

Safety and tolerability of esketamine nasal spray versus quetiapine extended release in patients with treatment resistant depression

Roger S. McIntyre^{a,b,*}, Istvan Bitter^c, Jozefien Buyze^d, Andrea Fagiolini^e, Yordan Godinov^f, Philip Gorwood^{g,h}, Tetsuro Itoⁱ, Albino J. Oliveira-Maia^{j,k}, Eduard Vieta^l, Tamara Werner-Kiechle^m, Allan H. Young^{n,o}, Andreas Reif^{p,q}

^a University of Toronto, Toronto, Ontario, Canada

^b Braxia Scientific, Toronto, Ontario, Canada

^c Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

^d Janssen Pharmaceutica NV, Beerse, Belgium

^e Department of Molecular Medicine, University of Siena School of Medicine, Siena, Italy

^f Janssen EMEA, Sofia, Bulgaria

^g Université Paris Cité, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, Paris, France

^h GHU-Paris Psychiatrie et Neurosciences, Hôpital Sainte Anne, CMME, F-75014 Paris, France

ⁱ Janssen EMEA, High Wycombe, UK

^j Champalimaud Research and Clinical Centre, Champalimaud Foundation, Lisbon, Portugal

^k NOVA Medical School, Faculdade de Ciências Médicas, NMS, FCM, Universidade NOVA de Lisboa, Lisbon, Portugal

^l Institute of Neuroscience, University of Barcelona, Hospital Clinic, IDIBAPS, CIBERSAM, Barcelona, Spain

^m Janssen EMEA, Neuss, Germany

ⁿ Institute of Psychiatry, Psychology and Neuroscience, King's College London, Department of Psychological Medicine, London, United Kingdom

^o South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Beckenham, United Kingdom

^p Goethe University Frankfurt, University Hospital, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Frankfurt, Germany

^q Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Frankfurt am Main, Germany

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ABSTRACT

In ESCAPE-TRD (NCT04338321), esketamine nasal spray (NS) significantly increased the probability of remission at Week 8, and of being relapse-free through Week 32 after remission at Week 8, versus quetiapine extended release (XR) in patients with treatment resistant depression (TRD). Here, we explore the time course, burden and consequences of treatment emergent adverse events (TEAEs) in the phase IIIb ESCAPE-TRD trial. Patients with TRD were randomised 1:1 to esketamine NS or quetiapine XR, dosed per label alongside an ongoing selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor. In this secondary publication, safety analyses (comprising patients who received ≥ 1 dose of study treatment) included incidence, severity and durations (Kaplan-Meier method) of TEAEs, and subsequent dispositional changes. P values were not adjusted for multiple testing. 336 patients were randomised to esketamine NS and 340 to quetiapine XR; 334 and 336 received ≥ 1 dose of study treatment, respectively. TEAEs were significantly more common with esketamine NS than quetiapine XR (91.9 % versus 78.0 %; $p < 0.001$), but were typically mild/moderate and transient in nature: a greater proportion resolved on the same-day (92.0 % versus 12.1 %) and lead to treatment discontinuation in significantly fewer patients (4.2 % versus 11.0 %, respectively; $p < 0.001$). The proportion of days spent with TEAEs was significantly lower with esketamine NS than quetiapine XR (median: 11.9 % versus 21.3 %; $p < 0.001$). Although more frequent with esketamine NS, TEAEs were typically transient and mild, with discontinuation less likely versus quetiapine XR. Data were consistent with established safety profiles, with no new safety signals identified. Alongside greater efficacy, the demonstrably more favourable tolerability profile of esketamine NS versus quetiapine XR further supports its use for TRD.

* Correspondence to Brain and Cognition Discovery Foundation, 77 Bloor St W., Suite 617, Toronto, ON M5S 1M2, Canada.

E-mail address: roger.mcintyre@bcdcf.org (R.S. McIntyre).

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1. Introduction

Treatment resistant depression (TRD) is commonly defined as non-response to two or more pharmacological treatments of adequate duration and dose during the current major depressive episode (MDE) (European Medicines Agency, 2013), and affects approximately 30 % of patients with major depressive disorder (MDD) (McIntyre et al., 2023). While numerous therapeutic options are available to patients with MDD, few have good evidence or are approved specifically for the treatment of adults with TRD (McIntyre et al., 2023; Voineskos et al., 2020). The paucity of TRD-specific therapeutic options, alongside the high burden of illness in the TRD population, underscores the unmet clinical need of objective response for these patients (Heerlein et al., 2021). The likelihood of a patient continuing treatment is closely linked with the efficacy and safety profile of that treatment (Rosenblat et al., 2018, 2019). Notably, the most common reason for changing treatment in patients with MDD is ineffectiveness, while both side effects and ineffectiveness are the most common reasons for discontinuing a medication (Rosenblat et al., 2018). Weight gain is the adverse event most commonly reported to lead to discontinuation (McIntyre et al., 2024). Thus, safe and effective TRD-specific therapeutic options that are well tolerated and acceptable to patients are needed (Rosenblat et al., 2018; Voineskos et al., 2020).

In clinical practice, pharmacologic treatments approved for major depressive disorder, including oral antidepressants and augmentation medications, are used in various treatment strategies (European Medicines Agency, 2013; Heerlein et al., 2021). Amongst these pharmacological options are augmentation with second-generation antipsychotics including aripiprazole, brexpiprazole, cariprazine and quetiapine extended release (XR), which have demonstrable efficacy when administered in conjunction with antidepressant treatments in partial responders (McIntyre et al., 2023). Quetiapine XR, an antipsychotic augmentation agent, is variously indicated for, and supported by guidelines for use in, the treatment of patients with TRD, being one of the most commonly utilised treatments in real-world practice (European Medicines Agency, 2014, 2019a; Heerlein et al., 2022; National Institute for Health and Care Excellence, 2022; Nationale Versorgungs Leitlinien, 2022; U.S. Food and Drug Administration, 2020). Commonly reported treatment-emergent adverse events (TEAEs) in patients receiving quetiapine XR include sedation, dizziness, hypotension and weight gain (European Medicines Agency, 2019a; Osborne et al., 2020; U.S. Food and Drug Administration, 2020). Esketamine nasal spray (NS) is approved specifically for TRD when given in combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) (European Medicines Agency, 2019b; U.S. Food and Drug Administration, 2023). Common TEAEs include headache, dizziness, nausea, dissociation, somnolence and nasopharyngitis (Zaki et al., 2023).

