 6*). However, the confidence interval includes values above 1, so it is plausible that patients who receive rituximab actually experience CDP at the same rate or sooner than those who receive placebo.

Based on the number of patients who experienced CDP, we calculated anticipated absolute risk of CDP and the risk difference of rituximab versus placebo. Of 1000 patients receiving placebo, 425 patients would be anticipated to CDP. When receiving rituximab, 78 fewer patients (i.e. 347 patients) would be anticipated to CDP The 95% CI shows that it is plausible that between 163 *fewer* patients (i.e. 262 patients) and 28 *more* patients (i.e. 453 patients) would be anticipated to experience CDP when receiving rituximab than when receiving placebo (*Table 6*).

Based on the assumed threshold of minimal clinically important difference (green line in *Figure 3*) and our GRADE assessment, we summarised the results of hazard ratio using standardised sentences (43) as follows: ocrelizumab may reduce the risk of CDP more than placebo (low certainty evidence). It is uncertain whether fingolimod and rituximab reduces the risk of CDP more than placebo because the certainty of this evidence is very low.

Discussion

Key findings and conclusions

We have systematically reviewed the literature on clinical efficacy for disease modifying treatment of PPMS. The evidence base comprised of three RCTs, all studying the effect of either fingolimod, ocrelizumab or rituximab on CDP (7;35;36).

Our results are heavily influenced by the lack of direct comparisons. None of the relevant drugs have been compared with another relevant drug. The three trials each compare one drug with placebo. The largest trial with 823 patients and the longest follow-up period, i.e. three years, had the tightest confidence interval (36). The smallest trial with 439 patients and the shortest follow-up period; i.e. two years had the widest confidence interval (7).

We find that ocrelizumab and rituximab may reduce the risk of CDP more than placebo. In total, the results do not give us good reason to assume that one drug is better than the other. Fingolimod may also reduce the risk of CDP, although to a lesser degree than for ocrelizumab and rituximab. We find these results to be less convincing than for ocrelizumab and rituximab.

Certainty of evidence

In the GRADE approach RCTs are, as a starting point, considered to provide high quality evidence. The rating of the quality of evidence may be reduced after further assessment, thereby reducing the confidence of the effect estimate (*Table 2*) (44). As all the included studies in our HTA are RCTs, our outcome (CDP) was set to start out at high certainty of evidence for each intervention: fingolimod, ocrelizumab and rituximab, respectively. The quality was then further assessed with regards to the following factors: 1) risk of bias (*Appendix 7*), 2) inconsistency, 3) indirectness, 4) imprecision, and 5) publication bias (44).

GRADEing the evidence for confirmed disease progression

We did not downgrade the quality of evidence with regards to risk of bias (*Appendix 7)*, indirectness, or publication bias, as we assessed that our outcome was not (substantially) influenced by either of these factors.

With regards to inconsistency, we downgraded the quality of evidence by one, seeing as our outcome is only based on a relatively small, single RCT for each treatment.

We found imprecision especially difficult to assess. We looked at the results in light of the set threshold of 10% minimal clinically important difference (*Figure 3*), and used Cochrane's "Reporting the Effects of an Intervention in EPOC Reviews" as guidance for our assessment (43).

Assessment of imprecision – risk ratio

Fingolimod

For risk ratio calculations for CDP for fingolimod, we considered the following:

- The point estimate of 0.93 is between no effect (=1) and the assumed threshold level (=0.90)
- The upper level of 95% CI crosses 1 substantially

Based on the point estimate alone, we would assume that fingolimod does not have an important effect. However, due to a large 95% CI, there is uncertainty regarding the true effect. Still, we assume that this research provide some indication of the likely effect of fingolimod, but we acknowledge that further research may reveal the effect to be substantially different. As such, we chose to rate one down for imprecision for risk ratio for fingolimod.

Ocrelizumab and rituximab

For risk ratio calculations for ocrelizumab and rituximab, we considered the following:

- The point estimates of 0.84 and 0,78 respectively, are below no effect (=1) and the assumed threshold level (=0,90)
- The upper levels of both 95% CIs cross 1

Based on the point estimates alone, we would assume both ocrelizumab and rituximab to have an important effect in reducing CDP. However, these estimates are imprecise, as both have large 95% CIs. Still, we assume that this research provide some indication of the likely effect of both ocrelizumab and rituximab, but we acknowledge that further research may reveal the effect to be substantially different. As such, we chose to rate one down for imprecision for risk ratios for ocrelizumab and rituximab.

As a result, the certainty of evidence of CDP for all three interventions is assessed to be low, i.e. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Assessment of imprecision – hazard ratio

Fingolimod and rituximab

For hazard ratio calculations for fingolimod and rituximab, we considered the following:

- The point estimates of 0.88 and 0.77 resepectively, are below no effect (=1) and the assumed threshold level (=0.90)
- The upper levels of both 95% CIs cross 1 substantially
- The 95% CIs are very wide

Based on the point estimates alone, we would assume both fingolimod and rituximab to have an important effect. However, these estimates are highly imprecise, as both have very large 95% CIs that cross 1 substantially. We therefore assume that this research does not provide a reliable indication of the likely effect of either fingolimod or rituximab, and acknowledge that further research may reveal the effects to be substantially different. Therefore, we chose to rate down twice for imprecision for hazard ratio CDP for both fingolimod and rituximab.

Ocrelizumab

For hazard ratio calculations for ocrelizumab, we considered the following:

- The point estimate of 0.76 is below no effect (=1) and the assumed threshold level (=0.90)
- The upper level of 95% CI does not cross 1
- The 95% CI is very large

Based on the point estimate alone, we would assume ocrelizumab to have an important effect in reducing CDP. Even though the entire 95% CI is below 1, it is still very wide, indicating a large uncertainty of the effect. We therefore assume that this research provide some indication of the likely effect of ocrelizumab, but we still acknowledge that further research may reveal the effect to be substantially different. As such, we chose to rate one down for imprecision for ocrelizumab.

As a result, the certainty of evidence of CDP for ocrelizumab is assessed to be low, whereas the certainty of evidence of CDP for both fingolimod and rituximab is assessed to be very low; i.e. any estimate of effect is very uncertain.

