**SUPPLEMENTARY MATERIAL**

**Figure e-1** Flowchart of patients’ selection

DMT = disease-modifying treatments.

Immagine che contiene screenshot

Descrizione generata automaticamente

**Figure e-2** Comparison of each DMT vs placebo

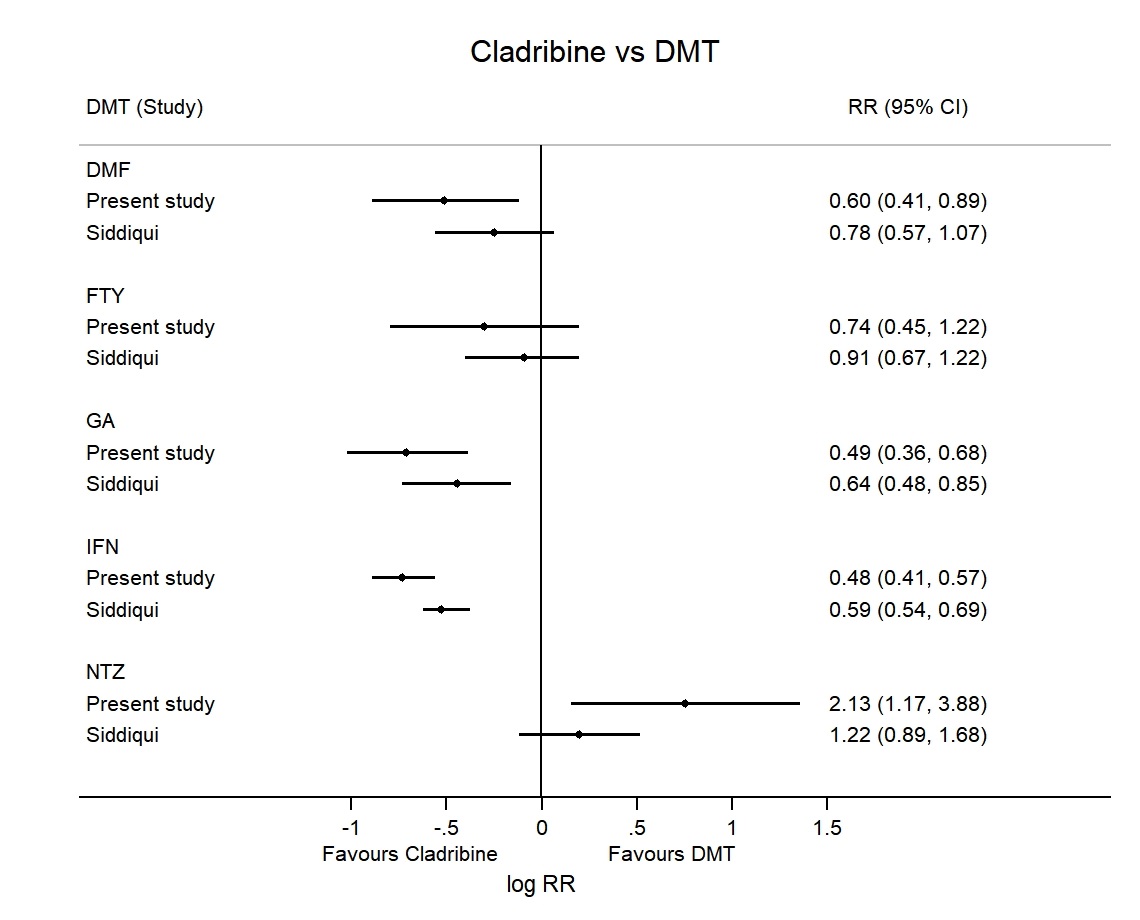
Forest plot for the comparison of each DMT vs placebo in our study and in the previous network meta-analyses of randomized clinical trials. DMF = dimethyl fumarate; DMT = disease-modifying treatment; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; NTZ = natalizumab; RR = relapse ratio.18–20

Immagine che contiene screenshot

Descrizione generata automaticamente

**Figure e-3** Comparison of the effectiveness of cladribine vs other DMTs

Forest plot to compare the effectiveness of cladribine vs the other DMT in our study with those reported in a previous network meta-analysis. DMF = dimethyl fumarate; DMT = disease-modifying treatment; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; NTZ = natalizumab; RR = relapse ratio.



**Figure e-4** Comparative effectiveness of cladribine vs other DMTs on time to disability progression

Forest plot for HR of cladribine vs each other DMT on time to disability progression. DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; HR = hazard ratio; IFN = interferon β; NTZ = natalizumab; TERI = teriflunomide.

**Immagine che contiene testo, mappa, sedendo, tavolo

Descrizione generata automaticamente**

**Figure e-5** EDSS progression-free survival over 2 years from treatment start

DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; NTZ = natalizumab.

**Immagine che contiene mappa, testo

Descrizione generata automaticamente**

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| **Table e-1** Number of patients, unweighted baseline characteristics, and follow-up duration in each treatment group for all patients included in the analysis | | | | | | | | | | | | | |
|  | **CLARITY (n=945)** | **IFN  (n=1168)** | **STD DIFF vs CLARITY** | **GA (n=402)** | **STD DIFF vs CLARITY** | **FTY (n=113)** | **STD DIFF vs CLARITY** | **NTZ (n=149)** | **STD DIFF vs CLARITY** | **DMF (n=295)** | **STD DIFF vs CLARITY** | **TERI (n=77)** | **STD DIFF vs CLARITY** |
| Age, years, mean (SD) | 38.7 (10.3) | 35 (10) | 0.37 | 39.9 (11.5) | 0.11 | 35.3 (10.8) | 0.33 | 32.2 (9.7) | 0.64 | 36.3 (10.2) | 0.23 | 46.3 (12) | 0.73 |
| Females, n (%) | 622 (65.8) | 762 (65.2) | 0.012 | 293 (72.9) | 0.15 | 64 (56.6) | 0.19 | 82 (55) | 0.22 | 181 (61.4) | 0.09 | 39 (50.7) | 0.31 |
| EDSS, mean (SD); median (IQR) | 2.90 (1.28);3 (2–4) | 1.81 (1.00);1.5 (1–2.5) | 0.96 | 1.82 (1.07);1.5 (1–2) | 0.88 | 2.47 (1.15);2.5 (1.5–3) | 0.34 | 2.63 (1.14);2.5 (2–3.5) | 0.21 | 1.59 (1.02);1.5 (1–2) | 1.07 | 2.47 (1.26);2 (1.5–3.5) | 0.34 |
| Disease duration, mean (SD); median (IQR) | 4.15 (5.42);2(0.56–5.86) | 2.33 (4.21);0.62 (0.2–2.3) | 0.38 | 3.07 (5.55);0.97 (0.3–3.1) | 0.20 | 3.27 (5.6);1.23 (0.21–3.96) | 0.16 | 1.83 (3.44);0.51 (0.15–2.1) | 0.45 | 2.27 (4.16);0.54 (0.2–2.1) | 0.37 | 5.93 (7.51);2.29 (0.5–9.8) | 0.32 |
| ARR in previous year, mean (SD) | 1.34 (0.59) | 1.26 (0.49) | 0.15 | 1.25 (0.49) | 0.16 | 1.45 (0.70) | 0.18 | 1.55 (0.73) | 0.34 | 1.21 (0.46) | 0.23 | 1.09 (0.33) | 0.44 |
| Active lesions, n (%) | 292 (30.9) | 457/1023 (44.7) | 0.29 | 174/376 (46.3) | 0.32 | 51/90 (56.7) | 0.54 | 95/128 (74.2) | 0.96 | 153/276 (55.4) | 0.51 | 31/72 (43.1) | 0.24 |
| Follow-up duration, mean (SD); median (IQR) | 1.74 (0.34); 1.83 (1.82–1.84) | 1.48 (0.64); 2 (0.93–2) | - | 1.31 (0.68); 1.40 (0.67–2) | - | 1.29 (0.71); 1.43 (0.67–2) | - | 1.49 (0.65); 1.92 (1.03–2) | - | 1 (0.63); 0.98 (0.45–1.51) | - | 1.07 (0.66); 0.97 (0.47–1.75) | - |
| Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; IQR = interquartile range; NTZ = natalizumab; STD DIFF = standardized mean difference according to Cohen’s d; TERI = teriflunomide. | | | | | | | | | | | | | |

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| **Table e-2** Baseline characteristics and the follow-up duration for all patients in the CLARITY study | | | |
|  | **Placebo  (n=305)** | **Cladribine 3.5 (n=322)** | **Cladribine 5.25  (n=318)** |
| Age, years, mean (SD) | 39 (10.1) | 38 (10.7) | 39.1 (10) |
| Females, n (%) | 201 (65.9) | 210 (65.2) | 213 (67) |
| EDSS, mean (SD); median (IQR) | 2.88 (1.30);  3 (2–4) | 2.88 (1.20);  2.5 (2–3.5) | 2.95 (1.36);  3 (2–4) |
| Disease duration, mean (SD); median (IQR) | 4.26 (5.61);  2 (0.6–5.8) | 4.05 (5.57);  1.8 (0.6–5.6) | 4.16 (5.06);  2.3 (0.5–6.4) |
| ARR in previous year, mean (SD) | 1.35 (0.56) | 1.35 (0.61) | 1.33 (0.61) |
| Active lesions, n (%) | 91 (29.8) | 102 (31.7) | 99 (31.1) |
| Follow-up duration, mean (SD); median (IQR) | 1.72 (0.37);  1.83 (1.82–1.84) | 1.78 (0.27);  1.83 (1.82–1.84) | 1.74 (0.34);  1.83 (1.82–1.84) |

Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IQR = interquartile range.

