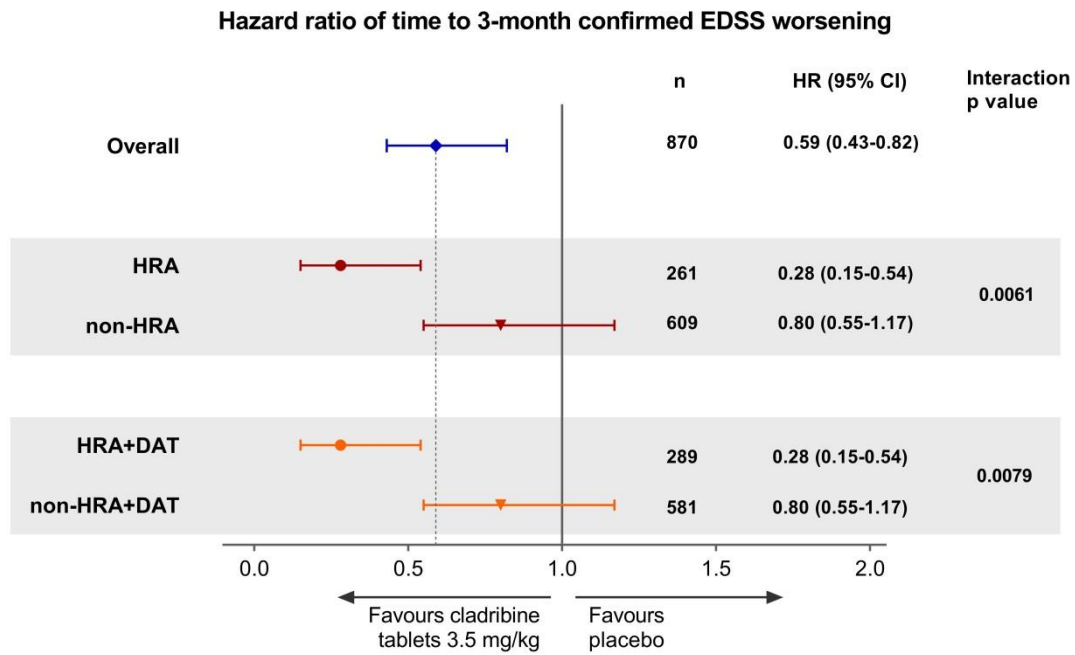
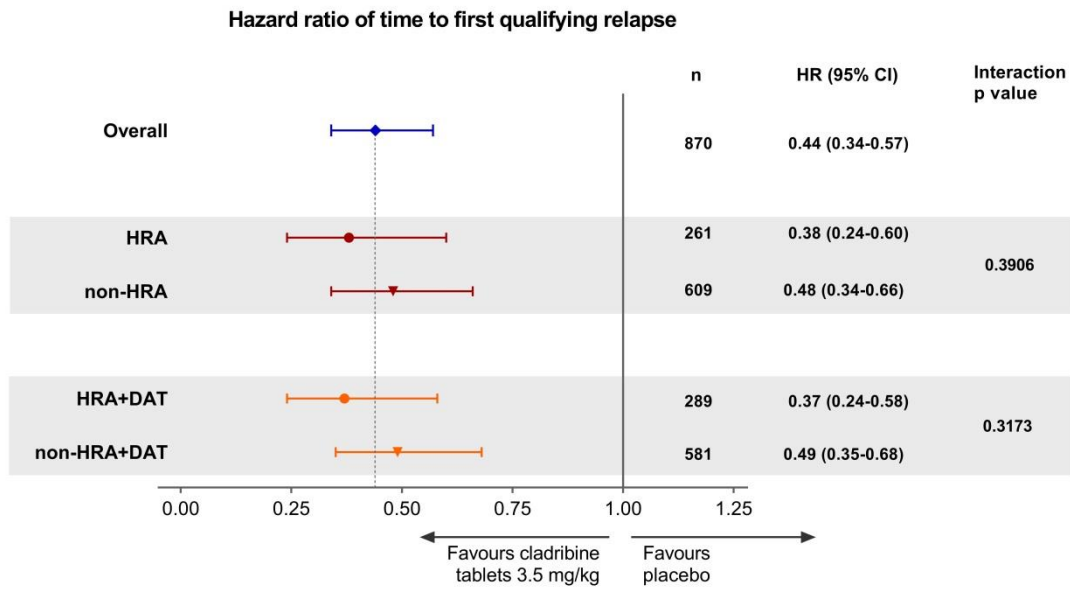


