SPRAVATO® (esketamine)
Comparison of SPRAVATO to atypical antipsychotics

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ESCAPE-TRD

- An international, randomized, open-label, rater-blinded, phase 3b study compared the efficacy of SPRAVATO and quetiapine XR, both in combination with an oral AD, in 676 patients with TRD.[1]
- The remission rate (MADRS total score ≤10) at wk 8 (primary endpoint) was significantly higher in the SPRAVATO+AD group compared with the quetiapine XR+AD group (27.1% vs 17.6%; *P*=0.003).[1]
- On the key secondary endpoint, a higher proportion of patients achieved remission at wk 8 and remained relapse-free through wk 32 in the SPRAVATO+AD group vs the quetiapine XR+AD group (21.7% vs 14.1%, respectively).[1]
- Significantly more patients in the SPRAVATO+AD group achieved functional remission vs the quetiapine XR+AD group (HR [95% CI], 1.82 [1.42 to 2.34]; *P*<0.001).[2]
- SPRAVATO+AD significantly improved presenteeism, work productivity loss, and activity impairment compared with quetiapine XR+AD.[2]
- HR-QoL outcomes were measured over time, including SF-36. At week 32, the following domains were improved with SPRAVATO+AD vs quetiapine XR+AD, returning to levels close to general population norms: Role Emotional (difference: 2.8), Mental Health (2.1), and Social Functioning (2.1), returning to levels close to general population norms.[3]
- There were numerically higher rates of dizziness, headache, dysgeusia, paresthesia, nausea, vomiting, dissociation, and vertigo in the SPRAVATO+AD group while there were higher rates of somnolence, fatigue, and weight increase in the quetiapine XR+AD arm. More patients discontinued due to AEs in the quetiapine XR+AD group (11.0% vs 4.2%).[1]

ESCAPE-LTE

- ESCAPE-LTE, a phase 4, single-arm, 2-year, open-label extension study to ESCAPE-TRD, was conducted in 183 patients to evaluate the long-term safety and efficacy of SPRAVATO.[4]
- TEAEs were reported in 88.0% and 96.7% of patients in ESCAPE-LTE alone and pooled ESCAPE-LTE and ESCAPE-TRD, respectively. Headache (44.3% and 51.9%), dizziness (27.3% and 48.6%), and nausea (20.2% and 40.4%) were the most commonly reported TEAEs in ESCAPE-LTE alone and across the pooled studies, respectively.[4]
- A rapid reduction in the mean (SE) MADRS total scores from baseline (31.5 [0.4]) was reported at wk 8 (14.7 [0.6]), and improvement continued over time to wk 136 (6.8 [0.5]). Of the 149 patients who achieved remission in ESCAPE-TRD, 118 (79.2%) patients continued without relapse during ESCAPE-LTE, 9 (6.0%) relapsed, and 22 (14.8%) had no relapse but discontinued treatment.[4]

Meta-analyses

- A meta-analysis of 25 short-term, DB, RCTs that compared add-on treatment of ADs to AAPs (AAP+AD) or SPRAVATO (SPRAVATO+AD) in the intervention groups and add-on PBO (PBO+AD) in the control group was conducted.[5] The analysis included studies with adult patient with non-psychotic MDD and at least one inadequate response to an AD trial prior to randomization.
  - Compared to PBO+AD, the pooled add-on SPRAVATO studies had a higher mean difference in MADRS total score than the pooled AAP augmentation studies with an effect size for SPRAVATO nearly twice that of AAPs.
- A meta-analysis of 12 short-term, DB, pivotal studies using adjunctive or conjunctive medications, including SPRAVATO, combination olanzapine/fluoxetine, and AAPs for the treatment of MDD, including TRD, found that patients treated with SPRAVATO+AD had larger improvements in MADRS total score and response rate compared to those treated with AAP+AD.[6] No significant difference in remission rate was found between the two arms.

Note: AAP, atypical antipsychotic; AD, antidepressant; AE, adverse event; DB, double blind; CI, confidence interval; HR, hazard ratio; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; PBO, placebo; RCT, randomized controlled trial; SE, standard error; TEAE, treatment-emergent adverse event; TRD, treatment resistant depression; WPAI:D, Work Productivity and Activity Impairment: Depression; XR, extended release.

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Overview[1]

A randomized, open-label, rater-blinded, active-controlled, phase 3b clinical study was conducted to compare the efficacy of SPRAVATO and quetiapine XR, both in combination with an oral AD (SSRI or SNRI), in patients with TRD across 171 sites in 24 countries.

Eligibility criteria[1,7]

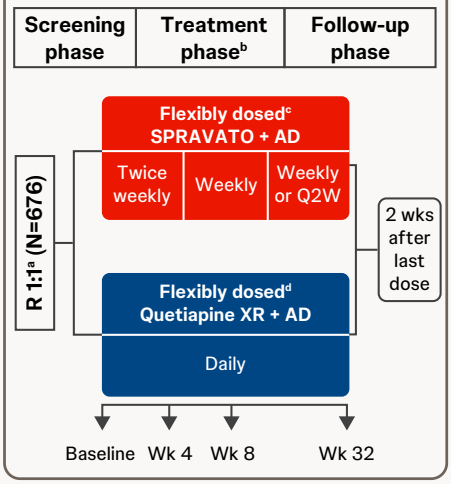
Key inclusion criteria:

- Age 18-≤74 years
- DSM-5 diagnosis of single episode or recurrent MDD
- IDS-C30 total score ≥34
- Prior treatment failure on ≥2 different AD classes

Key exclusion criteria:

- First episode onset of MDD at ≥55 years of age
- Diagnosis of psychotic disorder or psychotic features, obsessive compulsive disorder, intellectual disability, autism spectrum disorder, or borderline, antisocial, histrionic,

Study design[1,7]



Primary and key secondary endpoints[1]

Patients achieving endpoints

	SPRAVATO + AD (n=336)	Quetiapine XR + AD (n=340)
Remission at wk 8 (*P*=0.003)		
n (%)	91 (27.1)	60 (17.6)
OR (95% CI)	1.74 (1.20-2.52)	
Both in remission at wk 8 and relapse-free[e] through wk 32		
n (%)	73 (21.7)	48 (14.1)
OR (95% CI)	1.72 (1.15-2.57)	
Relapse[e]		
n (%)	8 (2.4)	6 (1.8)

Remission and response rate at wk 32[f1]

- At wk 32, the proportion of patients in remission was numerically higher in the SPRAVATO+AD vs quetiapine XR+AD arm (49.1% vs 32.9%; OR [95% CI], 1.96 [1.44-2.68]).
- At wk 32, the proportion of patients experiencing response was higher in the SPRAVATO+AD vs quetiapine XR+AD arm (65.5% vs 47.1%; OR [95% CI], 2.13 [1.57-2.91]).

