Table S1. Baseline values and changes of each efficacy measure at weeks 1, 2, 3, 4, and 6 for patients with schizophrenia receiving polypharmacy (N = 138) vs. monotherapy (N = 132 )

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline score |  |  Score change at Week 1 |  | Score change at Week 2 |  | Score change at Week 3 |  | Score change at Week 4 |  | Score change at Week 6 |
| Measure | Mean (SD) | p a |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |
| CGI-ScPolypharmacy  Monotherapy | 5.4 (0.8)5.5 (1.0) | 0.47 |  | -0.5 (0.6)-0.5 (0.7) | 0.65 |  | -0.9 (0.9)-0.9 (0.9) | 0.61 |  | -1.1 (1.0)-1.1 (1.0) | 0.84 |  | -1.3 (1.0)-1.3 (1.1) | 0.55 |  | -1.4 (1.1)-1. 5 (1.1) | 0.86 |
| PANSSd-TotalPolypharmacy  Monotherapy | 88.2 (17.8)87.7 (18.9) | 0.80 |  | -7.2 (8.9)-7.8 (9.4) | 0.59 |  | -11. 7 (12.5)-12.2 (12.3) | 0.69 |  | -14.5 (14.4)-14.8 (14.0) | 0.79 |  | -16.5 (15.8)-17.0 (15.1) | 0.70 |  | -19.5 (17.6)-19.3 (17.3) | 0.93 |
| PANSS-PositivePolypharmacyMonotherapy | 23.9 (6.1)24.0 (6.0) | 0.92 |  | -2.6 (3.2)-2.7 (3.3) | 0.79 |  | -3.9 (4.5)-4.4 (4.2) | 0.38 |  | -4.9 (4.7)-5.4 (4.7) | 0.42 |  | -5.6 (5.2)-6.1 (5.0) | 0.45 |  | -6.6 (5.9)-6.8 (5.6) | 0.79 |
| PANSS-NegativePolypharmacy  Monotherapy | 19.9 (6.1)19.6 (6.0) | 0.66 |  | -1.1 (2.1)-1.2 (2.0) | 0.55 |  | -1.9 (3.1)-2.1 (2.8) | 0.52 |  | -2.5 (3.7)-2.4 (3.4) | 0.94 |  | -2. 9 (3.9)-2.7 (3.8) | 0.85 |  | -3.4 (4.2)-3.2 (4.4) | 0.78 |
| PANSS-General psychopathologyPolypharmacy  Monotherapy | 44.4 (8.5)44.1 (10.0) | 0.78 |  | -3.5 (4.7)-3.9 (5.4) | 0.55 |  | -5.9 (6.4)-5.7 (6.8) | 0.94 |  | -7.1 (7.4)-7.0 (7.5) | 0.99 |  | -8.0 (8.2)-8.2 (8.1) | 0.70 |  | -9.5 (9.0)-9.2 (9.0) | 0.84 |
| CDSS ePolypharmacy  Monotherapy | 2.0 (3.4)2.5 (4.0) | 0.34 |  | -0.9 (2.1)-1.0 (2.2) | 0.56 |  | -1.1 (2.5)-1.0 (2.7) | 0.13 |  | -1.3 (2.9)-1.1 (2.6) | 0.05 |  | -1.3 (2.9)-1.2 (2.9) | 0.10 |  | -1.4 (3.1)-1.3 (3.0) | 0.06 |
| GAF fPolypharmacy  Monotherapy | 32.8 (7.5)33.8 (7.8) | 0.29 |  | 5.2 (5.4)6.2 (6.5) | 0.18 |  | 9.0 (7.6)9.9 (8.1) | 0.34 |  | 12.1 (9.0)12.2 (9.3) | 0.85 |  | 14.5 (10.5)14.8 (10.6) | 0.80 |  | 17.3 (11.6)16.9 (12.6) | 0.85 |

aIndependent t-test; bp values were determined by analysis of covariance (ANCOVA), with sex, age, age at onset, and baseline value as covariate;

cCGI-S = Clinical Global Impression-Severity of Illness; dPANSS = Positive and Negative Syndrome Scale; eCDSS = Calgary Depression Scale for Schizophrenia; fGAF = Global Assessment of Functioning