**Supplementary Figure 1. Forest plot of Hazard Ratio of time to 3-month confirmed EDSS worsening by HDA subgroups for cladribine tablets 3.5 mg/kg vs placebo.**



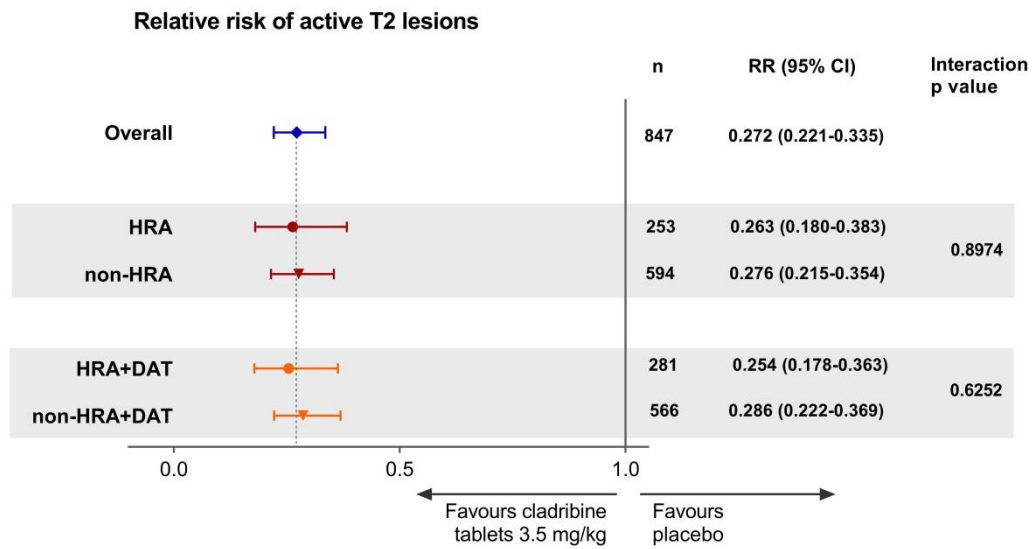
EDSS, Expanded Disability Status Scale; HDA, high disease activity; HRA, high relapse activity; HRA+DAT, high relapse activity plus disease activity on treatment

**Supplementary Figure 2. Forest plot of Hazard Ratio of time to first qualifying relapse by HDA subgroup for cladribine tablets 3.5 mg.kg vs placebo.**



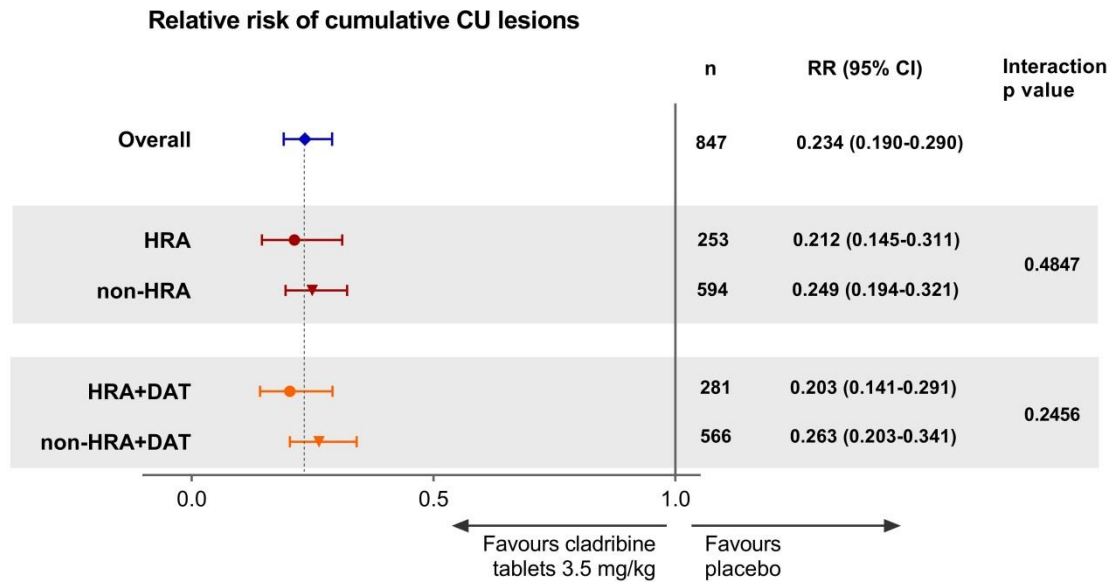
HDA, high disease activity; HRA, high relapse activity; HRA+DAT, high relapse activity plus disease activity on treatment

**Supplementary Figure 3. Forest plot of Relative Risk of cumulative number of active T2 lesions by HDA subgroups of cladribine tablets 3.5 mg/kg vs placebo**



HDA, high disease activity; HRA, high relapse activity; HRA+DAT, high relapse activity plus disease activity on treatment

**Supplementary Figure 4. Forest plot of Relative Risk of cumulative number of combined unique lesions by HDA subgroup for cladribine tablets 3.5 mg/kg vs placebo.**



CU, combined unique; HDA, high disease activity; HRA, high relapse activity; HRA+DAT, high relapse activity plus disease activity on treatment

**Supplementary Table 1. Baseline demographics and disease characteristics of patients in the ITT population treated with placebo or cladribine tablets 3.5 mg/kg by subgroup**