General comments on our GRADE judgement

We had several discussions both within the author group and with other colleagues about the GRADEing in general, and the assessment of imprecision in particular. There was broad agreement that there is no obvious or clear answer, and that the quality of evidence for all outcomes (all interventions, both risk ratio and hazard ratio) could be reasonably judged as low or very low. Although GRADE provides a framework for a systematic approach to evaluate the certainty of evidence, it still relies on subjective judgement. As such, we acknowledge that others may rate the evidence differently than we have. The main advantage of using GRADE to assess the certainty of the evidence is that it makes our judgements transparent and open to criticism.

One consideration that may lead to different judgements is the emphasis of statistical significance, i.e. whether the 95% CI crosses the line of no effect. One could argue that it makes little sense to slavishly use an arguably arbitrary level, such as 95% CI or p-value <0.05 as a cut-off point (45). For example, we downgraded the risk ratio estimate for ocrelizumab partly because the upper 95% confidence level (1.02) only just crossed the line of no effect, but we did not downgrade the hazard ratio estimate where the upper 95% confidence level (0.98) nearly crossed the line of no effect. Others may reasonably disagree.

Another consideration that we chose to disregard is the risk that these medications may have a negative impact on disease progression. We have disregarded this possibility in our GRADE-assessments as the clinical experts we consulted believe that a negative effect is unlikely.

Strengths and limitations

A general strength of this HTAs is that the work has been performed in a systematic manner and in accordance with our project plan (*Appendix 3*). Throughout the process, at least two researchers independently performed study selection, data extraction, and data analysis. In addition, they also independently assessed the methodological quality of the included studies (Cochrane risk of bias tool), and the quality of the outcome (GRADE). Based on this, we are confident that we have taken reasonable steps to produce a trustworthy HTA.

As our literature search was performed in February 2019, we cannot exclude the possibility that other relevant studies may have been published since that time. However, our search strategy was thorough and we are confident that we have identified all relevant studies published prior to February 2019. To ensure that we would find as many relevant studies as possible, our search strategy had also included non-randomised registry studies. Still, the only relevant studies we identified were RCTs. The RCT design is considered the gold standard of primary medical research. However, as there were only *three* relevant RCTs, the evidence base is very limited, and the resulting confidence intervals are therefore wide.

Because only three studies were included, each on a different treatment, we did not perform meta-analysis. This work is therefore limited relative to systematic reviews and HTAs that are able to synthesise results from multiple studies to more precisely estimate effects and assess and potentially explain heterogeneity between studies and possible publication bias.

In principle, because the included studies used a common comparator (placebo), it would have been possible to perform network meta-analysis. However, we judged that such an analysis would be of very limited benefit and a poor use of our resources. We therefore reported the study data as risk ratios, and opted to deviate from our protocol to also include hazard ratios as reported in the studies.

The relative risk of CDP is lowest (RR=0.78) in the shortest study (2 years of follow-up) and highest (RR=0.93) in the longest study (3 years of follow-up). Assuming a constant risk of CDP, we would expect more patients to experience CDP over longer periods of time. This observation plausibly explains the findings for relative risk. Readers should therefore be careful not to over-interpret comparisons between the treatments in terms of relative risk. Comparisons of hazard ratios are likely to be more robust to differences in study duration.

Health economic aspects

A full health economic evaluation is necessary in situations where the intervention is both more effective and more costly than the comparator, or both less effective and less costly than the comparator.

We have not conducted a full health economic evaluation as we do not have strong reasons to believe that one specific drug is better or worse than the other (in terms of CDP), and because rituximab is substantially less costly than the two other treatments.

Yearly treatment cost of fingolimod, ocrelizumab and rituximab based on current list and net prices, and also drug administration and monitoring costs are presented in *Table 7*.

Table 7: *Annual treatments cost including VAT and drug administration and monitoring cost (NOK)*

Treatment	List prices	Net prices	Drug administration and monitoring cost* 1. year	Drug administration and monitoring cost* Beyond 1. year
Fingolimod	242 467	[redacted]	19 758	7 883
Ocrelizumab	289 727	[redacted]	22 872	14 205
Rituximab	1. year 39 412 +1. year 26 274	[redacted]	20 750	14 205

**incl. travel costs (3)*

Generalizability

As previously described, patient characteristics vary somewhat between the three studies. The patients in the rituximab-trial are older and had been diagnosed with MS for a longer period of time than the patients in the fingolimod-trial and especially the ocrelizumab-trial (7;35;36). Based on the results from a pre-planned subgroup analysis in the rituximab-trial, Hawker *et al* suggest that the treatment may be more beneficial in younger patients (<51 years), particularly those with inflammatory lesions (7). The population in the ocrelizumab-trial is slightly younger, with shorter disease duration (35). Accordingly, the Summary of Product Characteristics (SPC) for ocrelizumab specifies the therapeutic indication to be "*… for the treatment of adult patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity*" (46). Given the limitations of the study's eligibility criteria, the effect of ocrelizumab in an older PPMS-population with longer disease duration is currently unknown (25).

The goal of systematic reviews is to summarise available evidence that meet a defined set of criteria. Regardless of the amount and quality of evidence that can be included in a systematic review, it is important to remember that systematic reviews and meta-analyses, as well as single studies, typically report average treatment effects, which do not necessarily reflect the treatment effect for an individual patient.

Consistency with other reviews

Because there were no treatments with market authorisation for PPMS available until ocrelizumab was approved in 2018 (in Norway), it is unsurprising that there are very few systematic reviews or meta-analyses regarding disease-modifying treatments for PPMS. We identified a systematic review that explores the use of rituximab in various immune-mediated diseases, including PPMS (47). Similar to this report, that systematic review identified only one relevant study of rituximab and PPMS: i.e. Hawker et al (7). Although the authors did not perform statistical analyses, their narrative discussion/conclusion regarding the efficacy of rituximab is similar to the one we present in this report.

There are several non-systematic reviews discussing various potential treatment options for PPMS (31;48). We interpret their assessments of the same studies we have included in this HTA, as similar to ours.

Need for further research

As evident in this HTA, the general lack of data makes it difficult to compare the relative efficacy of the included medications. All drugs that are in use as a treatment for PPMS should be studied further in randomised, controlled trials to provide longer-term efficacy and safety data. A more solid evidence base would also enable us to perform a meaningful health economic evaluation.

Many different drugs have been studied as potential disease-modifying treatments for PPMS (31;48). With the recent exception of ocrelizumab, most of these studies have failed to meet their primary endpoints (31;48). However, based on the results of the ocrelizumab-study (35), there might be a potential for studying the effect of different immune-modulating therapies in younger PPMS-populations.