Safety[1]

TEAEs

n (%)	SPRAVATO + AD (n=334)	Quetiapine XR + AD (n=336)
Any TEAE	307 (91.9)	262 (78.0)
Serious TEAEs	19 (5.7)	17 (5.1)
TEAEs leading to death	1 (0.3)	1 (0.3)
≥1 TEAE leading to DC	14 (4.2)	37 (11.0)

AD, antidepressant; CI, confidence interval; DC, discontinuation; IDS-C30, Inventory of Depressive Symptomatology, Clinician-Rated 30-item scale; LOCF, last observation carried forward; MDD, major depressive disorder; OR, odds ratio; R, randomization; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse event; TRD, treatment resistant depression; Wk, week; XR, extended release. [a]Randomization stratified by age and number of prior treatment failures. [b]Treatment phase consisted of an acute treatment phase (8 wks) and maintenance phase (24 wks). [c]SPRAVATO was dosed twice weekly (56 mg on day 1, increased to 56 or 84 mg from day 4) from wks 1–4, weekly (56 or 84 mg) from wks 5–8 and weekly or every 2 wks (56 or 84 mg) from wks 9–32, all in addition to an ongoing AD that elicited non-response at baseline.[c]Elderly patients (65-74 years) and adults of Japanese ancestry had a starting dose of 28 mg; patients could remain on a dose of 28 mg at the investigator's discretion. [d]Quetiapine XR was dosed daily, starting at 50 mg and titrated up to ≥150 mg/day by the end of wk 2. Quetiapine XR was then flexibly dosed (150–300 mg/day) from wks 3–32, all in addition to an ongoing AD that elicited non-response at baseline. [e]Relapse was defined as MADRS score ≥22 at 2 consecutive assessments within 5-15 days; hospitalization for worsening depression, suicide prevention, suicide attempt, completed suicide, or any other event indicative of relapse per investigator's judgment. [f]Using non-responder imputation.

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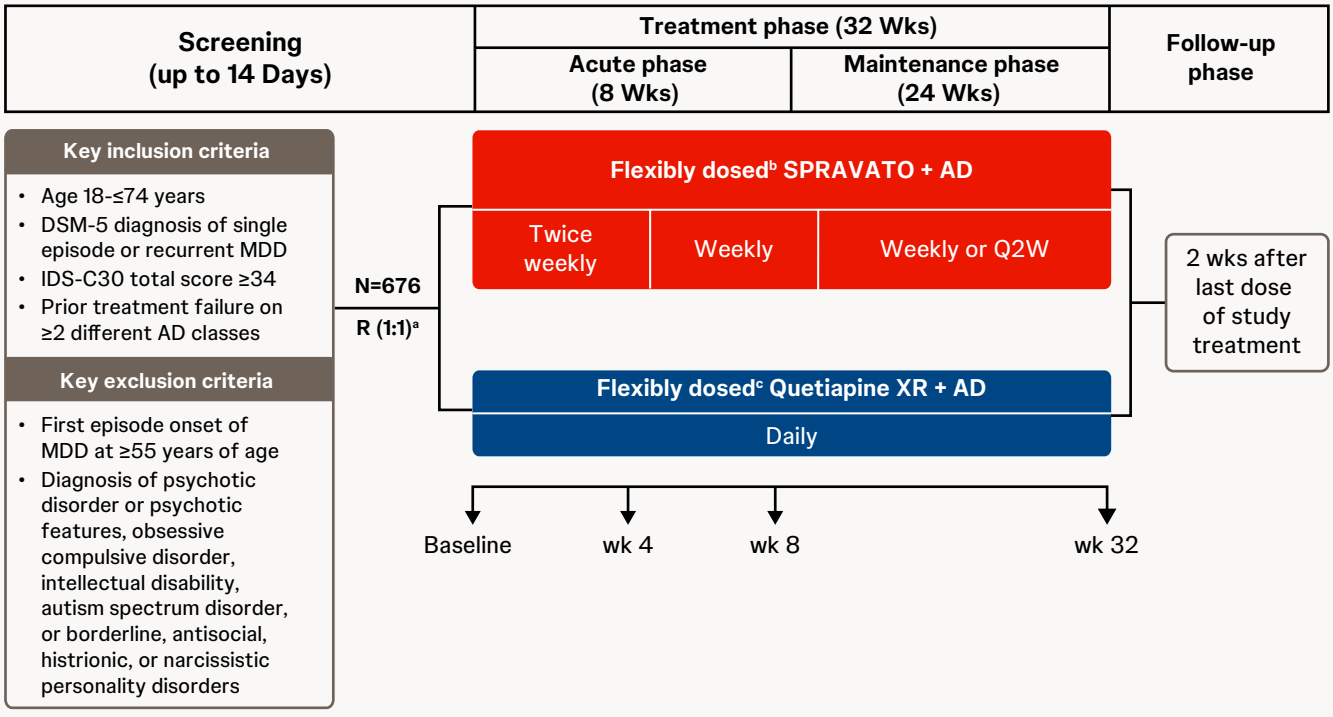
A randomized, open-label, rater-blinded, active-controlled, phase 3b clinical study was conducted to compare the efficacy, safety, and tolerability of SPRAVATO and quetiapine XR, both in combination with an oral AD (SSRI or SNRI), in adult patients with TRD in across 171 sites in 24 countries.[1]

- Eligible patients had <25% symptom improvement from ≥2 different AD classes, including the current AD, for ≥6 wks during the current depressive episode. SPRAVATO and quetiapine XR were added onto this existing ineffective oral AD (SSRI or SNRI) regimen while all the other ADs, including augmentation agents, were discontinued.[1]
- The treatment phase consisted of an 8-wk acute phase and a 24-wk maintenance phase.[1]
- Quetiapine XR was selected as the antipsychotic for comparison because its use is supported by multiple guidelines[8,9], it is widely used in patients with previous treatment failures, and it is approved by the European Medicines Agency as an add-on treatment for patients with MDD who have inadequate response to antidepressant monotherapy.[10]

Study design[1,7]



[a]Randomization stratified by age and number of prior treatment failures.
[b]SPRAVATO was dosed twice weekly (56 mg on day 1, increased to 56 or 84 mg from day 4) from wk 1–4, weekly (56 or 84 mg) from wks 5–8 and weekly or every 2 wks (56 or 84 mg) from wks 9–32, all in addition to an ongoing AD that elicited non-response at baseline. Elderly patients (65-74 years) and adults of Japanese ancestry had a starting dose of 28 mg; patients could remain on a dose of 28 mg at the investigator's discretion.
[c]Quetiapine XR was dosed daily, starting at 50 mg and titrated up to 150-≤300 mg/day by the end of wk 2. Quetiapine XR was then flexibly dosed (150–300 mg/day) from wks 3–32, all in addition to an ongoing AD that elicited non-response at baseline.

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- 336 patients were randomized to SPRAVATO and 340 to quetiapine XR study arms.[1]
- Baseline characteristics were comparable between the two groups.[1]

Baseline characteristics[1]

	SPRAVATO + AD (n=336)	Quetiapine XR + AD (n=340)
Baseline characteristics		
Age, years, mean (SD)	44.3 (13.6)	45.7 (13.4)
18-64 years, n (%)	317 (94.3)	322 (94.7)
≥65 years, n (%)	19 (5.7)	18 (5.3)
Sex, female, n (%)	225 (67.0)	222 (65.3)
BMI,[a] kg/m^2, n (%)		
Underweight (<18.5)	6 (2.1)	5 (1.7)
Normal (18.5-<25)	110 (39.0)	90 (31.0)
Overweight (25-<30)	100 (35.5)	102 (35.2)
Obese (≥30)	66 (23.4)	93 (32.1)
Number of treatment failures, n (%)		
2	204 (60.7)	211 (62.1)
≥3	132 (39.3)	129 (37.9)
Psychiatric history, mean (SD)		
Total number of episodes	3.4 (2.4)	3.6 (4.1)
Duration of current depressive episode	68.8 (84.2)	64.6 (65.7)
MADRS total score[a]	31.4 (6.1)	31.0 (5.8)
CGI-S score	4.8 (0.6)	4.9 (0.7)
IDS-C30 total score	44.6 (6.6)	45.0 (6.9)

Full analysis set (includes all randomized patients). [a]Baseline MADRS score data were missing for 1 quetiapine XR patient.