ESCAPE-TRD was an open-label, 32-week, rater-blinded, randomised controlled trial that compared the efficacy and safety of flexibly-dosed esketamine NS with quetiapine XR, both in combination with an ongoing SSRI/SNRI, in patients with TRD (Reif et al., 2023). Of the few existing head-to-head studies in TRD, ESCAPE-TRD was the first comparison of esketamine NS with an augmentation strategy. ESCAPE-TRD demonstrated the superiority of esketamine NS over quetiapine XR for treatment efficacy in both the short and long term (Reif et al., 2023). Specifically, esketamine NS significantly increased the odds of achieving remission at Week 8 (primary endpoint), and of being relapse-free through Week 32 after achieving remission at Week 8 (key secondary endpoint), versus quetiapine XR (Reif et al., 2023). Although the total number of TEAEs was higher in the esketamine NS arm, fewer patients reported TEAEs leading to treatment discontinuation with esketamine NS versus quetiapine XR (Reif et al., 2023).

Since TRD is associated with high rates of non-recovery, chronicity and recurrence, prolonged treatment is often considered beyond acute resolution of symptoms (Hirschfeld, 2001; McIntyre et al., 2014; Rush

et al., 2006; Voineskos et al., 2020). The need for a longer-term treatment paradigm in patients with TRD thus invites the need to characterise not only the rate of reported TEAEs, but also the subjective experience and tolerability of a prescribed agent. Nevertheless, few studies have explored the long-term safety profile of antidepressant therapies in depth (Lunghi et al., 2020). Results from long-term studies have repeatedly documented the favourable long-term safety profile of esketamine NS, reporting that treatment-emergent dissociative symptoms were generally transient, with no reported events suggestive of abuse (Wajs et al., 2020; Young et al., 2023; Zaki et al., 2023). The present 32-week study, comparing esketamine NS to quetiapine XR in combination with conventional antidepressants, is to our awareness the longest comparative trial of its kind. This head-to-head design therefore provides a unique opportunity to characterise the long-term comparative effectiveness of esketamine NS versus quetiapine XR, which will be crucial in providing comprehensive information to both patients and clinicians in the context of shared decision-making processes.

To further extend our knowledge from what has been previously documented in the ESCAPE-TRD trial (Reif et al., 2023), in this secondary publication, we report key safety and tolerability findings, exploring the time course, burden and consequences of esketamine NS versus quetiapine XR treatment in patients with TRD.

2. Experimental procedures

2.1. Study design

ESCAPE-TRD (NCT04338321) was an open-label, rater-blinded, active-controlled, phase IIb, randomised study, comparing the efficacy and safety of esketamine NS versus quetiapine XR, both alongside an ongoing SSRI/SNRI, in patients with TRD, as reported previously (Reif et al., 2023). Patients were randomised 1:1 to esketamine NS or quetiapine XR, both flexibly dosed per label (European Medicines Agency, 2019b, 2019a). Randomisation was stratified by age (18–≤64 years; 65–≤74 years) and number of prior treatment failures (2; ≥3). Full inclusion and exclusion criteria are reported in **Supplementary Material S1**.

ESCAPE-TRD was conducted in accordance with the Declaration of Helsinki (World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects, 2013), and approved by country-specific ethics review boards. All patients provided written informed consent and the study was registered at ClinicalTrials.gov.

2.2. Safety analysis

Safety analyses included patients who received ≥1 dose of study treatment. TEAEs were determined per investigators' clinical judgment and defined as events occurring or worsening at or after the first dose, and within 14 days (non-serious) or 30 days (serious) of the last dose of study treatment. Evaluation of TEAEs, clinical laboratory tests, pregnancy tests, vital signs (including blood pressure [BP] measurements), 12-lead electrocardiograms (ECGs), nasal examinations and body weight were performed throughout the study to monitor participant safety, as recorded by the treating physician. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) versions 23–25 (MedDRA, 2024). In the esketamine NS arm, vital sign measurements (supine BP, pulse and respiratory rate) were recorded before and after each dose of study treatment; in the quetiapine XR arm they were recorded weekly (Weeks 1–4), every two weeks (Weeks 4–8), or every four weeks (Weeks 8–32).

2.3. Common TEAEs and TEAEs of special interest

Incidence of the most common TEAEs, defined as those occurring in ≥5 % of patients in either treatment arm, are reported. In a post-hoc

analysis, odds ratios (with 95 % confidence intervals) of TEAE incidence summary data were calculated, and incidence rates were compared between treatment arms using chi-squared tests. In addition, pre-specified TEAEs of special interest (preferred terms) were grouped by the following MedDRA-based categories: sedation, dissociation, suicidality, suggestive of abuse potential, cystitis and hepatic impairment (see **Supplementary Material S2** for a full list of TEAEs in each special interest category) and are reported by system organ class and preferred term.

2.4. Time course of TEAEs

In a post-hoc analysis, the median (95 % confidence interval [CI]) duration of each of the most common TEAEs (those occurring in ≥5 % of patients in either treatment arm) was calculated using the Kaplan-Meier method; missing or incomplete TEAE start/end dates were imputed (**Supplementary Material S3**). Proportions of TEAEs that resolved within the following windows of time are reported by treatment arm: ≤1 hour (h); >1 h to ≤2 h; >2 h to ≤3 h; >3 h to ≤8 h; >8 h but same day; unknown but same day; 2 days to ≤7 days; 8 days to ≤28 days; >28 days or AE ongoing.

