Alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, and teriflunomide for the treatment of adult patients with highly active relapsing remitting multiple sclerosis[1]

EXTRACT

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According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed Form for disclosure of potential conflicts of interest from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A13 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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Patient and family involvement

Patients or family members were consulted during the preparation of the report. Nathalie Beßler, Ulf Blohm, André Kalesse, Elly Seeger and 3 further persons participated in the discussion. Its aim was to obtain information on the following topics: The impact of the condition on life and daily activities and how people cope, treatment preferences including treatment goals, and experiences and concerns about treatment.

IQWiG would like to thank the participants for taking part in the discussion. They were not involved in the actual writing of the report.

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Key statement

Research question

The objective of this investigation is to

- comparatively assess the benefits of the drugs alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, and teriflunomide with each other

in the treatment of adult patients with highly active relapsing-remitting multiple sclerosis despite complete and adequate treatment with at least 1 disease-modifying therapy. The assessment was conducted based on patient-relevant outcomes.

Due to the highly variable clinical courses of multiple sclerosis (MS) as discussed in Section 1 of the report, different treatment strategies are conceivable in the comparison of benefit:

- escalation from basic therapy (e.g. interferons or glatiramer acetate) to high-efficacy therapy (e.g. fingolimod, ocrelizumab)

- deescalation, i.e. treatment pause or switch to a basic therapy in the absence of disease activity or in case of intolerable side effects, planned pregnancy, or advanced age

- switch to another basic or escalation therapy

This results in the following research questions:

Table 1: Research questions of the benefit assessment

Research question	Comparison
1	Escalation therapy versus basic therapy
2	Escalation therapy with the possibility of deescalation vs. basic therapy
3	Escalation therapy versus escalation therapy with the possibility of deescalation
4	Comparison of different drugs within the same treatment strategy

Conclusion

Comparison of the treatment strategies of escalation therapy versus basic therapy (research question 1)

For research question 1, meaningful data are available from only 1 study which compares escalation therapy with alemtuzumab versus interferon-beta 1a. The results for patients who switched from another basic therapy to interferon-beta 1a at the start of the study are decisive for answering the research question. The overall analysis of all outcomes for which

results are available shows superiority of escalation to alemtuzumab versus switching to the basic therapy of IFN-β 1a. On the basis of the available data, no conclusions can be drawn for other escalation therapeutics.

Research questions on escalation therapies with the possibility of deescalation (questions 2 and 3)

No relevant studies were identified for the following research questions of the present benefit assessment:

- Research question 2: escalation therapy with the possibility of deescalation versus basic therapy

- Research question 3: escalation therapy versus escalation therapy with the possibility of deescalation

For these 2 care-relevant research questions, it therefore remains unclear whether there is an advantage for one of the treatment strategies mentioned or, within one of the treatment strategies, for one of the drugs investigated.

Comparison of different drugs within a treatment strategy (research question 4)

Based on the available data, a comparison of different drugs within a treatment strategy was possible only for escalation therapy. Within escalation therapy, study data were available on the drugs alemtuzumab, cladribine, fingolimod, ofatumumab, ozanimod, ponesimod, and teriflunomide. For the drugs dimethyl fumarate and ocrelizumab, the manufacturers submitted no data for the present assessment. No relevant studies were identified for the drug natalizumab.

Direct comparative studies were available for the drugs ofatumumab and ponesimod, each in comparison with teriflunomide. Based on the available data, greater or lesser benefit or harm can be derived only from the direct comparisons of the escalation therapies. For the majority of the other comparisons, data are either completely missing or were not provided by the responsible manufacturers. In some cases, relevant outcomes were not recorded in individual studies, or no advantages or disadvantages were found between the investigated drugs.

For the comparison of ofatumumab versus teriflunomide, there are only indications in favour of ofatumumab, namely in the outcomes of confirmed relapses (annual relapse rate, patients with confirmed relapse), confirmed disability progression, and discontinuation due to adverse events. Altogether, this results in an indication of greater harm from ofatumumab in comparison with teriflunomide.

For the comparison of ponesimod versus teriflunomide, this results in (1) a hint of greater benefit for the outcome of confirmed relapses (annual relapse rate) and (2) a hint of a greater harm from ponesimod for the outcome of discontinuation due to adverse events. However, only a few events occurred overall for the outcome of discontinuation due to adverse events. All things considered, this results in a hint of greater benefit of ponesimod in comparison with teriflunomide.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (Association of the Scientific Medical Societies in Germany)
CNS	central nervous system
EDSS	Extended Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Gd+	gadolinium enhancing
HR	hazard ratio
IFN-β	interferon beta
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAGNIMS	Magnetic Resonance Imaging in Multiple Sclerosis
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
NMA	network metaanalysis
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
PRO	patient-reported outcome
RCT	randomized controlled trial
RR	relative risk
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse events
SPMS	secondary progressive multiple sclerosis
T25FW	Timed 25-Foot Walk test

1 Background

Epidemiology and course of multiple sclerosis

At a prevalence of over 200,000 patients in Germany, multiple sclerosis (MS) is one of the most common neuroinflammatory neurodegenerative disorders [1]. For those affected, MS is often associated with lifelong and far-reaching consequences in daily life because, in addition to causing acute symptoms (e.g. motor disorders, visual disturbances, pain, incontinence), MS can frequently lead to progressive disability and even the need for long-term care [2-4]. Furthermore, "invisible" but burdensome symptoms such as fatigue, depression, or cognitive impairments, which considerably restrict activities of daily life, are common. The disease onset is typically between the ages of 20 and 40 years, although, in recent years, there has been an increasing number of first-time MS diagnoses in people over the age of 40. Women are 2 to 3 times more likely to be affected by MS than men [5].

MS essentially occurs in 3 forms. Alongside primary progressive MS (PPMS), which is rare overall (< 10%) and characterized by disability progression from the onset of disease, relapsing remitting multiple sclerosis (RRMS) affects the vast majority of MS patients [2]. RRMS is characterized by recurrent relapses. These involve episodes with clinical symptoms typical of MS which last for at least 24 hours and are due to focal or multifocal inflammatory demyelinating events in the central nervous system (CNS) which are not caused by an increase in body temperature (Uhthoff phenomenon) or infections [6]. Symptom intensity, time of onset, duration, and type vary from person to person. When a relapse ends, the impairments caused by the relapse often subside. In some cases, however, relapses leave residual effects which may lead to permanent disability or worsening of existing disabilities. In addition, RRMS sometimes leads to disability progression independently from relapse activity [7]. In at least 50% of people with RRMS, the disease eventually progresses to a secondary progressive form of MS (SPMS). Similar to PPMS, this involves steady disability progression during which further relapses may occur [8]. In addition, active and inactive courses are distinguished in both RRMS and the progressive forms, with activity being characterized by the occurrence of relapses and/or lesions on magnetic resonance imaging (MRI) [9].

The symptoms are varied and may include movement disorders (ataxia, tremor, spasticity), bladder and bowel disorders, visual disorders, sexual disorders, and pain, but also neuropsychological symptoms such as fatigue, sleep disorders, cognitive impairment, and depression [2]. In addition to neurological disabilities, fatigue is a particularly common cause of restricted activities of daily living, incapacity for work, and early retirement [10]. Depression, for example, occurs more frequently among people with MS than in the general population, and its pathophysiology is presumed to originate from MS [11,12]. It is primarily these neuropsychiatric and neuropsychological symptoms which reduce psychosocial well-being as well as the functions and activities of patients' everyday and professional lives. In

addition to the common symptom of fatigue, MS patients often mention visual disturbances, cognitive impairments, and motor disorders as being particularly relevant symptoms [13].

The progressive forms of MS and non-highly active RRMS are not discussed further below because, as commissioned, the present benefit assessment covers exclusively highly active RRMS.

Definition of highly active RRMS

No generally recognized definition of highly active RRMS has been established yet. In addition, other different terms, e.g. aggressive and malignant MS, are also vaguely defined, each representing a subset of RRMS [14-16]. The current S2 guideline issued by the German Neurological Society likewise defines highly active RRMS only for treatment-naïve patients [5].

In the approval studies for the drugs investigated herein, the definition of highly active RRMS is essentially based on the relapse rate and/or the number of new lesions found in MRI. The patient populations in these studies are often not limited to the highly active form of MS (e.g. natalizumab, cladribine, alemtuzumab). In some cases, however, the authorities have restricted the marketing authorization due to safety concerns and/or reduced effectiveness in patients without active disease. The use of these medicinal products was therefore restricted to patients with (highly) active disease. However, the definition of activity in clinical trials varies [17]. As a rule, it involves at least 1 or 2 relapses in the previous year plus several T2 lesions and/or at least 1 gadolinium-enhancing (Gd+) T1 lesion despite appropriate disease-modifying therapy. Other definitions of high disease activity are based on disability progression or the degree of disability at diagnosis, usually determined using the Extended Disability Status Scale (EDSS) [14,16]. Where a restriction to highly active RRMS exists, the SPCs of the individual drugs do not explicitly define the therapeutic indication [18-28].

For the present assessment, a definition of disease activity based on patient-relevant characteristics is preferred [29]. The occurrence of relapses is one such characteristic. The literature contains examples of high disease activity being characterized solely on the basis of relapse rates [30-32]. Spelman 2020 has shown that a definition of high activity based on relapse rates exhibits a higher association with disability progression than an MRI-based definition [31].

Several studies demonstrate that under treatment with beta-interferons or glatiramer acetate, the formation of several new T2 lesions (≥ 3) is prognostic for an unfavourable course of disease [33-35]. To assess disease activity, MRI activity is therefore taken into account alongside the occurrence of relapses. New lesions are about 5 to 10 times more common than clinically apparent relapses [36]. However, the detection of newly occurring lesions is subject to relevant uncertainties, as the informative value of MRI diagnostics depends, among other things, on the protocol used, the standardization of the MRI sequences in follow-up

examinations, and the handling of contrast agents as well as whether all affected CNS regions are shown in the imaging [33]. Gd+ lesions can be visualised only for a short period of time (as a rule, a lesion accumulates gadolinium for a maximum of 4 to 6 weeks [37]) and are therefore not sufficiently sensitive to assess the inflammatory process over a longer period of time. MRI scans using gadolinium as a contrast agent may be associated with a higher risk for patients than scans without additional contrast agent [38,39]. It appears to be unclear to what extent a short-term worsening of the EDSS score under therapy is predictive of long-term, irreversible disability progression; at least it is discussed but used inconsistently for scoring systems such as the modified Rio or the Magnetic Resonance Imaging in MS (MAGNIMS) [40,41].

Despite the described uncertainties, in the presence of very high MRI activity, it can be assumed that at least hidden clinical symptoms have developed but may not have been documented or diagnosed. For studies with enrolled patients in whom relapse events were not recorded during prior therapy, the comparability of the investigated populations must be ensured. To this end, MRI acquisition must be reported adequately and in a comparable manner, i.e. performed according to recognized standards and protocols [33,42]. Within the same study, all MRI scans must have been performed longitudinally with the same sequences and sequence parameters and on scanners of the same field strength to ensure intra-individual comparability of the scans in individual patients. Under these conditions, defining highly active disease based exclusively on high MRI activity is also conceivable.

There is currently no generally recognized definition based solely on MRI activity which is suitable for defining highly active disease. A threshold of 9 T2 lesions was investigated more closely as part of the marketing authorization procedure for natalizumab [43]. In addition, the SPCs of other drugs include the presence of ≥ 9 T2 lesions in their definition of highly active disease [20,22]. This threshold can therefore serve as a guideline for a purely MRI-based definition of highly active RRMS for the purpose of the benefit assessment. In the benefit assessment, no distinction is made between T1-Gd+ and T2 lesions (as in combined unique active lesions), and only new or enlarged lesions are taken into account. The current MAGNIMS recommendations [44], deem the inclusion of T1-Gd+ lesions to determine disease activity to be optional. Furthermore, the use of gadolinium as a contrast agent is recommended only under certain conditions, e.g. if the detection of T2 lesions alone is insufficient.

In summary, various definitions of highly active RRMS based on the occurrence of relapses and/or MRI activity are taken into account in the present assessment. Applicable definitions include either only clinical, only MRI-based, or combined definitions:

- Based exclusively on clinical parameters, the disease can be assumed to be highly active if ≥ 1 relapse has occurred in the past 12 months or ≥ 2 relapses in the past 24 months, each associated with significant functional impairment (e.g. deterioration of visual

acuity, deterioration of individual EDSS components). Due to the clinical relevance of the relapse, additional imaging is not necessary.

- Where relapses do not lead to marked functional impairment, the development of new or enlarged lesions may be used as a supporting criterion. The occurrence of ≥ 1 relapse in the past 12 months and additionally ≥ 3 new or enlarged T2 lesions or ≥ 1 new T1 Gd+ lesion in a follow-up MRI may serve as an approximate guideline.
- A purely MRI-based definition without regard to clinical manifestations may be based on a benchmark of ≥ 9 new or enlarged lesions within the past 12 months.

In all definitions, disease activity should always be assessed via the occurrence of relapses or MRI activity but not until full effectiveness of sufficient and appropriate prior therapy has been reached. Complete and appropriate prior treatment is defined as a disease-modifying therapy under full effectiveness of the respective drug. The latency periods of the administered drugs must be taken into account. Interferon beta, glatiramer acetate, teriflunomide, and dimethyl fumarate are particularly suitable prior therapies. Interferon beta, teriflunomide, and dimethyl fumarate reach their full effectiveness after approximately 3 months of continuous therapy, while glatiramer acetate reaches it after approximately 6 months [33,45]. Provided that the drugs have been administered at a sufficient and stable dosage, this results in a therapy duration of approximately 3 to 6 months for complete and appropriate prior therapy. Relapse events or newly occurring lesions which fall within this latency period are of limited value for the evaluation of effectiveness, and the assessment of relapse activity and MRI-detected changes should therefore be based on the period after full effectiveness has been achieved. For the assessment of MRI activity, it is therefore necessary to re-record the lesion status after full effectiveness has been achieved (re-baselining) [44]. Highly active RRMS is then diagnosed after immunomodulatory therapy has been completed.

The above-described definitions of highly active RRMS must be generally distinguished from merely active disease in the absence of a response to appropriate and sufficient prior therapy. Active disease may already be present when 1 new T2 or T1 Gd+ lesion develops or when a relapse occurs within a certain period of time [46].

Highly active RRMS is a separate entity from SPMS, which may occur with or without superimposed relapses. It is difficult to make an exact distinction between them because there are no clear boundaries and no validated biomarkers exist. The diagnosis of SPMS is mainly based on the duration of disease. Therefore, it can be reliably diagnosed only retrospectively on the basis of the clinical course [9]. Forms of SPMS with superimposed relapses were previously categorised as relapsing forms of multiple sclerosis (RMS) because it was assumed that the increase in disability may be linked to incompletely remitted relapses [47]. However, it has recently been shown that even in patients with RRMS, a marked proportion of disability

progression can occur independently of relapse events (known as progression independent of relapse activity [PIRA]) [7,48].

Goals of treatment

MS treatment essentially comprises therapy of acute relapses, treatment of disease symptoms, and modification of the course of the disease, i.e. disability progression and relapse rate. Glucocorticoids, especially methylprednisolone, are generally used for relapse therapy to alleviate symptoms and shorten relapse duration. In parallel, permanent disease-modifying or progression-modifying therapy is implemented independently of relapses with the aim of reducing the frequency of relapses and preventing or delaying disability progression. Immunomodulatory agents are used for this purpose [2,49-51].

Since the 1990s, interferon beta-1a and -1b and glatiramer acetate have been used as immunomodulatory therapies [52]. With the approval of alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, and teriflunomide in 2005, further immunomodulatory agents have become available. These drugs are not the subject of the present assessment.

MS was originally treated using an incremental strategy which differentiated between basic therapies and escalation therapies used in the event of insufficient response or severe courses of disease [53]. The basic therapeutic agents included beta-interferons and glatiramer acetate in particular, but also teriflunomide and dimethyl fumarate. The current S2 guideline issued by the Association of the Scientific Medical Societies in Germany (AWMF) now places the available drugs into effectiveness categories. For disease courses which are not highly active, it recommends beta-interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide, among others, which are now in effectiveness category 1 [5]. In addition to beta interferons and glatiramer acetate, the Disease-Oriented Competence Network Multiple Sclerosis (KKNMS) recommends the use of dimethyl fumarate and teriflunomide for mild and moderate courses, although both are also suitable for highly active MS or as escalation therapy [20,26,53]. According to the incremental therapy strategy, the new drugs investigated here are hence predominantly escalation therapies, which are used when prior treatment has failed and the disease is persistently (highly) active. Their authorizations are not identical and cover the therapeutic indication in question either in full or in part.

The present assessment compares the drugs alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, and teriflunomide. The current guideline categorizes these drugs, which the incremental therapy strategy predominantly classified as escalation therapies, into 3 effectiveness categories, with the drugs of the different categories being recommended in different therapeutic scenarios [5]. The concept of basic and escalation therapy has largely been replaced by an "early

intensive" treatment strategy. This is due to the fact that in recent years, the primary use of highly active substances has been increasingly discussed as the standard of treatment for all patients in the early stages of disease (induction therapy, hit hard and early) [5]. As per current guideline, this idea is based on several large cohort studies from recent years, which are, however, the subject of debate, particularly due to their retrospective (non-randomized) design [5]. Two large prospective randomized studies (DELIVER-MS [54], TREAT-MS [55]) are currently ongoing to investigate the different approaches.

Since at the time the commission for the present assessment was received (16 July 2020), treatment was typically categorized into basic and escalation therapy as per the incremental therapy strategy, these categories were chosen for the research questions in the report. The drugs alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, and teriflunomide are deemed escalation therapies. For the present assessment, other drugs such as beta-interferons or glatiramer acetate serve only as common comparators in indirect comparisons or networks. Although switching within the basic therapeutic agents of effectiveness category 1 (e.g. from dimethyl fumarate to teriflunomide) is no longer recommended by the current AWMF guideline [5], it may be a treatment option depending on the individual course of the disease and patient preference and is covered by the authorizations of the respective drugs. Irrespective of whether such a switch is common in clinical practice, its potential advantages or disadvantages for patients remain unclear and are therefore analysed in this assessment.

Requirements for studies in the therapeutic indication of RRMS

In recent years, the need for individualized MS therapy has been increasingly discussed [5,56,57]. Alongside relapse reduction, the severity of relapses, disability progression, side effects, and patient-reported outcomes regarding MS symptoms and health-related quality of life should be taken into account because these factors may also independently influence treatment decisions [45].

Treatment decisions to be made by patients and treating physicians depend on a variety of factors which include the effectiveness and safety of individual drugs as well as the patient's life circumstances and personal preferences [57]. Studies on patient preferences have also shown that it is by no means only the reduction in relapse rate and disability progression which are important for those affected, but also side effects, symptoms of disease, and health-related quality of life [58-62].

The spectrum of clinical studies should reflect the aforementioned requirements in order to allow drawing patient-relevant conclusions for routine care. Different treatment strategies must be taken into account [63]. Randomized controlled trials (RCTs) which compare escalation therapy (e.g. fingolimod, ocrelizumab) versus basic therapy (e.g. interferon,

glatiramer acetate) with a fixed treatment regimen do not meet this requirement on their own [64]. Instead, the relapse rate, severity of relapses, general symptoms, health-related quality of life, and side effects should be used to assess whether long-term escalation therapy is appropriate for individual patients. In the absence of disease activity, the current AWMF guideline on MS likewise recommends, for various drugs, to consider a treatment pause, suspend therapy, and inform patients about the benefits and risks of various strategies (continuation, suspension, de-escalation) [5]. This results in the need for study designs which enable the comparison not only of individual drugs, but also of entire treatment strategies (see Section 2).