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- A total of 676 patients were included in the full study analysis from SPRAVATO and quetiapine XR treatment arms.[1]
- The primary endpoint was remission (defined as MADRS total score of ≤10) at wk 8.[1]
- Based on the retrieved dropout analysis, 27.7% of patients receiving SPRAVATO+AD vs 17.9% of patients receiving quetiapine XR+AD achieved remission at wk 8 (OR [95% CI], 1.76 [1.22-2.54]; RR [95% CI], 1.55 [1.16-2.07]).[1]
- Sensitivity analyses conducted on both primary and key secondary endpoints continued to favor SPRAVATO over quetiapine XR.[15]

Proportion of patients achieving primary and key secondary endpoints[1]

	SPRAVATO + AD (n=336)	Quetiapine XR + AD (n=340)
Primary endpoint		
Remission at wk 8, n (%)	91 (27.1)	60 (17.6)
Adjusted *P* value[a]	0.003	
OR (95% CI)	1.74 (1.20-2.52)	
Key secondary endpoint		
Both in remission at wk 8 and relapse-free[b] through wk 32[c], n (%)	73 (21.7)	48 (14.1)
OR (95% CI)	1.72 (1.15-2.57)	
Relapse[b], n (%)	8 (2.4)	6 (1.8)
Hospitalized for worsening depression or suicide	2 (0.6)	3 (0.9)
MADRS total score ≥22	6 (1.8)	3 (0.9)
Without relapse but discontinued after being in remission at wk 8, n (%)	10 (3.0)	6 (1.8)

[a]Treatment groups were compared using a CMH chi-square test, adjusted for age group (18–64 years; 65–<75 years) and total number of treatment failures.
[b]Relapse was defined as MADRS score ≥22 at 2 consecutive assessments within 5-15 days; hospitalization for worsening depression, suicide prevention, suicide attempt, completed suicide, or any other event indicative of relapse per investigator's clinical judgment.
[c]Patients who discontinued treatment were imputed as non-responders, LOCF was used for patients with missing MADRS assessment at wk 8 but remained in the study.

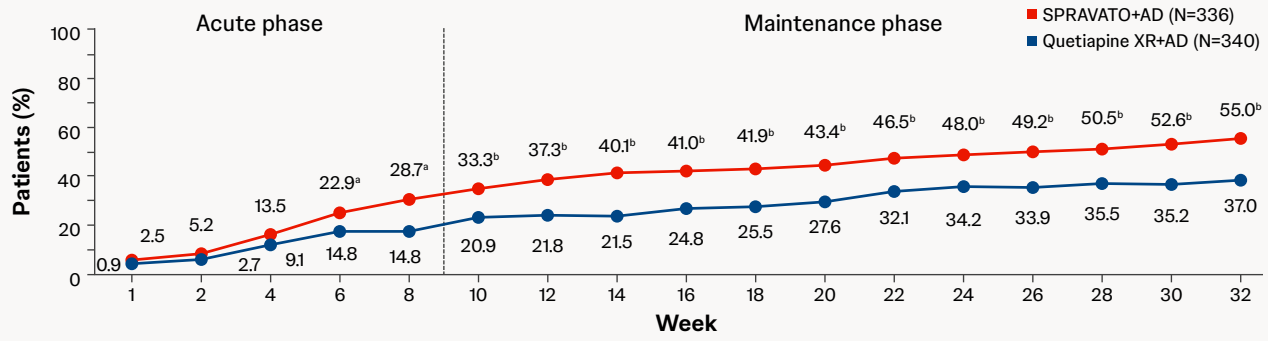
Response and remission rate over time

Change in MADRS total score over time

Response and remission rate over time

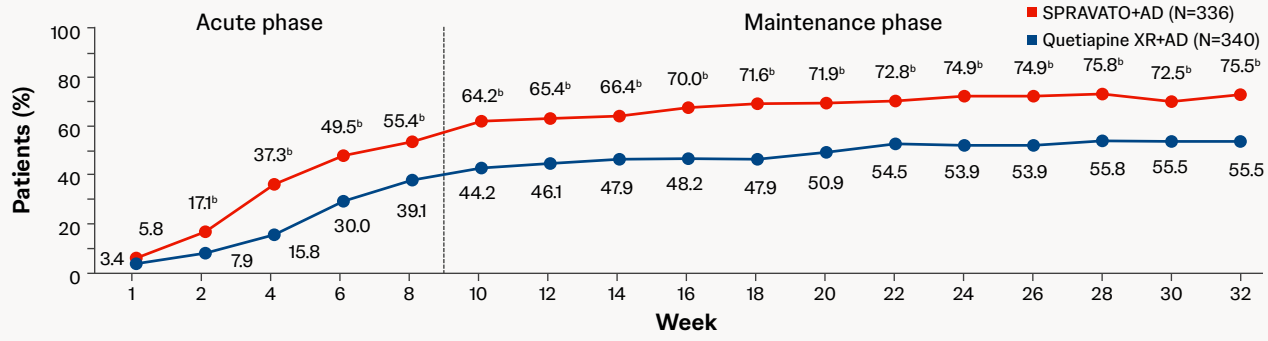
- Remission rates increased over time in both treatment arms. At wk 32, the proportion of patients in remission was numerically higher in the SPRAVATO+AD vs quetiapine XR+AD arm (per NRI, 49.1% vs 32.9%; per LOCF, 55.0% vs 37.0%) with an OR (95% CI [using NRI]) of 1.96 (1.44-2.68).[1]
- Using an alternative definition of remission (MADRS ≤12), 38.7% vs 22.9% of patients achieved remission at wk 8 (OR [95% CI], 2.14 [1.53-3.00]) in SPRAVATO+AD vs quetiapine XR+AD arm, and 32.1% vs 17.6% of patients were relapse free at wk 32 after remission at wk 8 (OR [95% CI], 2.28 [1.58-3.29]).[7]
- At wk 32, the proportion of patients experiencing response (≥50% improvement from baseline in MADRS total score or MADRS ≤10) was higher in the SPRAVATO+AD vs quetiapine XR+AD arm (per NRI, 65.5% vs 47.1%; per LOCF, 75.5% vs 55.5%) with an OR (95% CI [using NRI]) of 2.13 (1.57-2.91).[1]

Remission rate over time (LOCF)[7,11]



	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
SPRAVATO+AD:	325	327	327	327	327	327	327	327	327	327	327	327	327	327	327	327	327
Quetiapine XR+AD:	326	330	330	330	330	330	330	330	330	330	330	330	330	330	330	203	330

Response rate over time (LOCF)[7,11]



	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
SPRAVATO+AD:	325	327	327	327	327	327	327	327	327	327	327	327	327	327	327	327	327
Quetiapine XR+AD:	326	330	330	330	330	330	330	330	330	330	330	330	330	330	330	203	330

Full analysis set includes all randomized patients; data were missing for 1 patient in the quetiapine XR + AD arm at baseline. Percentages are based on the number of patients at each timepoint, using LOCF for missing data (on-treatment visits only). Tested at a two-sided 0.05 significance level without adjustment for multiple testing.

