Esketamine Nasal Spray Demonstrated Robust Efficacy over Quetiapine Extended Release over the Short- and Long-term: Sensitivity Analyses of ESCAPE-TRD, a Randomised Phase IIIb Clinical Trial

Young A.H. (MBChB, PhD),[1,2] Llorca P.M. (MD, PhD),[3] Fagiolini A. (MD, PhD),[4] Falkai P. (MD),[5] Cardoner N. (MD, PhD),[6] Nielsen R.E. (MD, PhD),[7] Blomqvist O. (MD, PhD),[8] Godinov Y. (MD),[9] Rive B. (PhD),[10] Diels J.,[11] Mulhern-Haughey S. (PhD),[12] Reif A. (MD)[13,14]

[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London, Department of Psychological Medicine, London, United Kingdom; [2]South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Beckenham, United Kingdom; [3]CHU Clermont-Ferrand, Department of Psychiatry, University of Clermont Auvergne, UMR 6602 Institut Pascal (IP), Clermont-Ferrand, France; [4]Department of Molecular Medicine, University of Siena School of Medicine, Siena, Italy; [5]Department of Psychiatry, Medical Faculty, LMU Munich, Munich, Germany; [6]Hospital de la Santa Creu i Sant Pau Universitat Autònoma de Barcelona (UAB), CIBERSAM, Barcelona, Spain; [7]Aalborg University Hospital, Psychiatry, Aalborg, Denmark & Aalborg University, Aalborg, Denmark; [8]Capio Lundby Hospital, Gothenburg, Sweden; [9]Janssen EMEA, Sofia, Bulgaria; [10]Janssen EMEA, Paris, France; [11]Janssen Pharmaceutica NV, Beerse, Belgium; [12]Janssen EMEA, Dublin, Ireland; [13]Goethe University Frankfurt, University Hospital, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Frankfurt, Germany; [14]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Frankfurt am Main, Germany.

Correspondence to: Professor Allan H. Young; allan.young@kcl.ac.uk, +44 (0)20 7848 0088

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SUPPLEMENTARY MATERIALS

Supplementary Appendix 1. ESCAPE-TRD Methods: Study Design and Patient Inclusion & Exclusion Criteria

Study Design

ESCAPE-TRD (NCT04338321) was a randomised, open-label, rater-blinded, active-controlled phase IIIb study that aimed to evaluate the efficacy and safety of esketamine nasal spray (NS) versus quetiapine extended release (XR), both in combination with a continuing selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI), in patients with treatment resistant depression (TRD). ESCAPE-TRD comprised an up-to-14-day screening phase, 8-week acute treatment phase, 24-week maintenance phase, and a safety follow-up 2 weeks after the last dose of study treatment.

Both esketamine NS and quetiapine XR were dosed as per the respective summary of product characteristics, valid at the time of study conduct.[1, 2] Esketamine NS treatments were administered at a dose of 56 mg on Day 1, 56/84 mg twice weekly from Day 4 during Weeks 1–4, weekly during Weeks 5–8, and weekly or every 2 weeks during Weeks 9–32; 150–300 mg of quetiapine XR was taken once daily (quetiapine XR dose at Day 1 was 50 mg, patients were then titrated up to 150–300 mg daily by the end of Week 2).

Montgomery-Åsberg Depression Rating Scale (MADRS) scores were collected at Day 1 (baseline), Week 1 and every 2 weeks from Week 2 to Week 32, inclusive.

Patients

Patients aged 18–≤74 years with TRD were eligible for inclusion. Patients met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for major depressive disorder,[3] with Inventory of Depressive Symptomatology – Clinician-rated, 30-item scale (IDS-C30) score ≥34.

In the current major depressive episode, patients had experienced 2–6 consecutive treatment failures (<25% symptom improvement), including the current treatment, from ≥2 different antidepressant classes. Patients were receiving a current antidepressant treatment including an SSRI/SNRI that resulted in non-response, but

had shown signs of minimal clinical improvement, after ≥6 weeks of treatment at adequate dosage with up-titration to the maximum tolerated dose. One current SSRI/SNRI treatment was continued whilst any other current antidepressant treatments, including augmentation agents, were discontinued. Full inclusion and exclusion criteria have been published previously.[4]

Patients were randomised 1:1 to esketamine NS or quetiapine XR, stratified by age (18–≤64 years; 65–≤74 years) and total number of prior treatment failures (2; ≥3).

