### Supplemental Table 1.

| **Key Inclusion criteria**                                                                 |
|---------------------------------------------------------------------------------------------|
| • Male or female outpatients 18 to 65 years of age, inclusive, at time of consent            |
| • Met DSM-IV-TR criteria for a principal diagnosis of bipolar I or II disorder (without psychotic features) |
| • A current major depressive episode $\geq$ 4 weeks and not exceeding 12 months             |
| • Fewer than 8 episodes of a mood disturbance (depression, mania, hypomania, or mixed state) in the previous 12 months |
| • Verified lifetime history of at least one bipolar manic or mixed episode (bipolar I disorder patients) or hypomanic or mixed episode (bipolar II disorder patients) |
| • Scores $\geq 20$ on the HAMD$_{17}$ and $\geq 2$ on Item 1 of the HAMD$_{24}$               |
| • Women of childbearing potential with a negative serum β-human chorionic gonadotropin pregnancy test |
| • Normal physical examination findings, clinical laboratory test results, and ECG results or abnormal results that were judged not clinically significant by the investigator |
| • Body mass index between 18 and 40, inclusive                                               |

| **Key Exclusion criteria**                                                                 |
|---------------------------------------------------------------------------------------------|
| • YMRS score $>$ 12                                                                         |
| • Principal DSM-IV-TR-based diagnosis of an axis I disorder other than bipolar disorder or any axis I disorder other than bipolar disorder that was the primary focus of treatment within 6 months |
| • History of meeting DSM-IV-TR criteria for cognitive disorder (eg, delirium, dementia, amnesia), psychotic disorder (eg, schizophrenia, schizoaffective disorder) or mental retardation |
| • DSM-IV-TR–based diagnosis of borderline or antisocial personality disorder or other axis II disorder of sufficient severity to interfere with study participation |
| • History of meeting DSM-IV-TR criteria for alcohol or substance abuse or dependence within the 6 months of the study |
| • Positive drug screen for any prohibited medication                                         |
| • Patients at imminent risk of injuring self or others or causing significant damage to property (investigator judged) |
| • Suicide risk (any of the following criteria: suicide attempt within the past year, significant risk based on the psychiatric interview and/or information collected in the Columbia–Suicide Severity Rating Scale [investigator judged]; score $\geq 5$ on item 10 of the MADRS) |
| • Pregnant, breastfeeding, plan to become pregnant/breastfeed during the study, not at least 2 years postmenopausal, surgically sterile, abstinent, or practicing a reliable method of contraception |
| • A concurrent medical condition that may have interfered with the conduct of the study, confounded the interpretation of the study results, or endangered the patient’s well-being |
| • Patients requiring concomitant treatment with any prohibited medication; psychotropic drugs were prohibited except for eszopiclone, zolpidem, zolpidem extended-release, or zaleplon for sleep; |
lorazepam for severe anxiety; or diphenhydramine, benztpine, or propranolol for EPS

- History of nonresponse to two or more adequate treatment trials (≥4 weeks at an adequate dose based on Package Insert recommendations) with fluoxetine + olanzapine combination, quetiapine, or a mood stabilizer (lithium, valproate, lamotrigine, carbamazepine, or oxycarbamazepine) in combination with an antidepressant used to treat the current depressive episode

- Use of any antipsychotic, antidepressant, anticonvulsant/mood stabilizer, anxiolytic, sedative/hypnotic medication, or investigational drug within 1 week or 5 half-lives; history of being treated with clozapine (within 5 years)

HAMD=Hamilton Depression Rating Scale (17- or 24-item version); MADRS=Montgomery-Åsberg Depression Rating Scale; YMRS=Young Mania Rating Scale.

**Supplemental Table 2.** Change from baseline to the end of the study in clinical laboratory and vital sign parameters in the safety population