2.5. Burden of TEAEs

In a post-hoc analysis, summary statistics were calculated for the number and proportion of days during study intervention on which a patient had any TEAE, where patients without a TEAE are counted with a duration of zero days. In a post-hoc analysis, a linear regression model with treatment arm as an independent variable was fitted to calculate the estimated mean difference between study arms in the proportion of days during study intervention on which a patient had any TEAE; 95 % CI and p value are reported. Frequencies of each event are reported by maximum severity (mild, moderate, or severe). The proportion of patients in each arm with a TEAE of weight change (increase or decrease), as considered clinically relevant and reportable by the attending physician, is reported. A post-hoc analysis of the proportion of patients with weight change of at least 7 % (increase or decrease) was also reported (described in **Supplementary Material S4**). Treatment-emergent abnormalities in vital sign measurements compared to baseline were calculated and their incidences are reported. Available data were used without imputation of missing values.

2.6. Consequences of TEAEs

Concomitant therapies were recorded and coded using the World Health Organization Drug Dictionary ([WHO Collaborating Centre for International Drug Monitoring, 1992](#)). The proportion of patients with at least one TEAE who received any concomitant medication as a result of a TEAE (post-hoc analysis) are reported by treatment arm. The proportion of TEAEs that led to dose reduction or interruption (post-hoc analysis), as well as the proportion of patients with a TEAE that led to treatment discontinuation, are also reported by treatment arm.

2.7. Statistical analysis

Odds ratios (ORs) and 95 % confidence intervals (CIs) between treatment arms are reported for the following TEAE summaries: incidence of TEAEs, TEAEs possibly related to treatment, TEAEs leading to death, incidence of ≥1 serious TEAE, TEAEs leading to treatment discontinuation, TEAEs leading to dose interruption or reduction and proportion of study intervention days with TEAEs. All p values reported were not adjusted for multiple testing.

3. Results

3.1. Patient disposition and common TEAEs

Overall, 336 patients were randomised to esketamine NS and 340 patients to quetiapine XR; 334 and 336 patients, respectively, received ≥1 dose of study treatment. Baseline characteristics were comparable between arms, as reported previously ([Reif et al., 2023](#)).

TEAEs were reported in 307 (91.9 %) patients treated with esketamine NS and 262 (78.0 %) with quetiapine XR (OR: 3.211; 95 % CI: 2.006, 5.141; $p < 0.001$; **Table 1**). Serious TEAEs occurred in 19 (5.7 %) patients treated with esketamine NS, and 17 (5.1 %) of those treated with quetiapine XR (OR: 1.132; 95 % CI: 0.578, 2.218; $p = 0.718$; **Table 1, Supplementary Table 1**). The most common TEAE with esketamine NS was dizziness, occurring in 156 (46.7 %) esketamine NS-treated and 28 (8.3 %) quetiapine XR-treated patients (**Table 2**). The most common TEAE with quetiapine XR was somnolence, occurring in 78 (23.2 %) quetiapine XR-treated and 50 (15.0 %) esketamine NS-treated patients; other common TEAEs (occurring in ≥5 % of patients in either treatment arm) are reported in **Table 2**. No clinically relevant hepatic, renal, cardiac, or metabolic signals were identified from laboratory results or electrocardiograms in either arm. Treatment-emergent suicidal ideation was reported in 5 (1.5 %) and 7 (2.1 %) of patients treated with esketamine NS and quetiapine XR, respectively; treatment-emergent suicide attempts were reported in 2 (0.6 %) patients and 1 (0.3 %) patient, respectively.

Table 1
Summary and consequences of TEAEs.

n (%), unless stated otherwise	Esketamine NS + SSRI/SNRI N = 334	Quetiapine XR + SSRI/SNRI N = 336	Odds ratio ^a (95 % CI), p value
≥1 TEAE	307 (91.9)	262 (78.0)	3.211 (2.006, 5.141), $p < 0.001$
TEAE possibly related to treatment	283 (84.7)	208 (61.9)	3.415 (2.357, 4.947), $p < 0.001$
TEAE leading to death	1 (0.3)	1 (0.3)	1.006 (0.063, 16.15), $p = 0.997$
≥1 serious TEAE	19 (5.7)	17 (5.1)	1.132 (0.578, 2.218), $p = 0.718$
TEAE leading to treatment discontinuation	14 (4.2)	37 (11.0)	0.354 (0.187, 0.667), $p < 0.001$
TEAE leading to dose interruption/reduction	35 (10.5)	43 (12.8)	0.798 (0.496, 1.282), $p = 0.350$
Proportion of study intervention days with TEAE (%)			
Mean (SD)	23.8 (30.33)	37.8 (38.56)	Mean difference: ^a -13.9
Median	11.9	21.3	
Range	(0 – 100)	(0 – 100)	(-19.2, -8.7), $p < 0.001$

Safety analysis set (patients received ≥1 dose of study treatment). Adverse events were coded using MedDRA preferred terms. An adverse event was counted as treatment emergent if it started after taking first dose and on or before 14 days after last dose of study medication. A serious adverse event was also counted as TEAE if it started within 30 days of last dose. Esketamine NS and quetiapine XR were both dosed per label and taken in addition to an ongoing SSRI/SNRI ([European Medicines Agency, 2019b, 2019a](#)). P values are for row mean differences.

^a Mean difference between study arms in the proportion of days during study intervention on which a patient had any TEAE. CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TEAE: treatment emergent adverse event; XR: extended release.

Table 2Common TEAEs with esketamine NS and quetiapine XR (occurring in ≥ 5 % of patients in either treatment arm).