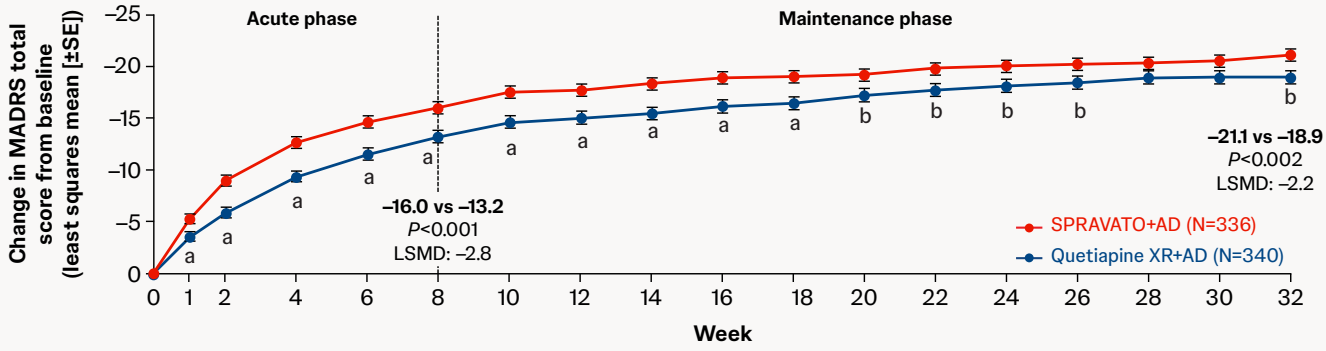
[a]$P<0.01$; [b]$P<0.001$.

AD, antidepressant; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; XR, extended release.

Change in MADRS total score over time

- MADRS total score decreased over time in both treatment arms; however, a greater reduction was observed in the SPRAVATO+AD vs quetiapine XR+AD arm with an estimated mean difference (95% CI) of -2.2 (-3.6 to -0.8) between the 2 arms at wk 32.[1]

Change in MADRS total score over time (MMRM)[1,11]



SPRAVATO+AD:	325	324	317	312	300	288	285	280	277	267	269	263	259	257	252	250	255
Quetiapine XR+AD:	326	315	295	285	265	242	235	232	223	219	214	214	209	206	205	200	203

NOTE: the higher the rise of the curve, the greater the symptom improvement from baseline.

Full analysis set includes all randomized patients. Total MADRS score at baseline was missing for 1 patient receiving quetiapine XR. Error bars depict SE. *P* values, LS means, and SE were based on MMRM (based on OC; on-treatment visits only), with treatment, age group, number of treatment failures, time, time by treatment, and baseline value as covariates. Modeled with an unstructured covariance structure. Tested at a two-sided 0.05 significance level without adjustment for multiple testing.

[a]*P*<0.001; [b]*P*<0.01.

AD, antidepressant; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed models for repeated measures; OC, observed case; SE, standard error; XR, extended release.

PHQ-9 remission and response

- SPRAVATO-treated patients achieved higher PHQ-9 remission and response rates at weeks 8 and 32.[3]
- The time to first remission (PHQ-9 ≤4 at 1 visit; HR [95% CI]: 1.88 [1.50-2.36) and the time to confirmed remission (PHQ ≤4 at 2 consecutive visits; HR [95% CI]: 1.76 [1.36-2.29]) were shorter in the SPRAVATO+AD group vs quetiapine XR+AD group.[3]

PHQ-9 remission and response[3]

Outcome	SPRAVATO + AD (n=336)	Quetiapine XR + AD (n=340)	OR (95% CI)
PHQ-9 remission (≤4), %			
Week 8	20.2	12.4	1.80 (1.19-2.74)
Week 32	34.5	18.2	2.39 (1.67-3.41)
PHQ-9 response (≥50% or ≤4), %			
Week 8	50	32.6	2.06 (1.51-2.81)
Week 32	58	40.6	2.03 (1.50-2.76)

AD, antidepressant; CI, confidence interval; OR, odds ration; PHQ-9, Patient Health Questionnaire-9; XR, extended release

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- A total of 676 patients were included from the SPRAVATO and quetiapine XR treatment groups for functionality and productivity assessments. There were similar baseline SDS total scores and WPAI:D scores between treatment arms, with ~53% who had marked functional impairment and who had an overall work time loss of ~75%.[2]
- Functionality was measured by the SDS with remission defined as a total score of ≤6 and was assessed every 4 weeks through week 32.[2]
- Productivity was determined by the change from baseline to 32 weeks in all four domain scores of the WPAI:D questionnaire, including absenteeism, presenteeism, work productivity loss, and activity impairment.[2]
- *P*-values reported were nominal and not adjusted for multiple testing.

Functionality

- Treatment with SPRAVATO+AD shortened the time to functional remission compared with quetiapine XR+AD.[2]
- Significantly higher number of patients achieved functional remission in the SPRAVATO+AD group vs the quetiapine XR+AD group (HR [95% CI], 1.82 [1.42 to 2.34]; *P*<0.001).[2]
  - Functional remission rates were numerically higher in the SPRAVATO+AD group vs the quetiapine XR+AD group at every timepoint.
  - A significant benefit was observed in the SPRAVATO+AD group vs the quetiapine XR+AD group from week 16 onwards (OR [95% CI], 1.71 [1.14 to 2.56]; *P*=0.009).
- Patients in the SPRAVATO+AD group had more cumulative time spent in functional remission (6.7 weeks vs 4.7 weeks; difference [95% CI], 2.0 weeks [0.7-3.3]; *P*=0.0023; 43.2% relative increase).[2]
- Overall, clinical response preceded or occurred at the same time as functional remission in 92.2% of cases. In patients who achieved both, the average time between clinical response and functional remission was 57.6 days.[2]

Productivity

- Over the 32-week period, patients receiving SPRAVATO+AD vs quetiapine XR+AD lost less time in all four domains of WPAI:D, with significant improvement in presenteeism, work productivity loss, and activity impairment[2]:
  - Absenteeism: 8.1 weeks vs 9.2 weeks (difference [95% CI], -1.1 weeks [-2.9 to 0.7]; *P*=0.229)
  - Presenteeism: 12.7 weeks vs 14.7 weeks (difference [95% CI], -1.9 weeks [-3.4 to -0.5]; *P*=0.001)
  - Work productivity loss: 13.9 weeks vs 16.2 weeks (difference [95% CI], -2.3 weeks [-3.9 to -0.7]; *P*=0.005)
  - Activity impairment: 14.2 weeks vs 15.5 weeks (difference [95% CI], -1.3 weeks [-2.3 to -0.2]; *P*=0.017)

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- Baseline SF-36, QLDS, and EQ-5D-5L scores were similar between groups.[3]

SF-36

- SPRAVATO+AD produced greater improvements across SF-36 Role Emotional, Mental Health, and Social Functioning domains compared with quetiapine XR, with differences of +2.8, +2.1, and +2.1 points, respectively, at Week 32.[3]
  - There was a trend favoring the SPRAVATO+AD arm for all other domains.