| Serum chemistry                  | Number assessed | Placebo mean (SD) n=77 | Number assessed | 0.25-0.75 mg/d mean (SD) n=75 | Number assessed | 1.5-3.0 mg/d mean (SD) n=75 |
|----------------------------------|----------------|------------------------|----------------|-----------------------------|----------------|-----------------------------|
| Total cholesterol, mmol/L        | 70             | -0.107 (0.69)          | 64             | -0.042 (0.72)               | 65             | -0.124 (0.78)               |
| HDL cholesterol, mmol/L          | 70             | -0.038 (0.21)          | 64             | -0.014 (0.19)               | 65             | -0.020 (0.22)               |
| LDL cholesterol, mmol/L          | 70             | -0.085 (0.53)          | 64             | -0.061 (0.65)               | 65             | -0.226 (0.59)               |
| Triglycerides, mmol/L            | 70             | -0.114 (0.85)          | 64             | -0.022 (0.68)               | 65             | 0.200 (0.99)                |
| Fasting glucose, mmol/L          | 59             | 0.028 (0.64)           | 58             | -0.136 (0.74)               | 56             | 0.022 (0.71)                |
| ALT, U/L                         | 70             | 0.2 (8.9)              | 64             | 1.4 (11.2)                  | 65             | 2.8 (10.9)                  |
| AST, U/L                         | 70             | 0.3 (5.9)              | 64             | -0.1 (7.9)                  | 65             | 1.0 (7.8)                   |
| Alkaline phosphatase, U/L        | 70             | -2.5 (9.3)             | 64             | 0.2 (10.9)                  | 65             | 0.1 (9.8)                   |
| Creatine phosphokinase, U/L      | 70             | 27.40 (126.15)         | 64             | -1.20 (279.61)              | 65             | 75.72 (422.58)              |
| Prolactin, ng/mL                 | 70             | 0.39 (4.25)            | 64             | 2.36 (3.49)                 | 65             | 3.16 (4.95)                 |
| Total bilirubin, mmol/L          | 70             | -0.538 (4.69)          | 64             | -0.748 (4.29)               | 65             | -0.816 (2.79)               |

**Vital signs**

| Vital signs                      | Number assessed | Placebo mean (SD) | Number assessed | 0.25-0.75 mg/d mean (SD) | Number assessed | 1.5-3.0 mg/d mean (SD) |
|----------------------------------|-----------------|------------------|----------------|--------------------------|----------------|------------------------|
| Supine systolic blood pressure, mm Hg | 76               | 0.8 (12.3)       | 75             | -1.3 (10.8)              | 74             | 0.5 (10.2)              |
| Supine diastolic blood pressure, mm Hg | 76               | 0.9 (8.9)        | 75             | -0.1 (8.7)               | 74             | 0.1 (6.4)               |
| Supine pulse, bpm                 | 76               | 0.4 (10.7)       | 75             | 3.6 (11.3)               | 74             | 1.4 (11.6)              |
|                                | 76     | 0.30 (2.16) | 75      | 0.62 (2.76) | 74      | 1.42 (2.93) |
|--------------------------------|--------|-------------|---------|-------------|---------|-------------|
| Body weight change, kg         |        |             |         |             |         |             |
| Weight gain ≥7%                | 0/76   | 0.0%        | 4/75    | 5.3%        | 5/74    | 6.8%        |
| Body mass index, kg/m²         | 76     | 0.11 (0.74) | 75      | 0.21 (0.94) | 74      | 0.50 (1.05) |
| Orthostatic hypotension        | 16/76  | 21.1%       | 17/72   | 23.6%       | 7/73    | 9.6%        |

**Electrocardiogram parameters**

|                                | 76     | 3.2 (11.5)  | 75      | 3.7 (11.2)  | 74      | 5.4 (12.2)  |
|--------------------------------|--------|-------------|---------|-------------|---------|-------------|
| Ventricular heart rate, bpm    |        |             |         |             |         |             |
| QRS interval, msec             | 76     | 0.1 (6.2)   | 75      | -0.8 (6.7)  | 74      | 0.6 (7.0)   |
| PR interval, msec              | 76     | -1.0 (10.8) | 75      | 1.6 (11.6)  | 74      | 0.9 (12.7)  |
| QT interval, msec              | 76     | -5.8 (22.7) | 75      | -6.4 (25.7) | 74      | -12.2 (27.6)|
| QTcB interval, msec            | 76     | 3.1 (21.9)  | 75      | 3.9 (19.7)  | 74      | 3.4 (19.4)  |
| QTcF interval, msec            | 76     | -0.1 (15.8) | 75      | 0.4 (16.2)  | 74      | -2.1 (15.9) |

Data are mean (SD) except for body weight increase ≥7% and orthostatic hypotension (≥20 mm Hg reduction in systolic blood pressure or ≥10 mm Hg reduction in diastolic blood pressure while changing from a supine to standing position), which are reported as percentages. Baseline is defined as the last assessment before the start of the double-blind treatment phase. ALT=alanine aminotransferase; AST=aspartate aminotransferase, QTcB=QT interval corrected for heart rate using the Bazett formula; QTcF=QT interval corrected for heart rate using the Fridericia formula.