Appendix

1 Information retrieval from marketing authorisation holders (MAHs)

Information about clinical trials on the disease modifying therapies (DMTs) of interest was requested directly from the MAHs. As a prerequisite for the use of unpublished data from MAHs, IQWiG asked the MAHs to sign an agreement requiring the submission of a list of all sponsored published and unpublished studies investigating the DMT concerned, as well as CONSORT compliant documents, in general, the complete clinical study reports (CSRs), on all relevant studies selected by IQWiG. This procedure was required to avoid bias due to selective provision of data. The Common Technical Documents, as submitted to the EMA, were screened for relevant studies. For potentially relevant studies, CSRs were requested from the MAHs.

If a study population was not limited to our target population as outlined above, patient characteristics and study results for the relevant subpopulation were requested from the MAHs. This procedure was also aimed at obtaining patient populations with sufficient similarity across studies and drugs, as the assessment of similarity is an important prerequisite for network meta-analysis (NMA).

2 Data synthesis and statistical methods

The prerequisite for conducting the NMA was an adequate structural quality of the study pool — that is, the availability of a study pool meeting the assumptions of similarity, homogeneity, and consistency. In general, an indirect comparison allows the simultaneous estimation of an effect between two treatments (A and B). This is possible even in the absence of head-to-head trials if other trials comparing A or B with a common comparator C (intermediate comparator)

are available [103,104]. The validity of an indirect comparison requires the assumption of similar study characteristics, such as the study design applied or the population investigated [105]. If this assumption is not met, possible effect modifiers may affect the indirect estimate. A consequence of this assumption is that both the direct and the indirect estimates of the effect of A versus B produce comparable results. While the conceptual assumption is called "similarity" or "transitivity," the statistical consequence is called "consistency" [106].

While the similarity assumption focuses on similarity of populations, interventions, comparators, outcomes, comparable design, and inclusion and exclusion criteria, the homogeneity assumption relates to treatment effects, as substantial heterogeneity makes a combined statement about the effect difficult. Both are also required in conventional meta-analyses [107-110].

Risk ratios and mean differences were the effect measures used for binary and continuous outcomes, respectively. Risk ratios and their standard errors were normalised by taking the logarithms of the data from contingency tables. In the case of zero events in either treatment group, a factor of 0.5 was added to each cell. Estimates of mean differences and their standard errors were extracted from the original scales used in the primary studies. In the case of statistically significant effects, the final NMA results of a continuous outcome analysis were supported by an additional analysis based on standardised effects using Hedges' g to assess the relevance of the effect. A relevant difference was assumed if the effect of the NMA based on standardised data was outside the interval (−0.2 to 0.2) [111]. All NMAs were conducted in a frequentist setting using random-effects models [112]. We used the netmeta software package in R [113] (Supplement 3 includes the programming code). Each hypothesis of no

difference between any two treatments was tested locally at the 0.05 level. We did not adjust for multiple testing. The resulting estimates from the NMA are presented with 95% confidence intervals.

We aimed to estimate differences between DMTs quantitatively. We refrained from ranking the NMA results, because our focus was on estimating actual treatment contrasts. In addition, each ranking method responds to a different question of interest and various methodological problems can hamper interpretation [114,115]. For example, ranking methods have been shown to be sensitive to network composition [116], do not reflect a treatment's effect size [117], and cannot always be accompanied by confidence or credible intervals [114]. In contrast to the presentation of effect estimates and confidence or credible intervals, there is no standard recommendation on whether the results should be ranked and, if so, which method should be used.

3 Comments and modifications to the original protocol

After publication of the protocol, an open commenting process was conducted. The MAHs of the DMTs studied, German medical societies with a focus on multiple sclerosis and neurology (German Neurological Society, German Multiple Sclerosis Society, Disease-Related Competence Network Multiple Sclerosis) and patient organisations commented on the protocol. The comments and the resulting changes to the protocol are discussed in detail in IQWiG's final report [118]. These comments led to the publication of an updated protocol. The main changes to the original protocol were the revision of the criteria for high disease activity and the exclusion of studies with a treatment duration of less than approximately 2 years, whereas the original version excluded studies with a duration of less than 1 year. After

publication of the preliminary report, an identical commenting process was initiated, the results of which are also documented in the final report.

4 Programming code for network meta-analyses

```
# Prerequisites: install and load package netmeta,
# if required, load packages required for netmeta are usually automatically loaded.
library(netmeta)

# data input:
# create a data frame nmadata containing
# - study name (StName)
# - treatment effect (md)
# - standard error (se)
# - name of first treatment (T1)
# - name of second treatment/comparator (T2)
# values in brackets are variable names that appear in the following programming statements
# binary data: enter the logarithms of effects and standard error

# network meta-analysis for binary outcome, relative risk:
object.nma.results.bin <- netmeta(te ,se , T1, T2, StName, data=nmadata, sm="RR",
comb.random=TRUE)
# effect measure for binary outcomes: Relative Risk
effect <- "RR"
# effect measure for continuous outcomes : Mean Difference:
```

```
effect <- "MD"


# calculation of network meta-analysis:
nma.net <- netmeta(te, se, B1, B2, StName, data = nmadata,
sm = "effect", level = 0.95, fixed = FALSE)


# results output (relative risk):
exp(nma.net$TE.random)    # treatment effect
exp(nma.net$lower.random) # 95% confidence interval lower bound
exp(nma.net$upper.random) # 95% confidence interval upper bound


# results output (mean difference):
nma.net$TE.random    # treatment effect
nma.net$lower.random # 95% confidence interval lower bound
nma.net$upper.random # 95% confidence interval upper bound
```

