Supplemental Data

*Follow-Up Characteristics by Diagnosis.*

Table S1. Follow-up characteristics for MS and NMOSD patients.

| Follow Up Characteristics                      | MS N=907 |          | NMOSD N=77 |          | p-value<sup>a</sup> |
|------------------------------------------------|----------|----------|------------|----------|--------------------|
| cumulative rituximab dose (mg)                 | 3,713 (median=3,000) 3015 |          | 7,526 (median=6,000) 6,272 |          | <0.001             |
| patients who switched to ocrelizumab           | 169 18.9% |          | 0 0.0%     |          | -                  |
| cumulative ocrelizumab dose (mg)<sup>*</sup>   | 1,141 (median= 1,200) 414 |          | - -      |          | -                  |
| time on rituximab/ocrelizumab (months)         | 29.7 21.0 |          | 47.2 40.0 |          | <0.001             |

Bold p-values indicate p>0.05 and are considered statistically significant.

*Calculated of those who switched to ocrelizumab

<sup>a</sup>Comparing MS and NMOSD patients
Baseline Characteristics by Study Center

Table S2. Baseline characteristics by study center.

| Baseline Characteristics | RMMSC N=725 | NYUMSCC N=275 | p-value<sup>a</sup> |
|--------------------------|-------------|---------------|---------------------|
| Age (Years, SD)          | 44.3 12.4   | 39.3 12.5     | <0.001              |
| Gender – Female          | 496 68.4%   | 191 69.5%     | 0.751               |
| Race                     |             |               | <0.001              |
| White                    | 560 77.2%   | 118 42.9%     |                     |
| Black                    | 57 7.9%     | 82 29.8%      |                     |
| Other                    | 57 7.9%     | 60 21.8%      |                     |
| Unknown                  | 51 7.0%     | 15 5.5%       |                     |
| Ethnicity                |             |               | <0.001              |
| Hispanic                 | 64 8.8%     | 43 15.6%      |                     |
| Non-Hispanic             | 604 83.3%   | 185 67.3%     |                     |
| Unknown                  | 57 7.9%     | 47 17.1%      |                     |
| Smoking Status           |             |               | 0.029               |
| Current Smoker           | 106 14.6%   | 25 9.2%       |                     |
| Former Smoker            | 199 27.5%   | 67 24.7%      |                     |
| Never Smoker             | 420 57.9%   | 179 66.1%     |                     |
| Body Mass Index          | 26.8 6.5    | 26.9 6.4      | 0.928               |
| Disability               |             |               | 0.019               |
| No walking device needed | 438 60.4%   | 188 69.9%     |                     |
| Unilateral support (Cane)| 105 14.5%   | 22 8.2%       |                     |
| Bilateral support (Walker)| 77 10.6%   | 27 10.4%      |                     |
| Wheelchair               | 105 14.5%   | 32 11.9%      |                     |
| Diagnosis                |             |               | <0.001              |
| Relapsing-Remitting MS   | 426 58.8%   | 147 53.5%     |                     |
| Secondary Progressive MS | 176 24.3%   | 39 14.2%      |                     |
| Primary Progressive MS   | 98 13.5%    | 21 7.6%       |                     |
| NMOSD                    | 23 3.2%     | 54 19.6%      |                     |
| Other                    | 2 0.3%      | 14 5.1%       |                     |
| Disease Duration         | 9.2 8.7     | 6.6 6.5       | <0.001              |
| Last DMT Used            |             |               | <0.001              |
| Azathioprine             | 2 0.3%      | 13 4.7%       |                     |
| Dimethyl fumarate        | 106 14.6%   | 47 17.1%      |                     |
| Fingolimod               | 127 17.5%   | 28 10.2%      |                     |
| Glatiramer Acetate       | 82 11.3%    | 18 6.5%       |                     |
| Interferon               | 56 7.7%     | 10 3.6%       |                     |
| Mycophenolate mofetil    | 0 0.0%      | 10 3.6%       |                     |
| Natalizumab              | 210 29.0%   | 68 24.7%      |                     |
| None                     | 102 14.1%   | 61 22.2%      |                     |
| Other/Missing            | 29 0.4%     | 16 5.8%       |                     |
| Teriflunomide            | 11 1.5%     | 4 1.5%        |                     |
| Time Since Last DMT (Months) | 7.8 19.8 | 5.5 20.6 | 0.171 |

Bold p-values indicate p>0.05 and are considered statistically significant. RMMSC: Rocky Mountain Multiple Sclerosis Clinic; NYUMSCC: New York University Multiple Sclerosis Care Center; N: number; SD: standard deviation; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; DMT: disease modifying therapy.