Patient-reported outcomes (PROs) are of particular importance in the benefit assessment due to the variety of symptoms and their impact on patients' daily lives. Health-related quality of life and symptom burden must be analysed together in order to draw conclusions about the benefits of MS therapies. The severity of relapses in terms of (permanent) functional impairment, which is not depicted by simply surveying the relapse rate, is additionally relevant.

As RRMS is a lifelong disease which sometimes leads to significant disability only after years, observations for several years are necessary. This particularly applies to the survey of the progression of disability. Although "confirmed" progression is often detected after 12 to 24 weeks, very short observation periods can lead to an overestimation of the treatment effect because relapse-related and progression-related increases in disability cannot be reliably differentiated [5,65].

A network metaanalysis (NMA) which includes all 10 commissioned drugs for highly active RRMS does not yet exist. Previous publications cover only parts of the drug spectrum or do not investigate highly active RRMS [66-71].

2 Research question

The objective of this investigation is to

- comparatively assess the benefits of the drugs alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, and teriflunomide with each other

in the treatment of adult patients with highly active relapsing-remitting multiple sclerosis despite complete and adequate treatment with at least 1 disease-modifying therapy. The assessment was conducted based on patient-relevant outcomes.

Due to the highly variable clinical courses of MS as discussed in Section 1, different treatment strategies are conceivable in the comparison of benefit:

- escalation from basic therapy (e.g. interferons or glatiramer acetate) to high-efficacy therapy (e.g. fingolimod, ocrelizumab)
- deescalation, i.e. treatment pause or switch to a basic therapy in the absence of disease activity or in case of intolerable side effects, planned pregnancy, or advanced age
- switch to another basic or escalation therapy

This results in the following research questions:

Table 2: Research questions of the benefit assessment

Research question	**Comparison**
1	Escalation therapy versus basic therapy
2	Escalation therapy with the possibility of deescalation vs. basic therapy
3	Escalation therapy versus escalation therapy with the possibility of deescalation
4	Comparison of different drugs within the same treatment strategy

3 Methods

The target population of the benefit assessment consisted of adult patients with highly active RRMS who had received complete and adequate prior treatment with at least 1 disease-modifying therapy.

Highly active RRMS was defined as follows:

1) Exclusively clinically: severe relapses with substantial functional impairment, irrespective of lesions
2) Clinically in conjunction with MRI activity: relapses without substantial functional impairment in conjunction with the development of new or enlarged lesions
3) Exclusively MRI-based: based on the development of numerous new or enlarged lesions

despite complete and appropriate prior treatment. For a more detailed specification of the possible definitions, see Chapter 1.

Alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, or teriflunomide were to be compared with each other in the treatment of this patient group and were therefore deemed both investigational and comparator interventions. In order to allow an indirect comparison of the drugs within a joint analysis, the benefit assessment includes not only studies which directly compare 2 of the identified drugs with each other, but also studies which compare at least 1 of these drugs versus 1 possible common comparator.

The following patient-relevant outcomes were taken into account in the assessment:

- All-cause mortality
- Confirmed relapses
  - annualized relapse rate
  - patients with confirmed relapse
- Disability
  - confirmed disability progression (confirmed after at least 24 weeks) using the EDSS[2]
  - disability severity (Multiple Sclerosis Functional Composite [MSFC])
  - walking ability, e.g. via the 6-minute walk test

[2] Results for the EDSS should be supplemented with data from other instruments such as the MSFC to obtain a complete picture of disability progression.

- Fatigue
- Vision disorders
- Health-related quality of life
- Overall rate of serious adverse events (SAEs)
- Overall rate of discontinuations due to adverse events (AEs)
- Progressive multifocal leukoencephalopathy (PML)
- Serious infections
- Serious neoplasms
- Serious secondary autoimmune diseases

Subjective outcomes (e.g. HrQoL) were taken into account only if they had been recorded using valid measurement instruments (e.g. validated scales).

The benefit assessment was to include only RCTs and routine practice randomised trials from registries. In addition, at least part of the study population had to be observed for at least 24 months.

The information retrieval is largely based on manufacturer queries on the drugs alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, and teriflunomide. Searches in study registers and a focussed search in MEDLINE were used to check the information provided by the manufacturers for completeness and to identify relevant studies conducted by third parties. In addition, the website of the Federal Joint Committee (G-BA) and the Institute for Quality and Efficiency in Health Care (IQWiG) as well as documents provided as comments to the report plan and the preliminary report were taken into account as sources of information. Where necessary, direct enquiries were also made with study authors.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, outcome-specific and study-level criteria for the risk of bias were assessed, and the risk of bias was rated as high or low in each case. For studies whose control intervention was included only as a common comparator in a network metaanalysis (NMA), the risk of bias at outcome level was assessed only if a comparison of at least 2 of the drugs to be assessed was possible for the outcome when taking the study into account. The results of the individual studies were described, organized by outcomes.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were to be conducted and effect modifiers investigated, provided that the methodological prerequisites had been met. For each outcome, a conclusion was to be drawn regarding the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was to be the case if no data were available, or the available data did not allow any of the other 3 conclusions to be drawn. In that case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was to be drawn.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

In order to be able to compare the experimental interventions within a joint analysis, NMAs were carried out where possible. This also enabled comparisons to be made for which no direct comparative evidence was available. Where conducting an NMA was impossible, the analysis is based exclusively, if available, on direct comparisons of 2 of the aforementioned experimental interventions or pairwise adjusted indirect comparisons according to Bucher. Sufficient structural quality is a prerequisite for conducting and interpreting an NMA or indirect comparisons. This quality is present if the assumption of similarity, homogeneity, and consistency was either met or not obviously violated in each case.

If individual aspects of structural quality cannot be assessed, the certainty of the results of an indirect comparison is low at best. Furthermore, where an indirect comparison is conducted based on only 1 study for at least 1 of the 2 compared drugs, no hint can be derived if this 1 study is subject to a high risk of bias.

4 Results

4.1 Results of the information retrieval

Initially, potentially relevant studies which meet the inclusion criteria of the present assessment were identified for the information retrieval. These studies comprise potentially, but not exclusively, a subpopulation relevant for the present assessment as per G-BA commission (patients with highly active RRMS despite complete and adequate treatment with at least 1 disease-modifying therapy). Studies with a relevant subpopulation were therefore subsequently identified via a data request on additional analyses. Furthermore, not all potentially relevant studies contained a direct comparison of drugs to be assessed or a suitable common comparator, i.e. not all potentially relevant studies were suitable for inclusion in the analyses.

The information retrieval revealed a total of 29 RCTs potentially relevant for the present benefit assessment, including 22 main studies and 7 associated extension studies. In addition, 11 RCTs without reported results were identified. These are exclusively studies that had not yet been completed at the time of the last search. Moreover, the majority of these studies (6 out of 11) investigated new drugs exclusively in comparison with teriflunomide and consequently contained neither a direct comparison of drugs as commissioned by the G-BA nor a suitable common comparator.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search in study registries and bibliographic databases was conducted on 2 November 2021. In addition, studies without reported results were reviewed to determine whether there were any changes in the registry entry or whether results are now available. The review was conducted on 22 July 2023.

The potentially relevant studies investigate the drugs alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, and teriflunomide. Pharmaceutical companies sponsored 27 of 29 potentially relevant studies.

Of the 29 potentially relevant studies, 15 were excluded from the assessment because their respective control intervention was not a suitable common comparator, and they did not implement a direct comparison of drugs investigated in this assessment. These 15 studies, which also include the 7 extension studies, were therefore disregarded in the further steps of the assessment.

The remaining 14 relevant studies each investigated the drugs of the present assessment (except natalizumab) as escalation therapy in comparison with each other (3 studies) or in comparison with placebo (7 studies) or interferon beta (IFN-β) 1a (4 studies). These studies are therefore relevant for research question 4 comparing the different drugs within escalation

therapy, with placebo and IFN-β 1a representing suitable common comparators within the study pool for research question 4. The studies using IFN-β 1a as a comparator intervention are furthermore relevant for investigations comparing the treatment strategies of escalation therapy versus basic therapy under research question 1.

The 3 studies with a direct comparison of drugs as per G-BA commission versus teriflunomide can be taken into account both for the comparison of drugs within escalation therapy (research question 4) and for the comparison of the treatment strategies escalation therapy versus basic therapy (research question 1). In the present assessment, these studies are used to answer research question 4 because in line with its authorization, teriflunomide is viewed as an escalation therapy for the population as commissioned by the G-BA.

No relevant studies are available for the drug natalizumab because the only potentially relevant study on this drug had no suitable common comparator. The approval studies for this drug, AFFIRM and SENTINEL, are irrelevant because they deviate from the inclusion criteria of the present assessment with regard to either the investigated population or the intervention. The AFFIRM study is irrelevant for the present assessment because it included only patients who were either treatment-naïve or had been untreated for at least 6 to 12 months prior to enrolment [72]. Consequently, this study does not include a subpopulation of patients with highly active disease despite complete and appropriate prior treatment. The SENTINEL study investigated only treatment with natalizumab in combination with IFN-β 1a [73]. However, natalizumab is explicitly not approved in combination with IFN-β 1a [18,19].

No relevant studies were identified for research questions 2 and 3, which investigate escalation therapy with the possibility of deescalation in comparison with basic therapy (research question 2) or escalation therapy without the possibility of deescalation (research question 3).

Since for research question 1, in contrast to research question 4, only a small proportion of the included studies are relevant, research question 4 on the comparison of different drugs within escalation therapy is discussed first, followed by research question 1 on the comparison of the treatment strategies of escalation therapy versus basic therapy.

All 14 relevant studies were conducted as part of the authorization procedure for the respective drugs and were identified accordingly via manufacturer enquiries. No relevant investigator-initiated studies were identified for the present assessment.

Table 3: Overview of studies potentially relevant for the benefit assessment from all search steps (multipage table)

Drug Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Other documents**
Alemtuzumab				
CARE-MS II	Yes [74-78]	Yes [79,80] / yes [79,80]	Yes [81]	No
Cladribine				
CLARITY	Yes [82-95]	Yes [96,97] / yes [96,97]	Yes [98]	Yes [99]
Dimethyl fumarate				
CONFIRM	Yes [100-105]	Yes [106-108] / yes [106,107]	Yes [109]	Yes [110]
DEFINE	Yes [104,105,111-115]	Yes [116-119] / yes [116,117]	Yes [120]	Yes [110]
Extension study for CONFIRM and DEFINE: ENDORSE[a]	Yes [121-123]	Yes [124-126] / yes [124,125]	Yes [127]	Yes [110]
RIFUND-MS[a]	No[b]	Yes [128,129] / no	No	No
Fingolimod				
CFTY720D1201[a]	No	Yes [130] / yes [130]	Yes [131]	Yes [132,133]
Extension study: CFTY720D1201E1[a]	No	Yes [134] / yes [134]	Yes [135]	Yes [132,133]
FREEDOMS	Yes [105,136-148]	Yes [149,150] / yes [149,150]	Yes [151]	Yes [132,133]
Extension study: CFTY720D2301E1[a]	Yes [147,152]	Yes [153] / yes [153]	Yes [154]	Yes [132,133]
FREEDOMS II	Yes [144,145,148,155,156]	Yes [157,158] / yes [157,158]	Yes [159]	Yes [132,133]
Extension study: CFTY720D2309E1[a]	No	Yes [157] / yes [157]	Yes [160]	Yes [132,133]
TRANSFORMS[a]	Yes [145,146,161-167]	Yes [168,169] / yes [168,169]	Yes [170]	Yes [132,133]
Extension study: CFTY720D2302E1[a]	Yes [166,171-173]	Yes [168,169] / yes [168,169]	Yes [174]	Yes [132,133]
Natalizumab				
IQUALYSEP[a]	No	Yes [175] / no	No	No
Ocrelizumab				
OPERA I	Yes [7,176-180]	Yes [181-184] / yes [183,184]	Yes [185]	Yes [186]
OPERA II	Yes [7,176-180,187]	Yes [188,189] / yes [188,189]	Yes [190]	Yes [186]

Table 3: Overview of studies potentially relevant for the benefit assessment from all search steps (multipage table)

Drug Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Other documents**
Ocrelizumab				
WA21493[a]	No	Yes [191,192] / yes [191,192]	Yes [193]	Yes [186]
Ofatumumab				
ASCLEPIOS I	Yes [194]	Yes [195-197] / yes [195,196]	Yes [198]	No
ASCLEPIOS II	Yes [194]	Yes [199-202] / yes [199,200]	Yes [203]	No
Ozanimod				
RADIANCE B	Yes [204,205]	Yes [206,207] / yes [206,207]	Yes [208]	Yes [209]
Ponesimod				
OPTIMUM	Yes [210]	Yes [211,212] / yes [211,212]	Yes [213]	Yes [214]

Table 3: Overview of studies potentially relevant for the benefit assessment from all search steps (multipage table)

Drug Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Other documents**
Teriflunomide				
HMR1726D/2001[a]	Yes [215]	Yes [216] / no	Yes [217]	Yes [218]
Extension study: LTS6048[a]	Yes [215]	Yes [219] / no	Yes [220]	Yes [218]
TEMSO	Yes [221-225]	Yes [226,227] / yes [226,227]	Yes [228]	Yes [218]
Extension study: LTS6050[a]	Yes [229]	Yes [230] / yes [230]	Yes [231]	Yes [218]
TOWER	Yes [105,232-235]	Yes [236-238] / yes [236,237]	Yes [239]	Yes [218]
ULTIMATE 1[a]	No[c]	Yes [240,241] / yes [240,241]	No	No
ULTIMATE 2[a]	No[c]	Yes [242,243] / yes [242,243]	No	No

a. These studies are disregarded from the benefit assessment because they do not include a direct comparison of the drugs to be assessed, and the respective control intervention of these studies does not represent a suitable common comparator. (No other study analyses a sufficiently similar comparator intervention.)
b. After the last search in bibliographic databases, a full paper [244] was published on the RIFUND-MS study identified via the search in study registers. As there is neither a direct comparison of the drugs to be assessed nor a suitable common comparator, no author enquiry was made for this study.
c. After the last search in bibliographic databases, a full paper [245] was published on the ULTIMATE 1 and ULTIMATE 2 studies identified via the search in study registers. As there is neither a direct comparison of the drugs to be assessed nor a suitable common comparator, no manufacturer enquiries were made for these studies.

Additional analyses of relevant subpopulations

The populations of the 14 relevant studies were not limited to the population of the present assessment as commissioned by the G-BA. Additional analyses for the relevant subpopulations were therefore requested from the manufacturers. The manufacturers provided them for the majority of the 14 relevant studies. However, no additional analyses were submitted by the manufacturers for the relevant studies on dimethyl fumarate and ocrelizumab (2 studies each). Due to these reporting gaps, it is impossible to include these studies in the analyses for the present assessment. In total, results from 10 studies on 7 drugs are therefore available for the present assessment.

4.2 Comparison of different drugs within a treatment strategy (research question 4)

4.2.1 Characteristics of the studies included in the assessment

Based on the available data, a comparison of different drugs within a treatment strategy was possible only for escalation therapy. In the context of this research question, therefore, different drugs are compared only within escalation therapy.

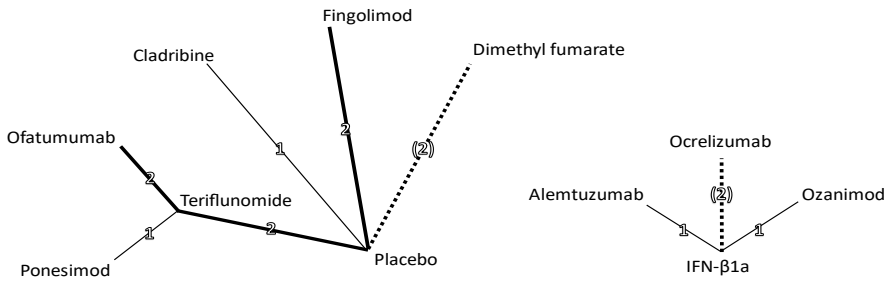
The 14 studies listed in the following table are relevant for the comparison of different drugs within escalation therapy, with no additional analyses of the relevant subpopulation having been submitted by the manufacturers for 4 studies on dimethyl fumarate and ocrelizumab.

Table 4: Study pool comparing different drugs within escalation therapy (research question 4)

Comparison **Drugs**[a]	**Study (study start)**	**Transmission of additional analyses**	**Primary publication**
Studies with IFN-β 1a in the comparator arm			
Alemtuzumab vs. IFN-β 1a	CARE-MS II (2007)	Yes	[77]
Ocrelizumab vs. IFN-β 1a	OPERA I (2011)	No	[177]
Ocrelizumab vs. IFN-β 1a	OPERA II (2011)	No	[177]
Ozanimod vs. IFN-β1a	RADIANCE B (2013)	Yes	[204]
Placebo-controlled studies			
Cladribine vs. placebo	CLARITY (2005)	Yes	[87]
Dimethyl fumarate vs. placebo	CONFIRM (2007)	No	[100]
Dimethyl fumarate vs. placebo	DEFINE (2007)	No	[114]
Fingolimod vs. placebo	FREEDOMS (2006)	Yes	[138]
Fingolimod vs. placebo	FREEDOMS II (2006)	Yes	[155]
Teriflunomide vs. placebo	TEMSO (2004)	Yes	[222]
Teriflunomide vs. placebo	TOWER (2008)	Yes	[234]
Direct comparisons			
Ofatumumab vs. teriflunomide	ASCLEPIOS I (2016)	Yes	[194]
Ofatumumab vs. teriflunomide	ASCLEPIOS II (2016)	Yes	[194]
Ponesimod vs. teriflunomide	OPTIMUM (2015)	Yes	[210]

a. No studies relevant for the benefit assessment were identified for natalizumab.
IFN: interferon; vs: versus

Based on this study pool, the comparisons shown in Figure 1 would be possible if the requirements for a joint analysis of all studies were met and data on an outcome were available from all studies. To illustrate the reporting gaps, the studies for which the manufacturers did not provide any analyses for the present assessment's relevant subpopulation are shown as well.



Dotted lines show comparisons for which no data were provided by the manufacturer. Numbers in parentheses indicate the number of relevant studies for these comparisons.
IFN: interferon

Figure 1: Possible comparisons taking into account all relevant studies

In the present study pool, it is possible to conduct an NMA taking into account the direct comparative and placebo-controlled studies as well as an indirect comparison on the studies with IFN-β 1a in the comparator arm. Even when taking into account the studies for which no analyses were submitted for the relevant subpopulations, a joint NMA considering all escalation therapies would be impossible on the basis of the available comparisons. This is due to the fact that (a) no multi-arm studies were identified which conducted comparisons with both placebo and IFN-β 1a, and (b) only a few direct comparisons of escalation therapies are available.

Study design and study populations

The included studies comparing different drugs within escalation therapy were reviewed for similarity. This resulted in a sufficiently similar study pool, taking into account all 10 studies for which analyses of the relevant subpopulation were submitted as commissioned by the G-BA. A central aspect of the review was the definition of the relevant subpopulation, i.e. which criteria were to be met by patients with highly active RRMS who had received complete and appropriate prior treatment with at least 1 disease-modifying therapy. The definitions used by the manufacturers for high disease activity or complete and appropriate prior treatment only in part corresponded to the criteria specified in the data request. This is mainly due to the fact that the studies provide neither information on functional impairment due to relapses nor information on lesion status over the course of disease. In addition, some of the studies disallowed prior therapies for a certain period of time prior to study inclusion.

Definition of the relevant subpopulation

For the majority of the studies, the manufacturers provided analyses of patients in whom highly active disease was defined by a combination of clinical criteria and the presence of Gd+ lesions at baseline. Some of them also included patients for whom a purely clinical definition was applied without taking into account functional impairment caused by relapses. In addition to using the combined definition, one of the manufacturers also included patients who had only a high number of Gd+ lesions at baseline.