Additionally, there is still a need for continuous research to develop new and better treatments that hopefully will meet the ultimate goal of treating PPMS; to halt and reverse disease progression.

Conclusion

The risk ratio results indicate that both ocrelizumab and rituximab may reduce the risk of disease progression, but there is substantial uncertainty about the extent of the effect, mainly owing to the imprecise results (wide 95% CIs). The point estimates slightly favour rituximab, but the two estimates are similar, and so is the imprecision. A reasonable interpretation is therefore that the two treatments may be similarly effective, but it is also likely that one is more effective than the other, although it is not possible to say which one is the better drug.

For the hazard ratio results, the certainty of evidence for ocrelizumab versus placebo is slightly more convincing than for rituximab versus placebo, although the effect estimates are practically identical.

Thus, in our judgement the results for ocrelizumab and rituximab (risk ratio and hazard ratio) do not give us good reason to believe that one drug is better than the other.

The interpretation is slightly different with regards to fingolimod: the risk ratio result indicates a slight effect on disease progression, while the effect based on the hazard ratio is highly uncertain. As such, we find the results for fingolimod less convincing than for ocrelizumab and rituximab.

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Appendix 1. Progress log

Logg og tid brukt i rapporten		
LOGG	Forslag til metode innsendt/ metodevarsel publisert på nyemetoder.no	30.01.2018
	Metodevurdering bestilt av Bestillerforum RHF (spesifisert på PPMS, utvidelse av første innsendelse på MS generelt)	28.01.2019
	Start metodevurdering	Mars 2019
	Fageksperter kontaktet første gang (på epost om prosjektplan til PPMS)	05.02.2019
	Brukerrepresentant kontaktet første gang	Ikke involvert
	Prosjektplan til internt godkjenning	26.03.2019
	Prosjektplan publisert	28.08.2019
	Dato for rapport sendt til eksterne fagfeller	09.12.2019
	Dato for rapport sendt til ekstern produsent	Ikke aktuelt
	Dato for rapport sendt til sekretariatet for Bestillerforum RHF	31.01.2020
TID	Tid brukt til å innhente ytterligere dokumentasjon fra produsent	Ikke aktuelt
	Tid brukt til å innhente ytterligere dokumentasjon fra andre aktører	Ikke aktuelt
	Totalt antall dager i påvente av dokumentasjon	Ikke aktuelt
	Totalt antall dager til saksbehandling (total tid hos utrederinstans)	

Appendix 2. Table of abbreviation

CDP	Confirmed disability progression
CNS	Central nervous system
EDSS	Expanded Disability Status Scale
HTA	Health technology assessment
HR MA	Market authorization
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
PPMS	Primary progressive multiple sclerosis
RR RRMS	Relapse remitting multiple sclerosis
SPMS	Secondary progressive multiple sclerosis

Appendix 3. Project plan

The project plan was published in August 2019, and is found here:

https://www.fhi.no/globalassets/dokumenterfiler/prosjekter/id2019_018-project-plan-ppms.pdf

Appendix 4. Search strategy

Detailed search strategy

In February 2019 we performed electronic searches in relevant databases for published and ongoing 1) systematic reviews, Health Technology Assessments and clinical guidelines, and 2) randomised controlled trials and register studies (*Table 1, this appendix*). The full search strategies for all databases with number of hits are found in *Table 2* (*this appendix*).

Table 1. *Search result*

Name of database	**Hits exported to EndNote**
Search 1: Publication type: Systematic Review, HTAs, Guidelines Year of publication: -> 2019 Search date: 07.02.2019	
Cochrane Library: Reviews (11), CDSR Protocols (5),	16
Epistemonikos: Broad Synthesis (1); Structured Summary (4); Systematic Review (28)	33
Other: • Statens beredning för medicinsk och social utvärdering (0) • Socialstyrelsen (1) • Sundhedsstyrelsen (0) • National Institute of Health and Care Excellence: NICE Guidelines (1)	2
PROSPERO Prospective international register of systematic reviews	13
EUnetHTA Planned and Ongoing Projects (POP) database	10
Search 2: Publication type: Randomised Controlled Trial, Register study Year of publication: -> 2019 Search date: 07.02.2019	
Cochrane Library: Cochrane Central Register of Controlled Trials	276
Embase (Ovid)	342
Ovid MEDLINE	399
Web of Science	555
Epistemonikos: primary studies	74
National Institute of Health Clinical Trials (clinicaltrials.gov)	60
International Clinical Trials Registry Platform (ICTRP)	48
Total hits	1828
Total hits without duplicates	1200
Total hits without duplicates and conference abstracts	913

