**Supplemental Material.**

**Lurasidone Improves Psychopathology and Cognition in Treatment Resistant Schizophrenia**

**Supplemental Table 1A – Reasons for Discontinuation Phase 1 and 2**

|  |  |
| --- | --- |
| **Phase 1 – Reasons for Discontinuation** | |
|  | **80 mg Open Label (N=101)** |
| Investigator Withdrew | 11 |
| Subject Withdrew – Other Reasons | 15 |
| Subject Withdrew – Lack of Efficacy | 2 |
| Subject Withdrew – Adverse Event | 2 |
| Symptoms Improved (3 at completion of Phase 1, 1 earlier in Phase 1) | 4 |

|  |  |  |
| --- | --- | --- |
| **Phase 2 – Reasons for Discontinuation** | | |
|  | **80 mg (N=34)** | **240 mg (N=33)** |
| Completed Study | 22 | 22 |
| Investigator Withdrew | 4 | 3 |
| Subject Withdrew – Adverse Event | 3 | 3 |
| Subject Withdrew – Other Reasons | 2 | 3 |
| Subject Withdrew – Lack of Efficacy | 3 | 1 |
| Death | 0 | 1 |

**Supplemental Table 1B – Adverse Events (AE)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Adverse Events** | **80 mg (n=34)** | | **240 mg (n=33)** | |
| Frequency | % Report AE | Frequency | % Report AE |
| **Nausea** | 8 | 23.5% | 9 | 30.3% |
| **Insomnia** | 6 | 17.6% | 4 | 12.1% |
| **Vomiting** | 4 | 11.8% | 2 | 6.1% |
| **Back pain** | 4 | 11.8% | 2 | 6.1% |
| **Headache** | 3 | 8.8% | 5 | 15.2% |
| **Suicidality** | 3 | 8.8% | 3 | 9.1% |
| **Dry mouth** | 3 | 8.8% | 1 | 3.0% |
| **Akathisia** | 2 | 5.9% | 3 | 9.1% |
| **Coughing** | 2 | 5.9% | 2 | 6.1% |
| **Emesis** | 2 | 5.9% | 1 | 3.0% |
| **Weight gain** | 2 | 5.9% | 0 | 0.0% |
| **Aggression** | 0 | 0.0% | 2 | 6.1% |
| **Hyponatremia** | 0 | 0.0% | 2 | 6.1% |

**The most common AEs were nausea and insomnia, not dose related**

**AEs leading to discontinuation: Increased psychosis, insomnia, emesis, akathisia, and leg cramps**

**Supplemental Table 1C – Extrapyramidal symptoms (EPS), Prolactin level, and Body Mass Index (BMI) at Phase 1 and 2**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | EPS( Mean ± SD) | | Prolactin Level ( Mean ± SD) | | BMI( Mean ± SD) |
| **80 mg group** | Simpson Angus Scale | Akathisia  Rating Scale | Male (N) | Female (N) |
| Phase 1 baseline | 9.5 ± 2.5 | 2.9 ± 4.8 | 31.5 ± 32.5 (14) | 17.6 ± 15.0 (18) | 30.4 ± 7.8 |
| Phase 2 baseline | 9.3 ± 2.0 | 1.3 ± 2.7 | 14.8± 16.0 (14) | 17.6 ± 16.6 (19) | 30.5 ± 7.8 |
| 6 week | 9.0 ± 1.6 | 2 ± 5.6 | 9.6 ± 6.8   (13) | 12.5 ± 14.1 (15) | 30.0 ± 7.9 |
| 12 week | 8.5 ± 0.6 | 1.1 ± 3.5 | 28.1 ± 30.7 (9) | 10.1 ± 5.7 (14) | 30.6 ± 8.3 |
| 24 week | 8.7 ± 1.0 | 0.6 ± 2.2 | 13.0 ± 11.4 (10) | 12.3 ± 9.6 (11) | 30.9 ± 8.6 |
| **240 mg group** |  |  |  |  |  |
| Phase 1 baseline | 9.3 ± 3.5 | 1.5 ± 3.8 | 35.7 ± 78.5 (15) | 18.0 ± 16.6 (16) | 32.6 ± 7.8 |
| Phase 2 baseline | 9.7 ± 3.0 | 1.8 ± 3.5 | 25.0 ± 32.7 (15) | 11.6 ± 13.9 (16) | 32.4 ± 7.8 |
| 6 week | 9.6 ± 2.6 | 1.0 ± 3.5 | 32.8 ± 36.4 (14) | 21.7 ± 32.0 (11) | 32.9 ± 8.6 |
| 12 week | 9.4 ± 2.1 | 1.5 ± 3.5 | 34.5 ± 34.3 (13) | 11.6 ± 8.0 (9) | 32.9 ± 9.2 |
| 24 week | 9.8 ± 2.8 | 1.4 ± 4.2 | 32.3 ± 44.4 (14) | 14.4 ± 9.9 (8) | 33.6 ± 8.1 |

No significant group difference in EPS, prolactin levels (male and female analysed separately), and BMI at any time points.