Most manufacturers included patients with prior therapies which ended within 12 months prior to the start of the study. This is partly due to the fact that in some studies, patients were not allowed treatment with beta-interferon or glatiramer acetate for 3 to 4 months before the start of the study. Only for the OPTIMUM study's subpopulation were patients included who had been treated continuously for at least 2 months prior to study inclusion. However, the proportion of patients with longer treatment-free intervals before study start is presumably not high enough to limit the analyses' certainty of results. According to the manufacturers, it was ensured for all relevant subpopulations that highly active disease was detected after complete and appropriate prior treatment, taking into account the drug-specific latency period.

Overall, the subpopulations submitted represent a sufficient approximation of the target population for this assessment. They are also deemed sufficiently similar for conducting a joint analysis.

Study design and characteristics of the relevant subpopulations

In 3 of the 10 relevant studies for which data on the relevant subpopulation were submitted, direct comparisons between escalation therapies were conducted (ofatumumab versus teriflunomide or ponesimod versus teriflunomide). The other studies investigated the comparison of drugs in the present assessment versus the common comparators of placebo (5 studies) and IFN-β 1a (2 studies). According to the study protocols, the included studies' treatment durations were predominantly around 2 years.

In the relevant subpopulations, the mean patient age was between 32 and 42 years. In most subpopulations, 65% to 75% of participants were female. The majority of patients (mostly over 70%) came from OECD countries.

According to the criteria from the data request, all patients in the relevant subpopulations had received prior treatment. In the majority of studies, prior treatment involved predominantly IFN-β 1a, IFN-β 1b, and/or glatiramer acetate. The proportions of the various drugs fluctuate. In addition, some studies exhibit differences between study arms due to the small size of the subpopulations. However, these are not deemed essential for the interpretability of results. In addition, the differences do not violate the assumption of similarity. For 1 study comparing

ponesimod directly with teriflunomide (OPTIMUM), no information was provided on prior treatment.

With regard to disease-specific characteristics at baseline, the analysed subpopulations are largely comparable. Although the mean time since the first diagnosis of MS varies from around 4 to just over 9 years, this does not per se indicate anything about the current state of the disease. Based on the criterion of highly active disease despite prior therapy, the subpopulations are presumably comparable in terms of current disease status, regardless of the duration of the disease. The mean EDSS scores at baseline in all studies were around 2.5 to 3 out of a maximum of 10 possible points, with higher scores indicating greater severity of disability. Most patients therefore had at most moderate disability. Relapse activity was very uniform across all subpopulations, with a median of 1 relapse in the last year before study inclusion and a median of 2 relapses within the last 2 years. Not all studies supply information on lesion occurrence. The median number of Gd+ lesions at baseline for the studies with available data was 0 to 2 at baseline, in some cases with large ranges within the individual populations. This is likely due to (a) different definitions used by the manufacturers to form the subpopulations, and (b) the heterogeneity of disease progression.

Overall, despite individual missing data or observed differences, the relevant subpopulations are presumably sufficiently similar since the submission of the additional analyses by the manufacturers suggests that all patients have highly active disease despite complete and appropriate prior treatment with at least 1 disease-modifying therapy. The review of the similarity assumption did not identify any differences between the relevant subpopulations which lead to the exclusion of individual studies from the analysis or call into question the interpretability of the results.

4.2.2 Overview of patient-relevant outcomes

In principle, data on patient-relevant outcomes were available from 10 studies on 7 drugs for the relevant subpopulation of the present assessment. Table 5 shows an overview of the patient-relevant outcomes for which data on the respective drugs are included in the analyses.

Data on all-cause mortality were reported for all 7 drugs but were not used for comparisons between escalation therapies because only very few events occurred in the studies. Data on confirmed relapses (annual relapse rate and patients with confirmed relapse) are available for all 7 drugs. Data on confirmed disability progression based on EDSS were also reported for all 7 drugs, but 1 drug (cladribine) was impossible to include in the analyses because the available data did not allow calculating a hazard ratio (HR) (no events in the intervention arm and few events in the placebo arm). Calculating the NMA using relative risk (RR) as an approximation would be subject to additional uncertainty in this data scenario. Results on the severity of disability based on the MSFC from placebo-controlled studies were not included in the

analyses because analyses of placebo-controlled studies were submitted for only 1 drug (fingolimod). Thus, placebo was not a suitable common comparator for this outcome. The same applies to the walking ability outcome using the timed 25-foot walk test (T25FW), one of the components of the MSFC.

Data on the outcome of visual disturbances were provided only for isolated comparisons, leaving no suitable common comparator for a comparison of escalation therapies. No usable data on the outcome of fatigue were available for any drug because either no analyses were submitted for the relevant subpopulation or the analyses submitted were unusable. For the outcome of health-related quality of life, usable data were available for only 1 direct comparison because for other comparisons, either (a) no analyses were submitted for the relevant subpopulation, (b) the submitted analyses were unusable, or (c) no comparable analyses were available.

For the outcomes of SAEs and discontinuations due to AEs, data were reported on all 7 drugs. Due to a lack of events in the studies, no adjusted indirect comparison of alemtuzumab versus ozanimod were possible for the outcome of SAEs. For the outcome of discontinuation due to AEs, studies on the 2 drugs alemtuzumab and cladribine were disregarded for comparability reasons because in contrast to the other drugs in studies comparing them with IFN-β 1a or placebo, these are so-called interval therapies which are administered only during short treatment phases at intervals of approximately 1 year. Due to substantial heterogeneity for the comparison of teriflunomide versus placebo and very imprecise estimates in the NMAs, it was likewise impossible to draw any conclusions regarding this outcome on the basis of the available data for drugs for which only placebo-controlled studies are available. Overall, therefore, only the direct comparisons were usable for analysing this outcome.

For specific AEs (PML, serious infections, serious neoplasms, serious secondary autoimmune diseases), only sporadic data were submitted, or no events occurred, so that comparisons between the escalation therapies for these outcomes were possible only in isolated cases.

Table 5: Matrix of patient-relevant outcomes available for comparisons per drug (multipage table)

Comparisons / Drug	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability[a]	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Comparisons with IFN-β 1a															
Alemtuzumab	(●)	●	●	●	●	●	x	–	(●)	(●)	(●)[b]	x	x	x	x
Ocrelizumab	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ozanimod	(●)	●	●	●	●	●	(●)	–	(●)	(●)	(●)	(●)	(●)	(●)	–
Comparisons with placebo															
Cladribine	(●)	●	●	(●)	–	–	–	–	x	●	(●)[b]	(●)	(●)	(●)	(●)
Dimethyl fumarate	x	x	x	x	x	x	x	–	x	x	x	x	x	x	x
Fingolimod	(●)	●	●	●	(●)	(●)	(●)	–	x	●	(●)[c]	(●)	x	x	x
Teriflunomide	(●)	●	●	●	x	x	–	○	○	●	(●)[c]	x	x	x	x
Direct comparisons															
Ofatumumab vs. teriflunomide	(●)	●	●	●	●	●	–	–	–	●	●	●	x	x	x
Ponesimod vs. teriflunomide	(●)	●	●	●	●	●	–	○	●	●	●	●	●	●	x

Table 5: Matrix of patient-relevant outcomes available for comparisons per drug (multipage table)

Comparisons / Drug	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability[a]	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Natalizumab	No studies relevant for the benefit assessment were identified.														

●: Data were sent and are usable.
(●): Data were submitted and are generally usable but cannot be taken into account in the analyses of the present assessment because (a) no comparison of 2 drugs is possible, (b) the homogeneity assumption has been violated, or (c) only few events in 1 arm or no events at all on the outcome were present.
○: Data were submitted but are unusable for the benefit assessment.
x: No data on the drug were submitted by the manufacturer for the relevant subpopulation.
–: The outcome was not surveyed.
a. Surveyed using the T25FW of the MSFC.
b. Comparison with other drugs not meaningful due to the treatment regime.
c. Due to very imprecise estimates when considering the placebo-controlled studies in NMAs, the evidence base for the outcome is derived exclusively from the results of the direct comparisons.

AE: adverse event; EDSS: Expanded Disability Status Scale; IFN: interferon; MSFC: Multiple Sclerosis Functional Composite; MSIS: Multiple Sclerosis Impact Scale; NMA: network metaanalysis; PML: progressive multifocal leukoencephalopathy; QoL: health-related quality of life; SAE: serious adverse event; T25FW: timed 25-foot walk

4.2.3 Assessment of the risk of bias of the results

The risk of bias was classified as low across all outcomes for all 10 studies for which additional analyses of the relevant subpopulation were submitted.

The outcome-specific risk of bias was assessed only if a comparison of at least 2 of the drugs to be assessed was possible on the basis of the study for 1 outcome. In these cases, the outcome-specific risk of bias was assessed for all studies with available results on this outcome, irrespective of whether it was decisive for the derivation of the evidence base. However, if no comparison with other escalation therapies was possible on the basis of a study, the outcome-specific risk of bias was not assessed.

Based on the data for the relevant subpopulations, the outcome-specific risk of bias of the results was assessed as high for the majority of studies and outcomes for which the assessment was not foregone. An outcome-specific low risk of bias was found only for the results of the studies RADIANCE B (for almost all outcomes except severity of disability and walking ability) and OPTIMUM (only for the outcomes of severity of disability and walking ability). In all cases, the risk of bias of the results was high because (a) the proportions of patients who were excluded from the analyses were high and possibly differential or (b) it remains unclear how many patients were included in the analyses over the course of the study.

4.2.4 Results on patient-relevant outcomes

Results of the tests of homogeneity and consistency assumption

A test of the homogeneity assumption was possible only for the comparisons for which more than 1 study was available. In the present study pool, this was true for the following comparisons of different drugs within escalation therapy: fingolimod and teriflunomide (each versus placebo) as well as ofatumumab versus teriflunomide. For other comparisons, the homogeneity assumption was not tested because only 1 study was available in each case.

The test of the homogeneity assumption for the preliminary analysis showed substantial heterogeneity only for the comparison of teriflunomide versus placebo in pairwise metaanalyses, in each case for the outcomes of confirmed relapses (annual relapse rate) and discontinuation due to AEs. The possible reasons for heterogeneity were analysed separately for each outcome. For both outcomes, the TEMSO study's placebo arm showed significantly higher event rates and frequencies than all other studies in the study pool. Against this background, the TEMSO study presumably deviates from the other studies in the study pool regarding these outcomes in a manner which cannot be identified on the basis of the available characteristics of the relevant subpopulations. For both outcomes, 1 NMA was conducted excluding the TEMSO study and 1 NMA excluding the TOWER study. The results of both NMAs were then checked for consistency. In the case of qualitatively different results, the NMA

excluding the TEMSO study was deemed decisive for the derivation of the evidence base. For the outcome of discontinuation due to AEs, however, both NMAs exhibited several very imprecise estimates, and therefore, only the results of the direct comparative studies were used for this outcome.

It is impossible to test the consistency assumption in this study pool because there are no closed loops. This means that for none of the comparisons of 2 escalation therapies are any studies available which simultaneously enable a direct and an indirect comparison of the same drugs with each other, or studies which independently enable 2 indirect comparisons of the same drugs via different common comparators.

Potential strength of evidence given the available data

Direct comparison available

On the basis of the available data, at most proof of greater or lesser benefit or harm can be derived for the direct comparison of 2 drugs. In order to derive proof, the following requirements must generally be met: the existence of a metaanalysis of studies of high qualitative certainty of results which shows a corresponding statistically significant effect or, if a metaanalysis is not feasible, the existence of at least 2 independently conducted studies of high qualitative certainty of results which exhibit a statistically significant effect and the result of which is not called into question by other studies of comparable certainty of results. Accordingly, despite statistically significant effects, a metaanalysis of studies of moderate qualitative certainty of results or a single study of high qualitative certainty of results can generally provide only an indication [29].

No direct comparison available

If no direct comparison of escalation therapies is available, at most hints of greater or lesser benefit or harm can be derived on the basis of the available data. This is because in the absence of direct comparisons, it is generally not possible to check the consistency assumption. Furthermore, where an indirect comparison is conducted based on only 1 study for at least 1 of the 2 compared drugs, no hint can be derived if this 1 study is subject to a high risk of bias.

Time points taken into account

For the 10 studies for which additional analyses of the relevant subpopulation are available, results were reported at Week 96, Week 108, and Month 24. The time periods are deemed sufficiently similar to be analysed together.

Subgroup characteristics and other effect modifiers

In addition to the results for the relevant subpopulations, subgroup analyses on the characteristics of age, sex, severity of disease, definition of highly active disease, and

geographical region were also requested from the manufacturers for these populations. For studies with IFN-β 1a treatment in the comparator arm, subgroup analyses of prior treatment with IFN-β 1a versus other prior therapies were additionally requested.

Subgroup analyses were submitted by the respective manufacturers for all studies for which basic data on the relevant subpopulation were provided. For the characteristics analysed, 6 interactions were found across all studies and outcomes based on the results of the individual studies. These interactions are also evident in the individual studies across different characteristics (prior treatment, age, severity as per EDSS, geographical region). Against this background, comparative analyses of the outcomes at subgroup level are not meaningful. The evidence base is therefore derived at the level of the relevant subpopulations, without taking into account subgroup characteristics.

Summary presentation of the results

Table 6 shows an overview of the available data for the comparisons of different drugs within escalation therapy. A distinction is made between comparisons which are possible on the basis of the available study pool and those which are not possible because the available studies do not allow a comparison. For comparisons which are possible in principle, it is also stated whether data were submitted for the drugs in the comparison or whether results with sufficient certainty of results are available for at least 1 of the outcomes in the indirect comparison.

Table 6: Overview of the available data for the comparisons of different drugs within escalation therapy

Comparison: Drug 1 vs. Drug 2	Alemtuzumab	Cladribine	Dimethyl fumarate	Fingolimod	Natalizumab	Ocrelizumab	Ofatumumab	Ozanimod	Ponesimod	Teriflunomide
Alemtuzumab										
Cladribine	–									
Dimethyl fumarate	–	x								
Fingolimod	–	○	x							
Natalizumab	–	–	–	–						
Ocrelizumab	x	–	–	–	–					
Ofatumumab	–	○	x	●	–	–				
Ozanimod	○	–	–	–	–	x	–			
Ponesimod	–	○	x	○	–	–	●	–		
Teriflunomide	–	○	x	●	–	–	●[a]	–	●[a]	

See Figure 1 for a visual representation of the possible comparisons.

●: Analyses for comparative purposes are possible on the basis of the available studies; results with sufficient certainty are available for at least 1 of the outcomes.

○: Analyses for comparative purposes are possible on the basis of the available studies; no results of sufficient certainty are available for any of the outcomes investigated.

–: Comparison impossible on the basis of the available studies.

x: Comparison would be possible on the basis of the available studies but cannot be carried out because no data for the relevant subpopulation were provided by the manufacturer for at least 1 drug.

a. The comparative analyses show favourable or unfavourable effects for 1 of the drugs for at least 1 outcome.

Table 7 summarizes the results of patient-relevant outcomes for the comparisons which are generally possible on the basis of the study pool. The available results of sufficient certainty are presented.

Table 7: Overview of the results of the patient-relevant outcomes for the comparison of different drugs within escalation therapy based on the relevant studies (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (first-named vs. second-named drug)**	
	Direct comparison	**NMA**
Alemtuzumab vs.		
ocrelizumab	–[b]	x
ozanimod	–[b]	–[c]
Cladribine vs.		
dimethyl fumarate	–[b]	x
fingolimod	–[b]	–[c]
ofatumumab	–[b]	–[c]
ponesimod	–[b]	–[c]
teriflunomide	–[b]	–[c]
Dimethyl fumarate vs.		
cladribine	–[b]	x
fingolimod	–[b]	x
ofatumumab	–[b]	x
ponesimod	–[b]	x
teriflunomide	–[b]	x
Fingolimod vs.		
cladribine	–[b]	–[c]
dimethyl fumarate	–[b]	x
ofatumumab	▪ All-cause mortality –[b] ▪ Confirmed relapses (annual relapse rate); rate ratio: –[b] ▪ Confirmed relapses (patients with confirmed relapse); RR: –[b] ▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: –[b] ▪ Severity of disability based on the MSFC, walking ability –[b] ▪ Visual disturbances, fatigue, health-related quality of life –[b] ▪ SAEs, RR: –[b]	–[d] 1.03 [0.45; 2.39][e] / 2.41 [0.98; 5.93][f] 1.08 [0.55; 2.12] 2.09 [0.44; 10.00] x –[g] 1.83 [0.60; 5.60]

Table 7: Overview of the results of the patient-relevant outcomes for the comparison of different drugs within escalation therapy based on the relevant studies (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (first-named vs. second-named drug)**	
	Direct comparison	**NMA**
Fingolimod vs.		
ofatumumab	▪ Discontinuation due to AEs –[b]	–[h]
	▪ PML, serious infections, serious neoplasms, serious secondary autoimmune diseases –[b]	x
ponesimod	–[b]	–[c]
teriflunomide	▪ All-cause mortality –[b]	–[d]
	▪ Confirmed relapses (annual relapse rate): –[b]	–[i]
	▪ Confirmed relapses (patients with confirmed relapse); RR: –[b]	0.65 [0.37; 1.17]
	▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: –[b]	0.98 [0.25; 3.88]
	▪ Severity of disability based on the MSFC, walking ability –[b]	x
	▪ Visual disturbances, fatigue, health-related quality of life –[b]	–[g]
	▪ SAEs, RR: –[b]	1.61 [0.60; 4.29]
	▪ Discontinuation due to AEs –[b]	–[h]
	▪ PML, serious infections, serious neoplasms, serious secondary autoimmune diseases –[b]	x
Ocrelizumab vs.		
alemtuzumab	–[b]	x
ozanimod	–[b]	x
Ofatumumab vs.		
cladribine	–[b]	–[c]
dimethyl fumarate	–[b]	x

Table 7: Overview of the results of the patient-relevant outcomes for the comparison of different drugs within escalation therapy based on the relevant studies (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (first-named vs. second-named drug)**	
	Direct comparison	**NMA**
Ofatumumab vs.		
fingolimod	▪ All-cause mortality –[b]	–[d]
	▪ Confirmed relapses (annual relapse rate); rate ratio: –[b]	0.97 [0.42; 2.24][e] / 0.41 [0.17; 1.02][f]
	▪ Confirmed relapses (patients with confirmed relapse); RR: –[b]	0.92 [0.47; 1.81]
	▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: –[b]	0.48 [0.10; 2.28]
	▪ Severity of disability based on the MSFC, walking ability –[b]	x
	▪ Visual disturbances, fatigue, health-related quality of life –[b]	–[g]
	▪ SAEs, RR: –[b]	0.55 [0.18; 1.68]
	▪ Discontinuation due to AEs –[b]	–[h]
	▪ PML, serious infections, serious neoplasms, serious secondary autoimmune diseases –[b]	x
ponesimod	▪ All-cause mortality –[b]	–[d]
	▪ Confirmed relapses (annual relapse rate / patients with confirmed relapse), confirmed disability progression based on EDSS, confirmed after 24 weeks –[b]	–[i]
	▪ Severity of disability based on the MSFC (MSFC z-score), MD –[b]	-0.13 [-0.29; 0.03]
	▪ Walking ability (T25FW of the MSFC); MD: –[b]	1.03 [-0.22; 2.28]
	▪ Visual disturbances, fatigue, health-related quality of life –[b]	–[g]
	▪ SAEs, discontinuation due to AEs –[b]	–[i]