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| **Table e-3** Inverse probability weighted demographic and clinical characteristics for the comparison of IFN with placebo and cladribine | | | | | | | |
|  | | **IFN vs cladribine vs placebo** | | | | **STD DIFF  IFN vs placebo** | **STD DIFF  IFN vs cladribine 3.5** | **STD DIFF  IFN vs cladribine 5.25** |
| **Placebo (n=305)** | **Cladribine 3.5 (n=322)** | **Cladribine 5.25 (n=318)** | **IFN (n=1168)** |
| Age, years, mean (SD) | | 37.6 (9.5) | 36.9 (10.7) | 37.5 (10) | 36.6 (10.7) | 0.096 | 0.028 | 0.085 |
| Females, n (%) | | 202 (66.2) | 203 (63.2) | 222 (69.8) | 768 (65.7) | 0.01 | 0.057 | 0.087 |
| EDSS, mean (SD); median (IQR) | | 2.46 (1.26); 2 (1.5–3) | 2.50 (1.14); 2 (1.5–3.5) | 2.42 (1.35); 2 (1.5–3.5) | 2.11 (1.17); 2 (1–3) | 0.29 | 0.34 | 0.25 |
| Disease duration, mean (SD); median (IQR) | | 2.56 (4.62); 0.6 (0.2–2.6) | 2.51 (4.6); 0.63 (0.22–2.45) | 2.34 (4.15); 0.39 (0.18–2.70) | 2.75 (4.68); 0.7 (0.2–2.9) | 0.04 | 0.05 | 0.089 |
| ARR in previous year, mean (SD) | | 1.32 (0.56) | 1.35 (0.58) | 1.30 (0.56) | 1.33 (0.58) | 0.017 | 0.034 | 0.052 |
| Active lesions, n (%) | | 96 (31.5) | 101 (31.5) | 109 (34.3) | 435/1023 (42.5) | 0.23 | 0.23 | 0.17 |

Sensitivity analysis including in the calculation of IPTW also MRI lesions.

Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IFN = interferon β; IPTW = inverse probability of treatment weighting; STD DIFF = standardized mean difference according to Cohen’s d.

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| **Table e-4** Inverse probability weighted demographic and clinical characteristics for the comparison of GA with placebo and cladribine | | | | | | | |
|  | **GA vs cladribine vs placebo** | | | | **STD DIFF GA vs placebo** | **STD DIFF GA vs cladribine 3.5** | **STD DIFF GA vs cladribine 5.25** |
| **Placebo (n=305)** | **Cladribine 3.5 (n=322)** | **Cladribine 5.25 (n=318)** | **GA (n=402)** |
| Age, years, mean (SD) | 38.9 (9.8) | 38.3 (10.7) | 39 (10) | 39.5 (11.8) | 0.054 | 0.11 | 0.045 |
| Females, n (%) | 204 (66.9) | 209 (64.9) | 215 (67.6) | 269 (66.9) | 0.0006 | 0.042 | 0.015 |
| EDSS, mean (SD); median (IQR) | 2.69 (1.30); 2.5 (1.5–3.5) | 2.71 (1.17); 2.5 (2–3.5) | 2.74 (1.36); 2.5 (1.5–3.5) | 2.28 (1.32); 2 (1–3) | 0.31 | 0.34 | 0.34 |
| Disease duration, mean (SD); median (IQR) | 3.46 (5.22); 1.18 (0.36–4.44) | 3.36 (5.20); 1.08 (0.33–4.39) | 3.32 (4.74); 1.19 (0.26–4.84) | 3.10 (5.57); 1.00 (0.17–3) | 0.066 | 0.048 | 0.042 |
| ARR in previous year, mean (SD) | 1.34 (0.56) | 1.35 (0.60) | 1.32 (0.58) | 1.32 (0.56) | 0.036 | 0.052 | 0.000 |
| Active lesions, n (%) | 92 (30.1) | 99 (30.7) | 101 (31.8) | 146/376 (38.7) | 0.18 | 0.17 | 0.15 |
| Sensitivity analysis including in the calculation of IPTW also MRI lesions  Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IPTW = inverse probability of treatment weighting; STD DIFF = standardized mean difference according to Cohen’s d. | | | | | | | |

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| **Table e-5** Inverse probability weighted demographic and clinical characteristics for the comparison of FTY with placebo and cladribine | | | | | | | | | | | |
|  | | | **FTY vs cladribine vs placebo** | | | | | | | **STD DIFF FTY vs placebo** | **STD DIFF FTY vs cladribine 3.5** | **STD DIFF FTY vs cladribine 5.25** |
| **Placebo (n=305)** | | **Cladribine 3.5 (n=322)** | | **Cladribine 5.25 (n=318)** | | **FTY (n=113)** |
| Age, years, mean (SD) | | 38.7 (10.1) | | 37.7 (10.8) | | 38.8 (10) | | 38.1 (11.6) | | 0.056 | 0.039 | 0.063 |
| Females, n (%) | | 198 (64.9) | | 207 (64.3) | | 209 (65.7) | | 69 (61.1) | | 0.079 | 0.067 | 0.097 |
| EDSS, mean (SD); median (IQR) | | 2.84 (1.30); 2.5(2–4) | | 2.83 (1.18); 2.5(2–3.5) | | 2.90 (1.37); 3 (2–4) | | 2.81 (1.23); 2.5 (2–3.5) | | 0.025 | 0.022 | 0.072 |
| Disease duration, mean (SD); median (IQR) | | 4.18 (5.55); 1.9 (0.6–5.8) | | 3.97 (5.50); 1.76 (0.5–5.5) | | 4.09 (5.03); 2.31 (0.5–6.3) | | 3.90 (6.11); 1.79 (0.3–5.6) | | 0.047 | 0.010 | 0.034 |
| ARR in previous year, mean (SD) | | 1.36 (0.57) | | 1.36 (0.62) | | 1.34 (0.61) | | 1.36 (0.57) | | 0.006 | 0.005 | 0.029 |
| Active lesions, n (%) | | 92 (30.2) | | 102 (31.8) | | 100 (31.5) | | 48/90 (53.3) | | 0.48 | 0.45 | 0.45 |

Sensitivity analysis including in the calculation of IPTW also MRI lesions.

Abbreviations: ARR = annualized relapse-rate; EDSS = Expanded Disability Status Scale; FTY = fingolimod; IPTW = inverse probability of treatment weighting.

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| **Table e-6** Inverse probability weighted demographic and clinical characteristics for the comparison of NTZ with placebo and cladribine | | | | | | | | | |
|  | **NTZ vs cladribine vs placebo** | | | | | | | **STD DIFF  NTZ vs placebo** | **STD DIFF  NTZ vs cladribine 3.5** | | **STD DIFF  NTZ vs cladribine 5.25** |
| **Placebo (n=305)** | **Cladribine 3.5 (n=322)** | | **Cladribine 5.25 (n=318)** | | **NTZ (n=149)** | |
| Age, years, mean (SD) | 38.2 (10.2) | | 37.1 (10.8) | | 38.4 (10.1) | | 36.6 (10.9) | 0.15 | 0.039 | | 0.16 |
| Females, n (%) | 195 (63.9) | | 204 (63.3) | | 209 (65.7) | | 84 (56.4) | 0.15 | 0.14 | | 0.19 |
| EDSS, mean (SD); median (IQR) | 2.85 (1.29); 3 (2–4) | | 2.84 (1.18); 2.5 (2–3.5) | | 2.91 (1.37); 3 (2–4) | | 2.74 (1.10); 2.5 (2–3.5) | 0.093 | 0.087 | | 0.14 |
| Disease duration, mean (SD); median (IQR) | 3.96 (5.37); 1.82 (0.55–5.21) | | 3.74 (5.31); 1.62 (0.51–4.85) | | 3.90 (4.88); 1.98 (0.46–6.06) | | 3.28 (5.10); 0.95 (0.17–4.58) | 0.13 | 0.089 | | 0.12 |
| ARR in previous year, mean (SD) | 1.37 (0.58) | | 1.38 (0.63) | | 1.36 (0.63) | | 1.42 (0.66) | 0.088 | 0.076 | | 0.094 |
| Active lesions, n (%) | 94 (30.8) | | 104 (32.3) | | 102 (32) | | 89/128 (69.5) | 0.49 | 0.47 | | 0.47 |
| Sensitivity analysis including in the calculation of IPTW also MRI lesions.  Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IPTW = inverse probability of treatment weighting; NTZ = natalizumab; STD DIFF = standardized mean difference according to Cohen’s d. | | | | | | | | | |

