### Table 1. Baseline Characteristics

|                                | Bexarotene | Placebo |
|--------------------------------|------------|---------|
| **Total number of participants** |            |         |
| Cambridge, number (%)           | 25         | 24      |
| Edinburgh, number (%)           | 16 (64)    | 15 (63) |
| **Age, years; mean (SD)**       | 40·4 (6·2) | 38 (6·8) |
| **Sex**                        |            |         |
| Female                         | 15         | 13      |
| Male                           | 10         | 11      |
| **Disease duration, years; mean (SD)** | 11 (5·9)   | 8·4 (5·8) |
| **Number of relapses in last 2 years; median (quartiles)** | 0 (0, 1)  | 0·5 (0, 1·3) |
| **EDSS; median (quartiles)**   | 2·5 (1·5, 3·5) | 2·0 (1·5, 3·0) |
| **Duration receiving dimethyl fumarate, years; median (quartiles)** | 2·2 (1·1, 3·2) | 1·6 (0·9, 2·3) |
| **MRI**                        |            |         |
| Within-patient number of T2 lesions; median (quartiles) | 63 (51, 111) | 43 (19·5, 66) |
| Within-patient size of T2 lesions, mm$^2$; median (quartiles) | 90·6 (67·7, 146·0) | 83·96 (55·4, 119·3) |
| Within-group total number of contrast-enhancing lesions at baseline | 3 | 0 |
| Within-patient lesional MTR, pu; mean (SD) | 41·83 (2·03) | 41·73 (2·08) |
| Within-patient brain parenchymal fraction; mean (SD) | 0·74 (0·02) | 0·75 (0·01) |
| **VEP**                        |            |         |
| Total number of VEP recordings with sufficient quality for inclusion; number of eyes (number of patients) | 42 (22) | 44 (23) |
| Participants with history of ON (number of eyes) | 11 (12) | 14 (20) |
| Time since ON, years; median (quartiles) | 12·2 (4·4, 15·5) | 3·3 (1·6, 8·6) |
| VEP P100 latency, ms; mean (SD) | 126·2 (18·6) | 119·3 (18·1) |

**Table 1. Comparison of baseline variables between the two trial arms for all participants in the intention-to-treat analyses.** One further participant randomised to bexarotene (who withdrew before month 2) and two further participants randomised to placebo (withdrawn before commencing the IMP) had no follow-up MRI or VEP so could not be included in the intention to treat analyses. EDSS: expanded disability status scale; MTR: magnetization transfer ratio; ON: optic neuritis; VEP: visual-evoked potential.
Table 2. Adverse events in the safety sample

|                        | Bexarotene (n=26) | Placebo (n=24) |
|------------------------|--------------------|---------------|
| **All adverse events** |                    |               |
| Number of adverse events (mean per person) | 159 (6·12) | 39 (1·63) |
| Number of participants with ≥1 adverse event (%) | 26 (100%) | 17 (71%) |
| Number of participants who discontinued study drug because of adverse event (%) | 5 (19%) | 2 (8%) |
| **Serious adverse events** |        |               |
| Hospitalisation        | 0      | 1 (4%) *      |
| **Expected Adverse Effects** |              |               |
| **Metabolic and nutrition disorders** |              |               |
| Hypertriglyceridaemia  | 24 (92%) | 0             |
| Secondary (central) hypothyroidism | 26 (100%) | 0             |
| **Blood and lymphatic system disorders** |              |               |
| Neutropenia             | 10 (38%) | 0             |
| Lymphopenia             | 1 (4%)   | 1 (4%)        |
| **Nervous system disorders** |          |               |
| Headache                | 14 (54%) | 8 (33%)       |
| **Skin and subcutaneous tissue disorders** |          |               |
| Rash                    | 13 (50%) | 1 (4%)        |
| Pruritis                | 7 (27%)  | 0             |
| **Emergent Adverse Effects** |          |               |
| **Nervous system disorders** |          |               |
| MS Relapse              | 1 (4%)   | 0             |
| MS Pseudorelapse        | 1 (4%)   | 4 (17%)       |
| Lhermitte’s sign        | 1 (4%)   | 0             |
| Cerebellar infarction   | 1 (4%)   | 0             |
| Neuropathic pain        | 1 (4%)   | 1 (4%)        |
| Muscle spasticity aggravated | 1 (4%) | 0             |
| Dizziness               | 1 (4%)   | 0             |
| Low mood                | 1 (4%)   | 0             |
| Memory disturbance      | 0        | 1 (4%)        |
| **Skin and subcutaneous tissue disorders** |          |               |
| Skin desquamation       | 5 (19%)  | 0             |
| Dry skin                | 4 (15%)  | 0             |
| Acne                    | 1 (4%)   | 0             |
| Alopecia                | 1 (4%)   | 0             |
| Facial flushing         | 0        | 2 (8%)        |
| Dry eyes                | 1 (4%)   | 0             |
| **Infections and infestations** |          |               |
| Upper respiratory tract infection | 2 (8%) | 1 (4%) |
| Lower respiratory tract infection | 1 (4%) | 0             |
| Urinary tract infection  | 2 (8%)   | 1 (4%)        |
| Shingles                | 0        | 1 (4%)        |
### Table 2. Adverse events in each of the two trial arms for participants who received at least one IMP dose

Unless otherwise stated, values are numbers of participants (%) with at least one event of the stated type. *One patient, on placebo, was hospitalised overnight for treatment of cholecystitis. Expected adverse effects of bexarotene, identified from the Summary of Product Characteristics was listed in the trial protocol.

