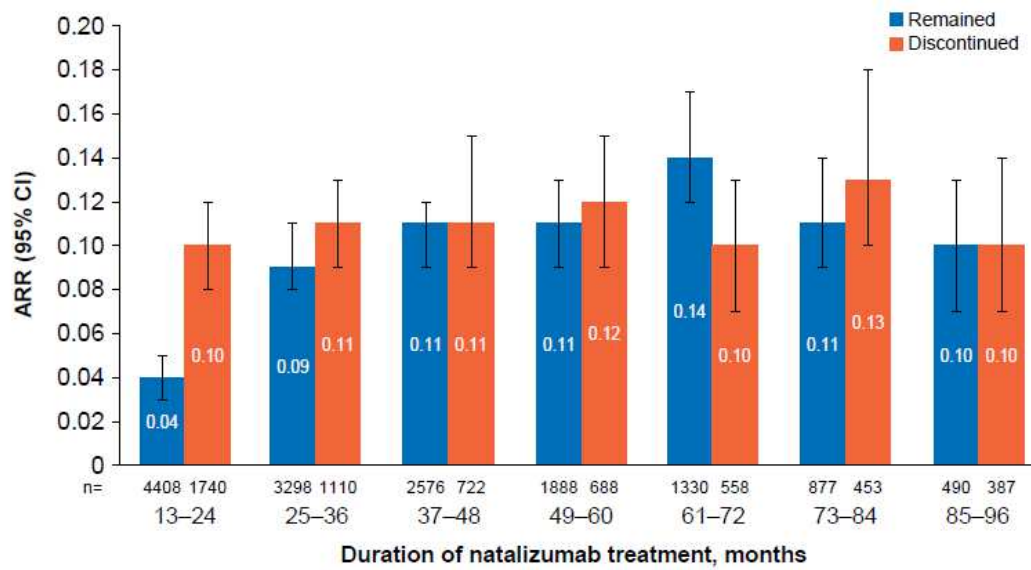
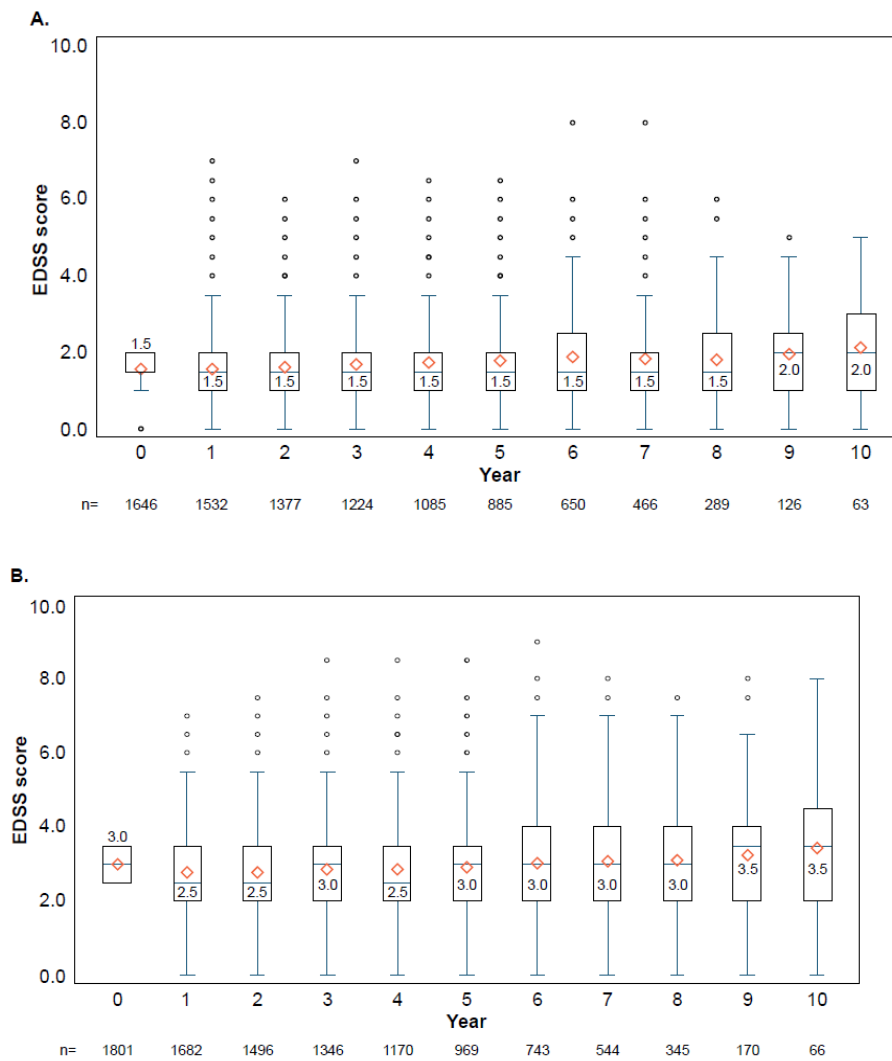
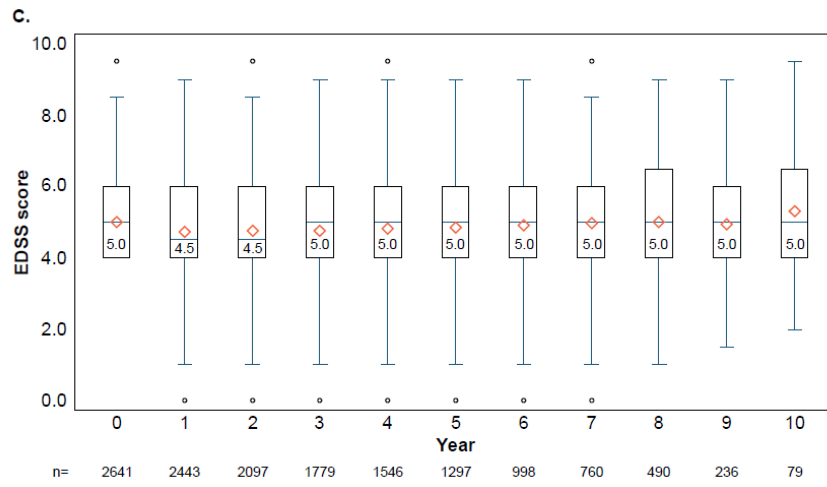