Table 2. *Detailed search strategies*

Embase (Ovid) 1974 to 6th February 2019 Ovid **MEDLINE**(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to 6th February 2019		
1	Multiple Sclerosis, Chronic Progressive/ use ppezv	1792
2	((progressive adj2 (MS or multiple sclerosis)) or PPMS or SPMS).tw,kw,kf.	13330
3	or/1-2	13994
4	Dimethyl Fumarate/ use ppezv or Fumaric acid dimethyl ester/ use oemezd	3525
5	(dimethyl fumarate* or dimethylfumarate*).tw,kw,kf.	3010
6	Teriflunomide/ use oemezd	2287
7	teriflunomide.tw,kw,kf.	1438
8	exp Interferon-beta/ use ppezv or Beta interferon/ use oemezd	32108
9	((interferon adj1 beta*) or IFN-beta*).tw,kw,kf.	32684
10	Glatiramer Acetate/ use ppezv or Glatiramer/ use oemezd	9184
11	(glatirameracetat* or glatiramer acetat*).tw,kw,kf.	4975
12	Natalizumab/ use ppezv or Natalizumab/ use oemezd	10605
13	natalizumab.tw,kw,kf.	6960
14	Fingolimod Hydrochloride/ use ppezv or Fingolimod/ use oemezd	10156
15	fingolimod.tw,kw,kf.	5474
16	Alemtuzumab/ use ppezv or Alemtuzumab/ use oemezd	16496
17	alemtuzumab.tw,kw,kf.	7945
18	Rituximab/ use ppezv or Rituximab/ use oemezd	81941
19	rituximab.tw,kw,kf.	58195
20	Cladribine/ use ppezv or Cladribine/ use oemezd	7731
21	cladribin*.tw,kw,kf.	3396
22	Ocrelizumab/ use oemezd	1200
23	ocrelizumab.tw,kw,kf.	696
24	or/4-23	177913
25	"Multiple Sclerosis, Chronic Progressive"/dt use ppezv	460
26	((Randomized Controlled Trial or Controlled Clinical Trial or "Clinical Trial, Phase II" or "Clinical Trial, Phase III" or "Clinical Trial, Phase IV").pt. or randomi?ed.ti,ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) use ppezv	1251586
27	(Randomized Controlled Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or Crossover-Procedure/ or Double-Blind Procedure/ or Single-Blind Procedure/ or randomi?ed.ab. or placebo.ab. or randomly.ab. or trial.ti.) use oemezd	1454231
28	(Registries/ or "Medical Record Linkage"/ or "Medical Records Systems, Computerized"/) use ppezv or Register/ use oemezd	209738
29	(((registry or registries or register or registers or database* or databank* or repositor*) adj3 multiple sclerosis) or (MS* adj (regist* or database or databank or repositor*)) or (regist* adj2 (stud* or data or analys* or report*)) or register based or panel data or (cohort adj2 (prospective or longitudinal)) or (longitudinal adj1 prospective) or ((real world or real life) adj2 (data or evidence or stud* or result* or outcome*)) or ((real world or real life) adj5 (research or registry or registries or register or registers))).tw,kw,kf.	303424
30	((medical or patient) adj2 (register or registers or registry or registries)).tw,kw,kf.	18718
31	or/26-29	3141353
32	((3 and 24) or 25) and (or/26-29)	955
33	remove duplicates from 32	741
34	33 use ppezv	399
35	33 use oemezd	342
PROSPERO Prospective international register of systematic reviews		
1	(((progressive AND (MS OR "multiple sclerosis")) OR PPMS OR SPMS) AND ("dimethyl fumarate" OR dimethylfumarate* OR teriflunomide OR (interferon AND beta*) OR IFN-beta* OR "IFN beta" OR "glatiramer acetate" OR glatirameraceta* OR natalizumab OR fingolimod OR alemtuzumab OR rituximab OR cladribin* OR ocrelizumab))	13
EUnetHTA Planned and Ongoing Projects (**POP) database**		
1	[Search for keywords "all (AND)"] "multiple sclerosis"	9
2	[Browse by MeSH term] **C10.314.350** Demyelinating Autoimmune Diseases, CNS	4
	Unique hits	10
Epistemonikos		
1	(((progressive AND (MS OR "multiple sclerosis")) OR PPMS OR SPMS) AND ("dimethyl fumarate" OR dimethylfumarate* OR teriflunomide OR (interferon AND beta*) OR IFN-beta* OR "IFN beta" OR "glatiramer acetate" OR glatirameraceta* OR natalizumab OR fingolimod OR alemtuzumab OR rituximab OR cladribin* OR ocrelizumab)) [Advanced search - Title/Abstract]	Broad Synthesis: 1 Structured Summary: 4 Systematic Review: 28 Primary Studies: 74
Cochrane Library Cochrane Database of Systematic Reviews: Issue 2 of 12, February 2019 Cochrane Central Register of Controlled Trials: Issue 2 of 12, February 2019		