Table S2. Baseline values and changes of AIM, SAS, BAS, body weight, BMI, pulse rate, systolic BP, and diastolic BP at weeks 1, 2, 3, 4, and 6 for patients with schizophrenia receiving

 polypharmacy (N = 138) vs. monotherapy (N = 132 ) (cont’s)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline score |  | Score changeat Week 1 |  | Score changeat Week 2 |  | Score changeat Week 3 |  | Score changeat Week 4 |  | Score changeat Week 6 |
| Measure | Mean (SD) | p a |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |
| AIMSc Polypharmacy  Monotherapy | 0.5 (2.0)0.4 (1.4) | 0.67 |  | 0.1 (0.8)-0.001 (0.5) | 0.30 |  | 0.01 (1.1)0.03 (1.0) | 0.96 |  | 0.03 (1.2)0.1 (1.1) | 0.94 |  | 0.1 (1.2) 0.1 (1.1) | 0.85 |  | 0.1 (1.2) -0.03 (1.3) | 0.42 |
| SASdPolypharmacy  Monotherapy | 1.4 (2.4)1.4 (2.1) | 0.86 |  | 0.3 (1.9)0.4 (1.9) | 0.66 |  | -0.1 (1.8)0.7 (2.8) | **0.01** |  | 0.03 (2.1) 0.9 (3.0) | **0.01** |  | 0.1 (1.8) 0.8 (2.9) | **0.01** |  | 0.1 (2.2) 0.7 (3.0) | 0.07 |
| BASePolypharmacy  Monotherapy | 0.8 (1.4)0.8 (1.3) | 0.95 |  | 0.1 (1.1) 0.1 (1.4) | 0.86 |  | 0.1 (1.4) 0.3 (1.7) | 0.25 |  | 0.1 (1.5) 0.2 (1.7) | 0.37 |  | 0.1 (1.7) 0.1 (1.6) | 0.94 |  | -0.04 (1.6) 0.03 (1.6) | 0.72 |
| Body weight (kg)Polypharmacy  Monotherapy | 67.7 (15.1)67.6 (14.8) | 0.96 |  | -0.1 (1.6)-0.1 (1.4) | 0.64 |  | 0.1 (2.1)0.2 (2.2) | 0.79 |  | 0.1 (2.4)0.1 (2.2) | 0.97 |  | 0.3 (2.7)0.1 (2.5) | 0.59 |  | 0.4 (3.0) 0.2 (2.7) | 0.59 |
| BMIf (kg/m2)Polypharmacy  Monotherapy | 25.0 (4.8)25.2 (5.2) | 0.72 |  | -0.05 (0.6)-0.02 (0.5) | 0.66 |  | 0.1 (0.8)0.1 (0.8) | 0.77 |  | 0.04 (0.9)0.04 (0.9) | 0.94 |  | 0.1 (1.0)0.1 (0.9) | 0.70 |  | 0.2 (1.1)0.1 (1.0) | 0.68 |
| Pulse rate (beat/min) Polypharmacy  Monotherapy | 84.1 (13.7)83.3 (13.3) | 0.64 |  | -1.6 (13.4) 0.2 (13.7) | 0.47 |  | -3.1 (14.8) -1.5 (13.7) | 0.47 |  | -3.5 (14.7)-2.6 (13.7) | 0.80 |  | -3.5 (15.1) -2.4 (14.1) | 0.68 |  | -4.6 (15.1)-3.3 (14.3) | 0.52 |
| Systolic BPg (mm Hg) Polypharmacy  Monotherapy | 113.4 (15.8)113.7 (17.3) | 0.87 |  | -1.2 (14.7)-0.7 (15.8) | 0.67 |  | -1.1 (16.7)-3.0 (15.9) | 0.29 |  | -2.3 (16.6)-2.6 (15.4) | 0.94 |  | -1.3 (17.4)-3.9 (14.2) | 0.14 |  | 0.1 (15.6)-2.5 (16.5) | 0.15 |
| Diastolic BP (mm Hg)Polypharmacy  Monotherapy | 75.9 (12.6)76.2 (11.5) | 0.82 |  | -1.9 (12.4) -1.6 (10.8) | 0.69 |  | -3.1 (13.8)-2.9 (12.2) | 0.77 |  | -2.7 (12.5)-2.0 (10.5) | 0.50 |  | -1.9 (13.0)-3.0 (11.1) | 0.45 |  | -1.5 (12.4)-0.6 (11.4) | 0.34 |

