

Real-world outcomes of esketamine in major depressive disorder with comorbid anxiety or trauma and stress-related disorders (ELLIPSE Study)

INTRODUCTION

Psychiatric comorbidities, including anxiety disorders and trauma and stress-related disorders (TSRD), are frequent in major depressive disorder (MDD) and may worsen symptom burden, suicidality, functioning and treatment outcomes¹⁻³. Esketamine nasal spray was approved in Europe in December 2019 for treatment-resistant depression (two previous antidepressant failures), but real-world data in MDD patients with these comorbidities remain limited⁴.

ELLIPSE previously provided prospective real-world evidence on esketamine use, effectiveness and safety in adults with unipolar MDD in France⁵. The present analysis focuses on patients with baseline anxiety disorder or TSRD.

OBJECTIVES

To describe 12-month clinical and safety outcomes after esketamine initiation in adults with unipolar MDD and baseline anxiety or TSRD treated in routine French practice.

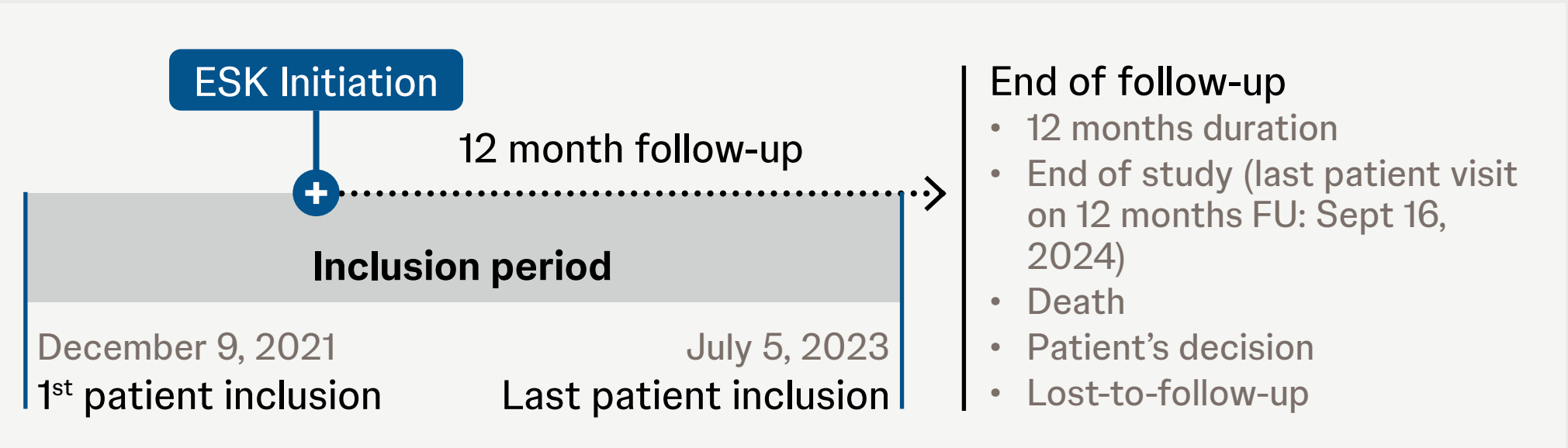
METHODS

ELLIPSE is a French, prospective, multicenter, observational study of adults with unipolar MDD initiating esketamine in routine care⁵.

Study population

All patients who received at least one dose of ESK, who meet study inclusion/exclusion criteria:

- Inclusion criteria:** adult (≥18 years) patients diagnosed with unipolar depression who not objected the collection of their data.
- Exclusion criteria:** patients who have participated, or planned to participate, in a clinical trial at the time of enrollment or within the 30 days prior to enrollment.



Visits were scheduled at baseline, D8, M1, M2, M3, M6, M9, M12.

Anxiety disorder and TSRD subgroups were investigator-defined from the overall cohort using DSM-5 criteria.

Effectiveness analyses included the prospective overall cohort (N=200); safety analyses included patients receiving ≥1 esketamine dose (N=207).

Scales

- MADRS:** 10-item clinician-rated depression-severity scale; range 0–60, with higher scores indicating greater severity
- QLDS:** 34-item patient-reported quality-of-life scale; range 0–34, with higher scores indicating poorer quality of life
- CGI-SS-R:** Clinician-rated suicidality-severity scale; range 0–6, with higher scores indicating greater severity.