<sup>a</sup>Comparing RMMSC and NYUMSCC patients
Table S3. Percentage of patients who experienced a serious safety event on rituximab/ocrelizumab by study center.

| Event                                         | Total N (%) | Diagnosis RMMSC N (%) | Diagnosis NYUMSCC N (%) | p-value<sup>a</sup> |
|-----------------------------------------------|-------------|-----------------------|-------------------------|---------------------|
| Infections resulting in:                     | 100 (8.6%)* | 85 (9.7%)             | 15 (5.5%)               | 0.019               |
| Hospitalization                              | 79 (6.5%)*  | 70 (7.7%)             | 9 (3.3%)                | 0.012               |
| IV antibiotics (without hospitalization)     | 6 (0.6%)    | 6 (0.8%)              | 0 (0.0%)                | 0.196               |
| Extended dosing antibiotics                  | 15 (1.5%)   | 9 (1.2%)              | 6 (2.2%)                | 0.260               |
| Infusion reaction requiring hospitalization  | 0 (0.0%)    | 0 (0.0%)              | 0 (0.0%)                |                     |
| Malignant Cancer                             | 9 (0.9%)    | 8 (1.1%)              | 1 (0.4%)                | 0.458               |
| New autoimmune disease diagnosis             | 6 (0.6%)    | 3 (0.4%)              | 3 (1.1%)                | 0.355               |
| Thromboembolic event (Non-superficial)       | 8 (0.8%)    | 6 (0.8%)              | 2 (0.7%)                | 0.372               |
| Lymphopenia                                   |             |                       |                         |                     |
| <500 cells/mm³                                | 48 (5.1%)   | 29 (4.3%)             | 19 (7.4%)               | 0.056               |
| <200 cells/mm³                                | 2 (0.2%)    | 1 (0.1%)              | 1 (0.4%)                | 0.476               |
| Neutropenia                                   |             |                       |                         |                     |
| <1000 cells/mm³                               | 14 (1.5%)   | 9 (1.3%)              | 5 (2.0%)                | 0.483               |
| <500 cells/mm³                                | 11 (1.2%)   | 8 (1.2%)              | 3 (1.2%)                | 1.000               |
| Low IgG Values                                |             |                       |                         |                     |
| <500 mg/dL                                    | 38 (5.2%)   | 30 (5.4%)             | 8 (4.3%)                | 0.545               |
| <300 mg/dL                                    | 8 (1.1%)    | 3 (0.5%)              | 5 (2.6%)                | 0.023               |
| Mortality                                     | 14 (1.4%)   | 12 (1.7%)             | 2 (0.7%)                | 0.372               |

Bold p-values indicate p>0.05 and are considered statistically significant. N: number of events occurred; %: percent of patients who experienced event; RMMSC: Rocky Mountain Multiple Sclerosis Center; NYUMSCC: New York University Multiple Sclerosis Care Center

* Sixty-five patients were hospitalized a total of 79 times. Nine patients were hospitalized multiple times due to infections.

<sup>a</sup>Comparing RMMSC and NYUMSCC patients
| Follow-Up Characteristics                      | RMMSC N=725 | NYUMSCC N=275 | p-value<sup>a</sup> |
|-----------------------------------------------|-------------|---------------|---------------------|
| Cumulative rituximab dose (mg)                | 3,152 (median=2,500) 2,261 | 6,410 (median=5,000) 4,984 | <0.001 |
| Patients who switched to ocrelizumab          | 131 18.1% | 38 13.8% | 0.109 |
| Cumulative ocrelizumab dose (mg)<sup>*</sup>  | 1,191 (median= 1,200) 413 | 971 (median= 1,200) 378 | 0.004 |
| Cumulative anti-CD20 dose                     | 3,368 (median= 2,700) 2,287 | 6,551 (median= 5,000) 4,947 | <0.001 |
| Time on rituximab/ocrelizumab (months)       | 28.7 (median=23) 21.5 | 37.6 (median=29) 27.1 | <0.001 |

Bold p-values indicate p>0.05 and are considered statistically significant. RMMSC: Rocky Mountain Multiple Sclerosis Clinic; NYUMSCC: New York University Multiple Sclerosis Care Center

<sup>*</sup>Calculated of those who switched to ocrelizumab

<sup>a</sup>Comparing RMMSC and NYUMSCC patients
Types of Infections

Table S5. Number of infections resulting in hospitalizations, IV antibiotics (without hospitalization) and extended dosing antibiotics.