**Supplemental Table 2 – PANSS-Total and Subscales in Phase 2**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Assessment | Time  Point | LS-Mean (SE) | | LS-Mean | | Source | | |
| 80 mg | 240 mg | Diff (SE) | P | Dose group  F | Time  F | Tx group by Time F |
| PANSS Total | Baseline | 81.8(1.3) | 82.4 (1.3) | 0.6 (1.8) | 0.74 | 0.38 | 50.59\*\*\*\*(ES=1.17) | 0.79 |
|  | 6 Week | 73.0(1.3) | 76.1 (1.4) | 3.0 (2.0) | 0.13 |  |  |  |
|  | 12 week | 69.4(1.5) | 69.6 (1.5) | 0.2 (2.1) | 0.91 |  |  |  |
|  | 24 week | 69.1(1.5) | 68.3(1.5) | -0.7 (2.1) | 0.73 |  |  |  |
| PANSS Positive (Items P1-P7) | Baseline | 21.9 (0.5) | 22.3 (0.5) | 0.4 ( 0.7 ) | 0.60 | 0.01 | 27.33\*\*\*\*(ES=0.86) | 1.34 |
|  | 6 Week | 20.0 (0.5) | 20.5 (0.5) | 0.6 (0.7 ) | 0.44 |  |  |  |
|  | 12 week | 19.2 (0.5) | 19.1 (0.6) | -0.08 ( 0.8) | 0.91 |  |  |  |
|  | 24 week | 19.0 (0.6) | 17.8 (0.6) | -1.1 (0.8) | 0.16 |  |  |  |
| PANSS Negative  (Items N1-N7) | Baseline | 18.1 (0.4) | 18.3 (0.4) | 0.2 (0.6) | 0.78 | 0.12 | 19.78\*\*\*\*(ES=0.74) | 0.19 |
|  | 6 Week | 16.6 (0.4) | 16.4 (0.5) | -0.1 (0.6) | 0.82 |  |  |  |
|  | 12 week | 15.6 (0.5) | 15.4 (0.5) | -0.1 (0.7) | 0.85 |  |  |  |
|  | 24 week | 15.9 (0.5) | 15.4 (0.5) | -0.5 (0.7) | 0.51 |  |  |  |
| PANSS General  (Items G1-G16) | Baseline | 41.9 (0.8) | 41.8 (0.8) | -0.04 (1.1) | 0.97 | 1.51 | 41.43\*\*\*\*(ES=1.06) | 1.17 |
|  | 6 Week | 36.6 (0.8) | 39.1 (0.8) | 2.5 (1.2) | 0.03\* |  |  |  |
|  | 12 week | 34.7 (0.9) | 35.0 (0.9) | 0.4 (1.2) | 0.77 |  |  |  |
|  | 24 week | 34.3 (0.9) | 35.1(0.9) | 0.8 (1.3) | 0.55 |  |  |  |
| PANSS Cognition  (Items P2, N5, N7, G7, G10, G11, G12, G14, G15) | Baseline | 27.8 (0.5) | 28.1 (0.5) | 0.4 (0.7) | 0.63 | 0.71 | 42.21\*\*\*\*(ES=1.07) | 0.10 |
|  | 6 Week | 24.5 (0.5) | 25.2 (0.6) | 0.7 (0.8) | 0.38 |  |  |  |
|  | 12 week | 23.3 (0.6) | 23.9 (0.6) | 0.6 (0.8) | 0.51 |  |  |  |
|  | 24 week | 22.9 (0.6) | 23.1 (0.6) | 0.2 (0.9) | 0.84 |  |  |  |