Online supplementary efigure 1 Relapse rates in the year prior to the indicated treatment epoch for patients who remained on natalizumab past the epoch or discontinued natalizumab during the epoch. ARR, annualised relapse rate; CI, confidence interval.

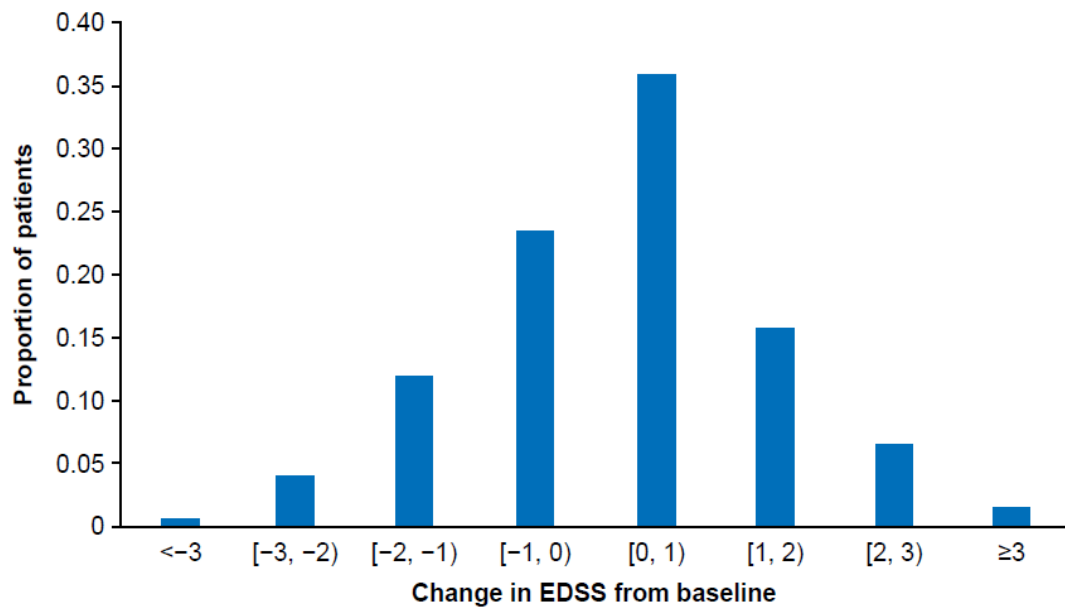


Online supplementary figure 2 Box plots of Expanded Disability Status Scale (EDSS) scores from enrolment to year 10, stratified by baseline EDSS score: (A) baseline EDSS <2.5, (B) baseline EDSS \geq 2.5 to <4.0 and (C) baseline EDSS \geq 4.0. The bottom and top edges of each box represent the interquartile range (IQR). The line inside each box represents the median value, which is also indicated by the number. The diamond inside each box indicates the mean value. The whiskers of each box are drawn from the box to the most extreme point that is $\leq 1.5 \times$ IQR. Circles above the whiskers indicate outliers.





Online supplementary efigure 3 Distribution of Expanded Disability Status Scale (EDSS) score change from baseline in the ≥ 8 -year treatment cohort at year 8. [a,b) indicates that the interval is inclusive of the endpoint on the left and is not inclusive of the endpoint on the right.