aIndependent t-test; bp values were determined by analysis of covariance (ANCOVA), with sex, age, age at onset, and baseline value as covariates

cAIMS = Abnormal Involuntary Movement Scale; dSAS = Simpson-Angus Rating Scale; eBAS = Barnes Akathisia Scale; fBMI = body mass index; gBP = blood pressure

Table S3. Baseline values and changes of safety measure and quality of life between week 0 and week 6 for patients treated with

polypharmacy vs. those treated with monotherapy

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Measure | Baseline value |  |  | Value change at week 6 |  |
| n | Mean (SD) | pa | n | Mean (SD) | pb |
| QTc c interval (ms)Polypharmacy  Monotherapy | 138130 | 408.9 (22.4)407.9 (25.3) | 0.75 |  | 9588 | -2.2 (22.9)0.6 (29.2) | 0.35 |
| Fasting glucose level (mg/dL)Polypharmacy  Monotherapy | 138132 | 82.6 (20.4)82.9 (19.0) | 0.90 |  | 9690 | 2.7 (19.7)1.6 (25.4) | 0.56 |
| ALT e (GPT) (U/L)Polypharmacy  Monotherapy | 138132 | 28.8 (18.4)29.6 (19.4) | 0.74 |  | 9489 | 3.4 (29.9)-0.8 (15.6) | 0.37 |
| AST f (GOT) (U/L)Polypharmacy  Monotherapy | 138132 | 25.5 (12.0)25.8 (11.8) | 0.87 |  | 9489 | 1.1 (20.9)-1.8 (11.5) | 0.30 |
| BUN g (mg/dL)Polypharmacy  Monotherapy | 138132 | 9.9 (3.1)10.5 (3.7) | 0.14 |  | 9489 | -0.5 (3.3)-0.6 (4.1) | 0.87 |
| Creatinine (mg/dL)Polypharmacy  Monotherapy | 138132 | 0.8 (0.2)0.9 (0.2) | 0.45 |  | 9489 | -0.01 (0.1)0.01 (0.2) | 0.37 |
| Cholesterol (mg/dL)Polypharmacy  Monotherapy | 134126 | 174.8 (38.9)174.3 (37.9) | 0.92 |  | 9383 | 6.2 (36.4)9.6 (41.9) | 0.94 |
| Triglycerides (mg/dL)Polypharmacy  Monotherapy | 134127 | 124.2 (58.6)129.1 (75.2) | 0.55 |  | 9084 | 27.4 (71.3)15.8 (69.9) | 0.29 |
| HDL h (mg/dL)Polypharmacy  Monotherapy | 132125 | 48.0 (18.5)49.1 (17.6) | 0.62 |  | 9382 | 1.0 (9.0)1.5 (9.3) | 0.62 |
| LDL i (mg/dL)Polypharmacy  Monotherapy | 132123 | 103.9 (33.9)104.4 (29.7) | 0.90 |  | 9380 | -1.3 (31.6)1.6 (27.8) | 0.62 |
| Prolactin (ng/ml)Polypharmacy  Monotherapy | 134128 | 35.4 (46.8)37.5 (45.0) | 0.71 |  | 9488 | 21.2 (56.1)36.5 (55.9) | 0.07 |
| PCS jPolypharmacy Monotherapy | 137132 | 51.1 (7.4)49.9 (6.8) | 0.18 |  | 9991 | 1.5 (6.1)1.6 (6.2) | 0.69 |
| MCS kPolypharmacy  Monotherapy | 137132 | 40.2 (11.0)39.4 (11.0) | 0.56 |  | 9991 | 2.6 (9.3)2.4 (9.1) | 0.59 |