Supplementary Appendix 2. Remote vs in-person MADRS assessment

As the ESCAPE-TRD study was conducted during the coronavirus-19 (COVID-19) pandemic, additional flexibility (e.g. video assessments) had to be permitted to maintain follow-up of patients, and accommodate for the COVID-19 pandemic and related restrictions. This analysis provides an estimation of the impact of COVID-related additional flexibility provided to patients on the MADRS results.

Methodology

Whilst MADRS score was normally assessed in in-person interviews between the patient and the independent rater, remote assessments (via video call) were allowed to accommodate for COVID-19-related restrictions. Remote assessments were still able to ensure proper follow-up of patients. The influence of the remote assessments on MADRS change from baseline (CfB) was explored in sensitivity analyses.

The MADRS CfB at each visit was analysed using a mixed model for repeated measurements (MMRM) based on observed cases (on-treatment visits only). The model included baseline score as a covariate, study intervention, stratification factors (age [18–≤64 years; 65–≤74 years], total number of treatment failures [2; ≥3]), visit and visit-by-study intervention interaction as fixed effects applying an unstructured covariance matrix.

The analysis was run with and without an additional time-varying adjustment variable that indicated the type of MADRS assessment at the visit: in-person versus remote (MADRS assessment at baseline was always in-person). This determined the influence of this adjustment on the estimated difference between treatment arms at each visit and also estimated the direct impact of remote assessments on MADRS scores compared with an in-person assessment.

Results

Of the 8,868 MADRS assessments conducted during the on-treatment phase of the study, 120 (1.35%) were completed remotely. The proportion of remote evaluations of MADRS was well balanced between the esketamine NS (71/4780; 1.49%) and quetiapine XR (49/4088; 1.20%) treatment arms.

Analyses with or without the time-varying adjustment on the type of MADRS assessment showed very little impact of this adjustment on the estimated difference between esketamine NS and quetiapine XR on MADRS CfB at each visit (**Supplementary Table 3**).

Remote assessments were estimated to yield MADRS scores 0.645 points lower (95% CI [–0.164, 1.455]; p=0.1179) than in-person assessments.

Discussion

Conducting an in-person study during the COVID-19 pandemic was difficult due to the related restrictions, and adaptations had to be made to adjust. To properly comply with these restrictions whilst maintaining sufficient data quality for clinical follow up, a remote option was offered which allowed the patient to complete the MADRS assessment via a video call. Only a small number of patients used this option. This appeared to have been a suitable solution to meet both goals, and given the marginal difference in remote MADRS assessment, was unlikely to have created any bias in the results. Despite different assessment methods to accommodate for COVID-19-related restrictions, evaluating TRD severity using the MADRS was found to be robust.

Supplementary Table 1. Sensitivity analyses

Sensitivity analysis category	Description	Performed on primary/key secondary endpoint:
Alternative thresholds	The remission cut-off was reduced to a MADRS total score of ≤8	Primary
	Patients were relapse-free through Week 32; the remission cut-off was reduced to a MADRS total score of ≤8	Key Secondary
	The remission cut-off was raised to a MADRS total score of ≤12	Primary
	Patients were relapse-free through Week 32; the remission cut-off was raised to a MADRS total score of ≤12	Key Secondary
	The relapse cut-off was reduced to a MADRS total score of ≥18	Key Secondary
	The relapse cut-off was redefined as CGI-S ≥5	Key Secondary
Alternative timepoints	The temporal cut-off for remission was reduced to Week 6	Primary
	Patients were relapse-free through Week 32; the temporal cut-off for remission was reduced to Week 6	Key Secondary
	The temporal cut-off for remission was raised to Week 10	Primary
	Patients were relapse-free through Week 32; the temporal cut-off for remission was raised to Week 10	Key Secondary
	The definition of remission was changed to remission any point at or before 8 weeks	Primary
	Patients were relapse-free through Week 32; the definition of remission was changed to remission any point at or before 8 weeks	Key Secondary
	The temporal cut-off for relapse was decreased to 4 months	Key Secondary

The primary endpoint was achieving remission (MADRS total score ≤10) at Week 8. The key secondary endpoint was remaining relapse-free (MADRS total score ≤22) through Week 32 after achieving remission at Week 8. CGI-S: Clinical Global Impression-Severity scale; MADRS: Montgomery-Åsberg Depression Rating Scale; SA: sensitivity analysis.