Supplementary Table 1 Relevant studies for comparison of escalation therapies in patients with highly active RRMS despite previous DMT

DMT[a]	Study	Publications	Registry	Clinical study report provided (unpublished)	Additional analyses for subpopulation with highly active RRMS despite previous DMT provided [unpublished]
vs. interferons					
Alemtuzumab vs. IFN-β 1a	CARE-MS II	[1-5]	[6,7]	yes	yes
Ocrelizumab vs. IFN-β 1a	OPERA I	[8-13]	[14-17]	yes	no
Ocrelizumab vs. IFN-β 1a	OPERA II	[8-13,18]	[19,20]	yes	no
Ozanimod vs. IFN-β 1a	RADIANCE B	[21,22]	[23,24]	yes	yes
vs. placebo					
Cladribine vs. placebo	CLARITY	[25-38]	[39,40]	yes	yes
Dimethyl fumarate vs. placebo	CONFIRM	[41-46]	[47-49]	yes	no
Dimethyl fumarate vs. placebo	DEFINE	[42,43,50-54]	[55-58]	yes	no
Fingolimod vs. placebo	FREEDOMS	[42,59-71]	[72,73]	yes	yes
Fingolimod vs. placebo	FREEDOMS II	[62,67,71,74,75]	[76,77]	yes	yes
Teriflunomide vs. placebo	TEMSO	[78-82]	[83,84]	yes	yes
Teriflunomide vs. placebo	TOWER	[42,85-88]	[89-91]	yes	yes
vs. DMT					
Ofatumumab vs. teriflunomide	ASCLEPIOS I	[92]	[93-95]	yes	yes
Ofatumumab vs. teriflunomide	ASCLEPIOS II	[92]	[96-99]	yes	yes
Ponesimod vs. teriflunomide	OPTIMUM	[100]	[101,102]	yes	yes

a. No relevant studies investigating natalizumab were identified.

DMT: disease modifying therapy; IFN: Interferon; RRMS: relapsing-remitting multiple sclerosis; vs.: versus

Supplementary Table 2 Definitions of highly active RRMS despite previous DMT as applied by MAHs for additional analyses of study data

DMT Study	Definition of adequate and complete previous DMT treatment	Highly active RRMS diagnosed after complete course of previous DMT	Definition of high disease activity[a]		
			Exclusively by clinical criteria	By clinical and MRT-based criteria	Exclusively by MRT-based criteria
Studies comparing DMT vs IFN-β 1a					
Alemtuzumab vs. IFN-β 1a CARE-MS II	▪ Previous DMT ≥ 3 months (IFN) or ≥ 6 months (GA) within the last year before determination of high disease activity	yes	▪ ≥ 1 relapse in last 12 months or ≥ 2 relapses in last 24 months before randomisation and no Gd+ lesion at baseline ▪ Information on severity of relapses not available	≥ 1 relapse in last 12 months and ≥ 1 new Gd+ lesion at baseline	–
Ozanimod vs IFN-β 1a RADIANCE B	▪ Previous DMT ≥ 3 months (IFN) or ≥ 6 months (other DMT) ▪ Complete course of therapy within 12 months before baseline	yes	–	≥ 1 relapse in last 12 months and ≥ 1 Gd+ lesion at baseline	–
Placebo-controlled studies					
Cladribine vs. placebo CLARITY	▪ Previous DMT ≥ 3 months (IFN) or ≥ 6 months (GA) ▪ End of previous DMT within 12 months before baseline	yes	–	≥ 1 relapse in last 12 months and ≥ 1 Gd+ lesion in MRT scan	≥ 9 Gd+ lesions within the last 12 months in MRT scan

Supplementary Table 2 Definitions of highly active RRMS despite previous DMT as applied by MAHs for additional analyses of study data

DMT **Study**	**Definition of adequate and complete previous DMT treatment**	**Highly active RRMS diagnosed after complete course of previous DMT**	**Definition of high disease activity[a]**		
			Exclusively by clinical criteria	**By clinical and MRT-based criteria**	**Exclusively by MRT-based criteria**
Fingolimod vs. placebo FREEDOMS I / FREEDOMS II	▪ Previous DMT of ≥ 90 days or 180 days before relapse ▪ End date of previous DMT within 12 months before baseline (if date of relapse available)	yes	▪ ≥ 1 relapse in last 12 months or ≥ 2 relapses in last 24 months before inclusion in study ▪ Information on functional impairment not available	–	–
Teriflunomide vs. placebo TEMSO	▪ Previous DMT ≥ 3 months (IFN) or ≥ 6 months (GA) within the last year before determination of high disease activity ▪ Last 365 days before screening were considered for duration of treatment	yes	▪ ≥ 1 relapse in last 12 months or ≥ 2 relapses in last 24 months before randomisation and no Gd+ lesion at baseline ▪ Information on severity of relapses not available	≥ 1 relapse in last 12 months and ≥ 1 new Gd+ lesion at baseline	–
Teriflunomide vs. placebo TOWER	▪ Previous DMT ≥ 3 months (IFN) or ≥ 6 months (GA) within the last year before determination of high disease activity ▪ Last 365 days before screening were considered for duration of treatment	yes	▪ ≥ 1 relapse in last 12 months or ≥ 2 relapses in last 24 months before randomisation ▪ Information on severity of relapses not available	–	–

Supplementary Table 2 Definitions of highly active RRMS despite previous DMT as applied by MAHs for additional analyses of study data

DMT Study	Definition of adequate and complete previous DMT treatment	Highly active RRMS diagnosed after complete course of previous DMT	Definition of high disease activity[a]		
			Exclusively by clinical criteria	By clinical and MRT-based criteria	Exclusively by MRT-based criteria
Studies comparing DMTs directly					
Ofatumumab vs. Teriflunomide ASCLEPIOS I / ASCLEPIOS II	▪ Previous DMT ≥ 90 days or 180 days before last relapse ▪ End date of previous DMT within 12 months before baseline (if date of relapse available)	yes	▪ ≥ 1 relapse in last 12 months or ≥ 2 relapses in last 24 months before inclusion in study ▪ Information on functional impairment not available	–	–
Ponesimod vs. teriflunomide OPTIMUM	▪ Previous DMT ≥ 6 months in the year before inclusion into the study; end date 2 months before relapse at most	yes	–	≥ 1 relapse in last year before and ≥ 1 Gd+ lesion at baseline	–

a. If MAHs provided > 1 definition of high disease activity per study, these definitions represent mutually exclusive subpopulations, i. e. patients are counted in only one category; for our analysis we used the combined populations of all patients with highly active RRMS despite previous DMT per study.

DMT: disease modifying therapy; GA: glatiramer acetate; Gd+: gadolinium-enriching; IFN: interferon; MAH: market authorisation holder; MRT: magnetic resonance tomography; RRMS: relapsing-remitting multiple sclerosis

Supplementary Table 3 Patient-relevant outcomes included in the studies and data availability for analyses

DMT	Outcome														
	Overall mortality	**Annual relapse rate**	**Number of patients with confirmed relapse**	**Confirmed disability progression (EDSS-based), confirmed after 24 weeks**	**Severity of disability (MSFC-score)**	**Mobility[a]**	**Visual impairment**	**Fatigue**	**Health-related quality of life**	**SAE**	**Discontinuation due to AE**	**PML**	**Serious infections**	**Serious neoplasms**	**Serious autoimmune disorders**
Versus 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	(●)	●	●	●	●	●	(●)	–	(●)	(●)	(●)	(●)	(●)	(●)	–
Versus 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 comparison															
Ofatumumab vs. teriflunomide	(●)	●	●	●	●	●	–	–	–	●	●	●	x	x	x
Ponesimod vs. teriflunomide	(●)	●	●	●	●	●	–	○	●	●	●	●	●	●	x
Natalizumab	No relevant studies were identified.														

Supplementary Table 3 Patient-relevant outcomes included in the studies and data availability for analyses

DMT	Outcome															
	Overall mortality	Annual relapse rate	Number of patients with confirmed relapse	Confirmed disability progression (EDSS-based), confirmed after 24 weeks	Severity of disability (MSFC-score)	Mobility[a]	Visual impairment	Fatigue	Health-related quality of life	SAE	Discontinuation due to AE	PML	Serious infections	Serious neoplasms	Serious autoimmune disorders

●: Data were provided.

(●): Data were provided, but could not be considered for the analysis, since pairwise comparison between 2 DMTs was not possible (e. g. because no data from studies on other DMTs were available), assumption of homogeneity was violated, or because no events or only few events in 1 study arm occurred

○: Data were provided, but were not suitable for analysis (e. g. because > 30% of the study population were missing from the analysis).

x: Data for the subpopulation of patients with highly active disease despite previous DMT were not provided.

–: Outcome not assessed.

a. Evaluated using the 25-foot walk test.

b. Comparison to other DMTs was inconclusive due to deviating treatment regimens.

c. Consideration of placebo-controlled studies led to imprecise estimations in the NMA; therefore, only direct comparisons of DMTs were considered.

AE: adverse event; DMT: disease modifying therapy; EDSS: Expanded Disability Status Scale; IFN: Interferon; MSFC: Multiple Sclerosis Functional Composite; MSIS: Multiple Sclerosis Impact Scale; NMA: network meta-analysis; PML: progressive multifocal leukoencephalopathy; SAE: serious adverse event

Supplementary Table 4 Patient characteristics of the relevant subpopulations including treatment and study discontinuation