QLDS

- A higher proportion of patients treated with SPRAVATO+AD achieved clinically meaningful improvement in QLDS at all timepoints, reaching 60.7% at Week 32 versus 41.8% with quetiapine XR+AD.[3]
- Patients treated with SPRAVATO+AD had a shorter time to meaningful QLDS improvement (median, 7.86 weeks vs 12.14 weeks).[3]
  - Clinically meaningful improvement in QLDS was defined as reduction of ≥8 points.

EQ-5D-5L

- Proportions of patients reporting an EQ-5D-5L score of 1 (no problems) increased from baseline to Week 32 across all domains in both study arms.[3]
  - A higher proportion of SPRAVATO-treated patients reported no problems across EQ-5D-5L domains: Self-Care (77.7% vs 65.3%), Pain/Discomfort (44.0% vs 32.1%), Mobility (73.2% vs 63.2%), Anxiety/Depression (25.3 vs 16.8) and Usual activities (39.3% vs 30.9%) at Week 32.
- SPRAVATO-treated patients showed greater improvement from baseline in EQ-VAS overall health state at Week 8 (least squares mean +19.0 vs +15.0 with quetiapine XR) which was more pronounced than at Week 32 (+24.5 vs +22.2).[3]

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- All randomized patients who took at least 1 dose of study treatment were included in the safety analysis.[1]
- Study discontinuations were mostly due to TEAEs and lack of efficacy and were numerically higher in the quetiapine XR+AD arm compared with the SPRAVATO+AD arm (40.3% vs 23.2%, respectively).[1]
- There was one TEAE-related death in each treatment arm.[1]

Summary of TEAEs[1,7]

n (%)	SPRAVATO + AD (n=334)	Quetiapine XR + AD (n=336)
≥1 TEAE, n (%)	307 (91.9)	262 (78.0)
≥1 serious TEAE	19 (5.7)	17 (5.1)
TEAE leading to death[a]	1 (0.3)	1 (0.3)
TEAE leading to dose interruption/reduction	35 (10.5)	43 (12.8)
Most common TEAEs (occurring in ≥10% of patients in either treatment arm)		
Dizziness	156 (46.7)	28 (8.3)
Somnolence	50 (15.0)	78 (23.2)
Headache	82 (24.6)	43 (12.8)
Dysgeusia	40 (12.0)	1 (0.3)
Paresthesia	37 (11.1)	2 (0.6)
Nausea	98 (29.3)	12 (3.6)
Vomiting	36 (10.8)	5 (1.5)
Fatigue	19 (5.7)	34 (10.1)
Dissociation	94 (28.1)	2 (0.6)
Weight increased	9 (2.7)	42 (12.5)
Vertigo	63 (18.9)	3 (0.9)

[a]Death in SPRAVATO+AD arm was from an undetermined cause at wk 9 and death in quetiapine+AD arm was due to cerebrovascular accident at wk 17. Neither were considered to be treatment-related by investigator.

TEAEs leading to discontinuation

Number and duration of most common TEAEs

TEAEs leading to discontinuation

- Fewer SPRAVATO-treated patients (4.2%) discontinued treatment due to TEAEs vs quetiapine XR-treated patients (11.0%).[1]

TEAEs leading to discontinuation (reported in ≥2 patients in either treatment arm)[7]

n (%)	SPRAVATO + AD (n=334)	Quetiapine XR + AD (n=336)
TEAEs leading to treatment discontinuation	14 (4.2)	37 (11.0)
Nervous system disorders	3 (0.9)	18 (5.4)
Sedation	0 (0.0)	7 (2.1)
Dizziness	2 (0.6)	4 (1.2)
Somnolence	0 (0.0)	5 (1.5)
Psychiatric disorders	4 (1.2)	4 (1.2)
Dissociation	2 (0.6)	0 (0.0)
Investigations	0 (0.0)	7 (2.1)
Weight increased	0 (0.0)	6 (1.8)
General disorders and administration site conditions	0 (0.0)	6 (1.8)
Fatigue	0 (0.0)	4 (1.2)
Hangover	0 (0.0)	2 (0.6)
Gastrointestinal disorders	2 (0.6)	2 (0.6)
Vomiting	2 (0.6)	(0.0)

Safety analysis set (includes all randomized participants who received at ≥1 dose of any study intervention). An AE was considered a TEAE if it started between the first dose and up to 14 days after the last study dose, or ≤30 days after the last dose if it was a serious AE.

AD, antidepressant; AE, adverse event; TEAE, treatment-emergent adverse event; XR, extended release.

Number and duration of most common TEAEs

- Across all TEAEs, 91.8% resolved on the same day in the SPRAVATO+AD group compared to 11.6% in the quetiapine XR+AD group[12]:
  - Based on the top 3 most frequently reported AEs in the SPRAVATO+AD group, 99.2% of dizziness, 91.4% of nausea, and 99.6% of dissociation resolved on the same dosing day.
  - Likewise, in the quetiapine XR+AD group, 7.8% of somnolence, 49.2% of headache, and 2.6% of weight increases resolved on the same dosing day.

Number and median duration of most common TEAEs (reported in ≥10% of patients)[13]

	SPRAVATO + AD (n=334)			Quetiapine XR + AD (n=336)		
	n[a] (% of patients)	Number of events[b]	Median duration[c] (Days, 95% CI)	n[a] (% of patients)	Number of events[b]	Median duration[c] (Days, 95% CI)
Dizziness	156 (46.7)	1510	1.0 (NE)	28 (8.3)	29	14.0 (7.0-27.0)
Somnolence	50 (15.0)	570	1.0 (NE)	78 (23.2)	110	15.0 (12.0-20.0)
Headache	82 (24.6)	169	1.0 (NE)	43 (12.8)	63	1.0 (1.0-2.0)
Dysgeusia	40 (12.0)	405	1.0 (NE)	1 (0.3)	1	42.0 (NE)
Paresthesia	37 (11.1)	219	1.0 (NE)	2 (0.6)	2	NE (48.0-NE)
Nausea	98 (29.3)	239	1.0 (NE)	12 (3.6)	12	9.0 (2.0-19.0)
Vomiting	36 (10.8)	48	1.0 (NE)	5 (1.5)	5	1.0 (1.0-NE)
Dissociation	94 (28.1)	825	1.0 (NE)	2 (0.6)	2	NE (34.0-NE)
Fatigue	19 (5.7)	61	1.0 (NE)	34 (10.1)	42	25.0 (14.0-62.0)
Weight increase	9 (2.7)	9	122.5 (15.0-NE)	42 (12.5)	42	197.0 (112.0-NE)
Vertigo	63 (18.9)	411	1.0 (NE)	3 (0.9)	3	4.0 (4.0-NE)

[a]Safety analysis set (patients received ≥1 dose of study treatment).

[b]An adverse event was counted as treatment emergent if it occurred after taking the first dose and on or before 14 days after the last dose of study medication. A serious adverse event was also counted as TEAE if it occurred within 30 days of the last dose. Adverse events were coded using MedDRA preferred terms.

[c]The median duration of TEAEs was evaluated using Kaplan-Meier analyses.

AD, antidepressant; MedDRA, Medical Dictionary for Regulatory Activities; NE, not estimable; TEAE, treatment-emergent adverse event; XR, extended release.