| Infection                  | Hospitalization* n=65 (6.5% of patients) | IV Antibiotics (without Hospitalization) n=6 (0.6% of patients) | Extended Dosing Antibiotics n=15 (1.5% of patients) |
|----------------------------|------------------------------------------|---------------------------------------------------------------|---------------------------------------------------|
|                            | N            | N                        | N            |
| Urinary Tract Infection    | 35           | 2                        | 10           |
| Sepsis                     | 22           | -                        | -            |
| Pneumonia                  | 20           | -                        | 1            |
| Cellulitis                 | 5            | 1                        | -            |
| Abscess                    | 3            | -                        | -            |
| C. Diff. Colitis           | 2            | -                        | -            |
| Kidney infection           | 2            | -                        | -            |
| Appendicitis               | 2            | -                        | -            |
| Influenza                  | 1            | -                        | -            |
| Respiratory syncytial virus| 1            | -                        | -            |
| Sinusitis / Bronchitis     | 1            | 1                        | -            |
| Non-specific fever         | 1            | -                        | --           |
| Wound infection            | 2            | 1                        | -            |
| Stomach infection          | 1            | -                        | -            |
| Bacteremia                 | 1            | -                        | 1            |
| Hep B reactivation         | 1            | -                        | -            |
| Pulmonary aspergillosis    | 1            | -                        | -            |
| Osteomyelitis              | 1            | -                        | 1            |
| Viral pleural & pericardial effusion | 1 | - | - |
| Skin and joint infection   | -            | 1                        | 1            |
| Bacterial Vaginosis        | -            | -                        | 1            |

*Some patients may have had multiple infections resulting in hospitalization.
Association between Hypogammaglobulinemia and Infections

**Table S6.** Descriptive statistics and odds ratio for patients experiencing first infection who had an IgG value <500 mg/dL at any time compared to those with IgG values always ≥500 mg/dL

| Infections resulting in Hospitalization Only* | Infections (Hospitalization) | No Infection | Total |
|---------------------------------------------|-------------------------------|--------------|-------|
| IgG Value: <500 mg/dL                       | 8 (21.1%)                    | 30 (78.9%)   | 38    |
| IgG Value: Always ≥500 mg/dL                | 40 (5.7%)                    | 660 (94.3%)  | 700   |

*Chi-square test p-value: 0.002

| Logistic Regression Analysis               | N | Odds Ratio (95% CI) | p-value |
|--------------------------------------------|---|---------------------|---------|
| Unadjusted Logistic Regression             | 738 | 4.40 (1.89, 10.22)  | <0.001  |
| Adjusted Logistic Regression*              | 646 | 3.29 (1.13, 9.58)   | 0.029   |

| Infections resulting in Hospitalization, Extended Dosing Antibiotics or IV Antibiotics^ | All Infections | No Infection | Total |
|---------------------------------------------------------------------------------------|---------------|--------------|-------|
| IgG Value: <500 mg/dL                                                               | 9 (23.7%)     | 29 (76.3%)   | 38    |
| IgG Value: Always ≥500 mg/dL                                                        | 52 (7.4%)     | 648 (92.6%)  | 700   |

^ Chi-square test p-value: 0.004

| Logistic Regression Analysis               | N | Odds Ratio (95% CI) | p-value |
|--------------------------------------------|---|---------------------|---------|
| Unadjusted Logistic Regression             | 738 | 3.87 (1.74, 8.60)  | 0.002   |
| Adjusted Logistic Regression*              | 646 | 3.15 (1.16, 8.55)  | 0.024   |

Note: Lab value<500 mg/dL at least once at any time, not necessarily at time of infection
Bold p-values indicate p>0.05 and are considered statistically significant.
*Adjusting for age at first infusion, gender, disease duration, diagnosis (Relapsing MS, Progressive MS or Other), and disability at baseline
Association between Lymphopenia and Infections

**Table S7.** Descriptive statistics and odds ratio for patients experiencing first infection who had lymphopenia at any time compared to those without.

| Infections resulting in Hospitalization Only* | Infections (Hospitalization) | No Infection | Total |
|---------------------------------------------|------------------------------|--------------|-------|
| Lymphopenia <500 cells/mm³                  | 8 (16.7%)                   | 40 (83.3%)   | 48    |
| No Lymphopenia                              | 56 (6.3%)                   | 832 (93.7%)  | 888   |

^Chi-square test p-value: 0.013

**Logistic Regression Analysis**

| N | Odds Ratio (95% CI) | p-value |
|---|---------------------|---------|
| Unadjusted Logistic Regression              | 936     | 2.97 (1.33, 6.65) | 0.008 |
| Adjusted Logistic Regression*               | 926     | 2.27 (0.93, 5.54) | 0.006 |

**Infections resulting in Hospitalization, Extended Dosing Antibiotics or IV antibiotics^**

| All Infections | No Infection | Total |
|----------------|--------------|-------|
| Lymphopenia <500 cells/mm³ | 10 (20.8%) | 38 (79.2%) | 48 |
| No Lymphopenia | 69 (77.7%)  | 819 (92.2%) | 888 |

^ Chi-square test p-value: 0.005

**Logistic Regression Analysis**

| N | Odds Ratio (95% CI) | p-value |
|---|---------------------|---------|
| Unadjusted Logistic Regression              | 936     | 3.12 (1.49, 6.53) | 0.003 |
| Adjusted Logistic Regression*               | 926     | 2.55 (1.12, 5.81) | 0.012 |

