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Comparability of blinded remote and site-based assessments of response to adjunctive esketamine or placebo nasal spray in patients with treatment resistant depression

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ABSTRACT

Functional unblinding due to treatment emergent adverse events (TEAEs) may occur with any investigational drug and poses a challenge for double-blind, placebo-controlled studies. This pilot study compared site-based Montgomery-Asberg Depression Rating Scale (MADRS) scores to remote, site-independent scores by blinded raters.

Audio-digital recordings of site-based MADRS interviews were obtained from a subset of patients during a double-blind, placebo-controlled study of esketamine nasal spray or placebo spray in treatment resistant depression (Clinical Trials Registration: NCT01998958). Fourteen of 67 patients (21%) in the ITT population were randomly selected from 3 clinical trial sites. The site-based MADRS interviews were recorded at the baseline and 2 h post-dose assessments on the first intranasal dosing day. Site-independent raters scored the recordings and were blinded to treatment and all reported TEAEs, including any transient dissociative/perceptual symptoms.

None of the 7 placebo-assigned patients achieved a treatment response or remission at the 2-h post-dose assessment. Four of the 7 esketamine-assigned patients (57.1%) achieved a treatment response at 2-h post-dose, and 3 patients (42.9%) achieved remission. Three esketamine-treated patients experienced transient dissociative symptoms.

The remote site-independent raters essentially replicated the site-based MADRS scores and yielded a 92.9% predictive value for matching treatment response and remission rates.

This small pilot study affirms that blinded remote ratings (without the likelihood of functional unblinding) are comparable to site-based ratings of efficacy of esketamine nasal spray. The audio-digital recording method offers a reasonable strategy for other studies that may also be vulnerable to functional unblinding due to distinctive TEAEs.

1. Introduction

The possibility of functional unblinding due to treatment emergent adverse events (TEAEs) associated with an experimental drug poses a methodological challenge in double-blind, placebo-controlled clinical trials. Functional unblinding may occur with any investigational drug that induces marked gastrointestinal symptoms, sedation, dizziness, or other distinctive somatic symptoms. Esketamine, a medication being developed for treatment resistant depression (TRD), is a case in point because it may induce transient dissociation in some patients (Zarate et al., 2006; Salvadore and Singh, 2013; Singh et al., 2016; Daly et al., 2017; Canuso et al., 2018).

Several studies have shown antidepressant efficacy with the N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine (Zarate et al., 2006; Salvadore and Singh, 2013; Murrough et al., 2013). Esketamine, the S-enantiomer of ketamine, has a higher affinity for the NMDA receptor than the R-enantiomer and is being developed as an intranasal formulation for the treatment of TRD (Domino, 1965). In a recent study, each of 3 different doses of esketamine nasal spray (28 mg, 56 mg, and 84 mg) given twice per week achieved significant benefit over placebo on the Montgomery-Asberg Depression Rating Scale (MADRS) at day 8, the primary endpoint (Daly et al., 2017; Montgomery and Asberg, 1979). All participants continued the antidepressants they were receiving at study entry during the study.

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Esketamine induced more TEAEs (including transient dissociation/perceptual symptoms, dizziness, and headache) than placebo-assigned patients (Daly et al., 2017). The transient dissociative effects occurred in 21.3% of patients in the safety analysis set and were noted approximately 30 min after the initial treatment (day 1) and lasted between 2 and 3 h in most affected patients. Although subsequent nasal spray treatments at days 4, 8, and 11 during the double blind phase generated less dissociation, it is recognized that it is difficult to completely blind esketamine treatment in the early stages of a placebo-controlled trial.

One strategy to reduce the potential bias in efficacy assessment introduced by functional unblinding is to employ site-independent (remote) raters who are blinded to any adverse events. Remote, site-independent blinded ratings can be obtained via live telephone interviews or by remote raters listening to recorded site-based interviews (Targum et al., 2014). The use of recorded site-based interviews (audio digital recordings) enables the use of existing interview material, which is less burdensome for a patient than a second live interview. This recording method has been shown to yield high intra-class correlations between site-based and site-independent MADRS ratings and replicate treatment outcomes (Targum et al., 2014; Leigh-Pemberton et al., 2014).

The primary focus of the pilot study reported here was to evaluate the utility of paired site-independent (remote) ratings of recorded site-based MADRS interviews to monitor site-based ratings and assure ratings quality. Further, the blinded, remote ratings allowed us to examine the effect, if any, of possible site-based functional unblinding by TEAEs, specifically related to transient dissociative/perceptual symptoms that might occur follow esketamine administration.