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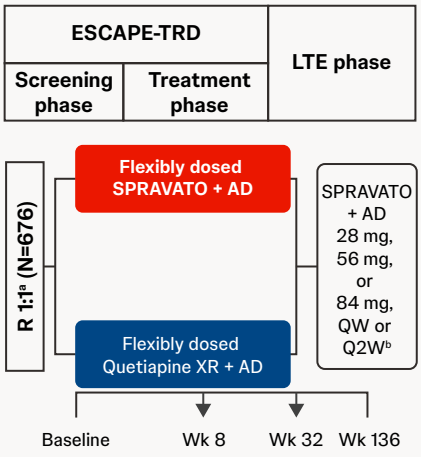
Overview[4]

ESCAPE-LTE, a phase 4, single-arm, 2-year, open-label extension study to the ESCAPE-TRD study, was conducted to assess the long-term safety, tolerability, and efficacy of SPRAVATO in combination with an oral AD (SSRI or SNRI).

Eligibility criteria[4]

Patients who completed 32 wks of SPRAVATO treatment in combination with an oral AD in the ESCAPE-TRD study were able to enroll in the ESCAPE-LTE study.

Study design[4]



Safety[4]

	ESCAPE-LTE (n=183)	Pooled ESCAPE-LTE + ESCAPE-TRD (n=183)
Any TEAE	161 (88.0)	177 (96.7)
≥1 serious TEAE	11 (6.0)	15 (8.2)
TEAEs leading to death[c]	1 (0.6)	1 (0.6)[d]
TEAE leading to treatment discontinuation	6 (3.3)	6 (3.3)[d]

MADRS total scores over Wk 136[4]

- A rapid reduction in the mean (SE) MADRS total scores from baseline was reported at wk 8, and improvement continued through to wk 136.

	SPRAVATO + AD (n=183)
Baseline	31.5 (0.4)
Wk 8	14.7 (0.6)
Wk 136	6.8 (0.5)

Remission[e] and relapse[f] rate[4]

- Of the 149 patients who achieved remission in ESCAPE-TRD, 118 (79.2%) continued without relapse, while 9 (6.0%) relapsed during ESCAPE-LTE.
- 24 patients who did not achieve remission in ESCAPE-TRD experienced remission during ESCAPE-LTE, with an average time to remission of 60.2 wks from treatment initiation. Of these, 21 patients continued without relapse.

AD, antidepressant; MADRS, Montgomery-Åsberg Depression Rating Scale; Q2W, every 2 weeks; QW, once weekly; R, randomization; SE, standard error; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse event; TRD, treatment resistant depression; Wk, week; XR, extended release.
[a]Randomization stratified by age and number of prior treatment failures. [b]Patients enrolled in the ESCAPE-LTE study were randomized to SPRAVATO, received their last dose at wk 30 or 31, completed the wk 32 visit, continued to benefit from SPRAVATO, and for whom SPRAVATO is not available in their home country. [c]One death was reported due to a TEAE because of multiple injuries that were found unrelated to the study drug. [d]As per the design, all deaths/withdrawals reported here occurred in ESCAPE-LTE, as the analysis includes patients who enrolled in the LTE phase. [e]Remission was defined as MADRS total score ≤10, no drug or study discontinuation before wk 8. [f]Relapse was defined as MADRS score ≥22 on 2 consecutive assessments within 5-31 days: hospitalization for worsening depression, suicide prevention, suicide attempt, or any other event indicative of relapse.

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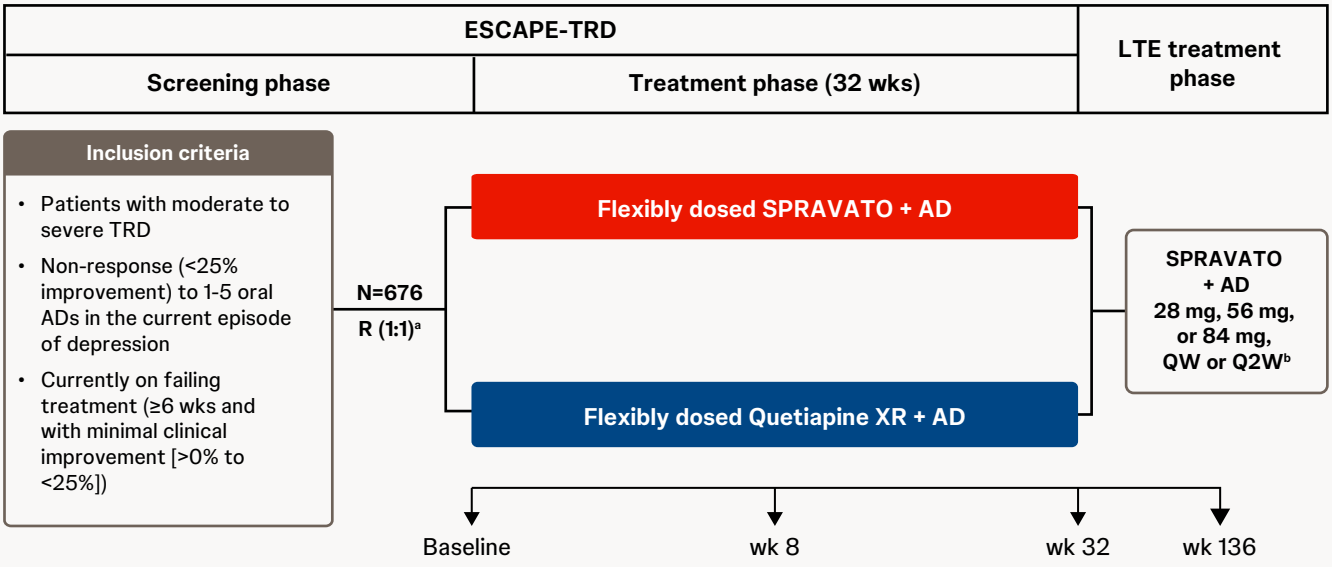
ESCAPE-LTE, a phase 4, single-arm, 2-year, open-label extension study to the ESCAPE-TRD study, was conducted to assess the long-term safety, tolerability, and efficacy of SPRAVATO in combination with an oral AD (SSRI or SNRI).[4]

- Patients who completed 32 wks of SPRAVATO treatment in combination with an oral AD in the ESCAPE-TRD study were eligible for ESCAPE-LTE.
- The primary endpoint was assessment of TEAEs.
- The secondary endpoints included percentage of patients who did not report relapse through wk 136 and change in MADRS from baseline in ESCAPE-TRD through wk 136.

Study design of ESCAPE-TRD and ESCAPE-LTE[4]



[a]Randomization stratified by age and number of prior treatment failures.
[b]Patients enrolled in the ESCAPE-LTE study were randomized to SPRAVATO, received their last dose at wk 30 or 31, completed the wk 32 visit, continued to benefit from SPRAVATO, and for whom SPRAVATO is not available in their home country.

