**SUPPLEMENTAL DATA**

**SUPPLEMENTAL TABLES**

**Table e-1. Exploratory endpoints at Week 48**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Laquinimod 0.6 mg vs. placebo** | **N** | **Output** | **Estimate** | **Standard error** | **95% CI** | ***P* value** |
| BICAMS, adjusted mean (95% CI) | | | | | | |
| CVLT-II – Verbal memory  BVMT – Nonverbal memory  SDMT – Processing speed  LCVA (chart type 100%)a  MSWS-12  9HPT | 224  199  232  218  232  235 | Treatment effect  Treatment effect  Treatment effect  Treatment effect  Treatment effect  Treatment effect | 0.340  0.382  1.987  0.785  -2.045  -0.525 | 1.0323  0.7957  0.9716  0.7708  1.1972  0.5102 | –1.6945, 2.3750  –1.1876, 1.9510  0.0812, 3.8934  –0.7295, 2.3002  –4.3936, 0.3036  –1.5250, 0.4750 | 0.742  0.632  0.41  0.309  0.088  0.412 |
| CDP alternatives, n (%)  12-week EDSS CDP  24-week EDSS CDP  12-week CDP (EDSS or T25FW)  12-week T25FW CDP  12-week CDP (EDSS, T25FW, 9HPT, or SDMT) | 276  279  276  276  276 | Hazard ratio  Hazard ratio  Hazard ratio  Hazard ratio  Hazard ratio | 0.9  0.7  1.0  0.9  1.0 |  | 0.52, 1.41  0.39, 1.24  0.69, 1.52  0.56, 1.48  0.68, 1.45 | 0.541  0.215  0.906  0.711  0.989 |

Abbreviations: 9HPT = 9-Hole Peg test; BICAMS = Brief International Cognitive Assessment for Multiple Sclerosis; BVMT = Brief Visuospatial Memory Test; CDP = confirmed disability progression; CI = confidence interval; CVLT-II = California Verbal Learning Test–II; EDSS = Expanded Disability Status Scale; N = number of patients included in the analysis; LCVA = low-contrast visual acuity; MSWS-12 = 12-Item Multiple Sclerosis Walking Scale; SDMT = Symbol Digit Modalities Test; T25FW = timed 25-foot walk.

a Estimated mean.

**Table e-2. Patients with prior use of MS disease-modifying treatment (ITT population)**

|  | | **Placebo (n = 140)** | | **Laquinimod 0.6 mg (n = 139)** | **Laquinimod 1.5 mg (n = 95)** | **Total (n = 374)** |
| --- | --- | --- | --- | --- | --- | --- |
| **Patients with prior DMT use, n (%)** | | 31 (22) | | 28 (20) | 30 (32) | 89 (24) |
| Investigational drug | | 4 (3) | | 10 (7) | 12 (13) | 26 (7) |
| Antineoplastic agents | | 0 | | 1 (<1) | 2 (2) | 3 (<1) |
| Mitoxantrone | | 0 | | 0 | 2 (2) | 2 (<1) |
| Rituximab | | 0 | | 1 (<1) | 0 | 1 (<1) |
| Corticosteroids for systemic use | | 1 (<1) | | 0 | 0 | 1 (<1) |
| Methylprednisolone | | 1 (<1) | | 0 | 0 | 1 (<1) |
| Immune sera and immunoglobulins | | 0 | | 1 (<1) | 1 (1) | 2 (<1) |
| Immunoglobulins NOS | | 0 | | 1 (<1) | 1 (1) | 2 (<1) |
| Immunostimulants | | 17 (12) | | 10 (7) | 12 (13) | 39 (10) |
| Glatiramer acetate | | 8 (6) | | 3 (2) | 7 (7) | 18 (5) |
| Interferon beta-1a | | 8 (6) | | 6 (4) | 3 (3) | 17 (5) |
| Interferon beta-1b | | 5 (4) | | 2 (1) | 2 (2) | 9 (2) |
| Interferon beta | | 0 | | 0 | 1 (1) | 1 (<1) |
| Immunosuppressants | | 8 (6) | | 10 (7) | 13 (14) | 31 (8) |
| Fingolimod | | 3 (2) | | 5 (4) | 10 (11) | 18 (5) |
| Azathioprine | | 1 (<1) | | 2 (1) | 2 (2) | 5 (1) |
| Fingolimod hydrochloride | | 3 (2) | | 1 (<1) | 1 (1) | 5 (1) |
| Methotrexate | | 1 (<1) | | 0 | 0 | 1 (<1) |
| Methotrexate sodium | | 0 | | 1 (<1) | 0 | 1 (<1) |
| Ocrelizumab | | 0 | | 1 (<1) | 0 | 1 (<1) |
| Teriflunomide | | 1 (<1) | | 0 | 0 | 1 (<1) |
| Muscle relaxants | | 1 (<1) | | 0 | 0 | 1 (<1) |
| Baclofen | | 1 (<1) | | 0 | 0 | 1 (<1) |
| Tizanidine hydrochloride | | 1 (<1) | | 0 | 0 | 1 (<1) |
| Other nervous system drugs | | 2 (1) | | 4 (3) | 2 (2) | 8 (2) |
| Fampridine | | 2 (1) | | 4 (3) | 0 | 6 (2) |
| Dimethyl fumarate | | 0 | | 0 | 2 (2) | 2 (<1) |
| Unspecified herbal and traditional medicine | | 1 (<1) | | 0 | 0 | 1 (<1) |
| *Camellia sinensis* | | 1 (<1) | | 0 | | 0 | 1 (<1) |
| Urologicals | | 1 (<1) | | 0 | | 0 | 1 (<1) |
| Fesoterodine fumarate | | 1 (<1) | | 0 | | 0 | 1 (<1) |
| Uncoded | | 4 (3) | | 1 (<1) | | 1 (1) | 6 (2) |
| Blood and blood-forming organs | | 4 (3) | | 1 (<1) | | 1 (1) | 6 (2) |