Supplementary Table 2. Patient disposition in ESCAPE-TRD

All randomised patients	N=676	
	Esketamine NS +SSRI/SNRI	Quetiapine XR +SSRI/SNRI
All randomised patients	n=336	n=340
Treatment discontinuation during acute phase	n=41, 12.2% • AE (n=9) • Lack of efficacy (n=13) • Refused further treatment (n=16) • Other[a] (n=3)	n=90, 26.5% • AE (n=29) • Lack of efficacy (n=32) • Refused further treatment (n=19) • Other[a] (n=10)
Patients that discontinued treatment during the acute phase but entered follow-up	n=26, 7.7%	n=73, 21.5%
Patients completing acute phase (Week 8)	n=295, 87.8%	n=250, 73.5%
Treatment discontinuation during maintenance phase	n=37, 11.0% • AE (n=5) • Lack of efficacy (n=15) • Refused further treatment (n=12) • Death (n=1) • Other[a] (n=4)	n=47, 13.8% • AE (n=10) • Lack of efficacy (n=19) • Refused further treatment (n=10) • Death (n=1) • Other[a] (n=7)
Patients that discontinued treatment during the maintenance phase but entered follow-up	n=31, 9.2%	n=35, 10.3%
Patients completing maintenance phase (Week 32)	n=258, 76.8%	n=203, 59.7%

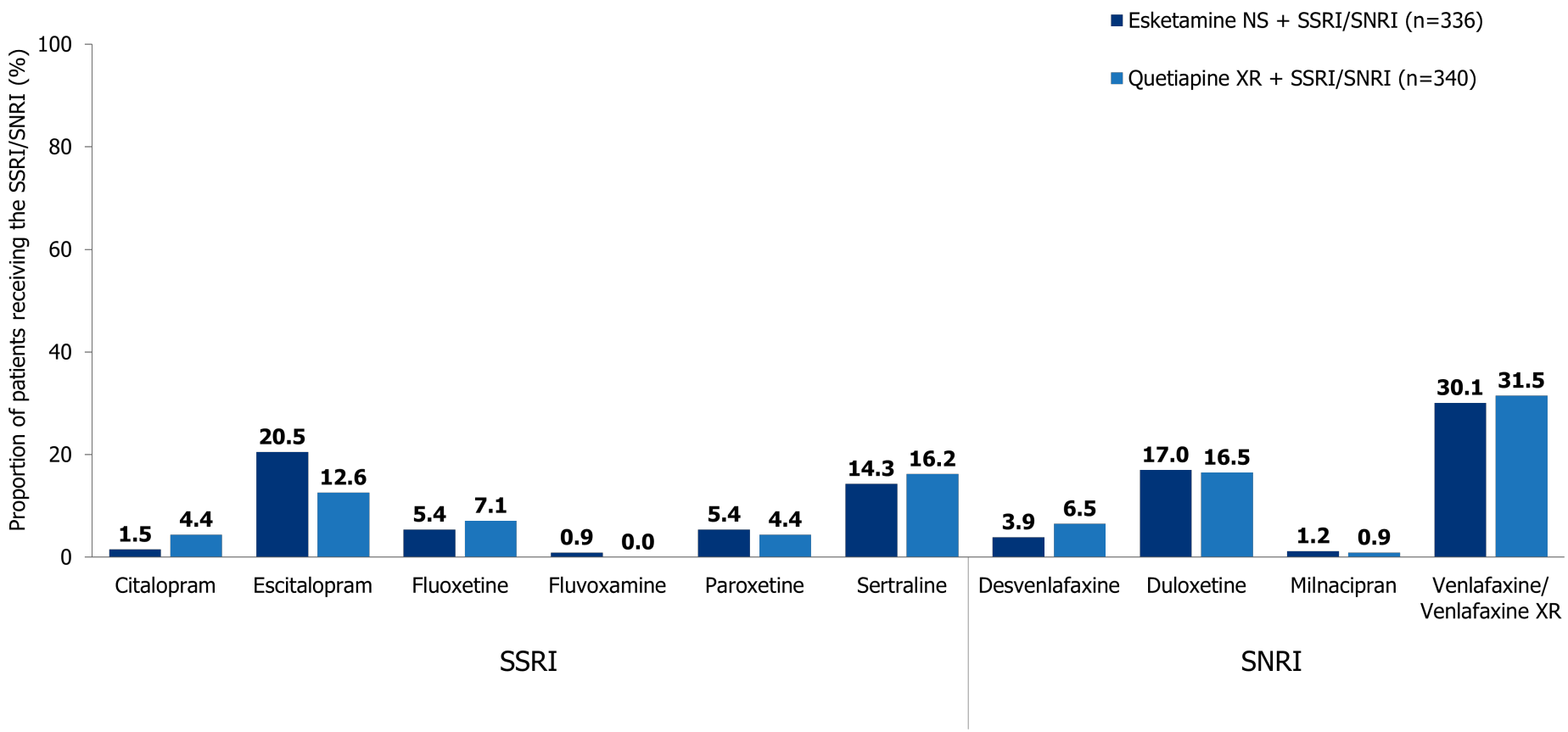
Full analysis set (includes all randomised patients). The study included an 8-week acute phase followed by a 24-week maintenance phase. Patients who terminated the trial treatment before Day 64 were considered to have discontinued the study treatment by Week 8. Percentages were based on the number of patients in the indicated population. [a]'Other' included: discontinuation of underlying SSRI/SNRI treatment, lost to follow-up, minimal required study treatment dose could not be tolerated, non-compliance with study treatment, physician decision, pregnancy, and other. AE: adverse event; NS: nasal spray; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; XR: extended release.