Comparison Study Study arm	N	Age [years] Mean (SD)	Sex [f / m] %	Region n (%)		Previous DMT n (%)				Treatment discontinu-ation n (%)	Study discontinu-ation n (%)
				OECD	Non-OECD	IFN-β 1a	IFN-β 1b	Glatiramer acetate	Other DMT[a]		
Studies comparing DMT vs. IFN-β 1a											
Alemtuzumab vs. IFN-β 1a											
CARE-MS II											
Alemtuzumab	363	35 (9)	65 / 35	283 (78)	80 (22)	155 (43)	99 (27)	85 (23)	n/a[b]	n/a	13 (4)
IFN-β 1a	199	36 (9)	66 / 34	160 (80)	39 (20)	87 (44)	48 (24)	53 (27)	n/a[b]	n/a	44 (22)
Ocrelizumab vs. IFN-β 1a											
OPERA I				Data for the relevant subpopulation were not provided							
OPERA II				Data for the relevant subpopulation were not provided							
Ozanimod vs. IFN-β 1a											
RADIANCE B											
Ozanimod	17	36 (9)	77 / 24	n/a	n/a	3 (18)	11 (65)	6 (35)	0 (0)[c]	2 (12)[d]	2 (12)[d]
IFN-β 1a	17	33 (7)	71 / 29	n/a	n/a	5 (29)	9 (53)	2 (12)	1 (6)[c]	2 (12)[d]	2 (12)[d]
Placebo-controlled studies											
Cladribine vs. placebo											
CLARITY											
Cladribine	13	32 (5)	62 / 38	7 (54)	6 (46)	8 (62)[e]	4 (31)[e]	1 (8)[e]	n/a	n/a	4 (31)
Placebo	17	34 (7)	82 / 18	12 (71)	5 (29)	11 (65)[e]	5 (29)[e]	1 (6)[e]	n/a	n/a	3 (18)
Dimethyl fumarate vs. placebo											
CONFIRM				Data for the relevant subpopulation were not provided							
DEFINE				Data for the relevant subpopulation were not provided							

Supplementary Table 4 Patient characteristics of the relevant subpopulations including treatment and study discontinuation

Comparison Study Study arm	N	Age [years] Mean (SD)	Sex [f / m] %	Region n (%)		Previous DMT n (%)				Treatment discontinu-ation n (%)	Study discontinu-ation n (%)
				OECD	Non-OECD	IFN-β 1a	IFN-β 1b	Glatiramer acetate	Other DMT[a]		
Fingolimod vs. placebo											
FREEDOMS											
Fingolimod	34	38 (10)	74 / 27	33 (97)	1 (3)	22 (65)	6 (18)	6 (18)	0 (0)	9 (27)	7 (21)
Placebo	28	39 (8)	79 / 21	27 (96)	1 (4)	16 (57)	6 (21)	6 (21)	0 (0)	10 (36)	8 (29)
FREEDOMS II											
Fingolimod	75	41 (8)	79 / 21	75 (100)	0 (0)	40 (53)	14 (19)	26 (35)	0 (0)	24 (32)	17 (23)
Placebo	69	42 (7)	73 / 28	69 (100)	0 (0)	33 (48)	11 (16)	29 (42)	3 (4)[f]	21 (30)	15 (22)
Teriflunomide vs. placebo											
TEMSO											
Teriflunomide	39	38 (7)	72 / 28	37 (95)	2 (5)	29 (74)	6 (15)	5 (13)	n/a	n/a	12 (31)
Placebo	32	37 (9)	84 / 16	30 (94)	2 (6)	21 (66)	3 (9)	7 (22)	n/a	n/a	19 (59)
TOWER											
Teriflunomide	66	39 (10)	73 / 27	61 (92)	5 (8)	37 (56)	15 (23)	18 (27)	n/a	n/a	24 (36)
Placebo	68	37 (10)	72 / 28	58 (85)	10 (15)	29 (43)	15 (22)	26 (38)	n/a	n/a	14 (21)
Studies comparing DMTs directly											
Ofatumumab vs. teriflunomide											
ASCLEPIOS I											
Ofatumumab	121	39 (8)	64 / 36	88 (73)	33 (27)	29 (24)	17 (14)	39 (32)	39 (32)	n/a	14 (12)
Teriflunomide	122	38 (10)	67 / 33	90 (74)	32 (26)	32 (26)	18 (15)	35 (29)	44 (36)	n/a	22 (18)

Supplementary Table 4 Patient characteristics of the relevant subpopulations including treatment and study discontinuation

Comparison Study Study arm	N	Age [years] Mean (SD)	Sex [f / m] %	Region n (%)		Previous DMT n (%)				Treatment discontinu-ation n (%)	Study discontinu-ation n (%)
				OECD	Non-OECD	IFN-β 1a	IFN-β 1b	Glatiramer acetate	Other DMT[a]		
ASCLEPIOS II											
Ofatumumab	135	38 (9)	67 / 33	83 (62)	52 (39)	36 (27)	27 (20)	45 (33)	40 (30)	n/a	18 (13)
Teriflunomide	147	39 (9)	73 / 27	99 (67)	48 (33)	41 (28)	18 (12)	44 (30)	58 (40)	n/a	36 (25)
Ponesimod vs. teriflunomide											
OPTIMUM											
Ponesimod	33	36 (9)	61 / 39	19 (58)	14 (42)	n/a	n/a	n/a	n/a	n/a	8 (24)
Teriflunomide	45	37 (9)	58 / 42	28 (62)	17 (38)	n/a	n/a	n/a	n/a	n/a	9 (20)
Natalizumab	No relevant studies were identified.										

a. Alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, teriflunomide.
b. Other DMTs were used in < 1% of patients.
c. Teriflunomide.
d. Authors' own calculation.
e. No data on time frame for assessment before baseline.
f. Natalizumab.

DMT: disease modifying therapy; f: female; IFN: interferon; m: male; N: number of randomised patients; n: number of patients with event; n/a: not available; OECD: Organisation for Economic Co-operation and Development; SD: standard deviation; vs.: versus

Supplementary Table 5 Disease-specific characteristics of the relevant subpopulations at baseline

Comparison Study Study arm	N	EDSS at baseline Mean (SD)	Time since diagnosis of MS [years] Mean (SD)	Nunber of relapses before baseline Median [Q1; Q3] or (Min; Max) Within 1 year	 Within 2 years	Number of lesions at baseline Median [Q1; Q3] or (Min; Max) T1 Gd+	 T1 Hypointense	 T2
Studies comparing DMT vs IFN-β 1a								
Alemtuzumab vs. IFN-β 1a								
CARE-MS II								
Alemtuzumab	363	2.6 (1.2)	4.3 (2.6)	2.0 (0; 5)	2,0 (1; 9)	0 (0; 36)	n/a	n/a
IFN-β 1a	199	2.7 (1.2)	4.4 (2.7)	1.0 (0; 5)	2.0 (1; 7)	0 (0; 41)	n/a	n/a
Ocrelizumab vs. IFN-β 1a								
OPERA I				Data for the relevant subpopulation were not provided				
OPERA II				Data for the relevant subpopulation were not provided				
Ozanimod vs. IFN-β 1a								
RADIANCE B								
Ozanimod	17	2.6 (1.2)	5.8 (4.0)	1.0 (0.0; 2.0)	2.0 (1.0; 4.0)	2 (1; 13)	n/a	59 (36; 183)
IFN-β 1a	17	2.6 (1.1)	5.9 (4.2)	1.0 (0.0; 3.0)	2.0 (1.0; 4.0)	2 (1; 22)	n/a	53 (33; 145)
Placebo-controlled studies								
Cladribine vs. placebo								
CLARITY								
Cladribine	13	3.0 (1.7)	7.2 (4.4)	2.0 [1.0; 2.0]	n/a	1 [1; 2]	4 [2; 7]	26 [20; 32]
Placebo	17	2.7 (1.2)	8.3 (4.2)	1.0 [1.0; 2.0]	n/a	2 [1; 3]	3 [2; 8]	36 [20; 45]
Dimethyl fumarate vs. placebo								
CONFIRM				Data for the relevant subpopulation were not provided				
DEFINE				Data for the relevant subpopulation were not provided				

Supplementary Table 5 Disease-specific characteristics of the relevant subpopulations at baseline

Comparison Study Study arm	N	EDSS at baseline Mean (SD)	Time since diagnosis of MS [years] Mean (SD)	Nunber of relapses before baseline Median [Q1; Q3] or (Min; Max)		Number of lesions at baseline Median [Q1; Q3] or (Min; Max)		
				Within 1 year	Within 2 years	T1 Gd+	T1 Hypointense	T2
Fingolimod vs. placebo								
FREEDOMS								
Fingolimod	34	2.6 (1.0)	7.4 (6.3)	1.0 [1.0; 1.0]	2.0 [1.0; 3.0]	0 [0; 1]	n/a	n/a
Placebo	28	3.1 (1.8)	6.4 (4.6)	1.0 [1.0; 1.0]	2.0 [1.0; 3.0]	0 [0; 2]	n/a	n/a
FREEDOMS II								
Fingolimod	75	2.7 (1.3)	7.0 (6.0)	1.0 [1.0; 2.0]	2.0 [1.0; 3.0]	0 [0; 1]	n/a	n/a
Placebo	69	2.7 (1.3)	8.1 (6.7)	1.0 [1.0; 2.0]	2.0 [1.5; 3.0]	0 [0; 1]	n/a	n/a
Teriflunomide vs. placebo								
TEMSO								
Teriflunomide	39	2.7 (1.2)	8.4 (5.9)	1.0 (0; 4)	2.0 (1; 6)	n/a	n/a	n/a
Placebo	32	2.6 (1.3)	7.3 (5.4)	1.0 (0; 3)	2.0 (1; 7)	n/a	n/a	n/a
TOWER								
Teriflunomide	66	2.9 (1.4)	7.4 (6.2)	1.0 (0; 4)	2.0 (1; 6)	n/a	n/a	n/a
Placebo	68	2.8 (1.4)	6.4 (5.1)	1.0 (0; 4)	2.0 (1;7)	n/a	n/a	n/a
Studies comparing DMTs directly								
Ofatumumab vs. teriflunomide								
ASCLEPIOS I								
Ofatumumab	121	3.2 (1.3)	7.4 (5.5)	1.0 [1.0; 2.0]	1,0 [0,0; 2.0][a]	0 [0; 1]	n/a	n/a
Teriflunomide	122	3.1 (1.3)	7.5 (5.8)	1.0 [1.0; 2.0]	1.0 [0,0; 2.0][a]	0 [0; 1]	n/a	n/a
ASCLEPIOS II								
Ofatumumab	135	3.1 (1.2)	7.4 (6.5)	1.0 [1.0; 2.0]	1.0 [0.0; 2.0][a]	0 [0; 1]	n/a	n/a
Teriflunomide	147	3.1 (1.3)	7.4 (6.3)	1.0 [1.0; 2.0]	1.0 [0.0; 2.0][a]	0 [0; 1]	n/a	n/a

Supplementary Table 5 Disease-specific characteristics of the relevant subpopulations at baseline

Comparison Study Study arm	N	EDSS at baseline Mean (SD)	Time since diagnosis of MS [years] Mean (SD)	Nunber of relapses before baseline Median [Q1; Q3] or (Min; Max) Within 1 year	 Within 2 years	Number of lesions at baseline Median [Q1; Q3] or (Min; Max) T1 Gd+	 T1 Hypointense	 T2
Ponesimod vs. teriflunomide								
OPTIMUM								
Ponesimod	33	2.7 (1.0)	6.3 (4.7)	1.0 [1.0; 1.0]	2.0 [1.0; 3.0]	1 [1; 5]	n/a	n/a (number of patients with lesions [n %]: < 9: 0 (0) ≥ 9: 33 (100))
Teriflunomide	45	3.0 (1.2)	9.4 (6.8)	1.0 [1.0; 1.0]	1.0 [1.0; 2.0]	2 [1; 4]	n/a	n/a (number of patients with lesions [n (%)]: < 9: 1 (2) ≥ 9: 44 (98))
Natalizumab	No relevant studies were identified.							

a. Refers to the time period of 12 to 24 months prior to screening.

EDSS: Expanded Disability Status Scale; Gd+: gadolinium enriching T1-lesion; IFN: interferon; Max: Maximum; Min: Minimum; MS: multiple sclerosis; N: number of randomised patients; n: number of patients with event; n/a: not available; Q1: 1st quartile; Q3: 3rd quartile; SD: standard deviation; vs.: versus

Supplementary Table 6 Results for the outcomes "number of patients with confirmed relapse" (RR, 95% CI), "time to disability progression by EDSS" (HR, 95% CI), and "treatment discontinuation due to AE" (RR, 95% CI) from analyses in patients with highly active RRMS despite previous DMT

Comparison of DMTs (horizontal vs. vertical)	Alemtuzumab	Cladribine	Dimethyl fumarate	Fingolimod	Natalizumab	Ocrelizumab	Ofatumumab	Ozanimod	Ponesimod	Teriflunomide
Alemtuzumab		–	–	–	–	x	–	–	–	–
Cladribine	–		x	–	–	–	–	–	–	–
Dimethyl fumarate	–	x		x	–	–	x	–	x	x
Fingolimod	–	–	x		–	–	Confirmed relapse: 1.08 [0.55; 2.12] Disability progression: 2.09 [0.44; 10.00] Discontinuation due to AE: –	–	–	Confirmed relapse: 0.65 [0.37; 1.17] Disability progression: 0.98 [0.25; 3.88] Discontinuation due to AE: –
Natalizumab	–	–	–	–		–	–	–	–	–
Ocrelizumab	x	–	–	–	–		–	x	–	–
Ofatumumab	–	–	x	Confirmed relapse: 0.92 [0.47; 1.81] Disability progression: 0.48 [0.10; 2.28] Discontinuation due to AE: –	–	–		–	–	**Confirmed relapse: 0.60 [0.43; 0.86]** **Disability progression: 0.47 [0.22; 0.98]** **Discontinuation due to AE: 0.32 [0.13; 0.78]**[a]
Ozanimod	–	–	–	–	–	x	–		–	–
Ponesimod	–	–	x	–	–	–	–	–		Confirmed relapse: 0.61 [0.32; 1.17] Disability progression: 0.17 [0.02; 1.47] **Discontinuation due to AE: 4.77 [1.06; 21.52]**[a]

Supplementary Table 6 Results for the outcomes "number of patients with confirmed relapse" (RR, 95% CI), "time to disability progression by EDSS" (HR, 95% CI), and "treatment discontinuation due to AE" (RR, 95% CI) from analyses in patients with highly active RRMS despite previous DMT

Comparison of DMTs (horizontal vs. vertical)	**Alemtuzumab**	**Cladribine**	**Dimethyl fumarate**	**Fingolimod**	**Natalizumab**	**Ocrelizumab**	**Ofatumumab**	**Ozanimod**	**Ponesimod**	**Teriflunomide**
Teriflunomide	–	–	x	Confirmed relapse: 1.53 [0.86; 2.72] Disability progression: 1.02 [0.26; 4.06] Discontinuation due to AE: –	–	–	**Confirmed relapse: 1.65 [1.17; 2.34]** **Disability progression: 2.14 [1.02; 4.49]** **Discontinuation due to AE: 3.14 [1.29; 7.64]**[a]	–	Confirmed relapse: 1.63 [0.86; 3.11] Disability progression: 6.02 [0.68; 53.39] **Discontinuation due to AE: 0.21 [0.05; 0.94]**[a]	

Entries printed in **bold** indicate statistically significant effects.

–: Based on the available studies, either no comparative analysis is possible, or results are not interpretable, because only one study with high risk of bias on at least one comparison of an indirect comparison was available.

x: Data for the subpopulation of patients with highly active RRMS despite previous DMT were not provided.

a. Result from direct comparison between the two DMTs.