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| **Table e-7** Inverse probability weighted demographic and clinical characteristics for the comparison of DMF with placebo and cladribine | | | | | | | |
|  | **DMF vs cladribine vs placebo** | | | | **STD DIFF  DMF vs placebo** | **STD DIFF  DMF vs cladribine 3.5** | **STD DIFF DMF vs cladribine 5.25** |
| **Placebo (n=305)** | **Cladribine 3.5 (n=322)** | **Cladribine 5.25 (n=318)** | **DMF (n=295)** |
| Age, years, mean (SD) | 38.6 (10) | 37.7 (10.7) | 38.5 (10) | 38.1 (10.2) | 0.050 | 0.038 | 0.039 |
| Females, n (%) | 199 (65.3) | 209 (64.9) | 210 (66) | 197 (66.8) | 0.032 | 0.04 | 0.016 |
| EDSS, mean (SD); median (IQR) | 2.65 (1.31); 2.5 (1.5–3.5) | 2.68 (1.19);2.5 (2–3.5) | 2.69 (1.39); 2.5 (1.5–3.5) | 2.38 (1.23); 2.5 (1.5–3) | 0.21 | 0.25 | 0.24 |
| Disease duration, mean (SD); median (IQR) | 3.90 (5.27); 1.8 (0.5–5.2) | 3.73 (5.26); 1.62 (0.51–4.85) | 3.89 (4.85); 1.98 (0.44–6.07) | 3.59 (5.61); 0.76 (0.3–4.4) | 0.057 | 0.025 | 0.056 |
| ARR in previous year, mean (SD) | 1.33 (0.55) | 1.34 (0.59) | 1.31 (0.58) | 1.29 (0.53) | 0.074 | 0.089 | 0.036 |
| Active lesions, n (%) | 92 (30.2) | 102 (31.7) | 100 (31.5) | 134/276 (48.6) | 0.38 | 0.35 | 0.35 |

Sensitivity analysis including in the calculation of IPTW also MRI lesions

Abbreviations: ARR = annualized relapse-rate; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; IPTW = inverse probability of treatment weighting; STD DIFF = standardized mean difference according to Cohen’s d.

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| **Table e-8** Inverse probability weighted demographic and clinical characteristics for the comparison of TERI with placebo and cladribine | | | | | | |
|  | **TERI vs cladribine vs placebo** | | | | **STD DIFF  TERI vs placebo** | **STD DIFF TERI vs cladribine 3.5** | | **STD DIFF TERI vs cladribine 5.25** |
| **Placebo (n=305)** | **Cladribine 3.5 (n=322)** | **Cladribine 5.25 (n=318)** | **TERI (n=77)** |
| Age, years, mean (SD) | 39.4 (10.2) | 38.4 (10.2) | 39.4 (10) | 39.3 (11.8) | 0.009 | 0.086 | | 0.01 |
| Females, n (%) | 200 (65.6) | 207 (64.3) | 208 (65.4) | 45 (58.4) | 0.15 | 0.12 | | 0.14 |
| EDSS, mean (SD); median (IQR) | 2.85 (1.30); 3 (2–4) | 2.85 (1.19); 2.5 (2–3.5) | 2.91 (1.36); 3 (2–4) | 2.56 (1.34); 2 (1.5–3.5) | 0.22 | 0.24 | | 0.26 |
| Disease duration, mean (SD); median (IQR) | 4.31 (5.64); 2.08 (0.63–5.90) | 4.16 (5.71); 1.81 (0.57–5.63) | 4.21 (5.15); 2.32 (0.51–6.38) | 3.76 (5.88); 1.05 (0.54–3.98) | 0.097 | 0.07 | | 0.085 |
| ARR in previous year, mean (SD) | 1.33 (0.55) | 1.34 (0.60) | 1.32 (0.59) | 1.32 (0.57) | 0.018 | 0.034 | | 0.000 |
| Active lesions, n (%) | 92 (30.2) | 100 (31.1) | 97 (30.5) | 19/72 (26.4) | 0.084 | 0.10 | | 0.09 |

Sensitivity analysis including in the calculation of IPTW also MRI lesions

Abbreviations: ARR: annualized relapse-rate; EDSS = Expanded Disability Status Scale; IPTW = inverse probability of treatment weighting; STD DIFF = standardized mean difference according to Cohen’s d; TERI = teriflunomide.

**Table e-9** Summary of the results of the treatment effects vs placebo in pivotal clinical trials18–20

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| All patients | IFN-1a (44) | IFN-1b (250) | IFN-1a (30) | GA (20) | GA (40) | FTY | NTZ | DMF (240) |
| ARR ratio (95% CI) | 0.69  (0.60–0.79) | 0.70  (0.61–0.82) | 0.84  (0.77–0.93) | 0.69  (0.62–0.76) | 0.66  (0.55–0.78) | 0.47  (0.41–0.53) | 0.31  (0.27–0.36) | 0.48  (0.42–0.55) |

Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; NTZ = natalizumab.

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| **Table e-10** ARR ratio of the two doses of cladribine vs other drugs | | |
|  | **IPTW clinical variables** | **IPTW clinical + MRI variables** |
|  | **ARR ratio (95% CI)** | **ARR ratio (95% CI)** |
| IFN vs placebo | 0.764 (0.644–0.907); *p*=0.002 | 0.792 (0.662–0.947); *p*=0.011 |
| Cladribine 3.5 mg vs IFN | 0.489 (0.392–0.609); *p*<0.001 | 0.474 (0.376–0.597); *p*<0.001 |
| Cladribine 5.25 mg vs IFN | 0.470 (0.378–0.584); *p*<0.001 | 0.443 (0.352–0.557); *p*<0.001 |
|  |  |  |
| GA vs placebo | 0.783 (0.568–1.077); *p*=0.13 | 0.786 (0.569–1.085); *p*=0.14 |
| Cladribine 3.5 mg vs GA | 0.489 (0.337–0.71); *p*<0.001 | 0.488 (0.335–0.712); *p*<0.001 |
| Cladribine 5.25 mg vs GA | 0.498 (0.343–0.722); *p*<0.001 | 0.491 (0.336–0.716); *p*<0.001 |
|  |  |  |
| FTY vs placebo | 0.54 (0.32–0.89); *p*=0.016 | 0.47 (0.28–0.79); *p*=0.005 |
| Cladribine 3.5 mg vs FTY | 0.73 (0.43–1.25); *p*=0.25 | 0.83 (0.48–1.45); *p*=0.52 |
| Cladribine 5.25 mg vs FTY | 0.75 (0.44–1.28); *p*=0.29 | 0.85 (0.49–1.47); *p*=0.56 |
|  |  |  |
| NTZ vs placebo | 0.17 (0.09–0.31); *p*<0.001 | 0.15 (0.08–0.29); *p*<0.001 |
| Cladribine 3.5 mg vs NTZ | 2.28 (1.22–4.27); *p*=0.009 | 2.55 (1.34–4.86); *p*=0.004 |
| Cladribine 5.25 mg vs NTZ | 2.32 (1.24–4.35); *p*=0.009 | 2.49 (1.30–4.76); *p*=0.006 |
|  |  |  |
| DMF vs placebo | 0.65 (0.44–0.97); *p*=0.036 | 0.64 (0.43–0.94); *p*=0.024 |
| Cladribine 3.5 mg vs DMF | 0.6 (0.39–0.94); *p*=0.024 | 0.64 (0.42–0.99); *p*=0.043 |
| Cladribine 5.25 mg vs DMF | 0.6 (0.39–0.93); *p*=0.023 | 0.62 (0.40–0.96); *p*=0.031 |

Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; IPTW = inverse probability of treatment weighting; NTZ = natalizumab.