Supplementary Table 3. Estimated difference in MADRS change from baseline between esketamine NS and quetiapine XR at each visit

Week	Model adjusted based on remote assessment MADRS CfB (95% CI) p value	Model without adjustment based on remote assessment MADRS CfB (95% CI) p value
1	−1.606 (−2.389, −0.822) <0.0001	−1.618 (−2.401, −0.834) <0.0001
2	−3.018 (−4.026, −2.010) <0.0001	−3.026 (−4.034, −2.018) <0.0001
4	−3.275 (−4.408, −2.142) <0.0001	−3.275 (−4.408, −2.141) <0.0001
6	−3.092 (−4.342, −1.843) <0.0001	−3.091 (−4.340, −1.842) <0.0001
8	−2.772 (−4.084, −1.459) <0.0001	−2.761 (−4.072, −1.449) <0.0001
10	−2.920 (−4.170, −1.671) <0.0001	−2.922 (−4.171, −1.672) <0.0001
12	−2.700 (−4.018, −1.382) <0.0001	−2.707 (−4.026, −1.388) <0.0001
14	−2.913 (−4.196, −1.630) <0.0001	−2.910 (−4.194, −1.627) <0.0001
16	−2.814 (−4.132, −1.496) <0.0001	−2.812 (−4.131, −1.493) <0.0001
18	−2.589 (−3.958, −1.221) 0.0002	−2.598 (−3.966, −1.230) 0.0002
20	−2.041 (−3.438, −0.645) 0.0043	−2.040 (−3.437, −0.643) 0.0043
22	−2.047 (−3.405, −0.689) 0.0032	−2.051 (−3.409, −0.693) 0.0031
24	−1.846 (−3.223, −0.469) 0.0087	−1.850 (−3.228, −0.473) 0.0086
26	−1.856 (−3.218, −0.494) 0.0077	−1.864 (−3.226, −0.501) 0.0074
28	−1.424 (−2.829, −0.020) 0.0469	−1.425 (−2.831, −0.020) 0.0469
30	−1.633 (−3.051, −0.214) 0.0241	−1.646 (−3.065, −0.226) 0.0232
32	−2.194 (−3.580, −0.808) 0.0020	−2.196 (−3.583, −0.810) 0.0020

