*Supplementary Table 1. Number (%) of patients with most frequent (at least 2% in any group) AEs regardless of study drug relationship during Weeks 1 to 16 (safety population)*

| Preferred term | 1-step titration N=107 n (%) | 3-step titration N=108 n (%) |
| --- | --- | --- |
| Patients with an AE | 73 (68.2) | 73 (67.6) |
| Application site pruritus | 20 (18.7) | 20 (18.5) |
| Application site erythema | 16 (15.0) | 14 (13.0) |
| Dermatitis contact | 12 (11.2) | 12 (11.1) |
| Nasopharyngitis | 8 (7.5) | 9 (8.3) |
| Vomiting | 5 (4.7) | 2 (1.9) |
| Decreased appetite | 5 (4.7) | 6 (5.6) |
| Nausea | 4 (3.7) | 4 (3.7) |
| Weight decreased | 4 (3.7) | 2 (1.9) |
| Restlessness | 4 (3.7) | 1 (0.9) |
| Constipation | 3 (2.8) | 2 (1.9) |
| Application site dermatitis | 3 (2.8) | 3 (2.8) |
| Application site rash | 3 (2.8) | 5 (4.6) |
| Eczema | 2 (1.9) | 3 (2.8) |
| Hypertension | 2 (1.9) | 4 (3.7) |

*Supplementary Table 2. ADAS-J cog change from baseline (FAS-LOCF)*

|  | 1-Step titration N = 104 | | 3-Step titration N = 105 | | 1-Step titration vs  3-Step titration | |
| --- | --- | --- | --- | --- | --- | --- |
| n | Mean (SD) | n | Mean (SD) | DLSM | 95% CI |
| Week 8 |  |  |  |  |  |  |
| Baseline | 99 | 23.7 (8.53) | 100 | 23.7 (9.96) |  |  |
| Post baseline | 99 | 22.4 (8.38) | 100 | 22.9 (10.13) |  |  |
| Change | 99 | −1.3 (3.94) | 100 | −0.9 (4.49) | −0.4 | (−1.6, 0.8) |
| Week 16 |  |  |  |  |  |  |
| Baseline | 100 | 23.7 (8.48) | 100 | 23.7 (9.96) |  |  |
| Post baseline | 100 | 22.1 (8.54) | 100 | 22.5 (10.06) |  |  |
| Change | 100 | −1.6 (5.01) | 100 | −1.2 (5.48) | −0.3 | (−1.7, 1.1) |
| Week 24 |  |  |  |  |  |  |
| Baseline | 100 | 23.7 (8.48) | 100 | 23.7 (9.96) |  |  |
| Post baseline | 100 | 22.1 (8.91) | 100 | 22.0 (9.88) |  |  |
| Change | 100 | −1.6 (4.66) | 100 | −1.8 (5.58) | 0.2 | (−1.2, 1.6) |

- 'n' is the number of patients with an assessment at baseline and the corresponding visit.

- Difference of least square means (DLSM) and 95% confidence interval (CI), are based on ANCOVA model including titration group as a factor and baseline ADAS-J cog score as a covariate.

- A negative change indicates an improvement from baseline. A negative difference (DLSM) indicates greater improvement in 1-Step titration as compared to 3-Step titration.

*Supplementary Table 3. MMSE change from baseline (FAS-LOCF)*

|  | 1-Step titration N = 104 | | 3-Step titration N = 105 | | 1-Step titration vs  3-Step titration | |
| --- | --- | --- | --- | --- | --- | --- |
| n | Mean (SD) | n | Mean (SD) | DLSM | 95% CI |
| Week 24 |  |  |  |  |  |  |
| Baseline | 94 | 17.3 (2.44) | 88 | 16.9 (2.91) |  |  |
| Post baseline | 94 | 17.9 (4.00) | 88 | 17.4 (4.38) |  |  |
| Change | 94 | 0.6 (2.91) | 88 | 0.5 (3.15) | 0.1 | (−0.8, 1.0) |

- 'n' is the number of patients with an assessment at baseline and the corresponding visit.

- Difference of least square means (DLSM) and 95% confidence interval (CI), are based on ANCOVA model including titration group as a factor and baseline MMSE score as a covariate.

- A positive change indicates an improvement from baseline. A positive difference (DLSM) indicates greater improvement in 1-Step titration as compared to 3-Step titration.

*Supplementary Table 4. Percentage of patients (and 95% CI) with no worsening in J-CGIC (FAS-LOCF)*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 1-Step titration N = 104 | | | 3-Step titration N = 105 | | | | 1-Step titration vs  3-Step titration | |
|  | n | (%) | 95% CI | | n | (%) | 95% CI | Difference | 95% CI |
| Week 4 | 97 | 93.3 | (88.0, 98.6) | | 98 | 93.3 | (88.1, 98.6) | −0.1 | (−7.8, 7.7) |
| Week 8 | 94 | 90.4 | (84.2, 96.5) | | 91 | 86.7 | (79.7, 93.6) | 3.7 | (−5.9, 13.3) |
| Week 12 | 92 | 88.5 | (81.8, 95.1) | | 94 | 89.5 | (83.2, 95.9) | −1.1 | (−10.5, 8.4) |
| Week 16 | 92 | 88.5 | (81.8, 95.1) | | 88 | 83.8 | (76.3, 91.3) | 4.7 | (−5.7, 15.0) |
| Week 20 | 92 | 88.5 | (81.8, 95.1) | | 89 | 84.8 | (77.4, 92.1) | 3.7 | (−6.5, 13.9) |
| Week 24 | 94 | 90.4 | (84.2, 96.5) | | 86 | 81.9 | (74.1, 89.7) | 8.5 | (−1.8, 18.7) |

- 'n (%)' refers to the number (percent) of patients with no change or improvement in J-CGIC total score at the corresponding time point.

- 95% confidence interval (CI) is based on the normal approximation.

*Supplementary Table 5. Percentage of patients (and 95% CI) with improvement in J-CGIC (FAS-LOCF)*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 1-Step titration N = 104 | | | | 3-Step titration N = 105 | | | 1-Step titration vs  3-Step titration | |
|  | n | (%) | | 95% CI | n | (%) | 95% CI | Difference | 95% CI |
| Week 4 | 22 | 21.2 | (12.8, 29.5) | | 23 | 21.9 | (13.5, 30.3) | −0.8 | (−12.9, 11.4) |
| Week 8 | 35 | 33.7 | (24.1, 43.2) | | 26 | 24.8 | (16.0, 33.5) | 8.9 | (−4.3, 22.1) |
| Week 12 | 37 | 35.6 | (25.9, 45.3) | | 33 | 31.4 | (22.1, 40.8) | 4.1 | (−9.6, 17.9) |
| Week 16 | 35 | 33.7 | (24.1, 43.2) | | 31 | 29.5 | (20.3, 38.7) | 4.1 | (−9.4, 17.7) |
| Week 20 | 32 | 30.8 | (21.4, 40.1) | | 32 | 30.5 | (21.2, 39.8) | 0.3 | (−13.2, 13.7) |
| Week 24 | 39 | 37.5 | (27.7, 47.3) | | 38 | 36.2 | (26.5, 45.9) | 1.3 | (−12.7, 15.3) |

- 'n (%)' refers to the number (percent) of patients with improvement in J-CGIC total score at the corresponding time point.

- 95% confidence interval (CI) is based on the normal approximation.