**Contents of On-Line Supplement**

Figure S1. Study Design and Disposition of Patients

Figure S2. Least-Square Mean Change (±SE) from Baseline for MADRS Total Score During the Follow-up Phase (MMRM; Observed Cases)

Figure S3. Remission Rate During the Double-Blind Treatment Phase

Figure S4. Response Rate During the Double-Blind Treatment Phase

Figure S5. Least-Squares Mean (95% CI) Treatment Difference on CGI SS r and Other Suicidality Indices During the Double-Blind Treatment Phasea

Table S1. Summary of Most Frequently Reported Adverse Events During the Follow-up Phase

Table S2. Treatment-Emergent Serious Adverse Events During the Double-Blind Treatment Phase

Table S3. Serious Adverse Events During the Follow-up Phase

**Figure S1. Study Design and Disposition of Patients**

**Diagram

Description automatically generated**

a14 days in certain countries within the European Union

bPatients who completed the double-blind phase and either entered the follow-up phase or had adverse events evaluated after the double-blind treatment phase.

cStandard antidepressant was initiated or optimized on day 1.

Note: Five patients were not included in the efficacy analysis dataset due to discontinuing prior to receiving study drug or not providing postbaseline efficacy data.

**Figure S2. Least-Squares Mean Change (**±**SE) from Baseline for MADRS Total Score During the Follow-up Phase (MMRM; Observed Cases)**

Graphical user interface, chart

Description automatically generated

LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model using repeated measures; SE = standard error

1. Includes patients who had their dose reduced due to tolerability issues.

Notes: Negative change in score indicates improvement.

During the follow-up phase, these were patients formerly treated with placebo and patients formerly treated with esketamine.

**Figure S3. Remission Rate During the Double-Blind Treatment Phase**

Chart, bar chart

Description automatically generated

MADRS = Montgomery-Åsberg Depression Rating Scale; SE = standard error

1. Includes patients who had their dose reduced due to tolerability issues.

Notes: Remission defined as MADRS total score ≤12. Patients who did not meet such criterion or discontinued prior to the time point for any reason were not be considered to be in remission. Negative change in score indicates improvement.

**Figure S4. Response Rate During the Double-Blind Treatment Phase**

**Chart, bar chart

Description automatically generated**

MADRS = Montgomery-Åsberg Depression Rating Scale; SE = standard error

aIncludes patients who had their dose reduced due to tolerability issues.

Notes: Response defined as ≥50% reduction in MADRS total score. Patients who did not meet such criterion or discontinued prior to the time point for any reason were not considered a responder.

**Figure S5. Least-Squares Mean (95% CI) Treatment Difference on CGI‑SS‑r and Other Suicidality Indices During the Double-Blind Treatment Phasea**

Table

Description automatically generated

ANCOVA = analysis of covariance, CGI-SR-I = Clinical Global Impression–Imminent Suicide Risk, CGI-SS-r = Clinical Global Impression of Severity of Suicidality Revised version, FoST = Frequency of Suicidal Thinking, LOCF = last observation carried forward, LS = least-squares, MADRS = Montgomery-Åsberg Depression Rating Scale

aChange in suicidal indices score was analyzed using ANCOVA with LOCF.

bIncludes patients who had their dose reduced due to tolerability issues.

cAt baseline, 1 patient had missing MADRS data and another patient had missing CGI-SS-r, CGI-SR-I, and clinician‑rated FoST data, two other patients had missing patient-reported FoST data.

Note: The SIBAT contains 8 modules, including the clinician-reported CGI-SS-r, rated on a 0–6 scale (0=normal, not at all suicidal to 6=among the most extremely suicidal patients), CGI-SR-I, rated on a 0–6 scale (0=no imminent suicidal risk to 6=extreme imminent suicidal risk), clinician-reported FoST, rated on a 0–5 scale (0=never to 5=all of the time), and patient-reported FoST, rated on a 0–4 scale (0=no suicidal thoughts to 4=suicidal thoughts all the time).