#1	[mh ^"Multiple Sclerosis, Chronic Progressive"]	210
#2	((progressive NEAR/2 (MS OR multiple NEXT sclerosis)) OR PPMS OR SPMS):ab,kw,ti	886
#3	((progressive NEAR/2 (MS OR multiple NEXT sclerosis)) OR PPMS OR SPMS)	931
#4	[mh ^"Dimethyl Fumarate"] OR [mh "Interferon-beta"] OR [mh ^" Glatiramer Acetate"] OR [mh ^Natalizumab] OR [mh ^"Fingolimod Hydrochloride"] OR [mh ^Alemtuzumab] OR [mh ^Rituximab] OR [mh ^Cladribine]	1957
#5	(dimethyl NEXT fumarate* OR dimethylfumarate* OR teriflunomide OR (interferon NEXT beta*) OR IFN-beta* OR IFN NEXT beta* OR glatiramer NEXT aceta* OR glatirameraceta* OR natalizumab OR fingolimod OR alemtuzumab OR rituximab OR cladribin* OR ocrelizumab):ti,ab,kw	6271
#6	(dimethyl NEXT fumarate* OR dimethylfumarate* OR teriflunomide OR (interferon NEXT beta*) OR IFN-beta* OR IFN NEXT beta* OR glatiramer NEXT aceta* OR glatirameraceta* OR natalizumab OR fingolimod OR alemtuzumab OR rituximab OR cladribin* OR ocrelizumab)	6393
#7	[mh ^"Multiple Sclerosis, Chronic Progressive"/DT]	113
	((#1 or #2) and (#4 or #5)) or #7 [in Cochrane Reviews]	11
	((#1 or #3) and (#4 or #6)) or #7 [in Cochrane Protocols or Cochrane Trials]	281
Web of Science		
#1	TS=(("progressive" NEAR/1 ("MS" OR "multiple sclerosis")) OR "PPMS" OR "SPMS")	7062
#2	TS=("dimethyl fumarate*" OR dimethylfumarate* OR "teriflunomide" OR "interferon beta*" OR IFN-beta* OR "glatiramer aceta*" OR glatirameraceta* OR "natalizumab" OR "fingolimod" OR "alemtuzumab" OR "rituximab" OR cladribin* OR "ocrelizumab")	61388
#3	TI="trial" OR TS=(randomised OR randomized OR randomly OR placebo) OR TS=((("registry" OR "registries" OR "register" OR "registers" OR database* OR databank* OR repositor*) NEAR/2 "multiple sclerosis") OR ("MS" NEAR/0 (regist* OR "database" OR "databank" OR repositor*)) OR (regist* NEAR/1 (stud* OR "data" OR analys* OR report*)) OR "register based" OR "panel data" OR ("cohort" NEAR/1 ("prospective" OR "longitudinal")) OR ("longitudinal" NEAR/0 "prospective") OR (("real world" OR "real life") NEAR/1 ("data" OR "evidence" OR stud* OR result* OR outcome*)) OR (("real world" OR "real life") NEAR/4 ("research" OR "registry" OR "registries" OR "register" OR "registers")))	1333915
#4	#1 AND #2 AND #3 [Indexes=SCI-EXPANDED, ESCI Timespan=All years]	555
NIH Clinical Trials (Search > other terms)		
((cladribine OR RWJ-26251 OR RWJ26251 OR rituximab OR IDEC-C2B8 OR GP-2013 OR GP2013) AND (PPMS OR SPMS OR "progressive multiple sclerosis" OR "progressive MS"))		9
((dimethyl fumarate OR BG-00012 OR BG00012 OR FAG-201 OR FAG201 OR teriflunomide OR HMR-1726 OR HMR1726) AND (PPMS OR SPMS OR "progressive multiple sclerosis" OR "progressive MS"))		6
((glatiramer acetate OR TV-5010 OR TV5010 OR fingolimod OR FTY-720 OR FTY720) AND (PPMS OR SPMS OR "progressive multiple sclerosis" OR "progressive MS"))		9
((natalizumab OR AN-100226 OR alemtuzumab OR ocrelizumab OR PR-070769 OR PR070769 OR R-1594 OR R1594) AND (PPMS OR SPMS OR "progressive multiple sclerosis" OR "progressive MS"))		16
((interferon-beta OR beta-interferon OR INF-beta) AND (PPMS OR SPMS OR "progressive multiple sclerosis" OR "progressive MS"))		20
International Clinical Trials Registry Platform		
cladribine AND PPMS OR cladribine AND SPMS OR cladribine AND "progressive multiple sclerosis" OR cladribine AND "progressive MS" OR RWJ-26251 AND PPMS OR RWJ-26251 AND SPMS OR RWJ-26251 AND "progressive multiple sclerosis" OR RWJ-26251 AND "progressive MS" OR RWJ26251 AND PPMS OR RWJ26251 AND SPMS OR RWJ26251 AND "progressive multiple sclerosis" OR RWJ26251 AND "progressive MS"		0
rituximab AND PPMS OR rituximab AND SPMS OR rituximab AND "progressive multiple sclerosis" OR rituximab AND "progressive MS" OR IDEC-C2B8 AND PPMS OR IDEC-C2B8 AND SPMS OR IDEC-C2B8 AND "progressive multiple sclerosis" OR IDEC-C2B8 AND "progressive MS" OR GP-2013 AND PPMS OR GP-2013 AND SPMS OR GP-2013 AND "progressive multiple sclerosis" OR GP-2013 AND "progressive MS" OR GP2013 AND PPMS OR GP2013 AND SPMS OR GP2013 AND "progressive multiple sclerosis" OR GP2013 AND "progressive MS" OR ocrelizumab AND PPMS OR ocrelizumab AND SPMS OR ocrelizumab AND "progressive multiple sclerosis" OR ocrelizumab AND "progressive MS" OR PR-070769 AND PPMS OR PR-070769 AND SPMS OR PR-070769 AND "progressive multiple sclerosis" OR PR-070769 AND "progressive MS" OR PR070769 AND PPMS OR PR070769 AND SPMS OR PR070769 AND "progressive multiple sclerosis" OR PR070769 AND "progressive MS" OR R-1594 AND PPMS OR R-1594 AND SPMS OR R-1594 AND "progressive multiple sclerosis" OR R-1594 AND "progressive MS" OR R1594 AND PPMS OR R1594 AND SPMS OR R1594 AND "progressive multiple sclerosis" OR R1594 AND "progressive MS"		21
dimethyl fumarate AND PPMS OR dimethyl fumarate AND SPMS OR dimethyl fumarate AND "progressive multiple sclerosis" OR dimethyl fumarate AND "progressive MS" OR BG-00012 AND PPMS OR BG-00012 AND SPMS OR BG-00012 AND "progressive multiple sclerosis" OR BG-00012 AND "progressive MS" OR BG00012 AND PPMS OR BG00012 AND SPMS OR BG00012 AND "progressive multiple sclerosis" OR BG00012 AND "progressive MS" OR FAG-201 AND PPMS OR FAG-201 AND SPMS OR FAG-201 AND "progressive multiple sclerosis" OR FAG-201 AND "progressive MS" OR FAG201 AND PPMS OR FAG201 AND SPMS OR FAG201 AND "progressive multiple sclerosis" OR FAG201 AND "progressive MS" OR glatiramer acetate AND PPMS OR glatiramer acetate AND SPMS OR glatiramer acetate AND "progressive multiple sclerosis" OR glatiramer acetate AND "progressive MS" OR TV-5010 AND PPMS OR TV-5010 AND SPMS OR TV-5010 AND "progressive multiple sclerosis" OR TV-5010 AND "progressive MS" OR TV5010 AND PPMS OR TV5010 AND SPMS OR TV5010 AND "progressive multiple sclerosis" OR TV5010 AND "progressive MS"		7

fingolimod AND PPMS OR fingolimod AND SPMS OR fingolimod AND "progressive multiple sclerosis" OR fingolimod AND "progressive MS" OR FTY-720 AND PPMS OR FTY-720 AND SPMS OR FTY-720 AND "progressive multiple sclerosis" OR FTY-720 AND "progressive MS" OR FTY720 AND PPMS OR FTY720 AND SPMS OR FTY720 AND "progressive multiple sclerosis" OR FTY720 AND "progressive MS" OR natalizumab AND PPMS OR natalizumab AND SPMS OR natalizumab AND "progressive multiple sclerosis" OR natalizumab AND "progressive MS" OR AN-100226 AND PPMS OR AN-100226 AND SPMS OR AN-100226 AND "progressive multiple sclerosis" OR AN-100226 AND "progressive MS" OR alemtuzumab AND PPMS OR alemtuzumab AND SPMS OR alemtuzumab AND "progressive multiple sclerosis" OR alemtuzumab AND "progressive MS"	10
teriflunomide AND PPMS OR teriflunomide AND SPMS OR teriflunomide AND "progressive multiple sclerosis" OR teriflunomide AND "progressive MS" OR HMR-1726 AND PPMS OR HMR-1726 AND SPMS OR HMR-1726 AND "progressive multiple sclerosis" OR HMR-1726 AND "progressive MS" OR HMR1726 AND PPMS OR HMR1726 AND SPMS OR HMR1726 AND "progressive multiple sclerosis" OR HMR1726 AND "progressive MS" OR interferon-beta* AND PPMS OR interferon-beta* AND SPMS OR interferon-beta* AND "progressive multiple sclerosis" OR interferon-beta* AND "progressive MS" OR beta interferon AND PPMS OR beta interferon AND SPMS OR beta interferon AND "progressive multiple sclerosis" OR beta interferon AND "progressive MS" OR INF-beta AND PPMS OR INF-beta AND SPMS OR INF-beta AND "progressive multiple sclerosis" OR INF-beta AND "progressive MS"	10

Appendix 5. Excluded studies with reasons

List of 21 excluded references with reason for exclusion.