Note: Lab value<500 mg/dL at least once at any time, not necessarily at time of infection
Bold p-values indicate p>0.05 and are considered statistically significant.
*Adjusting for age at first infusion, gender, disease duration, diagnosis (Relapsing MS, Progressive MS or Other), and disability at baseline
### Characteristics of Patients who Experienced an SSE

**Table S8.** Baseline characteristics for those who experience an SSE and those who do not.

| Baseline Characteristics          | No SSE N=823  | SSE* N=177 | p-value\(^{\beta}\) |
|----------------------------------|---------------|------------|-------------------|
| **Age (Years, SD)**              | 42.3 12.5     | 45.8 13.0  | 0.001\(^{\beta}\) |
| **Gender – Female**              | 572 69.5%     | 115 65.0%  | 0.238\(^{\beta}\) |
| **Race**                         |               |            | 0.616\(^{\beta}\) |
| White                            | 553 67.2%     | 125 70.6%  |                   |
| Black                            | 116 14.1%     | 23 13.0%   |                   |
| Other                            | 96 11.7%      | 21 11.9%   |                   |
| Unknown                          | 58 7.1%       | 8 4.5%     |                   |
| **Ethnicity**                    |               |            | 0.267\(^{\beta}\) |
| Hispanic                         | 90 10.9%      | 17 9.6%    |                   |
| Non-Hispanic                     | 642 78.0%     | 147 83.1%  |                   |
| Unknown                          | 91 11.1%      | 13 7.3%    |                   |
| **Smoking Status**               |               |            | 0.515\(^{\beta}\) |
| Current Smoker                   | 111 13.6%     | 20 11.3%   |                   |
| Former Smoker                    | 222 27.1%     | 44 24.9%   |                   |
| Never Smoker                     | 486 59.3%     | 113 63.8%  |                   |
| **Body Mass Index**              | 27.1 6.6      | 25.8 6.0   | 0.022\(^{\beta}\) |
| **Disability**                   |               |            | <0.001\(^{\beta}\) |
| No walking device needed         | 548 67.1%     | 78 44.1%   |                   |
| Unilateral support (Cane)        | 103 12.6%     | 24 13.6%   |                   |
| Bilateral support (Walker)       | 81 9.9%       | 23 13.0%   |                   |
| Wheelchair                       | 85 10.4%      | 52 29.4%   |                   |
| **Diagnosis**                    |               |            | <0.001\(^{\beta}\) |
| Relapsing-Remitting MS           | 507 61.6%     | 66 37.3%   |                   |
| Secondary Progressive MS         | 154 18.7%     | 61 34.5%   |                   |
| Primary Progressive MS           | 101 12.3%     | 18 10.2%   |                   |
| NMOSD                            | 45 5.5%       | 32 18.1%   |                   |
| Other                            | 16 1.9%       | 0 0.0%     |                   |
| **Disease Duration**             | 8.2 8.0       | 10.1 9.3   | 0.006\(^{\beta}\) |
| **Last DMT Used**                |               |            | 0.102\(^{\beta}\) |
| Azathioprine                     | 10 1.2%       | 5 2.8%     |                   |
| Dimethyl fumarate                | 128 15.6%     | 25 14.1%   |                   |
| Fingolimod                       | 130 15.8%     | 25 14.1%   |                   |
| Glatiramer Acetate               | 86 10.5%      | 14 7.9%    |                   |
| Interferon                       | 54 6.6%       | 5 7.9%     |                   |
| Mycophenolate mofetil            | 5 0.6%        | 5 2.8%     |                   |
| Natalizumab                      | 220 26.7%     | 58 32.8%   |                   |
| None                             | 140 17.0%     | 23 13.0%   |                   |
| Other/Missing                    | 37 4.5%       | 8 4.5%     |                   |
| Teriflunomide                    | 13 1.6%       | 2 1.1%     |                   |
| **Time Since Last DMT (Months, SD)**| 7.7 20.6    | 5.0 17.0  | 0.141\(^{\beta}\) |

Bold p-values indicate p>0.05 and are considered statistically significant. SSE: serious safety event; N: number; SD: standard deviation; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; DMT: disease modifying therapy.

*includes infusion reaction resulting in hospitalization, new diagnosis of malignant cancer, new diagnosis of an autoimmune disease, thromboembolic event (non-superficial), lymphopenia (<500 cells/mm\(^3\)), neutropenia (<1000 cells/mm\(^3\)), IgG values (<500 mg/dL), death or infections resulting in hospitalization, extended dosing antibiotics or IV antibiotics.