AE: adverse event; CI: confidence interval; DMT: disease modifying therapy; EDSS: Expanded Disability Status Scale; HR: hazard ratio; RR: relative risk; RRMS: relapsing-remitting multiple sclerosis

Supplementary Table 7 Results for the outcomes MSFC (z-score: MD, 95% CI) and T25FW (metres: MD, 95% CI) from analyses in patients with highly active RRMS despite previous DMT

Comparison of DMTs (horizontal vs. vertical	Alemtuzumab	Cladribine	Dimethyl fumarate	Fingolimod	Natalizumab	Ocrelizumab	Ofatumumab	Ozanimod	Ponesimod	Teriflunomide
Alemtuzumab		–	–	–	–	x	–	–	–	–
Cladribine	–		x	–	–	–	–	–	–	–
Dimethyl fumarate	–	x		x	–	–	x	–	x	x
Fingolimod	–	–	x		–	–	x	–	–	x
Natalizumab	–	–	–	–		–	–	–	–	–
Ocrelizumab	x	–	–	–	–		–	x	–	–
Ofatumumab	–	–	x	x	–	–		–	MSFC: -0.13 [-0.29; 0.03] T25FW: 1.03 [-0.22; 2.28]	MSFC: -0.01 [-0.10; 0.07][a] T25FW: 0.57 [-0.35; 1.48][a]
Ozanimod	–	–	–	–	–	x	–		–	–
Ponesimod	–	–	x	–	–	–	MSFC: 0.13 [-0.03; 0.29] T25FW: -1.03 [-2.28; 0.22]	–		MSFC: 0.12 [-0.02; 0.25][a] T25FW: -0.46 [-1.31; 0.40][a]
Teriflunomide	–	–	x	x	–	–	MSFC: 0.01 [-0.07; 0.10][a] T25FW: -0.57 [-1.48; 0.35][a]	–	MSFC: -0.12 [-0.25; 0.02][a] T25FW: 0.46 [-0.40; 1.31][a]	

Entries printed in **bold** indicate statistically significant effects.

–: Based on the available studies, either no comparative analysis is possible, or results are not interpretable, because only one study with high risk of bias on at least one comparison of an indirect comparison was available.

x: Data for the subpopulation of patients with highly active disease RRMS previous DMT were not provided.

a. Result from direct comparison between the two DMTs.

CI: confidence interval; DMT: disease modifying therapy; MD: mean difference from baseline; MSFC: Multiple Sclerosis Functional Composite; RRMS: relapsing-remitting multiple sclerosis; T25FW: Timed 25-foot Walk Test

Supplementary Table 8 Results for the outcome health-related quality of life (SF-36: RR, 95% CI) from analyses in patients with highly active RRMS despite previous DMT

Comparison of DMTs (horizontal vs. vertical	Alemtuzumab	Cladribine	Dimethyl fumarate	Fingolimod	Natalizumab	Ocrelizumab	Ofatumumab	Ozanimod	Ponesimod	Teriflunomide
Alemtuzumab		–	–	–	–	x	–	–	–	–
Cladribine	–		x	–	–	–	–	–	–	–
Dimethyl fumarate	–	x		x	–	–	x	–	x	x
Fingolimod	–	–	x		–	–	–	–	–	–
Natalizumab	–	–	–	–		–	–	–	–	–
Ocrelizumab	x	–	–	–	–		–	x	–	–
Ofatumumab	–	–	x	–	–	–		–	–	–
Ozanimod	–	–	–	–	–	x	–		–	–
Ponesimod	–	–	x	–	–	–	–	–		MCS (improvement)[a]: 1.58 [0.69; 3.65][c] PCS (improvement)[b]: 1.93 [0.40; 9.19][c] MCS (deterioration)[a]: 0.66 [0.23; 1.94][c] PCS (deterioration)[b]: 0.30 [0.06; 1.41][c]
Teriflunomide	–	–	x	–	–	–	–	–	MCS (improvement)[a]: 0.63 [0.27; 1.45][c] PCS (improvement)[b]: 0.52 [0.11; 2.50][c] MCS (deterioration)[a]: 1.52 [0.52; 4.35][c] PCS (deterioration)[b]: 3.33 [0.71; 16.67][c]	

Entries printed in **bold** indicate statistically significant effects.

–: Based on the available studies, either no comparative analysis is possible, or results are not interpretable, because only one study with high risk of bias on at least one comparison of an indirect comparison was available.

x: Data for the subpopulation of patients with highly active RRMS despite previous DMT were not provided.

a. Change by ≥ 15% of the scale range (10.8 points).

b. Change by ≥ 15% of the scale range (10.05 points).