Table 7: Overview of the results of the patient-relevant outcomes for the comparison of different drugs within escalation therapy based on the relevant studies (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (first-named vs. second-named drug)**	
	Direct comparison	**NMA**
Ofatumumab vs.		
ponesimod	▪ PML –[b]	–[d]
	▪ Serious infections, serious neoplasms, serious secondary autoimmune diseases –[b]	x
teriflunomide	▪ All-cause mortality –[d]	–[d]
	▪ Confirmed relapses (annual relapse rate); rate ratio: **0.46 [0.33; 0.64]**	**0.46 [0.31; 0.68]**
	▪ Confirmed relapses (patients with confirmed relapse); RR: **0.61 [0.46; 0.80]**	**0.60 [0.43; 0.86]**
	▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: **0.48 [0.27; 0.84]**	**0.47 [0.22; 0.98]**
	▪ Severity of disability based on the MSFC (MSFC z-score), MD -0.01 [-0.10; 0.07]	–[j]
	▪ Walking ability (T25FW of the MSFC); MD: 0.57 [-0.35; 1.48]	–[j]
	▪ Visual disturbances, fatigue, health-related quality of life –[g]	–[g]
	▪ SAEs, RR: 0.88 [0.51; 1.51]	0.88 [0.51; 1.51]
	▪ Discontinuation due to AEs, RR: **0.32 [0.13; 0.78]**	–[k]
	▪ PML –[d]	–[d]
	▪ Serious infections, serious neoplasms, serious secondary autoimmune diseases x	x
Ozanimod vs.		
alemtuzumab	–[b]	–[c]
ocrelizumab	–[b]	x

Table 7: Overview of the results of the patient-relevant outcomes for the comparison of different drugs within escalation therapy based on the relevant studies (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (first-named vs. second-named drug)**	
	Direct comparison	**NMA**
Ponesimod vs.		
cladribine	–[b]	–[c]
dimethyl fumarate	–[b]	x
fingolimod	–[b]	–[c]
ofatumumab	▪ All-cause mortality –[b]	–[d]
	▪ Confirmed relapses (annual relapse rate / patients with confirmed relapse), confirmed disability progression based on EDSS, confirmed after 24 weeks –[b]	–[i]
	▪ Severity of disability based on the MSFC (MSFC z-score), MD –[b]	0.13 [-0.03; 0.29]
	▪ Walking ability (T25FW of the MSFC), MD: –[b]	-1.03 [-2.28; 0.22]
	▪ Visual disturbances, fatigue, health-related quality of life –[b]	–[g]
	▪ SAEs, discontinuation due to AEs –[b]	–[i]
	▪ PML –[b]	–[d]
	▪ Serious infections, serious neoplasms, serious secondary autoimmune diseases –[b]	x
teriflunomide	▪ All-cause mortality –[d]	–[d]
	▪ Confirmed relapses (annual relapse rate); rate ratio: **0.45 [0.22; 0.92]**	**0.45 [0.21; 0.97]**
	▪ Confirmed relapses (patients with confirmed relapse); RR: 0.61 [0.35; 1.09]	0.61 [0.32; 1.17]
	▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: 0.17 [0.02; 1.34]	0.17 [0.02; 1.47]
	▪ Severity of disability based on the MSFC (MSFC z-score), MD 0.12 [-0.02; 0.25]	–[j]

Table 7: Overview of the results of the patient-relevant outcomes for the comparison of different drugs within escalation therapy based on the relevant studies (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (first-named vs. second-named drug)**	
	Direct comparison	**NMA**
Ponesimod vs.		
teriflunomide	▪ Walking ability (T25FW of the MSFC); MD: -0.46 [-1.31; 0.40] ▪ Vision disorders –[g] ▪ Fatigue x ▪ Health-related quality of life (recorded with the SF-36v2); RR: ▫ MCS, improvement by ≥ 10.8 points: 1.58 [0.69; 3.65] ▫ PCS, improvement by ≥ 10.05 points: 1.93 [0.40; 9.19] ▫ MCS, worsening by ≥ 10.8 points: 0.66 [0.23; 1.94] ▫ PCS, worsening by ≥ 10.05 points: 0.30 [0.06; 1.41] ▪ SAEs, RR: 1.63 [0.41; 6.44] ▪ Discontinuation due to AEs, RR: **4.77 [1.06; 21.52]** ▪ PML, serious infections, serious neoplasms –[d] ▪ Serious secondary autoimmune diseases x	▪ Walking ability (T25FW of the MSFC); MD: –[j] ▪ Vision disorders –[g] ▪ Fatigue –[j] ▪ Health-related quality of life (recorded with the SF-36v2); RR: –[j] ▪ SAEs, RR: 1.36 [0.43; 4.33] ▪ Discontinuation due to AEs, RR: –[k] ▪ PML, serious infections, serious neoplasms –[d] ▪ Serious secondary autoimmune diseases x
Teriflunomide vs.		
cladribine	–[b]	–[c]
dimethyl fumarate	–[b]	x
fingolimod	▪ All-cause mortality –[b] ▪ Confirmed relapses (annual relapse rate): –[b] ▪ Confirmed relapses (patients with confirmed relapse); RR: –[b] ▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: –[b] ▪ Severity of the disability based on the MSFC, walking ability –[b]	▪ All-cause mortality –[d] ▪ Confirmed relapses (annual relapse rate): –[i] ▪ Confirmed relapses (patients with confirmed relapse); RR: 1.53 [0.86; 2.72] ▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: 1.02 [0.26; 4.06] ▪ Severity of the disability based on the MSFC, walking ability x

Table 7: Overview of the results of the patient-relevant outcomes for the comparison of different drugs within escalation therapy based on the relevant studies (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (first-named vs. second-named drug)**	
	Direct comparison	**NMA**
Teriflunomide vs.		
fingolimod	▪ Visual disturbances, fatigue, health-related quality of life –[b]	–[g]
	▪ SAEs, RR: –[b]	0.62 [0.23; 1.66]
	▪ Discontinuation due to AEs –[b]	–[h]
	▪ PML, serious infections, serious neoplasms, serious secondary autoimmune diseases –[b]	x
ofatumumab	▪ All-cause mortality –[d]	–[d]
	▪ Confirmed relapses (annual relapse rate); rate ratio: **2.18 [1.57; 3.02]**	**2.18 [1.48; 3.21]**
	▪ Confirmed relapses (patients with confirmed relapse); RR: **1.65 [1.25; 2.18]**	**1.65 [1.17; 2.34]**
	▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: **2.08 [1.18; 3.64]**	**2.14 [1.02; 4.49]**
	▪ Severity of disability based on the MSFC (MSFC z-score), MD 0.01 [-0.07; 0.10]	–[i]
	▪ Walking ability (T25FW of the MSFC); MD: -0.57 [-1.48; 0.35]	–[i]
	▪ Visual disturbances, fatigue, health-related quality of life –[g]	–[g]
	▪ SAEs, RR: 1.13 [0.66; 1.94]	1.14 [0.66; 1.95]
	▪ Discontinuation due to AEs, RR: **3.14 [1.29; 7.64]**	–[k]
	▪ PML –[d]	–[d]
	▪ Serious infections, serious neoplasms, serious secondary autoimmune diseases x	x

Table 7: Overview of the results of the patient-relevant outcomes for the comparison of different drugs within escalation therapy based on the relevant studies (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (first-named vs. second-named drug)**	
	Direct comparison	**NMA**
Teriflunomide vs.		
ponesimod	▪ All-cause mortality –[d]	–[d]
	▪ Confirmed relapses (annual relapse rate); rate ratio: **2.22 [1.09; 4.55]**	**2.22 [1.03; 4.81]**
	▪ Confirmed relapses (patients with confirmed relapse); RR: 1.64 [0.92; 2.86]	1.63 [0.86; 3.11]
	▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: 6.02 [0.75; 47.62]	6.02 [0.68; 53.39]
	▪ Severity of disability based on the MSFC (MSFC z-score), MD -0.12 [-0.25; 0.02]	–[j]
	▪ Walking ability (T25FW of the MSFC), MD: 0.46 [-0.40; 1.31]	–[j]
	▪ Vision disorders –[g]	–[g]
	▪ Fatigue x	–[j]
	▪ Health-related quality of life (recorded with the SF-36v2); RR: ▫ MCS, improvement by ≥ 10.8 points: 0.63 [0.27; 1.45] ▫ PCS, improvement by ≥ 10.05 points: 0.52 [0.11; 2.50] ▫ MCS, worsening by ≥ 10.8 points: 1.52 [0.52; 4.35] ▫ PCS, worsening by ≥ 10.05 points: 3.33 [0.71; 16.67]	–[j]
	▪ SAEs, RR: 0.61 [0.16; 2.44]	0.73 [0.23; 2.33]
	▪ Discontinuation due to AEs, RR: **0.21 [0.05; 0.94]**	–[k]
	▪ PML, serious infections, serious neoplasms –[d]	–[d]
	▪ Serious secondary autoimmune diseases x	x

Statistically significant differences are shown **in bold** .
–: No hint of greater or lesser benefit or harm
x: A comparison of the drugs is impossible because for at least 1 drug, no data for the relevant subpopulation were provided by the manufacturer.

Table 7: Overview of the results of the patient-relevant outcomes for the comparison of different drugs within escalation therapy based on the relevant studies (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (first-named vs. second-named drug)**	
	Direct comparison	**NMA**
a. Effects are specified for both directions and are therefore listed twice. b. No directly comparative studies were identified. c. In the indirect comparison, sufficient certainty of results is not available for any of the analysed outcomes. Therefore, the results for the individual outcomes are not summarized for the comparison (see Table 9 for detailed information on the outcomes for which data were available for the comparison). d. A comparison is not possible or cannot be meaningfully interpreted because events for this outcome occurred only sporadically in the studies or only in 1 study arm. e. Results of the NMA excluding the TEMSO study. f. Results of the NMA excluding the TOWER study. g. No data on the outcome were collected or no usable data on the outcome are available for at least 1 of the drugs in the comparison. h. No valid conclusions on the comparison of escalation therapies can be drawn on the basis of the NMAs. i. There is insufficient certainty of results in the indirect comparison. Therefore, the results for the outcome(s) are not presented. j. No NMA was possible for the outcome based on the available data. k. Due to very imprecise estimates when taking into account the placebo-controlled studies in NMAs, the evidence base for the outcome is derived exclusively from the results of the direct comparisons. AE: adverse event; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; MCS: Mental Component Summary; MD: mean difference; MSFC: Multiple Sclerosis Functional Composite; NMA: network metaanalysis; PCS: Physical Component Summary; PML: progressive multifocal leukoencephalopathy; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form 36 Health Survey, version 2; T25FW: timed 25-foot walk		

Favourable and unfavourable effects for the comparison of different drugs within escalation therapy (research question 4)

For the comparison of different drugs within escalation therapy, Table 8 shows for which outcomes favourable or unfavourable effects were present on the basis of which conclusions were derived for greater or lesser benefit or harm.

Table 8: Comparison of different drugs within escalation therapy, favourable and unfavourable effects related to patient-relevant outcomes (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (drug listed first vs. drug listed second)**			
	In favour of the drug listed first		**To the disadvantage of the drug listed first**	
	Direct comparison	**NMA**	**Direct comparison**	**NMA**
Alemtuzumab vs.				
cladribine	–		–	
dimethyl fumarate	–		–	
fingolimod	–		–	
natalizumab	–		–	
ocrelizumab	x		x	
ofatumumab	–		–	
ozanimod	–[b]		–[b]	
ponesimod	–		–	
teriflunomide	–		–	
Cladribine vs.				
alemtuzumab	–		–	
dimethyl fumarate	x		x	
fingolimod	–[b]		–[b]	
natalizumab	–		–	
ocrelizumab	–		–	
ofatumumab	–[b]		–[b]	
ozanimod	–		–	
ponesimod	–[b]		–[b]	
teriflunomide	–[b]		–[b]	
Dimethyl fumarate vs.				
alemtuzumab	–		–	
cladribine	x		x	
fingolimod	x		x	
natalizumab	–		–	
ocrelizumab	–		–	
ofatumumab	x		x	
ozanimod	–		–	
ponesimod	x		x	
teriflunomide	x		x	

Table 8: Comparison of different drugs within escalation therapy, favourable and unfavourable effects related to patient-relevant outcomes (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (drug listed first vs. drug listed second)**			
	In favour of the drug listed first		**To the disadvantage of the drug listed first**	
	Direct comparison	**NMA**	**Direct comparison**	**NMA**
Fingolimod vs.				
alemtuzumab	–		–	
cladribine	–[b]		–[b]	
dimethyl fumarate	x		x	
natalizumab	–		–	
ocrelizumab	–		–	
ofatumumab[c]	–[b]		–[b]	
ozanimod	–		–	
ponesimod	–[b]		–[b]	
teriflunomide[c]	–[b]		–[b]	
Natalizumab vs.				
alemtuzumab	–		–	
cladribine	–		–	
dimethyl fumarate	–		–	
fingolimod	–		–	
ocrelizumab	–		–	
ofatumumab	–		–	
ozanimod	–		–	
ponesimod	–		–	
teriflunomide	–		–	
Ocrelizumab vs.				
alemtuzumab	x		x	
cladribine	–		–	
dimethyl fumarate	–		–	
fingolimod	–		–	
natalizumab	–		–	
ofatumumab	–		–	
ozanimod	x		x	
ponesimod	–		–	
teriflunomide	–		–	

Table 8: Comparison of different drugs within escalation therapy, favourable and unfavourable effects related to patient-relevant outcomes (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (drug listed first vs. drug listed second)**	
	In favour of the drug listed first	**To the disadvantage of the drug listed first**
	Direct comparison NMA	**Direct comparison NMA**
Ofatumumab vs.		
alemtuzumab	–	–
cladribine	–[b]	–[b]
dimethyl fumarate	x	x
fingolimod[c]	–[b]	–[b]
natalizumab	–	–
ocrelizumab	–	–
ozanimod	–	–
ponesimod[c]	–[b]	–[b]
teriflunomide[d]	▪ Confirmed relapses (annual relapse rate); rate ratio: 0.46 [0.33; 0.64] 0.46 [0.31; 0.68] ▪ Confirmed relapses (patients with confirmed relapse); RR: 0.61 [0.46; 0.80] 0.60 [0.43; 0.86] ▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: 0.48 [0.27; 0.84] 0.47 [0.22; 0.98] ▪ Discontinuation due to AEs, RR: 0.32 [0.13; 0.78] –[e]	–[f]
Ozanimod vs.		
alemtuzumab	–[b]	–[b]
cladribine	–	–
dimethyl fumarate	–	–
fingolimod	–	–
natalizumab	–	–
ocrelizumab	x	x
ofatumumab	–	–
ponesimod	–	–
teriflunomide	–	–

Table 8: Comparison of different drugs within escalation therapy, favourable and unfavourable effects related to patient-relevant outcomes (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (drug listed first vs. drug listed second)**	
	In favour of the drug listed first	**To the disadvantage of the drug listed first**
	Direct comparison **NMA**	**Direct comparison** **NMA**
Ponesimod vs.		
alemtuzumab	–	–
cladribine	–[b]	–[b]
dimethyl fumarate	x	x
fingolimod	–[b]	–[b]
natalizumab	–	–
ocrelizumab	–	–
ofatumumab[c]	–[b]	–[b]
ozanimod	–	–
teriflunomide[d]	▪ Confirmed relapses (annual relapse rate); rate ratio: 0.45 [0.22; 0.92] 0.45 [0.21; 0.97]	▪ Discontinuation due to AEs, RR: 4.77 [1.06; 21.52] –[e]
Teriflunomide vs.		
alemtuzumab	–	–
cladribine	–[b]	–[b]
dimethyl fumarate	x	x
fingolimod[c]	–[b]	–[b]
natalizumab	–	–
ocrelizumab	–	–
ofatumumab[d]	–[g]	▪ Confirmed relapses (annual relapse rate); rate ratio: 2.18 [1.57; 3.02] 2.18 [1.48; 3.21] ▪ Confirmed relapses (patients with confirmed relapse); RR: 1.65 [1.25; 2.18] 1.65 [1.17; 2.34] ▪ Confirmed disability progression based on the EDSS, confirmed after 24 weeks; HR: 2.08 [1.18; 3.64] 2.14 [1.02; 4.49] ▪ Discontinuation due to AEs, RR: 3.14 [1.29; 7.64] –[f]
ozanimod	–	–
ponesimod[d]	▪ Discontinuation due to AEs, RR: 0.21 [0.05; 0.94] –[e]	▪ Confirmed relapses (annual relapse rate); rate ratio: 2.22 [1.09; 4.55] 2.22 [1.03; 4.81]

Table 8: Comparison of different drugs within escalation therapy, favourable and unfavourable effects related to patient-relevant outcomes (multipage table)

Comparisons[a] **Drug**	**Outcome, effect measure: effect estimate [95% CI] (drug listed first vs. drug listed second)**			
	In favour of the drug listed first		**To the disadvantage of the drug listed first**	
	Direct comparison	**NMA**	**Direct comparison**	**NMA**

-: No hint of greater or lesser benefit or harm; unless otherwise stated, this is due to the fact that a comparison between the drugs is impossible because no relevant study was identified for at least 1 drug or no common comparator is available for an indirect comparison.
x: A comparison of the drugs is impossible because for at least 1 drug, no data for the relevant subpopulation were provided by the manufacturer.

a. Effects are specified for both directions and are therefore listed twice.
b. A comparison of the drugs is possible for individual outcomes because data on both drugs are available for 1 or more outcomes; however, based on the available data, there is no hint of greater or lesser benefit or harm from 1 of the drugs (Table 9 shows the outcomes for which data are available).
c. For this drug comparison, data were available for some outcomes and there was sufficient certainty of results in the indirect comparison. There were no statistically significant differences in favour or to the disadvantage of any of the drugs (for detailed results, see Table 7).
d. For this drug comparison, data from the direct comparison were available on other outcomes. There were no further statistically significant differences in favour or to the disadvantage of 1 of the drugs (for detailed results, see Table 7).
e. Due to very imprecise estimates when taking into account the placebo-controlled studies in NMAs, the evidence base for the outcome is derived exclusively from the results of the direct comparisons.
f. Based on the available data comparing the drugs, there are no differences in favour of the first-mentioned drug.
g. Based on the available data comparing the drugs, there are no differences in favour of the first-mentioned drug.

AE: adverse event; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; NMA: network metaanalysis; RR: relative risk

For the comparison within escalation therapy, the available data allow deriving favourable and unfavourable effects only for direct comparisons between the different drugs. Favourable effects were found for ofatumumab versus teriflunomide for the outcomes of confirmed relapses (annual relapse rate and patients with confirmed relapse), confirmed disability progression based on the EDSS, and discontinuation due to AEs, for ponesimod versus teriflunomide for the outcome of confirmed relapses (annual relapse rate), and for teriflunomide versus ponesimod for the outcome of discontinuation due to AEs. For all other outcomes, the direct comparisons showed neither favourable nor unfavourable effects between the escalation therapies.

Based on the available data, greater benefit of a drug compared to other escalation therapies cannot be proven from indirect comparisons. However, this is not proof of equivalence of the compared therapies. The available data from indirect comparisons are unsuitable for ruling out an advantage or disadvantage of individual therapies. This is due in particular to the

insufficient data available for the indirect comparisons in the present study pool. In addition, the effect estimates are imprecise in many cases. In indirect comparisons, the drugs and common comparators are furthermore not always linked via at least 2 studies, but in some cases only via 1 study with a high risk of bias. The certainty of results for these indirect comparisons is therefore insufficient, so that no hint, e.g. of a higher benefit, can be derived from the available data.

4.2.5 Overall evaluation of results

Evidence map

The following Table 9 shows the evidence map regarding patient-relevant outcomes.