| Disorder                                                                 | IMP | Placebo |
|-------------------------------------------------------------------------|-----|---------|
| **Ear infection**                                                       | 1 (4%) | 0       |
| Coryzal symptoms                                                        | 3 (12%) | 4 (17%) |
| Sinusitis                                                               | 0    | 1 (4%)  |
| **Gastrointestinal and hepatobiliary disorders**                        |     |         |
| Nausea                                                                  | 5 (19%) | 0       |
| Diarrhoea                                                               | 4 (15%) | 4 (17%) |
| Constipation                                                            | 2 (8%) | 0       |
| Epigastric pain                                                         | 1 (4%) | 0       |
| Dry lips                                                                | 2 (8%) | 0       |
| Ulceration of mouth                                                     | 2 (8%) | 0       |
| Cholecystitis                                                           | 0    | 1 (4%)  |
| **Respiratory, thoracic and mediastinal disorders**                     |     |         |
| Cough                                                                   | 1 (4%) | 1 (4%)  |
| Shortness of breath                                                     | 0    | 1 (4%)  |
| Sore throat                                                             | 1 (4%) | 1 (4%)  |
| **Musculoskeletal and connective tissue disorders**                     |     |         |
| Stiffness joints                                                        | 1 (4%) | 1 (4%)  |
| Myalgia                                                                 | 1 (4%) | 0       |
| **Renal and urinary disorders**                                          |     |         |
| Nocturia                                                                | 2 (8%) | 0       |
| Urinary frequency                                                       | 2 (8%) | 0       |
| **Vascular disorders**                                                  |     |         |
| Epistaxis                                                               | 1 (4%) | 0       |
| **General disorders**                                                   |     |         |
| Fatigue                                                                 | 6 (23%) | 4 (17%) |
| **Investigations**                                                      |     |         |
| Transaminitis                                                           | 3 (12%) | 0       |
| Weight loss                                                             | 1 (4%) | 0       |
Table 3. Trial MRI outcomes in the intention to treat sample

| Subgroup of lesions | Bexarotene | Placebo | Bexarotene-placebo change |
|---------------------|------------|---------|---------------------------|
| Patient number      | Unadjusted mean (SD) change in lesional MTR (pu) | Unadjusted mean (SD) change in lesional MTR (pu) | Adjusted bexarotene-placebo difference (95% CI) | p-value |
| Primary Efficacy Endpoint (Patient-level) | | | | |
| Patient submedian lesion mean** | 25 | 0.25 (0.98) | 24 | 0.09 (0.84) | 0.16 (-0.39, 0.71) | 0.554 |
| Pre-specified Exploratory MRI Analyses (Lesion-level) | | | | |
| Lesion number | Unadjusted mean (SD) change in lesional MTR (pu) | Lesion number | Unadjusted mean (SD) change in lesional MTR (pu) | Adjusted bexarotene-placebo difference (95% CI) | p-value |
| Submedian lesions (defined by cohort-level median) | 923 | 0.35 (2.09) | 662 | -0.07 (1.68) | 0.30 (-0.18, 0.78) | 0.223 |
| Supramedian lesions (defined by cohort-level median) | 1023 | -0.31 (1.74) | 562 | -0.18 (1.51) | -0.04 (-0.52, 0.43) | 0.854 |
| Interaction test comparing treatment group differences between submedian and supramedian lesions | .. | .. | .. | .. | .. | 0.007 |
| Periventricular lesions | 205 | -0.31 (1.70) | 151 | -0.18 (1.33) | -0.02 (-0.58, 0.55) | 0.953 |
| Deep WM lesions | 593 | -0.03 (1.72) | 356 | 0.01 (1.39) | -0.06 (-0.56, 0.44) | 0.810 |
| Juxtacortical lesions | 82 | 0.09 (1.71) | 53 | -0.16 (2.15) | 0.29 (-0.44, 1.01) | 0.441 |
| Leucocortical lesions | 650 | 0 (2.08) | 393 | -0.02 (1.62) | -0.04 (-0.54, 0.46) | 0.867 |
| CGM lesions | 46 | 0.69 (2.58) | 39 | -0.42 (3.20) | 1.00 (0.12, 1.75) | 0.023 |
| DGM lesions | 7 | 0.49 (2.81) | 9 | -1.41 (1.25) | 1.93 (0.28, 3.59) | 0.027 |
| Mixed DGM and WM lesions | 217 | 0.10 (1.80) | 158 | -0.24 (1.43) | 0.41 (-0.15, 0.97) | 0.160 |
| Brainstem lesions | 64 | 0.24 (2.62) | 24 | -1.21 (1.59) | 1.75 (0.86, 2.63) | 0.0003 |
| Cerebellar lesions | 82 | 0.04 (2.28) | 41 | -0.31 (1.54) | -0.03 (-0.79, 0.74) | 0.947 |
| Interaction test comparing treatment group differences between lesion locations | .. | .. | .. | .. | .. | <0.0001 |
| Prespecified Exploratory Whole-brain MRI Analyses (Patient level) | | | | | | |
| Patient number | Unadjusted mean (SD) change | Patient number | Unadjusted mean (SD) change | Adjusted bexarotene-placebo difference (95% CI) | p-value |
Table 3. Trial MRI and visual evoked potential (VEP) outcomes for intention to treat analysis. *p* values and CIs are for the adjusted (for baseline value and prespecified covariates) bexarotene – placebo differences. For the VEP outcomes, one participant in the bexarotene group, and two in the placebo group, contributed one eye to each of the ≤118 ms and >118 ms subgroups. As described in the main text, we prospectively substituted an analysis of BPF for the measure of T1 volume. BPF: brain parenchymal fraction; CGM: cortical grey matter; DGM: deep grey matter; MTR: magnetization transfer ratio; ON: optic neuritis; pu: percentage units; NAWM: normal-appearing white matter; WM: white matter.