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| **Table e-11** Risk of 24-week disability progression of cladribine 3.5 mg and cladribine 5.25 mg vs other drugs | | |
|  | **IPW clinical variables** | **IPW clinical + MRI variables** |
|  | **HR (95% CI)** | **HR (95% CI)** |
| IFN (n=1128) vs placebo | 0.72 (0.55–0.94); *p*=0.017 | 0.75 (0.57–0.99); *p*=0.046 |
| Cladribine 3.5 mg vs IFN | 0.77 (0.56–1.06); *p*=0.11 | 0.72 (0.51–1.01); *p*=0.055 |
| Cladribine 5.25 mg vs IFN | 0.95 (0.71–1.27); *p*=0.71 | 0.90 (0.66–1.22); *p*=0.48 |
|  |  |  |
| GA (n=379) vs placebo | 0.93 (0.58–1.47); *p*=0.74 | 1.00 (0.63–1.59); *p*=0.99 |
| Cladribine 3.5 mg vs GA | 0.59 (0.35–0.99); *p*=0.045 | 0.53 (0.31–0.90); *p*=0.018 |
| Cladribine 5.25 mg vs GA | 0.69 (0.42–1.14); *p*=0.15 | 0.63 (0.38–1.04); *p*=0.073 |
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| FTY (n=108) vs placebo | 0.61 (0.30–1.27); *p*=0.19 | 0.65 (0.32–1.30); *p*=0.23 |
| Cladribine 3.5 mg vs FTY | 0.80 (0.37–1.73); *p*=0.57 | 0.76 (0.36–1.59); *p*=0.47 |
| Cladribine 5.25 mg vs FTY | 0.99 (0.47–2.11); *p*=0.99 | 0.92 (0.45–1.90); *p*=0.83 |
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| NTZ (n=134) vs placebo | 0.45 (0.22–0.92); *p*=0.028 | 0.35 (0.16–0.78); *p*=0.01 |
| Cladribine 3.5 mg vs NTZ | 1.09 (0.51–2.31); *p*=0.83 | 1.40 (0.61–3.22); *p*=0.43 |
| Cladribine 5.25 mg vs NTZ | 1.32 (0.63–2.78); *p*=0.46 | 1.63 (0.71–3.73); *p*=0.25 |
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| DMF (n=262) vs placebo | 0.54 (0.29–1.00); *p*=0.051 | 0.68 (0.38–1.19); *p*=0.18 |
| Cladribine 3.5 mg vs DMF | 0.95 (0.49–1.84); *p*=0.87 | 0.75 (0.41–1.39); *p*=0.36 |
| Cladribine 5.25 mg vs DMF | 1.19 (0.63–2.26); *p*=0.60 | 0.86 (0.47–1.56); *p*=0.61 |

Abbreviations: DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; HR = hazard ratio; IFN = interferon β; IPW = inverse probability weighting; NTZ = natalizumab.

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| **Table e-12** Inverse probability weighted demographic and clinical characteristics for the comparison of IFN, GA, and FTY vs CLARITY study in low and highly active groups | | | | | | | | | | | | | | | | | | | | | | |
|  | **CLARITY (n=945)** | | | **IFN  (n=1168)** | | **STD DIFF IFN vs CLARITY** | | **CLARITY (n=945)** | | **GA  (n=402)** | | **STD DIFF GA vs CLARITY** | | | **CLARITY (n=945)** | | | **FTY  (n=113)** | | **STD DIFF FTY vs CLARITY** | |
| **HDA N**  **(n=670)** | **HDA Y**  **(n=275)** | **HDA N**  **(n=896)** | | **HDA Y**  **(n=272)** | **HDA N** | **HDA Y** | **HDA N**  **(n=670)** | **HDA Y**  **(n=275)** | **HDA N**  **(n=312)** | **HDA Y**  **(n=90)** | | **HDA N** | **HDA Y** | | **HDA N**  **(n=670)** | **HDA Y**  **(n=275)** | **HDA N**  **(n=72)** | **HDA Y**  **(n=41)** | **HDA N** | **HDA Y** | |
| Age | 38 (10) | 35.7 (10.1) | 36.3 (10.5) | | 37.4 (11.3) | 0.17 | 0.16 | 39.5 (10.1) | 37 (10.1) | 40 (12.6) | 38.2 (9.5) | | 0.047 | 0.12 | | 39.2 (10.3) | 36.5 (10.2) | 38.8 (12) | 36.6 (10) | 0.038 | 0.006 | |
| Females, n (%) | 443 (66.1) | 186 (67.7) | 581 (64.8) | | 187 (68.8) | 0.027 | 0.024 | 447 (66.7) | 182 (66.3) | 199 (63.8) | 70 (77.8) | | 0.07 | 0.23 | | 438 (65.3) | 176 (64.1) | 42 (58) | 27 (66.5) | 0.089 | 0.013 | |
| EDSS, mean (SD); median (IQR) | 2.47 (1.21) | 2.43 (1.37) | 2.03 (1.11) | | 2.32 (1.29) | 0.38 | 0.08 | 2.71 (1.25) | 2.72 (1.36) | 2.21 (1.24) | 2.45 (1.52) | | 0.40 | 0.19 | | 2.84 (1.26) | 2.88 (1.35) | 2.85 (1.23) | 2.69 (1.10) | 0.007 | 0.16 | |
| Disease duration, mean (SD); median (IQR) | 2.67 (4.67) | 1.93 (3.78) | 2.77 (4.60) | | 2.69 (4.88) | 0.022 | 0.17 | 3.71 (5.29) | 2.55 (4.30) | 3.46 (6.07) | 2.14 (3.81) | | 0.043 | 0.10 | | 4.54 (5.60) | 2.98 (4.56) | 4.43 (6.93) | 2.64 (3.49) | 0.018 | 0.08 | |
| ARR in previous year, mean (SD) | 1 (0.04) | 2.16 (0.42) | 1 (0) | | 2.19 (0.46) | 0.058 | 0.07 | 1 (0.05) | 2.17 (0.44) | 1 (0) | 2.18 (0.39) | | 0.069 | 0.028 | | 1 (0.06) | 2.18 (0.47) | 1 (0) | 2.22 (0.65) | 0.079 | 0.069 | |
| Active lesions, n (%) | 208 (31.1) | 99 (36) | 338/795 (42.6) | | 96/228 (42.1) | 0.24 | 0.13 | 196 (29.2) | 95 (34.5) | 114/298 (38.1) | 32/78 (40.5) | | 0.19 | 0.12 | | 197 (29.4) | 97 (35.2) | 32/63 (50.8) | 19/32 (59) | 0.45 | 0.49 | |
| Abbreviations: ARR = annualized relapse rate; FTY = fingolimod; GA = glatiramer acetate; HDA = high disease activity (N = no; Y = yes); IFN = interferon β; STD DIFF = standardized difference. | | | | | | | | | | | | | | | | | | | | | | |

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| **Table e-13** Inverse probability weighted demographic and clinical characteristics for the comparison of NTZ, DMF vs CLARITY study in low and highly active groups | | | | | | | | | | | | |
|  | **CLARITY (n=945)** | | **NTZ** | | **STD DIFF NTZ vs CLARITY** | | **CLARITY (n=945)** | | **DMF** | | **STD DIFF DMF vs CLARITY** | |
| **HDA N (n=670)** | **HDA Y (n=275)** | **HDA N (n=86)** | **HDA Y (n=63)** | **HDA N** | **HDA Y** | **HDA N (n=670)** | **HDA Y (n=275)** | **HDA N (n=238)** | **HDA Y (n=57)** | **HDA N** | **HDA Y** |
| Age, years, mean (SD) | 38.8 (10.4) | 35.9 (10.2) | 37.7 (11.7) | 34.5 (9.1) | 0.09 | 0.14 | 39 (10.2) | 36.4 (10.1) | 38.4 (10.5) | 37.4 (9.2) | 0.06 | 0.10 |
| Females, n (%) | 433 (64.7) | 176 (63.9) | 49 (57) | 35 (55.6) | 0.14 | 0.15 | 441 (65.9) | 175 (63.8) | 154 (64.7) | 43 (75.3) | 0.038 | 0.25 |
| EDSS, mean (SD); median (IQR) | 2.86 (1.25) | 2.89 (1.35) | 2.67 (1.08) | 2.86 (1.12) | 0.16 | 0.023 | 2.66 (1.26) | 2.73 (1.38) | 2.40 (1.29) | 2.32 (1.01) | 0.20 | 0.34 |
| Disease duration, mean (SD); median (IQR) | 4.34 (5.45) | 2.80 (4.35) | 3.35 (5.20) | 3.15 (4.94) | 0.19 | 0.075 | 4.23 (5.33) | 2.80 (4.38) | 4.23 (6.11) | 1.69 (3.04) | 0.001 | 0.30 |
| ARR in previous year, mean (SD) | 1 (0.06) | 2.19 (0.48) | 1 (0) | 2.25 (0.50) | 0.08 | 0.11 | 1.00 (0.05) | 2.17 (0.44) | 1 (0) | 2.15 (0.36) | 0.078 | 0.042 |
| Active lesions, n (%) | 200 (29.8) | 99 (35.8) | 51/75 (68.5) | 39/53 (72.7) | 0.83 | 0.79 | 197 (29.5) | 96 (35.1) | 110/222 (49.5) | 25/54 (45.9) | 0.42 | 0.22 |
| Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; HDA = high disease activity (N = No; Y = Yes); NTZ = natalizumab; STD DIFF = standardized difference. | | | | | | | | | | | | |