Abbreviations: DMT = disease-modifying treatment; ITT = intention-to-treat; MS = multiple sclerosis; NOS = not otherwise specified.

**Table e-3. Trial comparison**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **INFORMS17** | **ORATORIO19, 26** | **PROMISE27** | **OLYMPUS21** | **SPRINT22** | **ARPEGGIO** |
| **Study characteristics** |  |  |  |  |  |  |
| Study drug | Fingolimod | Ocrelizumab | Glatiramer acetate | Rituximab | Ibudilast | Laquinimod |
| Study period | 36 months | 120 weeks | 36 months | 96 weeks | 96 weeks | 48 weeks |
| N | 823 | 732 | 943 | 439 | 255 | 374 |
| **Baseline characteristics** | | | | | | |
| Age, mean years (SD) | 48.5 (8.4) | 44.6 | 50.4 (8.3) | 49.9 (8.9) | 56 | 46.3 (7.0) |
| Male, n (%) | 425 (52) | 371 (50.7) | 460 (48.8) | 218 (49.7) | 133 (66.5) | 205 (55.0) |
| White, n (%) | 791 (96) | 94.1 | 747 (89.8) | 402 (91.6) | 236 (92.5) | 362 (97) |
| Time since symptom onset, mean years (SD) | 5.8 (2.4) | 6.5 (3.89) | 10.9 (7.5) | 9.1 (6.6) | Median 9 years placebo, 11 years treatment arm | 8.0 (5.8) |
| EDSS score, mean (SD) | 4.67 (1.03) | 4.70 (1.7) | 4.9 (1.2) | 4.8 (1.4) | Median 6 both arms | 4.5 (0.9) |
| Prior use of DMT, n (%) | 179 (22) | 85 (12.0) | NR | 154 (35.1) | NR | 89 (24) |
| **Study endpoint baseline values** | | | | | | |
| T25FW score (seconds), mean (SD) | 9.08 (6.87) | NR | 12.4 (13.8) | 8.08 median | Median 9.93 placebo, median 9.35 treatment arm | 9.7 (8.4) |
| 9-HPT dominant hand score (s), mean (SD) | 28.65 (14.62) | NR | 29.1 (19.3) | NR | Median 30.31 placebo, median 28.68 treatment arm | 32.4 (22.4) |
| Gd-enhancing lesions count, mean (SD) | 0.3 (1.06) | 1.0 (4.31) | 0.45 (2.7) | NR | NR | 0.3 (1.3) |
| Free of Gd+, n (%) | 260 (87.0) | 534 (73.0) | 85.9 | 75.5 | NR | 84.2 |
| Total volume of T2 lesions (mm3), mean (SD) | 9794.5 (11943.5) | 12, 100 | NR | 9173.3 (13114.0) | 10000 | 6129.0 (8885.1) |
| Normalized brain volume (cm3), mean (SD) | 1491.4 (85.5) | 1465.0 (86.0) | NR | 1205.8 (123.3) | NR | 1458.5 (102.7) |

Abbreviations: 9-HPT = 9-Hole Peg Test; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; Gd = gadolinium; NR = not reported; SD = standard deviation; T25FW = timed 25-foot walk.