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- A total of 183 patients were enrolled in the ESCAPE-LTE study. Baseline characteristics of patients were presented from the first visit of the ESCAPE-TRD study.[4]

Baseline characteristics[4]

	ESCAPE-LTE (n=183)
Age, years, mean (SD)	44.6 (13.1)
Female sex, n (%)	128 (69.9)
Number of treatment failures, n (%)	
2	125 (68.3)
≥3	58 (31.7)
Age at MDD diagnosis (years)	34.5 (11.2)
Baseline MADRS total score	31.5 (5.6)
Duration of current episodes (wks)	52.4 (51.9)

Safety analysis set of the ESCAPE-LTE only (patients who received ≥1 dose of study treatment).

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- TEAEs were reported in 161 (88.0%) and 177 (96.7%) patients in ESCAPE-LTE alone and pooled ESCAPE-LTE and ESCAPE-TRD, respectively.[4]
- Nearly all TEAEs that were reported on dosing days subsided on the same day.[4]
- Headaches, dizziness, and nausea were the most commonly reported TEAEs.[4]

Summary of TEAEs[4]

n (% [95% CI])	ESCAPE-LTE alone (n=183)	Pooled ESCAPE-LTE and ESCAPE-TRD (n=183)
All TEAEs	161 (88.0 [82.4-92.3])	177 (96.7 [93.0-98.8])
TEAEs possibly related to study treatment	128 (70.0 [62.7-76.5])	163 (89.1 [83.6-93.2])
TEAEs leading to death[a]	1 (0.6 [0.0-3.0])	1 (0.6 [0.0-3.0])[b]
≥1 serious TEAEs	11 (6.0 [3.0-10.5])	15 (8.2 [4.7-13.2])
TEAEs leading to study treatment withdrawal	6 (3.3 [1.2-7.0])	6 (3.3 [1.2-7.0])[b]
TEAEs leading to dose interruption/modification	24 (13.1 [8.6-18.9])	37 (20.2 [14.7-26.8])
Most frequent TEAEs, n (%)		
Headache	81 (44.3)	95 (51.9)
Dizziness	50 (27.3)	89 (48.6)
Nausea	37 (20.2)	74 (40.4)
Vertigo	32 (17.5)	48 (26.2)
Dissociation	19 (10.4)	43 (23.5)
Nasopharyngitis	37 (20.2)	40 (21.9)
COVID-19 infection	30 (16.4)	39 (21.3)

Safety analysis set of ESCAPE-LTE (patients who received ≥1 dose of study treatment).
[a]One death was reported due to a TEAE because of multiple injuries that were found unrelated to the study drug.
[b]As per the design, all deaths/withdrawals reported here occurred in ESCAPE-LTE, as the analysis includes patients who enrolled in the LTE phase.

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- Of 149 patients who achieved remission in the ESCAPE-TRD study, 118 (79.2%) patients continued without relapse, while 9 (6.0%) patients experienced relapse during ESCAPE-LTE.[4]
- 24 patients who did not achieve remission in ESCAPE-TRD experienced remission during ESCAPE-LTE, with an average time to remission of 60.2 wks from treatment initiation. Of these, 21 patients continued without relapse.[4]
- During both studies, the overall relapse rate was 6.9%.[4]

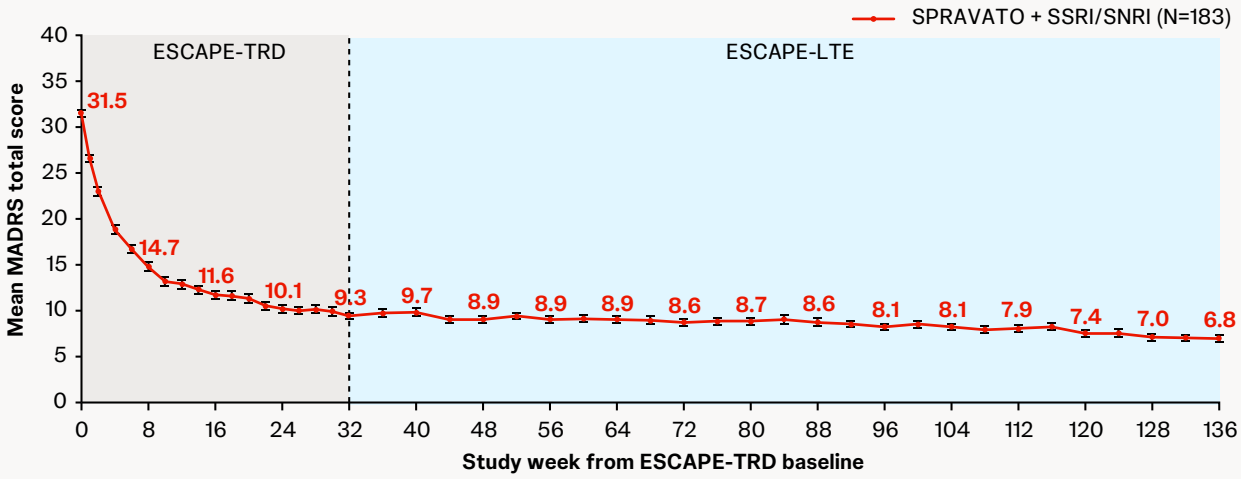
Proportion of patients achieving remission and relapse during ESCAPE-LTE[4]

n (%)	ESCAPE-LTE
Patients achieved remission in ESCAPE-TRD[a] (N=183)	149 (81.4)
Continued treatment without relapse in ESCAPE-LTE (N=149)	118 (79.2)
Relapsed in ESCAPE-LTE[b] (N=149)	9 (6.0)
Discontinued treatment without relapse (N=149)	22 (14.8)
Patients not in remission during ESCAPE-TRD who achieved remission in ESCAPE-LTE (N=183)	24 (13.1)
Experienced no relapse in ESCAPE-LTE (N=24)	21 (87.5)
Relapsed after achieving remission in ESCAPE-LTE (N=24)	3 (12.5)
Patients not achieving remission in ESCAPE-TRD or ESCAPE-LTE (N=183)	10 (5.5)

[a]Defined as MADRS total score ≤10, no treatment or study discontinuation before wk 8.
[b]Defined as MADRS score ≥22 at 2 consecutive assessments within 5-31 days; hospitalization for worsening depression, suicide prevention, suicide attempt, or any other event indicative of relapse.

- Rapid reduction in mean (SE) MADRS total scores from baseline was reported at wk 8, and improvement continued over wk 136.[4]

Mean (SE) change in the MADRS total score during ESCAPE-TRD and ESCAPE-LTE[4]



SPRAVATO+AD: N=183	182	181	181	182	177	175	177	166	163	159	148	151	143	139	134	132	127

Efficacy set (patients who received ≥1 dose of study treatment; observed case). Error bars depict SE.

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A meta-analysis was conducted to evaluate the efficacy of SPRAVATO or AAPs compared to PBO as add-on treatment to oral ADs in patients with non-psychotic MDD with inadequate response to prior AD treatment.[5]

- A comprehensive systematic literature survey of published and unpublished acute-phase, DB, RCTs that compared add-on treatment of ADs to AAPs (AAP+AD) or SPRAVATO (SPRAVATO+AD) in the intervention groups and add-on PBO (PBO+AD) in the control group was conducted.
- This analysis included studies with an adult population (age ≥18 years, no restriction in terms of gender, ethnicity, and comorbidities) with non-psychotic MDD and at least one inadequate response to an AD trial prior to randomization.
- The primary outcome was the mean change (baseline to endpoint) in MADRS total score (if change was not available, mean values at study endpoint were considered).