\*p ≤ .05, \*\*\*\*p ≤ .0001

**Supplemental Table 3 – Neurocognitive Battery in Phase 2**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Assessment | Time  Point | LS-Mean (SE) | | LS-Mean | | Source | | |
| 80 mg | 240 mg | Diff (SE) | P | Dose group  F | T Time  F F | Tx group by Time F |
| REY Trial1 | Baseline | 5.4 (0.2) | 5.4 (0.2) | -0.01 (0.3) | 0.99 | 0.08 | 1.99 | 1.80 |
|  | 6 Week | 5.5 (0.2) | 5.9 (0.3) | 0.4 (0.4) | 0.31 |  |  |  |
|  | 24 week | 6.2 (0.3) | 5.6 (0.3) | -0.6 (0.4) | 0.15 |  |  |  |
| REY Trial5 | Baseline | 9.6 (0.3) | 9.6 (0.3) | -0.02 (0.4) | 0.96 | 0.00 | 0.71 | 0.11 |
|  | 6 Week | 9.3 (0.3) | 9.2 (0.43) | -0.1 (0.4) | 0.74 |  |  |  |
|  | 24 week | 9.4 (0.3) | 9.6 (0.4) | 0.1 (0.5) | 0.77 |  |  |  |
| REY Total Trial1\_5 | Baseline | 40.1 (1.0) | 40.0 (0.1) | -0.05 (1.4) | 0.97 | 0.24 | 0.09 | 0.19 |
|  | 6 Week | 39.7 (1.0) | 40.9 (1.1) | 1.1 (1.5) | 0.46 |  |  |  |
|  | 24 week | 40.3 (1.2) | 40.7 (1.2) | 0.4 (1.7) | 0.83 |  |  |  |
| REY Immediate Recall | Baseline | 7.6 (0.3) | 7.6 (0.3) | -0.07 (0.4) | 0.85 | 0.45 | 0.81 | 0.48 |
|  | 6 Week | 7.9 (0.3) | 8.0 (0.3) | 0.1 (0.4) | 0.79 |  |  |  |
|  | 24 week | 7.6 (0.3) | 8.1 (0.3) | 0.5 (0.5) | 0.29 |  |  |  |
| REY Delayed Recall | Baseline | 7.3 (0.3) | 7.2 (0.3) | -0.1 (0.4) | 0.83 | 4.63\*(ES=0.55) | 0.20 | 2.12 |
|  | 6 Week | 6.9 (0.3) | 7.9 (0.3) | 1.0 (0.4) | 0.02\* |  |  |  |
|  | 24 week | 7.0 (0.3) | 7.9 (0.3) | 0.8 (0.5) | 0.08 |  |  |  |
| WISC Maze | Baseline | 19.1 (0.6) | 19.1 (0.6) | -0.02 (0.9) | 1.00 | 6.35\*(ES=0.65) | 1.46 | 3.34\*(ES=0.38) |
|  | 6 Week | 18.3 (0.6) | 21.5 (0.7) | 3.2 (1.0) | 0.01\*\* |  |  |  |
|  | 24 week | 19.5 (0.7) | 20.8 (0.7) | 1.3 (1.1) | 0.24 |  |  |  |
| WCST Categories | Baseline | 2.8 (0.2) | 2.7 (0.2) | -0.02 (0.3) | 0.94 | 1.85 | 4.10\*(ES=0.43) | 0.52 |
|  | 6 Week | 2.9 (0.2) | 2.6 (0.2) | -0.3 (0.3) | 0.22 |  |  |  |
|  | 24 week | 3.4 (0.2) | 3.1 (0.2) | -0.3 (0.3) | 0.27 |  |  |  |
| WCST Percent Perseveration | Baseline | 25.1 (1.7) | 25.2 (1.8) | 0.07 (2.5) | 0.97 | 9.87\*\*(ES=0.81) | 1.52 | 3.48\*(ES=0.39) |
|  | 6 Week | 24.4 (1.9) | 31.7 (2.0) | 7.4 (2.7) | 0.01\*\* |  |  |  |
|  | 24 week | 21.2 (2.1) | 29.9 (2.1) | 8.7 (3.0) | 0.01\*\* |  |  |  |
| Control Word Association | Baseline | 32.7 (1.0) | 32.2 (1.0) | -0.5 (1.5) | 0.74 | 0.44 | 0.28 | 0.08 |
|  | 6 Week | 33.7 (1.1) | 32.5 (1.2) | -1.2 (1.6) | 0.46 |  |  |  |
|  | 24 week | 33.3 (1.3) | 33.0 (1.2) | -0.4 (1.8) | 0.82 |  |  |  |
| Category Generation | Baseline | 16.2 (0.5) | 16.0 (0.5) | -0.1 (0.8) | 0.86 | 0.02 | 0.118 | 0.04 |
|  | 6 Week | 16.0 (0.5) | 15.7 (0.6) | -0.2 (0.8) | 0.79 |  |  |  |
|  | 24 week | 16.1 (0.7) | 16.2 (0.6) | 0.1 (0.9) | 0.90 |  |  |  |
| Digit Symbol Test | Baseline | 38.8 (1.1) | 38.7 (1.1) | -0.1 (1.5) | 0.94 | 2.89 | 5.70\*\*(ES=0.49) | 1.64 |
|  | 6 Week | 42.4 (1.1) | 40.0 (1.2) | -2.7 (1.6) | 0.09 |  |  |  |
|  | 24 week | 43.4 (1.2) | 40.1 (1.2) | -3.3 (1.7) | 0.06 |  |  |  |
| ACT without  first 5 | Baseline | 24.8 (1.0) | 24.9 (1.0) | 0.04 (1.4) | 0.98 | 1.32 | 0.07 | 0.63 |
|  | 6 Week | 25.7 (1.1) | 24.6 (1.1) | -1.1 (1.5) | 0.47 |  |  |  |
|  | 24 week | 26.3 (1.2) | 24.0 (1.2) | -2.3 (1.7) | 0.18 |  |  |  |
| ACT with  first 5 | Baseline | 39.3 (1.1) | 39.3 (1.1) | 0.01 (1.6) | 1.00 | 0.22 | 0.21 | 0.74 |
|  | 6 Week | 39.5 (1.2) | 40.0 (1.3) | 0.5 (1.7) | 0.77 |  |  |  |
|  | 24 week | 41.1 (1.3) | 38.9 (1.3) | -2.2 (1.9) | 0.26 |  |  |  |