\(^{a}\) Comparing those with no SSE to those with an SSE

\(^{\beta}\) T-test

\(^{\beta}\) Chi-squared tests
Table S9. Follow-up characteristics for those who experience an SSE and those who do not.

| Follow Up Characteristics          | No SSEs N=823 | SSE^ N=177 | p-value^a |
|-----------------------------------|--------------|------------|-----------|
| **Cumulative rituximab Dose (mg)** |              |            |           |
| N or Mean                         | 3,749        | 5,215      | <0.001^b  |
| SD or %                           | (median=3,000)| (median=4,000) |           |
| **Patients who switched to ocrelizumab** |              |            | 0.985^i   |
| N or Mean                         | 139          | 30         |           |
| SD or %                           | 16.9%        | 17.0%      |           |
| **Cumulative ocrelizumab dose (mg)^* |              |            | 0.788^b   |
| N or Mean                         | 1,137        | 1,160      |           |
| SD or %                           | (median=1,200)| (median=1,200) |           |
| **Time on rituximab/ocrelizumab (months)** |              |            | <0.001^b  |
| N or Mean                         | 28.8         | 42.0       |           |
| SD or %                           | (median=24)  | (median=32) |           |

Bold p-values indicate p>0.05 and are considered statistically significant. SSE: serious safety event; N: number; SD: standard deviation.

作品内容包括：
- 表格：比较了没有严重安全事件（SSE）和有严重安全事件的患者在随访期间的特征。
- 表格内容包括：累计利妥昔单抗剂量（mg）、转到奥泽利单抗的患者人数和比例、累计奥泽利单抗剂量（mg）、用药时间（个月）。
- 结果表明，有严重安全事件的患者在累计利妥昔单抗剂量和用药时间上与没有严重安全事件的患者有显著差异。

注释：
- ^a includes infusion reaction resulting in hospitalization, new diagnosis of malignant cancer, new diagnosis of an autoimmune disease, thromboembolic event (non-superficial), lymphopenia (<500 cells/mm³), neutropenia (<1000 cells/mm³), IgG values (<500 mg/dL), death or infections resulting in hospitalization, extended dosing antibiotics or IV antibiotics.
- ^b Calculated of those who switched to ocrelizumab.
- ^c Comparing those with no SSE to those with an SSE.
- ^T-test
- ^Chi-squared tests.
Table S10. Follow-up characteristics for those who experience an SSE by type at time of SSE.

| Follow Up Characteristics | First Serious Infection (N=86) | Cancer (N=9) | Autoimmune disease (N=6) | Thromboembolic event (N=8) |
|---------------------------|--------------------------------|--------------|--------------------------|---------------------------|
| **Cumulative rituximab Dose (mg)** | 3,705 [3,346] Median=2,500 | 3,167 [2,511] Median=4,000 | 4,667 [4,761] Median=3,000 | 3,643 [2,116] Median=3,000 |
| **Patients who switched to ocrelizumab** | 2 (2.3%) Median=600 | 1 (11.1%) Median=1,200 | 0 (0.0%) Median=0 | 0 (0.0%) Median=0 |
| **Cumulative ocrelizumab dose (mg)*** | 600 [.] Median=600 | 1,200 [.] Median=1,200 | - | - |
| **Time on rituximab/ocrelizumab (months)** | 25.1 [28.9] Median=19.0 | 38.8 (34.3) Median=50.0 | 19.0 (15.6) Median=16.5 | 31.5 [28.3] Median=27.0 |

| Follow Up Characteristics | Lymphopenia (N=48) | Neutropenia (N=14) | Low IgG Values (N=38) | Mortality (N=14) |
|---------------------------|--------------------|--------------------|-----------------------|-----------------|
| **Cumulative rituximab Dose (mg)** | 2,593 [2,408] Median=2,000 | 2,923 [1,801] Median=2,500 | 5,454 [4,812] Median=3,500 | 2,962 [1,738] Median=2,500 |
| **Patients who switched to ocrelizumab** | 3 (6.3%) Median=600 | 1 (7.1%) Median=300 | 5 (13.2%) Median=1200 | 0 (0.0%) Median=0 |
| **Cumulative ocrelizumab dose (mg)*** | 500 [173] Median=600 | 300 [.] Median=300 | 1140 [537] Median = 1200 | - |
| **Time on rituximab/ocrelizumab (months)** | 17.8 [20.6] Median=11.0 | 17.9 [13.3] Median=15.0 | 44.8 [32.8] Median=42.0 | 30.4 [21.6] Median=28.0 |

*Calculated of those who switched to ocrelizumab

SSE: serious safety event; N: number; SD: standard deviation.
Table S11. Percentage of patients who experienced a serious safety event while on rituximab/ocrelizumab by age.