**Table S1. Summary of Most Frequently Reporteda Adverse Events During the Follow-up Phase**

|  |  |  |
| --- | --- | --- |
|  | **Number (%) of Patients** | |
| **Adverse Event** | **Placebo + Standard-of-Care N = 185** | **Esketamine 84 mgb + Standard-of-Care N = 190** |
| Depression | 6 (3.2) | 13 (6.8) |
| Headache | 17 (9.2) | 13 (6.8) |
| Insomnia | 11 (5.9) | 12 (6.3) |
| Anxiety | 18 (9.7) | 11 (5.8) |
| Suicidal ideation | 12 (6.5) | 10 (5.3) |

a Most frequently reported is defined as ≥5% of patients in either treatment group during the follow-up phase. Events are presented in descending order in the esketamine group and in alphabetical order for events with same incidence.

b Includes patients who had their dose reduced due to tolerability issues.

**Table S2. Treatment-Emergent Serious Adverse Events During the Double-Blind Treatment Phase**

|  |  |  |
| --- | --- | --- |
|  | **Number (%) of Patients** | |
| **Adverse Eventa** | **Placebo + Standard-of-Care N = 225** | **Esketamine 84 mgb + Standard-of-Care N = 227** |
| Suicide attempt | 4 (1.8) | 4 (1.8) |
| Depression suicidal | 1 (0.4) | 2 (0.9) |
| Depersonalisation/derealisation disorder | 0 | 1 (0.4) |
| Depression | 2 (0.9) | 1 (0.4) |
| Diabetic ketoacidosis | 0 | 1 (0.4) |
| Suicidal ideation | 4 (1.8) | 1 (0.4) |
| Aggression | 1 (0.4) | 0 |
| Arrhythmia | 1 (0.4) | 0 |
| Hypertransaminasemia | 1 (0.4) | 0 |
| Pericardial effusion | 1 (0.4) | 0 |
| Pneumothorax | 1 (0.4) | 0 |

a Events are presented in descending order in the esketamine group and in alphabetic order for events with same incidence.

b Includes patients who had their dose reduced due to tolerability issues.

Note: A serious adverse event is any untoward medical occurrence that, at any dose: resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; was a suspected transmission of any infectious agent via a medicinal product; or was medically important.

**Table S3. Serious Adverse Events During the Follow-up Phase**

|  |  |  |
| --- | --- | --- |
|  | **Number (%) of Patients** | |
| **Adverse Event** | **Placebo + Standard-of-Care N = 185** | **Esketamine 84 mgb + Standard-of-Care N = 190** |
| Suicide attempt | 3 (1.6) | 7 (3.7) |
| Depression suicidal | 5 (2.7) | 5 (2.6) |
| Suicidal ideation | 6 (3.2) | 5 (2.6) |
| Depression | 1 (0.5) | 2 (1.1) |
| Major depression | 0 | 2 (1.1) |
| Acute stress disorder | 0 | 1 (0.5) |
| Completed suicide | 0 | 1 (0.5) |
| Hemothorax | 0 | 1 (0.5) |
| Encephalopathy | 1 (0.5) | 0 |
| Erysipelas | 1 (0.5) | 0 |
| Homicidal ideation | 1 (0.5) | 0 |
| Overdose | 1 (0.5) | 0 |
| Papillary thyroid cancer | 1 (0.5) | 0 |
| Pyelonephritis | 1 (0.5) | 0 |
| Rhabdomyolysis | 1 (0.5) | 0 |
| Staphylococcal bacteremia | 1 (0.5) | 0 |

a Events are presented in descending order in the esketamine group and in alphabetic order for events with same incidence.

b Includes patients who had their dose reduced due to tolerability issues.

Note: A serious adverse event is any untoward medical occurrence that, at any dose: resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; was a suspected transmission of any infectious agent via a medicinal product; or was medically important.