\*p ≤ .05, \*\*p ≤ .01

**Supplemental Table 4: Clinical Global Impression (CGI)-Severity and Personal and Social Performance (PSP) scales in**

**Phase 2**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Assessment | Time  Point | LS-Mean (SE) | | LS-Mean | | Source | | |
| 240 mg | 80 mg | Diff (SE) | P | Dose group  F | Time  F | Dose group by Time F |
| CGI-Severity | Baseline | 4.6 (0.1) | 4.5 (0.1) | 0.01 (0.1) | 0.97 | 1.17 | 14.70\*\*\*\*(ES=0.65) | 0.36 |
|  | 6 Week | 4.2 (0.1) | 4.3 (0.1) | -0.1 (0.2) | 0.34 |  |  |  |
|  | 12 week | 3.9 (0.1) | 4.1 (0.1) | -0.2 (0.2) | 0.28 |  |  |  |
|  | 24 week | 3.9 (0.1) | 4.0 (0.1) | -0.1 (0.2) | 0.57 |  |  |  |
| PSP Total | Baseline | 46.1 (1.1) | 46.2 (1.1) | -0.1 (1.6) | 0.93 | 0.25 | 13.22\*\*\*\*(ES=0.60) | 0.19 |
|  | 6 Week | 47.2 (1.2) | 48.5 (1.1) | -1.3 (1.7) | 0.44 |  |  |  |
|  | 12 week | 50.6 (1.3) | 50.5 (1.3) | 0.01 (1.8) | 0.99 |  |  |  |
|  | 24 week | 51.5 (1.3) | 52.4 (1.3) | -0.9 (1.8) | 0.62 |  |  |  |

\*\*\*\* p<0.0001

Medication Administration in Phase 2

In Phase 2, patients received blister card kits with 10 rows (1 week +3 days per kit) with six columns. Those randomized to 80 mg received columns with two 40 mg and four placebo tablets. Those randomized to 240 mg received columns with three 40 mg tablets and three placebo tablets at week 1. At beginning of week 2, 3 and 4, the dose of lurasidone was increased to 160, 200 and 240 mg (six 40 mg tablets)/day.

**Legend for Figure S1**: Changes in CGI and PSA during Phase 1 and 2.

\* or +: denote significant or a trend of differences compared to Phase 2 baseline of each group.

\*\*\* p <0.001, \*\* p<0.01, \* p<0.05, + p<0.10

#: denotes time effect of lurasidone in combined groups. ### p<0.001, ## p<0.01, # p<0.05.