| Characteristic                             | Value     | Placebo (N=437) |               |               |               |                   | Cladribine tablets 3.5 mg/kg (N=433) |               |               |               |                   |
|--|-----------|-----------------|---------------|---------------|---------------|-------------------|--------------------------------------|---------------|---------------|---------------|-------------------|
|  |           | Overall N=437   | HRA N=131     | Non-HRA N=306 | HRA+DAT N=149 | Non-HRA+DAT N=288 | Overall N=433                        | HRA N=130     | Non-HRA N=303 | HRA+DAT N=140 | Non-HRA+DAT N=293 |
| HDA subgroup (N)                           |           |                 |               |               |               |                   |                                      |               |               |               |                   |
| Age, years                                 | Mean (SD) | 38.7 (9.9)      | 36.7 (10.3)   | 39.5 (9.6)    | 37.1 (10.2)   | 39.6 (9.6)        | 37.9 (10.3)                          | 36.5 (9.5)    | 38.6 (10.6)   | 36.3 (9.5)    | 38.7 (10.6)       |
| Female                                     | n (%)     | 288 (65.9)      | 82 (62.6)     | 206 (67.3)    | 94 (63.1)     | 194 (67.4)        | 298 (68.8)                           | 96 (73.8)     | 202 (66.7)    | 102 (72.9)    | 196 (66.9)        |
| Disease duration, years                    | Mean (SD) | 5.18 (5.45)     | 4.51 (5.48)   | 5.47 (5.43)   | 4.75 (5.34)   | 5.41 (5.51)       | 4.68 (5.51)                          | 3.90 (5.07)   | 5.01 (5.67)   | 3.94 (4.92)   | 5.03 (5.75)       |
| Prior use of DMDs                          | n (%)     | 132 (30.2)      | 38 (29.0)     | 94 (30.7)     | 56 (37.6)     | 76 (26.4)         | 110 (25.4)                           | 36 (27.7)     | 74 (24.4)     | 46 (32.9)     | 64 (21.8)         |
| Relapses in prior 12 months, n             | n (%)     |                 |               |               |               |                   |                                      |               |               |               |                   |
| 0  |           | 0 (0.0)         | 0 (0.0)       | 0 (0.0)       | 0 (0.0)       | 0 (0.0)           | 0 (0.0)                              | 0 (0.0)       | 0 (0.0)       | 0 (0.0)       | 0 (0.0)           |
| 1  |           | 306 (70.0)      | 0 (0.0)       | 306 (100.0)   | 18 (12.1)     | 288 (100.0)       | 302 (69.7)                           | 0 (0.0)       | 302 (99.7)    | 10 (7.1)      | 292 (99.7)        |
| 2  |           | 110 (25.2)      | 110 (84.0)    | 0 (0.0)       | 110 (73.8)    | 0 (0.0)           | 106 (24.5)                           | 105 (80.8)    | 1 (0.3)       | 105 (75.0)    | 1 (0.3)           |
| ≥3   |           | 21 (4.8)        | 21 (16.0)     | 0 (0.0)       | 21 (14.1)     | 0 (0.0)           | 25 (5.8)                             | 25 (19.2)     | 0 (0.0)       | 25 (17.9)     | 0 (0.0)           |
| EDSS score at baseline                     | Mean (SD) | 2.94 (1.31)     | 2.91 (1.37)   | 2.95 (1.29)   | 2.97 (1.35)   | 2.92 (1.30)       | 2.83 (1.25)                          | 2.90 (1.33)   | 2.81 (1.22)   | 2.86 (1.32)   | 2.82 (1.22)       |
| Number of T1 Gd+ lesions at baseline       | Mean (SD) | 0.8 (2.1)       | 1.1 (3.0)     | 0.7 (1.5)     | 1.0 (2.8)     | 0.7 (1.5)         | 1.0 (2.7)                            | 1.4 (3.6)     | 0.8 (2.2)     | 1.3 (3.5)     | 0.8 (2.2)         |
| Patients with ≥1 T1 Gd+ lesion at baseline | n (%)     | 128 (29.3)      | 41 (31.3)     | 87 (28.4)     | 47 (31.5)     | 81 (28.1)         | 138 (31.9)                           | 50 (38.5)     | 88 (29.0)     | 52 (37.1)     | 86 (29.4)         |
| Number of T2 lesions at baseline           | Mean (SD) | 27.4 (17.7)     | 30.0 (20.3)   | 26.2 (16.4)   | 29.9 (19.8)   | 26.0 (16.4)       | 25.3 (16.3)                          | 25.3 (17.4)   | 25.3 (15.9)   | 25.2 (17.2)   | 25.3 (15.9)       |
| T2 Lesion                                  | Mean      | 14.31 (13.13)   | 15.31 (14.07) | 13.87 (12.7)  | 14.84         | 14.03             | 14.84 (16.28)                        | 14.67 (16.86) | 14.91 (16.06) | 14.99 (17.54) | 14.77 (15.68)     |

| Characteristic                      | Value | Placebo<br>(N=437) |  |  |         | Cladribine tablets 3.5 mg/kg<br>(N=433) |  |  |  |  |
|-------------------------------------|-------|--------------------|--|--|---------|---|--|--|--|--|
|                                     |       |                    |  |  |         |   |  |  |  |  |
| volume at baseline, cm <sup>2</sup> | (SD)  |                    |  |  | (13.58) | (12.91)                                 |  |  |  |  |

EDSS, expanded disability status scale; Gd+, gadolinium enhancing; HRA, high relapse activity; HRA+DAT, high relapse activity plus disease activity on treatment