| Infections resulting in:                  | Total N (%) | Age N=808 (%) | Age N=192 (%) | p-value<sup>a</sup> |
|-------------------------------------------|-------------|---------------|---------------|---------------------|
| Hospitalization                           | 79 (6.5%)*  | 53 (5.3%)*    | 26 (11.5%)*   | 0.005               |
| IV antibiotics (without hospitalization)  | 6 (0.6%)    | 4 (0.5%)      | 2 (1.0%)      | 0.325               |
| Extended dosing antibiotics               | 15 (1.5%)   | 12 (1.5%)     | 3 (1.6%)      | 1.000               |
| Infusion reaction requiring hospitalization| 0 (0.0%)    | 0 (0.0%)      | 0 (0.0%)      | -                   |
| Malignant Cancer                          | 9 (0.9%)    | 6 (0.7%)      | 3 (1.6%)      | 0.386               |
| New autoimmune disease diagnosis         | 6 (0.6%)    | 5 (0.6%)      | 1 (0.5%)      | 1.000               |
| Thromboembolic event (Non-superficial)    | 8 (0.8%)    | 4 (0.5%)      | 4 (2.1%)      | 0.049               |
| Lymphopenia                               |             |               |               |                     |
| <500 cells/mm3                            | 48 (5.1%)   | 29 (3.8%)     | 19 (10.7%)    | <0.001              |
| <200 cells/mm3                            | 2 (0.2%)    | 2 (0.3%)      | 0 (0.0%)      | 0.656               |
| Neutropenia                               |             |               |               |                     |
| <1000 cells/mm3                           | 14 (1.5%)   | 11 (1.5%)     | 3 (1.7%)      | 0.736               |
| <500 cells/mm3                            | 11 (1.2%)   | 8 (1.1%)      | 3 (1.7%)      | 0.445               |
| Low IgG Values                            |             |               |               |                     |
| <500 mg/dL                                | 38 (5.2%)   | 28 (4.7%)     | 10 (7.0%)     | 0.256               |
| <300 mg/dL                                | 8 (1.1%)    | 5 (0.8%)      | 3 (2.1%)      | 0.186               |
| Mortality                                 | 14 (1.4%)   | 10 (1.2%)     | 4 (2.1%)      | 0.323               |

Bold p-values indicate p>0.05 and are considered statistically significant. N: number of events occurred; %: percent of patients who experienced event; RMMSC: Rocky Mountain Multiple Sclerosis Center; NYUMSCC: New York University Multiple Sclerosis Care Center

* Sixty-five patients (43 <55 years; 22 ≥55 years) were hospitalized a total of 79 times (53 <55 years; 26 ≥55 years).

<sup>a</sup> Comparing those with <55 years to those ≥55 years

Nine patients (6 <55 years; 3 ≥55 years) were hospitalized multiple times due to infections.
# Subgroup Analysis - By Disability