Excluded studies	Reason for exclusion
Alcala C, Gascon F, Perez-Miralles F, Gil-Perotin S, Navarre A, Bosca I, et al. Efficacy and safety of rituximab in relapsing and progressive multiple sclerosis: a hospital-based study. JNeurol 2018;265(7):1690-7.	Study population not relevant (only 14 of 90 patients had PPMS)
Beutler E, Sipe J, Romine J, McMillan R, Zyroff J, Koziol J. Treatment of multiple sclerosis and other autoimmune diseases with cladribine. Seminars in Hematology 1996;33(1):45-52.	Full text not available, study is from 1996
Borràs C, Porcel J, Brieva L, Tintore M, Rio J, Arévalo MJ, et al. Double blind, pilot clinical trial in primary progressive and transitional progressive multiple sclerosis patients treated with interferon beta-1b or placebo. Neuropsychological results. Neurología 2002;17(9):491.	Full text not available, study is from 2002
Disanto G, Benkert P, Lorscheider J, Mueller S, Vehoff J, Zecca C, et al. The Swiss Multiple Sclerosis Cohort-Study (SMSC): a prospective Swiss wide investigation of key phases in disease evolution and new treatment options. Plos one 2016;11(3).	Study population not relevant (3.5% PPMS)
Fox EJ, Markowitz C, Applebee A, Montalban X, Wolinsky JS, Belachew S, et al. Ocrelizumab reduces progression of upper extremity impairment in patients with primary progressive multiple sclerosis: Findings from the phase III randomized ORATORIO trial. MultScler 2018;24(14):1862-70.	Outcome (CDP) not reported
Leary SM, Miller DH, Stevenson VL, Brex PA, Chard DT, Thompson AJ. Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial. Neurology 2003;60(1):44-51.	Data is not intelligible: presented only in Kaplan-Meier survival plot, in total: only 50 patients (20+15+15), and study is from 2003.
Lorscheider J, Kuhle J, Izquierdo G, Lugaresi A, Havrdova E, Horakova D, et al. Anti-inflammatory disease-modifying treatment and disability progression in primary progressive multiple sclerosis: a cohort study. European Journal of Neurology 2019;26(2):363-70.	Observational study. Different DMTs included in "treated" group.
Miller DH, Lublin FD, Sormani MP, Kappos L, Yaldizli O, Freedman MS, et al. Brain atrophy and disability worsening in primary progressive multiple sclerosis: insights from the INFORMS study. Ann Clin Transl Neurol 2018;5(3):346-56.	INFORMS-study, studies other outcome
Montalbán X, Brieva L, Tintoré M, Borras C, Río J, Nos C, et al. Clinical trial, DCPC, randomized single center with interferon beta 1b in primary and transitional progressive multiple sclerosis: an exploratory study in phase II. Neurología 2002;17(9):490.	Full text not available, study is from 2002
Montalban X, Sastre-Garriga J, Tintore M, Brieva L, Aymerich FX, Rio J, et al. A single-center, randomized, double-blind, placebo-controlled study of interferon beta-1b on primary progressive and transitional multiple sclerosis. MultScler 2009;15(10):1195-205.	Population is a mix of PPMS and transitional MS. Small patient group (36 + 37).
Rice GPA, Filippi M, Comi G. Cladribine and progressive MS: Clinical and MRI outcomes of a multicenter controlled trial. Neurology 2000;54(5):1145-55.	Study population not relevant (only 30% had PPMS)
Salzer J, Svenningsson R, Alping P, Novakova L, Bjorck A, Fink K, et al. Rituximab in multiple sclerosis A retrospective observational study on safety and efficacy. Neurology 2016;87(20):2074-81.	Observational study. No comparator.
Scotti B, Disanto G, Sacco R, Guigli M, Zecca C, Gobbi C. Effectiveness and safety of Rituximab in multiple sclerosis: an observational study from Southern Switzerland. Plos One 2018;13(5):11.	Study population not relevant (only 12 of 82 patients had PPMS)
Sipe JC, Romine J, Zyroff J, Koziol J, McMillan R, Beutler E. Cladribine favorably alters the clinical course of progressive multiple sclerosis (MS). Neurology 1994;44:A357.	Full text not available, study is from 1994
Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J, Beutler E. Cladribine in treatment of chronic progressive multiple sclerosis. Lancet 1994;344(8914):9-13.	Study population not relevant.
Strassburger-Krogias K, Ellrichmann G, Krogias C, Altmeyer P, Chan A, Gold R. Fumarate treatment in progressive forms of multiple sclerosis: first results of a single-center observational study. Therapeutic Advances in Neurological Disorders 2014;7(5):232-8.	Study population not relevant (combined PPMS and SPMS)

Tur C, Montalban X, Tintore M, Nos C, Rio J, Aymerich FX, et al. Interferon beta-1b for the treatment of primary progressive multiple sclerosis: five-year clinical trial follow-up. Archives of Neurology 2011;68(11):1421-7.	Follow-up study after ended DMT-treatment
Wajgt A, Strzyzewska S, Ochudlo S. The treatment of chronic progressive multiple sclerosis with cladribine. Journal of the neurological sciences 1997:S116.	Full text not available, study is from 1997
Wolinsky JS, Montalban X, Hauser SL, Giovannoni G, Vermersch P, Bernasconi C, et al. Evaluation of no evidence of progression or active disease (NEPAD) in patients with primary progressive multiple sclerosis in the ORATORIO trial. AnnNeurol 2018;84(4):527-36.	No additional data from the core study (Montalban 2017)
Wolinsky JS, Narayana PA, O'Connor P, Coyle PK, Ford C, Johnson K, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. AnnNeurol 2007;61(1):14-24.	Study terminated because of lack of effect
Yamout BI, El-Ayoubi NK, Nicolas J, El Kouzi Y, Khoury SJ, Zeineddine MM. Safety and Efficacy of Rituximab in Multiple Sclerosis: A Retrospective Observational Study. Journal of Immunology Research 2018:9.	Study population not relevant (only 2 of 121 patients had PPMS)

