Supplemental Table A. Adverse events by MedDRA system organ classification by study phase.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Placebo-controlled Phase  (0-6 months) | | Delay-start Phase  (6-12 months) | | Both Phases  (0-12 months) | |
| System Organ Classification | Early starters  N=62 | Delayed starters  N=63 | Early starters  N=59 | Delayed starters  N=60 | Early starters  N=62 | Delayed starters  N=63 |
| Blood and lymphatic system disorders | 2 | 0 | 0 | 1 | 2 | 1 |
| Cardiac disorders | 0 | 1 | 0 | 2 | 0 | 3 |
| Ear and labyrinth disorders | 0 | 1 | 0 | 0 | 0 | 1 |
| Eye disorders | 0 | 1 | 0 | 0 | 0 | 1 |
| Gastrointestinal disorders | 11 | 5 | 8 | 5 | 19 | 10 |
| General disorders and administration site conditions | 3 | 6 | 3 | 1 | 6 | 7 |
| Hepatobiliary disorders | 1 | 0 | 0 | 0 | 1 | 0 |
| Immune system disorders | 0 | 0 | 1 | 0 | 1 | 0 |
| Infections and infestations | 14 | 13 | 15 | 8 | 29 | 21 |
| Injury, poisoning and procedural complications | 12 | 15 | 9 | 11 | 21 | 26 |
| Investigations | 3 | 3 | 3 | 3 | 6 | 6 |
| Metabolism and nutrition disorders | 3 | 1 | 0 | 0 | 3 | 1 |
| Musculoskeletal and connective tissue disorders | 4 | 3 | 0 | 3 | 4 | 6 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0 | 1 | 0 | 0 | 0 | 1 |
| Nervous system disorders | 11 | 3 | 1 | 2 | 12 | 5 |
| Product issues | 1 | 0 | 0 | 0 | 1 | 0 |
| Psychiatric disorders | 3 | 3 | 1 | 3 | 4 | 6 |
| Renal and urinary disorders | 3 | 1 | 0 | 0 | 3 | 1 |
| Reproductive system and breast disorders | 0 | 0 | 2 | 0 | 2 | 0 |
| Respiratory, thoracic and mediastinal disorders | 5 | 6 | 5 | 2 | 10 | 8 |
| Skin and subcutaneous tissue disorders | 0 | 1 | 5 | 1 | 5 | 2 |
| Surgical and medical procedures | 0 | 0 | 0 | 1 | 0 | 1 |
| Vascular disorders | 3 | 3 | 3 | 3 | 6 | 6 |
| Total | 79 | 67 | 56 | 46 | 135 | 113 |

Supplemental Table B. Sensitivity analysis of mean difference and 95% confidence interval of improvement from baseline in ADAS-Cog scores between early and delayed starters at months 3, 6, 9 and 12 using the intention-to-treat (ITT) population, per-protocol population (PP), without last observation carried forward method (w/o LOCF), and after adjustment for potential confounders.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ITT (LOCF) | PP | ITT (w/o LOCF) | ITT adjusted\* |
| Month 3 | -0.59 (-2.60, 1.41) | -1.45 (-4.16, 1.27) | -0.61 (-2.67, 1.45) | -0.72 (-2.67, 1.23) |
| Month 6 | -0.99 (-3.28, 1.29) | -1.89 (-4.81, 1.03) | -1.00 (-3.31, 1.31) | -1.09 (-3.33, 1.15) |
| Month 9 | -3.36 (-5.64, -1.09) | -3.66 (-6.42, -0.89) | -3.01 (-5.29, -0.73) | -3.22 (-5.50, -0.94) |
| Month 12 | -2.35 (-5.45, 0.74) | -4.75 (-8.92, -0.59) | -3.06 (-6.61, 0.48) | -2.07 (-4.96, 0.82) |
| *\*adjusted for age, sex, educational level, baseline ADAS-Cog score, baseline MMSE score, and standard AD treatment used* | | | | |

Supplemental Table C. Change from baseline scores (mean ± SD) on Alzheimer’s Disease Cooperative Study - Activities of Daily Living Scale (ADCS-ADL), Neuropsychiatric Inventory (NPI), and Mini–Mental State Examination (MMSE) over time in the ITT population.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Early starters  (N = 62) | Delayed starters  (N = 63) | Mean difference  (95 CI) |
| ADCS-ADL |  |  |  |
| M3 | -1.7 (6.75) | -1.0 (5.61) | -0.74 (-2.95, 1.48) |
| M6 | -3.2 (8.18) | -2.7 (7.29) | -0.52 (-3.32, 2.28) |
| M9 | -3.7 (9.82) | -4.5 (8.47) | 0.78 (-2.56, 4.13) |
| M12 | -4.6 (9.28) | -6.1 (9.46) | 1.54 (-1.88, 4.95) |
| NPI |  |  |  |
| M3 | -0.2 (7.67) | 1.0 (10.38) | -1.13 (-4.39, 2.12) |
| M6 | 2.7 (12.48) | 0.5 (10.51) | 2.18 (-1.99, 6.35) |
| M9 | 0.9 (13.34) | 4.1 (13.18) | -3.20 (-8.04, 1.63) |
| M12 | 3.0 (11.64) | 3.6 (13.13) | -0.60 (-5.12, 3.92) |
| MMSE |  |  |  |
| M3 | 0.1 (2.37) | -0.0 (2.79) | 0.15 (-0.78, 1.07) |
| M6 | 0.1 (2.66) | -0.5 (3.02) | 0.57 (-0.46, 1.60) |
| M9 | 0.6 (3.24) | -0.1 (2.98) | 0.70 (-0.43, 1.84) |
| M12 | -0.4 (3.12) | -1.2 (4.02) | 0.81 (-0.50, 2.12) |