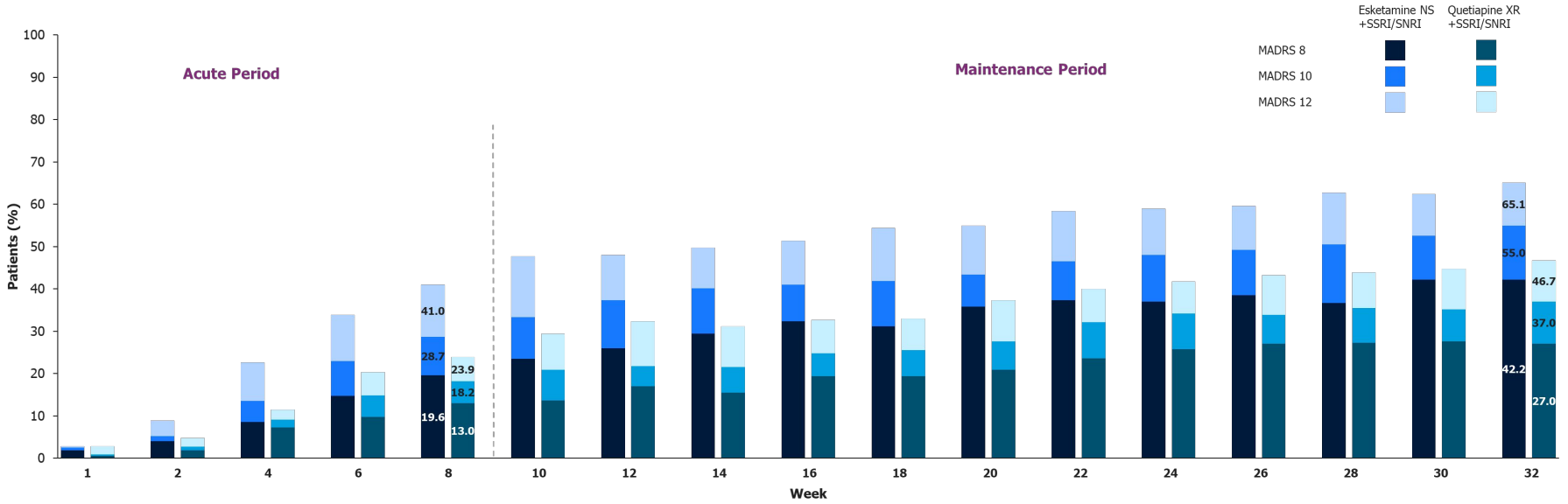
1 Full analysis set. Models were adjusted on the type of MADRS assessment (in person versus remote),
2 where noted. CfB: change from baseline; CI: confidence interval; MADRS: Montgomery-Åsberg
3 Depression Rating Scale.

Supplementary Figure 1. Adjunctive antidepressant treatment (SSRI/SNRIs) at baseline



Full analysis set, includes all randomised patients. NS: nasal spray; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; XR: extended release.