**Supplementary Table 2. Baseline demographics and disease characteristics of patients in the safety population treated with placebo or cladribine tablets 3.5 mg/kg by subgroup**

| Characteristic                             | Value     | Placebo          |              |                  | Cladribine tablets 3.5 mg/kg |              |                  |
|--|-----------|------------------|--------------|------------------|------------------------------|--------------|------------------|
|  |           | Overall<br>N=433 | HRA<br>N=131 | HRA+DAT<br>N=148 | Overall<br>N=442             | HRA<br>N=131 | HRA+DAT<br>N=142 |
| HDA subgroup (N)                           |           |                  |              |                  |                              |              |                  |
| Age, years                                 | Mean (SD) | 38.7 (9.9)       | 36.7 (10.3)  | 37.1 (10.2)      | 37.8 (10.4)                  | 36.5 (9.5)   | 36.2 (9.5)       |
| Female                                     | n (%)     | 284 (65.6)       | 82 (62.6)    | 93 (62.8)        | 307 (69.5)                   | 97 (74.0)    | 104 (73.2)       |
| Disease duration, years                    | Mean (SD) | 5.20 (5.47)      | 4.51 (5.48)  | 4.77 (5.36)      | 4.65 (5.48)                  | 3.94 (5.05)  | 3.98 (4.88)      |
| Prior use of DMDs                          | n (%)     | 130 (30)         | 38 (29.0)    | 55 (37.2)        | 113 (25.6)                   | 36 (27.5)    | 47 (33.1)        |
| Relapses in prior 12 months, n             | n (%)     |                  |              |                  |                              |              |                  |
| 0  |           | 0                | 0            | 0                | 0                            | 0            | 0                |
| 1  |           | 302 (69.7)       | 0            | 17 (11.5)        | 310 (70.1)                   | 0            | 11 (7.7)         |
| 2  |           | 110 (25.4)       | 110 (84.0)   | 110 (74.3)       | 108 (24.4)                   | 107 (81.7)   | 107 (75.4)       |
| ≥3   |           | 21 (4.8)         | 21 (16.0)    | 21 (14.2)        | 24 (5.4)                     | 24 (18.3)    | 24 (16.9)        |
| EDSS score at baseline                     | Mean (SD) | 2.94 (1.31)      | 2.91 (1.37)  | 2.98 (1.36)      | 2.83 (1.26)                  | 2.87 (1.33)  | 2.84 (1.31)      |
| Number of T1 Gd+ lesions at baseline       | Mean (SD) | 0.8 (2.1)        | 1.1 (3.0)    | 1.0 (2.9)        | 1.0 (2.7)                    | 1.4 (3.6)    | 1.3 (3.5)        |
| Patients with ≥1 T1 Gd+ lesion at baseline | n (%)     | 126 (29.1)       | 41 (31.3)    | 46 (31.1)        | 143 (32.4)                   | 49 (37.4)    | 52 (36.6)        |
| Number of T2 lesions at baseline           | Mean (SD) | 27.4 (17.7)      | 30.0 (20.3)  | 29.8 (19.8)      | 25.4 (16.3)                  | 25.3 (17.4)  | 25.3 (17.2)      |

|   |           |               |               |               |               |              |               |
|---|-----------|---------------|---------------|---------------|---------------|--------------|---------------|
| T2 Lesion volume at baseline, cm <sup>2</sup> | Mean (SD) | 14.38 (13.17) | 15.31 (14.07) | 14.86 (13.62) | 15.04 (16.49) | 14.89 (16.9) | 15.16 (17.51) |
|---|-----------|---------------|---------------|---------------|---------------|--------------|---------------|

EDSS, expanded disability status scale; Gd+, gadolinium enhancing; HRA, high relapse activity; HRA+DAT, high relapse activity plus disease activity on treatment