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| **Table e-14** Inverse probability weighted demographic and clinical characteristics for the comparison of IFN with placebo and cladribine according to HDA subgroups | | | | | | | | | | | | | | | | | | | | | | |
|  | **IFN vs cladribine vs placebo** | | | | | | | | | | **STD DIFF IFN vs placebo** | | | | **STD DIFF IFN vs cladribine 3.5** | | | | **STD DIFF IFN vs cladribine 5.25** | | | |
| **Placebo** | | **Cladribine 3.5** | | | **Cladribine 5.25** | | | **IFN** | |
| **HDA N (n=212)** | **HDA Y (n=93)** | **HDA N (n=228)** | **HDA Y (n=94)** | **HDA N (n=230)** | | **HDA Y (n=88)** | **HDA N (n=896)** | | **HDA Y (n=272)** |
| **HDA N** | | **HDA Y** | | | **HDA N** | | **HDA Y** | | **HDA N** | | **HDA Y** |
| Age, years, mean (SD) | 38.2 (9.3) | 36.3 (10) | 37.6 (10.9) | 35.2 (10.3) | 38.1 (9.9) | | 35.7 (10) | 36.3 (10.5) | | 37.4 (11.3) | 0.18 | 0.10 | | 0.12 | | | 0.20 | | 0.17 | | 0.15 | |
| Females, n (%) | 145 (68.4) | 57 (61) | 136 (59.6) | 67 (71.3) | 161 (70) | | 61 (69.3) | 581 (64.8) | | 187 (68.8) | 0.075 | 0.16 | | 0.11 | | | 0.055 | | 0.11 | | 0.012 | |
| EDSS, mean (SD); median (IQR) | 2.46 (1.19) | 2.45 (1.43) | 2.55 (1.13) | 2.37 (1.15) | 2.41 (1.28) | | 2.47 (1.54) | 2.03 (1.11) | | 2.32 (1.29) | 0.38 | 0.098 | | 0.47 | | | 0.040 | | 0.33 | | 0.11 | |
| Disease duration, mean (SD); median (IQR) | 2.72 (4.72) | 2.14 (4.34) | 2.81 (4.94) | 1.79 (3.63) | 2.50 (4.38) | | 1.88 (3.37) | 2.77 (4.60) | | 2.69 (4.88) | 0.01 | 0.12 | | 0.009 | | | 0.20 | | 0.059 | | 0.18 | |
| ARR in previous year, mean (SD) | 1 (0) | 2.16 (0.37) | 1.0 (0.05) | 2.16 (0.44) | 1 (0.05) | | 2.16 (0.45) | 1 (0) | | 2.19 (0.46) | - | 0.068 | | - | | | 0.066 | | - | | 0.066 | |
| Active lesions, n (%) | 69 (32.5) | 37 (40) | 77 (33.8) | 33 (35.3) | 80 (34.8) | | 38 (43) | 338/795 (42.6) | | 96/228 (42.1) | 0.16 | 0.08 | | 0.13 | | | 0.18 | | 0.11 | | 0.013 | |
| Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; HDA = high disease activity (N = no; Y = yes); IFN = interferon β; STD DIFF = standardized mean difference according to Cohen’s d. | | | | | | | | | | | | | | | | | | | | | | |

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| **Table e-15** Inverse probability weighted demographic and clinical characteristics for the comparison of GA with placebo and cladribine according to HDA subgroups | | | | | | | | | | | | | | |
|  | | **GA vs cladribine vs placebo** | | | | | | | | **STD DIFF GA vs placebo** | | **STD DIFF GA vs cladribine 3.5** | | **STD DIFF GA vs cladribine 5.25** | |
| **Placebo** | | **Cladribine 3.5** | | **Cladribine 5.25** | | **GA** | |
| **HDA N (n=212)** | **HDA Y (n=93)** | **HDA N (n=228)** | **HDA Y (n=94)** | **HDA N (n=230)** | **HDA Y (n=88)** | **HDA N (n=312)** | **HDA Y (n=90)** |
| **HDA N** | **HDA Y** | **HDA N** | **HDA Y** | **HDA N** | **HDA Y** |
| Age, years, mean (SD) | | 39.7 (9.5) | 37.1 (10.4) | 39 (10.9) | 36.4 (10.1) | 39.7 (9.9) | 37.4 (10) | 40 (12.6) | 38.2 (9.5) | 0.026 | 0.11 | 0.082 | 0.18 | 0.031 | 0.08 |
| Females, n (%) | | 148 (69.8) | 56 (60) | 141 (61.8) | 68 (72.6) | 157 (68.3) | 58 (65.9) | 199 (63.8) | 70 (77.8) | 0.14 | 0.36 | 0.033 | 0.091 | 0.10 | 0.24 |
| EDSS, mean (SD); median (IQR) | | 2.68 (1.24) | 2.73 (1.43) | 2.75 (1.15) | 2.60 (1.22) | 2.70 (1.34) | 2.85 (1.45) | 2.2 (1.24) | 2.45 (1.52) | 0.37 | 0.19 | 0.45 | 0.11 | 0.38 | 0.27 |
| Disease duration, mean (SD); median (IQR) | | 3.77 (5.34) | 2.71 (4.87) | 3.75 (5.53) | 2.41 (4.19) | 3.60 (5.01) | 2.54 (3.82) | 3.46 (6.07) | 2.14 (3.81) | 0.054 | 0.13 | 0.049 | 0.067 | 0.026 | 0.10 |
| ARR in previous year, mean (SD) | | 1 (0) | 2.15 (0.36) | 1.0 (0.06) | 2.19 (0.48) | 1 (0.06) | 2.17 (0.49) | 1 (0) | 2.18 (0.39) | - | 0.08 | 0.085 | 0.01 | 0.082 | 0.023 |
| Active lesions, n (%) | | 63 (30) | 33 (35.4) | 71 (31) | 33 (35) | 70 (30.4) | 34 (38.1) | 114/298 (38.1) | 32/78 (40.5) | 0.20 | 0.13 | 0.18 | 0.15 | 0.18 | 0.08 |
| Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; HDA = high disease activity (N = no; Y = yes); STD DIFF = standardized mean difference according to Cohen’s d. | | | | | | | | | | | | | | |

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| **Table e-16** Inverse probability weighted demographic and clinical characteristics for the comparison of FTY with placebo and cladribine according to HDA subgroups | | | | | | | | | | | | | | | |
|  | **FTY vs cladribine vs placebo** | | | | | | | | | **STD DIFF FTY vs placebo** | | **STD DIFF FTY vs cladribine 3.5** | | **Std difference FTY vs cladribine 5.25** | | |
| **Placebo** | | **Cladribine 3.5** | | | **Cladribine 5.25** | | **FTY** | |
| **HDA N (n=212)** | **HDA Y (n=93)** | | **HDA N (n=228)** | **HDA Y (n=94)** | **HDA N (n=230)** | **HDA Y (n=88)** | **HDA N (n=72)** | **HDA Y (n=41)** | **HDA N** | **HDA Y** | **HDA N** | **HDA Y** | **HDA N** | **HDA Y** | |
| Age, years, mean (SD) | 39.8 (9.7) | 36.5 (10.6) | | 38.5 (11) | 35.8 (10) | 39.5 (10) | 37.2 (10) | 38.8 (12) | 36.6 (10) | 0.088 | 0.004 | 0.027 | 0.07 | 0.061 | 0.06 | |
| Females, n (%) | 145 (68.5) | 53 (57.1) | | 139 (61) | 68 (72.2) | 154 (67) | 55 (62.8) | 42 (58) | 27 (66.5) | 0.15 | 0.16 | 0.01 | 0.16 | 0.12 | 0.039 | |
| EDSS, mean (SD); median (IQR) | 2.81 (1.25) | 2.9 (1.4) | | 2.88 (1.16) | 2.73 (1.23) | 2.85 (1.35) | 3 (1.4) | 2.85 (1.23) | 2.69 (1.10) | 0.034 | 0.16 | 0.018 | 0.033 | 0.005 | 0.27 | |
| Disease duration, mean (SD); median (IQR) | 4.65 (5.65) | 3.13 (5.18) | | 4.46 (5.84) | 2.80 (4.41) | 4.52 (5.32) | 3.02 (4.03) | 4.43 (6.93) | 2.64 (3.49) | 0.035 | 0.11 | 0.005 | 0.039 | 0.015 | 0.095 | |
| ARR in previous year, mean (SD) | 1 (0) | 2.14 (0.35) | | 1.01 (0.07) | 2.21 (0.50) | 1 (0.07) | 2.20 (0.54) | 1 (0) | 2.22 (0.65) |  | 0.15 | 0.099 | 0.029 | 0.092 | 0.034 | |
| Active lesions, n (%) | 64 (30.3) | 33 (35.5) | | 74 (32.2) | 35 (37.4) | 71 (31) | 34 (38.5) | 32/63 (50.8) | 19/32 (59) | 0.47 | 0.52 | 0.43 | 0.48 | 0.45 | 0.45 | |
| Abbreviations: ARR: annualized relapse rate; EDSS = Expanded Disability Status Scale; FTY = fingolimod; HDA = high disease activity (N = no; Y = Yes); STD DIFF = standardized mean difference according to Cohen’s d. | | | | | | | | | | | | | | | | |