2. Material and methods

This pilot study was conducted in a sub-set of patients during a phase 2 double-blind, 2 panel, placebo-controlled, delayed-start study, evaluating efficacy and safety of nasal spray esketamine in patients with TRD (clinicaltrials.gov identifier: NCT01998958). The main study was conducted from January 28, 2014, to September 25, 2015 (Daly et al., 2017). This first of 2 panels (Panel A) included 14 study sites (13 in the United States, 1 in Belgium). The pilot study reported here was conducted at 3 of the 13 U.S. trial sites participating in Panel A.

2.1. Study population

The study enrolled medically stable adults (aged 20–64 years) based on physical examination, medical history, vital signs, and 12-lead electrocardiogram performed at screening who met diagnostic criteria for Major Depressive Disorder (MDD), according to the DSM-IV-TR (APA, 2000). All eligible participants had TRD, defined as an inadequate response to at least 2 adequate antidepressant treatments of which at least one failure was documented by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ) in the current major depressive episode (Chandler et al., 2010). All participants continued the antidepressants they were receiving at study entry during the trial. At screening and before the first dose of nasal spray medication on day 1, eligible participants required a score of 34 or more on the 30-item, clinician rated Inventory of Depressive Symptomatology (IDSc30) corresponding to moderate to severe depression (Rush et al., 2000; Trivedi et al., 2004).

Key exclusion criteria included recent or current suicidal ideation with intent to act, suicidal behavior, or homicidal ideation or intent, bipolar or related disorders, intellectual disability, psychotic disorder, MDD with psychosis, posttraumatic stress disorder, obsessive-compulsive disorder, substance/alcohol use disorders in the past year, and a positive test result for cannabinoids predose on Day 1.

The study was conducted in accordance with ethical principles based on the Declaration of Helsinki consistent with Good Clinical Practices and applicable regulatory requirements (World Medical Association, 2013). The protocol and all amendments were reviewed and approved by Independent review boards in the United States and Belgium. All participating individuals provided written informed consent before participating in the study. Financial compensation was provided to the participating patients.

The pilot study randomly selected 14 of the 67 patients who were eligible for the intent to treat (ITT) set (21%) from 3 investigative sites in Panel A of the study for audio-digital recording of site-based MADRS interviews. All participating patients provided written informed consent for the use of the audio-digital recordings for quality assurance to affirm site-based rater scoring. A blinded randomization algorithm selected 7 patients at the 3 participating trial sites who were randomly assigned to placebo nasal spray and 7 patients assigned to one of 3 different esketamine doses for the MADRS recordings. The recordings were conducted pre-dose and repeated at 2-h post-dose on Day 1 of Period 1 in these 14 patients.

2.2. Study design

The study consisted of 4 phases: (1) screening; (2) a double-blind treatment phase (days 1–15) composed of two 1-week periods (Period 1, Period 2); (3) an optional open-label treatment (days 15-74) with tapering of intranasal dosing frequency; and (4) a post treatment follow-up phase (8 weeks). Based on prior studies of ketamine in which efficacy was reported after 1 to 2 doses, the duration of each period in the double-blind phase was 1 week, during which time it was expected that efficacy could be achieved. At the beginning of the double-blind Period 1, eligible participants were randomized (3:1:1:1) to placebo nasal spray or esketamine 28, 56, or 84 mg, twice weekly (days 1 and 4) based on computer-generated randomization schedules for periods 1 and 2).

2.3. Study drug and administration

To maintain blinding, the placebo solution (intranasal solution of water for injection) had a bittering agent (denatonium benzoate) added to simulate the taste of esketamine nasal spray solution. As described above, the antidepressant that participants had been receiving immediately before study entry was continued unchanged. On each dosing day during the double-blind phase, participant's self-administered the assigned nasal spray treatment (esketamine 28, 56, or 84 mg or placebo) into each nostril at 3 time points, each separated by 5 min. To maintain blinding, each subject used 2 sprays per device per time point. For example, patients assigned to 28 mg esketamine received 2 sprays of esketamine (14 mg per spray) at t = 0 min, followed by 2 sprays of placebo at t = 5 min and t = 10 min.

2.4. Site-based assessments

The MADRS was the primary efficacy measure and was assessed on day 1 (pre dose and 2 h post dose), day 2, day 8 (pre dose), day 9, and day 15, using the SIGMA, a structured interview guide (Williams and Kobak, 2008). The MADRS rating at the 2-h post dose visit was modified for the appetite and sleep items to account for the brevity between the drug administration and assessment. Therefore, the scores for these 2 items were carried over from the baseline assessment.