CONCLUSION

Esketamine was associated with improvements in depressive symptoms, health-related quality of life and suicidality severity in patients with unipolar MDD and baseline anxiety disorder or TSRD. Safety findings in anxiety were broadly aligned with the overall safety population, while TEAEs and dissociative states were more frequently reported in TSRD without higher TEAE-related discontinuation. Findings are descriptive and should be interpreted cautiously due to the post hoc design and decreasing sample sizes over follow-up.

Reference
¹Kalin NH. The Critical Relationship Between Anxiety and Depression. AJP 2020; 177: 365–367
²Angelakis S, Nixon RDV. The Comorbidity of PTSD and MDD: Implications for Clinical Practice and Future Research. Behav change 2015; 32: 1–25
³Wang S-M, Pae C-U. Major depressive disorder: how to evaluate and manage patients with psychiatric and medical comorbidities. In: Carvalho AF, McIntyre RS (eds)
⁴European Medicines Agency. Spravato : EPAR - Product Information, https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf (December2019)
⁵Llorca P-M, Mékaoui L, Rotharmel M, et al. Real world clinical practice, efficacy and safety of esketamine nasal spray in MDD patients: the French ELLIPSE study. Eur Psychiatr 2025; 68: S317–S317

RESULTS

Patients characteristics

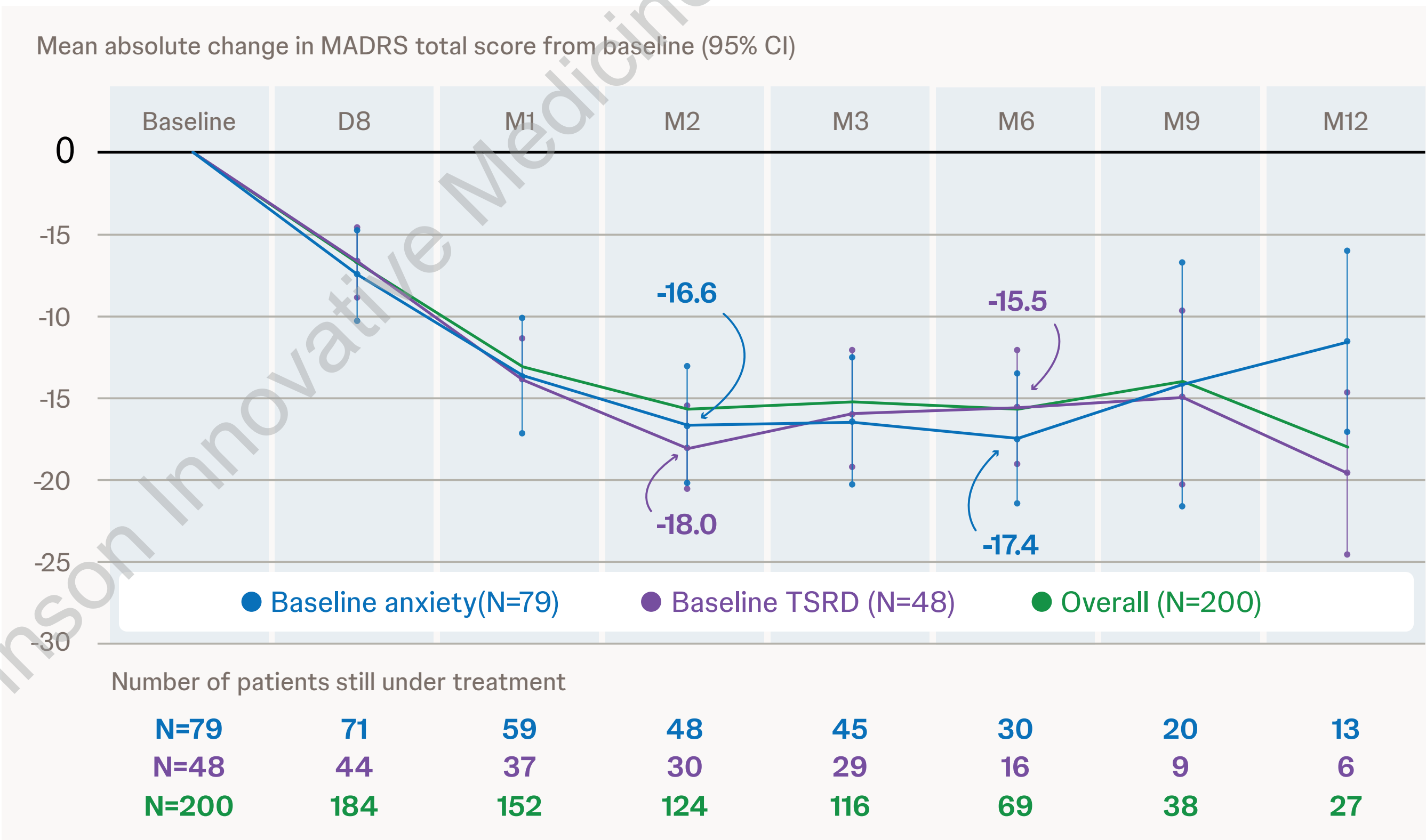
In the overall cohort (N=200), 79 patients (39.5%) had baseline anxiety disorder, 48 (24.0%) had TSRD, and 17 (8.5%) had both.