System Organ Class Preferred Term	Esketamine NS + SSRI/SNRI N = 334			Quetiapine XR + SSRI/SNRI N = 336		
	n (% of patients)	Number of events	Median duration (days [95 % CI])	n (% of patients)	Number of events	Median duration (days [95 % CI])
Nervous system disorders	231 (69.2)			161 (47.9)		
Dizziness	156 (46.7)	1510	1.0 (-, -)	28 (8.3)	29	14.0 (7.0, 27.0)
Somnolence	50 (15.0)	570	1.0 (-, -)	78 (23.2)	110	15.0 (12.0, 20.0)
Headache	82 (24.6)	169	1.0 (-, -)	43 (12.8)	63	1.0 (1.0, 2.0)
Sedation	22 (6.6)	136	1.0 (-, -)	29 (8.6)	43	8.0 (4.0, 14.0)
Dysgeusia	40 (12.0)	405	1.0 (-, -)	1 (0.3)	1	42.0 (-, -)
Paraesthesia	37 (11.1)	219	1.0 (-, -)	2 (0.6)	2	- (48.0, -)
Hypoesthesia	19 (5.7)	112	1.0 (-, -)	1 (0.3)	2	- (1.0, -)
Gastrointestinal disorders	141 (42.2)			68 (20.2)		
Nausea	98 (29.3)	240	1.0 (-, -)	12 (3.6)	12	9.0 (2.0, 19.0)
Vomiting	36 (10.8)	48	1.0 (-, -)	5 (1.5)	5	1.0 (1.0, -)
Dry mouth	3 (0.9)	14	1.0 (-, -)	22 (6.5)	27	37.0 (16.0, 91.0)
Psychiatric disorders	156 (46.7)			44 (13.1)		
Dissociation	94 (28.1)	825	1.0 (-, -)	2 (0.6)	2	- (34.0, -)
Confusional state	20 (6.0)	46	1.0 (-, -)	1 (0.3)	1	6.0 (-, -)
Infections and infestations	70 (21.0)			69 (20.5)		
COVID-19	24 (7.2)	25	10.0 (8.0, 11.0)	29 (8.6)	31	11.0 (9.0, 15.0)
Nasopharyngitis	21 (6.3)	27	6.0 (4.0, 8.0)	11 (3.3)	14	6.0 (5.0, 8.0)
General disorders and administration site conditions	66 (19.8)			53 (15.8)		
Fatigue	19 (5.7)	61	1.0 (-, -)	34 (10.1)	42	25.0 (14.0, 62.0)
Investigations	51 (15.3)			54 (16.1)		
Weight increased	9 (2.7)	9	122.5 (15.0, -)	42 (12.5)	42	197.0 (112.0, -)
Blood pressure increased	28 (8.4)	135	1.0 (-, -)	4 (1.2)	4	39.5 (1.0, -)
Ear and labyrinth disorders	67 (20.1)			5 (1.5)		
Vertigo	63 (18.9)	411	1.0 (-, -)	3 (0.9)	3	4.0 (4.0, -)
Musculoskeletal and connective tissue disorders	40 (12.0)			26 (7.7)		
Back pain	17 (5.1)	26	3.0 (1.0, 3.0)	9 (2.7)	11	11.0 (4.0, 44.0)
Eye disorders	32 (9.6)			5 (1.5)		
Vision blurred	21 (6.3)	177	1.0 (-, -)	3 (0.9)	4	56.5 (22.0, -)

Safety analysis set (patients received ≥ 1 dose of study treatment). Adverse events were coded using MedDRA preferred terms. An adverse event was counted as treatment emergent if it started after taking first dose and on or before 14 days after last dose of study medication. A serious adverse event was also counted as TEAE if it started within 30 days of last dose. Median durations were not estimable when there were only two incidences of TEAEs and the TEAE with the longest duration was ongoing. CI limits were not estimable either due to a small sample size or because the majority of TEAEs had a duration of one day. Esketamine NS and quetiapine XR were both dosed per label and taken in addition to an ongoing SSRI/SNRI (European Medicines Agency, 2019a, 2019b). CI: confidence interval; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TEAE: treatment emergent adverse event; XR: extended release.

3.2. Time course of TEAEs

Although TEAEs were more common with esketamine NS than quetiapine XR, they were typically transient in nature: 92.0 % of all TEAEs resolved on the same day with esketamine NS, versus 12.1 % with quetiapine XR (Fig. 1). The duration of common TEAEs was generally shorter with esketamine NS versus quetiapine XR, with TEAEs experienced by esketamine NS-treated patients typically resolving within hours or 1 day (Fig. 1). Indeed, the majority of the most common TEAEs (occurring in ≥ 5 % of patients in either arm) most frequently resolved within ≤ 1 hour. For example, for dizziness, the most frequent TEAE reported with esketamine NS, 47.0 % of events resolved within 1 hour with esketamine NS versus 0.0 % of events with quetiapine XR, while 1.1 % and 93.1 %, respectively, lasted 2 days or more. Similarly for somnolence, the most frequent TEAE reported with quetiapine XR, 84.0 % of events resolved within 1 hour with esketamine NS, versus just 3.6 % of events with quetiapine XR.

3.3. Burden of TEAEs

TEAEs of special interest that occurred with both esketamine NS and quetiapine XR were typically mild or moderate in severity (Supplementary Table 2). The median number of study intervention days with TEAEs was lower with esketamine NS versus quetiapine XR: 16.0 versus 18.0 days, respectively (Table 3), culminating in a significantly lower overall proportion of study intervention days with TEAEs with

esketamine NS versus quetiapine XR (median: 11.9 % versus 21.3 % of days, respectively; mean difference [95 % CI]: -13.9 [-19.2, -8.7]; $p < 0.001$).

Baseline weight and body mass index (BMI) were comparable between treatment arms (Table 3). Relative to patients who received esketamine NS, who generally maintained a stable weight and BMI over 32 weeks of treatment, patients treated with quetiapine XR more commonly experienced a TEAE of weight increased: 42 (12.5 %) versus 9 (2.7 %) patients, respectively (Table 3). Incidences of weight increase TEAEs were balanced across patients categorised as normal, overweight or obese by baseline BMI (Supplementary Figure 1). Weight gain led to treatment discontinuation in 6 (1.8 %) patients treated with quetiapine XR, versus 0 (0.0 %) patients treated with esketamine NS. The proportion of patients with weight change of at least 7 % (increase or decrease) is also reported in Supplementary Table 3.

With regards to abnormal vital sign measurements (Table 4), abnormally high systolic blood pressure relative to baseline was observed in 2 (0.6 %) patients treated with esketamine NS versus 0 (0.0 %) with quetiapine XR. Abnormally high diastolic blood pressure was observed in 15 (4.5 %) and 1 (0.3 %) patient, respectively; hypertension did not lead to discontinuation in either treatment arm. 10 (3.0 %) patients in the esketamine NS arm versus 1 (0.3 %) patient in the quetiapine XR arm experienced an abnormally low respiratory rate; however no clinically significant decreases in respiratory rate were reported as TEAEs. 6 (1.8 %) and 1 (0.3 %) patient in each arm, respectively, experienced an abnormal high respiratory rate.

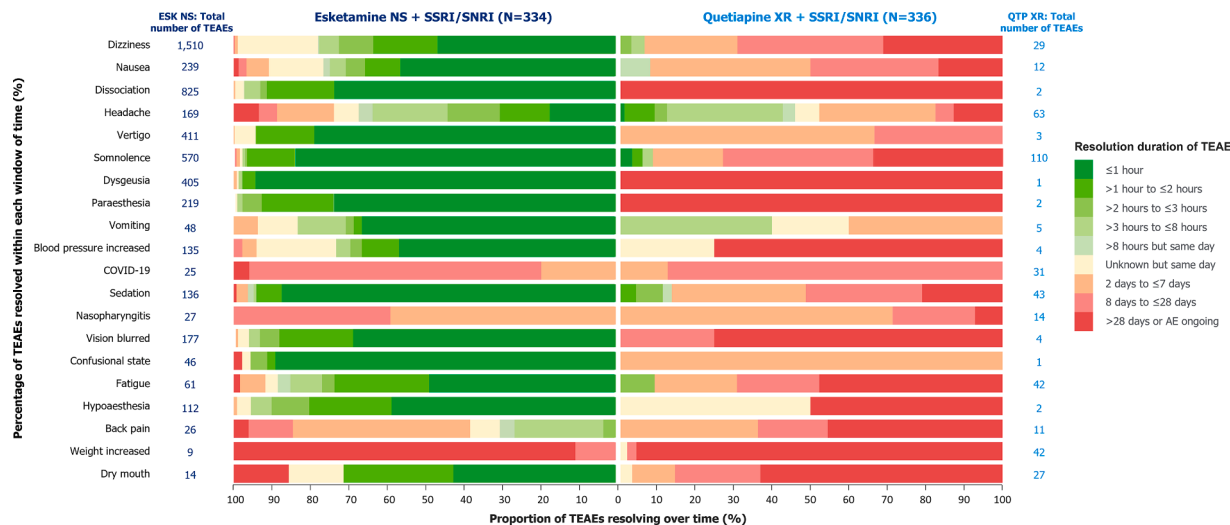


Fig. 1. Time course profiles of the most common TEAEs with esketamine NS and quetiapine XR. Safety analysis set (patients received ≥ 1 dose of study treatment). Data are reported as the proportions of most common TEAEs (occurring in $\geq 5\%$ of patients in either treatment arm) resolving over time, by duration of time to resolution. Adverse events were coded using MedDRA preferred terms. An adverse event was counted as treatment emergent if it started after taking the first dose and on or before 14 days after taking the last dose of study medication. A serious adverse event was also counted as a TEAE if it started within 30 days of taking the last dose. Esketamine NS and quetiapine XR were both dosed per label and taken in addition to an ongoing SSRI/SNRI (European Medicines Agency, 2019b, 2019a). COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; NS: nasal spray; TEAE: treatment emergent adverse event; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; XR: extended release.

Table. 3
Burden of TEAEs with esketamine NS and quetiapine XR.

	Esketamine NS + SSRI/ SNRI N = 334	Quetiapine XR + SSRI/ SNRI N = 336
Patients with TEAE during treatment, n (%)	307 (91.9)	256 (76.2)
Number of study intervention days with AE, days		
Mean (SD)	36.6 (52.85)	55.9 (71.86)
Median	16.0	18.0
Range	(0 – 220)	(0 – 225)
Patients with TEAE weight change, n (%)		
Weight increased	9 (2.7)	42 (12.5)
Weight decreased	7 (2.1)	0 (0.0)
Weight, kg, mean (SD)		
Patients with weight measurements at baseline, n	334	336
Baseline	76.4 (16.17)	79.1 (16.88)
Patients with weight measurements at Week 32, n	249	203
Week 32	76.5 (16.30)	80.7 (15.59)
BMI ^a kg/m ² , mean (SD)		
Patients with BMI measurements at baseline, n	280	286
Baseline	26.6 (4.93)	27.5 (5.07)
Patients with BMI measurements at Week 32, n	211	178
Week 32	26.7 (5.25)	28.5 (4.94)

^a BMI data were missing for 104 patients (54 for esketamine NS and 50 for quetiapine XR). Safety analysis set (patients received ≥ 1 dose of study treatment). Patients without TEAE would be counted with duration=0. Adverse events were coded using MedDRA preferred terms. An adverse event was counted as treatment emergent if it started after taking first dose and on or before 14 days after last dose of study medication. A serious adverse event was also counted as a TEAE if it started within 30 days of taking the last dose. Esketamine NS and quetiapine XR were both dosed per label and taken in addition to an ongoing SSRI/SNRI (European Medicines Agency, 2019b, 2019a). AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TEAE: treatment emergent adverse event; XR: extended release.

Table. 4
Patients who experienced treatment emergent abnormally low/high vital sign measurements.

Vital sign, n (%)	Esketamine NS + SSRI/SNRI N = 334	Quetiapine XR + SSRI/SNRI N = 336
Systolic BP, mmHg		
Decrease ≥ 20 and value ≤ 90	10 (3.0)	8 (2.4)
Increase ≥ 20 and value ≥ 180	2 (0.6)	0 (0.0)
Diastolic BP, mmHg		
Decrease ≥ 15 and value ≤ 50	6 (1.8)	2 (0.6)
Increase ≥ 15 and value ≥ 105	15 (4.5)	1 (0.3)
Pulse rate, beats/min		
Decrease ≥ 15 and value ≤ 50	6 (1.8)	0 (0.0)
Increase ≥ 15 and value ≥ 100	21 (6.3)	21 (6.3)
Respiratory rate, breaths/min		
Value < 10	10 (3.0)	1 (0.3)
Value > 24	6 (1.8)	1 (0.3)
Treatment emergent acute hypertension		
Systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg	7 (2.1)	0 (0.0)

Safety analysis set (patients received ≥ 1 dose of study treatment). Post-baseline vital sign values were considered treatment emergent if they met both the relevant value and change criteria reported in the table; for vital signs that did not include change from baseline criteria, treatment emergence was concluded if the post-baseline value was above the upper limit and the baseline value was below the upper limit (e.g. the value was normal or low) or if the post-baseline value was below the lower limit with the baseline value being above the lower limit (e.g. the value was normal or high); if the baseline value was missing, a post-baseline abnormality was always considered as treatment emergent. Esketamine NS and quetiapine XR were both dosed per label and taken in addition to an ongoing SSRI/SNRI (European Medicines Agency, 2019b, 2019a). BP: blood pressure; NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; XR: extended release.

3.4. Consequences of TEAEs

Of patients who experienced at least one TEAE, a similar proportion of patients in each arm received medication for a TEAE: 127 (41.1 %)

patients treated with esketamine NS, versus 111 (42.4 %) treated with quetiapine XR. Significantly fewer esketamine NS- than quetiapine XR-treated patients reported TEAEs leading to treatment discontinuation: 14 (4.2 %) versus 37 (11.0 %), respectively (OR: 0.354; 95 % CI: 0.187, 0.667; $p < 0.001$; Table 1). Similarly, we found a trend for fewer patients reporting a TEAE leading to dose interruption or reduction with esketamine NS than quetiapine XR: 35 (10.5 %) versus 43 (12.8 %), respectively (OR: 0.798; 95 % CI: 0.496, 1.282; $p = 0.350$; Table 1).

4. Discussion

The long-term safety and tolerability profile of esketamine NS was investigated previously in the SUSTAIN-2 and SUSTAIN-3 studies (Wajs et al., 2020; Zaki et al., 2023). However, ESCAPE-TRD is, to our knowledge, the first randomised comparative study reporting the long-term safety and tolerability of esketamine NS versus quetiapine XR, in combination with an ongoing SSRI/SNRI, in patients with TRD. The safety and tolerability of esketamine NS and quetiapine XR were consistent with their established safety profiles, with no new safety signals identified (Reif et al., 2023; Zaki et al., 2023). Importantly, however, when considering the time course, burden and consequences of TEAEs with each treatment over the 32-week treatment phase, esketamine NS exhibited a generally more favourable safety profile versus quetiapine XR, with patient dispositional changes demonstrating greater tolerability of adverse events with esketamine NS. Indeed, although the odds of a patient experiencing a TEAE was significantly (three times) higher with esketamine NS versus quetiapine XR, the odds of a patient discontinuing treatment due to TEAEs was significantly (three times) lower with esketamine NS versus quetiapine XR.

Although TEAEs occurred significantly more frequently in patients treated with esketamine NS, they were typically of shorter duration than those in patients treated with quetiapine XR, which may be related to differences in the pharmacokinetic profiles of the two drugs and to the fact that esketamine does not require daily administration. Most TEAEs in esketamine NS-treated patients occurred under clinical supervision in the immediate post-dosing period, commonly resolving within a few hours, and almost always on the same day that they occurred. These rapidly resolving TEAEs commonly included dizziness, nausea, dissociation and vertigo. In contrast, sedation, occurring with similar frequency in each arm, typically persisted substantially longer with quetiapine XR than esketamine NS, and led to treatment discontinuation in seven patients treated with quetiapine XR versus none receiving esketamine NS; a full listing of the incidence of individual TEAEs that lead to treatment discontinuation in the ESCAPE-TRD trial has been previously reported (Reif et al., 2023). Other common TEAEs with quetiapine XR also tended to be chronic and more frequently led to treatment discontinuation than those occurring with esketamine NS, including fatigue and increase in weight. Overall, therefore, reflective of the disparate time courses of common TEAEs between arms, the proportion of days spent with TEAEs was substantially and significantly lower with esketamine NS than quetiapine XR.

Importantly, TEAEs of special interest, spanning categories of sedation, dissociation, suicidality, suggestive of abuse potential and cystitis were seldom severe in either arm, with no incidences of pre-specified TEAEs of special interest related to hepatic impairment reported. Consistent with previous studies, events indicative of abuse potential, cystitis and suicidality were comparably infrequent in both the esketamine NS and quetiapine XR arms (Reif et al., 2023; Zaki et al., 2023). Furthermore, abnormalities in vital sign measurements were infrequent and generally comparable between arms. As described in the primary publication (Reif et al., 2023), two deaths were reported during the trial: one occurred during Week 9 in an esketamine NS-treated patient (undetermined cause), and one occurred during Week 17 in a quetiapine XR-treated patient (cerebrovascular accident); neither was considered by the investigator to be related to the trial treatment.

Consistent with the time course of common TEAEs in each arm, the

burdensome nature of TEAEs most often experienced with quetiapine XR may have more negatively impacted patients' quality of life and perception of treatment tolerability than those common to esketamine NS. Indeed, TEAEs reported with quetiapine XR resulted in dose reduction and/or subsequent treatment discontinuation significantly more often than those with esketamine NS. For instance, weight gain, being the adverse event that most commonly leads patients with MDD to discontinue a medication (Rosenblat et al., 2019), was relatively common with quetiapine XR and led to treatment discontinuation in 6 (1.8 %) patients. In contrast, fewer patients treated with esketamine NS experienced TEAEs of weight gain and no patients discontinued treatment due to TEAEs of weight gain. Sedation similarly occurred in a greater proportion of patients treated with quetiapine XR than esketamine NS. Given the potential for persistent sedation to substantially impact quality of life and productivity, its frequent occurrence in patients treated with quetiapine XR may have driven a ceiling effect of treatment effectiveness, since adequate doses may have been less tolerable to the patient than esketamine NS. Collectively, the temporal profile and nature of common TEAEs with esketamine NS are suggestive of greater tolerability and thus a reduced overall patient burden versus those experienced with quetiapine XR; this may have improved patients' perceptions of treatment favourability and their willingness to continue treatment (McIntyre et al., 2024; Reif et al., 2023). Since a recent consensus study reported that long-term maintenance of therapy is essential in patients with TRD, the apparent reduction in burden of continued esketamine NS versus quetiapine XR treatment over 32 weeks, as demonstrated here, further emphasises the preferentiality of esketamine NS as a therapeutic option in TRD (Maina et al., 2023).

While approximately half of patients with depression report treatment side effects as one of the main reasons for changing an antidepressant therapy, almost two thirds cite a lack of perceived therapeutic efficacy (Rosenblat et al., 2018). Treatment acceptability, as evidenced by the patient's choice to continue treatment, is influenced by multiple factors, none of which singularly or comprehensively explain acceptability (Rosenblat et al., 2019). For example, treatments that are considered by patients as providing a significant and meaningful improvement in target psychopathology are often adhered to at a higher rate despite the presence of adverse events that for other treatments may prevent acceptability (Rosenblat et al., 2019). Therefore, the significantly lower rate of treatment discontinuation due to TEAEs experienced with esketamine NS relative to those experienced with quetiapine XR may also have been influenced by a more positive patient perception of treatment efficacy with esketamine NS, since patients were more likely to achieve remission and response with esketamine NS than quetiapine XR (Reif et al., 2023; Rosenblat et al., 2018). Together, these data are suggestive of both more favourable TEAE tolerability and benefit:risk profiles for esketamine NS than quetiapine XR, which may be indicative of a greater overall treatment acceptability and effectiveness. Thus, given the chronic and resistant nature of TRD, the long-term acceptability of esketamine NS further facilitates its use as an effective antidepressant therapy and addresses the need for a long-term treatment in this population (Heerlein et al., 2021).

Key strengths of ESCAPE-TRD were its large sample size, long (32-week) duration and well-controlled head-to-head design, which facilitated direct comparison of the active compounds and provided improved generalisability and real-world relevance over a placebo-controlled study, which will be important for guiding future treatment recommendations (Vieta and Cruz, 2012). The visit schedule differed between patients receiving esketamine NS and quetiapine XR; since visits were conducted twice weekly in the esketamine NS arm and weekly in the quetiapine XR arm to Week 8, this increased frequency may have affected safety reporting. This difference, however, further supports the evidence of greater tolerability with esketamine NS, since increased visit frequency would likely increase sensitivity to detect TEAEs. Limitations include the open-label design, owing to the differing routes of administration between the two treatment arms, which was

selected to eliminate the need for placebo in the trial and reduce visit frequency (Reif et al., 2023). In addition, since both esketamine NS and quetiapine XR were administered in addition to an oral SSRI/SNRI, the treatment combination may have affected the overall safety profile reported for each arm and added a layer of complexity to the comparisons drawn (Ilzarbe and Vieta, 2023).

In ESCAPE-TRD, although TEAEs were more frequent with esketamine NS, they were typically short-lived, mild in nature and significantly less likely to result in treatment discontinuation versus quetiapine XR, suggesting they may have been less burdensome. Building upon the rapid onset and superior efficacy of esketamine NS versus quetiapine XR demonstrated in ESCAPE-TRD (Reif et al., 2023), and in conjunction with its favourable acute and long-term safety profile, these data reinforce the superiority of esketamine NS over quetiapine XR. Indeed, esketamine NS presents a valuable and well-tolerated treatment option with a highly positive benefit-risk profile for many patients with TRD, for whom treatment outcomes are notoriously poor and positive changes are hard to achieve. These findings will support physicians in their undertaking of risk-benefit assessments when making treatment recommendations to their patients.

Data sharing statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at <https://www.janssen.com/clinical-trials/transparency>. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at <http://yoda.yale.edu>.

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Janssen EMEA were responsible for study design and analysis of the data. Authors, including those affiliated with Janssen EMEA, were involved in drafting the outline of this manuscript and in reviewing subsequent drafts. Janssen EMEA did not provide any suggestions to authors. Final approval of the manuscript was the sole decision of the authors.

CRediT authorship contribution statement

Roger S. McIntyre: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Istvan Bitter:** Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Jozefien Buyze:** Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Andrea Fagiolini:** Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Yordan Godinov:** Conceptualization, Data curation, Formal analysis, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Philip Gorwood:** Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Tetsuro Ito:** Conceptualization, Data curation, Formal analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **Albino J. Oliveira-Maia:** Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Eduard Vieta:** Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Tamara Werner-Kiechle:** Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Allan H. Young:** Conceptualization, Investigation,

Visualization, Writing – original draft, Writing – review & editing. **Andreas Reif:** Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

AR: In the past 3 years, received speaker's honoraria from Janssen, Medice, Shire/Takeda and Das Fortbildungskolleg; participated in advisory boards for Boehringer Ingelheim, COMPASS, Cycleron, Janssen, LivaNova, Medice, SAGE/Biogen and Shire/Takeda; participated without financial compensation in a Data and Safety Monitoring Board for the GAINS study; participated without financial compensation in the Scientific and Ethics Advisory Board for the EU H2020 project, TIME-SPAN; received support for attending meetings from Janssen; board member of DGBS, DGPPN, ECNP and German Depression Foundation; aided in developing National Care Guidelines (NVL, S3) on major depression, bipolar disorder, ADHD and suicidal behaviour.

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Supplementary materials

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References

- European Medicines Agency. 2013. Guideline on clinical investigation of medicinal products in the treatment of depression. EMA/CHMP/185423/2010 Rev 2. Available at: https://www.ema.europa.eu/system/files/documents/scientific-guideline/wc_500143770_en.pdf.
- European Medicines Agency. 2014. Questions and answers on Seroquel, Seroquel XR and associated names (quetiapine). August 2014, Accessed August 2014. https://www.ema.europa.eu/en/documents/referral/questions-answers-seroquel-seroquel-xr-associated-names-quetiapine_en.pdf.
- European Medicines Agency. 2019a. Seroquel XR: summary of product characteristics 2019. Available at: https://www.ema.europa.eu/en/documents/referral/seroquel-xr-article-613-referral-annex-i-ii-iii-iv_en.pdf.
- European Medicines Agency. 2019b. Spravato: summary of product characteristics 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/spravato-epar-product-information_en.pdf.
- Heerlein, K., Godinov, Y., Kambarov, Y., Mulhern-Haughey, S., Ito, T., von Holt, C., 2022. HSD28 most common treatments in patients with treatment resistant depression based on European cohort study real-world evidence. *Value Health*, pp. S278–S279.
- Heerlein, K., Perugi, G., Otte, C., Frodl, T., Degraeve, G., Hagedoorn, W., et al., 2021. Real-world evidence from a European cohort study of patients with treatment resistant depression: treatment patterns and clinical outcomes. *J. Affect. Disord.* 290, 334–344.
- Hirschfeld, R.M., 2001. Clinical importance of long-term antidepressant treatment. *Br. J. Psychiatry Suppl.* 42, S4–S8.
- Ilzarbe, L., Vieta, E., 2023. The elephant in the room: medication as confounder. *Eur. Neuropsychopharmacol.* 71, 6–8.
- Lunghi, C., Auid-Orcid, Antonazzo, I.C., Burato, S., Auid-Orcid Raschi, E., Zoffoli, V., Forcesi, E., et al., 2020. Prevalence and determinants of long-term utilization of antidepressant drugs: a retrospective cohort study. *Neuropsychiatr. Dis. Treat.* 16, 1157–1170.
- Maina, G., Adami, M., Ascione, G., Bondi, E., De Berardis, D., Delmonte, D., et al., 2023. Nationwide consensus on the clinical management of treatment-resistant depression in Italy: a Delphi panel. *Ann. Gen. Psychiatry* 22, 48.
- McIntyre, R.S., Alsuwaidan, M., Baune, B.T., Berk, M., Demyttenaere, K., Goldberg, J.F., et al., 2023. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry* 22, 394–412.
- McIntyre, R.S., Filteau, M.J., Martin, L., Patry, S., Carvalho, A., Cha, D.S., et al., 2014. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J. Affect. Disord.* 156, 1–7.
- McIntyre, R.S., Kwan, A.T.H., Rosenblat, J.D., Teopiz, K.M., Mansur, R.B., 2024. Psychotropic drug-related weight gain and its treatment. *Am. J. Psychiatry* 181, 26–38.
- MedDRA. 2024. Medical dictionary for regulatory activities, Accessed January. <http://www.meddra.org/>.
- National Institute for Health and Care Excellence. 2022. NICE guideline NG222, Depression in adults, [E] Chronic depression.
- Nationale Versorgungs Leitlinien. 2022. Nationale versorgungs leitlinie: unipolare depression version 3.0.
- Osborne, V., Davies, M., Evans, A., Shakir, S.A.W., 2020. Observational assessment of safety in seroquel (OASIS): a specialist cohort event monitoring (SCEM) study in England. *Ther. Adv. Psychopharmacol.* 10, 2045125320954616.
- Reif, A., Bitter, I., Buyze, J., Cebulla, K., Frey, R., Fu, D.J., et al., 2023. Esketamine nasal spray versus quetiapine for treatment-resistant depression. *N. Engl. J. Med.* 389, 1298–1309.
- Rosenblat, J.D., Simon, G.E., Sachs, G.S., Deetz, I., Doederlein, A., DePeralta, D., et al., 2018. Factors that impact treatment decisions: results from an online survey of individuals with bipolar and unipolar depression. *Prim. Care Companion. CNS. Disord.* 20, 18m02340.
- Rosenblat, J.D., Simon, G.E., Sachs, G.S., Deetz, I., Doederlein, A., DePeralta, D., et al., 2019. Treatment effectiveness and tolerability outcomes that are most important to individuals with bipolar and unipolar depression. *J. Affect. Disord.* 243, 116–120.
- Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., et al., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am. J. Psychiatry* 163, 1905–1917.
- U.S. Food and Drug Administration. 2020. SEROQUEL XR (quetiapine fumarate extended release) prescribing information March 2020.
- U.S. Food and Drug Administration. 2023. SPRAVATO® (esketamine nasal spray) prescribing information October 2023.
- Vieta, E., Cruz, N., 2012. Head to head comparisons as an alternative to placebo-controlled trials. *Eur. Neuropsychopharmacol.* 22, 800–803.
- Voineskos, D., Daskalakis, Z.J., Blumberger, D.M., 2020. Management of treatment-resistant depression: challenges and strategies. *Neuropsychiatr. Dis. Treat.* 16, 221–234.
- Wajs, E., Aluisio, L., Holder, R., Daly, E.J., Lane, R., Lim, P., et al., 2020. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). *J. Clin. Psychiatry* 81, 19m12891.
- WHO Collaborating Centre for International Drug Monitoring. 1992. WHO drug dictionary.: uppsala: WHO collaborating centre for international drug monitoring.
- World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects, 2013. *JAMA* 310, 2191–2194.
- Young, A.H., Zaki, N., Chen, L., Lane, R., Doherty, T., Drevets, W.C., et al., 2023. Long-term safety and maintenance of response with Esketamine nasal spray in treatment-resistant depression: final results of the SUSTAIN-3 Study. In: Presented at 36th European College of Neuropsychopharmacology (ECNP) congress, p. P0636.
- Zaki, Naim, Chen, Li, Lane, Rosanne, Doherty, Teodora, Drevets, Wayne C., Morrison, Randall L., et al., 2023. Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment-resistant depression: interim results of the SUSTAIN-3 study. *Neuropsychopharmacology* 48, 1225–1233.