## Table S12. Baseline characteristics by disability.

| Baseline Characteristics       | No Walking Device N=626 | Unilateral Support N=127 | Bilateral Support N=104 | Wheelchair N=137 |
|-------------------------------|-------------------------|--------------------------|-------------------------|-----------------|
| **Age (Years, SD)**           | 39.8 ± 12.3             | 46.5 ± 11.6              | 49.3 ± 11.8             | 48.9 ± 10.6     |
| **Gender – Female**           | 439 (70.1%)             | 77 (60.6%)               | 78 (75.0%)              | 88 (64.2%)      |
| **Race**                      |                         |                          |                         |                 |
| White                         | 426 (68.1%)             | 90 (70.9%)               | 69 (66.4%)              | 89 (65.0%)      |
| Black                         | 73 (11.7%)              | 25 (19.7%)               | 17 (16.4%)              | 23 (16.8%)      |
| Other                         | 82 (13.1%)              | 7 (5.5%)                 | 10 (9.6%)               | 17 (12.4%)      |
| Unknown                       | 45 (7.2%)               | 5 (3.9%)                 | 8 (7.8%)                | 8 (5.8%)        |
| **Ethnicity**                 |                         |                          |                         |                 |
| Hispanic                      | 72 (11.5%)              | 12 (9.5%)                | 10 (9.6%)               | 11 (8.0%)       |
| Non-Hispanic                  | 487 (77.8%)             | 107 (84.3%)              | 77 (74.0%)              | 116 (84.7%)     |
| Unknown                       | 67 (10.7%)              | 8 (6.3%)                 | 17 (16.4%)              | 10 (7.3%)       |
| **Smoking Status**            |                         |                          |                         |                 |
| Current Smoker                | 78 (12.5%)              | 23 (181.1%)              | 12 (11.5%)              | 18 (13.2%)      |
| Former Smoker                 | 156 (24.9%)             | 39 (30.7%)               | 31 (29.8%)              | 40 (29.4%)      |
| Never Smoker                  | 392 (62.6%)             | 65 (51.2%)               | 61 (58.7%)              | 78 (57.4%)      |
| **Body Mass Index**           | 26.9 ± 6.2              | 28.2 ± 7.4               | 27.7 ± 6.5              | 25.0 ± 6.5      |
| **Diagnosis**                 |                         |                          |                         |                 |
| Relapsing-Remitting MS        | 480 (76.7%)             | 51 (40.2%)               | 24 (23.1%)              | 17 (12.4%)      |
| Secondary Progressive MS      | 41 (6.6%)               | 44 (34.7%)               | 44 (42.3%)              | 84 (61.3%)      |
| Primary Progressive MS        | 39 (6.2%)               | 25 (19.7%)               | 29 (27.9%)              | 26 (19.0%)      |
| NMOSD                         | 53 (8.5%)               | 6 (4.7%)                 | 7 (6.7%)                | 9 (6.6%)        |
| Other                         | 13 (2.1%)               | 1 (0.8%)                 | 0 (0.0%)                | 1 (0.7%)        |
| **Disease Duration**          | 6.7 ± 6.9               | 9.7 ± 8.2                | 11.5 ± 9.5              | 13.6 ± 9.9      |
| **Last DMT Used**             |                         |                          |                         |                 |
| Azathioprine                  | 8 (1.3%)                | 1 (0.0%)                 | 3 (2.9%)                | 2 (1.5%)        |
| Dimethyl fumarate             | 103 (16.5%)             | 16 (12.6%)               | 21 (20.2%)              | 12 (8.8%)       |
| Fingolimod                    | 92 (14.7%)              | 29 (22.8%)               | 18 (17.3%)              | 16 (11.7%)      |
| Glatiramer Acetate            | 63 (10.1%)              | 11 (8.7%)                | 5 (4.8%)                | 21 (15.3%)      |
| Interferon                    | 31 (5.0%)               | 11 (8.7%)                | 11 (10.6%)              | 13 (9.5%)       |
| Mycophenolate mofetil         | 5 (0.8%)                | 0 (0.0%)                 | 2 (1.9%)                | 3 (2.2%)        |
| Natalizumab                   | 161 (58.1%)             | 35 (12.6%)               | 31 (11.2%)              | 50 (18.1%)      |
| None                          | 130 (20.8%)             | 15 (11.8%)               | 6 (5.8%)                | 11 (8.0%)       |
| Other/Missing                 | 27 (4.3%)               | 6 (4.7%)                 | 5 (4.8%)                | 6 (4.4%)        |
| Teriflunomide                  | 6 (1.0%)                | 4 (3.2%)                 | 2 (1.9%)                | 3 (2.2%)        |
| **Time Since Last DMT (Months)** | 6.2 ± 16.0            | 8.2 ± 18.1               | 5.2 ± 9.0               | 12.8 ± 35.0     |

RMMSC: Rocky Mountain Multiple Sclerosis Clinic; NYUMSCC: New York University Multiple Sclerosis Care Center; N: number; SD: standard deviation; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; DMT: disease modifying therapy.
Table S13. Percentage of patients who experienced a serious safety event while on rituximab/ocrelizumab by disability at baseline.

| Infections resulting in: | Total N (%) | No Device N= 626 N (%) | Unilateral Support N=127 N (%) | Bilateral Support N=104 N (%) | Wheelchair-Bound N=137 N (%) | p-value<sup>a</sup> |
|--------------------------|-------------|------------------------|--------------------------------|-------------------------------|------------------------------|-------------------|
| **Hospitalization**      | 79 (6.5%)*  | 17 (2.7%)*             | 10 (7.1%)*                     | 13 (9.6%)*                    | 39 (21.2%)*                 | <0.001 |
| **IV antibiotics (without hospitalization)** | 6 (0.6%)    | 2 (0.3%)               | 0 (0.0%)                       | 2 (1.9%)                      | 2 (1.5%)                    | 0.078 |
| **Extended dosing antibiotics** | 15 (1.5%)  | 5 (0.8%)               | 2 (1.6%)                       | 2 (1.9%)                      | 6 (4.4%)                    | 0.016 |
| **Infusion reaction requiring hospitalization** | 0 (0.0%)    | 0 (0.0%)               | 0 (0.0%)                       | 0 (0.0%)                      | 0 (0.0%)                    | - |
| **Malignant Cancer**     | 9 (0.9%)    | 4 (0.6%)               | 0 (0.0%)                       | 1 (1.0%)                      | 4 (2.9%)                    | 0.066 |
| **New autoimmune disease diagnosis** | 6 (0.6%)    | 5 (0.8%)               | 0 (0.0%)                       | 0 (0.0%)                      | 1 (0.7%)                    | 0.916 |
| **Thromboembolic event (Non-superficial)** | 8 (0.8%)    | 0 (0.0%)               | 3 (2.4%)                       | 1 (1.0%)                      | 4 (2.9%)                    | 0.003 |
| **Lymphopenia**          |             |                        |                                |                               |                              |                   |
| <500 cells/mm³           | 48 (5.1%)   | 23 (4.0%)              | 10 (8.2%)                      | 5 (5.0%)                      | 10 (7.9%)                   | 0.098 |
| <200 cells/mm³           | 2 (0.2%)    | 0 (0.0%)               | 2 (1.6%)                       | 0 (0.0%)                      | 0 (0.0%)                    | 0.029 |
| **Neutropenia**          |             |                        |                                |                               |                              |                   |
| <1000 cells/mm³          | 14 (1.5%)   | 9 (1.6%)               | 2 (1.6%)                       | 2 (2.0%)                      | 1 (0.8%)                    | 0.888 |
| <500 cells/mm³           | 11 (1.2%)   | 7 (1.2%)               | 2 (1.6%)                       | 1 (1.0%)                      | 1 (0.8%)                    | 0.916 |
| **Low IgG Values**       |             |                        |                                |                               |                              |                   |
| <500 mg/dL               | 38 (5.2%)   | 18 (3.9%)              | 7 (7.5%)                       | 7 (8.1%)                      | 6 (4.4%)                    | 0.175 |
| <300 mg/dL               | 8 (1.1%)    | 5 (1.1%)               | 1 (1.1%)                       | 1 (1.2%)                      | 1 (1.1%)                    | 1.000 |
| **Mortality**            | 14 (1.4%)   | 2 (0.3%)               | 0 (0.0%)                       | 3 (2.9%)                      | 9 (6.6%)                    | <0.001 |