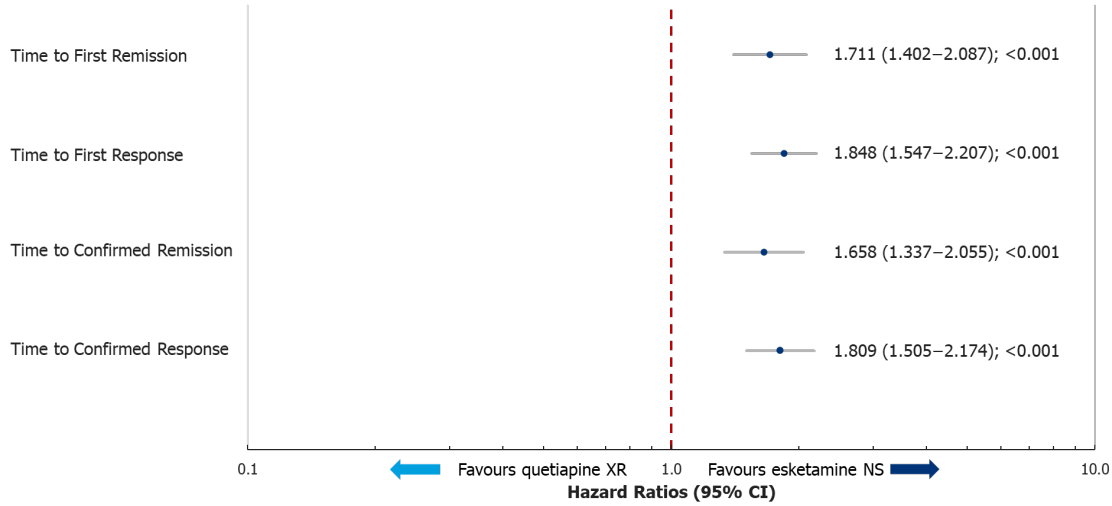
Supplementary Figure 2. Remission over time using MADRS 8, 10 and 12 cut-offs (LOCF)



Relative Risk (95% CI)	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
MADRS ≤8	3.106 (0.623–15.481) p=0.167	2.204 (0.840–5.782) p=0.108	1.182 (0.696–2.007) p=0.537	1.508 (0.987–2.305) p=0.057	1.506 (1.051–2.157) p=0.026	1.740 (1.242–2.438) p=0.001	1.544 (1.142–2.085) p=0.005	1.920 (1.420–2.595) p<0.001	1.679 (1.282–2.198) p<0.001	1.618 (1.233–2.124) p=0.001	1.721 (1.334–2.220) p<0.001	1.589 (1.253–2.016) p<0.001	1.444 (1.147–1.818) p=0.002	1.438 (1.151–1.797) p=0.001	1.353 (1.080–1.695) p=0.009	1.536 (1.238–1.905) p<0.001	1.572 (1.265–1.954) p<0.001
MADRS ≤10	2.754 (0.728–10.423) p=0.136	1.912 (0.857–4.262) p=0.113	1.481 (0.949–2.314) p=0.084	1.544 (1.111–2.147) p=0.010	1.591 (1.194–2.119) p=0.002	1.601 (1.233–2.079) p<0.001	1.717 (1.341–2.198) p<0.001	1.878 (1.471–2.398) p<0.001	1.659 (1.321–2.082) p<0.001	1.655 (1.324–2.068) p<0.001	1.585 (1.281–1.961) p<0.001	1.458 (1.202–1.769) p<0.001	1.411 (1.172–1.699) p<0.001	1.461 (1.215–1.758) p<0.001	1.432 (1.197–1.713) p<0.001	1.503 (1.257–1.797) p<0.001	1.495 (1.260–1.773) p<0.001
MADRS ≤12	1.029 (0.409–2.589) p=0.952	1.836 (1.011–3.333) p=0.046	1.979 (1.374–2.849) p<0.001	1.678 (1.291–2.180) p<0.001	1.722 (1.365–2.173) p<0.001	1.630 (1.333–1.994) p<0.001	1.486 (1.227–1.799) p<0.001	1.606 (1.325–1.948) p<0.001	1.579 (1.311–1.900) p<0.001	1.659 (1.385–1.987) p<0.001	1.486 (1.255–1.759) p<0.001	1.468 (1.253–1.720) p<0.001	1.418 (1.215–1.655) p<0.001	1.384 (1.192–1.608) p<0.001	1.433 (1.238–1.660) p<0.001	1.397 (1.208–1.616) p<0.001	1.401 (1.220–1.610) p<0.001

Full analysis set. CI: confidence interval; MADRS: Montgomery-Åsberg Depression Rating Scale; NS: nasal spray; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; XR: extended release.

Supplementary Figure 3. Hazard ratios for time to event outcomes



Full analysis set. Data are displayed as: hazard ratio (95% CI); p value. CI: confidence internal; NS: nasal spray; XR: extended release.

Supplementary References

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