Characteristic	Anxiety (N=79)	TSRD (N=48)	Overall (N=200)
Age, years, mean (SD)	46.7 (16.8)	42.1 (15.6)	46.6 (15.5)
Female, n (%)	48 (60.8%)	36 (75.0%)	113 (56.5%)
Follow-up duration , months, median (IQR)	11.9 (6.7-12.2)	12.0 (5.5-12.2)	11.8 (6.0-12.2)
Lifetime history of depression			
Duration of depression, years, median (IQR)	12.8 (4.0–23.0)	6.4 (2.2–10.3)	10.0 (3.2–22.9)
Lifetime MDE excluding current MDE, mean (SD)	3.5 (3.4)	2.4 (2.5)	3.0 (2.9)
≥1 suicide attempt among patients with ≥1 previous MDE, n/N (%)	29/65 (44.6%)	20/36 (55.6%)	78/160 (48.8%)
Current MDE			
Current MDE duration, years, median (IQR)	2.0 (1.0-3.4)	1.9 (0.7-3.8)	1.8 (0.9-3.2)
Treatment-resistant depression, clinician judgement, n (%)	78 (98.7%)	47 (97.9%)	195 (97.5%)
≥1 inpatient hospitalization since current MDE onset, n (%)	50/79 (63.3%)	30/48 (62.5%)	115/200 (57.5%)
Baseline MADRS, mean (SD)	32.2 (7.0)	33.4 (6.2)	31.9 (7.0)
Baseline QLDS, mean (SD)	20.4 (3.7)	21.2 (3.2)	20.8 (3.8)
Baseline CGI-SS-R, mean (SD)	1.9 (1.4)	2.4 (1.6)	1.9 (1.4)