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
Comparison	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Alemtuzumab vs.															
cladribine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
dimethyl fumarate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
fingolimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
natalizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ocrelizumab	x	x	x	x	x	x	x	–	x	x	x	x	x	x	x
ofatumumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ozanimod	–[a]	–[b]	–[b]	–[b]	–[b]	–[b]	x	–	–[c]	–[a]	–[c]	x	x	x	–
ponesimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
teriflunomide	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

Comparison	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Cladribine vs.															
alemtuzumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
dimethyl fumarate	x	x	x	x	–	–	–	–	x	x	x	x	x	x	x
fingolimod	–[a]	–[b]	–[b]	–[a]	–	–	–	–	x	–[b]	–[c]	–[a]	x	x	x
natalizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ocrelizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ofatumumab	–[a]	–[b]	–[b]	–[a]	–	–	–	–	–	–[b]	–[c]	x	x	x	x
ozanimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ponesimod	–[a]	–[b]	–[b]	–[a]	–	–	–	–	–	–[b]	–[c]	x	x	x	x
teriflunomide	–[a]	–[b]	–[b]	–[a]	–	–	–	–	–	–[b]	–[c]	x	x	x	x

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

Comparison	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Dimethyl fumarate vs.															
alemtuzumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
cladribine	x	x	x	x	–	–	–	–	x	x	x	x	x	x	x
fingolimod	x	x	x	x	x	x	x	–	x	x	x	x	x	x	x
natalizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ocrelizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ofatumumab	x	x	x	x	x	x	–	–	–	x	x	x	x	x	x
ozanimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ponesimod	x	x	x	x	x	x	–	–	x	x	x	x	x	x	x
teriflunomide	x	x	x	x	x	x	–	–	x	x	x	x	x	x	x

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

Comparison	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Fingolimod vs.															
alemtuzumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
cladribine	–[a]	–[b]	–[b]	–[a]	–	–	–	–	x	–[b]	–[c]	–[a]	x	x	x
dimethyl fumarate	x	x	x	x	x	x	x	–	x	x	x	x	x	x	x
natalizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ocrelizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ofatumumab	–[a]	(⇔)	⇔	(⇔)	x	x	–	–	–	⇔	–[d]	x	x	x	x
ozanimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ponesimod	–[a]	–[b]	–[b]	–[b]	x	x	–	–	–	–[b]	–[d]	x	x	x	x
teriflunomide	–[a]	–[b]	⇔	(⇔)	x	x	–	–	–	⇔	–[d]	x	x	x	x

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

Comparison	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Natalizumab vs.															
alemtuzumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
cladribine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
dimethyl fumarate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
fingolimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ocrelizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ofatumumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ozanimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ponesimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
teriflunomide	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

Comparison	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Ocrelizumab vs.															
alemtuzumab	x	x	x	x	x	x	x	–	x	x	x	x	x	x	x
cladribine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
dimethyl fumarate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
fingolimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
natalizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ofatumumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ozanimod	x	x	x	x	x	x	x	–	x	x	x	x	x	x	–
ponesimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
teriflunomide	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

Comparison	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Ofatumumab vs.															
alemtuzumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
cladribine	–[a]	–[b]	–[b]	–[a]	–	–	–	–	–	–[b]	–[c]	x	x	x	x
dimethyl fumarate	x	x	x	x	x	x	–	–	–	x	x	x	x	x	x
fingolimod	–[a]	(⇔)	⇔	(⇔)	x	x	–	–	–	⇔	–[d]	x	x	x	x
natalizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ocrelizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ozanimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ponesimod	–[a]	–[b]	–[b]	–[b]	⇔	⇔	–	–	–	–[b]	–[b]	–[a]	x	x	x
teriflunomide	–[a]	⇑	⇑	⇑	⇔	⇔	–	–	–	⇔	⇑	–[a]	x	x	x

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

Comparison	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Ozanimod vs.															
alemtuzumab	–[a]	–[b]	–[b]	–[b]	–[b]	–[b]	x	–	–[c]	–[a]	–[c]	x	x	x	–
cladribine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
dimethyl fumarate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
fingolimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
natalizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ocrelizumab	x	x	x	x	x	x	x	–	x	x	x	x	x	x	–
ofatumumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ponesimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
teriflunomide	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

Comparison	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Ponesimod vs.															
alemtuzumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
cladribine	–[a]	–[b]	–[b]	–[a]	–	–	–	–	–	–[b]	–[c]	x	x	x	x
dimethyl fumarate	x	x	x	x	x	x	–	–	x	x	x	x	x	x	x
fingolimod	–[a]	–[b]	–[b]	–[b]	x	x	–	–	–	–[b]	–[d]	x	x	x	x
natalizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ocrelizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ofatumumab	–[a]	–[b]	–[b]	–[b]	⇔	⇔	–	–	–	–[b]	–[b]	–[a]	x	x	x
ozanimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
teriflunomide	–[a]	⇗	⇔	⇔	⇔	⇔	–	x	⇔	(⇔)	⇘	–[a]	–[a]	–[a]	x

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

	Outcomes														
	Mortality	Morbidity							QoL	Side effects					
Comparison	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases
Teriflunomide vs.															
alemtuzumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
cladribine	–[a]	–[b]	–[b]	–[a]	–	–	–	–	–	–[b]	–[c]	x	x	x	x
dimethyl fumarate	x	x	x	x	x	x	–	–	x	x	x	x	x	x	x
fingolimod	–[a]	–[b]	⇔	(⇔)	x	x	–	–	–	⇔	–[d]	x	x	x	x
natalizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ocrelizumab	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ofatumumab	–[a]	⇓	⇓	⇓	⇔	⇔	–	–	–	⇔	⇓	–[a]	x	x	x
ozanimod	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ponesimod	–[a]	⇘	⇔	⇔	⇔	⇔	–	x	⇔	(⇔)	⇗	–[a]	–[a]	–[a]	x

Table 9: Evidence map regarding patient-relevant outcomes (multipage table)

Comparison	Outcomes															
	Mortality	Morbidity							QoL	Side effects					
	All-cause mortality	Confirmed relapses (annual relapse rate)	Confirmed relapses (patients with confirmed relapse)	Confirmed disability progression based on the EDSS, confirmed after 24 weeks	Severity of the disability based on the MSFC	Walking ability	Vision disorders	Fatigue	Health-related quality of life	SAEs	Discontinuation due to AEs	PML	Serious infections	Serious neoplasms	Serious secondary autoimmune diseases

⇧: Indication of (greater) benefit or indication of lesser harm
⇩: Indication of lesser benefit or indication of (greater) harm
⇗: Hint of (greater) benefit or hint of lesser harm
⇘: Hint of lesser benefit or hint of (greater) harm
⇔: No hint, indication, or proof
(⇔): No hint, indication, or proof; the 95% confidence interval for the relative effect is so imprecise that neither halving nor doubling of the effect can be ruled out
–: A comparison of the drugs is impossible because the available studies do not allow a comparison of the drugs or no outcome was recorded or no usable data are available for at least 1 drug. There is no hint, indication, or proof of (greater) benefit or lesser harm.
x: In principle, a comparison of the drugs would be possible on the basis of the available data, but it cannot be carried out because regarding this outcome, no data for the relevant subpopulation were provided by the manufacturer for at least 1 drug.
a. A comparison is not possible or cannot be meaningfully interpreted because in the studies, events for this outcome occurred only sporadically or only in 1 study arm.
b. The certainty of results is insufficient for the indirect comparison, so that no hint, e.g. of greater benefit, can be derived from the available data.
c. The available analyses are not deemed to be comparable.
d. No valid conclusions on the comparison of escalation therapies can be derived on the basis of the NMAs.

AE: adverse event; EDSS: Expanded Disability Status Scale; MSFC: Multiple Sclerosis Functional Composite; NMA: network metaanalysis; PML: progressive multifocal leukoencephalopathy; QoL: health-related quality of life; SAE: serious adverse event; T25FW: timed 25-foot walk

Assessment of the volume of unpublished data

The present report is based mainly on unpublished data because an assessment of the benefits and harms of the various escalation therapies for the population of the present assessment as commissioned by the G-BA (patients with highly active RRMS who have received complete and adequate prior treatment with at least 1 disease-modifying therapy) was possible only on the basis of additional analyses. Since the relevant studies identified for the present assessment were all sponsored by pharmaceutical companies, manufacturers were asked for additional analyses. The manufacturers provided them for the majority of the 14 relevant studies.

No additional analyses were submitted by the manufacturers for the relevant studies on dimethyl fumarate and ocrelizumab (2 studies each). For these 2 drugs, the present assessment can therefore draw no conclusions on greater benefit or harm from the analyses conducted. Overall, this means that previously unpublished results from manufacturer queries are available for the present assessment from 10 studies on 7 drugs. In addition to these studies, studies without reported results were identified for individual drugs. These are all ongoing studies for which no results have yet been reported. It is unclear to what extent these studies enrolled patients who correspond to the population of the present assessment as commissioned by the G-BA. Further, the majority of these studies investigate only new drugs for the treatment of MS in comparison with teriflunomide. The study arms investigating the new drugs, however, do not represent a suitable common comparator in the present study pool.

Weighing of benefits versus harms

Based on the available data, greater or lesser benefit or harm can be derived only from the direct comparisons of the escalation therapies. For the majority of the other comparisons, data are either completely missing or were not provided by the responsible manufacturers. In some cases, relevant outcomes were not recorded in individual studies, or no advantages or disadvantages were found between the investigated drugs.

The available direct comparative studies on the basis of which greater or lesser benefit or harm can be derived include the comparisons of ofatumumab and ponesimod, each versus teriflunomide. This results in greater benefit or lesser harm for each of the following outcomes:

- Indication of greater benefit or lesser harm from ofatumumab compared to teriflunomide:
  - confirmed relapses (annual relapse rate / patients with confirmed relapse)
  - confirmed disability progression surveyed by the EDSS

- discontinuation due to AEs

- Hint of greater benefit of ponesimod in comparison with teriflunomide:
  - confirmed relapses (annual relapse rate):
- Hint of lesser harm from teriflunomide compared to ponesimod:
  - discontinuation due to AEs

For the comparison of ofatumumab versus teriflunomide, there are indications of greater benefit for the outcomes of confirmed relapses and confirmed disability progression based on the EDSS. In contrast, there was no statistically significant difference for the outcome of severity of disability based on the MSFC or the components included in the MSFC. The greater benefit of ofatumumab with regard to this outcome is therefore based exclusively on aspects of disability, surveyed with the EDSS. No additional analyses were submitted for the comparison of ofatumumab versus teriflunomide regarding the outcomes of serious infections, serious neoplasms, or serious secondary autoimmune diseases. However, based on the data on the total populations of the ASCLEPIOS I and II studies and the analyses submitted on AEs overall (i.e. serious and non-serious), only isolated events presumably occurred for these outcomes. It is therefore not plausible for differences to exist to the disadvantage of ofatumumab compared to teriflunomide which would call into question the observed advantages. Altogether, this results in an indication of greater benefit of ofatumumab in comparison with teriflunomide in escalation therapy.

For the comparison of ponesimod versus teriflunomide, there is both a hint of greater benefit of ponesimod and a hint of greater harm from ponesimod. Ponesimod showed greater benefit for the operationalization of annual relapse rate in the outcome of confirmed relapses. In the operationalization of patients with confirmed relapse, the effect estimate pointed in the same direction, although no hint of greater benefit resulted there. For the outcome of discontinuation due to AEs, there was a disadvantage of ponesimod compared to teriflunomide, but few events occurred for this outcome. The results for this outcome do not call into question the benefit of ponesimod for the outcome of confirmed relapses (annual relapse rate). Unlike in the comparison of ofatumumab versus teriflunomide, in the comparison of ponesimod versus teriflunomide, data are also available for the majority of specific serious AEs, although only isolated events occurred. Overall, this results in a hint of greater benefit of ponesimod in comparison with teriflunomide in escalation therapy.

4.3 Comparison of the treatment strategies of escalation therapy versus basic therapy (research question 1)

For research question 1, 4 studies are available in which escalation therapy is compared with IFN-β 1a: CARE-MS II (alemtuzumab versus IFN-β 1a), RADIANCE B (ozanimod versus IFN-β 1a), and OPERA I and OPERA II (each ocrelizumab versus IFN-β 1a). As described in

Section 4.1, no analyses of the relevant subpopulations of the OPERA I and II studies were submitted by the manufacturer of ocrelizumab. Thus, only analyses of the CARE-MS II and RADIANCE B studies are available for research question 1. Furthermore, the studies comparing ofatumumab or ponesimod versus teriflunomide can also be taken into account as a comparison of escalation therapy versus basic therapy. In the present assessment, these studies are included as direct comparisons of escalation therapies because their application in this therapeutic situation is covered by the approval of teriflunomide.

In order to investigate the benefit of escalation therapy compared to the continuation of treatment with basic therapeutics, subgroup analyses were requested from the manufacturers for the studies comparing IFN-β 1a regarding the characteristic of prior treatment with IFN-β 1a versus other prior therapies. Decisive for research question 1 are the results for the subgroup in which a switch to a different basic therapy took place at the start of the study, in this case a switch from another prior therapy to IFN-β 1a.

The relevant subpopulation in the study comparing ozanimod versus IFN-β 1a (RADIANCE B) is of much smaller size than in the study comparing alemtuzumab versus IFN-β 1a (CARE-MS II). Meaningful data on research question 1 are therefore available only from the CARE-MS II study. For this study, only 1 outcome showed an effect modification by the characteristic of prior therapy. The results for the subgroup "prior therapies other than IFN-β 1a" are therefore not presented. The overall picture of all outcomes for which results are available shows superiority of escalation to alemtuzumab compared to switching to the basic therapy IFN-β 1a, despite an observed effect modification for 1 outcome. On the basis of the available analyses, no conclusions can be drawn for other escalation therapeutics.

4.4 Research questions on escalation therapies with the possibility of deescalation (questions 2 and 3)

No relevant studies were identified for the following research questions of the present benefit assessment:

- Research question 2: escalation therapy with the possibility of deescalation versus basic therapy
- Research question 3: escalation therapy versus escalation therapy with the possibility of deescalation

For these two care-relevant questions, it therefore remains unclear whether there is an advantage for one of the treatment strategies mentioned or, within one of the treatment strategies, for one of the drugs investigated.

5 Classification of the assessment result

This benefit assessment is the first investigation comparing the drugs approved until 2021 within escalation therapy in patients with highly active RRMS who have received complete and adequate prior treatment with at least 1 disease-modifying therapy. A central result of this investigation is that there is a substantial lack of study data for the research questions of this benefit assessment. This is due to the fact that (a) only a few direct comparative studies are available and indirect comparisons are possible only to a limited extent based on the available studies, and (b) no studies at all were carried out on individual care-related research questions.

All studies relevant for the present report also included other patient groups (in particular patients who had not received prior treatment). In each case, it was therefore necessary to analyse a subpopulation via additional analyses. These analyses were requested from the respective responsible manufacturers, and most, but not all, were provided.

The present assessment had the most comprehensive data available for the comparison of the drugs with each other within escalation therapy (research question 4), although the amount of available data for the individual drugs differed to a relevant extent. For the drug natalizumab, no relevant studies were found which investigated the patient population of the present assessment and thus that of the main therapeutic indication of natalizumab. For the relevant studies on the drugs dimethyl fumarate and ocrelizumab, the manufacturers did not submit any analyses of the relevant subpopulations for the present assessment. Consequently, results comparing the escalation therapies with each other are generally available for only 7 of the 10 drugs in this assessment.

In addition, the studies for which analyses were generally submitted suffered from data collection gaps in that some patient-relevant outcomes were not in all cases included in the study design. This applies in particular to the patient-reported outcomes of visual impairment, fatigue, and health-related quality of life. For these outcomes, only limited comparisons of individual drugs were possible on the basis of the study pool. In view of the high patient relevance of investigations on these outcomes, which also became evident during the hearing on the preliminary report, patient-reported outcomes on symptoms and health-related quality of life must in future be included in the study protocol in this therapeutic indication.

For the majority of the studies, the relevant subpopulations furthermore comprise between 4% and 30% of the individual study arms' original total population. These studies investigated a broad range of patients: patients with or without prior treatment as well as patients with or without highly active disease. In about half of the studies analysed, the present research question is therefore informed by less than 10% of the study population.

The results of the information retrieval for the present benefit assessment show that virtually no directly comparative studies on the various escalation therapeutics are available, and after marketing authorization has been granted, they are apparently not to be expected either from the manufacturers. This applies, firstly, in general to the present population of patients with high disease activity despite receiving prior treatment. Secondly, no studies at all are available on the research questions of targeted deescalation of treatment after initial escalation, which are important for patients. The fact that studies on this are of particular patient relevance to also became clear during the hearing on the preliminary report. From the patient perspective, relevant research gaps identified through the present benefit assessment exist not only for patient-reported outcomes, but also for research questions related to targeted deescalation. In addition, long-term observations from the patient perspective would be necessary.

The present assessment emphasizes the need for comparative studies with high certainty of results to inform the care of the patient population investigated in this assessment. One way of generating the evidence required for healthcare provision is through pragmatic, particularly registry-based RCTs, which can be used to address both proximity to care and certainty of results. It therefore seems crucial to improve the necessary framework conditions for conducting such register-based RCTs in Germany. The hearing on the preliminary report revealed that there are currently various obstacles to conducting such studies in Germany, not only regarding the financing of the often expensive study medication. In view of the needs of those affected, the deliberations on a Registry Act which are ongoing at the time of this assessment should be viewed favourably. As a further approach to addressing the research gaps, the idea of implementing a pragmatic RCT on deescalation in the MS registry of the German Multiple Sclerosis Society (DMSG) with the help of joint pool funding from the industry was formulated as part of the scientific discussion on the preliminary report. In view of the research gaps identified for the investigation of the research questions at hand and the particular importance of studies on research questions regarding deescalation, this approach as well should be further pursued.

6 Conclusion

Comparison of the treatment strategies of escalation therapy versus basic therapy (research question 1)

For research question 1, meaningful data are available from only 1 study which compares escalation therapy with alemtuzumab versus interferon-beta 1a. The results for patients who switched from another basic therapy to interferon-beta 1a at the start of the study are decisive for answering the research question. The overall analysis of all outcomes for which results are available shows superiority of escalation to alemtuzumab versus switching to the basic therapy of IFN-β 1a. On the basis of the available data, no conclusions can be drawn for other escalation therapeutics.

Research questions on escalation therapies with the possibility of deescalation (questions 2 and 3)

No relevant studies were identified for the following research questions of the present benefit assessment:

- Research question 2: escalation therapy with the possibility of deescalation versus basic therapy
- Research question 3: escalation therapy versus escalation therapy with the possibility of deescalation

For these 2 care-relevant research questions, it therefore remains unclear whether there is an advantage for one of the treatment strategies mentioned or, within one of the treatment strategies, for one of the drugs investigated.

Comparison of different drugs within a treatment strategy (research question 4)

Based on the available data, a comparison of different drugs within a treatment strategy was possible only for escalation therapy. Within escalation therapy, study data were available on the drugs alemtuzumab, cladribine, fingolimod, ofatumumab, ozanimod, ponesimod, and teriflunomide. For the drugs dimethyl fumarate and ocrelizumab, the manufacturers submitted no data for the present assessment. No relevant studies were identified for the drug natalizumab.

Direct comparative studies were available for the drugs ofatumumab and ponesimod, each in comparison with teriflunomide. Based on the available data, greater or lesser benefit or harm can be derived only from the direct comparisons of the escalation therapies. For the majority of the other comparisons, data are either completely missing or were not provided by the responsible manufacturers. In some cases, relevant outcomes were not recorded in individual studies, or no advantages or disadvantages were found between the investigated drugs.

For the comparison of ofatumumab versus teriflunomide, there are only indications in favour of ofatumumab, namely in the outcomes of confirmed relapses (annual relapse rate, patients with confirmed relapse), confirmed disability progression, and discontinuation due to adverse events. Altogether, this results in an indication of greater harm from ofatumumab in comparison with teriflunomide.