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- A total of 25 studies were included in analysis (SPRAVATO, N=3 studies; AAPs, N=22 studies). Calculations for all outcomes were separately performed for the pooled AAPs and pooled SPRAVATO groups, in comparison with PBO group.[5]
- Compared to AD+PBO, the pooled add-on SPRAVATO studies (mean difference=4.09, 95% CI, 2.01-6.17; n=641) had a higher mean difference than the pooled AAP augmentation studies (mean difference=2.05, 95% CI, 1.51-2.59; n=8363).[5]
- Individual AAP+AD itemization demonstrated superiority over PBO+AD for aripiprazole (mean difference=2.51, 95% CI, 1.81-3.21; n=2284), brexpiprazole (mean difference=1.46, 95% CI, 0.18-2.74; n=2393), cariprazine (mean difference=1.02, 95% CI, 0.12-1.91; n=1563), olanzapine (mean difference=3.19, 95% CI, 0.45-5.92; n=1012), and quetiapine (mean difference=1.89, 95% CI, 0.31-3.47; n=1088). Risperidone did not significantly differentiate from AD+PBO (n=23).[5]
- No significant heterogeneity was identified in the study comparisons.[5]
- Descriptive analysis showed a higher pooled mean reduction in the MADRS total score for SPRAVATO+AD (-18.08) than for AAP+AD treatment (-10.72) when the intervention and control group was analyzed separately.[5]
- A higher mean MADRS reduction was reported in the control AD+PBO groups of the SPRAVATO studies (-13.72, n=268) compared to the AAP studies (-8.45 points, n=3571).[5]

Limitations

- The authors noted that the methodological differences of the studies make direct comparisons of mean reductions in MADRS for AAP augmentation and SPRAVATO difficult.[5]
  - For example, in the SPRAVATO studies, patients with MDD with an inadequate response discontinued their current AD and initiated a new AD, while patients in the AAP studies continued their current AD medication in the DB phase.
- The lack of safety considerations, exclusion of 5 RCTs without MADRS assessments, and exclusion of RCTs with patients with MDD and psychotic symptoms were identified as additional limitations to this meta-analysis.[5]

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A meta-analysis was conducted to assess differences in AD efficacy of SPRAVATO and AAPs, both in combination with oral ADs. Medications included aripiprazole, brexpiprazole, and quetiapine for adjunctive treatment of MDD, combination olanzapine/fluoxetine for TRD, and SPRAVATO for treatment of TRD.[6]

- Studies included were phase 3, DB, RCTs that were 4-12 wks in length and were pivotal in supporting the FDA approved indications.[6]
- The study population included adult patients 18-65 years of age who had a current episode of diagnosed MDD with an inadequate response to at least 1 trial of AD treatment prior to study enrollment.[6]

Outcomes

- Mean change in total score on the MADRS[6]
- Response (proportion of patients who achieved at least 50% decrease in the MADRS total score from baseline to endpoint)[6]
- Remission (MADRS total score at DB endpoint that decreased below a prespecified threshold of 12, 10, or 8, depending on the study)[6]

Statistical Analysis

- The R package “metafor” was used for statistical analysis on summary-level data (i.e., mean, SD and group size) from each study.[6]
- The effect from multiple treatment arms were pooled using the Cochrane Handbook for Systematic Reviews of Interventions.[14]

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- Twelve studies were included in the analysis with 2,565 patients that received AAP+AD or SPRAVATO+AD and 1,711 patients that received PBO+AD; 2 of the 12 studies were for SPRAVATO.[6]
- Baseline demographics were similar between the pooled AAP+AD arm and the pooled SPRAVATO+AD arm, with the exception of patients in the SPRAVATO+AD arm having a higher mean MADRS total score (37.4 vs 28.0; *P*<0.0001), a longer duration of current MDD episode (152.8 wks vs 55.7 wks; *P*<0.0001), and they had significantly lower BMI (-1.5; *P*=0.02).[6]
- **LS mean MADRS total score reduction in the pooled active treatment arms of the SPRAVATO vs AAP studies:** At endpoint, the reduction in the estimated MADRS total score was 9.16 points greater with pooled SPRAVATO+AD vs pooled AAP+AD (*P*<0.0001).[6]
- **LS mean MADRS total score reduction in the pooled control arms of the SPRAVATO vs AAP studies:** A significantly greater reduction by 7.57 points in the estimated MADRS total score in the pooled PBO+AD arms of the SPRAVATO studies was observed vs that of the control arms of the AAP augmentation studies (*P*<0.0001).[6]
- **Mean differences in MADRS total score reduction between active and control arms:** The mean difference in MADRS total score reduction between pooled SPRAVATO+AD arms and pooled PBO+AD arms was 1.87 points greater than that for pooled AAP+AD and PBO+AD arms (95% CI, -4.49 to 0.74; *P*=0.16).[6]
- **Mean differences in response rates at endpoint:** The mean difference in response rates between SPRAVATO+AD and its control arms was significantly larger than that between AAPs and their control arms (+16% [95% CI: 0.07 to 0.25]; *P*=0.0004).[6]

Limitations

- Limitations of the meta-analysis include differences in study design/methodology (e.g., SPRAVATO studies initiated a new oral AD while AAPs were added to inadequate ADs), patient characteristics including the level of treatment resistance, study duration, and dosing (e.g., dosing frequency).[6]
- Patients in the SPRAVATO studies had a higher mean baseline MADRS score which may have affected the results of the analysis in favor of SPRAVATO; however, these patients were also treatment-resistant to at least 2 adequately dosed ADs and could have been more difficult to treat.[6]

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AAP	Atypical antipsychotics	**MDE**	Major depressive episode
AD	Antidepressant	**MedDRA**	Medical Dictionary for Regulatory Activities
AE	Adverse event	**OC**	Observed case
BMI	Body mass index	**OR**	Odds ratio
CGI-S	Clinical Global Impressions – Severity	**PBO**	Placebo
CI	Confidence interval	**PHQ-9**	Patient Health Questionnaire-9
CMH	Cochran–Mantel–Haenszel	**Q2W**	Every 2 weeks
DB	Double blind	**QLDS**	Quality of Life in Depression Scale
DC	Discontinuation	**QW**	Once weekly
DSM-5	Diagnostic and Statistical Manual of Mental Disorders	**RCT**	Randomized controlled trial
EQ-5D-5L	EuroQol 5-Dimension, 5-Level instrument	**SD**	Standard deviation
EQ-VAS	EuroQol Visual Analogue Scale	**SDS**	Sheehan Disability Scale
FDA	Food and Drug Administration	**SE**	Standard error
HR	Hazard ratio	**SF-36**	36-Item Short Form Health Survey
HRQoL	Health related quality of life	**SNRI**	Serotonin norepinephrine reuptake inhibitor
IDS-C30	Inventory of Depressive Symptomatology, Clinician-Rated	**SSRI**	Selective serotonin reuptake inhibitor
LOCF	Last observation carried forward	**TEAE**	Treatment-emergent adverse event
LS	Least squares	**TRD**	Treatment-resistant depression
LSMD	Least squares mean difference	**Wk**	Week
MADRS	Montgomery-Åsberg Depression Rating Scale	**WPAI:D**	Work Productivity and Activity Impairment: Depression
MDD	Major depressive disorder	**XR**	Extended release

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A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 25 December 2025.

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