Bold p-values indicate p>0.05 and are considered statistically significant. N: number of events occurred; %: percent of patients who experienced event.

* Sixty-five patients (17 no device; 9 unilateral support; 10 bilateral support; 29 wheelchair-bound) were hospitalized a total of 79 times (17 no device; 10 unilateral support; 13 bilateral support; 39 wheelchair-bound). Nine patients (0 no device; 1 unilateral support; 2 bilateral support; 6 wheelchair-bound) were hospitalized multiple times due to infections.

<sup>a</sup>Comparing all disability levels; Significance indicates outcomes are dependent on disability level.
**Subgroup Analysis- By Immunosuppression/Chemotherapy History**

**Table S14.** Percentage of patients who experienced a serious safety event on rituximab/ocrelizumab by immunosuppression/chemotherapy history.

| Infections resulting in:                          | Total N (%) | Immunosuppression/Chemotherapy History^ | p-value* |
|--------------------------------------------------|-------------|-----------------------------------------|----------|
|                                                  | N= 841      | N= 106                                  | N= 26    |           |
| **No history**                                   | 52 (5.6%)   | 25 (14.8%)                              | 2 (7.1%) | 0.001    |
| **Prior treatment**                              | 6 (0.6%)    | 2 (1.9%)                                | 0 (0.0%) | 0.278    |
| **Current treatment**                            | 11 (1.3%)   | 4 (3.7%)                                | 0 (0.0%) | 0.135    |
| **Infections resulting in:**                     |             |                                         |          |
| Hospitalization                                  | 52 (5.6%)   |                                         |          |
| IV antibiotics (without hospitalization)         | 0 (0.0%)    |                                         |          |
| Extended dosing antibiotics                      | 0 (0.0%)    |                                         |          |
| Infusion reaction requiring hospitalization       | 0 (0.0%)    |                                         |          |
| Malignant Cancer                                 | 9 (1.1%)    |                                         |          |
| New autoimmune disease diagnosis                 | 6 (0.6%)    |                                         |          |
| **Thromboembolic event (Non-superficial)**       | 4 (0.5%)    |                                         |          |
| Lymphopenia                                       | 48 (5.1%)   |                                         |          |
| <500 cells/mm³                                    | 31 (3.9%)   |                                         |          |
| <200 cells/mm³                                    | 0 (0.0%)    |                                         |          |
| <500 cells/mm³                                    | 1 (1.0%)    |                                         |          |
| Neutropenia                                       | 4 (0.5%)    |                                         |          |
| <1000 cells/mm³                                   | 11 (1.5%)   |                                         |          |
| <500 cells/mm³                                    | 8 (1.0%)    |                                         |          |
| Low IgG Values                                    | 38 (5.2%)   |                                         |          |
| <500 mg/dL                                        | 26 (4.1%)   |                                         |          |
| <300 mg/dL                                        | 1 (0.16%)   |                                         |          |
| Mortality                                         | 13 (1.5%)   |                                         |          |
| <500 mg/dL                                        | 1 (0.9%)    |                                         |          |

Bold p-values indicate p>0.05 and are considered statistically significant. N: number of events occurred; %: percent of patients who experienced event.

^Excluding MS therapies of natalizumab, dimethyl fumarate and fingolimod.

* Sixty-five patients (47 no history; 16 prior treatment; 2 current treatment) were hospitalized a total of 79 times (47 no history; 25 prior treatment; 2 current treatment). Nine patients (4 no history; 5 prior treatment; 0 current treatment) were hospitalized multiple times due to infections.

* Comparing no, prior and current treatment; Significance indicates outcomes are dependent on immunosuppression/chemotherapy History.