For the comparison of ponesimod versus teriflunomide, this results in (1) a hint of greater benefit for the outcome of confirmed relapses (annual relapse rate) and (2) a hint of a greater harm from ponesimod for the outcome of discontinuation due to adverse events. However, only a few events occurred overall for the outcome of discontinuation due to adverse events. All things considered, this results in a hint of greater benefit of ponesimod in comparison with teriflunomide.

References for English extract

Please see full final report for full reference list.

1. Holstiege J, Steffen A, Goffrier B, Bätzing J. Epidemiologie der Multiplen Sklerose – eine populationsbasierte deutschlandweite Studie [online]. 2018 [Accessed: 11.11.2020]. URL: https://www.versorgungsatlas.de/fileadmin/ziva_docs/86/VA-86-Multiple%20Sklerose-Bericht-V13_Cor..pdf.

2. Kip M, Schönfelder T, Bleß HH. Weißbuch Multiple Sklerose: Versorgungssituation in Deutschland [online]. 2016 [Accessed: 30.11.2020]. URL: https://link.springer.com/content/pdf/10.1007%2F978-3-662-49204-8.pdf.

3. Flachenecker P, Stuke K, Elias W et al. Multiple sclerosis registry in Germany: results of the extension phase 2005/2006. Dtsch Arztebl Int 2008; 105(7): 113-119. https://doi.org/10.3238/arztebl.2008.0113.

4. Kister I, Bacon TE, Chamot E et al. Natural history of multiple sclerosis symptoms. Int J MS Care 2013; 15(3): 146-158. https://doi.org/10.7224/1537-2073.2012-053.

5. Hemmer B. Diagnose und Therapie der Multiplen Sklerose, Neuromyelitis-optica-Spektrum-Erkrankungen und MOG-IgG-assoziierten Erkrankungen; 1. Aktualisierung als Living Guideline 2023 [online]. 2023 [Accessed: 11.07.2023]. URL: https://register.awmf.org/assets/guidelines/030-050l_S2k_Diagnose-Therapie-Multiple-Sklerose-Neuromyelitis-Optica-Spektrum-MOG-IgG-assoziierte-Erkrankungen_2023-05.pdf.

6. Thompson AJ, Banwell BL, Barkhof F et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018; 17(2): 162-173. https://doi.org/10.1016/S1474-4422(17)30470-2.

7. Kappos L, Wolinsky JS, Giovannoni G et al. Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials. JAMA Neurol 2020; 77(9): 1132-1140. https://doi.org/10.1001/jamaneurol.2020.1568.

8. Thompson AJ, Baranzini SE, Geurts J et al. Multiple sclerosis. Lancet 2018; 391(10130): 1622-1636. https://doi.org/10.1016/S0140-6736(18)30481-1.

9. Lublin FD. New multiple sclerosis phenotypic classification. Eur Neurol 2014; 72(Suppl 1): 1-5. https://doi.org/10.1159/000367614.

10. Krause I, Kern S, Horntrich A, Ziemssen T. Employment status in multiple sclerosis: impact of disease-specific and non-disease-specific factors. Mult Scler 2013; 19(13): 1792-1799. https://doi.org/10.1177/1352458513485655.

11. Pucak ML, Carroll KA, Kerr DA, Kaplin AI. Neuropsychiatric manifestations of depression in multiple sclerosis: neuroinflammatory, neuroendocrine, and neurotrophic mechanisms in the pathogenesis of immune-mediated depression. Dialogues Clin Neurosci 2007; 9(2): 125-139.

12. Vattakatuchery JJ, Rickards H, Cavanna AE. Pathogenic mechanisms of depression in multiple sclerosis. J Neuropsychiatry Clin Neurosci 2011; 23(3): 261-276. https://doi.org/10.1176/jnp.23.3.jnp261.

13. Heesen C, Haase R, Melzig S et al. Perceptions on the value of bodily functions in multiple sclerosis. Acta Neurol Scand 2018; 137(3): 356-362. https://doi.org/10.1111/ane.12881.

14. Diaz C, Zarco LA, Rivera DM. Highly active multiple sclerosis: An update. Mult Scler Relat Disord 2019; 30: 215-224. https://doi.org/10.1016/j.msard.2019.01.039.

15. Ellenberger D, Flachenecker P, Fneish F et al. Aggressive multiple sclerosis: a matter of measurement and timing. Brain 2020; 143(11): e97. https://doi.org/10.1093/brain/awaa306.

16. Iacobaeus E, Arrambide G, Pia Amato M et al. Aggressive multiple sclerosis (1): Towards a definition of the phenotype. Mult Scler 2020; 26(9): 1031-1044. https://doi.org/10.1177/1352458520925369.

17. Arrambide G, Iacobaeus E, Amato MP et al. Aggressive multiple sclerosis (2): Treatment. Mult Scler 2020; 26: 1045-1063. https://doi.org/10.1177/1352458520924595.

18. Biogen. Tysabri 300 mg [online]. 2022 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

19. Biogen. Tysabri 150 mg Injektionslösung in einer Fertigspritze [online]. 2022 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

20. Biogen. Tecfidera 120 mg/240 mg magensaftresistente Hartkapseln [online]. 2022 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

21. Janssen. Ponvory Filmtabletten [online]. 2022 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

22. Merck. Mavenclad 10 mg Tabletten [online]. 2022 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

23. Pharma N. Gilenya Hartkapseln [online]. 2023 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

24. Pharma N. Kesimpta 20 mg Injektionslösung in einer Fertigspritze; Kesimpta 20 mg Injektionslösung im Fertigpen [online]. 2023 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

25. Roche. Ocrevus [online]. 2023 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

26. Sanofi. AUBAGIO 7 mg Filmtabletten; AUBAGIO 14 mg Filmtabletten [online]. 2022 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

27. Sanofi Genzyme. LEMTRADA 12 mg Konzentrat zur Herstellung einer Infusionslösung [online]. 2022 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

28. Bristol Myers Squibb. Zeposia Hartkapseln [online]. 2023 [Accessed: 13.07.2023]. URL: https://www.fachinfo.de/.

29. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.0 [online]. 2020 [Accessed: 30.11.2020]. URL: https://www.iqwig.de/download/Allgemeine-Methoden_Version-6-0.pdf.

30. Ohlmeier C, Gothe H, Haas J et al. Epidemiology, characteristics and treatment of patients with relapsing remitting multiple sclerosis and incidence of high disease activity: Real world evidence based on German claims data. PLoS One 2020; 15(5): e0231846. https://doi.org/10.1371/journal.pone.0231846.

31. Spelman T, Freilich J, Anell B et al. Patients With High-disease-activity Relapsing-Remitting Multiple Sclerosis in Real-world Clinical Practice: A Population-based Study in Sweden. Clin Ther 2020; 42(2): 240-250. https://doi.org/10.1016/j.clinthera.2019.11.018.

32. NHS England. Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies [online]. 2019 [Accessed: 30.11.2020]. URL: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf.

33. Gasperini C, Prosperini L, Tintore M et al. Unraveling treatment response in multiple sclerosis: A clinical and MRI challenge. Neurology 2019; 92(4): 180-192. https://doi.org/10.1212/WNL.0000000000006810.

34. Rio J, Rovira A, Tintore M et al. Disability progression markers over 6-12 years in interferon-beta-treated multiple sclerosis patients. Mult Scler 2018; 24(3): 322-330. https://doi.org/10.1177/1352458517698052.

35. Rio J, Comabella M, Montalban X. Predicting responders to therapies for multiple sclerosis. Nat Rev Neurol 2009; 5(10): 553-560. https://doi.org/10.1038/nrneurol.2009.139.

36. Paty DW, McFarland H. Magnetic resonance techniques to monitor the long term evolution of multiple sclerosis pathology and to monitor definitive clinical trials. J Neurol Neurosurg Psychiatry 1998; 64 Suppl 1: S47-51.

37. Cotton F, Weiner HL, Jolesz FA, Guttmann CR. MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals. Neurology 2003; 60(4): 640-646. https://doi.org/10.1212/01.wnl.0000046587.83503.1e.

38. Gulani V, Calamante F, Shellock FG et al. Gadolinium deposition in the brain: summary of evidence and recommendations. Lancet Neurol 2017; 16(7): 564-570. https://doi.org/10.1016/S1474-4422(17)30158-8.

39. Deutsche Röntgengesellschaft. Gadolinium-haltige Kontrastmittel in der Magnetresonanztomographie [online]. 2019 [Accessed: 17.12.2020]. URL: https://www.drg.de/de-DE/3994/mrt-kt/.

40. Sormani MP, Gasperini C, Romeo M et al. Assessing response to interferon-beta in a multicenter dataset of patients with MS. Neurology 2016; 87(2): 134-140. https://doi.org/10.1212/WNL.0000000000002830.

41. Sormani MP, Truffinet P, Thangavelu K et al. Predicting long-term disability outcomes in patients with MS treated with teriflunomide in TEMSO. Neurol Neuroimmunol Neuroinflamm 2017; 4(5): e379. https://doi.org/10.1212/NXI.0000000000000379.

42. Saslow L, Li DKB, Halper J et al. An International Standardized Magnetic Resonance Imaging Protocol for Diagnosis and Follow-up of Patients with Multiple Sclerosis: Advocacy, Dissemination, and Implementation Strategies. Int J MS Care 2020; 22(5): 226-232. https://doi.org/10.7224/1537-2073.2020-094.

43. European Medicines Agency. Tysabri; EPAR; Scientific Discussion [online]. 2007 [Accessed: 15.07.2021]. URL: https://www.ema.europa.eu/documents/scientific-discussion/tysabri-epar-scientific-discussion_en.pdf.

44. Wattjes MP, Ciccarelli O, Reich DS et al. 2021 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. Lancet Neurol 2021. https://doi.org/10.1016/S1474-4422(21)00095-8.

45. Freedman MS, Devonshire V, Duquette P et al. Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. Can J Neurol Sci 2020; 47(4): 437-455. https://doi.org/10.1017/cjn.2020.66.

46. Lublin FD, Reingold SC, Cohen JA et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014; 83(3): 278-286. https://doi.org/10.1212/WNL.0000000000000560.

47. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis [online]. 2015 [Accessed: 10.08.2020]. URL: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-multiple-sclerosis_en-0.pdf.

48. Lublin FD, Haring DA, Ganjgahi H et al. How patients with multiple sclerosis acquire disability. Brain 2022; 145(9): 3147-3161. https://doi.org/10.1093/brain/awac016.

49. Krankheitsbezogenes Kompetenznetz Multiple Sklerose. Qualitätshandbuch [online]. [Accessed: 11.01.2023]. URL: https://ms-qualitaetshandbuch.de/.

50. Montalban X, Gold R, Thompson AJ et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Eur J Neurol 2018; 25(2): 215-237. https://doi.org/10.1111/ene.13536.

51. Freedman MS, Selchen D, Prat A, Giacomini PS. Managing Multiple Sclerosis: Treatment Initiation, Modification, and Sequencing. Can J Neurol Sci 2018; 45(5): 489-503. https://doi.org/10.1017/cjn.2018.17.

52. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med 2000; 343(13): 938-952. https://doi.org/10.1056/NEJM200009283431307.

53. Sklerose KM. Qualitätshandbuch MS / NMOSD. Empfehlungen zur Therapie der Multiplen Sklerose / Neuromyelitis-optica-Spektrum-Erkrankungen für Ärzte. [online]. [Accessed: 10.08.2029]. URL: https://www.kompetenznetz-multiplesklerose.de/wp-content/uploads/2020/03/KKNMS_Qualit%C3%A4tshandbuch-MSNMOSD_202001_webfrei-1.pdf.

54. Cleveland Clinic. Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for RRMS (DELIVER-MS) [online]. 2023 [Accessed: 28.08.2023]. URL: https://ClinicalTrials.gov/show/NCT03535298.

55. Johns Hopkins University. Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial (TREAT-MS) [online]. 2023 [Accessed: 28.08.2023]. URL: https://ClinicalTrials.gov/show/NCT03500328.

56. Marziniak M, Ghorab K, Kozubski W et al. Variations in multiple sclerosis practice within Europe - Is it time for a new treatment guideline? Mult Scler Relat Disord 2016; 8: 35-44. https://doi.org/10.1016/j.msard.2016.04.004.

57. Rotstein D, Montalban X. Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. Nat Rev Neurol 2019; 15(5): 287-300. https://doi.org/10.1038/s41582-019-0170-8.

58. Carlin CS, Higuera L, Anderson S. Improving Patient-Centered Care by Assessing Patient Preferences for Multiple Sclerosis Disease-Modifying Agents: A Stated-Choice Experiment. Perm J 2017; 21: 16-102. https://doi.org/10.7812/TPP/16-102.

59. Garcia-Dominguez JM, Munoz D, Comellas M et al. Patient preferences for treatment of multiple sclerosis with disease-modifying therapies: a discrete choice experiment. Patient Prefer Adherence 2016; 10: 1945-1956. https://doi.org/10.2147/PPA.S114619.

60. Lee Mortensen G, Rasmussen PV. The impact of quality of life on treatment preferences in multiple sclerosis patients. Patient Prefer Adherence 2017; 11: 1789-1796. https://doi.org/10.2147/PPA.S142373.

61. Poulos C, Wakeford C, Kinter E et al. Patient and physician preferences for multiple sclerosis treatments in Germany: A discrete-choice experiment study. Mult Scler J Exp Transl Clin 2020; 6(1): 2055217320910778. https://doi.org/10.1177/2055217320910778.

62. Wilson LS, Loucks A, Gipson G et al. Patient preferences for attributes of multiple sclerosis disease-modifying therapies: development and results of a ratings-based conjoint analysis. Int J MS Care 2015; 17(2): 74-82. https://doi.org/10.7224/1537-2073.2013-053.

63. Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. Mayo Clin Proc 2014; 89(2): 225-240. https://doi.org/10.1016/j.mayocp.2013.11.002.

64. Gehr S, Kaiser T, Kreutz R et al. Suggestions for improving the design of clinical trials in multiple sclerosis-results of a systematic analysis of completed phase III trials. EPMA J 2019; 10(4): 425-436. https://doi.org/10.1007/s13167-019-00192-z.

65. Kalincik T, Cutter G, Spelman T et al. Defining reliable disability outcomes in multiple sclerosis. Brain 2015; 138(Pt 11): 3287-3298. https://doi.org/10.1093/brain/awv258.

66. Huisman E, Papadimitropoulou K, Jarrett J et al. Systematic literature review and network meta-analysis in highly active relapsing-remitting multiple sclerosis and rapidly evolving severe multiple sclerosis. BMJ Open 2017; 7(3): e013430. https://doi.org/10.1136/bmjopen-2016-013430.

67. Tramacere I, Del Giovane C, Salanti G et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev 2015; (9): CD011381. https://doi.org/10.1002/14651858.CD011381.pub2.

68. Fogarty E, Schmitz S, Tubridy N et al. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: systematic review and network meta-analysis. Mult Scler Relat Disord 2016; 9: 23-30. https://doi.org/10.1016/j.msard.2016.06.001.

69. Li H, Hu F, Zhang Y, Li K. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. J Neurol 2020; 267(12): 3489-3498. https://doi.org/10.1007/s00415-019-09395-w.

70. Sladowska K, Kawalec P, Holko P, Osiecka O. Comparative safety of high-efficacy disease-modifying therapies in relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. Neurol Sci 2022; 43(9): 5479-5500. https://doi.org/10.1007/s10072-022-06197-3.

71. Liu Z, Liao Q, Wen H, Zhang Y. Disease modifying therapies in relapsing-remitting multiple sclerosis: A systematic review and network meta-analysis. Autoimmun Rev 2021; 20(6): 102826. https://doi.org/10.1016/j.autrev.2021.102826.

72. Polman CH, O'Connor PW, Havrdova E et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354(9): 899-910. https://doi.org/10.1056/NEJMoa044397.

73. Rudick RA, Stuart WH, Calabresi PA et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med 2006; 354(9): 911-923. https://doi.org/10.1056/NEJMoa044396.

74. Arroyo Gonzalez R, Kita M, Crayton H et al. Alemtuzumab improves quality-of-life outcomes compared with subcutaneous interferon beta-1a in patients with active relapsing-remitting multiple sclerosis. Mult Scler 2017; 23(10): 1367-1376. https://doi.org/10.1177/1352458516677589.

75. Giovannoni G, Cohen JA, Coles AJ et al. Alemtuzumab improves preexisting disability in active relapsing-remitting MS patients. Neurology 2016; 87(19): 1985-1992. https://doi.org/10.1212/wnl.0000000000003319.

76. Arnold DL, Fisher E, Brinar VV et al. Superior MRI outcomes with alemtuzumab compared with subcutaneous interferon beta-1a in MS. Neurology 2016; 87(14): 1464-1472. https://doi.org/10.1212/wnl.0000000000003169.

77. Coles AJ, Twyman CL, Arnold DL et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012; 380(9856): 1829-1839. https://doi.org/10.1016/s0140-6736(12)61768-1.

78. Ziemssen T, Bass AD, Berkovich R et al. Efficacy and Safety of Alemtuzumab Through 9 Years of Follow-up in Patients with Highly Active Disease: Post Hoc Analysis of CARE-MS I and II Patients in the TOPAZ Extension Study. CNS Drugs 2020; 34(9): 973-988. https://doi.org/10.1007/s40263-020-00749-x.

79. Genzyme. A Phase 3 Randomized, Rater- and Dose-Blinded Study Comparing Two Annual Cycles of Intravenous Low- and High-Dose Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1a (Rebif) in Patients with Relapsing-Remitting Multiple Scleroris Who Have Relapsed On Therapy [online]. [Accessed: 18.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-001162-32.

80. Genzyme a Sanofi Company. Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis, Study Two (CARE-MS II) [online]. 2017 [Accessed: 12.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00548405.

81. Genzyme. A Phase 3 Randomized, Rater- and Dose-Blinded Study Comparing Two Annual Cycles of Intravenous Low- and High-Dose Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1a (Rebif) in Patients with Relapsing-Remitting Multiple Sclerosis who Have Relapsed on Therapy (CARE-MS II); Study CAMMS32400507; Final Clinical Study Report [unpublished]. 2012.

82. Afolabi D, Albor C, Zalewski L et al. Positive impact of cladribine on quality of life in people with relapsing multiple sclerosis. Mult Scler 2018; 24(11): 1461-1468. https://doi.org/10.1177/1352458517726380.

83. Ali S, Paracha N, Cook S et al. Reduction in healthcare and societal resource utilization associated with cladribine tablets in patients with relapsing-remitting multiple sclerosis: analysis of economic data from the CLARITY Study. Clin Drug Investig 2012; 32(1): 15-27. https://doi.org/10.2165/11593310-000000000-00000.

84. Comi G, Cook SD, Giovannoni G et al. MRI outcomes with cladribine tablets for multiple sclerosis in the CLARITY study. J Neurol 2013; 260(4): 1136-1146. https://doi.org/10.1007/s00415-012-6775-0.

85. Cook S, Vermersch P, Comi G et al. Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) study. Mult Scler 2011; 17(5): 578-593. https://doi.org/10.1177/1352458510391344.

86. De Stefano N, Giorgio A, Battaglini M et al. Reduced brain atrophy rates are associated with lower risk of disability progression in patients with relapsing multiple sclerosis treated with cladribine tablets. Mult Scler 2018; 24(2): 222-226. https://doi.org/10.1177/1352458517690269.

87. Giovannoni G, Comi G, Cook S et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med 2010; 362(5): 416-426. https://doi.org/10.1056/NEJMoa0902533.

88. Giovannoni G, Cook S, Rammohan K et al. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. Lancet Neurol 2011; 10(4): 329-337. https://doi.org/10.1016/s1474-4422(11)70023-0.

89. Giovannoni G, Soelberg Sorensen P, Cook S et al. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Mult Scler 2019; 25(6): 819-827. https://doi.org/10.1177/1352458518771875.