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| **Table e-17** Inverse probability weighted demographic and clinical characteristics for the comparison of NTZ with placebo and cladribine according to HDA subgroups | | | | | | | | | | | | | | | | |
|  | **NTZ vs cladribine vs placebo** | | | | | | | | | | **STD DIFF NTZ vs placebo** | | **STD DIFF NTZ vs cladribine 3.5** | | **STD DIFF NTZ vs cladribine 5.25** | | |
| **Placebo** | | **Cladribine 3.5** | | | **Cladribine 5.25** | | | **NTZ** | |
| **HDA N (n=212)** | **HDA Y (n=93)** | **HDA N (n=228)** | **HDA Y (n=94)** | **HDA N (n=230)** | | **HDA Y (n=88)** | **HDA N (n=86)** | | **HDA Y (n=63)** |
| **HDA N** | **HDA Y** | **HDA N** | **HDA Y** | **HDA N** | **HDA Y** | |
| Age, years, mean (SD) | 39.4 (9.8) | 35.8 (10.7) | 37.9 (11.) | 35.2 (9.9) | 39.1 (10.1) | | 36.6 (10) | 37.7 (11.7) | | 34.5 (9.1) | 0.15 | 0.13 | 0.013 | 0.075 | 0.12 | 0.22 | |
| Females, n (%) | 143 (67.5) | 52 (55.9) | 137 (60) | 67 (71.6) | 154 (67) | | 55 (62.8) | 49 (57) | | 35 (55.6) | 0.20 | 0.01 | 0.035 | 0.32 | 0.19 | 0.13 | |
| EDSS, mean (SD); median (IQR) | 2.82 (1.24) | 2.91 (1.40) | 2.88 (1.16) | 2.73 (1.24) | 2.86 (1.35) | | 3 (1.40) | 2.67 (1.08) | | 2.86 (1.12) | 0.13 | 0.04 | 0.19 | 0.11 | 0.16 | 0.14 | |
| Disease duration, mean (SD); median (IQR) | 4.46 (5.53) | 2.93 (4.90) | 4.24 (5.66) | 2.63 (4.23) | 4.33 (5.19) | | 2.85 (3.87) | 3.35 (5.20) | | 3.15 (4.94) | 0.20 | 0.05 | 0.16 | 0.11 | 0.19 | 0.07 | |
| ARR in previous year, mean (SD) | 1 (0) | 2.15 (0.36) | 1.01 (0.07) | 2.21 (0.51) | 1 (0.06) | | 2.22 (0.55) | 1 (0) | | 2.25 (0.50) | - | 0.23 | 0.10 | 0.07 | 0.09 | 0.057 | |
| Active lesions, n (%) | 68 (32.1) | 37 (39.8) | 78 (34.4) | 39 (41) | 77 (33.5) | | 37 (42) | 51/75 (68.5) | | 39/53 (72.7) | 0.86 | 0.82 | 0.81 | 0.79 | 0.83 | 0.75 | |

Abbreviations: ARR: annualized relapse rate; EDSS = Expanded Disability Status Scale; HDA = high disease activity (N = no; Y = yes); NTZ = natalizumab; STD DIFF = standardized mean difference according to Cohen’s d.

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| **Table e-18** Inverse probability weighted demographic and clinical characteristics for the comparison of DMF with placebo and cladribine according to HDA subgroups | | | | | | | | | | | | | | |
|  | **DMF vs cladribine vs placebo** | | | | | | | | **STD DIFF DMF vs placebo** | | **STD DIFF DMF vs cladribine 3.5** | | **STD DIFF DMF vs cladribine 5.25** | |
| **Placebo** | | **Cladribine 3.5** | | **Cladribine 5.25** | | **DMF** | |
| **HDA N (n=212)** | **HDA Y (n=93)** | **HDA N (n=228)** | **HDA Y (n=94)** | **HDA N (n=230)** | **HDA Y (n=88)** | **HDA N (n=238)** | **HDA Y (n=57)** |
| **HDA N** | **HDA Y** | **HDA N** | **HDA Y** | **HDA N** | **HDA Y** |
| Age, years, mean (SD) | 39.5 (9.7) | 36.6 (10.6) | 38.5 (11) | 35.7 (9.9) | 39.1 (10) | 36.9 (10) | 38.4 (10.5) | 37.4 (9.2) | 0.11 | 0.082 | 0.009 | 0.17 | 0.069 | 0.049 |
| Females, n (%) | 145 (68.5) | 54 (58.1) | 142 (62.4) | 67 (71.1) | 154 (66.8) | 56 (63.1) | 154 (64.7) | 43 (75.3) | 0.10 | 0.39 | 0.034 | 0.095 | 0.058 | 0.27 |
| EDSS, mean (SD); median (IQR) | 2.62 (1.26) | 2.73 (1.43) | 2.71 (1.16) | 2.61 (1.24) | 2.64 (1.36) | 2.86 (1.47) | 2.40 (1.29) | 2.32 (1.01) | 0.17 | 0.33 | 0.25 | 0.26 | 0.18 | 0.43 |
| Disease duration, mean (SD); median (IQR) | 4.30 (5.35) | 2.90 (4.93) | 4.15 (5.56) | 2.64 (4.26) | 4.24 (5.10) | 2.87 (3.90) | 4.23 (6.11) | 1.69 (3.04) | 0.012 | 0.29 | 0.012 | 0.26 | 0.002 | 0.34 |
| ARR in previous year, mean (SD) | 1 (0) | 2.14 (0.35) | 1.01 (0.07) | 2.18 (0.47) | 1 (0.06) | 2.18 (0.50) | 1 (0) | 2.15 (0.36) | - | 0.04 | 0.099 | 0.08 | 0.089 | 0.07 |
| Active lesions, n (%) | 72 (34) | 35 (37.1) | 81 (35.5) | 37 (39.3) | 80 (34.8) | 35 (40) | 110/222 (49.5) | 25/54 (45.9) | 0.43 | 0.26 | 0.40 | 0.21 | 0.42 | 0.19 |

Abbreviations: ARR: annualized relapse rate; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; HDA = high disease activity (N = no; Y = yes); STD DIFF = standardized mean difference according to Cohen’s d.