MADRS Evolution

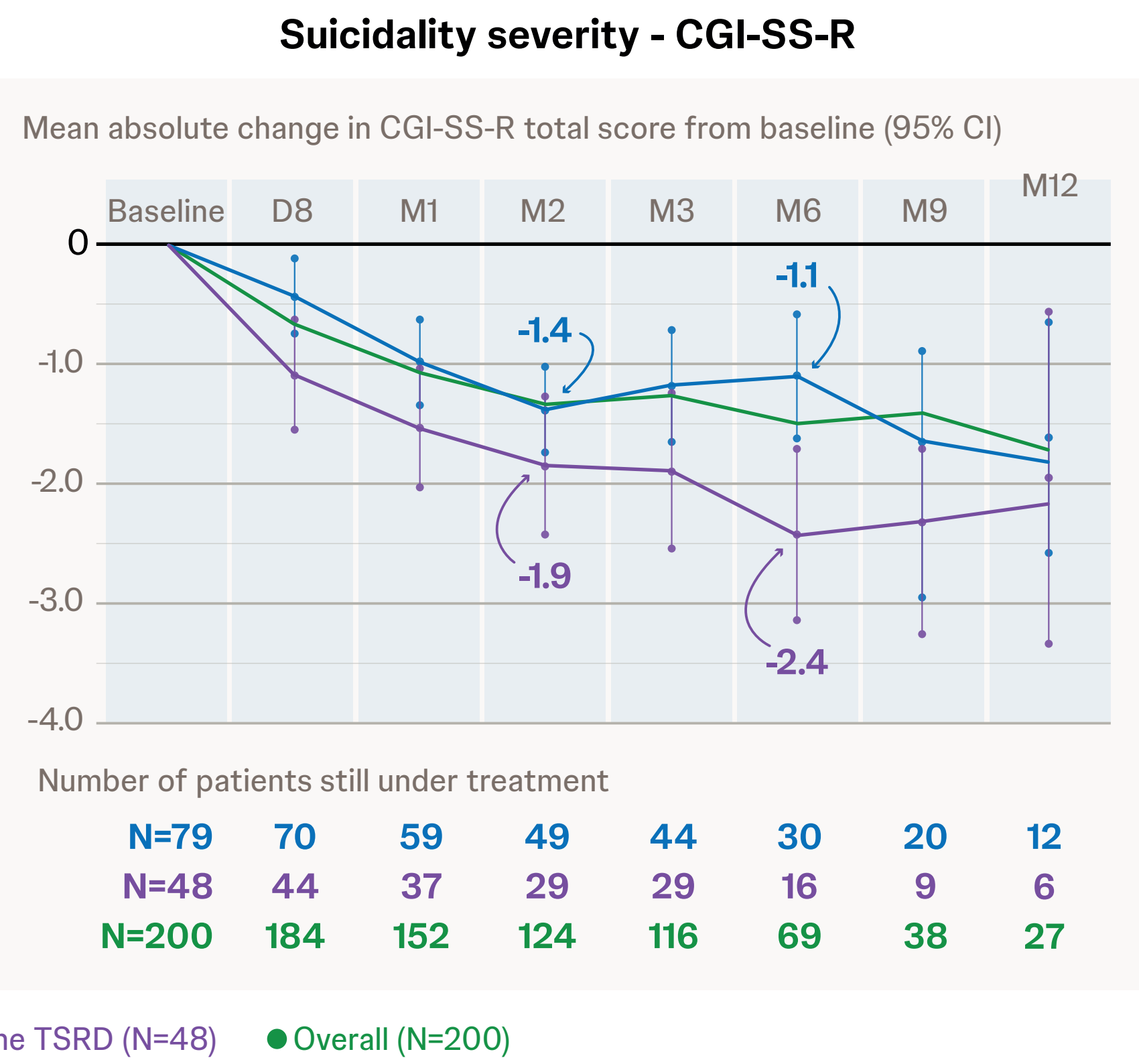
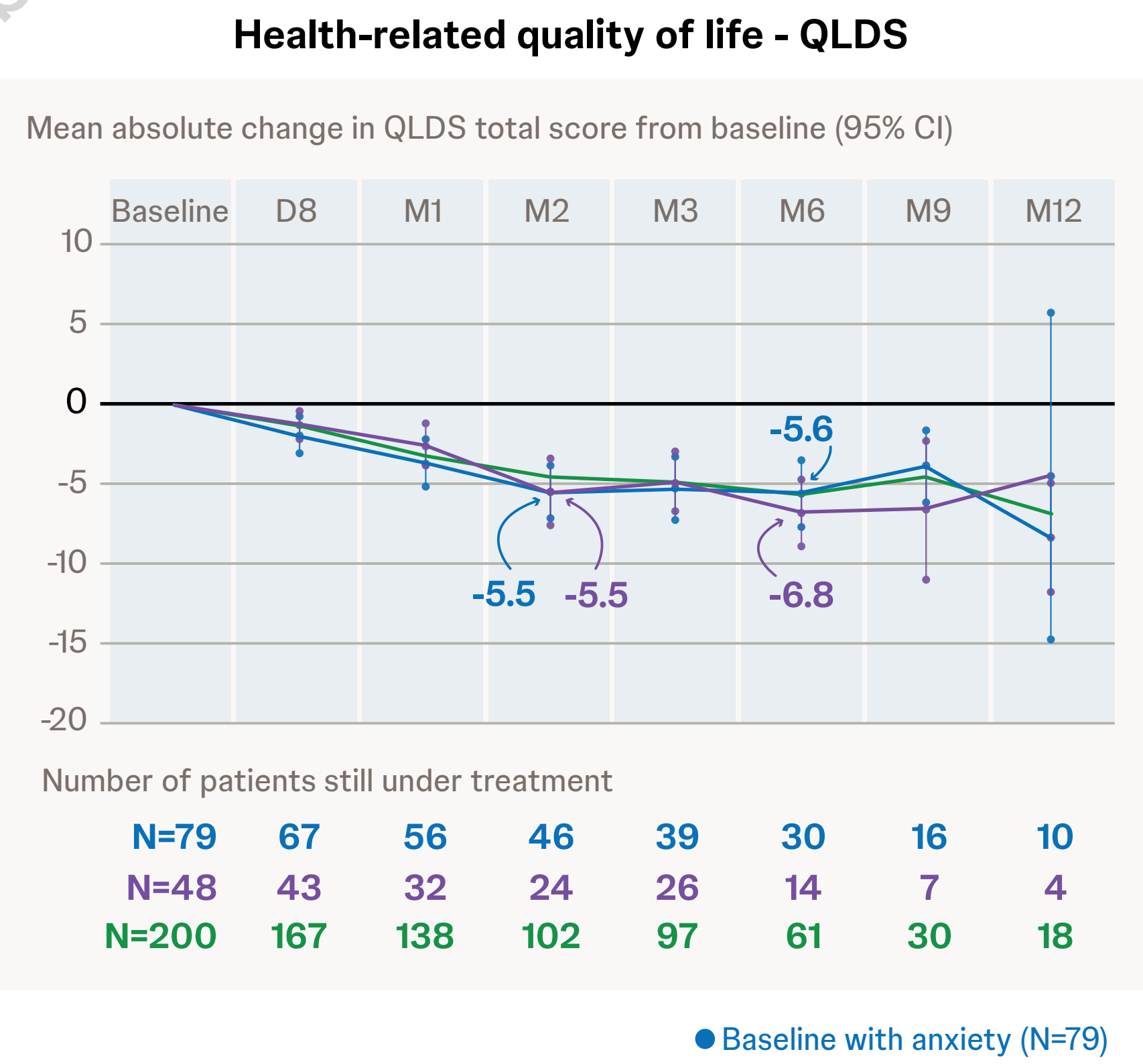
Among patients still receiving esketamine, mean MADRS decreases from baseline were observed in both comorbidity subgroups and in the overall cohort.