90. Hermann R, Litwin JS, Friberg LE et al. Effects of cladribine tablets on heart rate, atrio-ventricular conduction and cardiac repolarization in patients with relapsing multiple sclerosis. Br J Clin Pharmacol 2019; 85(7): 1484-1494. https://doi.org/10.1111/bcp.13919.

91. Rammohan K, Giovannoni G, Comi G et al. Cladribine tablets for relapsing-remitting multiple sclerosis: Efficacy across patient subgroups from the phase III CLARITY study. Multiple Sclerosis and Related Disorders 2012; 1(1): 49-54. https://doi.org/10.1016/j.msard.2011.08.006.

92. Terranova N, Hicking C, Dangond F, Munafo A. Effects of Postponing Treatment in the Second Year of Cladribine Administration: Clinical Trial Simulation Analysis of Absolute Lymphocyte Counts and Relapse Rate in Patients with Relapsing-Remitting Multiple Sclerosis. Clin Pharmacokinet 2019; 58(3): 325-333. https://doi.org/10.1007/s40262-018-0693-y.

93. Vermersch P, Galazka A, Dangond F et al. Efficacy of cladribine tablets in high disease activity patients with relapsing multiple sclerosis: Post hoc analysis of subgroups with and without prior disease-modifying drug treatment. Curr Med Res Opin 2020: 1. https://doi.org/10.1080/03007995.2020.1865888.

94. De Stefano N, Sormani MP, Giovannoni G et al. Analysis of frequency and severity of relapses in multiple sclerosis patients treated with cladribine tablets or placebo: The CLARITY and CLARITY Extension studies. Mult Scler 2021: 13524585211010294. https://doi.org/10.1177/13524585211010294.

95. Giovannoni G, Comi G, Rammohan K et al. Long-Term Disease Stability Assessed by the Expanded Disability Status Scale in Patients Treated with Cladribine Tablets 3.5 mg/kg for Relapsing Multiple Sclerosis: An Exploratory Post Hoc Analysis of the CLARITY and CLARITY Extension Studies. Adv Ther 2021; 38(9): 4975-4985. https://doi.org/10.1007/s12325-021-01865-w.

96. EMD Serono. A Safety and Efficacy Study of Oral Cladribine in Subjects With Relapsing-remitting Multiple Sclerosis (RRMS) (CLARITY) [online]. 2014 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00213135.

97. Merck Serono International. A phase III, randomised, double-blind, three-arm, placebo-controlled, multi-center study to evaluate the safety and efficacy of oral Cladribine in subjects with relapsing remitting multiple sclerosis [online]. [Accessed: 14.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004-005148-28.

98. Merck. A phase III, randomized, double-blind, three-arm, placebo-controlled, multi-center study to evaluate the safety and efficacy of oral cladribine in subjects with relapsing-remitting multiple sclerosis (RRMS); Study 25643; Clinical Trial Report [unpublished]. 2010.

99. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Cladribin (Hochaktive schubförmige Multiple Sklerose) [online]. 2018 [Accessed: 03.09.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/334/.

100. Fox RJ, Miller DH, Phillips JT et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012; 367(12): 1087-1097. https://doi.org/10.1056/NEJMoa1206328.

101. Hutchinson M, Fox RJ, Miller DH et al. Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the CONFIRM study. J Neurol 2013; 260(9): 2286-2296. https://doi.org/10.1007/s00415-013-6968-1.

102. Kita M, Fox RJ, Phillips JT et al. Effects of BG-12 (dimethyl fumarate) on health-related quality of life in patients with relapsing-remitting multiple sclerosis: findings from the CONFIRM study. Mult Scler 2014; 20(2): 253-257. https://doi.org/10.1177/1352458513507818.

103. Miller DH, Fox RJ, Phillips JT et al. Effects of delayed-release dimethyl fumarate on MRI measures in the phase 3 CONFIRM study. Neurology 2015; 84(11): 1145-1152. https://doi.org/10.1212/wnl.0000000000001360.

104. Havrdova E, Giovannoni G, Gold R et al. Effect of delayed-release dimethyl fumarate on no evidence of disease activity in relapsing-remitting multiple sclerosis: integrated analysis of the phase III DEFINE and CONFIRM studies. Eur J Neurol 2017; 24(5): 726-733. https://doi.org/10.1111/ene.13272.

105. Freedman MS, Montalban X, Miller AE et al. Comparing outcomes from clinical studies of oral disease-modifying therapies (dimethyl fumarate, fingolimod, and teriflunomide) in relapsing MS: Assessing absolute differences using a number needed to treat analysis. Multiple Sclerosis and Related Disorders 2016; 10: 204-212. https://doi.org/10.1016/j.msard.2016.10.010.

106. Biogen. Efficacy and Safety Study of Oral BG00012 With Active Reference in Relapsing-Remitting Multiple Sclerosis (CONFIRM) [online]. 2015 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00451451.

107. Biogen Idec. A Randomized, Multicenter, Placebo-Controlled and Active Reference (Glatiramer Acetate) Comparison Study to Evaluate the Efficacy and Safety of BG00012 in Subjects With Relapsing-Remitting Multiple Sclerosis [online]. [Accessed: 14.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-003697-10.

108. Biogen Idec. A Randomized, Multicenter, Placebo-Controlled and Active Reference (Glatiramer Acetate) Comparison Study to Evaluate the Efficacy and Safety of BG00012 in Subjects With Relapsing-Remitting Multiple Sclerosis [online]. 2013 [Accessed: 18.05.2021]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=380.

109. Biogen Idec. A Randomized, Multicenter, Placebo-Controlled and Active Reference (Glatiramer Acetate) Comparison Study to Evaluate the Efficacy and Safety of BG00012 in Subjects With Relapsing-Remitting Multiple Sclerosis; Study 109MS302; Clinical Study Report [unpublished]. 2012.

110. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Dimethylfumarat (Schubförmig remittierende Multiple Sklerose) [online]. 2014 [Accessed: 03.09.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/111/.

111. Arnold DL, Gold R, Kappos L et al. Effects of delayed-release dimethyl fumarate on MRI measures in the Phase 3 DEFINE study. J Neurol 2014; 261(9): 1794-1802. https://doi.org/10.1007/s00415-014-7412-x.

112. Arnold DL, Gold R, Kappos L et al. Magnetization transfer ratio in the delayed-release dimethyl fumarate DEFINE study. J Neurol 2014; 261(12): 2429-2437. https://doi.org/10.1007/s00415-014-7504-7.

113. Bar-Or A, Gold R, Kappos L et al. Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the DEFINE study. J Neurol 2013; 260(9): 2297-2305. https://doi.org/10.1007/s00415-013-6954-7.

114. Gold R, Kappos L, Arnold DL et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012; 367(12): 1098-1107. https://doi.org/10.1056/NEJMoa1114287.

115. Kappos L, Gold R, Arnold DL et al. Quality of life outcomes with BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: the DEFINE study. Mult Scler 2014; 20(2): 243-252. https://doi.org/10.1177/1352458513507817.

116. Biogen. Efficacy and Safety of Oral BG00012 in Relapsing-Remitting Multiple Sclerosis (DEFINE) [online]. 2015 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00420212.

117. Biogen Idec. A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Dose-Comparison Study to Determine the Efficacy and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis [online]. [Accessed: 14.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-003696-12.

118. Biogen Idec. A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Dose-Comparison Study to Determine the Efficacy and Safety of BG00012 in Subjects With Relapsing-Remitting Multiple Sclerosis [online]. 2015 [Accessed: 18.05.2021]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=356.

119. Biogen Idec. A Randomized, Multicentre, Double-Blind, Placebo-Controlled, Dose-Comparison Study to Determine the Safety and Efficacy of BG00012 in Subjects with Relapsing Remitting Multiple Sclerosis [online]. 2007 [Accessed: 18.05.2021]. URL: https://anzctr.org.au/ACTRN12607000124437.aspx.

120. Biogen Idec. A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Dose-Comparison Study to Determine the Efficacy and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis; Study 109MS301; Clinical Study Report [unpublished]. 2012.

121. Gold R, Arnold DL, Bar-Or A et al. Safety and efficacy of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis: 9 years'follow-up of DEFINE, CONFIRM, and ENDORSE. Ther Adv Neurol Disord 2020; 13: 1756286420915005. https://doi.org/10.1177/1756286420915005.

122. Gold R, Arnold DL, Bar-Or A et al. Long-term effects of delayed-release dimethyl fumarate in multiple sclerosis: Interim analysis of ENDORSE, a randomized extension study. Mult Scler 2017; 23(2): 253-265. https://doi.org/10.1177/1352458516649037.

123. Gold R, Arnold DL, Bar-Or A et al. Long-term safety and efficacy of dimethyl fumarate for up to 13 years in patients with relapsing-remitting multiple sclerosis: Final ENDORSE study results. Mult Scler 2021: 13524585211037909. https://doi.org/10.1177/13524585211037909.

124. Biogen. BG00012 Monotherapy Safety and Efficacy Extension Study in Multiple Sclerosis (MS) (ENDORSE) [online]. 2020 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00835770.

125. Biogen Idec. A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis [online]. [Accessed: 14.04.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-004753-14.

126. Biogen Idec. A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis [online]. 2015 [Accessed: 18.05.2021]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=1495.

127. Biogen. A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis; Study 109MS303; Clinical Study Report [unpublished]. 2020.

128. Svenningsson A. RItuximab Versus FUmarate in Newly Diagnosed Multiple Sclerosis. (RIFUND-MS) [online]. 2020 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT02746744.

129. Department of Clinical Sciences, Danderyd Hospital. RItuximab versus FUmarate in Newly Diagnosed Multiple Sclerosis – RIFUND-MS A randomized phase 3 study comparing Rituximab with Dimethyl Fumarate in early Relapsing-Remitting Multiple Sclerosis [online]. [Accessed: 18.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-004116-38.

130. Novartis. Efficacy and Safety of FTY720 in Patients With Relapsing Multiple Sclerosis (MS) [online]. 2011 [Accessed: 21.03.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT00537082.

131. Novartis / Mitsubishi Tanabe Pharma. A 6-month, double-blind, randomized, placebo-controlled, parallel-group, multicenter study comparing efficacy and safety of FTY720 0.5 mg and 1.25 mg administered orally once daily in patients with relapsing multiple sclerosis (MS); Study CFTY720D1201; Clinical Study Report [unpublished]. 2010.

132. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Fingolimod (neues Anwendungsgebiet: hochaktive schubförmig remittierende Multiple Sklerose, nach unzureichender Vorbehandlung) [online]. 2016 [Accessed: 03.09.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/202/.

133. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Fingolimod (Neubewertung nach Fristablauf: rasch fortschreitende schubförmig remittierende Multiple Sklerose) [online]. 2015 [Accessed: 03.09.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/165/.

134. Novartis. An Extension Study of the Efficacy and Safety of Fingolimod (FTY720) in Patients With Relapsing Multiple Sclerosis [online]. 2013 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00670449.

135. Novartis / Mitsubishi Tanabe Pharma. An extension of the 6-month, double-blind, randomized, placebo-controlled, parallel-group, multicenter study comparing efficacy and safety of FTY720 0.5 mg and 1.25 mg administered orally once daily in patients with relapsing multiple sclerosis; Study CFTY720D1201E1; Clinical Study Report [unpublished]. 2012.

136. Agius M, Meng X, Chin P et al. Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom. CNS Neurosci Ther 2014; 20(5): 446-451. https://doi.org/10.1111/cns.12235.

137. Devonshire V, Havrdova E, Radue EW et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol 2012; 11(5): 420-428. https://doi.org/10.1016/s1474-4422(12)70056-x.

138. Kappos L, Radue EW, O'Connor P et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010; 362(5): 387-401. https://doi.org/10.1056/NEJMoa0909494.

139. Kremenchutzky M, O'Connor P, Hohlfeld R et al. Impact of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod: Subgroup analyses of the Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study. Multiple Sclerosis and Related Disorders 2014; 3(3): 341-349. https://doi.org/10.1016/j.msard.2013.10.006.

140. Kuhle J, Disanto G, Lorscheider J et al. Fingolimod and CSF neurofilament light chain levels in relapsing-remitting multiple sclerosis. Neurology 2015; 84(16): 1639-1643. https://doi.org/10.1212/wnl.0000000000001491.

141. Radue EW, O'Connor P, Polman CH et al. Impact of fingolimod therapy on magnetic resonance imaging outcomes in patients with multiple sclerosis. Arch Neurol 2012; 69(10): 1259-1269. https://doi.org/10.1001/archneurol.2012.1051.

142. Sormani MP, De Stefano N, Francis G et al. Fingolimod effect on brain volume loss independently contributes to its effect on disability. Mult Scler 2015; 21(7): 916-924. https://doi.org/10.1177/1352458515569099.

143. Sormani MP, Haering DA, Kropshofer H et al. Blood neurofilament light as a potential endpoint in Phase 2 studies in MS. Ann Clin Transl Neurol 2019; 6(6): 1081-1089. https://doi.org/10.1002/acn3.795.

144. Gartner J, Chitnis T, Ghezzi A et al. Relapse Rate and MRI Activity in Young Adult Patients With Multiple Sclerosis: A Post Hoc Analysis of Phase 3 Fingolimod Trials. Mult Scler J Exp Transl Clin 2018; 4(2): 2055217318778610. https://doi.org/10.1177/2055217318778610.

145. Radue EW, Barkhof F, Kappos L et al. Correlation between brain volume loss and clinical and MRI outcomes in multiple sclerosis. Neurology 2015; 84(8): 784-793. https://doi.org/10.1212/wnl.0000000000001281.

146. Kuhle J, Kropshofer H, Haering DA et al. Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. Neurology 2019; 92(10): e1007-e1015. https://doi.org/10.1212/wnl.0000000000007032.

147. Jeffery DR, Di Cantogno EV, Ritter S et al. The relationship between the rate of brain volume loss during first 24 months and disability progression over 24 and 48 months in relapsing MS. J Neurol 2016; 263(2): 299-305. https://doi.org/10.1007/s00415-015-7959-1.

148. Vermersch P, Radue EW, Putzki N et al. A comparison of multiple sclerosis disease activity after discontinuation of fingolimod and placebo. Mult Scler J Exp Transl Clin 2017; 3(3): 2055217317730096. https://doi.org/10.1177/2055217317730096.

149. Novartis. Efficacy and Safety of Fingolimod in Patients With Relapsing-remitting Multiple Sclerosis (FREEDOMS) [online]. 2012 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00289978.

150. Novartis Pharma Services. A 24-month, double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis [online]. [Accessed: 14.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-000365-19.

151. Novartis. A 24-month double-blind, randomized, multicenter, active-controlled, parallel-group study comparing the efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing- remitting multiple sclerosis; Study FTY720D2301; Clinical Study Report [unpublished]. 2009.

152. Kappos L, O'Connor P, Radue EW et al. Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial. Neurology 2015; 84(15): 1582-1591. https://doi.org/10.1212/wnl.0000000000001462.

153. Novartis Pharma. An extension of the 24-month, double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis [online]. [Accessed: 14.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-004122-24.

154. Novartis. An extension of the 24-month, double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis; Study CFTY720D2301E1; Clinical Study Report [unpublished]. 2011.

155. Calabresi PA, Radue EW, Goodin D et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 2014; 13(6): 545-556. https://doi.org/10.1016/s1474-4422(14)70049-3.

156. Winges KM, Werner JS, Harvey DJ et al. Baseline retinal nerve fiber layer thickness and macular volume quantified by OCT in the North American phase 3 fingolimod trial for relapsing-remitting multiple sclerosis. J Neuroophthalmol 2013; 33(4): 322-329. https://doi.org/10.1097/WNO.0b013e31829c51f7.

157. Novartis. Efficacy and Safety of Fingolimod (FTY720) in Patients With Relapsing-remitting Multiple Sclerosis (FREEDOMS II) [online]. 2012 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00355134.

158. Novartis Pharma Services. A 24-month double-blind, randomized, multicenter, placebocontrolled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis [online]. [Accessed: 14.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-002096-27.

159. Novartis. A 24-month double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis; Study CFTY720D2309; Clinical Study Report [unpublished]. 2011.

160. Novartis. A 24-month double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis with optional Extension phase; Study CFTY720D2309E1; Clinical Study Report [unpublished]. 2012.

161. Barkhof F, de Jong R, Sfikas N et al. The influence of patient demographics, disease characteristics and treatment on brain volume loss in Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS), a phase 3 study of fingolimod in multiple sclerosis. Mult Scler 2014; 20(13): 1704-1713. https://doi.org/10.1177/1352458514532317.

162. Cohen JA, Barkhof F, Comi G et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010; 362(5): 402-415. https://doi.org/10.1056/NEJMoa0907839.

163. Cohen JA, Barkhof F, Comi G et al. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. J Neurol 2013; 260(8): 2023-2032. https://doi.org/10.1007/s00415-013-6932-0.

164. Haas J, Jeffery D, Silva D et al. Early initiation of fingolimod reduces the rate of severe relapses over the long term: Post hoc analysis from the FREEDOMS, FREEDOMS II, and TRANSFORMS studies. Multiple Sclerosis and Related Disorders 2019; 36: 101335. https://doi.org/10.1016/j.msard.2019.07.011.

165. Khatri BO, Pelletier J, Kappos L et al. Effect of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod vs. interferon beta-1a intramuscular: Subgroup analyses of the Trial Assessing Injectable Interferon vs. Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS). Multiple Sclerosis and Related Disorders 2014; 3(3): 355-363. https://doi.org/10.1016/j.msard.2013.11.006.

166. Agashivala N, Kim E. Cost-effectiveness of early initiation of fingolimod versus delayed initiation after 1 year of intramuscular interferon beta-1a in patients with multiple sclerosis. Clin Ther 2012; 34(7): 1583-1590. https://doi.org/10.1016/j.clinthera.2012.06.012.

167. Cree BA, Cohen JA, Reder AT et al. Disability improvement as a clinically relevant outcome in clinical trials of relapsing forms of multiple sclerosis. Mult Scler 2021: 13524585211000280. https://doi.org/10.1177/13524585211000280.

168. Novartis. Efficacy and Safety of Fingolimod in Patients With Relapsing-remitting Multiple Sclerosis With Optional Extension Phase (TRANSFORMS) [online]. 2017 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00340834.

169. Novartis Pharma Services. A 12-month double-blind, randomized, multicenter, active controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon β-1a (Avonex) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional Extension Phase [online]. [Accessed: 18.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-000704-17.

170. Novartis. A 12-month double-blind, randomized, multicenter, active-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon β-1a (Avonex) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional Extension Phase; Study CFTY720D2302; Clinical Study Report [unpublished]. 2009.

171. Cohen JA, Khatri B, Barkhof F et al. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. Journal of Neurology, Neurosurgery & Psychiatry 2016; 87(5): 468-475. https://doi.org/10.1136/jnnp-2015-310597.

172. Khatri B, Barkhof F, Comi G et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. Lancet Neurol 2011; 10(6): 520-529. https://doi.org/10.1016/s1474-4422(11)70099-0.

173. Meng X, Chin PS, Hashmonay R et al. Effect of switching from intramuscular interferon beta-1a to oral fingolimod on time to relapse in patients with relapsing-remitting multiple sclerosis enrolled in a 1-year extension of TRANSFORMS. Contemp Clin Trials 2015; 41: 69-74. https://doi.org/10.1016/j.cct.2014.12.011.

174. Novartis. A 12-month double-blind, randomized, multicenter, active-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720)administered orally once daily versus interferon β-1a (Avonex) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional Extension phase; Study FTY720D2302E1; Clinical Study Report [unpublished]. 2011.

175. Rennes University Hospital. Impact Study of 2 Therapeutic Strategy for Aggressive Remitting Multiple Sclerosis (IQUALYSEP) [online]. 2012 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT01065727.