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| **Table e-19** Relapse rate ratio of cladribine 3.5 mg vs each treatment according to HDA subgroups | | | | | | | |
|  | **HDA** | **N treatment** | **N MRI** | ***p* for interaction** | **N treatment** | **MRI** | ***p* for interaction** |
|  |  |  | **RR (95% CI)** |  |  | **RR (95% CI)** |  |
| Cladribine 3.5 mg vs GA | No | IFN: 896 CL: 228 | 0.62 (0.47–0.81); *p*=0.001 | *p*=0.0053 | IFN: 788 CL: 228 | 0.52 (0.40–0.69); *p*<0.001 | *p*=0.11 |
| Yes | IFN: 272 CL: 94 | 0.32 (0.22–0.47); *p*<0.001 | IFN: 219 CL: 94 | 0.35 (0.24–0.54); *p*<0.001 |
| Cladribine 3.5 mg vs GA | No | GA: 312 CL: 228 | 0.59 (0.37–0.94); *p*=0.028 | *p*=0.13 | GA: 298 CL: 228 | 0.55 (0.35–0.87); *p*=0.011 | *p*=0.28 |
| Yes | GA: 90 CL: 94 | 0.34 (0.19–0.61); *p*<0.001 | GA: 78 CL: 94 | 0.39 (0.21–0.73); *p*=0.003 |
| Cladribine 3.5 mg vs FTY | No | FTY: 72 CL: 228 | 0.74 (0.36–1.52); *p*=0.41 | *p*=0.92 | FTY: 59 CL: 228 | 0.64 (0.32–1.71); *p*=0.23 | *p*=0.28 |
| Yes | FTY: 41 CL: 94 | 0.72 (0.32–1.65); *p*=0.44 | FTY: 31 CL: 94 | 1.34 (0.50–3.72); *p*=0.56 |
| Cladribine 3.5 mg vs NTZ | No | NTZ: 86 CL: 228 | 2.43 (1.01–5.86); *p*=0.049 | *p*=0.56 | NTZ: 75 CL: 228 | 3.09 (1.19–7.99); *p*=0.02 | *p*=0.30 |
| Yes | NTZ: 63 CL: 94 | 1.57 (0.63–3.95); *p*=0.34 | NTZ: 53 CL: 94 | 1.48 (0.61–3.60); *p*=0.38 |
| Cladribine 3.5 mg vs DMF | No | DMF: 238 CL: 228 | 0.78 (0.44–1.40); *p*=0.41 | *p*=0.063 | DMF: 222 CL: 228 | 0.89 (0.51–1.57); *p*=0.70 | *p*=0.034 |
| Yes | DMF: 57 CL: 94 | 0.30 (0.12–0.70); *p*=0.006 | DMF: 54 CL: 94 | 0.31 (0.14–0.69); *p*=0.004 |

Abbreviations: CL = cladribine; DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; HDA = high disease activity; IFN = interferon β; NTZ = natalizumab; RR = relapse ratio.

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| **Table e-20** Effect of cladribine vs other drugs on disability progression in HDA subgroups | | | | | | | | | | |
|  |  | | | **IPW No MRI** | | | | **IPW MRI** | | |
|  | | **HDA** | **N treatment** | | **HR (95% CI)** | ***p* for interaction** | **N treatment** | | **HR (95% CI)** | ***p* for interaction** |
|  | |  |  | |  |  |  | |  |  |
| Cladribine vs IFN | | No | IFN: 869  CL: 458 | | 0.97 (0.73–1.30); *p*=0.86 | *p*=0.13 | IFN: 767  CL: 458 | | 0.80 (0.60–1.08); *p*=0.14 | *p*=0.89 |
| Yes | IFN: 259  CL: 182 | | 0.63 (0.40–0.98); *p*=0.043 | IFN: 208  CL: 182 | | 0.83 (0.48–1.41); *p*=0.49 |
| Cladribine vs GA | | No | GA: 293  CL: 458 | | 0.60 (0.37–0.98); *p*=0.042 | *p*=0.84 | GA: 279  CL: 458 | | 0.55 (0.33–0.88); *p*=0.013 | *p*=0.74 |
| Yes | GA: 86  CL: 182 | | 0.70 (0.25–1.93); *p*=0.49 | GA: 74  CL: 182 | | 0.68 (0.24–1.93); *p*=0.46 |
| Cladribine vs FTY | | No | FTY: 68  CL: 458 | | 0.76 (0.35–1.67); *p*=0.50 | *p*=0.65 | FTY: 56  CL: 458 | | 1.13 (0.43–2.95); *p*=0.81 | *p*=0.52 |
| Yes | FTY: 40  CL: 182 | | 1.22 (0.22–6.85); *p*=0.82 | FTY: 30  CL: 182 | | 0.68 (0.19–2.41); *p*=0.55 |
| Cladribine vs NTZ | | No | NTZ: 76  CL: 458 | | 1.19 (0.53–2.66); *p*=0.67 | *p*=0.94 | NTZ: 76  CL: 458 | | 3.01 (0.85–10.6); *p*=0.087 | *p*=0.05 |
| Yes | NTZ: 58  CL: 182 | | 1.11 (0.26–473); *p*=0.89 | NTZ: 58  CL: 182 | | 0.57 (0.19–1.72); *p*=0.32 |
| Cladribine vs DMF | | No | DMF: 212  CL: 228 | | 0.96 (0.51–1.81); *p*=0.90 | *p*=0.56 | DMF: 196  CL: 228 | | 0.70 (0.39–1.26); *p*=0.23 | *p*=0.63 |
| Yes | DMF: 50  CL: 94 | | 2.26 (0.26–19.5); *p*=0.46 | DMF: 47  CL: 94 | | 1.45 (0.27–7.81); *p*=0.67 |

Abbreviations: CL = cladribine; DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; HDA = high disease activity; HR = hazard ratio; IFN = interferon β; NTZ = natalizumab.

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| **Table e-21** Effect of cladribine 3.5 mg vs other drugs on disability progression in HDA subgroups | | | | | | | |
|  | **HDA** | **N treatment** | **IPW No MRI** | ***p* for interaction** | **N treatment** | **IPW MRI** | ***p* for interaction** |
|  |  |  | **HR (95% CI)** |  |  | **HR (95% CI)** |  |
| Cladribine 3.5 mg vs GA | No | GA: 869  CL: 228 | 1.00 (0.70–1.45); *p*=0.97 | *p*=0.0089 | GA: 767  CL: 228 | 0.83 (0.57–1.20); *p*=0.32 | *p*=0.15 |
| Yes | GA: 259  CL: 94 | 0.31 (0.15–0.67); *p*=0.003 | GA: 208  CL: 94 | 0.41 (0.18–0.96); *p*=0.039 |
| Cladribine 3.5 mg vs GA | No | GA: 293  CL: 228 | 0.61 (0.34–1.08); *p*=0.09 | *p*=0.60 | GA: 279  CL: 227 | 0.55 (0.31–0.97); *p*=0.04 | *p*=0.68 |
| Yes | GA: 86  CL: 94 | 0.41 (0.11–1.55); *p*=0.19 | GA: 74  CL: 95 | 0.39 (0.10–1.52); *p*=0.18 |
| Cladribine 3.5 mg vs FTY | No | FTY: 68  CL: 228 | 0.72 (0.31–1.68); *p*=0.45 | *p*=0.90 | FTY: 56  CL: 228 | 1.08 (0.39–2.95); *p*=0.89 | *p*=0.37 |
| Yes | FTY: 40  CL: 94 | 0.83 (0.13–5.49); *p*=0.85 | FTY: 30  CL: 94 | 0.47 (0.11–2.07); *p*=0.32 |
| Cladribine 3.5 mg vs NTZ | No | NTZ: 76  CL: 228 | 1.14 (0.48–2.69); *p*=0.76 | *p*=0.73 | NTZ: 76  CL: 228 | 2.94 (0.80–10.7); *p*=0.10 | *p*=0.046 |
| Yes | NTZ: 58  CL: 94 | 0.82 (0.16–4.16); *p*=0.81 | NTZ: 58  CL: 94 | 0.46 (0.12–1.70); *p*=0.24 |
| Cladribine 3.5 mg vs DMF | No | DMF: 212  CL: 228 | 0.91 (0.45–1.85); *p*=0.80 | *p*=0.83 | DMF: 196  CL: 228 | 0.66 (0.34–1.27); *p*=0.21 | *p*=0.88 |
| Yes | DMF: 50  CL: 94 | 1.52 (0.14–16); *p*=0.73 | DMF: 47  CL: 94 | 1.13 (0.17–7.49); *p*=0.90 |

Abbreviations: CL = cladribine; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; FTY = fingolimod; GA = glatiramer acetate; HDA: high-disease activity; HR = hazard ratio; IFN = interferon β; NTZ = natalizumab.

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| **Table e-22** Baseline characteristics of 1:1 matched patients for cladribine and each treatment | | | | | | | | | | | | | | | |
|  | **CLARITY (n=588)** | **IFN (n=588)** | **STD DIFF vs CLARITY** | **CLARITY (n=290)** | **GA (n=290)** | **STD DIFF vs CLARITY** | **CLARITY (n=109)** | **FTY (n=109)** | **STD DIFF vs CLARITY** | **CLARITY (n=146)** | **NTZ (n=146)** | **STD DIFF vs CLARITY** | **CLARITY (n=228)** | **DMF (n=228)** | **STD DIFF vs CLARITY** |
| Age, years, mean (SD) | 38.2 (10.3) | 38.7 (10.8) | 0.048 | 38.6 (10.3) | 38.2 (11.7) | 0.038 | 35.6 (10.4) | 35.3 (10.8) | 0.029 | 32.3 (8.6) | 32.2 (9.7) | 0.008 | 36.6 (10.2) | 36.7 (10.4) | 0.012 |
| Females, n (%) | 383 (65.1) | 375 (63.8) | 0.028 | 195 (67.2) | 195 (67.9) | 0.015 | 62 (56.9) | 62 (56.9) | 0.000 | 85 (58.2) | 80 (54.8) | 0.069 | 141 (61.8) | 139 (61) | 0.018 |
| EDSS, mean (SD) | 2.74 (1.17) | 2.66 (1.03) | 0.069 | 2.01 (0.94) | 2.02 (1.00) | 0.01 | 2.37 (1.17) | 2.49 (1.09) | 0.11 | 2.56 (1.26) | 2.66 (1.09) | 0.087 | 1.86 (0.89) | 1.81 (0.86) | 0.058 |
| Disease duration, mean (SD) | 3.89 (4.94) | 3.88 (5.96) | 0.001 | 3.48 (4.50) | 3.39 (6.11) | 0.017 | 3.60 (4.55) | 3.38 (5.75) | 0.04 | 2.14 (2.96) | 1.96 (3.44) | 0.054 | 2.71 (3.91) | 2.52 (4.44) | 0.045 |
| ARR in previous year, mean (SD) | 1.29 (0.53) | 1.37 (0.70) | 0.12 | 1.31 (0.56) | 1.29  (0.52) | 0.03 | 1.38 (0.59) | 1.47 (0.71) | 0.14 | 1.65 (0.83) | 1.56 (0.74) | 0.12 | 1.26 (0.5) | 1.25 (0.49) | 0.018 |
| Active lesions, n (%) | 181 (30.8) | 195/459 (42.5) | 0.24 | 91 (31.4) | 125/265 (47.2) | 0.33 | 33 (30.3) | 49/87 (56.3) | 0.54 | 52 (34.9) | 93/125 (74.4) | 0.86 | 67 (29.4) | 121/213 (56.8) | 0.57 |

Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; NTZ = natalizumab; STD DIFF = standardized mean difference according to Cohen’s d.

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| **Table e-23** ARR ratio between cladribine and iMUST treatment arms. Results are presented after 1:1 matching | |
|  | **1:1 Matching clinical variables** |
|  | **ARR ratio (95% CI)** |
| Cladribine vs IFN | 0.48 (0.36–0.62); *p*<0.001 |
| Cladribine vs GA | 0.36 (0.24–0.54); *p*<0.001 |
| Cladribine vs FTY | 0.52 (0.26–1.01); *p*=0.054 |
| Cladribine vs NTZ | 1.25 (0.62–2.48); *p*=0.53 |
| Cladribine vs DMF | 0.57 (0.33–0.98); *p*=0.043 |

Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; NTZ = natalizumab.

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| **Table e-24** Baseline characteristics of matched patients with a ratio up to 3:1 for cladribine and each treatment | | | | | | | | | | | | | | | | |
|  | **CLARITY(n=554)** | **IFN (n=1146)** | | **STD DIFF vs CLARITY** | **CLARITY(n=370)** | **GA (n=384)** | **STD DIFF vs CLARITY** | **CLARITY(n=233)** | **FTY (n=109)** | **STD DIFF vs CLARITY** | **CLARITY(n=210)** | **NTZ (n=146)** | **STD DIFF vs CLARITY** | **CLARITY(n=305)** | **DMF (n=267)** | **STD DIFF vs CLARITY** |
| Age, years, mean (SD) | 34.3(10.3) | 34.9 (10.8) | | 0.056 | 38.8 (10.7) | 39.9 (11.6) | 0.095 | 36 (10.4) | 35.3 (10.8) | 0.073 | 32 (9.6) | 32.2 (9.7) | 0.024 | 37.1 (9.9) | 36.4 (10.5) | 0.064 |
| Females, n (%) | 364(65.7) | 753 (65.7) | | 0.001 | 275 (74.2) | 281 (73.2) | 0.024 | 128 (55) | 62 (56.9) | 0.036 | 120 (57.3) | 80 (54.8) | 0.05 | 196 (64.2) | 159 (59.6) | 0.09 |
| EDSS, mean (SD) | 1.81(1.00) | 1.81 (1.00) | | 0.002 | 1.75 (1.03) | 1.79 (0.99) | 0.043 | 2.42 (1.17) | 2.49 (1.09) | 0.06 | 2.71 (1.26) | 2.66 (1.09) | 0.044 | 1.56 (1.03) | 1.55 (1.01) | 0.005 |
| Disease duration, mean (SD) | 2.35(3.62) | 2.38 (4.28) | | 0.007 | 3.02 (4.51) | 3.16 (5.69) | 0.028 | 3.57 (4.55) | 3.38 (5.75) | 0.036 | 2.06 (3.30) | 1.96 (3.57) | 0.031 | 2.67 (3.65) | 2.34 (4.30) | 0.082 |
| ARR in previous year, mean (SD) | 1.27(0.53) | 1.25 (0.49) | | 0.028 | 1.24 (0.48) | 1.24(0.52) | 0.004 | 1.41 (0.59) | 1.47 (0.71) | 0.084 | 1.63 (0.79) | 1.56 (0.74) | 0.092 | 1.20 (0.46) | 1.22 (0.47) | 0.051 |
| Active lesions, n (%) | 196 (35.3) | 448/1004 (44.6) | | 0.19 | 120 (32.6) | 166/358 (46.4) | 0.29 | 72 (31) | 49/87 (56.3) | 0.53 | 83 (39.5) | 93/125 (74.4) | 0.75 | 94 (30.7) | 138/248 (55.7) | 0.52 |

Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; NTZ = natalizumab; STD DIFF = standardized mean difference according to Cohen’s d.

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| **Table e-25** ARR ratio between cladribine and iMUST treatment arms. Results are presented after matching in a variable ratio up to 3:1 | |
|  | **3:1 Matching clinical variables** |
|  | **ARR ratio (95% CI)** |
| Cladribine vs IFN | 0.53 (0.44–0.63); *p*<0.001 |
| Cladribine vs GA | 0.43 (0.30–0.60); *p*<0.001 |
| Cladribine vs FTY | 0.63 (0.33–1.23); *p*=0.18 |
| Cladribine vs NTZ | 1.97 (1.08–3.58); *p*=0.027 |
| Cladribine vs DMF | 0.59 (0.36–0.96); *p*=0.033 |

Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; NTZ = natalizumab.

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| **Table e-26** Inverse probability weighted demographic and clinical characteristics for the comparison of IFN arms vs CLARITY study | | | | | | | | | |
|  | **CLARITY (n=945)** | **IFN-1a IM (n=318)** | **STD DIFF IFN vs CLARITY** | **CLARITY (n=945)** | **IFN-1b (n=236)** | **STD DIFF IFN-1b vs CLARITY** | **CLARITY (n=945)** | **IFN-1a SC (n=614)** | **STD DIFF IFN-1a vs CLARITY** |
| Age, years, mean (SD) | 38.1 (10.3) | 38.1 (11) | 0.002 | 38.3 (10.2) | 38.4 (11.8) | 0.004 | 36.7 (10.3) | 36.6 (10.3) | 0.025 |
| Females, n (%) | 639 (67.6) | 211 (66.3) | 0.028 | 611 (64.6) | 150 (63.6) | 0.02 | 617 (65.3) | 389 (63.1) | 0.05 |
| EDSS, mean (SD); median (IQR) | 2.53 (1.38) | 2.32 (1.09) | 0.17 | 2.74 (1.30) | 2.74 (1.27) | 0.003 | 2.44 (1.33) | 2.33 (1.11) | 0.094 |
| Disease duration, mean (SD) | 3.81 (5.1) | 3.61 (5.46) | 0.037 | 3.93 (5.22) | 3.93 (5.84) | 0.001 | 3.33 (4.69) | 3.45 (5.41) | 0.03 |
| ARR in previous year, mean (SD) | 1.35 (0.59) | 1.26 | 0.15 | 1.35 (0.59) | 1.31 (0.50) | 0.074 | 1.36 (0.6) | 1.28 (0.55) | 0.15 |
| Active lesions, n (%) | 304 (32.1) | 93/279 (33.2) | 0.21 | 294 (31.1) | 107/211 (50.6) | 0.40 | 312 (33) | 235/536 (43.9) | 0.23 |

Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IFN = interferon β; SC = subcutaneous.

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| **Table e-27** ARR ratio between cladribine and iMUST treatment arms of IFN. Results are presented after IPTW on demographic and clinical characteristics | |
|  | **ARR ratio (95% CI)** |
| Cladribine vs IFN-1a IM | 0.71 (0.51–0.99); *p*=0.044 |
| Cladribine vs IFN-1b | 0.43 (0.31–0.59); *p*<0.001 |
| Cladribine vs IFN-1a SC | 0.49 (0.38–0.63); *p*<0.001 |

Abbreviations: ARR = annualized relapse rate; IFN = interferon β; IPTW = inverse probability of treatment weighting; SC = subcutaneous.