At M2 and M6, mean changes were -18.0 and -15.5 in the anxiety subgroup, -16.6 and -17.4 in the TSRD subgroup, and -15.6 and -15.6 in the overall cohort, respectively.



Health-related Quality of Life

At M2 and M6, mean QLDS changes from baseline were -5.5 and -5.6 in anxiety, -5.5 and -6.8 in TSRD, and -4.6 and -5.7 overall. Mean baseline CGI-SS-R was 2.4 in TSRD versus 1.9 in both anxiety and the overall cohort; corresponding changes at M2 and M6 were -1.86 and -2.44 in TSRD, -1.39 and -1.10 in anxiety, and -1.34 and -1.50 overall.



Safety

Safety findings in anxiety were broadly aligned with the total safety population. In TSRD, TEAEs and dissociative states were reported more frequently. However, dissociative states were non-serious, recovered, and rarely led to treatment discontinuation.

Safety outcome	Anxiety N=82	TSRD N=49	Overall N=207
≥1 TEAE	51 (62.2)	42 (85.7)	136 (65.7)
Serious TEAE	7 (8.5)	7 (14.3)	25 (12.1)
Treatment-related TEAE	35 (42.7)	31 (63.3)	99 (47.8)
TEAE leading to discontinuation	10 (12.2)	5 (10.2)	23 (11.1)
Most frequent treatment-related TEAEs	Dissociative states		
	23 (28.0)	23 (46.9)	58 (28.0)
Blood pressure increased			
	10 (12.2)	10 (20.4)	24 (11.6)

	Anxiety N=82	TSRD N=49	Overall N=207
Dissociative states			
Dissociative states	25 (30.5)	24 (49.0)	61 (29.5)
Outcome	Non serious		
	25 (30.5)	24 (49.0)	61 (29.5)
	Related to treatment		
	23 (28.0)	23 (46.9)	58 (28.0)
	Recovered		
	25 (30.5)	24 (49.0)	61 (29.5)
Outcome	No change in treatment posology		
	25 (30.5)	23 (46.9)	60 (29.0)
	Dose decreased		
	1 (1.2)	1 (2.0)	3 (1.4)
Treatment discontinuation			
	0 (0.0)	1 (2.0)	1 (0.5)