Appendix 6. Description of included trials

	Hawker 2009 (7)	Lublin 2016 (36)	Montalban 2017 (35)
Study	**OLYMPUS**; NCT00087529; RCT; Phase 2/3; Double-blind placebo-controlled; Multicentre (60 centres in USA and Canada)	**INFORMS**; NCT00731692; RCT; Phase 3; double-blind placebo controlled; multicentre (148 centres in 18 countries	**ORATORIO**: NCT01194570; RCT; Phase 3; double-blind, parallel-group, stratified, placebo-controlled; multicentre (USA and other countries)
Interventions and control	Rituximab, n=292, two 1,000 mg i.v. every 24 weeks through 96 weeks (4 courses) Placebo, n=147, same regimen as with intervention	**Cohort 1**: Fingolimod, n=147, 1.25 mg Placebo, n=133. **Cohort 2**: Fingolimod, n=336, 0.5 mg Placebo n=354 **Protocol amendment**: fingolimod 1.25mg discontinued in 2009 and patients changed to 0.5mg in a masked manner and included in Cohort 2.	Ocrelizumab n=488, 600mg i.v. every 24 weeks for at least 120 weeks Placebo n=239
Follow-up	96 weeks course of active treatment, safety total 122 weeks. Completed 122 weeks: Rituximab 224 /92.9%), placebo 116 (93.5)	Treatment at least 36 months and maximum 5 years. Clinical assessments (EDSS, 25'TWT, and 9-HPT) were done at screening, at randomisation (baseline), and at study visits, including safety assessments at 2 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months during the first year after randomisation and then every 3 months until month 36.	Treatment for at least 120 weeks or until a pre-specified number of confirmed disability progression events had occurred.

	Hawker 2009 (7)	Lublin 2016 (36)	Montalban 2017 (35)
Eligibility criteria	**Age:** 18-65 years **Diagnosis:** PPMS **EDSS:** At baseline 2.0 - 6.5 points **Functional Systems scale:** Score of ≥2.0 **CSF:** presence of IgG oligoclonal bands or elevated CSF IgG, or or both obtained at screening or documented during the previous 24 months **Exclusion criteria:** Different MS-squalae, treatment therapies	**Age:** 25-65 years **Diagnosis:** PPMS **Disease duration:** One year or more **In addition:** one or more of the following - positive brain MRI, positive spinal cord MRI or positive cerebrospinal fluid	**Age:** 18-55 years **Diagnosis:** PPMS **EDSS:** 3.0-6.5 range (1-10.0) at screening **Functional Systems Scale:** at least 2 (range 0-6) **Duration of disease:** <15 years with EDSS >5.0, or <10 years with EDSS < 5.0 at screening **Immunology:** History or presence and IgG index or at least 1 IgG oligoclonal band in the cerebrospinal fluid. **Exclusion criteria:** history of RRMS/PMS, contraindication to MRI, contraindications/unacceptable side effects from oral or intravenous glucocorticoids, previous treatment with B-cell-targeted therapies and other immunosuppressive medications.
Baseline characteristics	Rituximab **Age:** 50.1 (±9.0) years mean (±SD); **Female:** 140; **EDSS:** 5.0 (2.0 - 6.5) median (min, max); **Duration from onset:** 9.2 (±6.4) years mean (±SD) Placebo **Age:** 49.6 (±8.7) years mean (±SD); **Female:** 81; **EDSS:** Median (min, max) 4.5 (2.0 - 6.5); **Duration from onset:** 9.0 (±6.8) years mean (±SD)	Fingolimod 0.5 mg **Age:** 48.5 (±8.6) years mean (±SD) **Female:** 163 (49%); **EDSS:** 4.50 (4.0-6.0) (median, range); **Disease duration:** 2.80 (±2.6) years mean (±SD) Placebo **Age:** 48.5 (±8.3) years mean (±SD); **Female:** 235 (48%); **EDSS:** 4.50 (4.0-6.0) (median, range); **Disease duration:** 2.91 (±2.3) years mean (±SD)	Ocrelizumab **Age:** 44.7 (±7.9) years mean (±SD); **Female:** 237 (48.6%); **EDSS:** 4.5 (2.5-7.0) (median, range); **Disease duration:** 2.9 (±3.2) years mean (±SD) Placebo **Age:** 44.4 (±8.3) years mean (±SD); **Female:** 124 (50.8%); **EDSS:** 4.5 (2.5-6.5) (median, range); **Disease duration:** 2.8 (±3.3) years mean (±SD)
Outcomes and definitions	Time to confirmed disease progression (CDP), defined as sustained EDSS increase of ≥1.0 point from baseline EDSS if EDSS was between 2.0 and 5.5 points (inclusive), or an EDSS increase of ≥0.5 points if the baseline EDSS was >5.5 points, for which change was not attributable to another aetiology sustained for ≥12 weeks	Delay of time to confirmed disability progression (CDP). CDP was defined as first occurrence of at least criteria: 1) Increase in baseline EDSS by 1 point if baseline EDSS = 5.0 or lower or by 0.5 points if baseline EDSS 5.5 or higher; 2) At least 20% increase in 25 TWT; 3) At least 20% increase in in time taken to complete 9-HTP. Progression in at least one of three components had to be confirmed for the same components at least 3 months later at scheduled visit.	Percentage of patients with disability progression confirmed at 12 weeks in a time-to-event analysis.

Appendix 7. Risk of bias of included studies

Risk of bias was assessed by using the Risk of Bias tool from Cochrane handbook (49). The following rating was used in the assessment:

Low risk of bias +
High risk of bias -
Unknown risk of bias ?

	*Hawker 2009 (7)	Lublin 2016 (36)	Montalban 2017 (35)
Random sequence generation (selection bias)	?	+	+
Allocation concealment (selection bias)	?	+	?
Blinding of participants and personnel (performance bias)	+	+	+
Blinding of outcome assessment (detection bias)	+	+	+
Incomplete outcome data (attrition bias)	+	?	+
Selective reporting (reporting bias)	+	+	+
Other bias	+	+	+
Overall risk of bias	+	+	+

*Although we assessed the study by Hawker et al to have unclear risk in terms of random sequence generation and allocation concealment, its overall risk of bias was still assessed to be low.