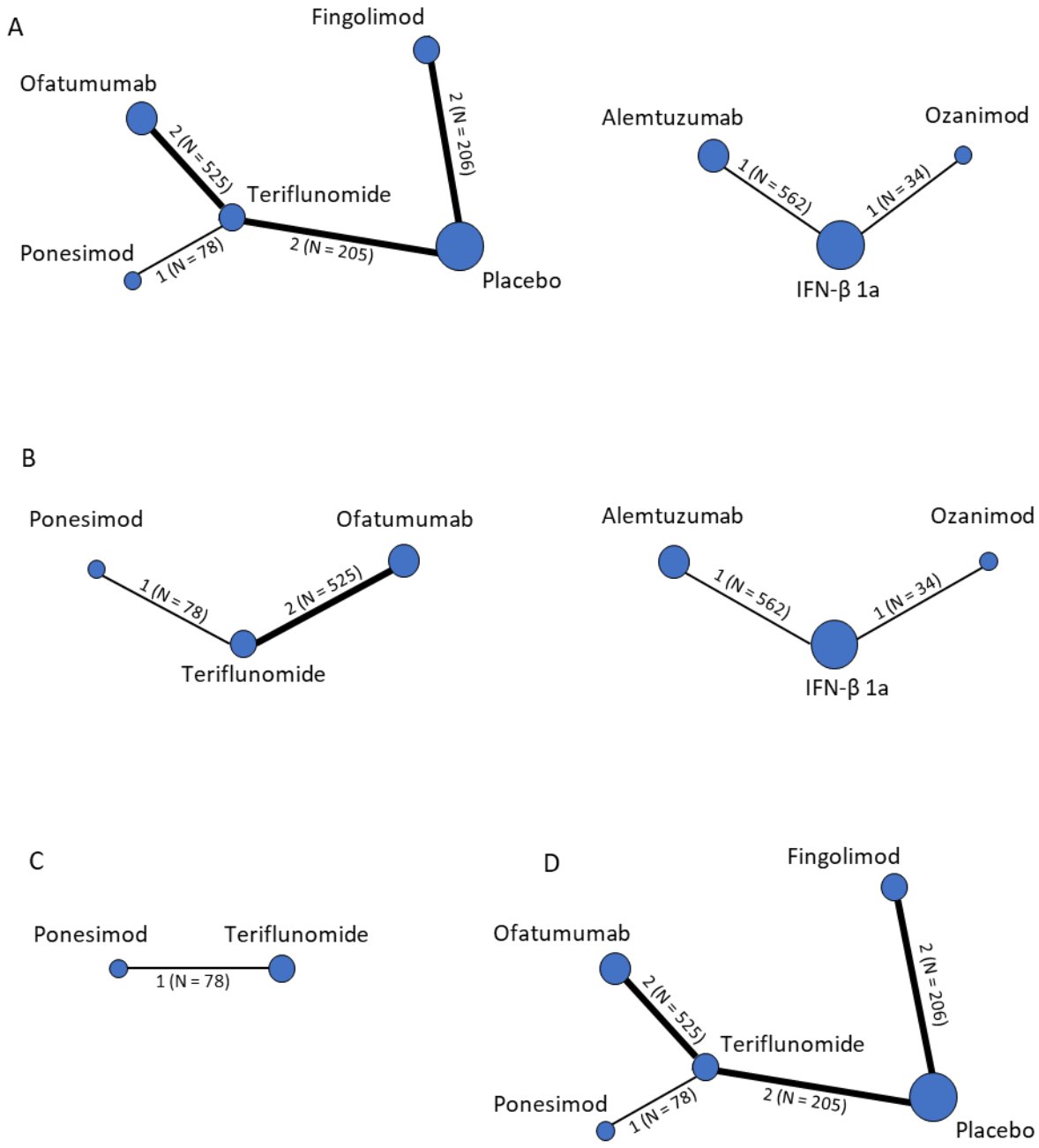
c. Direct comparison.

CI: confidence interval; DMT: disease modifying therapy; MCS: Mental Component Summary; PCS: Physical Component Summary; RR: relative risk; RRMS: relapsing-remitting multiple sclerosis; SF-36: Short Form 36

Supplementary Table 9 Studies without results published up to July 2023

Study	Study ID [Reference]	Planned sample size	Study status[a] (Study Completion, if available)
Cladribin			
ChariotMS	NCT04695080 [269], 2018-005038-39 [270]	200	ongoing (12/2027)
NOR-MS	NCT04121403 [271], 2019-001505-24 [272]	264	ongoing (12/2024)
Ocrelizumab			
BN42082	NCT04544436 [273], 2020-000893-69 [274], PER-056-20 [275]	865	ongoing (08/2028)
DanNORMS	NCT04688788 [276], 2020-002981-15 [277]	594	ongoing (04/2028)
Teriflunomide			
BCD-132-2	NCT04056897 [278]	270	unclear[a]
evolutionRMS 1 (MS200527_0080)	NCT04338022 [279], 2019-004972-20 [280], CTRI/2020/10/028457 [281]	1124	ongoing (06/2026)
evolutionRMS 2 (MS200527_0082)	NCT04338061 [282], 2019-004980-36 [283], CTRI/2020/10/028183 [284]	1124	ongoing (06/2026)
FENhance (GN41851)	NCT04586010 [285], 2019-004857-10 [286], PER-076-20 [287]	736	ongoing (11/2025)
FENhance 2 (GN42272)	NCT04586023 [288], 2020-001168-28 [289], CTRI/2021/03/031904 [290]	736	ongoing (11/2025)
GEMINI 1	NCT04410978 [291], 2020-000637-41 [292]	900	ongoing (09/2023)
GEMINI 2	NCT04410991 [293], 2020-000644-55 [294], CTRI/2020/11/029237 [295]	900	ongoing (08/2023)

a. status available in the registry on 22th July 2023
b. registries were checked in July 2023, last update in 2021, study was labelled ongoing



Supplementary Figure 1 Comparisons for outcomes other than relapse rate and serious adverse events for which data were available.

A: EDSS-based disability progression, confirmed after 24 weeks, B: severity of disability (assessed with MSFC z-score) and walking ability (assessed with T25FW), C: health-related quality of life, D: discontinuation due to adverse events. Numbers indicate the number of studies per comparison and total number of patients. EDSS = Expanded Disability Status Scale; IFN = interferon; MSFC = Multiple Sclerosis Functional Composite; N = total number of patients; T25FW = Timed 25-Foot Walk Test

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