aIndependent t-test; bp values were determined by analysis of covariance (ANCOVA), with sex, age, age at onset, and baseline value as covariates

cQTc interval = Bazett’s correction of QT interval; eALT (GPT) = alanine aminotransferase; f AST (GOT) = aspartate aminotransferase; gBUN = blood urea nitrogen; hHDL = high density lipoprotein; iLDL = low density lipoprotein; jPCS = physical component summary of SF-36; kMCS = mental component summary of SF-36

Table S4. Side effects (determined by individual item of UKU Scale) occurring in at least 10% of the patients in either group, N (%)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Polypharmacy (N = 138) |  | Monotherapy (N = 132) |  |  |
| Adverse event |  | N | % |  | N | % |  | *p* |
| At least one adverse event |  | 118 | 85.5 |  | 118 | 89.4 |  | 0.34 a  |
| Concentration difficulties |  | 18 | 13.0 |  | 16 | 12.1 |  | 0.82 a |
| Asthenia/increased fatiguability |  | 30 | 21.7 |  | 34 | 25.8 |  | 0.44 a |
| Sleepiness/sedation |  | 21 | 15.2 |  | 20 | 15.2 |  | 0.99 a |
| Failing memory |  | 20 | 14.5 |  | 22 | 16.7 |  | 0.62 a |
| Depression |  | 16 | 11.6 |  | 16 | 12.1 |  | 0.89 a |
| Tension /inner unrest |  | 28 | 20.3 |  | 26 | 19.7 |  | 0.90 a |
| Increased duration of sleep |  | 13 | 9.4 |  | 20 | 15.2 |  | 0.15 a |
| Reduced duration of sleep |  | 32 | 23.2 |  | 30 | 22.7 |  | 0.93 a |
| Increased dream activity |  | 17 | 12.3 |  | 26 | 19.7 |  | 0.10 a |
| Rigidity |  | 16 | 11.6 |  | 16 | 12.1 |  | 0.89 a |
| Hypokinesia /akinesia |  | 12 | 8.7 |  | 15 | 11.4 |  | 0.47 a |
| Tremor |  | 26 | 18.8 |  | 31 | 23.5 |  | 0.35 a |
| Akathisia |  | 26 | 18.8 |  | 20 | 15.2 |  | 0.42 a |
| Increased salivation |  | 23 | 16.7 |  | 24 | 18.2 |  | 0.74 a |
| Reduced salivation |  | 28 | 20.3 |  | 29 | 22.0 |  | 0.74 a |
| Constipation |  | 18 | 13.0 |  | 23 | 17.4 |  | 0.32 a |
| Polyuria/polydipsia |  | 21 | 15.2 |  | 24 | 18.2 |  | 0.51 a |
| Orthostatic dizziness |  | 11 | 8.0 |  | 17 | 12.9 |  | 0.19 a |
| Pruritus |  | 18 | 13.0 |  | 16 | 12.1 |  | 0.82 a |
| Weight gain |  | 44 | 31.9 |  | 39 | 29.5 |  | 0.68 a |
| Weight loss |  | 32 | 23.2 |  | 42 | 31.8 |  | 0.11 a |
| Headache |  | 15 | 10.9 |  | 16 | 12..1 |  | 0.75 a |

aPearson χ2 test