Online supplementary etable 1 List of reported cases of opportunistic infections (excluding PML)*

| Opportunistic infection | Number reported in TOP | CNS/Non-CNS | Type |
|---|-------------------------------|--------------------|-------------|
| Herpes zoster | 3 | CNS | Viral |
| Meningitis herpes | 2 | CNS | Viral |
| Encephalitis | 1 | CNS | Viral |
| Herpes simplex encephalitis | 1 | CNS | Viral |
| Herpes zoster disseminated | 1 | Non-CNS | Viral |
| Listeria meningitis (sepsis) | 1 | CNS | Bacterial |
| Pneumonia | 1 | Non-CNS | Bacterial |
| Pulmonary <i>Mycobacterium kansasii</i> infection | 1 | Non-CNS | Bacterial |

*Opportunistic infections are defined based on criteria related to an identified pathogen and clinical symptoms. In six cases the event resolved (herpes zoster [three cases], herpes simplex encephalitis, listeria meningitis [sepsis] and meningitis herpes), and in five (encephalitis, herpes zoster disseminated, meningitis herpes, pneumonia and pulmonary *Mycobacterium kansasii* infection) it did not resolve. In seven cases (herpes zoster [two cases], meningitis herpes [two cases], encephalitis, pneumonia and pulmonary *Mycobacterium kansasii* infection) natalizumab was discontinued. In two cases natalizumab was continued (herpes zoster and herpes zoster disseminated), and in two cases (herpes simplex encephalitis and listeria meningitis [sepsis]) the continuation of natalizumab was unknown. CNS, central nervous system; PML, progressive multifocal leukoencephalopathy.

Online supplementary etable 2 List of reported malignancies

| Malignancy | Number reported in TOP |
|---|-------------------------------|
| Breast cancer/breast cancer metastatic/invasive ductal breast carcinoma | 19 |
| Colon cancer/colon cancer metastatic/adenocarcinoma of colon | 4 |
| Papillary thyroid cancer | 4 |
| Chronic lymphocytic leukaemia | 3 |
| Renal cancer/clear cell renal cell carcinoma/renal cell carcinoma | 3 |
| Basal cell carcinoma | 2 |
| B-cell lymphoma | 2 |
| Cervix carcinoma | 2 |
| Chronic myeloid leukaemia | 2 |
| Leiomyosarcoma/leiomyosarcoma metastatic | 2 |
| Lung adenocarcinoma/lung neoplasm malignant | 2 |
| Malignant melanoma in situ | 2 |
| Acute promyelocytic leukaemia | 1 |
| Bladder cancer | 1 |
| Cervix carcinoma stage 0 | 1 |
| Chordoma | 1 |
| Choroid melanoma | 1 |
| Genital neoplasm malignant female | 1 |
| Glioblastoma | 1 |
| Hodgkin disease stage II | 1 |
| Intraocular melanoma | 1 |
| Lentigo maligna | 1 |
| Malignant neoplasm of ampulla of Vater | 1 |
| Oligodendroglioma | 1 |
| Oropharyngeal squamous cell carcinoma | 1 |
| Ovarian neoplasm | 1 |
| Pancreatic carcinoma metastatic | 1 |
| Pleomorphic adenoma | 1 |
| Rectal cancer | 1 |
| Testicular neoplasm | 1 |
| Waldenström macroglobulinaemia | 1 |

Online supplementary etable 3 Annualised relapse rates (ARRs) in the year prior to natalizumab treatment and after starting natalizumab by patient characteristics and treatment history at baseline

| Baseline characteristic | ARR | | p value (pre vs post natalizumab) |
|---|------------------------------------|----------------------------|-----------------------------------|
| | Year prior to starting natalizumab | After starting natalizumab | |
| Age | | | |
| ≤40 years (n=3876) | 2.09 | 0.14 | <0.001 |
| >40 years (n=2272) | 1.84 | 0.12 | <0.001 |
| p value (≤40 vs >40 years) | <0.001 | <0.001 | — |
| EDSS score category | | | |
| ≤3.0 (n=2843) | 1.96 | 0.11 | <0.001 |
| >3.0 (n=3245) | 1.96 | 0.15 | <0.001 |
| p value (≤3.0 vs >3.0) | 0.746 | <0.001 | — |
| Number of prior DMTs | | | |
| 0 (n=952) | 2.00 | 0.11 | <0.001 |
| 1 (n=2897) | 1.97 | 0.13 | <0.001 |
| ≥2 (n=2299) | 1.91 | 0.15 | <0.001 |
| p value (0 vs 1) | 0.493 | 0.013 | — |
| p value (0 vs ≥2) | 0.014 | <0.001 | — |
| p value (1 vs ≥2) | 0.020 | 0.003 | — |
| Relapses in the year prior to enrolment | | | |
| ≤1 (n=2094) | — | 0.10 | — |
| >1 (n=4054) | — | 0.16 | — |
| p value (≤1 vs >1) | — | <0.001 | — |

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale.