European Neuropsychopharmacology

Improvements in Functioning and Workplace Productivity with Esketamine Nasal Spray versus Quetiapine Extended Release in Patients with Treatment Resistant Depression: Findings from a 32-Week Randomised, Open-Label, Rater-Blinded Phase IIIb Study

--Manuscript Draft--

Manuscript Number:	ENP-24-682R1
Article Type:	Research article
Keywords:	esketamine; Major depressive disorder; quetiapine; functioning and productivity; Treatment Resistant Depression; workplace productivity
Corresponding Author:	Eduard Vieta, Ph.D., M.D. Universitat de Barcelona Facultat de Medicina i Ciencies de la Salut Barcelona, SPAIN
First Author:	Eduard Vieta, MD, PhD
Order of Authors:	Eduard Vieta, MD, PhD
	Nahida Ahmed, MD
	Celso Arango, MD, PhD
	Anthony J. Cleare, MBBS, PhD
	Koen Demyttenaere, MD, PhD
	Markus Dold, MD
	Tetsuro Ito, MSc, MBA
	Yerkebulan Kambarov, MD, MSc
	Stephanie Krüger, MD
	Pierre-Michel LLorca, MD, PhD
	Roger S. McIntyre, MD, FRCPC
	Gabriele Sani, MD
	Christian von Holt, MD
	Benoit Rive, MSc, PhD
Abstract:	Patients with treatment resistant depression (TRD) experience a greater negative impact on their functioning and productivity at home and in the workplace versus treatment-responsive patients. Here, we report the effects of esketamine nasal spray (NS) versus quetiapine extended release (XR) on functioning, work productivity and activity impairment. ESCAPE-TRD (NCT04338321) was a 32-week randomised, open-label, rater-blinded, active-controlled phase IIIb study comparing the efficacy and safety of esketamine NS versus quetiapine XR, both alongside an ongoing selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor (SSRI/SNRI), in patients with TRD. Patient functioning was assessed via the Sheehan Disability Scale (SDS; functional remission ≤6). Absenteeism, presenteeism, work productivity loss and activity impairment over time were assessed using the Work Productivity and Activity Impairment: Depression (WPAI:D) questionnaire. Results were cumulated over the entire study duration. Esketamine NS-treated patients (N=336) experienced 43.2% more weeks with functional remission versus quetiapine XR-treated patients (N=340) over the 32-week study period (difference: 2.0 weeks [95% CI: 0.7, 3.3]; p=0.0023 [ANCOVA models]). Up to Week 32, esketamine NS-treated patients experienced an 11.9% reduction in productivity loss due to absenteeism (difference: −1.1 weeks [95% CI: −2.9, 0.7]; p=0.2285) and a 14.2% reduction in overall work productivity loss (difference: –2.3 weeks, 95% CI: [–3.9, –0.7] p=0.0045) versus quetiapine XR-treated patients, based on mixed models for repeated measures. Patients receiving esketamine NS experienced greater improvements in functioning and productivity over 32 weeks versus quetiapine XR. These improvements

	demonstrate the clinical and functional benefit of treatment with esketamine NS for patients with TRD.

Eduard Vieta, MD, PhD
Hospital Clínic
170 Villarroel St
08036 Barcelona, Catalonia, Spain
+34 932275477
evieta@clinic.cat

Professor Eduard Vieta, Editor-in-Chief
European Neuropsychopharmacology
20 December 2024

RE: Improvements in Functioning and Workplace Productivity with Esketamine Nasal Spray versus Quetiapine Extended Release in Patients with Treatment Resistant Depression
Authors: Eduard Vieta, Nahida Ahmed, Celso Arango, Anthony J. Cleare, Koen Demyttenaere, Markus Dold, Tetsuro Ito, Yerkebulan Kambarov, Stephanie Krüger, Pierre-Michel Llorca, Roger S. McIntyre, Gabriele Sani, Christian von Holt, Benoit Rive

Dear Jose Sanchez-Moreno and the wider editorial team,

Thank you very much for providing detailed peer-review comments as well as the opportunity to revise our manuscript for consideration by *European Neuropsychopharmacology*.

We have now revised the manuscript according to the reviewers' recommendations (all changes are provided as 'tracked changes' in the revised manuscript) and have provided a detailed point-by-point response to each comment within this letter (please see below; where quoted, new additions are underlined).

We hope that this response addresses all the concerns raised by the reviewers and that you will now consider the manuscript suitable for publication.

We thank you again and look forward to hearing from you.

Sincerely,

Prof. Eduard Vieta, MD, PhD

Full Professor of Psychiatry
University of Barcelona
Head of the Department of Psychiatry and Psychology
Hospital Clínic
Lead investigator in Bipolar and Depressive Disorders
IDIBAPS, CIBERSAM

Reviewer 1:

General comments:

This study evaluates the impact of esketamine nasal spray versus quetiapine XR, alongside SSRIs/SNRIs, on functioning and workplace productivity in individuals with TRD over 32 weeks. Using data from the ESCAPE-TRD randomized, open-label, rater-blinded study, it highlights esketamine nasal spray's superiority in improving functional outcomes and reducing productivity loss compared to quetiapine XR. Functional remission, measured by the SDS, and work productivity, assessed through the WPAI:D questionnaire, showed statistically significant benefits with esketamine nasal spray. These findings underscore the clinical and functional advantages of esketamine for people with TRD. This article has a timely and innovative focus, going beyond symptom reduction to emphasize functional and workplace outcomes, addressing real-world challenges faced by people suffering from TRD. The length of follow-up and the use of validated tools like SDS and WPAI:D provide valuable insights into sustained treatment effects and strengthen the reliability of outcomes. Overall, this paper effectively bridges clinical efficacy with meaningful functional recovery in TRD management.

Authors' response: We thank the reviewer for their positive feedback. Responses to your specific comments can be found below.

Specific comments:

1. The title could be more specific about the type of study conducted (e.g., ": Findings from a 32-Week Randomized Open-Label Study").

   Authors' response: Thank you for this suggestion. We have updated the title accordingly, as below (page 1, lines 1–5):

   Improvements in Functioning and Workplace Productivity with Esketamine Nasal Spray versus Quetiapine Extended Release in Patients with Treatment Resistant Depression: Findings from a 32-Week Randomised, Open-Label, Rater-Blinded Phase IIIb Study

2. The abstract effectively summarizes the study but omits details on sample demographics and statistical methods. Including these could improve clarity and appeal to a broader audience.
   Authors' response: Thank you for raising this. We have made updates to the abstract to address these concerns (page 4, lines 4–5, 15–19, 23):

   Patients with treatment resistant depression (TRD) experience a greater negative impact on their functioning and productivity at home and in the workplace versus treatment-responsive patients. ~~It is unclear whether treatment of clinical symptoms reliably improves workplace and home-based functioning~~. Here, we report the effects of esketamine nasal spray (NS) versus quetiapine extended release (XR) on functioning, work productivity and activity impairment. ESCAPE-TRD (NCT04338321) was a 32-week randomised, open-label, rater-blinded, active-controlled phase IIIb study comparing the efficacy and safety of esketamine NS versus quetiapine XR, both alongside an ongoing selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor (SSRI/SNRI), in patients with TRD. Patient functioning was assessed via the Sheehan Disability Scale (SDS; functional remission ≤6). Absenteeism, presenteeism, work productivity loss and activity impairment over time were assessed using the Work Productivity and Activity Impairment: Depression (WPAI:D) questionnaire. Results were cumulated over the entire study duration. Esketamine NS-treated patients (N=336) experienced 43.2% more weeks with functional remission versus quetiapine

XR-treated patients (N=340) over the 32-week study period (difference: 2.0 weeks [95% CI: 0.7, 3.3]; p=0.0023 [ANCOVA models]). Up to Week 32, esketamine NS-treated patients experienced an 11.9% reduction in productivity loss due to absenteeism (difference: −1.1 weeks [95% CI: −2.9, 0.7]; p=0.2285) and a 14.2% reduction in overall work productivity loss (difference: −2.3 weeks, 95% CI: [−3.9, −0.7] p=0.0045) versus quetiapine XR-treated patients, based on mixed models for repeated measures. Patients receiving esketamine NS experienced greater improvements in functioning and productivity over 32 weeks versus quetiapine XR. These improvements demonstrate the clinical and functional benefit of treatment with esketamine NS for patients with TRD.

Reviewer 2:

Specific comments:

1. The baseline WPAI:D score differed between groups. What this difference impacted the outcomes?

   Authors' response: We thank the reviewer for this comment and acknowledge that there are indeed numerical differences at baseline between the two treatments arms, with more favourable scores observed in the quetiapine extended-release arm, indicating less productivity loss at baseline, for all four scores of the WPAI-D. The authors would also emphasise that baseline scores should be considered part of the outcome since total time lost for productivity was assessed using 4-week intervals. The first interval therefore incorporated the average productive time lost from baseline to Week 4, meaning that higher baseline productivity loss in the esketamine nasal spray arm would have resulted in an inflated productivity loss in this first interval (from baseline to Week 4). Since the analysis is based on a mixed model with repeated measures (MMRM) method applied to the WPAI:D scores at each visit, it is unfortunately not possible to adjust for this baseline imbalance by having baseline scores as a covariate since it would result in perfect collinearity and make the model impossible to estimate. Therefore, this baseline imbalance would have resulted in a conservative estimation of the actual difference between the esketamine and quetiapine arms.

   A note regarding this has also been added to the Discussion as follows (page 15, lines 10–14):

   Finally, since the first 4-week interval in which WPAI:D was assessed incorporated the average productive time lost from baseline to Week 4, the higher baseline productivity loss observed in the esketamine NS arm versus quetiapine XR arm would have resulted in an inflated productivity loss in this first interval. Therefore, the overall estimation of the actual difference between the arms was conservative.

2. The esketamine leads a similar effect in work function stratified by different baseline work impairment? Or in which condition esketamine may have the greater effect?

   Authors' response: The authors thank the reviewer for this query. It is not currently planned to conduct analyses stratified by baseline work impairment, since such analyses would no longer rely on baseline randomisation, which was based on age and number of prior treatment failures. However, analyses exploring how patients baseline characteristics may

have impacted their outcomes, and differences between different treatments, are ongoing and will be reported in future publications (please also see also our response to comment 6).

3. In addition, the authors mentioned the age, but I did not see the age-stratified sub-analyses. How were the findings applied to retired people? If not, the authors should focus on working people.

Authors' response: The authors thank the reviewer for this query. The WPAI:D questionnaire provides different scores quantifying the impairment of the patients with regards to patients' work productivity and daily activities (absenteeism, presenteeism, work productivity loss and activity impairment). While activity impairment can apply to patients of all ages, absenteeism, presenteeism, and work productivity loss apply only to working patients. Analyses on these parameters were therefore conducted only using data from working patients, regardless of their age (retired patients were excluded, as were non-working patients who were of working age). The decrease in sample size resulting from these adjustments can be seen in Table 1: Baseline Characteristics (page 22).

Clarification on patients included in the WPAI:D analysis has been added to the Methods section (page 9, lines 20–22):

Analyses on absenteeism, presenteeism and work impairment parameters were conducted using only data from working patients, regardless of their age (retired patients were excluded, as were non-working patients who were of working age).

4. "NS-treated patients experienced 8.1 weeks of absenteeism versus 9.2 weeks for quetiapine XR-treated patients, indicating an 11.9% reduction in productivity loss due to absenteeism (difference: −1.1 weeks [95% CI: −2.9, 0.7]; p=0.2285). Esketamine NS significantly improved presenteeism (-1.9 weeks, 95% CI: [-3.4, -20 0.5], p=0.0098, -13.1%)". Why was the absenteeism non-significant but presenteeism significant?

Authors' response: The authors thank the reviewer for raising this important point. While absenteeism and presenteeism both quantify productivity loss, absenteeism only accounts for missed days of work (i.e. sick leave), whilst presenteeism accounts for reductions in productivity while patients are working. Although these outcomes are expected to be correlated, the distinct differences in the way in which they are calculated may explain this difference. For example, absenteeism may be particularly susceptible to factors not directly related to disease severity or symptom evolution, such as the propensity for patients to request, or physician to prescribe, sick leave; this is supported by a study which found previous sick leave to be the strongest predictor of subsequent sick leave.[1] Further, in this study, absenteeism was associated with a smaller difference between treatment arms compared with presenteeism, but also greater variability, making statistical significance less likely. We have added some text to the Discussion to address these possibilities (page 14, lines 29–33; page 15, lines 1–9):

The difference for absenteeism did not reach statistical significance in this analysis, which may be due to larger variability in time lost compared with other WPAI:D domains. Esketamine NS-treated patients may also have required to use more sick days or time off, as these patients had to attend treatment sessions and could not work. An additional factor which could potentially explain why significant differences between treatments were observed on all WPAI:D scores except absenteeism could be found in the correlation analyses, which revealed a substantially lower correlation of the absenteeism score with depression severity

(as measured by MADRS score) compared to the other three WPAI:D scores (presenteeism, work productivity loss and activity impairment), making absenteeism less sensitive to improvement in depression symptoms and therefore to treatment effect. This is consistent with literature that found that other factors, such as previous history of sick leave, were the main predictors of future sick leaves.[1]

5. Was work function improvement associated with mood symptom improvement?

Authors' response: The authors thank the review for this query. We have conducted an additional analysis on the correlation between MADRS and each of the four WPAI:D parameters, which is now reported throughout the manuscript.

Methods (page 10; lines 1–3): Using all records where both MADRS and WPAI:D were assessed, Pearson correlation coefficients between MADRS and each of the four WPAI-D scores were also estimated.

Results (page 13; lines 1–3): Correlations between MADRS and the WPAI-D scores were less strong for absenteeism (Pearson correlation coefficient: 0.3413) compared with presenteeism (0.6497), work productivity loss (0.6118), and activity impairment (0.6826).

Discussion (page 14, line 33; page 15, lines 1–9): An additional factor which could potentially explain why significant differences between treatments were observed on all WPAI:D scores except absenteeism could be found in the correlation analyses, which revealed a substantially lower correlation of the absenteeism score with depression severity (as measured by MADRS score) compared to the other three WPAI:D scores (presenteeism, work productivity loss and activity impairment), making absenteeism less sensitive to improvement in depression symptoms and therefore to treatment effect. This is consistent with literature that found that other factors, such as previous history of sick leave, were the main predictors of future sick leaves.[1]

6. Was baseline TRD condition related to subsequent outcomes of work function? And vice versa?

Authors' response: The authors thank the reviewer for raising this interesting point. Baseline TRD condition may have impacted both treatment arms and may potentially modify the differences observed with each treatment. Additional analyses are ongoing to explore the effects of patients' baseline characteristics on treatment outcomes, and this will be reported in future manuscripts.

7. Finally, it is an important study, but it needs further clarification.

Authors' response: The authors thank the reviewer for acknowledging the importance of this study. We hope that the clarifications above and updates made to the manuscript have addressed your concerns.

1. Gasse C, Petersen L, Chollet J, et al. Pattern and predictors of sick leave among users of antidepressants: a Danish retrospective register-based cohort study. J Affect Disord 2013;151:959-66.

Additional Request from Authors: Please note that Prof Roger S. McIntyre requested an update to his affiliation, reflected in the tracked changes on page 2, lines 12–13, 26–30.

Improvements in Functioning and Workplace Productivity with Esketamine Nasal Spray versus Quetiapine Extended Release in Patients with Treatment Resistant Depression: Findings from a 32-Week Randomised, Open-Label, Rater-Blinded Phase IIIb Study

Journal Requirements

Proposed Journal: European Neuropsychopharmacology

Full details at: European Neuropsychopharmacology

- Word limit: 6,500 (includes tables and figure legends)
  - Abstract: 250
- Max tables/figures: N/A
- Max References: 80

- Submission to acceptance time: 68 days (72 with review)
- Impact factor: 6.1

Lead medical writer: Laura Mawdsley (laura.mawdsley@costellomedical.com)

Current manuscript

Word count: 4,020
Number of tables: 2 (+2 in Supplement)
Number of figures: 4 (+1 in Supplement)
Number of references: 33

Improvements in Functioning and Workplace Productivity with Esketamine Nasal Spray versus Quetiapine Extended Release in Patients with Treatment Resistant Depression: Findings from a 32-Week Randomised, Open-Label, Rater-Blinded Phase IIIb Study

Eduard Vieta (MD, PhD),[1] Nahida Ahmed (MD),[2] Celso Arango (MD, PhD),[3] Anthony J. Cleare (MBBS, PhD),[4] Koen Demyttenaere (MD, PhD),[5] Markus Dold,[6] Tetsuro Ito (MSc, MBA),[7] Yerkebulan Kambarov (MD, MSc),[8] Stephanie Krüger (MD),[9] Pierre-Michel Llorca (MD, PhD),[10] Roger S. McIntyre (MD, FRCPC),[11] Gabriele Sani (MD),[12,13] Christian von Holt (MD),[14] Benoit Rive (MSc, PhD)[15]

1. Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Institut de Neurociències (UBNeuro), Universitat de Barcelona (UB); Bipolar and Depressive Disorders Unit, Hospital Clínic de Barcelona; Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS); CIBERSAM, ISCIII, Barcelona, Spain ; 2. Sakina Mental Health & Wellbeing Services; College of Medicine, and Health Sciences (CMHS) of the United Arab Emirates University; Khalifa University, Abu Dhabi, UAE; 3. Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense de Madrid, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain; 4. Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; 5. University Psychiatric Center KU Leuven, Campus Leuven, Belgium; 6. Medical University of Vienna, Department of Psychiatry and Psychotherapy; 7. Janssen EMEA, High Wycombe, UK; 8. Janssen EMEA, Beerse, Belgium; 9. Department of Mental Health, Vivantes Humboldt Clinic, Berlin, Germany; 10. CHU Clermont-Ferrand, Department of Psychiatry, University of Clermont Auvergne, UMR 6602 Institut Pascal (IP), Clermont Ferrand, France; 11. Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; 12. Department of Neuroscience, Section of Psychiatry, Università Cattolica del Sacro Cuore, Rome, Italy; 13. Department of Psychiatry, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; 14. Janssen EMEA, Neuss, Germany; 15. Janssen EMEA, Paris, France

Correspondence to: Prof Eduard Vieta, EVIETA@clinic.cat

Short title: ESCAPE-TRD Functioning and Productivity

Trial registration: ClinicalTrials.gov identifier: NCT04338321

Funding: Janssen EMEA, Beerse, Belgium

Key words: esketamine, major depressive disorder, quetiapine, functioning and productivity, treatment resistant depression, workplace productivity

ABSTRACT (250/250 words)

Patients with treatment resistant depression (TRD) experience a greater negative impact on their functioning and productivity at home and in the workplace versus treatment-responsive patients. Here, we report the effects of esketamine nasal spray (NS) versus quetiapine extended release (XR) on functioning, work productivity and activity impairment. ESCAPE-TRD (NCT04338321) was a 32-week randomised, open-label, rater-blinded, active-controlled phase IIIb study comparing the efficacy and safety of esketamine NS versus quetiapine XR, both alongside an ongoing selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor (SSRI/SNRI), in patients with TRD. Patient functioning was assessed via the Sheehan Disability Scale (SDS; functional remission ≤6). Absenteeism, presenteeism, work productivity loss and activity impairment over time were assessed using the Work Productivity and Activity Impairment: Depression (WPAI:D) questionnaire. Results were cumulated over the entire study duration. Esketamine NS-treated patients (N=336) experienced 43.2% more weeks with functional remission versus quetiapine XR-treated patients (N=340) over the 32-week study period (difference: 2.0 weeks [95% CI: 0.7, 3.3]; p=0.0023 [ANCOVA models]). Up to Week 32, esketamine NS-treated patients experienced an 11.9% reduction in productivity loss due to absenteeism (difference: −1.1 weeks [95% CI: −2.9, 0.7]; p=0.2285) and a 14.2% reduction in overall work productivity loss (difference: −2.3 weeks, 95% CI: [−3.9, −0.7] p=0.0045) versus quetiapine XR-treated patients, based on mixed models for repeated measures. Patients receiving esketamine NS experienced greater improvements in functioning and productivity over 32 weeks versus quetiapine XR. These improvements demonstrate the clinical and functional benefit of treatment with esketamine NS for patients with TRD.

INTRODUCTION

Treatment resistant depression (TRD) is commonly defined as a lack of response to two or more pharmacological treatments of adequate duration and dose within the same major depressive episode (MDE),(European Medicines Agency, 2013) and affects 10–30% of patients with major depressive disorder (MDD) in research and real-world settings.(Rush *et al.*, 2006, McIntyre *et al.*, 2023, Al-Harbi, 2012) Relative to their treatment-responsive counterparts, patients with TRD have a worse prognosis, a higher rate of suicide,(McIntyre *et al.*, 2023) a greater negative impact on their functioning and productivity,(Jaffe *et al.*, 2019, Heerlein, Young*, et al.*, 2021) and experience a reduced health-related quality of life (HRQoL).(Johnston, Powell*, et al.*, 2019) Patients with TRD also face increased personal and economic costs when compared with treatment-responsive patients, driven by productivity loss and workplace impairment.(Heerlein *et al.*, 2022)

There are multiple objective, subjective and performance-based measures of functional impairment; one of the most widely used is the Sheehan Disability Scale (SDS). The SDS is a patient-reported outcome measure of functional disability that assesses the degree to which symptoms disrupt a patient's daily life. This scale assesses three domains: work and/or school work, social life and leisure activities, and family life and home responsibilities.(Florea *et al.*, 2017, Sheehan & Sheehan, 2008) Low SDS scores indicate minimal disruption in a patient's daily functioning and can be used to determine rates of functional remission. Previous studies using the SDS to measure functional remission have shown that most patients that achieved functional remission first achieved clinical response and remission,(Oliveira-Maia, Rive*, et al.*, 2024) suggesting that a reduction in disease symptoms may be required to reduce the impact of the disease on daily functioning.

In addition to functional remission, impairment in a patient's productivity at work and in their daily life is another method of measuring the impact of TRD. The Work Productivity and Activity Impairment for Depression (WPAI:D) questionnaire provides several measures of the extent to which TRD impacts daily functioning; absenteeism (the proportion of work time missed due to TRD), presenteeism (the degree of impairment while working due to TRD), work productivity loss (overall work impairment due to TRD, combining absenteeism and presenteeism) and activity impairment (the degree of impairment of regular, non-work activity due to TRD) are

all quantified. Previous studies using the WPAI have shown that patients with TRD experienced an overall mean impairment of work and activity of 60.5% and 73.3%, respectively.(Heerlein, Young*, et al.*, 2021, Oliveira-Maia, Bobrowska*, et al.*, 2024) These impairments lead to increased costs, and result in human capital erosion. It is currently unclear whether antidepressant treatment significantly and reliably improves measures of workplace functioning.(Lee *et al.*, 2018) Preliminary evidence from real-world data sets provides some support for improvements in workplace productivity in people with TRD following treatment,(Rodrigues *et al.*, 2021) however, no randomised-controlled study data are available in this regard, nor studies on how these improvements translate to workplace functionality. Furthermore, patients who achieve clinical remission when using second-line monoamine-based antidepressants continue to demonstrate impairment in workplace metrics,(Trivedi *et al.*, 2013) indicating a lack of solutions for workplace impairment and productivity loss in patients with TRD.

Esketamine nasal spray (NS), given in combination with either a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI), is approved for the treatment of TRD in Europe.(European Medicines Agency, 2019a)

ESCAPE-TRD is one of the few existing large, long-term head-to-head studies in TRD and was the first head-to-head study comparing esketamine NS with an augmentation strategy. ESCAPE-TRD demonstrated the superior efficacy of esketamine NS over quetiapine extended release (XR), both in combination with an ongoing SSRI/SNRI, in both the short and long term.(European Medicines Agency, 2019b, Reif *et al.*, 2023) The trial also showed a more favourable tolerability profile for esketamine NS as compared with quetiapine XR.(McIntyre *et al.*, 2024)

Here, we report the effects of esketamine NS versus quetiapine XR treatment on functioning, work productivity and impairment over 32 weeks in patients with TRD. Furthermore, we explore the sequential cascade from clinical response to clinical remission, through to functional remission and compare the temporal pattern of these transitions between treatments.

EXPERIMENTAL PROCEDURES

Study design

ESCAPE-TRD (NCT04338321) was a randomised, open-label, rater-blinded, active-controlled phase IIIb study comparing the efficacy and safety of esketamine NS versus quetiapine XR, both alongside an ongoing SSRI/SNRI, in patients with TRD; the full methodology was reported in the primary publication.(Reif *et al.*, 2023) Patients were randomised 1:1 to esketamine NS or quetiapine XR, both flexibly dosed per label.(European Medicines Agency, 2019a, b) Randomisation was stratified by age (18–≤64 years; 65–<75 years) and number of prior treatment failures in the current MDE (2; ≥3). Full inclusion and exclusion criteria were reported in the primary publication.(Reif *et al.*, 2023)

ESCAPE-TRD was conducted in accordance with the Declaration of Helsinki;(Association, 2013) country-specific ethics review boards provided approval. All patients provided written informed consent and the study was registered at ClinicalTrials.gov.

The Montgomery-Åsberg Depression Rating Scale (MADRS) was used to assess clinical symptom severity. Clinical remission was defined as MADRS total score ≤10. Clinical response was defined as an improvement in MADRS total score from baseline of ≥50%, or MADRS total score ≤10. Patient functioning was assessed via the SDS, with functional remission defined as SDS total score ≤6 (total SDS score range was 0–30, where higher scores indicated worse functioning).(Sheehan & Sheehan, 2008, Eaton *et al.*, 2008) SDS-based functional remission measures the state where depression symptoms only create a minimal disruption in the patient's daily functioning (versus whether a patient has achieved a "normal life"). The degree of absenteeism, presenteeism, work productivity loss and activity impairment experienced by patients over time were assessed as a proportion of time lost using the WPAI:D questionnaire.(Reilly *et al.*, 1993) The SDS and the WPAI:D were assessed every 4 weeks from baseline to Week 32. All p values reported here were not adjusted for multiple testing.

Time to event

Time to event, assessed for clinical response, clinical remission, and functional remission, was estimated using the Kaplan-Meier method. Patients can either reach the condition of the event while on treatment, where the time of the event is the

first time where the condition is satisfied, or complete the study without having ever satisfied the condition for the event, when they would be considered censored at the time of completion. Patients discontinuing study treatment before having ever satisfied the condition for the event were censored at an infinite (arbitrarily large) time and were assumed to never achieve the relevant event.

Hazard ratio (HR), 95% confidence intervals (CI) and corresponding p value were estimated using a Cox proportional hazards model adjusted for age (18–≤64, 65–<75 years) and number of prior treatment failures (2, ≥3).

Consistency between outcomes was explored (pooled treatments arms) by estimating the proportion of patients achieving functional remission (at any point in time) for patients having reached clinical response/remission and for those who did not reach these outcomes. For patients having reached both functional remission and clinical outcomes (response or remission), the length of time between the first occurrences of these events was estimated.

Events at each visit

At each visit where all endpoints were assessed (every 4 weeks), the proportions of patients that achieved clinical response, clinical remission and functional remission were analysed.

This analysis was based on observed data; patients that discontinued study treatment were imputed using non-responder imputation (NRI) and systematically considered as having a negative outcome at all timepoints following treatment discontinuation. For patients that were still receiving treatment but had missing values, data were imputed using local last observation carried forward (LOCF), where missing values were assigned the outcome of the last timepoint where data were collected.

Odds ratios (OR), corresponding 95% CIs and p values are reported based on Cochran-Mantel-Haenszel chi-square tests adjusted for age and number of prior treatment failures.

Cumulative time spent in health states

Cumulative time spent in either clinical response, clinical remission, or functional remission was estimated using the area under the curve (AUC) method, based on

status at on-treatment visits using NRI. If a patient had the same outcome (favourable or un-favourable) at both the beginning and end of an interval (two consecutive visits), they were considered to have spent the time between visits in the corresponding health state. If a patient had different outcomes at consecutive visits, a transition was assumed to have taken place at the midpoint of the interval.

For each patient, total time in a given health state was then calculated by adding the time in the health state on each 4-week interval (where both MADRS and SDS were assessed), from baseline to Week 32. Total time spent in each health state (and the corresponding 95% CI and p-value) was estimated by treatment arm and compared between treatment arms using analysis of covariance (ANCOVA) models with age and number of prior treatment failures as covariates.

Cumulative work productivity and impairment

Each of the four WPAI:D scores (calculated as a percentage of time lost) was analysed using a mixed model for repeated measures (with an unstructured covariance structure) based on observed cases. The model included study intervention, stratification factors (age [18–≤64 years; 65–<75 years] and number of prior treatment failures [2; ≥3]), visit (every 4 weeks from baseline to Week 32), and visit-by-study-intervention interaction as fixed effects. The analysis included both on-treatment visits and retrieved dropouts (post-study treatment discontinuation). Analyses on absenteeism, presenteeism and work impairment parameters were conducted using only data from working patients, regardless of their age (retired patients were excluded, as were non-working patients who were of working age).

In each 4-week time interval, patients were assumed to spend the first two weeks with their WPAI score at the start of the interval and the latter two weeks with their score at the end of the interval. Total time of productivity loss on each score (by treatment arm and difference between treatment arms, along with corresponding 95% CI and p-value) was then estimated by allocating weights to each visit and estimating the corresponding least-square means, with intermediate visits (every 4 weeks from Week 4 to Week 28) receiving a weight of 4 weeks as they each contributed to two intervals, and extreme visits (baseline and Week 32) receiving a weight of 2 weeks. Total time lost was then calculated as the proportion of time lost (WPAI:D scores) multiplied by the weighted time interval.

Using all records where both MADRS and WPAI:D were assessed, Pearson correlation coefficients between MADRS and each of the four WPAI-D scores were also estimated.

SDS imputation validity

Methods used to explore the validity of SDS imputation are reported in **Supplementary Material S1**.

Proxy for SDS functional remission based on MADRS

Methods used to explore a MADRS-based proxy for SDS functional remission are reported in **Supplementary Material S2.**

RESULTS

Patient disposition and baseline functioning and productivity

Overall, 336 patients were randomised to esketamine NS and 340 patients to quetiapine XR (N=676). Baseline demographics were comparable between arms,(Reif *et al.*, 2023) with similar MADRS, SDS total and WPAI:D scores in each arm (**Table 1**). Of all patients at baseline, the majority of patients (52.5%) had marked functional impairment, 28.1% had moderate impairment, 14.0% extreme impairment and 5.5% mild or no impairment. Patients experienced a mean 40.4% loss of work time due to absenteeism. When combined with presenteeism, this resulted in an overall work time loss of 74.6%.

Time to event

Significantly more esketamine NS-treated patients achieved clinical response (HR: 1.848, 95% CI: [1.547, 2.207], p<0.001), clinical remission (HR: 1.711, 95% CI: [1.402, 2.087], p<0.001) and functional remission (HR: 1.819, 95% CI: [1.416, 2.336], p<0.001) compared with quetiapine XR-treated patients. Esketamine NS-treated patients also achieved these outcomes faster than patients treated with quetiapine XR (**Figure 1**).

Within each treatment arm, at each time point, more patients reached clinical response than clinical remission, and more patients reached clinical remission than functional remission, indicating the increasing difficulty in achieving these outcomes.

Time to clinical remission in patients receiving esketamine NS was similar to time to clinical response with quetiapine XR; likewise, time to functional remission observed in patients receiving esketamine NS was similar to time to clinical remission in patients receiving quetiapine XR (**Figure 1**).

Among all patients (including both esketamine NS- and quetiapine XR-treated) who never reached clinical response (n=174), 2.3% (4) achieved functional remission. In contrast, among patients who did achieve clinical response (n=502), 51.0% (256) of patients achieved functional remission. The average time between achieving clinical response and functional remission (for patients who achieved both) was 57.6 days. Clinical response occurred before or at the same time as functional remission in 92.2% of cases.

Similarly, among patients who never achieved clinical remission (n=276), 8.7% (24) achieved functional remission. Among patients who reached clinical remission (n=400), 59.0% (236) of patients achieved functional remission. The average time between clinical remission and functional remission (for patients who achieved both) was 26.1 days. Clinical remission occurred before or at the same time as functional remission in 77.5% of cases.

The exploration of a potential MADRS cut-off for use as a proxy for SDS functional remission determined that no MADRS cut-off provided a high enough sensitivity or specificity (**Supplementary Material S2, Supplementary Table S2**).

Events at each visit

Across all outcomes, the proportion of patients with a favourable outcome (clinical response, clinical remission or functional remission) was numerically higher with esketamine NS compared to quetiapine XR at each visit (**Table 2**).

A statistically significant benefit for esketamine NS was seen as early as Week 4, where the OR for clinical response was 3.088 (95% CI: [2.131, 4.474]; p<0.001), which continued through every visit to Week 32 (**Figure 2A**).

For clinical remission, a significant benefit for esketamine NS versus quetiapine XR was observed from Week 8 onwards (OR: 1.740, 95% CI: [1.204, 2.515]; p=0.003) and for functional remission this benefit was observed from Week 16 onwards (OR: 1.709, 95% CI: [1.141, 2.559]; p=0.009; **Figure 2B–C**).

At each visit a similar number of esketamine NS-treated patients achieved clinical remission as quetiapine XR-treated patients who reached clinical response; likewise, a similar number of esketamine NS-treated patients achieved functional remission as quetiapine XR-treated patients who reached clinical remission (**Table 2**).

Cumulative time spent in health states

With respect to cumulative time spent in each of the three health states, a significant benefit of esketamine NS was seen when compared with quetiapine XR over the 32-week study period (**Figure 3**). Esketamine NS-treated patients experienced 17.0 weeks with clinical response versus 11.6 weeks for quetiapine XR-treated patients (difference: 5.4 weeks [95% CI: 3.7, 7.1]; p<0.0001), indicating a 46.4% relative increase. Esketamine NS-treated patients experienced 10.5 weeks with clinical remission versus 6.8 weeks for quetiapine XR-treated patients (difference: 3.7 weeks [95% CI: 2.2, 5.2]; p<0.0001), indicating a 55.0% relative increase. Finally, esketamine NS-treated patients experienced 6.7 weeks with functional remission versus 4.7 weeks for quetiapine XR-treated patients (difference: 2.0 weeks [95% CI: 0.7, 3.3]; p=0.0023), indicating a 43.2% relative increase.

Time spent in clinical remission with esketamine NS was similar to time in clinical response with quetiapine XR, whilst time in functional remission with esketamine NS was similar to time in clinical remission with quetiapine XR (**Figure 3A**).

Cumulative work productivity and impairment

Over the 32-week duration of the study, patients receiving esketamine NS lost numerically less time to work productivity and activity impairment (i.e. gained more productive time) compared to patients on quetiapine XR (**Figure 4A**). Esketamine NS-treated patients experienced 8.1 weeks of absenteeism versus 9.2 weeks for quetiapine XR-treated patients, indicating an 11.9% reduction in productivity loss due to absenteeism (difference: −1.1 weeks [95% CI: −2.9, 0.7]; p=0.2285). Esketamine NS significantly improved presenteeism (–1.9 weeks, 95% CI: [–3.4, –0.5], p=0.0098, –13.1%), work productivity loss (–2.3 weeks, 95% CI: [–3.9, –0.7] p=0.0045, –14.2%) and activity impairment (–1.3 weeks, 95% CI: [–2.3, –0.2] p=0.0172, –8.3%) compared to quetiapine-XR (**Figure 4B**).

Correlations between MADRS and the WPAI:D scores were less strong for absenteeism (Pearson correlation coefficient: 0.3413) compared with presenteeism (0.6497), work productivity loss (0.6118), and activity impairment (0.6826).

SDS imputation validity

The imputation of SDS scores was considered valid; the specifics pertaining to the validity of SDS imputation for partially missing data are reported in **Supplementary Material S1** (**Supplementary Figure S1, Supplementary Table S1**).

DISCUSSION

The functioning and productivity analyses reported here suggest that esketamine NS has a significant functional benefit over quetiapine XR for patients with TRD. These data reinforce the superiority of esketamine NS over the commonly used augmentation agent, quetiapine XR, when given in combination with an ongoing SSRI/SNRI, and further establish the importance of achieving clinical endpoints, such as clinical remission, to achieve functional treatment benefits.

As demonstrated previously, achieving functional remission often requires the achievement of both clinical response and clinical remission.(Oliveira-Maia, Rive*, et al.*, 2024) In ESCAPE-TRD, significantly more esketamine NS-treated patients achieved clinical response, clinical remission and functional remission compared with quetiapine XR-treated patients. Patients treated with esketamine NS also achieved these milestones faster than quetiapine XR-treated patients. These results suggest that patients treated with esketamine NS experience a greater clinical and functional benefit than patients treated with quetiapine XR, to the extent that similar number of patients treated with esketamine NS achieved clinical remission as quetiapine XR-treated patients did clinical response. The same pattern was observed with functional versus clinical remission and remains true at any timepoint. This is consistent with the findings of the primary analysis of ESCAPE-TRD, where patients treated with esketamine NS experienced more rapid reductions in MADRS total score and earlier onset of clinical remission and clinical response.(Reif *et al.*, 2023)

Though response trajectories are heterogeneous, these results support findings seen in other studies that show there is often a progression, or a "domino cascade", from clinical response to clinical remission, through to functional remission.(Oliveira-Maia, Rive*, et al.*, 2024) This suggests that functional remission is both harder for patients

to achieve and takes longer to achieve than clinical outcomes. The exploratory MADRS proxy analysis supports the view that severity and functioning are two distinct concepts and challenges the idea that functional remission is just a stricter definition of clinical remission. These analyses highlight the need for physicians to monitor both outcomes in their clinical practice.(Habert *et al.*, 2016)

It has been shown that the larger the amount of time that patients are considered to have achieved these three outcomes, the less likely they are to be experiencing decreased functioning, which is linked with poorer QoL, higher costs and a larger disease burden.(Heerlein, Perugi*, et al.*, 2021, Heerlein *et al.*, 2022, Jaffe *et al.*, 2019, Johnston, Powell*, et al.*, 2019) Patients treated with esketamine NS spent more time in clinical remission and functional remission when compared with quetiapine XR-treated patients. These results represent a relative increase in time of approximately 50% on each outcome over the 32-week study duration. For patients treated with esketamine NS, in addition to reaching each clinical outcome more quickly, treatment also enabled patients to spend more time having achieved each clinical outcome, demonstrating the persistent benefit of esketamine NS that results in better outcomes for patients.

Significant relationships between depression severity and both absenteeism and presenteeism have been demonstrated, showing indicated increases in absence and decreases in performance with increasing depression severity.(Johnston, Harvey*, et al.*, 2019) Improvements in workplace productivity are not commonly demonstrated in treatment with a second typical monoamine antidepressant, even when patients have achieved clinical remission.(Trivedi *et al.*, 2013, Gaynes BN, 2009) Over the 32-week duration of the study, patients receiving esketamine NS gained more productive time compared to patients on quetiapine XR, with this difference reaching statistical significance for presenteeism, work productivity loss and activity impairment. As presenteeism disproportionately accounts for disability and is costlier compared with absenteeism, improvements in presenteeism would have a real-world impact on patients.(Biron *et al.*, 2006) The difference for absenteeism did not reach statistical significance in this analysis, which may be due to larger variability in time lost compared with other WPAI:D domains. Esketamine NS-treated patients may also have required to use more sick days or time off, as these patients had to attend treatment sessions and could not work. An additional factor which could potentially

explain why significant differences between treatments were observed on all WPAI:D scores except absenteeism could be found in the correlation analyses, which revealed a substantially lower correlation of the absenteeism score with depression severity (as measured by MADRS score) compared to the other three WPAI:D scores (presenteeism, work productivity loss and activity impairment), making absenteeism less sensitive to improvement in depression symptoms and therefore to treatment effect. This is consistent with literature that found that other factors, such as previous history of sick leave, were the main predictors of future sick leaves.(Gasse *et al.*, 2013)

Finally, since the first 4-week interval in which WPAI:D was assessed incorporated the average productive time lost from baseline to Week 4, the higher baseline productivity loss observed in the esketamine NS arm versus quetiapine XR arm would have resulted in an inflated productivity loss in this first interval. Therefore, the overall estimation of the actual difference between the arms was conservative. The results presented here suggest a benefit of treatment with esketamine NS for improvements in workplace productivity, which could potentially lead to a reduction in the societal costs associated with TRD, highlighting the effective translation of clinical efficacy into meaningful improvements in patients' daily functioning and productivity.(Heerlein *et al.*, 2022, Mrazek DA, 2014)

Strengths and limitations

To our knowledge, ESCAPE-TRD is the first randomised comparative study reporting long-term esketamine NS use against an augmentation treatment for patients with TRD.

A strength of these analyses is that despite the varied methodology, all analyses reported a similar result; esketamine NS-treated patients consistently experienced better outcomes than quetiapine XR-treated patients. The different analyses reported here provide a complementary and extensive view of the relative benefit of esketamine NS over quetiapine XR in achieving clinical response, clinical remission and functional remission. Additionally, the validity of the SDS imputation for partially missing data was confirmed, lending robustness to the SDS score results. A feature of ESCAPE-TRD was the high degree of physician supervision which, while beneficial, may not be generalisable to a real-life setting.

A limitation of the first event analysis was that it could only address how fast patients first reached the outcome, not if they continued to achieve it. This limitation was addressed by subsequent analyses that determined the proportion of patients that achieved each outcome. This analysis provides conclusions at a population level but cannot be reported at an individual patient level. For example, any one patient could achieve functional remission at one time point, not achieve it at the next time point, then achieve it again at a third time point. Additionally, patients with less impairment in the workplace experience greater functional outcomes with treatment;(McIntyre *et al.*, 2017) however, results reported here are not adjusted for baseline functioning. Finally, a further limitation is related to the use of the SDS, which is a valid and reliable measure of functioning in patients with depression but lacks the granularity of other instruments such as the Functioning Assessment Short Test (FAST).(Rosa *et al.*, 2007)

Similar studies have shown that patients who have an improvement in functional recovery also demonstrate an improvement in anhedonia.(Vinckier *et al.*, 2017, Wong *et al.*, 2024) Thus, future work may investigate whether treatment with esketamine NS demonstrates a similar trend. Additional future analyses may include prognostic risk factors and their influence on outcomes.

Conclusions

Building upon the primary findings of ESCAPE-TRD, which reported improved rates of clinical remission and response from depressive symptoms, these data highlight their effective translation into meaningful improvements in patients' daily functioning and productivity. Patients receiving esketamine NS plus SSRI/SNRI experienced greater improvements in functioning and productivity over 32 weeks versus quetiapine XR plus SSRI/SNRI.

Furthermore, these findings demonstrate that the resolution of depressive symptoms (i.e. experiencing clinical response and remission) are typically a prerequisite to achieving functional remission and a reduction in functional impairment.

The combination of the superior clinical efficacy and the substantial improvements in functional impairment resulting from treatment with esketamine NS versus quetiapine XR, demonstrate the clinical and functional benefit of treatment with esketamine NS for patients with TRD.

ACKNOWLEDGEMENTS

The authors thank the patients, the investigators and their teams who took part in this study. The authors also acknowledge Ruth Milz, MD, MA, MSc, MBA, the physician responsible for the development of the study protocol, and Laura Mawdsley, MSc, from Costello Medical, UK, for medical writing and editorial assistance based on the authors' input and direction. This study was funded by Janssen EMEA.

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.

FUNDING

This study was sponsored by Janssen EMEA. Support for third-party writing assistance for this article, provided by Laura Mawdsley, MSc, Costello Medical, UK, was funded by Janssen EMEA in accordance with Good Publication Practice (GPP 2022) guidelines (https://www.ismpp.org/gpp-2022). Dr Arango has been supported by the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III (ISCIII), co-financed by the European Union, ERDF Funds from the European Commission, "A way of making Europe", financed by the European Union NextGenerationEU (PMP21/00051), PI19/01024, CIBERSAM, Madrid Regional Government (B2017/BMD-3740 AGES-CM-2), European Union Structural Funds, European Union Seventh Framework Program, European Union H2020 Program under the Innovative Medicines Initiative 2 Joint Undertaking: Project PRISM-2 (Grant agreement No. 101034377), Project AIMS-2-TRIALS (Grant agreement No. 777394), Horizon Europe, the National Institute of Mental Health of the National Institutes of Health under Award No. 1U01MH124639-01 (Project ProNET) and Award No. 5P50MH115846-03 (project FEP-CAUSAL), Fundación Familia Alonso, and Fundación Alicia Koplowitz.

ROLE OF SPONSOR

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.

AUTHORS' CONTRIBUTIONS

Substantial contributions to study conception and design: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**; substantial contributions to analysis and interpretation of the data: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**; drafting the article or revising it critically for important intellectual content: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**; final approval of the version of the article to be published: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**.

DISCLOSURES

EV: Received grants and served as consultant, advisor or CME speaker for AB-Biotics, AbbVie, Adamed, Angelini, BeckleyPsych, Biogen, Boehringer Ingelheim, Celon Pharma, Compass, Ethypharm, Ferrer, Gedeon Richter, GH Research, GSK, HMNC, Idorsia, Janssen, Lundbeck, Medincell, Merck, Newron, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva and Viatris.
NA: Received research Grants from Department of Health- Abu Dhabi; Janssen and Viatris; Honoraria for Speaking engagements from Lundbeck, Janssen, Viatris and Hikma; served as consultant/ advisor to MindTales & FeelWrite digital startups.
CA: Consultant to or has received honoraria or grants from Abbot, Acadia, Ambrosetti, Angelini, Biogen, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Medscape, Menarini, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion, Takeda and Teva.
AJC: In the last 3 years: grant funding from the MRC, ADM Protexin Ltd, NIHR, European Union Horizon Europe/Innovate UK, Beckley Psytech Ltd, and Wellcome Trust; honoraria for presentations and/or consulting from Janssen, Otsuka, COMPASS Pathways Plc, Viatris and Medscape; President of the International Society for Affective Disorders.
KD: Biogen, Boehringer Ingelheim, Johnson & Johnson, LivaNova, Lundbeck, Merck, Pfizer and Viatris.
MD: Received travel grants and consultant and speaker honoraria from Medizin Medien Austria, Janssen, and Universimed.
SK: Served on advisory boards, participated as an investigator and received speaker's honoraria from Janssen, Ketabon, Neurocrine and ROVI.
PML: In the past 3 years, participated in advisory boards for Eisai, Ethypharm, Janssen, Lundbeck, MSD, Neuraxpharm, Novartis, Otsuka, Roche and Rovi; received speaker's honoraria and consultation fees from Eisai, Ethypharm, Janssen, Lundbeck, MSD, Neuraxpharm, Novartis, Otsuka, Roche, and Rovi; member of the Executive Committee of Fondation FondaMental; involved in developing National Care Guidelines for the French Society for Biological Psychiatry and Neuropsychopharmacology on the treatment of major depression.
RSM: Received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from

Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Neurawell, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie and Atai Life Sciences. Dr. Roger S. McIntyre is a CEO of Braxia Scientific Corp.

GS: Received grants and honoraria from Angelini, Janssen, Lundbeck, Otsuka, Rovi, and Viatris.

TI, YK, CvH, BR: Employees of Janssen; hold Johnson & Johnson company stock/stock options.

REFERENCES

Al-Harbi, K. S. (2012). *Patient Prefer Adherence* **6**, 369-388.

Association, W. M. (2013). *Jama* **310**, 2191-2194.

Biron, C., Brun, J. P., Ivers, H. & Cooper, C. (2006). *Journal of Public Mental Health* **5**, 26-37.

Eaton, W. W., Martins, S. S., Nestadt, G., Bienvenu, O. J., Clarke, D. & Alexandre, P. (2008). *Epidemiologic Reviews* **30**, 1-14.

European Medicines Agency (2013).

European Medicines Agency (2019a).

European Medicines Agency (2019b).

Florea, I., Loft, H., Danchenko, N., Rive, B., Brignone, M., Merikle, E., Jacobsen, P. L. & Sheehan, D. V. (2017). *Brain Behav* **7**, e00622.

Gasse, C., Petersen, L., Chollet, J. & Saragoussi, D. (2013). *J Affect Disord* **151**, 959-966.

Gaynes BN, W. D., Trivedi MH, et al. (2009).

Habert, J., Katzman, M. A., Oluboka, O. J., McIntyre, R. S., McIntosh, D., MacQueen, G. M., Khullar, A., Milev, R. V., Kjernisted, K. D., Chokka, P. R. & Kennedy, S. H. (2016). *Prim Care Companion CNS Disord* **18**.

Heerlein, K., De Giorgi, S., Degraeve, G., Frodl, T., Hagedoorn, W., Oliveira-Maia, A. J., Otte, C., Perez Sola, V., Rathod, S., Rosso, G., Sierra, P., Vita, A., Morrens, J., Rive, B., Mulhern Haughey, S., Kambarov, Y. & Young, A. H. (2022). *J Affect Disord* **298**, 442-450.

Heerlein, K., Perugi, G., Otte, C., Frodl, T., Degraeve, G., Hagedoorn, W., Oliveira-Maia, A. J., Perez Sola, V., Rathod, S., Rosso, G., Sierra, P., Malynn, S., Morrens, J., Verrijcken, C., Gonzalez, B. & Young, A. H. (2021). *J Affect Disord* **290**, 334-344.

Heerlein, K., Young, A. H., Otte, C., Frodl, T., Degraeve, G., Hagedoorn, W., Oliveira-Maia, A. J., Perez Sola, V., Rathod, S., Rosso, G., Sierra, P., Morrens, J., Van Dooren, G., Gali, Y. & Perugi, G. (2021). *J Affect Disord* **283**, 115-122.

Jaffe, D. H., Rive, B. & Denee, T. R. (2019). *BMC Psychiatry* **19**, 247.

Johnston, D. A., Harvey, S. B., Glozier, N., Calvo, R. A., Christensen, H. & Deady, M. (2019). *Journal of Affective Disorders* **256**, 536-540.

Johnston, K. M., Powell, L. C., Anderson, I. M., Szabo, S. & Cline, S. (2019). *J Affect Disord* **242**, 195-210.

Lee, Y., Rosenblat, J. D., Lee, J., Carmona, N. E., Subramaniapillai, M., Shekotikhina, M., Mansur, R. B., Brietzke, E., Lee, J. H., Ho, R. C., Yim, S. J. & McIntyre, R. S. (2018). *J Affect Disord* **227**, 406-415.

McIntyre, R. S., Alsuwaidan, M., Baune, B. T., Berk, M., Demyttenaere, K., Goldberg, J. F., Gorwood, P., Ho, R., Kasper, S., Kennedy, S. H., Ly-Uson, J., Mansur, R. B., McAllister-Williams, R. H., Murrough, J. W., Nemeroff, C. B., Nierenberg, A. A., Rosenblat, J. D., Sanacora, G., Schatzberg, A. F., Shelton, R., Stahl, S. M., Trivedi, M. H., Vieta, E., Vinberg, M., Williams, N., Young, A. H. & Maj, M. (2023). *World Psychiatry* **22**, 394-412.

McIntyre, R. S., Bitter, I., Buyze, J., Fagiolini, A., Godinov, Y., Gorwood, P., Ito, T., Oliveira-Maia, A. J., Vieta, E., Werner-Kiechle, T., Young, A. H. & Reif, A. (2024). *Eur Neuropsychopharmacol* **85**, 58-65.

McIntyre, R. S., Florea, I., Tonnoir, B., Loft, H., Lam, R. W. & Christensen, M. C. (2017). *J Clin Psychiatry* **78**, 115-121.

Mrazek DA, H. J., Altar CA, et al. (2014).

Oliveira-Maia, A. J., Bobrowska, A., Constant, E., Ito, T., Kambarov, Y., Luedke, H., Mulhern-Haughey, S. & von Holt, C. (2024). *Advances in Therapy* **41**, 34-64.

Oliveira-Maia, A. J., Rive, B., Godinov, Y. & Mulhern-Haughey, S. (2024). *Frontiers in Psychiatry* **15**, 1459633.

Reif, A., Bitter, I., Buyze, J., Cebulla, K., Frey, R., Fu, D. J., Ito, T., Kambarov, Y., Llorca, P. M., Oliveira-Maia, A. J., Messer, T., Mulhern-Haughey, S., Rive, B., von Holt, C., Young, A. H. & Godinov, Y. (2023). *N Engl J Med* **389**, 1298-1309.

Reilly, M. C., Zbrozek, A. S. & Dukes, E. M. (1993). *Pharmacoeconomics* **4**, 353-365.

Rodrigues, N. B., McIntyre, R. S., Lipsitz, O., Lee, Y., Subramaniapillai, M., Kratiuk, K., Majeed, A., Nasri, F., Gill, H., Mansur, R. B. & Rosenblat, J. D. (2021). *Psychiatry Res* **300**, 113860.

Rosa, A. R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van Riel, W., Ayuso-Mateos, J. L., Kapczinski, F. & Vieta, E. (2007). *Clin Pract Epidemiol Ment Health* **3**, 5.

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J. & Fava, M. (2006). *Am J Psychiatry* **163**, 1905-1917.

Sheehan, K. H. & Sheehan, D. V. (2008). *Int Clin Psychopharmacol* **23**, 70-83.

Trivedi, M. H., Morris, D. W., Wisniewski, S. R., Lesser, I., Nierenberg, A. A., Daly, E., Kurian, B. T., Gaynes, B. N., Balasubramani, G. K. & Rush, A. J. (2013). *Am J Psychiatry* **170**, 633-641.

Vinckier, F., Gourion, D. & Mouchabac, S. (2017). *Eur Psychiatry* **44**, 1-8.

Wong, S., Le, G. H., Phan, L., Rhee, T. G., Ho, R., Meshkat, S., Teopiz, K. M., Kwan, A. T. H., Mansur, R. B., Rosenblat, J. D. & McIntyre, R. S. (2024). *J Affect Disord* **356**, 684-698.

TABLES AND FIGURES

Table 1. Baseline characteristics

Mean (SD), unless otherwise specified	Esketamine NS + SSRI/SNRI N=336	Quetiapine XR + SSRI/SNRI N=340	Total N=676
Baseline characteristics			
Age, years	44.3 (13.6)	45.7 (13.4)	45.0 (13.5)
Sex, female, n (%)	225 (67.0)	222 (65.3)	447 (66.1)
Number of treatment failures in the current MDE, n (%)			
2	204 (60.7)	211 (62.1)	415 (61.4)
≥3	132 (39.3)	129 (37.9)	261 (38.6)
Psychiatric history			
Age at diagnosis, years	33.5 (11.7)	34.8 (11.7)	34.2 (11.7)
Total number of episodes	3.4 (2.4)	3.6 (4.1)	3.5 (3.4)
Duration of current episode, weeks	68.8 (84.2)	64.6 (65.7)	66.7 (75.4)
Total MADRS baseline score	31.4 (6.1; n=336)	31.0 (5.8; n=339)	31.2 (5.9; n=675)
SDS total score	22.3 (5.0; n=326)	21.8 (5.6; n=333)	22.0 (5.3; n=659)
Not impaired (0–3), n (%)	1 (0.3)	4 (1.2)	5 (0.8)
Mild (4–11), n (%)	11 (3.4)	20 (6.0)	31 (4.7)
Moderate (12–19), n (%)	89 (27.3)	96 (28.8)	185 (28.1)
Marked (20–26), n (%)	178 (54.6)	168 (50.5)	346 (52.5)
Extreme (27–30), n (%)	47 (14.4)	45 (13.5)	92 (14.0)
WPAI:D score, % time lost			
Absenteeism	43.1 (38.1; n=153)	37.3 (34.7; n=134)	40.4 (36.6; n=287)
Presenteeism	70.9 (21.6; n=154)	66.1 (25.2 n=152)	68.5 (23.6; n=306)
Work productivity loss	76.8 (22.4; n=154)	72.4 (26.1; n=152)	74.6 (24.3; n=306)
Activity Impairment	74.3 (16.8; n=327)	73.0 (19.1; n=335)	73.6 (18.0; n=662)

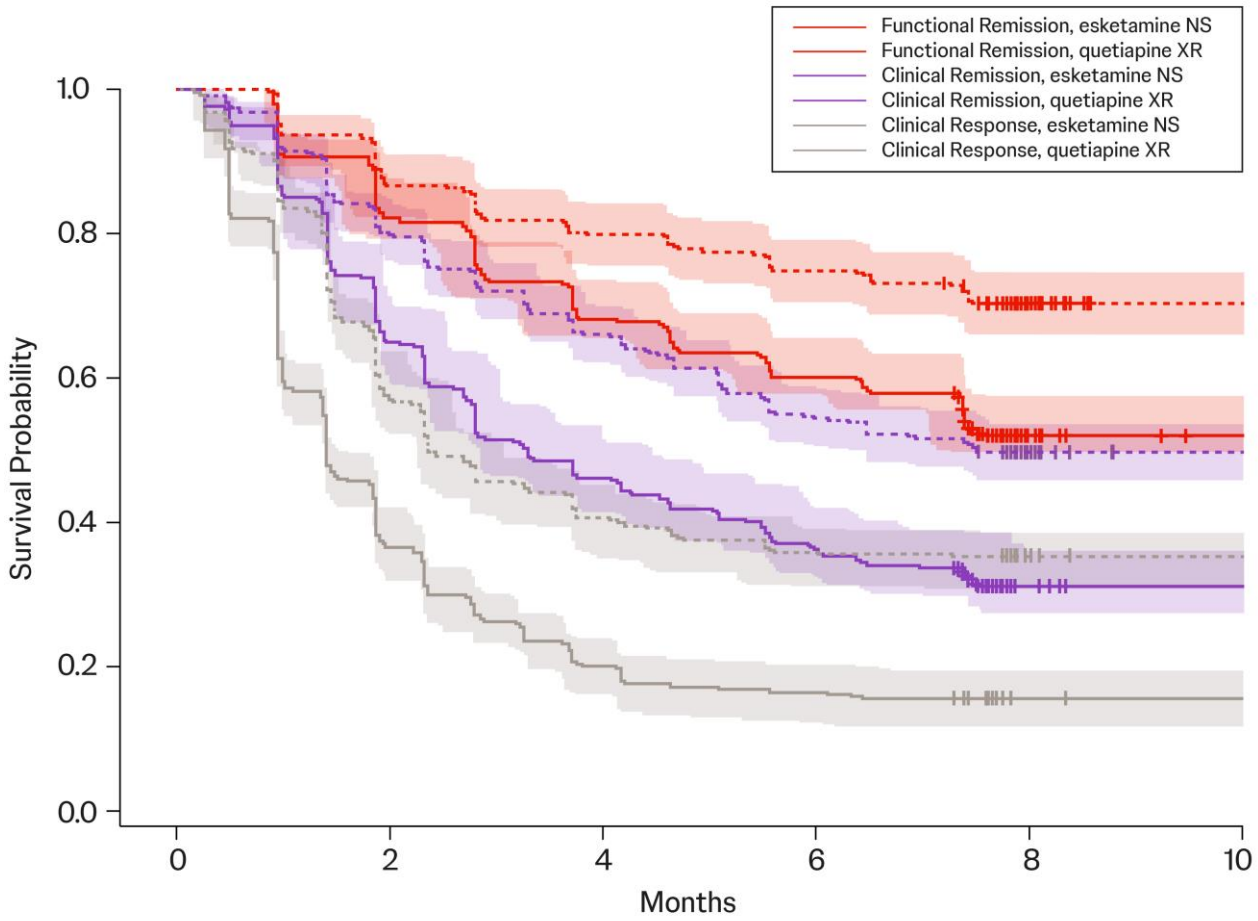
Full analysis set: includes all randomised patients. MADRS: Montgomery-Åsberg Depression Rating Scale; MDE: major depressive episode; NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SD: standard deviation; SDS: Sheehan Disability Scale; SSRI: selective serotonin reuptake inhibitor; WPAI:D: Work Productivity and Activity Impairment: Depression; XR: extended release.

Table 2. Summary of treatment effect estimates for clinical response, clinical remission and functional remission events at each visit

Visit	Clinical response, n (%)		Clinical remission, n (%)		Functional remission, n (%)	
	Esketamine NS + SSRI/SNRI N=336	Quetiapine XR + SSRI/SNRI N=340	Esketamine NS + SSRI/SNRI N=336	Quetiapine XR + SSRI/SNRI N=340	Esketamine NS + SSRI/SNRI N=336	Quetiapine XR + SSRI/SNRI N=340
Week 4	120 (35.7%)	52 (15.3%)	43 (12.8%)	30 (8.8%)	31 (9.2%)	22 (6.5%)
Week 8	174 (51.8%)	126 (37.1%)	91 (27.1%)	60 (17.6%)	49 (14.6%)	42 (12.4%)
Week 12	203 (60.4%)	145 (42.6%)	117 (34.8%)	70 (20.6%)	63 (18.8%)	46 (13.5%)
Week 16	213 (63.4%)	149 (43.8%)	127 (37.8%)	80 (23.5%)	72 (21.4%)	47 (13.8%)
Week 20	216 (64.3%)	155 (45.6%)	134 (39.9%)	86 (25.3%)	82 (24.4%)	52 (15.3%)
Week 24	221 (65.8%)	164 (48.2%)	145 (43.2%)	108 (31.8%)	87 (25.9%)	58 (17.1%)
Week 28	224 (66.7%)	167 (49.1%)	153 (45.5%)	111 (32.6%)	87 (25.9%)	64 (18.8%)
Week 32	222 (66.1%)	161 (47.4%)	167 (49.7%)	112 (32.9%)	115 (34.2%)	67 (19.7%)

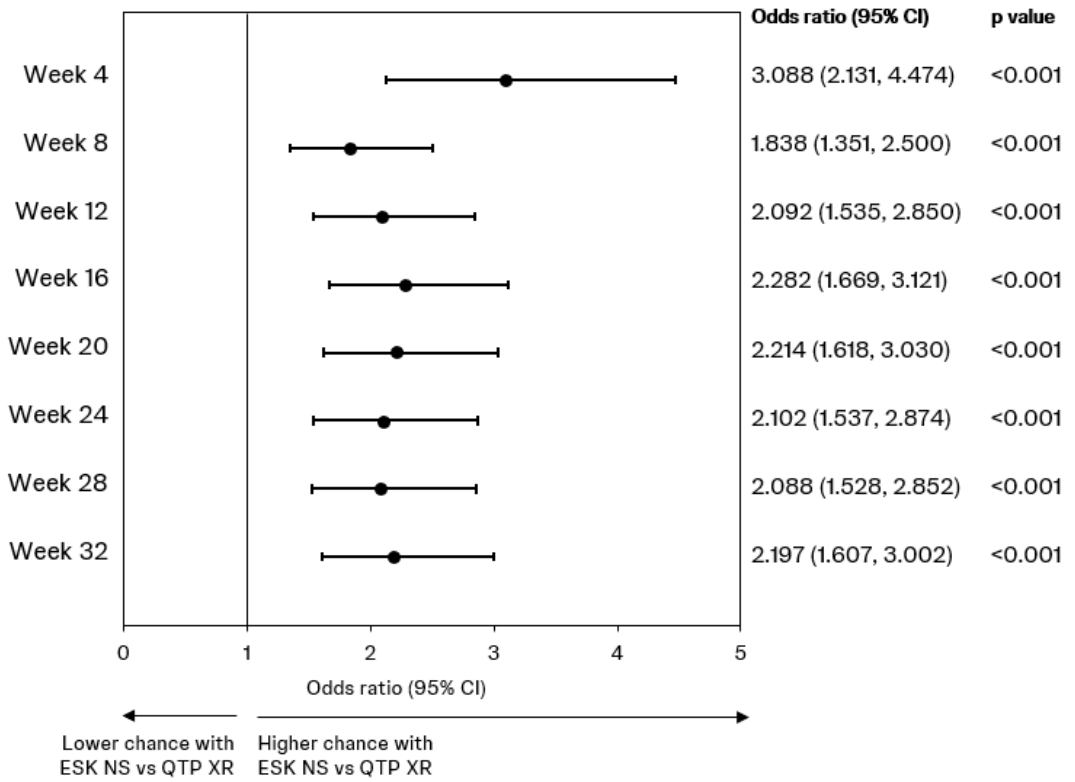
Full analysis set: includes all randomised patients. NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; XR: extended release.

Figure 1. Time to clinical response, clinical remission and functional remission



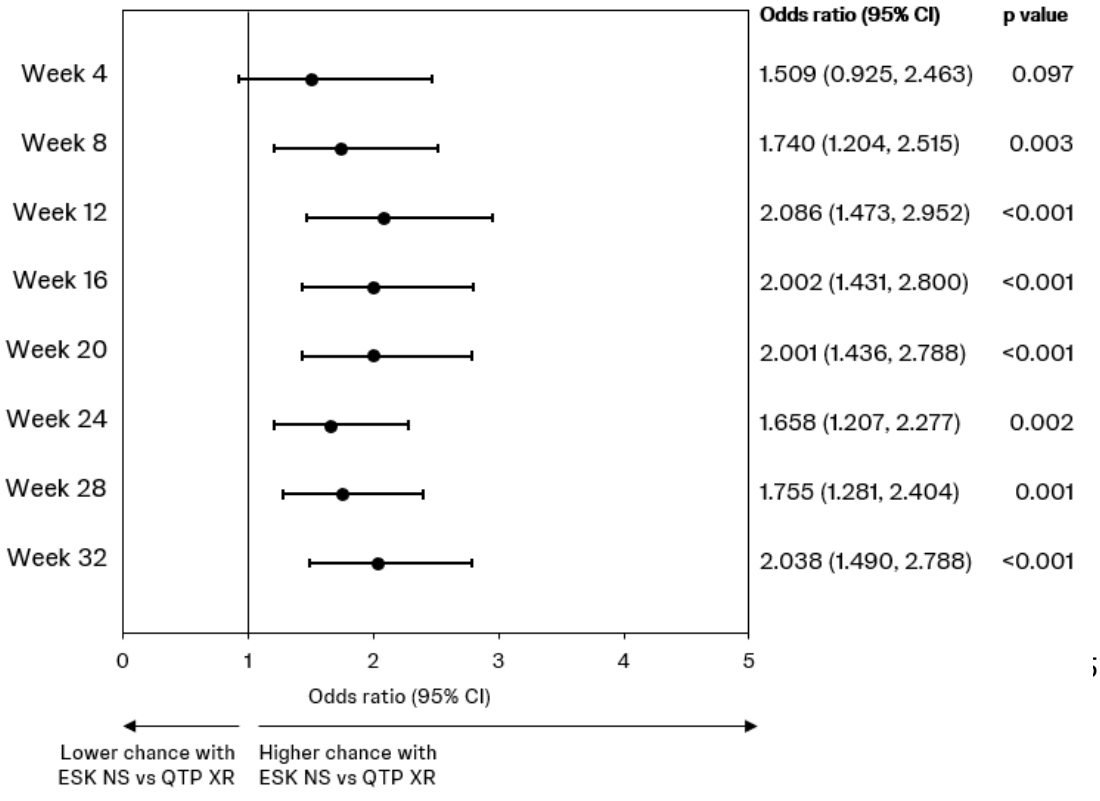
Full analysis set: includes all randomised patients (N=336 esketamine NS; N=340 quetiapine XR). NS: nasal spray; XR: extended release.

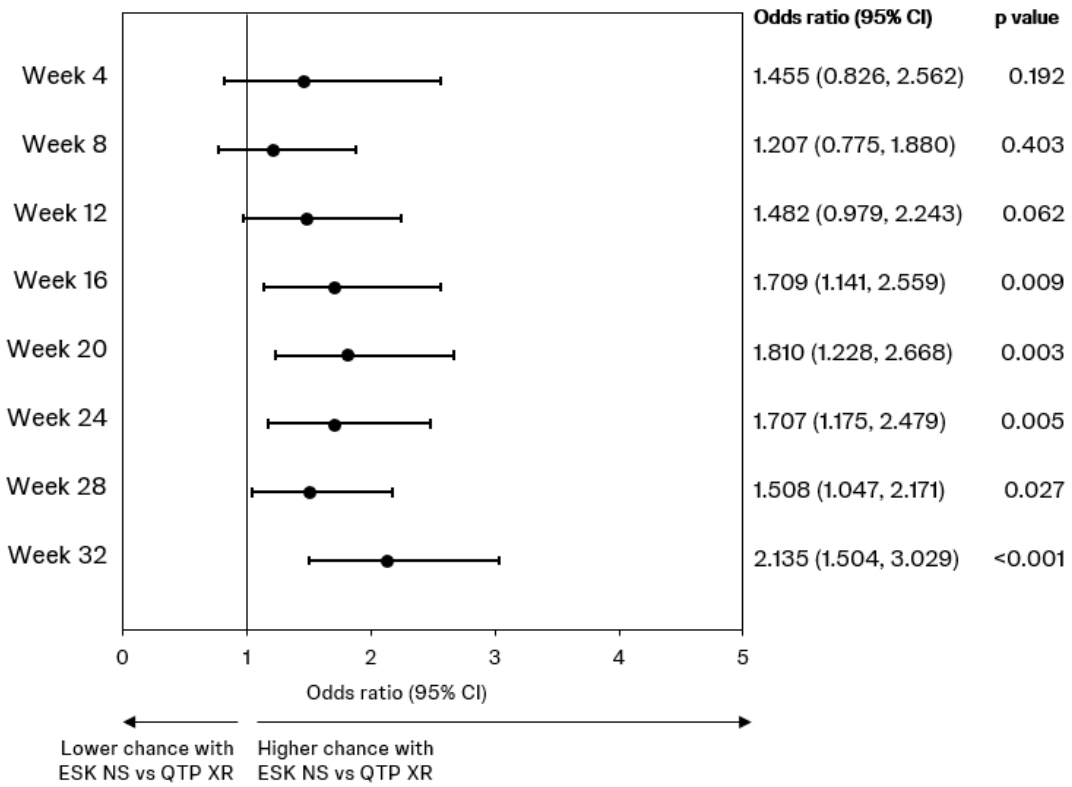
Figure 2. Chance of achieving clinical response, clinical remission and functional remission events at each visit



A) Clinical response

B) Clinical remission



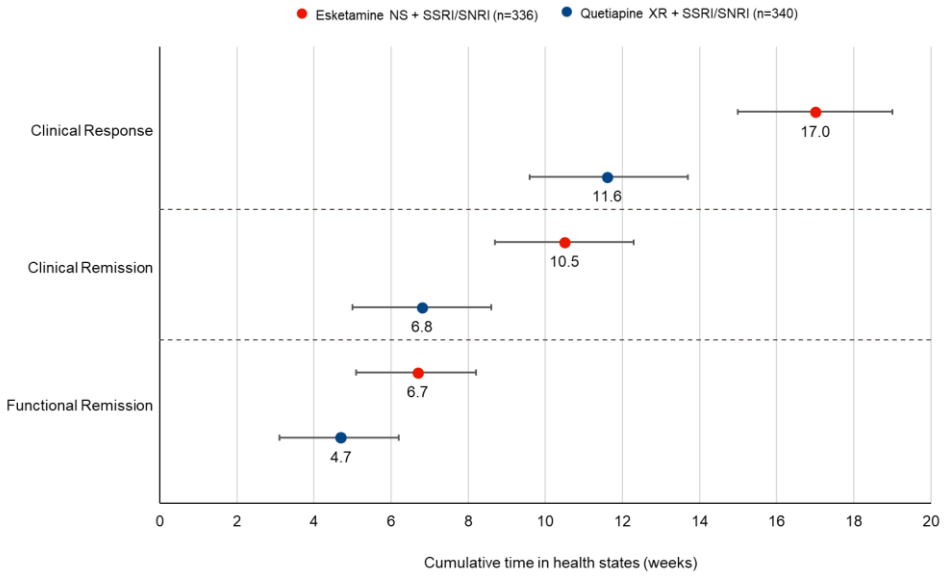


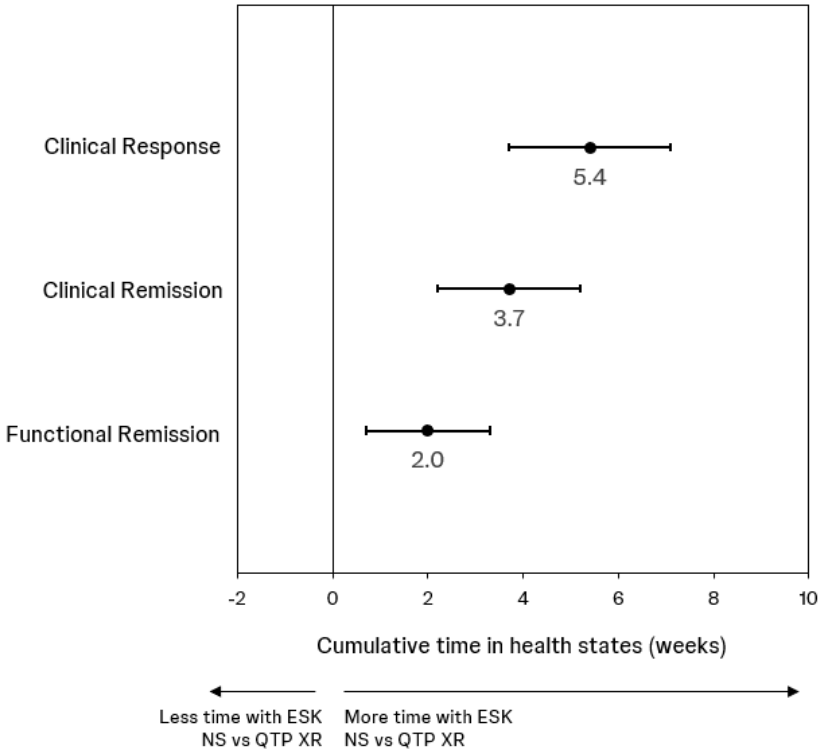
C) Functional remission

Full analysis set: includes all randomised patients (N=336 esketamine NS; N=340 quetiapine XR). Error bars represent 95% CIs. ESK: esketamine; NS: nasal spray; QTP: quetiapine; XR: extended release.

Figure 3. Time spent in clinical response, clinical remission and functional remission

A) By treatment arm at Week 32





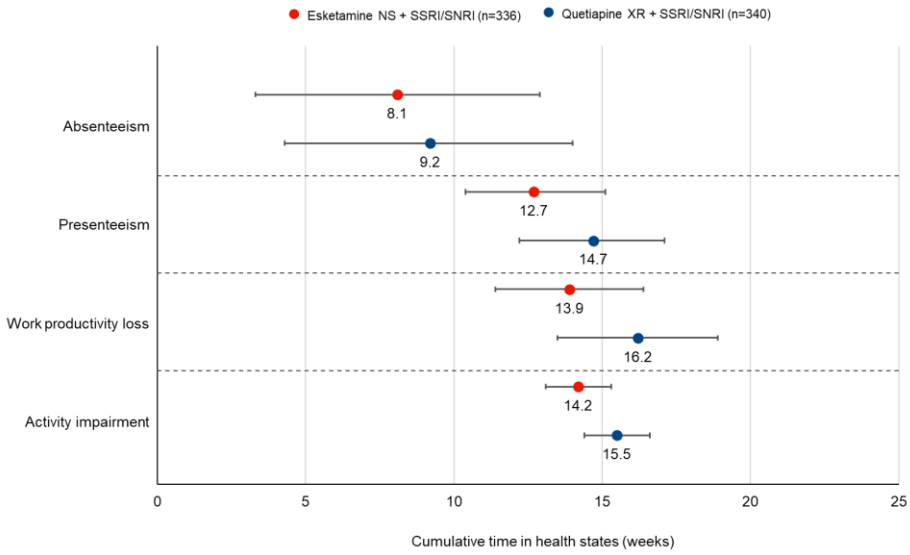
B) Difference between treatment arms at Week 32

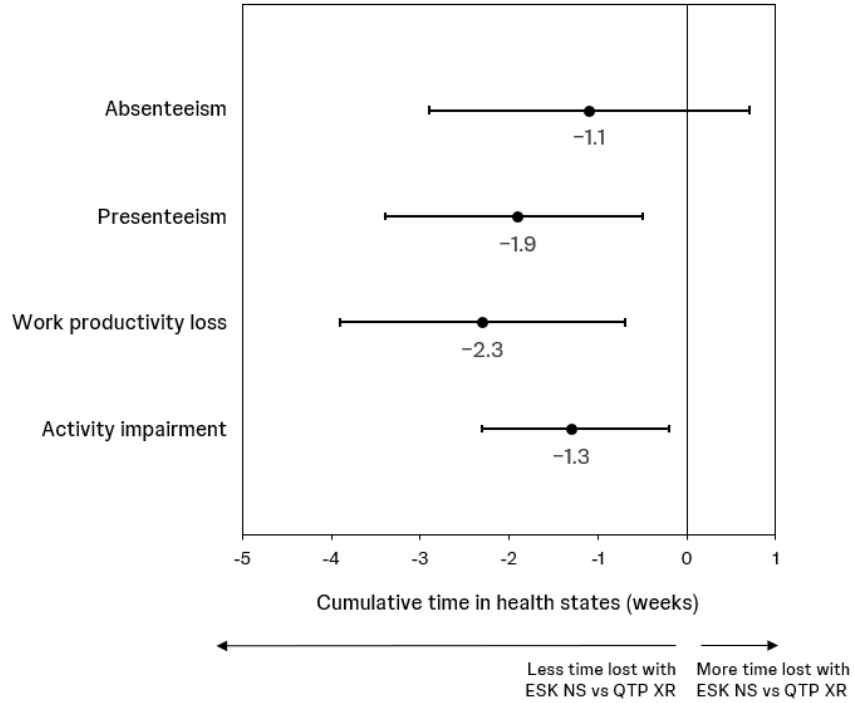
Full analysis set: includes all randomised patients (N=336 esketamine NS; N=340 quetiapine XR). Error bars represent 95% CIs. Time spent estimated using AUC, based on status at on-treatment visits using NRI. Comparisons made using ANCOVA models with age and number of prior treatment failures as covariates. Patients who achieved clinical remission also achieved clinical response. ANCOVA: analysis of

covariance; AUC: area under the curve; CI: confidence interval; ESK: esketamine; NRI: non-responder imputation; NS: nasal spray; QTP: quetiapine; XR: extended release.

Figure 4. Cumulative work productivity and impairment measured with WPAI:D

A) Results by treatment arm at Week 32





B) Difference between treatment arms at Week 32

Full analysis set: includes all randomised patients (N=336 esketamine NS; N=340 quetiapine XR). Error bars represent 95% CIs. CI: confidence interval; NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; WPAI:D: Work Productivity and Activity Impairment for Depression; XR: extended release.

SUPPLEMENTARY MATERIAL

Supplementary Material S1. Validity of SDS imputation

When a score for the school and/or work item of the SDS was missing, the social life and leisure activities and family life and home responsibilities items were used to compute the total score. This is an approach also used by authors of the SDS.(Sheehan & Sheehan, 2008) This score was computed by imputation by the mean. The objective of this analysis was to assess the validity of the imputation for partially missing SDS data. Using all records (all patients, all visits, observed cases) where all three items were present, total SDS score was computed both normally and without the school and/or work category score. The two scores were then compared using a distribution of each score and their difference.

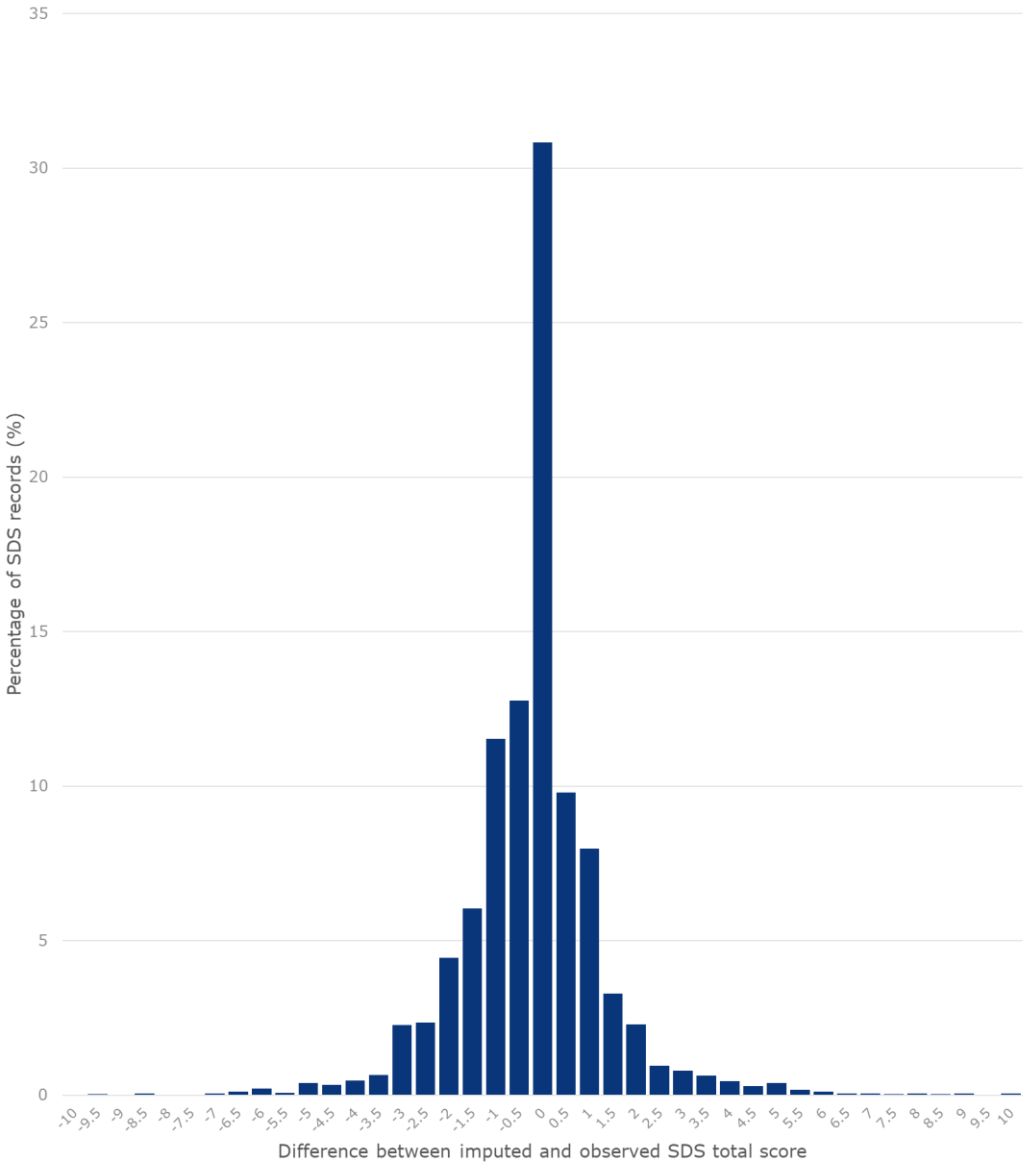
The SDS school and/or work category was highly correlated with the SDS social life and leisure activities score (Pearson correlation coefficient: 0.8401) and the SDS family life and home responsibilities score (0.8158). The imputed SDS scores were a good predictor of the observed SDS scores: 30.8% of observations had imputed scores equal to the observed scores, 72.9% were within one point of the observed score and 88.9% were within two points of the observed score (**Supplementary Table 1**). The distribution between the imputed scores and the observed scores were very similar and appeared symmetrical (**Supplementary Figure 1**), demonstrating no evidence of bias in either direction. Using the SDS imputed score to estimate functional remission (SDS total score ≤6) compared to the actual observed SDS score, was associated with a sensitivity of 96.4% and a specificity of 98.1%, thereby reinforcing the appropriateness of the imputation approach.

Supplementary Table 1. Imputed SDS scores as a predictor of total SDS scores

Threshold	Record within threshold	Percentage within threshold (%)
0.0	1174/3809	30.8
0.5	2033/3809	53.4
1.0	2776/3809	72.9
1.5	3131/3809	82.2
2.0	3387/3809	88.9
2.5	3512/3809	92.2
3.0	3628/3809	95.2

SDS: Sheehan Disability Scale.

Supplementary Figure 1. Distribution of the difference between imputed and observed scores



SDS: Sheehan Disability Scale.

Supplementary Material S2. Exploring proxy of functional remission based on MADRS

Results presented in this article support trends seen in other studies that show there is a progression, or a "domino cascade", from clinical response to clinical remission, through to functional remission.(Oliveira-Maia, Rive*, et al.*, 2024) This begs the question "could functional remission be defined as a stricter remission based on a lower MADRS threshold?".

The objective of this analysis was to assess the feasibility of approximating functional remission using MADRS only.

Using all records (all patients, all visits, observed cases) where both MADRS and SDS were assessed, functional remission and alternative definitions of clinical remission were computed using different thresholds on MADRS, varying from 0 to 15. For each cut-off, the sensitivity, specificity and Youden criterion (sensitivity + specificity – 1) were calculated to evaluate the ability for the corresponding alternative clinical remission criterion to represent a valid proxy of functional remission.

The highest Youden criterion values were observed for MADRS cut-offs of 8, 9 and 10. With cut-offs 9 and 10, both sensitivity and specificity were below 80%. For cut-off 8, specificity reached 84.1% but sensitivity was 69.2%. Sensitivity above 90% could only be reached by having specificity below 60% and specificity above 90% could only be reached by having sensitivity below 60% (**Supplementary Table 2**).

Supplementary Table 2. Sensitivity and specificity of MADRS scores as a proxy for functional remission

MADRS cut-off	Sensitivity (%)	Specificity (%)	Youden criterion
0	11.3	99.7	0.109
1	16.7	99.2	0.159
2	25.4	98.0	0.235
3	35.9	96.7	0.326
4	45.0	94.8	0.398
5	51.8	92.8	0.445
6	59.1	90.4	0.494
7	63.6	87.9	0.516
8	69.2	84.1	0.532
9	75.2	79.3	0.545
10	79.8	74.1	0.539
11	83.6	68.7	0.524
12	86.9	62.1	0.490
13	89.5	55.8	0.453
14	91.3	50.4	0.416
15	92.7	45.0	0.377

MADRS: Montgomery-Åsberg Depression Rating Scale.

References

Oliveira-Maia, A. J., Rive, B., Godinov, Y. & Mulhern-Haughey, S. (2024). *Frontiers in Psychiatry* **15**, 1459633.

Sheehan, K. H. & Sheehan, D. V. (2008). *Int Clin Psychopharmacol* **23**, 70-83.

-Improvements in Functioning and Workplace Productivity with Esketamine Nasal Spray versus Quetiapine Extended Release in Patients with Treatment Resistant Depression: Findings from a 32-Week Randomised, Open-Label, Rater-Blinded Phase IIIb Study

Journal Requirements

Proposed Journal: European Neuropsychopharmacology

Full details at: European Neuropsychopharmacology

- Word limit: 6,500 (includes tables and figure legends)
  - Abstract: 250
- Max tables/figures: N/A
- Max References: 80

- Submission to acceptance time: 68 days (72 with review)
- Impact factor: 6.1

Lead medical writer: Laura Mawdsley (laura.mawdsley@costellomedical.com)

Current manuscript

Word count: ~~3,773~~4,020
Number of tables: 2 (+2 in Supplement)
Number of figures: 4 (+1 in Supplement)
Number of references: ~~32~~33

Improvements in Functioning and Workplace Productivity with Esketamine Nasal Spray versus Quetiapine Extended Release in Patients with Treatment Resistant Depression: Findings from a 32-Week Randomised, Open-Label, Rater-Blinded Phase IIIb Study ~~Improvements in Functioning and Workplace Productivity with Esketamine Nasal Spray versus Quetiapine Extended Release in Patients with Treatment Resistant Depression~~

Eduard Vieta (MD, PhD),[1] Nahida Ahmed (MD),[2] Celso Arango (MD, PhD),[3] Anthony J. Cleare (MBBS, PhD),[4] Koen Demyttenaere (MD, PhD),[5] Markus Dold,[6] Tetsuro Ito (MSc, MBA),[7] Yerkebulan Kambarov (MD, MSc),[8] Stephanie Krüger (MD),[9] Pierre-Michel Llorca (MD, PhD),[10] Roger S. McIntyre (MD, FRCPC),[11,~~12~~] Gabriele Sani (MD),[1~~2~~3,1~~3~~4] Christian von Holt (MD),[1~~4~~5] Benoit Rive (MSc, PhD)[1~~5~~6]

1 Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Institut de Neurociències (UBNeuro), Universitat de Barcelona (UB); Bipolar and Depressive Disorders Unit, Hospital Clínic de Barcelona; Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS); CIBERSAM, ISCIII, Barcelona, Spain ; 2. Sakina Mental Health & Wellbeing Services; College of Medicine, and Health Sciences (CMHS) of the United Arab Emirates University; Khalifa University, Abu Dhabi, UAE; 3. Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense de Madrid, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain; 4. Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; 5. University Psychiatric Center KU Leuven, Campus Leuven, Belgium; 6. Medical University of Vienna, Department of Psychiatry and Psychotherapy; 7. Janssen EMEA, High Wycombe, UK; 8. Janssen EMEA, Beerse, Belgium; 9. Department of Mental Health, Vivantes Humboldt Clinic, Berlin, Germany; 10. CHU Clermont-Ferrand, Department of Psychiatry, University of Clermont Auvergne, UMR 6602 Institut Pascal (IP), Clermont Ferrand, France; 11. Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; ~~12. Braxia Scientific, Toronto, Ontario, Canada;~~ 1~~2~~3. Department of Neuroscience, Section of Psychiatry, Università Cattolica del Sacro Cuore, Rome, Italy; 1~~3~~4. Department of Psychiatry, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; 1~~4~~5. Janssen EMEA, Neuss, Germany; 1~~5~~6. Janssen EMEA, Paris, France

Formatted: English (United Kingdom)

1 **Correspondence to:** Prof Eduard Vieta, EVIETA@clinic.cat

2 **Short title:** ESCAPE-TRD Functioning and Productivity

3 **Trial registration:** ClinicalTrials.gov identifier: NCT04338321

4 **Funding:** Janssen EMEA, Beerse, Belgium

5 **Key words:** esketamine, major depressive disorder, quetiapine, functioning and
6 productivity, treatment resistant depression, workplace productivity

ABSTRACT (25045/250 words)

Patients with treatment resistant depression (TRD) experience a greater negative impact on their functioning and productivity at home and in the workplace versus treatment-responsive patients. ~~It is unclear whether treatment of clinical symptoms reliably improves workplace and home based functioning.~~ Here, we report the effects of esketamine nasal spray (NS) versus quetiapine extended release (XR) on functioning, work productivity and activity impairment. ESCAPE-TRD (NCT04338321) was a 32-week randomised, open-label, rater-blinded, active-controlled phase IIIb study comparing the efficacy and safety of esketamine NS versus quetiapine XR, both alongside an ongoing selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor (SSRI/SNRI), in patients with TRD. Patient functioning was assessed via the Sheehan Disability Scale (SDS; functional remission ≤6). Absenteeism, presenteeism, work productivity loss and activity impairment over time were assessed using the Work Productivity and Activity Impairment: Depression (WPAI:D) questionnaire. Results were cumulated over the entire study duration. Esketamine NS-treated patients (N=336) experienced 43.2% more weeks with functional remission versus quetiapine XR-treated patients (N=340) over the 32-week study period (difference: 2.0 weeks [95% CI: 0.7, 3.3]; p=0.0023 [ANCOVA models]). Up to Week 32, esketamine NS-treated patients experienced an 11.9% reduction in productivity loss due to absenteeism (difference: −1.1 weeks [95% CI: −2.9, 0.7]; p=0.2285) and a 14.2% reduction in overall work productivity loss (difference: −2.3 weeks, 95% CI: [−3.9, −0.7] p=0.0045) versus quetiapine XR-treated patients, based on mixed models for repeated measures. Patients receiving esketamine NS experienced greater improvements in functioning and productivity over 32 weeks versus quetiapine XR. These improvements demonstrate the clinical and functional benefit of treatment with esketamine NS for patients with TRD.

INTRODUCTION

Treatment resistant depression (TRD) is commonly defined as a lack of response to two or more pharmacological treatments of adequate duration and dose within the same major depressive episode (MDE),(European Medicines Agency, 2013) and affects 10–30% of patients with major depressive disorder (MDD) in research and real-world settings.(Rush *et al.*, 2006, McIntyre *et al.*, 2023, Al-Harbi, 2012) Relative to their treatment-responsive counterparts, patients with TRD have a worse prognosis, a higher rate of suicide,(McIntyre *et al.*, 2023) a greater negative impact on their functioning and productivity,(Jaffe *et al.*, 2019, Heerlein, Young*, et al.*, 2021) and experience a reduced health-related quality of life (HRQoL).(Johnston, Powell*, et al.*, 2019) Patients with TRD also face increased personal and economic costs when compared with treatment-responsive patients, driven by productivity loss and workplace impairment.(Heerlein *et al.*, 2022)

There are multiple objective, subjective and performance-based measures of functional impairment; one of the most widely used is the Sheehan Disability Scale (SDS). The SDS is a patient-reported outcome measure of functional disability that assesses the degree to which symptoms disrupt a patient's daily life. This scale assesses three domains: work and/or school work, social life and leisure activities, and family life and home responsibilities.(Florea *et al.*, 2017, Sheehan & Sheehan, 2008) Low SDS scores indicate minimal disruption in a patient's daily functioning and can be used to determine rates of functional remission. Previous studies using the SDS to measure functional remission have shown that most patients that achieved functional remission first achieved clinical response and remission,(Oliveira-Maia, Rive*, et al.*, 2024) suggesting that a reduction in disease symptoms may be required to reduce the impact of the disease on daily functioning.

In addition to functional remission, impairment in a patient's productivity at work and in their daily life is another method of measuring the impact of TRD. The Work Productivity and Activity Impairment for Depression (WPAI:D) questionnaire provides several measures of the extent to which TRD impacts daily functioning; absenteeism (the proportion of work time missed due to TRD), presenteeism (the degree of impairment while working due to TRD), work productivity loss (overall work impairment due to TRD, combining absenteeism and presenteeism) and activity impairment (the degree of impairment of regular, non-work activity due to TRD) are

all quantified. Previous studies using the WPAI have shown that patients with TRD experienced an overall mean impairment of work and activity of 60.5% and 73.3%, respectively.(Heerlein, Young*, et al.*, 2021, Oliveira-Maia, Bobrowska*, et al.*, 2024) These impairments lead to increased costs, and result in human capital erosion. It is currently unclear whether antidepressant treatment significantly and reliably improves measures of workplace functioning.(Lee *et al.*, 2018) Preliminary evidence from real-world data sets provides some support for improvements in workplace productivity in people with TRD following treatment,(Rodrigues *et al.*, 2021) however, no randomised-controlled study data are available in this regard, nor studies on how these improvements translate to workplace functionality. Furthermore, patients who achieve clinical remission when using second-line monoamine-based antidepressants continue to demonstrate impairment in workplace metrics,(Trivedi *et al.*, 2013) indicating a lack of solutions for workplace impairment and productivity loss in patients with TRD.

Esketamine nasal spray (NS), given in combination with either a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI), is approved for the treatment of TRD in Europe.(European Medicines Agency, 2019a)

ESCAPE-TRD is one of the few existing large, long-term head-to-head studies in TRD and was the first head-to-head study comparing esketamine NS with an augmentation strategy. ESCAPE-TRD demonstrated the superior efficacy of esketamine NS over quetiapine extended release (XR), both in combination with an ongoing SSRI/SNRI, in both the short and long term.(European Medicines Agency, 2019b, Reif *et al.*, 2023) The trial also showed a more favourable tolerability profile for esketamine NS as compared with quetiapine XR.(McIntyre *et al.*, 2024)

Here, we report the effects of esketamine NS versus quetiapine XR treatment on functioning, work productivity and impairment over 32 weeks in patients with TRD. Furthermore, we explore the sequential cascade from clinical response to clinical remission, through to functional remission and compare the temporal pattern of these transitions between treatments.

EXPERIMENTAL PROCEDURES

Formatted: Keep with next

Study design

ESCAPE-TRD (NCT04338321) was a randomised, open-label, rater-blinded, active-controlled phase IIIb study comparing the efficacy and safety of esketamine NS versus quetiapine XR, both alongside an ongoing SSRI/SNRI, in patients with TRD; the full methodology was reported in the primary publication.(Reif *et al.*, 2023) Patients were randomised 1:1 to esketamine NS or quetiapine XR, both flexibly dosed per label.(European Medicines Agency, 2019a, b) Randomisation was stratified by age (18–≤64 years; 65–<75 years) and number of prior treatment failures in the current MDE (2; ≥3). Full inclusion and exclusion criteria were reported in the primary publication.(Reif *et al.*, 2023)

ESCAPE-TRD was conducted in accordance with the Declaration of Helsinki;(Association, 2013) country-specific ethics review boards provided approval. All patients provided written informed consent and the study was registered at ClinicalTrials.gov.

The Montgomery-Åsberg Depression Rating Scale (MADRS) was used to assess clinical symptom severity. Clinical remission was defined as MADRS total score ≤10. Clinical response was defined as an improvement in MADRS total score from baseline of ≥50%, or MADRS total score ≤10. Patient functioning was assessed via the SDS, with functional remission defined as SDS total score ≤6 (total SDS score range was 0–30, where higher scores indicated worse functioning).(Sheehan & Sheehan, 2008, Eaton *et al.*, 2008) SDS-based functional remission measures the state where depression symptoms only create a minimal disruption in the patient's daily functioning (versus whether a patient has achieved a "normal life"). The degree of absenteeism, presenteeism, work productivity loss and activity impairment experienced by patients over time were assessed as a proportion of time lost using the WPAI:D questionnaire.(Reilly *et al.*, 1993) The SDS and the WPAI:D were assessed every 4 weeks from baseline to Week 32. All p values reported here were not adjusted for multiple testing.

Time to event

Time to event, assessed for clinical response, clinical remission, and functional remission, was estimated using the Kaplan-Meier method. Patients can either reach the condition of the event while on treatment, where the time of the event is the

first time where the condition is satisfied, or complete the study without having ever satisfied the condition for the event, when they would be considered censored at the time of completion. Patients discontinuing study treatment before having ever satisfied the condition for the event were censored at an infinite (arbitrarily large) time and were assumed to never achieve the relevant event.

Hazard ratio (HR), 95% confidence intervals (CI) and corresponding p value were estimated using a Cox proportional hazards model adjusted for age (18–≤64, 65–<75 years) and number of prior treatment failures (2, ≥3).

Consistency between outcomes was explored (pooled treatments arms) by estimating the proportion of patients achieving functional remission (at any point in time) for patients having reached clinical response/remission and for those who did not reach these outcomes. For patients having reached both functional remission and clinical outcomes (response or remission), the length of time between the first occurrences of these events was estimated.

Events at each visit

At each visit where all endpoints were assessed (every 4 weeks), the proportions of patients that achieved clinical response, clinical remission and functional remission were analysed.

This analysis was based on observed data; patients that discontinued study treatment were imputed using non-responder imputation (NRI) and systematically considered as having a negative outcome at all timepoints following treatment discontinuation. For patients that were still receiving treatment but had missing values, data were imputed using local last observation carried forward (LOCF), where missing values were assigned the outcome of the last timepoint where data were collected.

Odds ratios (OR), corresponding 95% CIs and p values are reported based on Cochran-Mantel-Haenszel chi-square tests adjusted for age and number of prior treatment failures.

Cumulative time spent in health states

Cumulative time spent in either clinical response, clinical remission, or functional remission was estimated using the area under the curve (AUC) method, based on

status at on-treatment visits using NRI. If a patient had the same outcome (favourable or un-favourable) at both the beginning and end of an interval (two consecutive visits), they were considered to have spent the time between visits in the corresponding health state. If a patient had different outcomes at consecutive visits, a transition was assumed to have taken place at the midpoint of the interval.

For each patient, total time in a given health state was then calculated by adding the time in the health state on each 4-week interval (where both MADRS and SDS were assessed), from baseline to Week 32. Total time spent in each health state (and the corresponding 95% CI and p-value) was estimated by treatment arm and compared between treatment arms using analysis of covariance (ANCOVA) models with age and number of prior treatment failures as covariates.

Cumulative work productivity and impairment

Each of the four WPAI:D scores (calculated as a percentage of time lost) was analysed using a mixed model for repeated measures (with an unstructured covariance structure) based on observed cases. The model included study intervention, stratification factors (age [18–≤64 years; 65–<75 years] and number of prior treatment failures [2; ≥3]), visit (every 4 weeks from baseline to Week 32), and visit-by-study-intervention interaction as fixed effects. The analysis included both on-treatment visits and retrieved dropouts (post-study treatment discontinuation). Analyses on absenteeism, presenteeism and work impairment parameters were conducted using only data from working patients, regardless of their age (retired patients were excluded, as were non-working patients who were of working age).

In each 4-week time interval, patients were assumed to spend the first two weeks with their WPAI score at the start of the interval and the latter two weeks with their score at the end of the interval. Total time of productivity loss on each score (by treatment arm and difference between treatment arms, along with corresponding 95% CI and p-value) was then estimated by allocating weights to each visit and estimating the corresponding least-square means, with intermediate visits (every 4 weeks from Week 4 to Week 28) receiving a weight of 4 weeks as they each contributed to two intervals, and extreme visits (baseline and Week 32) receiving a weight of 2 weeks. Total time lost was then calculated as the proportion of time lost (WPAI:D scores) multiplied by the weighted time interval.

Using all records where both MADRS and WPAI:D were assessed, Pearson correlation coefficients between MADRS and each of the four WPAI-D scores were also estimated.

SDS imputation validity

Methods used to explore the validity of SDS imputation are reported in **Supplementary Material S1**.

Proxy for SDS functional remission based on MADRS

Methods used to explore a MADRS-based proxy for SDS functional remission are reported in **Supplementary Material S2.**

RESULTS

Patient disposition and baseline functioning and productivity

Overall, 336 patients were randomised to esketamine NS and 340 patients to quetiapine XR (N=676). Baseline demographics were comparable between arms,(Reif *et al.*, 2023) with similar MADRS, SDS total and WPAI:D scores in each arm (**Table 1**). Of all patients at baseline, the majority of patients (52.5%) had marked functional impairment, 28.1% had moderate impairment, 14.0% extreme impairment and 5.5% mild or no impairment. Patients experienced a mean 40.4% loss of work time due to absenteeism. When combined with presenteeism, this resulted in an overall work time loss of 74.6%.

Time to event

Significantly more esketamine NS-treated patients achieved clinical response (HR: 1.848, 95% CI: [1.547, 2.207], p<0.001), clinical remission (HR: 1.711, 95% CI: [1.402, 2.087], p<0.001) and functional remission (HR: 1.819, 95% CI: [1.416, 2.336], p<0.001) compared with quetiapine XR-treated patients. Esketamine NS-treated patients also achieved these outcomes faster than patients treated with quetiapine XR (**Figure 1**).

Within each treatment arm, at each time point, more patients reached clinical response than clinical remission, and more patients reached clinical remission than functional remission, indicating the increasing difficulty in achieving these outcomes.

Time to clinical remission in patients receiving esketamine NS was similar to time to clinical response with quetiapine XR; likewise, time to functional remission observed in patients receiving esketamine NS was similar to time to clinical remission in patients receiving quetiapine XR (**Figure 1**).

Among all patients (including both esketamine NS- and quetiapine XR-treated) who never reached clinical response (n=174), 2.3% (4) achieved functional remission. In contrast, among patients who did achieve clinical response (n=502), 51.0% (256) of patients achieved functional remission. The average time between achieving clinical response and functional remission (for patients who achieved both) was 57.6 days. Clinical response occurred before or at the same time as functional remission in 92.2% of cases.

Similarly, among patients who never achieved clinical remission (n=276), 8.7% (24) achieved functional remission. Among patients who reached clinical remission (n=400), 59.0% (236) of patients achieved functional remission. The average time between clinical remission and functional remission (for patients who achieved both) was 26.1 days. Clinical remission occurred before or at the same time as functional remission in 77.5% of cases.

The exploration of a potential MADRS cut-off for use as a proxy for SDS functional remission determined that no MADRS cut-off provided a high enough sensitivity or specificity (**Supplementary Material S2, Supplementary Table S2**).

Events at each visit

Across all outcomes, the proportion of patients with a favourable outcome (clinical response, clinical remission or functional remission) was numerically higher with esketamine NS compared to quetiapine XR at each visit (**Table 2**).

A statistically significant benefit for esketamine NS was seen as early as Week 4, where the OR for clinical response was 3.088 (95% CI: [2.131, 4.474]; p<0.001), which continued through every visit to Week 32 (**Figure 2A**).

For clinical remission, a significant benefit for esketamine NS versus quetiapine XR was observed from Week 8 onwards (OR: 1.740, 95% CI: [1.204, 2.515]; p=0.003) and for functional remission this benefit was observed from Week 16 onwards (OR: 1.709, 95% CI: [1.141, 2.559]; p=0.009; **Figure 2B–C**).

At each visit a similar number of esketamine NS-treated patients achieved clinical remission as quetiapine XR-treated patients who reached clinical response; likewise, a similar number of esketamine NS-treated patients achieved functional remission as quetiapine XR-treated patients who reached clinical remission (**Table 2**).

Cumulative time spent in health states

With respect to cumulative time spent in each of the three health states, a significant benefit of esketamine NS was seen when compared with quetiapine XR over the 32-week study period (**Figure 3**). Esketamine NS-treated patients experienced 17.0 weeks with clinical response versus 11.6 weeks for quetiapine XR-treated patients (difference: 5.4 weeks [95% CI: 3.7, 7.1]; p<0.0001), indicating a 46.4% relative increase. Esketamine NS-treated patients experienced 10.5 weeks with clinical remission versus 6.8 weeks for quetiapine XR-treated patients (difference: 3.7 weeks [95% CI: 2.2, 5.2]; p<0.0001), indicating a 55.0% relative increase. Finally, esketamine NS-treated patients experienced 6.7 weeks with functional remission versus 4.7 weeks for quetiapine XR-treated patients (difference: 2.0 weeks [95% CI: 0.7, 3.3]; p=0.0023), indicating a 43.2% relative increase.

Time spent in clinical remission with esketamine NS was similar to time in clinical response with quetiapine XR, whilst time in functional remission with esketamine NS was similar to time in clinical remission with quetiapine XR (**Figure 3A**).

Cumulative work productivity and impairment

Over the 32-week duration of the study, patients receiving esketamine NS lost numerically less time to work productivity and activity impairment (i.e. gained more productive time) compared to patients on quetiapine XR (**Figure 4A**). Esketamine NS-treated patients experienced 8.1 weeks of absenteeism versus 9.2 weeks for quetiapine XR-treated patients, indicating an 11.9% reduction in productivity loss due to absenteeism (difference: −1.1 weeks [95% CI: −2.9, 0.7]; p=0.2285). Esketamine NS significantly improved presenteeism (–1.9 weeks, 95% CI: [–3.4, –0.5], p=0.0098, –13.1%), work productivity loss (–2.3 weeks, 95% CI: [–3.9, –0.7] p=0.0045, –14.2%) and activity impairment (–1.3 weeks, 95% CI: [–2.3, –0.2] p=0.0172, –8.3%) compared to quetiapine-XR (**Figure 4B**).

Correlations between MADRS and the WPAI:D scores were less strong for absenteeism (Pearson correlation coefficient: 0.3413) compared with presenteeism (0.6497), work productivity loss (0.6118), and activity impairment (0.6826).

SDS imputation validity

The imputation of SDS scores was considered valid; the specifics pertaining to the validity of SDS imputation for partially missing data are reported in **Supplementary Material S1** (**Supplementary Figure S1, Supplementary Table S1**).

DISCUSSION

The functioning and productivity analyses reported here suggest that esketamine NS has a significant functional benefit over quetiapine XR for patients with TRD. These data reinforce the superiority of esketamine NS over the commonly used augmentation agent, quetiapine XR, when given in combination with an ongoing SSRI/SNRI, and further establish the importance of achieving clinical endpoints, such as clinical remission, to achieve functional treatment benefits.

As demonstrated previously, achieving functional remission often requires the achievement of both clinical response and clinical remission.(Oliveira-Maia, Rive*, et al.*, 2024) In ESCAPE-TRD, significantly more esketamine NS-treated patients achieved clinical response, clinical remission and functional remission compared with quetiapine XR-treated patients. Patients treated with esketamine NS also achieved these milestones faster than quetiapine XR-treated patients. These results suggest that patients treated with esketamine NS experience a greater clinical and functional benefit than patients treated with quetiapine XR, to the extent that similar number of patients treated with esketamine NS achieved clinical remission as quetiapine XR-treated patients did clinical response. The same pattern was observed with functional versus clinical remission and remains true at any timepoint. This is consistent with the findings of the primary analysis of ESCAPE-TRD, where patients treated with esketamine NS experienced more rapid reductions in MADRS total score and earlier onset of clinical remission and clinical response.(Reif *et al.*, 2023)

Though response trajectories are heterogeneous, these results support findings seen in other studies that show there is often a progression, or a "domino cascade", from clinical response to clinical remission, through to functional remission.(Oliveira-Maia, Rive*, et al.*, 2024) This suggests that functional remission is both harder for patients

to achieve and takes longer to achieve than clinical outcomes. The exploratory MADRS proxy analysis supports the view that severity and functioning are two distinct concepts and challenges the idea that functional remission is just a stricter definition of clinical remission. These analyses highlight the need for physicians to monitor both outcomes in their clinical practice.(Habert *et al.*, 2016)

It has been shown that the larger the amount of time that patients are considered to have achieved these three outcomes, the less likely they are to be experiencing decreased functioning, which is linked with poorer QoL, higher costs and a larger disease burden.(Heerlein, Perugi*, et al.*, 2021, Heerlein *et al.*, 2022, Jaffe *et al.*, 2019, Johnston, Powell*, et al.*, 2019) Patients treated with esketamine NS spent more time in clinical remission and functional remission when compared with quetiapine XR-treated patients. These results represent a relative increase in time of approximately 50% on each outcome over the 32-week study duration. For patients treated with esketamine NS, in addition to reaching each clinical outcome more quickly, treatment also enabled patients to spend more time having achieved each clinical outcome, demonstrating the persistent benefit of esketamine NS that results in better outcomes for patients.

Significant relationships between depression severity and both absenteeism and presenteeism have been demonstrated, showing indicated increases in absence and decreases in performance with increasing depression severity.(Johnston, Harvey*, et al.*, 2019) Improvements in workplace productivity are not commonly demonstrated in treatment with a second typical monoamine antidepressant, even when patients have achieved clinical remission.(Trivedi *et al.*, 2013, Gaynes BN, 2009) Over the 32-week duration of the study, patients receiving esketamine NS gained more productive time compared to patients on quetiapine XR, with this difference reaching statistical significance for presenteeism, work productivity loss and activity impairment. As presenteeism disproportionately accounts for disability and is costlier compared with absenteeism, improvements in presenteeism would have a real-world impact on patients.(Biron *et al.*, 2006) The difference for absenteeism did not reach statistical significance in this analysis, which may be due to larger variability in time lost compared with other WPAI:D domains. ~~Additionally, e~~Esketamine NS-treated patients may also have required to use more sick days or time off, as these patients had to attend treatment sessions and could not work. An additional factor which

could potentially explain why significant differences between treatments were observed on all WPAI:D scores except absenteeism could be found in the correlation analyses, which revealed a substantially lower correlation of the absenteeism score with depression severity (as measured by MADRS score) compared to the other three WPAI:D scores (presenteeism, work productivity loss and activity impairment), making absenteeism less sensitive to improvement in depression symptoms and therefore to treatment effect. This is consistent with literature that found that other factors, such as previous history of sick leave, were the main predictors of future sick leaves.(Gasse *et al.*, 2013)

Finally, since the first 4-week interval in which WPAI:D was assessed incorporated the average productive time lost from baseline to Week 4, the higher baseline productivity loss observed in the esketamine NS arm versus quetiapine XR arm would have resulted in an inflated productivity loss in this first interval. Therefore, the overall estimation of the actual difference between the arms was conservative. The results presented here suggest a benefit of treatment with esketamine NS for improvements in workplace productivity, which could potentially lead to a reduction in the societal costs associated with TRD, highlighting the effective translation of clinical efficacy into meaningful improvements in patients' daily functioning and productivity.(Heerlein *et al.*, 2022, Mrazek DA, 2014)

Strengths and limitations

To our knowledge, ESCAPE-TRD is the first randomised comparative study reporting long-term esketamine NS use against an augmentation treatment for patients with TRD.

A strength of these analyses is that despite the varied methodology, all analyses reported a similar result; esketamine NS-treated patients consistently experienced better outcomes than quetiapine XR-treated patients. The different analyses reported here provide a complementary and extensive view of the relative benefit of esketamine NS over quetiapine XR in achieving clinical response, clinical remission and functional remission. Additionally, the validity of the SDS imputation for partially missing data was confirmed, lending robustness to the SDS score results. A feature of ESCAPE-TRD was the high degree of physician supervision which, while beneficial, may not be generalisable to a real-life setting.

A limitation of the first event analysis was that it could only address how fast patients first reached the outcome, not if they continued to achieve it. This limitation was addressed by subsequent analyses that determined the proportion of patients that achieved each outcome. This analysis provides conclusions at a population level but cannot be reported at an individual patient level. For example, any one patient could achieve functional remission at one time point, not achieve it at the next time point, then achieve it again at a third time point. Additionally, patients with less impairment in the workplace experience greater functional outcomes with treatment;(McIntyre *et al.*, 2017) however, results reported here are not adjusted for baseline functioning. Finally, a further limitation is related to the use of the SDS, which is a valid and reliable measure of functioning in patients with depression but lacks the granularity of other instruments such as the Functioning Assessment Short Test (FAST).(Rosa *et al.*, 2007)

Similar studies have shown that patients who have an improvement in functional recovery also demonstrate an improvement in anhedonia.(Vinckier *et al.*, 2017, Wong *et al.*, 2024) Thus, future work may investigate whether treatment with esketamine NS demonstrates a similar trend. Additional future analyses may include prognostic risk factors and their influence on outcomes.

Conclusions

Building upon the primary findings of ESCAPE-TRD, which reported improved rates of clinical remission and response from depressive symptoms, these data highlight their effective translation into meaningful improvements in patients' daily functioning and productivity. Patients receiving esketamine NS plus SSRI/SNRI experienced greater improvements in functioning and productivity over 32 weeks versus quetiapine XR plus SSRI/SNRI.

Furthermore, these findings demonstrate that the resolution of depressive symptoms (i.e. experiencing clinical response and remission) are typically a prerequisite to achieving functional remission and a reduction in functional impairment.

The combination of the superior clinical efficacy and the substantial improvements in functional impairment resulting from treatment with esketamine NS versus quetiapine XR, demonstrate the clinical and functional benefit of treatment with esketamine NS for patients with TRD.

ACKNOWLEDGEMENTS

The authors thank the patients, the investigators and their teams who took part in this study. The authors also acknowledge Ruth Milz, MD, MA, MSc, MBA, the physician responsible for the development of the study protocol, and Laura Mawdsley, MSc, from Costello Medical, UK, for medical writing and editorial assistance based on the authors' input and direction. This study was funded by Janssen EMEA.

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.

FUNDING

This study was sponsored by Janssen EMEA. Support for third-party writing assistance for this article, provided by Laura Mawdsley, MSc, Costello Medical, UK, was funded by Janssen EMEA in accordance with Good Publication Practice (GPP 2022) guidelines (https://www.ismpp.org/gpp-2022). Dr Arango has been supported by the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III (ISCIII), co-financed by the European Union, ERDF Funds from the European Commission, "A way of making Europe", financed by the European Union NextGenerationEU (PMP21/00051), PI19/01024, CIBERSAM, Madrid Regional Government (B2017/BMD-3740 AGES-CM-2), European Union Structural Funds, European Union Seventh Framework Program, European Union H2020 Program under the Innovative Medicines Initiative 2 Joint Undertaking: Project PRISM-2 (Grant agreement No. 101034377), Project AIMS-2-TRIALS (Grant agreement No. 777394), Horizon Europe, the National Institute of Mental Health of the National Institutes of Health under Award No. 1U01MH124639-01 (Project ProNET) and Award No. 5P50MH115846-03 (project FEP-CAUSAL), Fundación Familia Alonso, and Fundación Alicia Koplowitz.

ROLE OF SPONSOR

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.

AUTHORS' CONTRIBUTIONS

Substantial contributions to study conception and design: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**; substantial contributions to analysis and interpretation of the data: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**; drafting the article or revising it critically for important intellectual content: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**; final approval of the version of the article to be published: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**.

DISCLOSURES

EV: Received grants and served as consultant, advisor or CME speaker for AB-Biotics, AbbVie, Adamed, Angelini, BeckleyPsych, Biogen, Boehringer Ingelheim, Celon Pharma, Compass, Ethypharm, Ferrer, Gedeon Richter, GH Research, GSK, HMNC, Idorsia, Janssen, Lundbeck, Medincell, Merck, Newron, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva and Viatris.
NA: Received research Grants from Department of Health- Abu Dhabi; Janssen and Viatris; Honoraria for Speaking engagements from Lundbeck, Janssen, Viatris and Hikma; served as consultant/ advisor to MindTales & FeelWrite digital startups.
CA: Consultant to or has received honoraria or grants from Abbot, Acadia, Ambrosetti, Angelini, Biogen, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Medscape, Menarini, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion, Takeda and Teva.
AJC: In the last 3 years: grant funding from the MRC, ADM Protexin Ltd, NIHR, European Union Horizon Europe/Innovate UK, Beckley Psytech Ltd, and Wellcome Trust; honoraria for presentations and/or consulting from Janssen, Otsuka, COMPASS Pathways Plc, Viatris and Medscape; President of the International Society for Affective Disorders.
KD: Biogen, Boehringer Ingelheim, Johnson & Johnson, LivaNova, Lundbeck, Merck, Pfizer and Viatris.
MD: Received travel grants and consultant and speaker honoraria from Medizin Medien Austria, Janssen, and Universimed.
SK: Served on advisory boards, participated as an investigator and received speaker's honoraria from Janssen, Ketabon, Neurocrine and ROVI.
PML: In the past 3 years, participated in advisory boards for Eisai, Ethypharm, Janssen, Lundbeck, MSD, Neuraxpharm, Novartis, Otsuka, Roche and Rovi; received speaker's honoraria and consultation fees from Eisai, Ethypharm, Janssen, Lundbeck, MSD, Neuraxpharm, Novartis, Otsuka, Roche, and Rovi; member of the Executive Committee of Fondation FondaMental; involved in developing National Care Guidelines for the French Society for Biological Psychiatry and Neuropsychopharmacology on the treatment of major depression.
RSM: Received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from

Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Neurawell, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie and Atai Life Sciences. Dr. Roger S. McIntyre is a CEO of Braxia Scientific Corp.
GS: Received grants and honoraria from Angelini, Janssen, Lundbeck, Otsuka, Rovi, and Viatris.
TI, YK, CvH, BR: Employees of Janssen; hold Johnson & Johnson company stock/stock options.

REFERENCES

Al-Harbi, K. S. (2012). *Patient Prefer Adherence* **6**, 369-388.

Association, W. M. (2013). *Jama* **310**, 2191-2194.

Biron, C., Brun, J. P., Ivers, H. & Cooper, C. (2006). *Journal of Public Mental Health* **5**, 26-37.

Eaton, W. W., Martins, S. S., Nestadt, G., Bienvenu, O. J., Clarke, D. & Alexandre, P. (2008). *Epidemiologic Reviews* **30**, 1-14.

European Medicines Agency (2013).

European Medicines Agency (2019a).

European Medicines Agency (2019b).

Florea, I., Loft, H., Danchenko, N., Rive, B., Brignone, M., Merikle, E., Jacobsen, P. L. & Sheehan, D. V. (2017). *Brain Behav* **7**, e00622.

Gasse, C., Petersen, L., Chollet, J. & Saragoussi, D. (2013). *J Affect Disord* **151**, 959-966.

Gaynes BN, W. D., Trivedi MH, et al. (2009).

Habert, J., Katzman, M. A., Oluboka, O. J., McIntyre, R. S., McIntosh, D., MacQueen, G. M., Khullar, A., Milev, R. V., Kjernisted, K. D., Chokka, P. R. & Kennedy, S. H. (2016). *Prim Care Companion CNS Disord* **18**.

Heerlein, K., De Giorgi, S., Degraeve, G., Frodl, T., Hagedoorn, W., Oliveira-Maia, A. J., Otte, C., Perez Sola, V., Rathod, S., Rosso, G., Sierra, P., Vita, A., Morrens, J., Rive, B., Mulhern Haughey, S., Kambarov, Y. & Young, A. H. (2022). *J Affect Disord* **298**, 442-450.

Heerlein, K., Perugi, G., Otte, C., Frodl, T., Degraeve, G., Hagedoorn, W., Oliveira-Maia, A. J., Perez Sola, V., Rathod, S., Rosso, G., Sierra, P., Malynn, S., Morrens, J., Verrijcken, C., Gonzalez, B. & Young, A. H. (2021). *J Affect Disord* **290**, 334-344.

Heerlein, K., Young, A. H., Otte, C., Frodl, T., Degraeve, G., Hagedoorn, W., Oliveira-Maia, A. J., Perez Sola, V., Rathod, S., Rosso, G., Sierra, P., Morrens, J., Van Dooren, G., Gali, Y. & Perugi, G. (2021). *J Affect Disord* **283**, 115-122.

Jaffe, D. H., Rive, B. & Denee, T. R. (2019). *BMC Psychiatry* **19**, 247.

Johnston, D. A., Harvey, S. B., Glozier, N., Calvo, R. A., Christensen, H. & Deady, M. (2019). *Journal of Affective Disorders* **256**, 536-540.

Johnston, K. M., Powell, L. C., Anderson, I. M., Szabo, S. & Cline, S. (2019). *J Affect Disord* **242**, 195-210.

Lee, Y., Rosenblat, J. D., Lee, J., Carmona, N. E., Subramaniapillai, M., Shekotikhina, M., Mansur, R. B., Brietzke, E., Lee, J. H., Ho, R. C., Yim, S. J. & McIntyre, R. S. (2018). *J Affect Disord* **227**, 406-415.

McIntyre, R. S., Alsuwaidan, M., Baune, B. T., Berk, M., Demyttenaere, K., Goldberg, J. F., Gorwood, P., Ho, R., Kasper, S., Kennedy, S. H., Ly-Uson, J., Mansur, R. B., McAllister-Williams, R. H., Murrough, J. W., Nemeroff, C. B., Nierenberg, A. A., Rosenblat, J. D., Sanacora, G., Schatzberg, A. F., Shelton, R., Stahl, S. M., Trivedi, M. H., Vieta, E., Vinberg, M., Williams, N., Young, A. H. & Maj, M. (2023). *World Psychiatry* **22**, 394-412.

McIntyre, R. S., Bitter, I., Buyze, J., Fagiolini, A., Godinov, Y., Gorwood, P., Ito, T., Oliveira-Maia, A. J., Vieta, E., Werner-Kiechle, T., Young, A. H. & Reif, A. (2024). *Eur Neuropsychopharmacol* **85**, 58-65.

McIntyre, R. S., Florea, I., Tonnoir, B., Loft, H., Lam, R. W. & Christensen, M. C. (2017). *J Clin Psychiatry* **78**, 115-121.

Mrazek DA, H. J., Altar CA, et al. (2014).

Oliveira-Maia, A. J., Bobrowska, A., Constant, E., Ito, T., Kambarov, Y., Luedke, H., Mulhern-Haughey, S. & von Holt, C. (2024). *Advances in Therapy* **41**, 34-64.

Formatted: Spanish (Spain)

Formatted: Spanish (Spain)

Field Code Changed

Formatted: French (France)

Formatted: French (France)

Formatted: Italian (Italy)

Formatted: French (France)

Formatted: Italian (Italy)

Oliveira-Maia, A. J., Rive, B., Godinov, Y. & Mulhern-Haughey, S. (2024). *Frontiers in Psychiatry* **15**, 1459633.
Reif, A., Bitter, I., Buyze, J., Cebulla, K., Frey, R., Fu, D. J., Ito, T., Kambarov, Y., Llorca, P. M., Oliveira-Maia, A. J., Messer, T., Mulhern-Haughey, S., Rive, B., von Holt, C., Young, A. H. & Godinov, Y. (2023). *N Engl J Med* **389**, 1298-1309.
Reilly, M. C., Zbrozek, A. S. & Dukes, E. M. (1993). *Pharmacoeconomics* **4**, 353-365.
Rodrigues, N. B., McIntyre, R. S., Lipsitz, O., Lee, Y., Subramaniapillai, M., Kratiuk, K., Majeed, A., Nasri, F., Gill, H., Mansur, R. B. & Rosenblat, J. D. (2021). *Psychiatry Res* **300**, 113860.
Rosa, A. R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van Riel, W., Ayuso-Mateos, J. L., Kapczinski, F. & Vieta, E. (2007). *Clin Pract Epidemiol Ment Health* **3**, 5.
Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J. & Fava, M. (2006). *Am J Psychiatry* **163**, 1905-1917.
Sheehan, K. H. & Sheehan, D. V. (2008). *Int Clin Psychopharmacol* **23**, 70-83.
Trivedi, M. H., Morris, D. W., Wisniewski, S. R., Lesser, I., Nierenberg, A. A., Daly, E., Kurian, B. T., Gaynes, B. N., Balasubramani, G. K. & Rush, A. J. (2013). *Am J Psychiatry* **170**, 633-641.
Vinckier, F., Gourion, D. & Mouchabac, S. (2017). *Eur Psychiatry* **44**, 1-8.
Wong, S., Le, G. H., Phan, L., Rhee, T. G., Ho, R., Meshkat, S., Teopiz, K. M., Kwan, A. T. H., Mansur, R. B., Rosenblat, J. D. & McIntyre, R. S. (2024). *J Affect Disord* **356**, 684-698.

Formatted: Spanish (Spain)

TABLES AND FIGURES

Table 1. Baseline characteristics

Mean (SD), unless otherwise specified	Esketamine NS + SSRI/SNRI N=336	Quetiapine XR + SSRI/SNRI N=340	Total N=676
Baseline characteristics			
Age, years	44.3 (13.6)	45.7 (13.4)	45.0 (13.5)
Sex, female, n (%)	225 (67.0)	222 (65.3)	447 (66.1)
Number of treatment failures in the current MDE, n (%)			
2	204 (60.7)	211 (62.1)	415 (61.4)
≥3	132 (39.3)	129 (37.9)	261 (38.6)
Psychiatric history			
Age at diagnosis, years	33.5 (11.7)	34.8 (11.7)	34.2 (11.7)
Total number of episodes	3.4 (2.4)	3.6 (4.1)	3.5 (3.4)
Duration of current episode, weeks	68.8 (84.2)	64.6 (65.7)	66.7 (75.4)
Total MADRS baseline score	31.4 (6.1; n=336)	31.0 (5.8; n=339)	31.2 (5.9; n=675)
SDS total score	22.3 (5.0; n=326)	21.8 (5.6; n=333)	22.0 (5.3; n=659)
Not impaired (0–3), n (%)	1 (0.3)	4 (1.2)	5 (0.8)
Mild (4–11), n (%)	11 (3.4)	20 (6.0)	31 (4.7)
Moderate (12–19), n (%)	89 (27.3)	96 (28.8)	185 (28.1)
Marked (20–26), n (%)	178 (54.6)	168 (50.5)	346 (52.5)
Extreme (27–30), n (%)	47 (14.4)	45 (13.5)	92 (14.0)
WPAI:D score, % time lost			
Absenteeism	43.1 (38.1; n=153)	37.3 (34.7; n=134)	40.4 (36.6; n=287)
Presenteeism	70.9 (21.6; n=154)	66.1 (25.2 n=152)	68.5 (23.6; n=306)
Work productivity loss	76.8 (22.4; n=154)	72.4 (26.1; n=152)	74.6 (24.3; n=306)
Activity Impairment	74.3 (16.8; n=327)	73.0 (19.1; n=335)	73.6 (18.0; n=662)

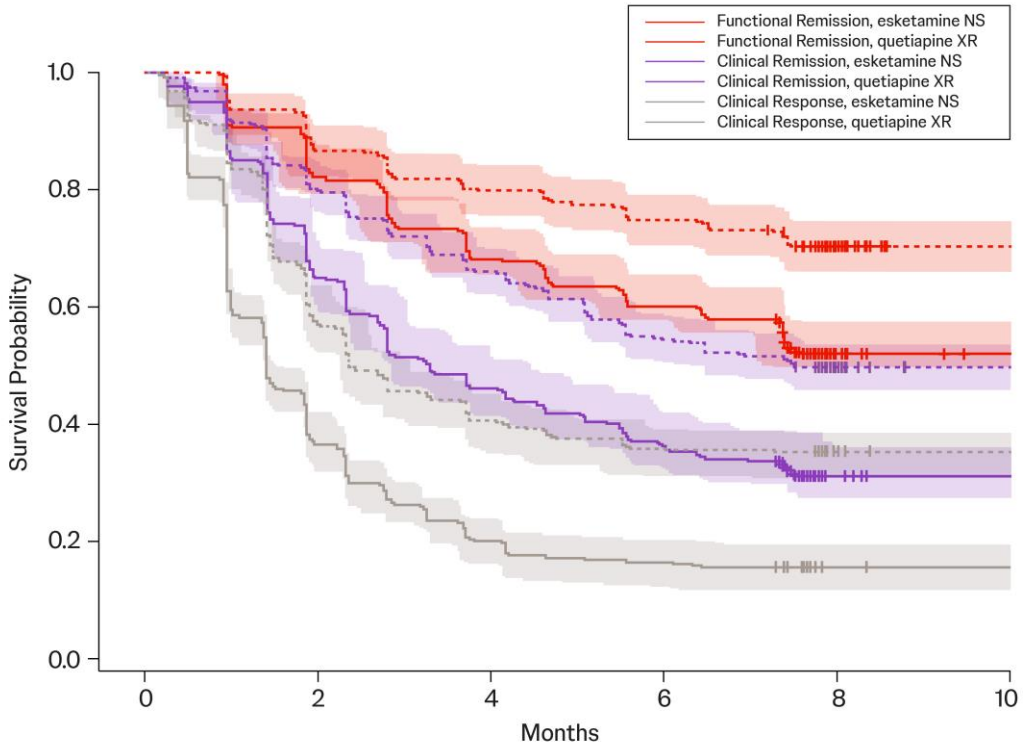
Full analysis set: includes all randomised patients. MADRS: Montgomery-Åsberg Depression Rating Scale; MDE: major depressive episode; NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SD: standard deviation; SDS: Sheehan Disability Scale; SSRI: selective serotonin reuptake inhibitor; WPAI:D: Work Productivity and Activity Impairment: Depression; XR: extended release.

Table 2. Summary of treatment effect estimates for clinical response, clinical remission and functional remission events at each visit

Visit	Clinical response, n (%)		Clinical remission, n (%)		Functional remission, n (%)	
	Esketamine NS + SSRI/SNRI N=336	Quetiapine XR + SSRI/SNRI N=340	Esketamine NS + SSRI/SNRI N=336	Quetiapine XR + SSRI/SNRI N=340	Esketamine NS + SSRI/SNRI N=336	Quetiapine XR + SSRI/SNRI N=340
Week 4	120 (35.7%)	52 (15.3%)	43 (12.8%)	30 (8.8%)	31 (9.2%)	22 (6.5%)
Week 8	174 (51.8%)	126 (37.1%)	91 (27.1%)	60 (17.6%)	49 (14.6%)	42 (12.4%)
Week 12	203 (60.4%)	145 (42.6%)	117 (34.8%)	70 (20.6%)	63 (18.8%)	46 (13.5%)
Week 16	213 (63.4%)	149 (43.8%)	127 (37.8%)	80 (23.5%)	72 (21.4%)	47 (13.8%)
Week 20	216 (64.3%)	155 (45.6%)	134 (39.9%)	86 (25.3%)	82 (24.4%)	52 (15.3%)
Week 24	221 (65.8%)	164 (48.2%)	145 (43.2%)	108 (31.8%)	87 (25.9%)	58 (17.1%)
Week 28	224 (66.7%)	167 (49.1%)	153 (45.5%)	111 (32.6%)	87 (25.9%)	64 (18.8%)
Week 32	222 (66.1%)	161 (47.4%)	167 (49.7%)	112 (32.9%)	115 (34.2%)	67 (19.7%)

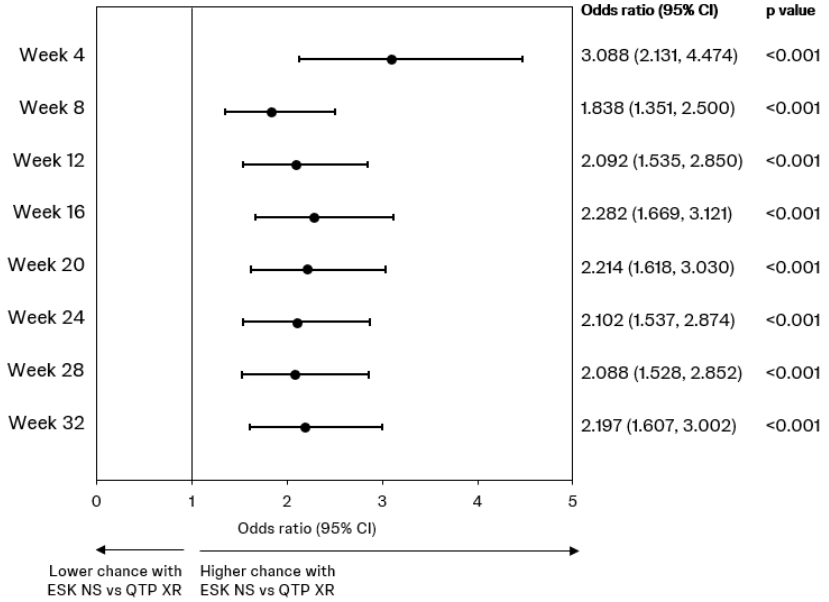
Full analysis set: includes all randomised patients. NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; XR: extended release.

Figure 1. Time to clinical response, clinical remission and functional remission



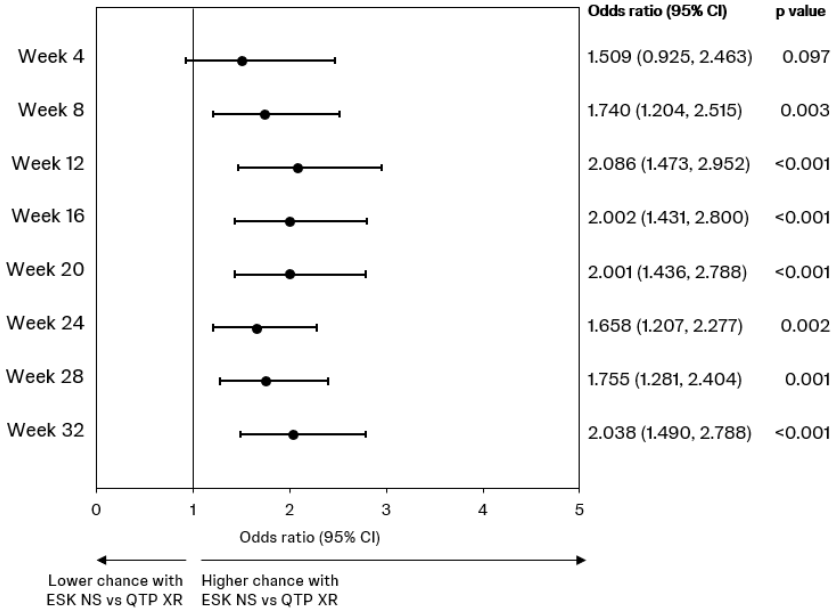
Full analysis set: includes all randomised patients (N=336 esketamine NS; N=340 quetiapine XR). NS: nasal spray; XR: extended release.

Figure 2. Chance of achieving clinical response, clinical remission and functional remission events at each visit

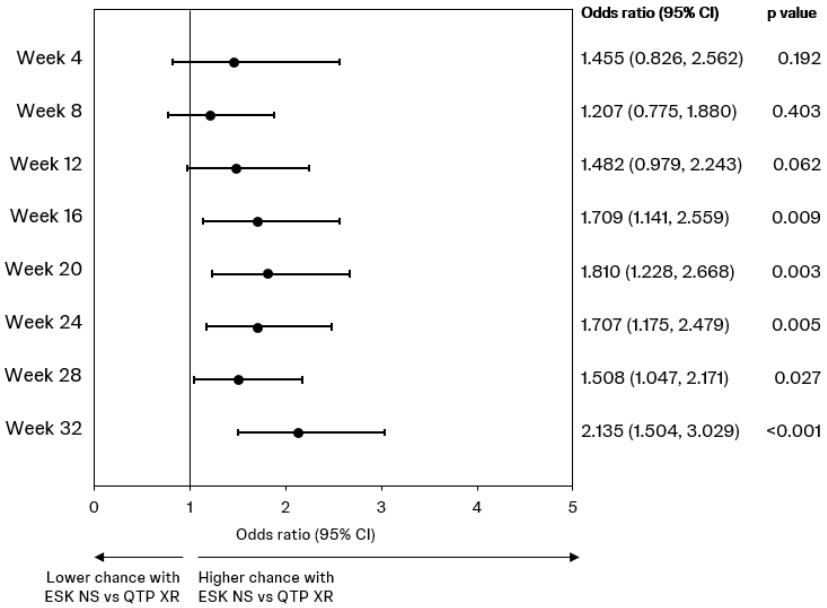


A) Clinical response

B) Clinical remission



;

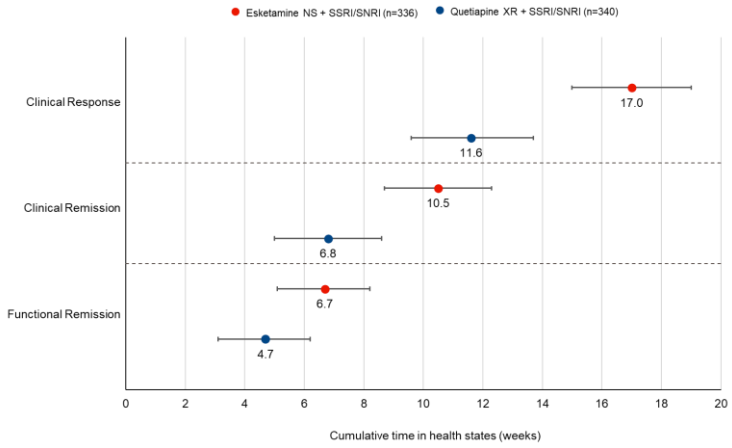


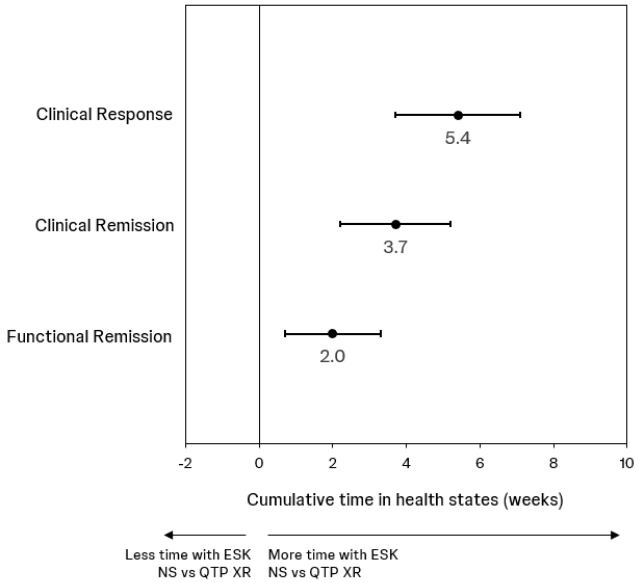
C) Functional remission

Full analysis set: includes all randomised patients (N=336 esketamine NS; N=340 quetiapine XR). Error bars represent 95% CIs. ESK: esketamine; NS: nasal spray; QTP: quetiapine; XR: extended release.

Figure 3. Time spent in clinical response, clinical remission and functional remission

A) By treatment arm at Week 32





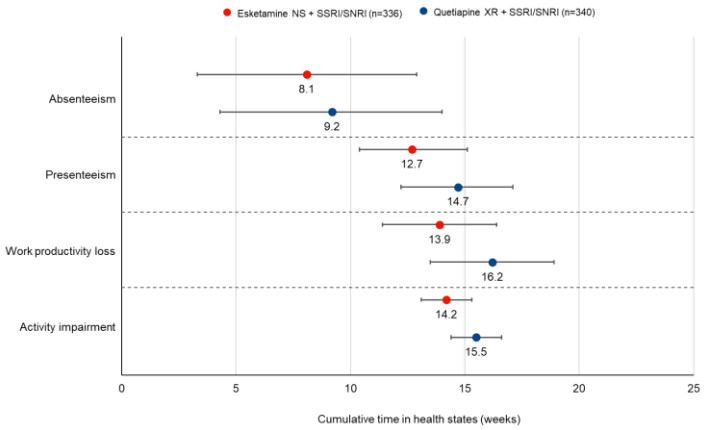
B) Difference between treatment arms at Week 32

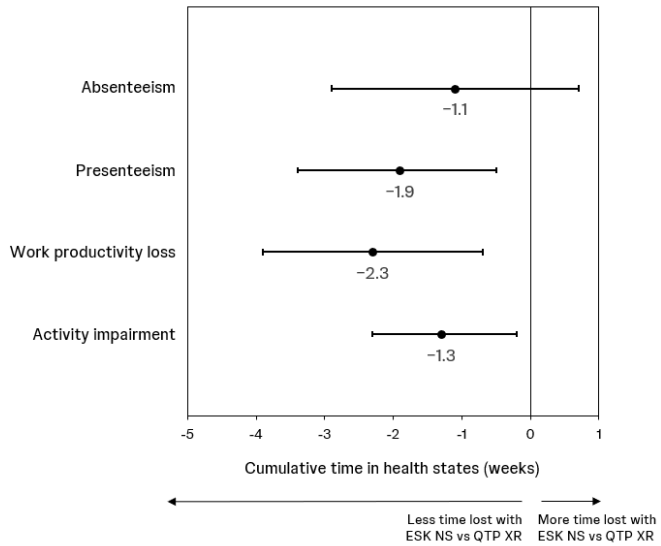
Full analysis set: includes all randomised patients (N=336 esketamine NS; N=340 quetiapine XR). Error bars represent 95% CIs. Time spent estimated using AUC, based on status at on-treatment visits using NRI. Comparisons made using ANCOVA models with age and number of prior treatment failures as covariates. Patients who achieved clinical remission also achieved clinical response. ANCOVA: analysis of

covariance; AUC: area under the curve; CI: confidence interval; ESK: esketamine; NRI: non-responder imputation; NS: nasal spray; QTP: quetiapine; XR: extended release.

Figure 4. Cumulative work productivity and impairment measured with WPAI:D

A) Results by treatment arm at Week 32





B) Difference between treatment arms at Week 32

Full analysis set: includes all randomised patients (N=336 esketamine NS; N=340 quetiapine XR). Error bars represent 95% CIs. CI: confidence interval; NS: nasal spray; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; WPAI:D: Work Productivity and Activity Impairment for Depression; XR: extended release.

SUPPLEMENTARY MATERIAL

Supplementary Material S1. Validity of SDS imputation

When a score for the school and/or work item of the SDS was missing, the social life and leisure activities and family life and home responsibilities items were used to compute the total score. This is an approach also used by authors of the SDS.(Sheehan & Sheehan, 2008) This score was computed by imputation by the mean. The objective of this analysis was to assess the validity of the imputation for partially missing SDS data. Using all records (all patients, all visits, observed cases) where all three items were present, total SDS score was computed both normally and without the school and/or work category score. The two scores were then compared using a distribution of each score and their difference.

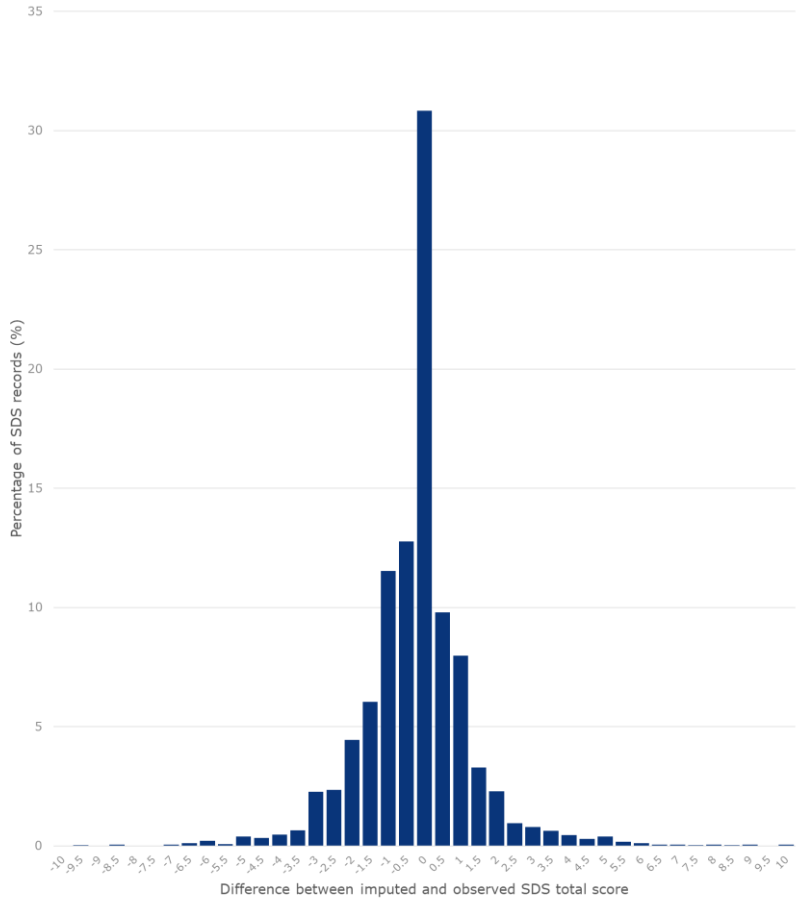
The SDS school and/or work category was highly correlated with the SDS social life and leisure activities score (Pearson correlation coefficient: 0.8401) and the SDS family life and home responsibilities score (0.8158). The imputed SDS scores were a good predictor of the observed SDS scores: 30.8% of observations had imputed scores equal to the observed scores, 72.9% were within one point of the observed score and 88.9% were within two points of the observed score (**Supplementary Table 1**). The distribution between the imputed scores and the observed scores were very similar and appeared symmetrical (**Supplementary Figure 1**), demonstrating no evidence of bias in either direction. Using the SDS imputed score to estimate functional remission (SDS total score ≤6) compared to the actual observed SDS score, was associated with a sensitivity of 96.4% and a specificity of 98.1%, thereby reinforcing the appropriateness of the imputation approach.

Supplementary Table 1. Imputed SDS scores as a predictor of total SDS scores

Threshold	Record within threshold	Percentage within threshold (%)
0.0	1174/3809	30.8
0.5	2033/3809	53.4
1.0	2776/3809	72.9
1.5	3131/3809	82.2
2.0	3387/3809	88.9
2.5	3512/3809	92.2
3.0	3628/3809	95.2

SDS: Sheehan Disability Scale.

Supplementary Figure 1. Distribution of the difference between imputed and observed scores



SDS: Sheehan Disability Scale.

Supplementary Material S2. Exploring proxy of functional remission based on MADRS

Results presented in this article support trends seen in other studies that show there is a progression, or a "domino cascade", from clinical response to clinical remission, through to functional remission.(Oliveira-Maia, Rive*, et al.*, 2024) This begs the question "could functional remission be defined as a stricter remission based on a lower MADRS threshold?".

The objective of this analysis was to assess the feasibility of approximating functional remission using MADRS only.

Using all records (all patients, all visits, observed cases) where both MADRS and SDS were assessed, functional remission and alternative definitions of clinical remission were computed using different thresholds on MADRS, varying from 0 to 15. For each cut-off, the sensitivity, specificity and Youden criterion (sensitivity + specificity – 1) were calculated to evaluate the ability for the corresponding alternative clinical remission criterion to represent a valid proxy of functional remission.

The highest Youden criterion values were observed for MADRS cut-offs of 8, 9 and 10. With cut-offs 9 and 10, both sensitivity and specificity were below 80%. For cut-off 8, specificity reached 84.1% but sensitivity was 69.2%. Sensitivity above 90% could only be reached by having specificity below 60% and specificity above 90% could only be reached by having sensitivity below 60% (**Supplementary Table 2**).

Supplementary Table 2. Sensitivity and specificity of MADRS scores as a proxy for functional remission

MADRS cut-off	Sensitivity (%)	Specificity (%)	Youden criterion
0	11.3	99.7	0.109
1	16.7	99.2	0.159
2	25.4	98.0	0.235
3	35.9	96.7	0.326
4	45.0	94.8	0.398
5	51.8	92.8	0.445
6	59.1	90.4	0.494
7	63.6	87.9	0.516
8	69.2	84.1	0.532
9	75.2	79.3	0.545
10	79.8	74.1	0.539
11	83.6	68.7	0.524
12	86.9	62.1	0.490
13	89.5	55.8	0.453
14	91.3	50.4	0.416
15	92.7	45.0	0.377

MADRS: Montgomery-Åsberg Depression Rating Scale.

References

Oliveira-Maia, A. J., Rive, B., Godinov, Y. & Mulhern-Haughey, S. (2024). *Frontiers in Psychiatry* **15**, 1459633.

Sheehan, K. H. & Sheehan, D. V. (2008). *Int Clin Psychopharmacol* **23**, 70-83.

Figure 1

Click here to access/download;Figure (300 dpi and editable format);Figure1_05Nov2024.png

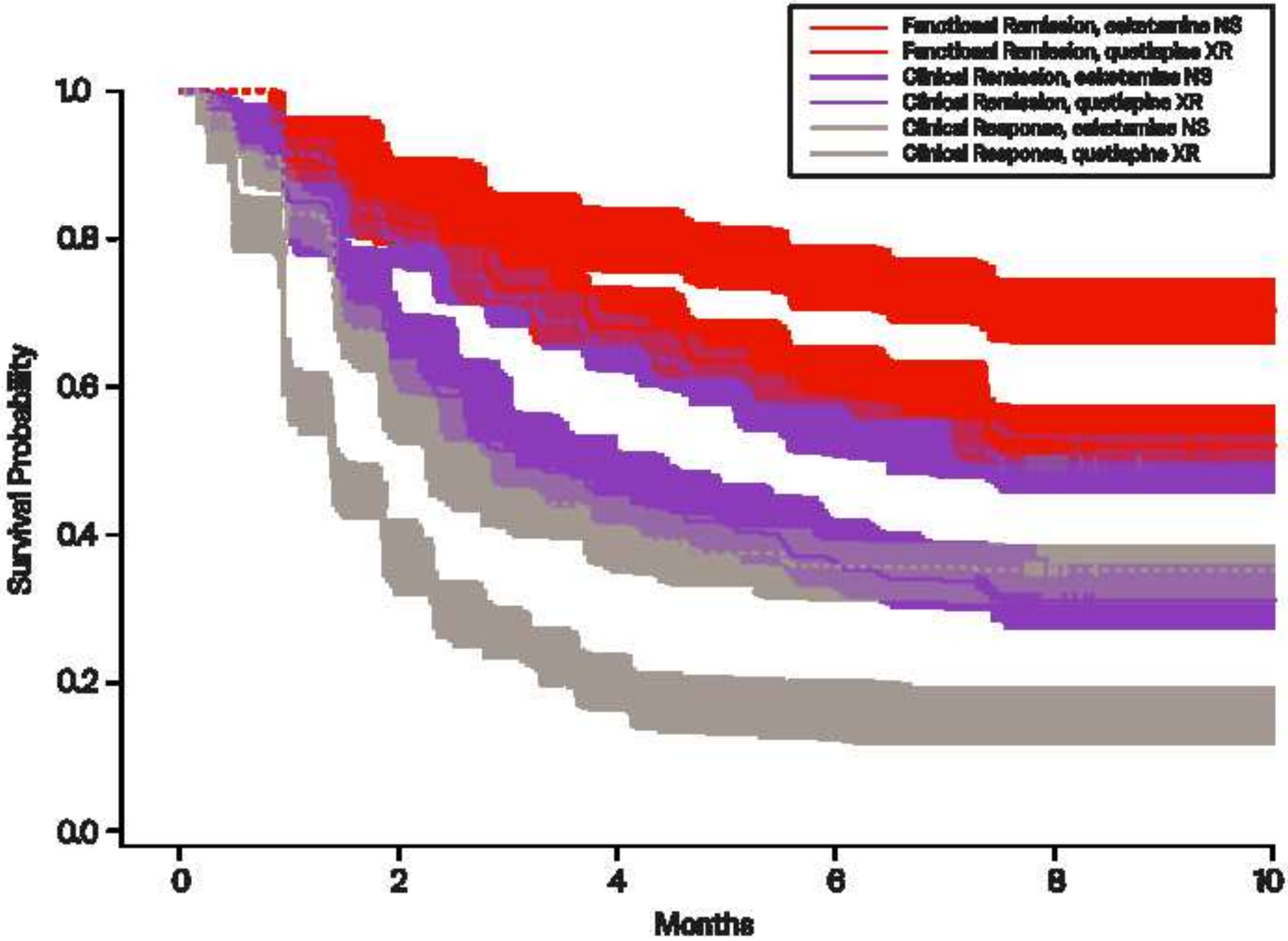


Figure 2A - response

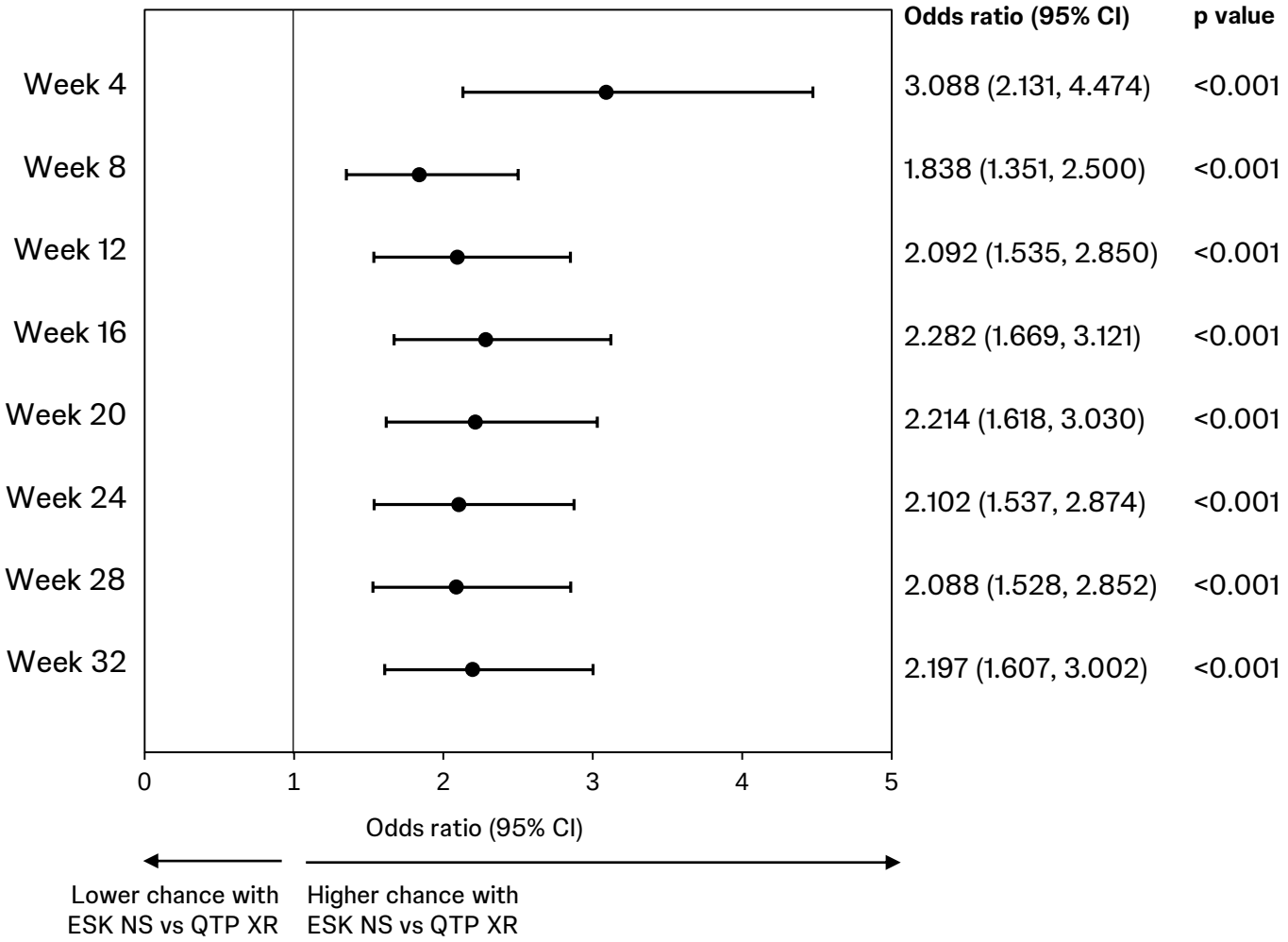


Figure 2A - remission

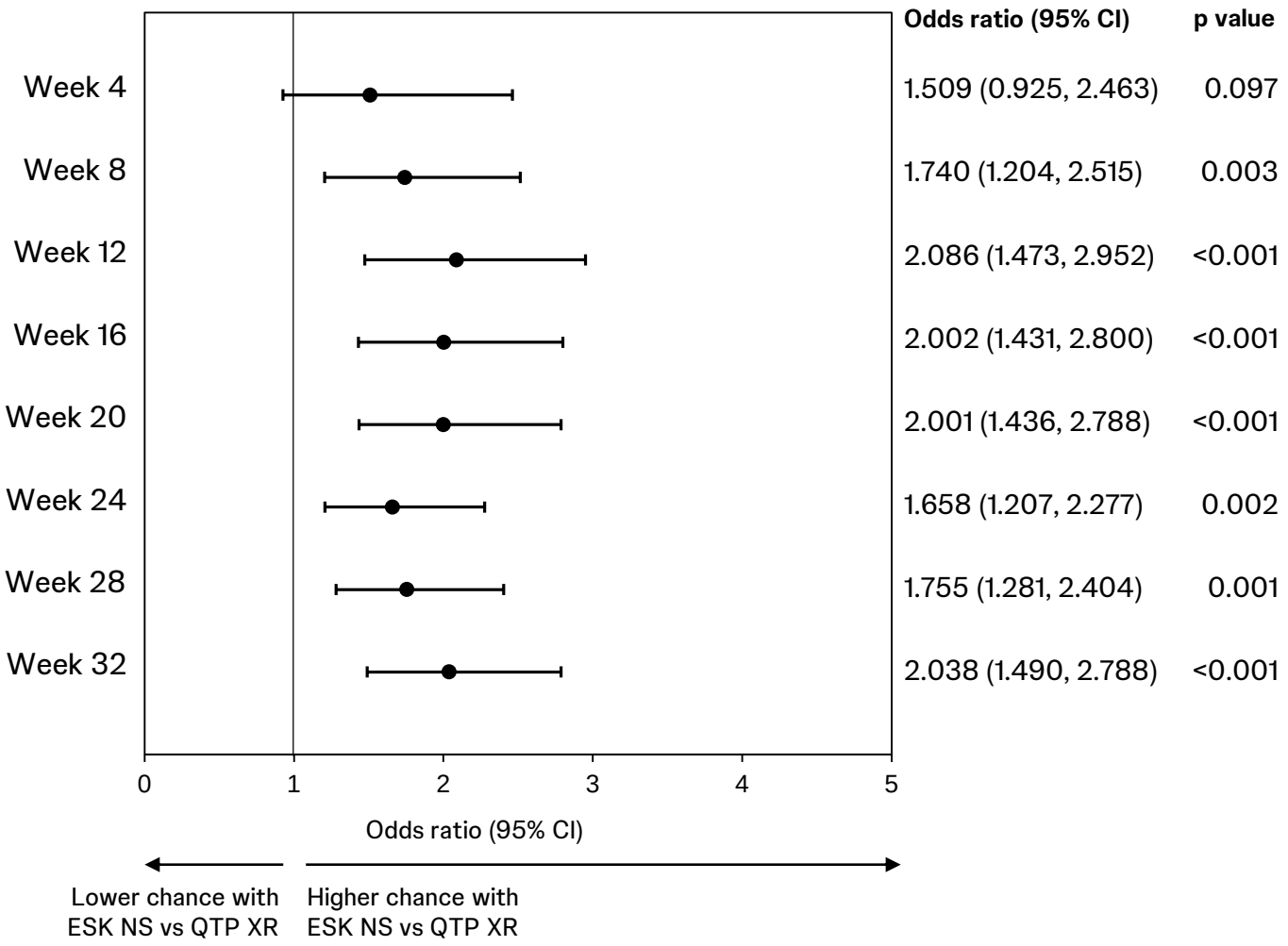


Figure 2A – functional remission

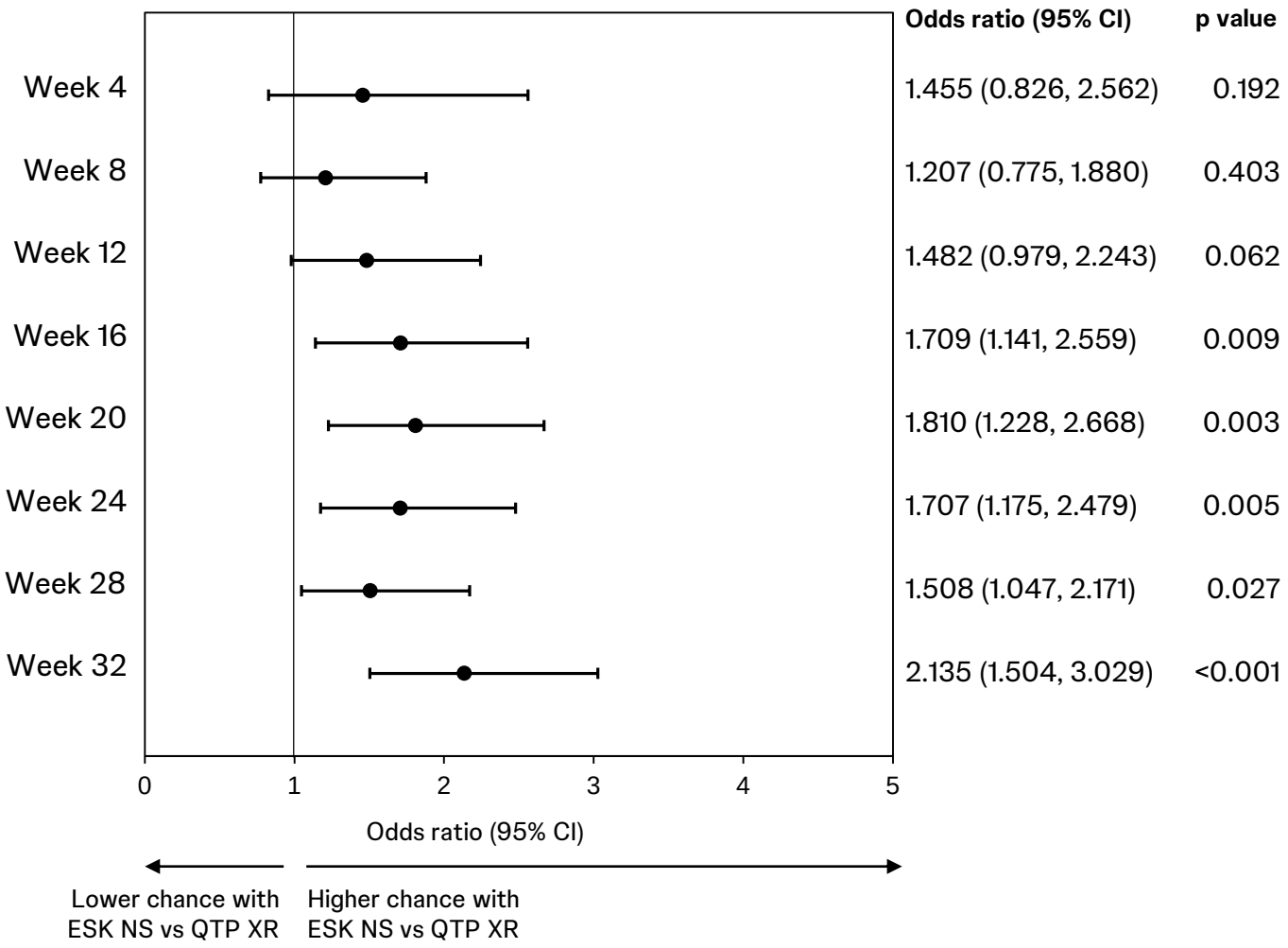


Figure 3A – results by treatment arm

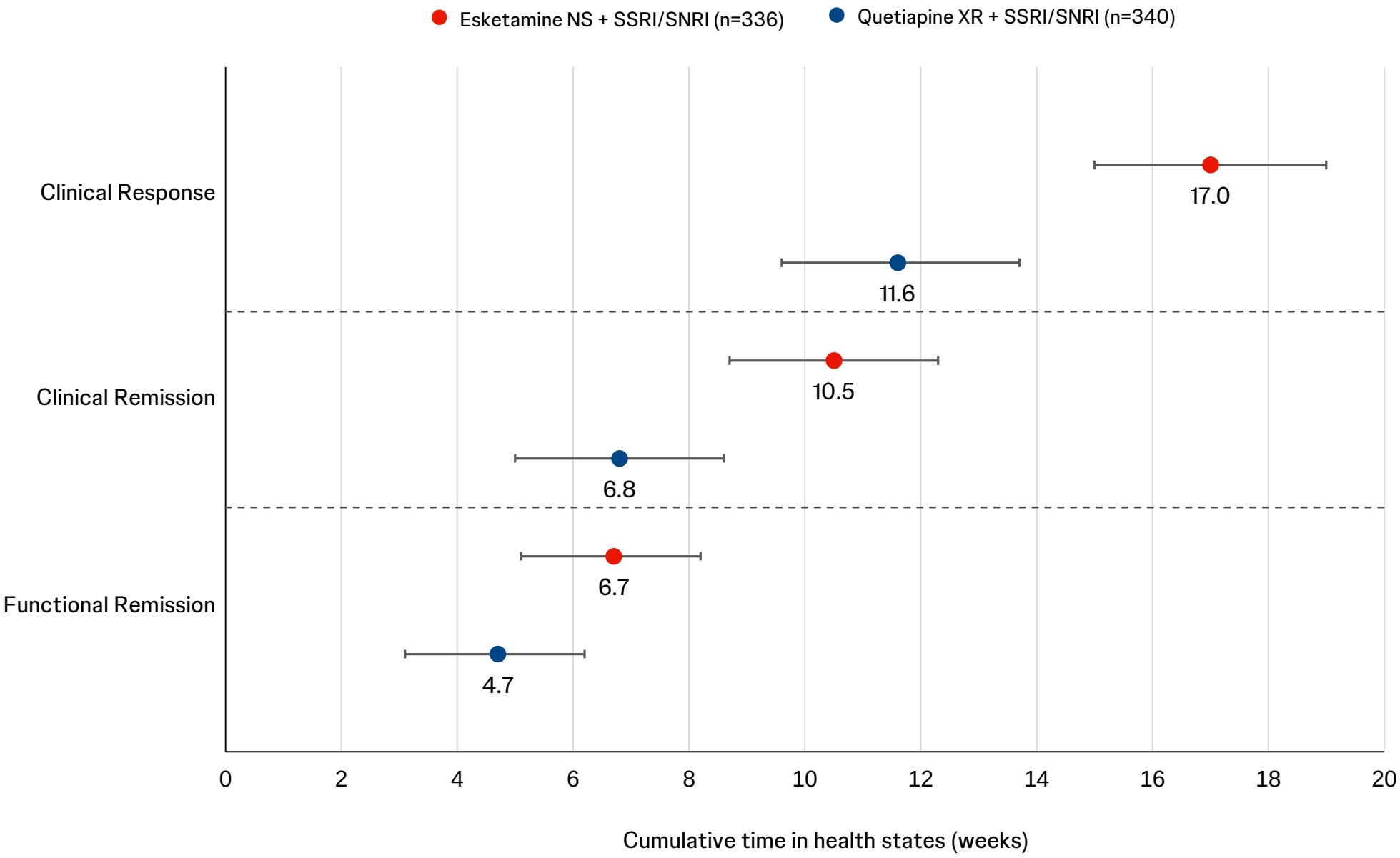


Figure 3B – difference between treatment arms

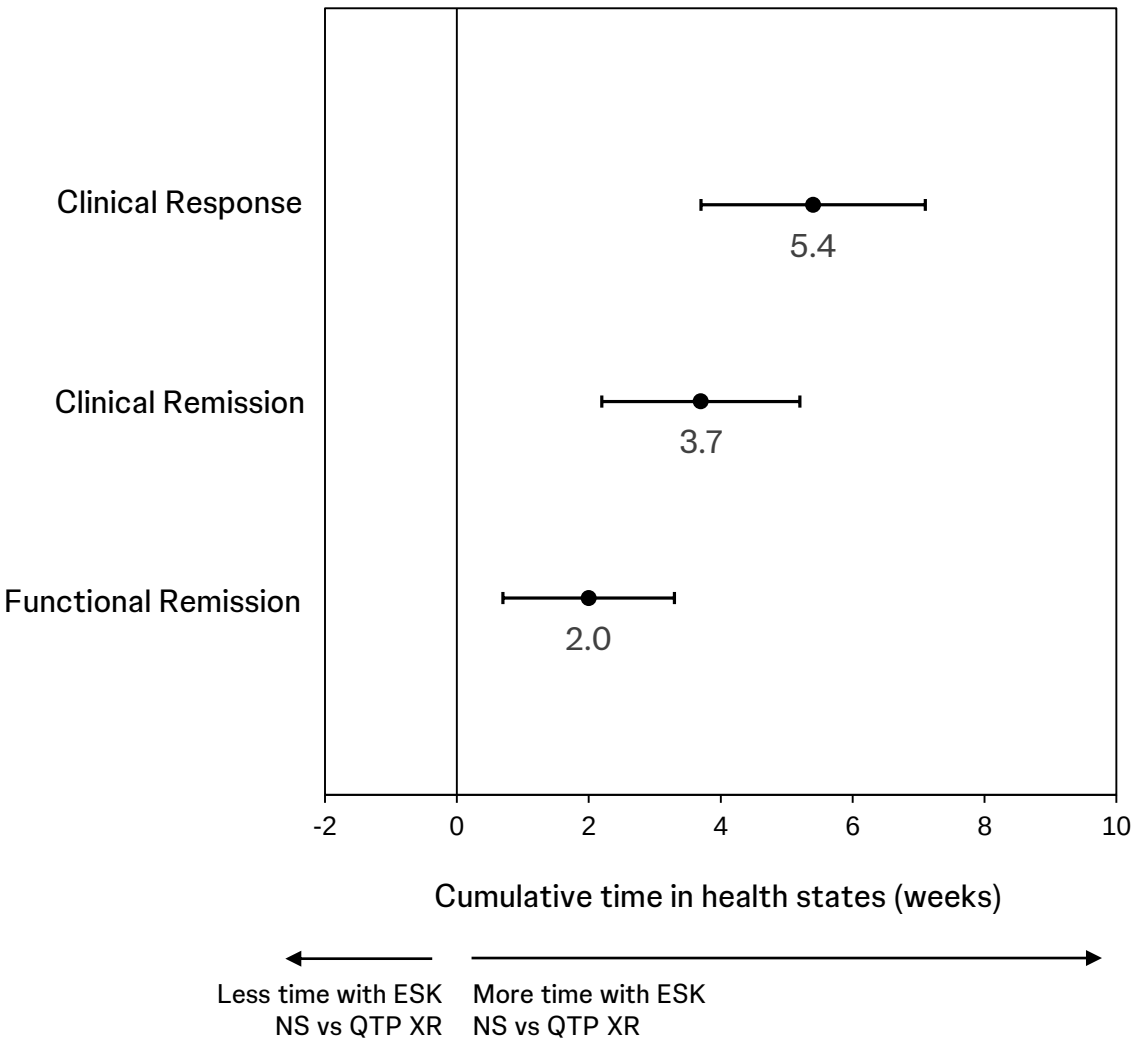


Figure 4A – WPAI results by treatment arm

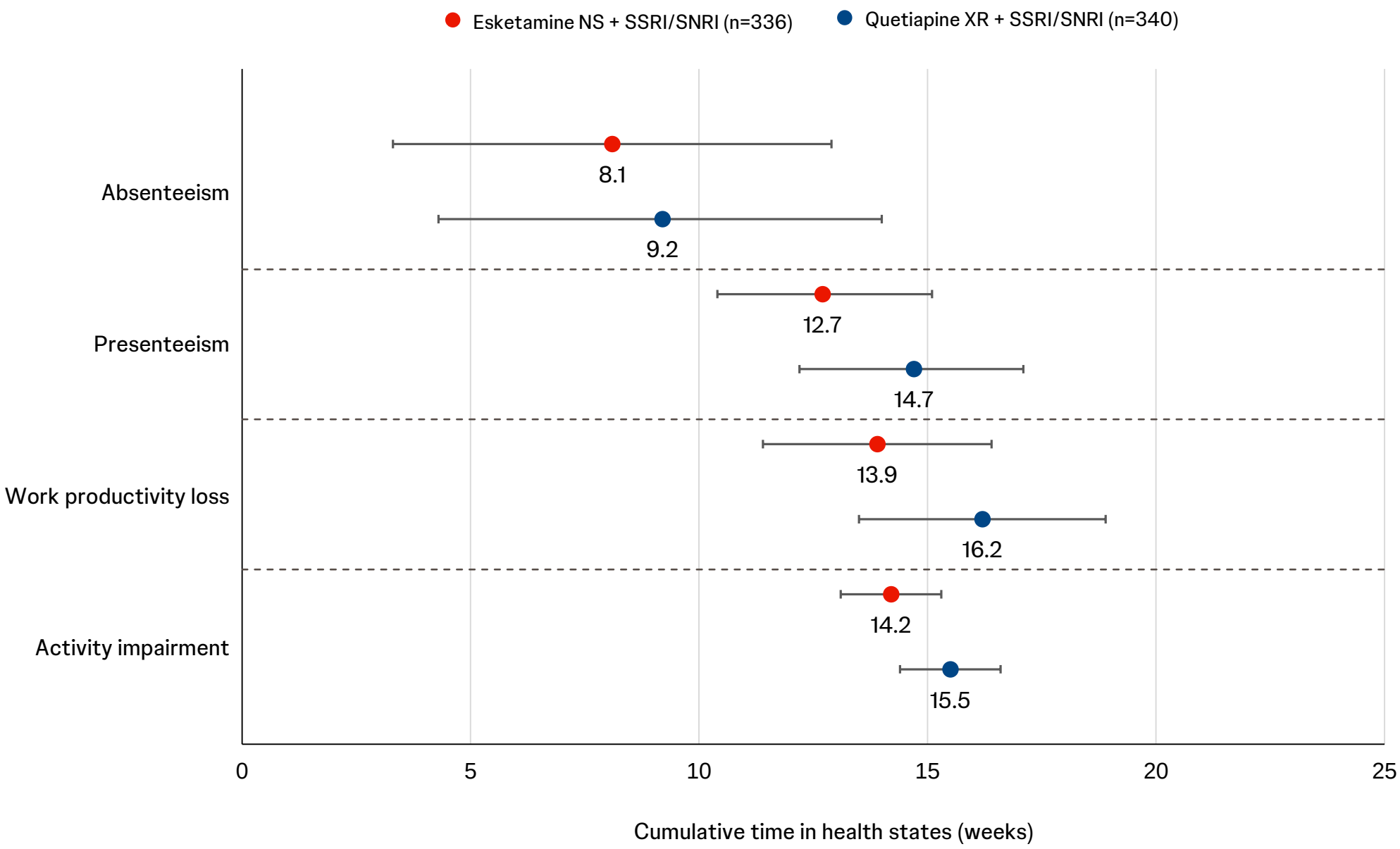
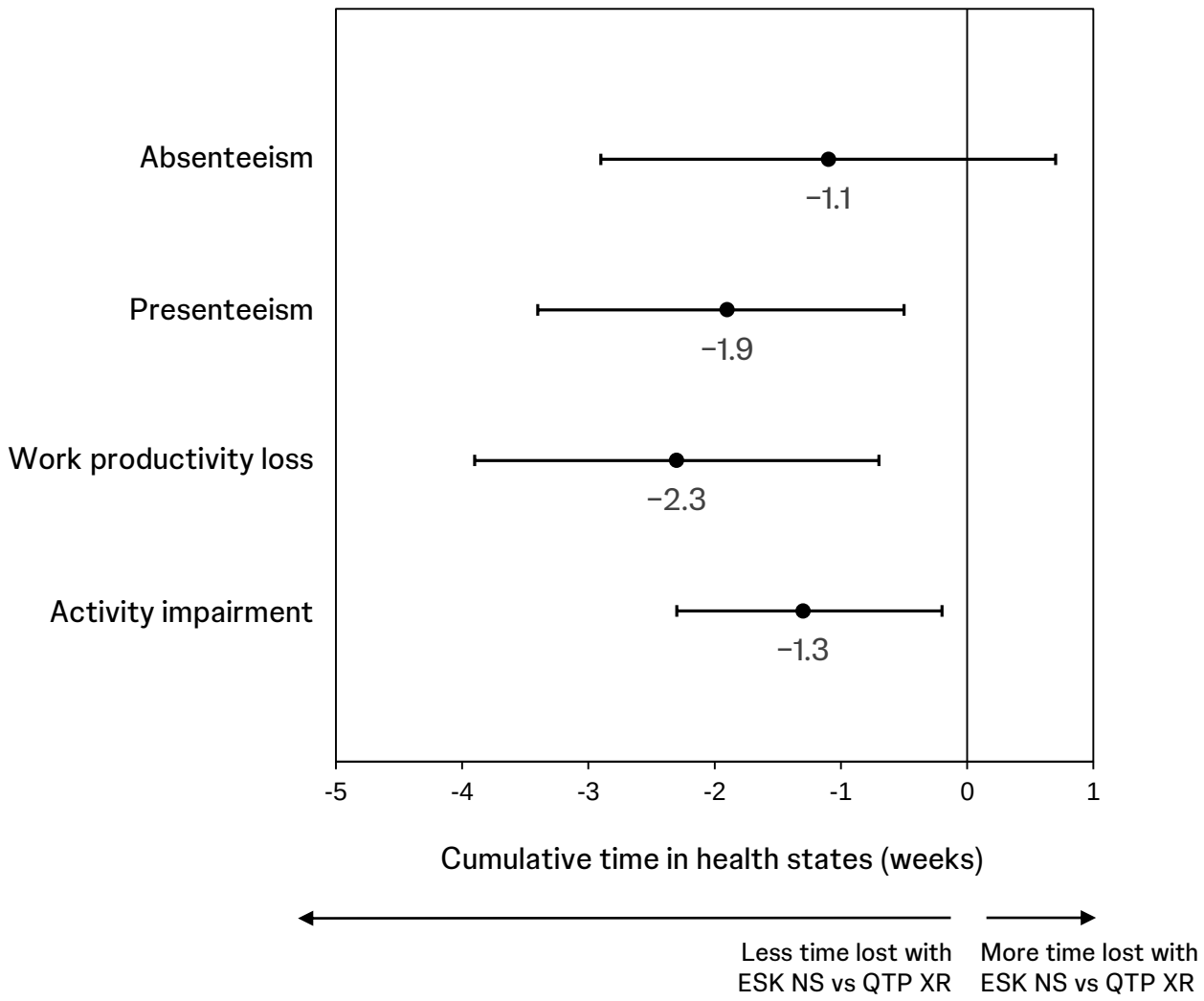


Figure 4B – WPAI difference between treatment arms



ROLE OF SPONSOR

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.

AUTHORS' CONTRIBUTIONS

Substantial contributions to study conception and design: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**; substantial contributions to analysis and interpretation of the data: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**; drafting the article or revising it critically for important intellectual content: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**; final approval of the version of the article to be published: **EV, NA, CA, AJC, KD, MD, TI, YK, SK, PML, RSM, GS, CvH, BR**.

DISCLOSURES

EV: Received grants and served as consultant, advisor or CME speaker for AB-Biotics, AbbVie, Adamed, Angelini, BeckleyPsych, Biogen, Boehringer Ingelheim, Celon Pharma, Compass, Ethypharm, Ferrer, Gedeon Richter, GH Research, GSK, HMNC, Idorsia, Janssen, Lundbeck, Medincell, Merck, Newron, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva and Viatris.

NA: Received research Grants from Department of Health- Abu Dhabi; Janssen and Viatris; Honoraria for Speaking engagements from Lundbeck, Janssen, Viatris and Hikma; served as consultant/ advisor to MindTales & FeelWrite digital startups.

CA: Consultant to or has received honoraria or grants from Abbot, Acadia, Ambrosetti, Angelini, Biogen, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Medscape, Menarini, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion, Takeda and Teva.

AJC: In the last 3 years: grant funding from the MRC, ADM Protexin Ltd, NIHR, European Union Horizon Europe/Innovate UK, Beckley Psytech Ltd, and Wellcome Trust; honoraria for presentations and/or consulting from Janssen, Otsuka, COMPASS Pathways Plc, Viatris and Medscape; President of the International Society for Affective Disorders.

KD: Biogen, Boehringer Ingelheim, Johnson & Johnson, LivaNova, Lundbeck, Merck, Pfizer and Viatris.

MD: Received travel grants and consultant and speaker honoraria from Medizin Medien Austria, Janssen, and Universimed.

SK: Served on advisory boards, participated as an investigator and received speaker's honoraria from Janssen, Ketabon, Neurocrine and ROVI.

PML: In the past 3 years, participated in advisory boards for Eisai, Ethypharm, Janssen, Lundbeck, MSD, Neuraxpharm, Novartis, Otsuka, Roche and Rovi; received speaker's honoraria and consultation fees from Eisai, Ethypharm, Janssen, Lundbeck, MSD, Neuraxpharm, Novartis, Otsuka, Roche, and Rovi; member of the Executive Committee of Fondation FondaMental; involved in developing National Care Guidelines for the French Society for Biological Psychiatry and Neuropsychopharmacology on the treatment of major depression.

RSM: Received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Neurawell, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie and Atai Life Sciences. Dr. Roger S. McIntyre is a CEO of Braxia Scientific Corp.

GS: Received grants and honoraria from Angelini, Janssen, Lundbeck, Otsuka, Rovi, and Viatris.

TI, YK, CvH, BR: Employees of Janssen; hold Johnson & Johnson company stock/stock options.

ACKNOWLEDGEMENTS

The authors thank the patients, the investigators and their teams who took part in this study. The authors also acknowledge Ruth Milz, MD, MA, MSc, MBA, the physician responsible for the development of the study protocol, and Laura Mawdsley, MSc, from Costello Medical, UK, for medical writing and editorial assistance based on the authors' input and direction. This study was funded by Janssen EMEA.