Appendix 8. Ongoing clinical trials

Table of ongoing clinical trials. Studies with fewer than 300 participants, non-randomised studies or studies without controls, are shaded

Study ID/ name	Status/ Estimated end	Drug/comparator	Study design/ Number of participants (n)	Main outcome
NCT01194570/ A Study of Ocrelizumab in Participants With Primary Progressive Multiple Sclerosis	Active/ 2021	Ocrelizumab/ Placebo	Interventional/ n =732	Time to Onset of Clinical Disability Progression
NCT01433497/ Efficacy and Safety of Masitinib in the Treatment of Progressive Multiple Sclerosis	Active/ 2020	Masitinib/ Placebo	Interventional/ n =656	EDSS
NCT02936037/ Effect of MD1003 in Progressive Multiple Sclerosis (SPI2) (SPI2)	Active/ 2023	MD1003/ Placebo	Interventional/ n =642	EDSS, Timed 25-Foot Walk
NCT02959658/ Dimethyl Fumarate Treatment of Primary Progressive Multiple Sclerosis (FUMAPMS)	Active/ 2019	Dimethyl fumarate/ Placebo	Interventional/ n =90	Changes in neuro filament light chain
NCT01854359/ Idebenone for Primary Progressive Multiple Sclerosis	Active/ 2019	Idebenone/ No comparator	Interventional/ n =61	Combinatorial Weight-Adjusted Disability Score
NCT03362294/ Safety and Efficacy of Monthly Long-acting IM Injection of 40 mg GA Depot in Subjects With PPMS	Recruiting/ 2020	Glatiramer acetate/ No comparator	Interventional/ n =24	Safety: adverse events (AE) and injection site reactions
NCT02913157/ Hydroxychloroquine in Primary Progressive Multiple Sclerosis	Recruiting/ 2020	Hydroxychloroquine/ no comparator	Interventional/ n =35	Timed 25-Foot Walk
NCT02688985/ Study to Explore the Mechanism of Action of Ocrelizumab and B-Cell Biology in Participants With Relapsing Multiple Sclerosis (RMS) or Primary Progressive Multiple Sclerosis (PPMS)	Recruiting/ 2023	Ocrelizumab/ No comparator	Interventional/ n =120	Changes in: neuro filament light chain, number of CD19+ B-Cells, number of CD3+ T-Cells
NCT03593590/ Non-interventional Study of Ocrelizumab in Participants With Relapsing or Primary Progressive Multiple Sclerosis (MuSicalE)	Recruiting/ 2025	Ocrelizumab/ No comparator	Observational/ n =1000	Changes in SymptoMScreen score
NCT03283826/ Phase 1 Study to Evaluate the Safety of ATA188 in Subjects With Progressive and Relapsing-Remitting Multiple Sclerosis	Recruiting/ 2021	ATA188/ No comapator	Interventional/ n =60	Safety and tolerability, dose finding
* **NCT03606460**/ A Study to Evaluate the Safety of Administering Ocrelizumab Per a Shorter Infusion Protocol in Participants With Primary Progressive Multiple Sclerosis (PPMS) and Relapsing Multiple Sclerosis (RMS)	Active/ 2019	Ocrelizumab/ Ocrelizumab other dose	Interventional/ n =150	% patients with AE
NCT03783416/ SIZOMUS Safety of Ixazomib Targeting Plasma Cells in Multiple Sclerosis (SIZOMUS)	Not yet recruiting/ 2023	Ixazomib/ Placebo	Interventional/ n =72	Safety: AE
NCT01950234/ ACTH in Progressive Forms of MS	Recruiting/ 2022	Adrenocorticotropic hormone (ACTH)/ Placebo	Interventional/ n =100	Timed 25-Foot Walk
NCT03691077/ Effect of Ocrelizumab on Brain Innate Immune Microglial Cells Activation in MS Using PET-MRI With 18F-DPA714 (INN-MS)	Recruiting/ 2022	Ocrelizumab/ No comparator	Interventional/ n =51	Change in 18FDPA714 positive voxels in the total white matter

Study ID/ name	Status/ Estimated end	Drug/comparator	Study design/ Number of participants (n)	Main outcome
NCT03562975/ Upper Extremity Function in Multiple Sclerosis Patients With Advanced Disability Treated With Ocrevus	Recruiting/ 2020	Ocrelizumab/ No control	Observational/ n =35	Performance Evaluation Test for the Elderly (TEMPA)
NCT02988401/ Intranasal Insulin for Improving Cognitive Function in Multiple Sclerosis	Recruiting/ 2020	Insulin/ Placebo	Interventional/ n =105	Change in cognitive function
NCT03523858/ A Study to Evaluate Ocrelizumab Treatment in Participants With Progressive Multiple Sclerosis (CONSONANCE)	Recruiting/ 2025	Ocrelizumab/ No comparator	Interventional/ n =600	% patients with no evidence of progression
NCT02583594/ A Study to Characterize Subcutaneous or Intravenous Alemtuzumab in Patients With Progressive Multiple Sclerosis (SCALA)	Active/ 2021	Alemtuzumab s.c./ Alemtuzumab i.v.	Interventional/ n =24	Change in CD3+ lymphocyte subset
NCT02545959/ Intrathecal Rituximab in Progressive Multiple Sclerosis (EFFRITE)	Active/ 2019	Rituximab i.t./ Rituximab i.v./ Placebo	Interventional/ n =10	Change in osteopontin level in CSF
NCT03552211/ Evaluation of the Incidence of Relapses in Patients With Biotin-treated Progressive Multiple Sclerosis (IPBio-SeP)	By invitation/ 2019	Biotin/ No comparator	Observational/ n =3000	Relapses
NCT03302806/ Study to Assess Effect and Safety of High Dose of Biotin (Qizenday®) in Progressive Multiple Sclerosis (BIOSEP)	Recruiting/ 2018	Biotin/ No comparator	Observational/ n =100	EDSS
NCT02313285/ A Long-term Follow-up Study Of Multiple Sclerosis Patients Who Participated In Genzyme-sponsored Studies of GZ402668	Recruiting/ 2019	GZ402668/ No comparator	Observational/ n =72	Safety, AE, thyroid function
NCT03161028/ Lipoic Acid for Progressive Multiple Sclerosis (MS)	Recruiting/ 2021	Lipoic acid/ Placebo	Interventional/ n =118	Timed 25-Foot Walk
NCT03737812/ A Study to Assess the Safety and Efficacy of Elezanumab When Added to Standard of Care in Progressive Forms of Multiple Sclerosis	Recruiting/ 2021	Elezanumab/ Placebo	Interventional/ n =18	Overall Response Score
NCT03540485/ Safety and Efficacy of Melatonin in Patients With Multiple Progressive Primary Sclerosis	Not yet recruiting/ 2020	Melatonin	Interventional/ n=50	EDSS, Multiple Sclerosis Functional Composite scale

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