176. Barkhof F, Kappos L, Wolinsky JS et al. Onset of clinical and MRI efficacy of ocrelizumab in relapsing multiple sclerosis. Neurology 2019; 93(19): e1778-e1786. https://doi.org/10.1212/wnl.0000000000008189.

177. Hauser SL, Bar-Or A, Comi G et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med 2017; 376(3): 221-234. https://doi.org/10.1056/NEJMoa1601277.

178. Mayer L, Kappos L, Racke MK et al. Ocrelizumab infusion experience in patients with relapsing and primary progressive multiple sclerosis: Results from the phase 3 randomized OPERA I, OPERA II, and ORATORIO studies. Multiple Sclerosis and Related Disorders 2019; 30: 236-243. https://doi.org/10.1016/j.msard.2019.01.044.

179. Turner B, Cree BAC, Kappos L et al. Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. J Neurol 2019; 266(5): 1182-1193. https://doi.org/10.1007/s00415-019-09248-6.

180. Wolinsky JS, Engmann NJ, Pei J et al. An exploratory analysis of the efficacy of ocrelizumab in patients with multiple sclerosis with increased disability. Mult Scler J Exp Transl Clin 2020; 6(1): 2055217320911939. https://doi.org/10.1177/2055217320911939.

181. F. Hoffmann La Roche / Genentech. A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study to Evaluate the Efficacy and Safety of Ocrelizumab in Comparison to Interferon Beta-1a (Rebif®) in Patients with Relapsing Multiple Sclerosis [online]. [Accessed: 18.05.2021]. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=024-14.

182. F. Hoffmann La Roche / Genentech. A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study to Evaluate the Efficacy and Safety of Ocrelizumab in Comparison to Interferon Beta-1a (REBIF) in Patients with Relapsing Multiple Sclerosis [online]. [Accessed: 18.05.2021]. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=128-11.

183. F. Hoffmann-La Roche. A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate The Efficacy And Safety Of Ocrelizumab In Comparison To Interferon Beta-1a (Rebif®) In Patients With Relapsing Multiple Sclerosis [online]. [Accessed: 18.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-020337-99.

184. Hoffmann-La Roche. A Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Participants With Relapsing Multiple Sclerosis [online]. 2020 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT01247324.

185. F. Hoffmann-La Roche / Genentech. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis; Study WA21092; Primary Clinical Study Report [unpublished]. 2016.

186. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Ocrelizumab [online]. 2018 [Accessed: 03.09.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/343/.

187. MacMillan EL, Schubert JJ, Vavasour IM et al. Magnetic resonance spectroscopy evidence for declining gliosis in MS patients treated with ocrelizumab versus interferon beta-1a. Mult Scler J Exp Transl Clin 2019; 5(4): 2055217319879952. https://doi.org/10.1177/2055217319879952.

188. F. Hoffmann-La Roche. A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate The Efficacy And Safety Of Ocrelizumab In Comparison To Interferon Beta-1a (REBIF) In Patients With Relapsing Multiple Sclerosis [online]. [Accessed: 18.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-020315-36.

189. Hoffmann-La Roche. A Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Participants With Relapsing Multiple Sclerosis [online]. 2020 [Accessed: 14.06.2021]. URL: https://ClinicalTrials.gov/show/NCT01412333.

190. F. Hoffmann-La Roche / Genentech. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif) in patients with relapsing multiple sclerosis; Study WA21093; Primary Clinical Study Report [unpublished]. 2016.

191. Genentech. A Study of the Efficacy and Safety of Ocrelizumab in Patients With Relapsing-Remitting Multiple Sclerosis [online]. 2020 [Accessed: 07.01.2021]. URL: https://ClinicalTrials.gov/show/NCT00676715.

192. Hoffman La Roche. Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex controlled dose finding study to evaluate the efficacy, as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with relapsing-remitting multiple sclerosis [online]. [Accessed: 07.01.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-006338-32.

193. F. Hoffmann-La Roche / Genentech. Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS; Study WA21493; Update Clinical Study Report [unpublished]. 2016.

194. Hauser SL, Bar-Or A, Cohen JA et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. N Engl J Med 2020; 383(6): 546-557. https://doi.org/10.1056/NEJMoa1917246.

195. Novartis Pharmaceuticals. Efficacy and Safety of Ofatumumab Compared to Teriflunomide in Patients With Relapsing Multiple Sclerosis (ASCLEPIOS I) [online]. 2021 [Accessed: 15.02.2022]. URL: https://ClinicalTrials.gov/show/NCT02792218.

196. Novartis Pharma. A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis [online]. [Accessed: 11.02.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-005418-31.

197. Novartis Healthcare. A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis [online]. 2019 [Accessed: 15.02.2022]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=16236.

198. Novartis. A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis (ASCLEPIOS I); Study COMB157G2301; Clinical Study Report [unpublished]. 2021.

199. Novartis Pharmaceuticals. Efficacy and Safety of Ofatumumab Compared to Teriflunomide in Patients With Relapsing Multiple Sclerosis. (ASCLEPIOS II) [online]. 2021 [Accessed: 15.02.2022]. URL: https://ClinicalTrials.gov/show/NCT02792231.

200. Novartis Pharma Services. A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis [online]. [Accessed: 11.02.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-005419-33.

201. Novartis Biosciense Peru. A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis [online]. [Accessed: 11.02.2022]. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=049-16.

202. Novartis Healthcare. A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis [online]. 2019 [Accessed: 15.02.2022]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=16414.

203. Novartis. A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis (ASCLEPIOS II); Study COMB157G2302; Clinical Study Report [unpublished]. 2021.

204. Cohen JA, Comi G, Selmaj KW et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. Lancet Neurol 2019; 18(11): 1021-1033. https://doi.org/10.1016/s1474-4422(19)30238-8.

205. Harris S, Comi G, Cree BAC et al. Plasma neurofilament light chain concentrations as a biomarker of clinical and radiologic outcomes in relapsing multiple sclerosis: Post hoc analysis of Phase 3 ozanimod trials. Eur J Neurol 2021; 28(11): 3722-3730. https://doi.org/10.1111/ene.15009.

206. Celgene. Efficacy and Safety Study of Ozanimod in Relapsing Multiple Sclerosis (RADIANCE) [online]. 2021 [Accessed: 15.02.2022]. URL: https://ClinicalTrials.gov/show/NCT02047734.

207. Receptos. A Phase 2/3, Multi-Center, Randomized, Double-Blind, Placebo Controlled (Part a) and Double-Blind, Double-Dummy, Active Controlled (Part B), Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients [online]. [Accessed: 15.02.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-002714-40.

208. Celgene International. A Phase 2/3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled (Part A) And Double-Blind, Double-Dummy, Active-Controlled (Part B), Parallel Group Study To Evaluate The Efficacy And Safety Of Rpc1063 Administered Orally To Relapsing Multiple Sclerosis Patients; Study RPC01-201B; Clinical Study Report [unpublished]. 2017.

209. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Ozanimod (Schubförmig remittierende Multiple Sklerose) [online]. 2020 [Accessed: 22.04.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/566/.

210. Kappos L, Fox RJ, Burcklen M et al. Ponesimod Compared With Teriflunomide in Patients With Relapsing Multiple Sclerosis in the Active-Comparator Phase 3 OPTIMUM Study: A Randomized Clinical Trial. JAMA Neurology 2021; 78(5): 558-567. https://doi.org/10.1001/jamaneurol.2021.0405.

211. Actelion. Oral Ponesimod Versus Teriflunomide In Relapsing MUltiple Sclerosis (OPTIMUM) [online]. 2021 [Accessed: 11.02.2022]. URL: https://ClinicalTrials.gov/show/NCT02425644.

212. Actelion Pharmaceuticals. Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with relapsing multiple sclerosis [online]. [Accessed: 15.02.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000540-10.

213. Janssen Research & Development. Multicenter, Randomized, Double-Blind, Parallel group, Active-Controlled, Superiority Study to Compare the Efficacy and Safety of Ponesimod to Teriflunomide in Subjects With Relapsing Multiple Sclerosis; OPTIMUM: Oral Ponesimod versus Teriflunomide In relapsing Multiple sclerosis; Study AC-058B301; Clinical Study Report [unpublished]. 2020.

214. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Ponesimod (Schubförmige Multiple Sklerose) [online]. 2022 [Accessed: 22.04.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/768/.

215. Confavreux C, Li DK, Freedman MS et al. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. Mult Scler 2012; 18(9): 1278-1289. https://doi.org/10.1177/1352458512436594.

216. Sanofi. Safety and Efficacy of Teriflunomide (HMR1726) in Multiple Sclerosis With Relapses [online]. 2012 [Accessed: 07.01.2021]. URL: https://clinicaltrials.gov/ct2/show/NCT01487096.

217. Aventia Pharma. A phase II study of the safety and efficacy of teriflunomide (HMR1726) in multiple sclerosis with relapses; Study HMR1726D/2001; Clinical Study Report [unpublished]. 2003.

218. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Teriflunomid (Schubförmig remittierende Multiple Sklerose) [online]. 2014 [Accessed: 03.09.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/81/.

219. Sanofi. Long Term Safety and Efficacy of Teriflunomide (HMR1726) in Multiple Sclerosis With Relapses [online]. 2015 [Accessed: 07.01.2021]. URL: https://ClinicalTrials.gov/show/NCT00228163.

220. Sanofi Aventis. Extension of Protocol HMR1726D/2001, A Phase II Study of the Safety and Efficacy of Teriflunomide (HMR 1726) in Multiple Sclerosis with Relapses; Study LTS6048; Clinical Study Report [unpublished]. 2011.

221. Miller AE, O'Connor P, Wolinsky JS et al. Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis. Mult Scler 2012; 18(11): 1625-1632. https://doi.org/10.1177/1352458512450354.

222. O'Connor P, Wolinsky JS, Confavreux C et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011; 365(14): 1293-1303. https://doi.org/10.1056/NEJMoa1014656.

223. O'Connor PW, Lublin FD, Wolinsky JS et al. Teriflunomide reduces relapse-related neurological sequelae, hospitalizations and steroid use. J Neurol 2013; 260(10): 2472-2480. https://doi.org/10.1007/s00415-013-6979-y.

224. Wolinsky JS, Narayana PA, Nelson F et al. Magnetic resonance imaging outcomes from a phase III trial of teriflunomide. Mult Scler 2013; 19(10): 1310-1319. https://doi.org/10.1177/1352458513475723.

225. Sprenger T, Kappos L, Radue EW et al. Association of brain volume loss and long-term disability outcomes in patients with multiple sclerosis treated with teriflunomide. Mult Scler 2020; 26(10): 1207-1216. https://doi.org/10.1177/1352458519855722.

226. Sanofi. Study of Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients With Multiple Sclerosis (TEMSO) [online]. 2013 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00134563.

227. Sanofi-Aventis US. A randomized, double-blind, placebo-controlled, parallel group design study to evaluate the efficacy and safety of teriflunomide (HMR1726D) in reducing the frequency of relapses and delaying the accumulation of physical disability in subjects with multiple sclerosis with relapses [online]. [Accessed: 14.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004-000555-42.

228. Sanofi-Aventis. A randomized, double-blind, placebo-controlled, parallel-group design study to evaluate the efficacy and safety of teriflunomide (HMR1726D) in reducing the frequency of relapses and delaying the accumulation of physical disability in subjects with multiple sclerosis with relapses; Study EFC6049; Clinical Study Report [unpublished]. 2011.

229. O'Connor P, Comi G, Freedman MS et al. Long-term safety and efficacy of teriflunomide: Nine-year follow-up of the randomized TEMSO study. Neurology 2016; 86(10): 920-930. https://doi.org/10.1212/wnl.0000000000002441.

230. Sanofi-Aventis Recherche & Développement. Long-term extension of the multinational, double-blind, placebo controlled study EFC6049 (HMR1726D/3001) to document the safety of two doses of teriflunomide (7 and 14 mg) in patients with multiple sclerosis with relapses [online]. [Accessed: 14.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-003361-14.

231. Sanofi. Long-term extension of the multinational, double-blind, placebo controlled study EFC6049 (HMR1726D/3001) to document the safety of two doses of teriflunomide (7 and 14 mg) in patients with multiple sclerosis with relapses; Study LTS6050; Clinical Study Report [unpublished].

232. Miller AE, Xu X, Macdonell R et al. Efficacy and safety of teriflunomide in Asian patients with relapsing forms of multiple sclerosis: A subgroup analysis of the phase 3 TOWER study. J Clin Neurosci 2019; 59: 229-231. https://doi.org/10.1016/j.jocn.2018.09.012.

233. Qiu W, Huang DH, Hou SF et al. Efficacy and Safety of Teriflunomide in Chinese Patients with Relapsing Forms of Multiple Sclerosis: A Subgroup Analysis of the Phase 3 TOWER Study. Chin Med J (Engl) 2018; 131(23): 2776-2784. https://doi.org/10.4103/0366-6999.246067.

234. Confavreux C, O'Connor P, Comi G et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014; 13(3): 247-256. https://doi.org/10.1016/s1474-4422(13)70308-9.

235. Miller AE, Macdonell R, Comi G et al. Teriflunomide reduces relapses with sequelae and relapses leading to hospitalizations: results from the TOWER study. J Neurol 2014; 261(9): 1781-1788. https://doi.org/10.1007/s00415-014-7395-7.

236. Sanofi. An Efficacy Study of Teriflunomide in Participants With Relapsing Multiple Sclerosis (TOWER) [online]. 2016 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT00751881.

237. Sanofi-Aventis Recherche & Développement. A multi-center double-blind parallel-group placebo-controlled study of the efficacy and safety of teriflunomide in patients with relapsing multiple sclerosis [online]. [Accessed: 14.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-004452-36.

238. Sanofi-Aventis Recherche & Development. A multi-center double-blind parallel-group placebo-controlled study of the efficacy and safety of teriflunomide in patients with relapsing multiple sclerosis [online]. [Accessed: 15.02.2022]. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=111-08.

239. Sanofi-Aventis. A multi-center double-blind parallel-group placebo-controlled study of the efficacy and safety of teriflunomide in patients with relapsing multiple sclerosis; Study EFC10531; Clinical Study Report [unpublished]. 2012.

240. Therapeutics T. Phase III: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE I STUDY) [online]. [Accessed: 18.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-000638-75.

241. TG Therapeutics. A Phase 3, Randomized, Multi-center, Double-blinded, Active-controlled Study to Assess the Efficacy and Safety/Tolerability of Ublituximab (TG-1101; UTX) as Compared to Teriflunomide in Subjects With Relapsing Multiple Sclerosis (RMS) (ULTIMATE 1) [online]. 2021 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT03277261.

242. TG Therapeutics. Phase III: UbliTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE II STUDY) [online]. [Accessed: 18.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-000639-15.

243. TG Therapeutics. A Phase 3, Randomized, Multi-center, Double-blinded, Active-controlled Study to Assess the Efficacy and Safety/Tolerability of Ublituximab (TG-1101; UTX) as Compares to Teriflunomide in Subjects With Relapsing Multiple Sclerosis (RMS) (ULTIMATE 2) [online]. 2021 [Accessed: 14.05.2021]. URL: https://ClinicalTrials.gov/show/NCT03277248.

244. Svenningsson A, Frisell T, Burman J et al. Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial. Lancet Neurol 2022; 21(8): 693-703. https://doi.org/10.1016/S1474-4422(22)00209-5.

245. Steinman L, Fox E, Hartung HP et al. Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis. N Engl J Med 2022; 387(8): 704-714. https://doi.org/10.1056/NEJMoa2201904.

246. Lefebvre C, Glanville J, Briscoe S et al. Cochrane Handbook for Systematic Reviews of Interventions; Version 6.2; Technical Supplement to Chapter 4: Searching for and selecting studies [online]. 2021 [Accessed: 27.05.2021]. URL: https://training.cochrane.org/handbook/version-6.1/chapter-4-tech-suppl.

The full report (German version) is published under

https://www.iqwig.de/en/projects/a20-60.html

Appendix A Search strategies

A.1 Searches in bibliographic databases

Search for primary studies in MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to November 01, 2021

The following filter was adopted:

- RCT: Lefebvre [246] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)

#	Searches
1	Multiple Sclerosis, Relapsing-Remitting/
2	(multiple sclerosis and (relapse or relapsing)).ti,ab.
3	or/1-2
4	(alemtuzumab or dimethyl fumarate or cladribine or fingolimod or natalizumab or ocrelizumab or teriflunomide or BG-12 or ofatumumab or ozanimod or ponesimod).mp.
5	randomized controlled trial.pt.
6	controlled clinical trial.pt.
7	(randomized or placebo or randomly).ab.
8	clinical trials as topic.sh.
9	trial.ti.
10	or/5-9
11	10 not (exp animals/ not humans.sh.)
12	and/3-4,11
13	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
14	hi.fs. or case report.mp.
15	or/13-14
16	12 not 15
17	16 and (english or german or multilingual or undetermined).lg.

A.2 Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Expert Search

Search strategy
multiple sclerosis AND (alemtuzumab OR LDP-03 OR GZ-402673 OR dimethyl fumarate OR FAG-201 OR BG-00012 OR BG-12 OR cladribine OR RWJ-26251 OR fingolimod OR FTY-720 OR natalizumab OR BG-00002 OR ocrelizumab OR PRO-70769 OR rhuMAb-2H7 OR teriflunomide OR HMR-1726 OR ofatumumab OR HUMAX-CD20 OR GSK-1841157 OR ozanimod OR RPC-1063 OR ponesimod OR ACT-128800)

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
(multiple sclerosis*) AND (alemtuzumab* OR LDP03 OR LDP-03 OR GZ402673 OR GZ-402673 OR campath OR lemtrada OR "dimethyl fumarate" OR FAG201 OR FAG-201 OR BG00012 OR BG-00012 OR BG12 OR BG-12 OR cladribin* OR RWJ26251 OR RWJ-26251 OR fingolimod* OR FTY720 OR FTY-720 OR natalizumab* OR BG00002 OR BG-00002 OR tysabri OR ocrelizumab* OR PRO70769 OR PRO-70769 OR rhuMAb2H7 OR rhuMAb-2H7 OR Teriflunomid* OR HMR1726 OR HMR-1726 OR ofatumumab* OR HUMAX-CD20 OR HUMAXCD20 OR GSK-1841157 OR GSK1841157 OR ozanimod* OR RPC-1063 OR RPC1063 OR ponesimod* OR ACT-128800 OR ACT128800)

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
multiple sclerosis AND (alemtuzumab OR LDP03 OR LDP-03 OR GZ402673 OR GZ-402673 OR campath OR lemtrada OR dimethyl fumarate OR FAG201 OR FAG-201 OR BG00012 OR BG-00012 OR BG12 OR BG-12 OR cladribine OR RWJ26251 OR RWJ-26251 OR fingolimod OR FTY720 OR FTY-720 OR natalizumab OR BG00002 OR BG-00002 OR tysabri OR ocrelizumab OR PRO70769 OR PRO-70769 OR rhuMAb2H7 OR rhuMAb-2H7 OR teriflunomide OR HMR1726 OR HMR-1726 OR ofatumumab OR HUMAX-CD20 OR HUMAXCD20 OR GSK-1841157 OR GSK1841157 OR ozanimod OR RPC-1063 OR RPC1063 OR ponesimod OR ACT-128800 OR ACT128800)

A.3 Further information sources and search techniques

G-BA website and IQWiG website

G-BA

URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/

Search terms
Alemtuzumab, Dimethylfumarat, Cladribin, Fingolimod, Natalizumab, Ocrelizumab, Ofatumumab, Ozanimod, Ponesimod, Teriflunomid

IQWiG

URL: https://www.iqwig.de/projekte/projekte-und-ergebnisse/

Search terms
Alemtuzumab, Dimethylfumarat, Cladribin, Fingolimod, Natalizumab, Ocrelizumab, Ofatumumab, Ozanimod, Ponesimod, Teriflunomid