Safety assessments (ie, laboratory tests, vital signs, physical examination) were performed at prespecified time points. Vital signs and the Clinician Administered Dissociative States Scale (CADSS) were also assessed at the pre dose visit, at 40 min, and at 2 h post dose (Bremner et al., 1998).

2.5. Site-independent (remote) assessments

The site-based MADRS interview recordings were obtained with a commercially available audio-digital pen (Targum et al., 2014). After

Table 1
Comparison of MADRS scores in period 1 between ITT and pilot study populations.

	ITT Population				Pilot study	
	Placebo	Esk 28	Esk 56	Esk 84	Placebo	All Esk[a]
n	33	11	11	12	7	7
MADRS Baseline ± SD	35.0 ± 5.2	31.3 ± 3.8	33.2 ± 6.3	35.0 ± 4.2	38.4 ± 4.7	35.9 ± 5.2
2 HRS post dose ± SD	26.3 ± 8.0	17.2 ± 9.2	20.5 ± 9.4	18.3 ± 11.1	30.3 ± 5.2	18.3 ± 12.8
Mean change at 2 HRS[b]	−8.7 ± 1.5	−14.1 ± 2.7	−12.7 ± 1.9	−16.7 ± 3.0	−8.1 ± 2.4	−17.6 ± 4.0
Mean difference from placebo (± SE)		−6.6 ± 3.0	−4.0 ± 3.0	−8.0 ± 2.8		−9.4 ± 2.6
Responders at 2 HRS	6 (18.2%)	6 (54.5%)	4 (36.4%)	7 (58.3%)	0 (0%)	4 (57.1%)
Remitters at 2 HRS	1 (3.0%)	3 (27.2%)	2 (18.2%)	3 (25.0%)	0 (0%)	3 (42.9%)
Mean change (Day 1)[b]	−5.1 ± 1.1	−12.2 ± 3.3	−14.2 ± 3.1	−15.8 ± 3.3	−4.0 ± 0.9	−17.7 ± 4.3
Mean change (Day 8)[b]	−4.4 ± 1.2	−7.5 ± 2.4	−11.1 ± 2.5	−14.9 ± 3.7	−3.4 ± 1.5	−17.4 ± 4.9
Responders at Day 8	2 (6.1%)	1 (9.1%)	2 (18.2%)	5 (41.7%)	0 (0%)	3 (42.9%)
Remitters at Day 8	1 (3.0%)	1 (9.1%)	1 (9.1%)	3 (25.0%)	0 (0%)	2 (28.6%)

[a] Includes patients randomly assigned to esketamine 28 mg (2), 56 mg, (3) and 84 mg. (2).
[b] Mean change (± SE) of total MADRS score from baseline (pre-dose).

collection, the data was transmitted to a central location (Clintara LLC) for distribution to the site-independent raters. Three site-independent raters received the 28 MADRS interview recordings. The site-independent raters met the same rater qualification requirements as the site-based raters. The site-independent raters were blinded to the study visit, to any visual observations made by the site-based rater, and blinded to any unsolicited TEAEs that were identified. An effort was made to minimize the possibility that the central MADRS raters might become aware of any transient dissociative side effects during the interviews. Therefore, the site-based raters were instructed to focus their interview on the queries contained in the structured MADRS interview (SIGMA) and not to assess adverse events. The semi-structured probes of the SIGMA do not assess transient dissociation or other esketamine-type adverse events. The site-independent MADRS ratings were randomly assigned. Three of the 14 treated patients had the same independent rater at both the baseline and 2-h visits.

2.6. Efficacy endpoints and statistical analysis

This pilot study used blinded, remote raters that allowed us to evaluate any potential bias in site-based assessment of efficacy as a result of functional unblinding by TEAEs, specifically transient dissociation or perceptual symptoms that might occur following esketamine administration. The transient dissociation symptoms are generally noted within 30 min of the initial esketamine administration and can last 2–3 h. Consequently, the pre-dose assessment and 2-h post-dose assessment following the initial intranasal administration at day 1 when these symptoms may be present were the key MADRS measurement time points in this pilot study. In addition, we examined the CADSS scores at baseline, 40 min, and 2-h post-dose.

We compared the clinical characteristics and treatment response of the 14 patients randomly selected for paired ratings with the total Panel A population. We used intra-class correlation (ICC) to compare MADRS scoring concordance between the site-based ratings and remote, site-independent ratings at the predose and 2 h time points as well as Cohen's effect size, treatment response and remission rates (Lakens, 2013). For this study, treatment response was defined as a MADRS score improvement ≥50% from the pre-dose baseline (Day 1) assessment and remission as a MADRS total score ≤10 at the 2 h post-dose assessment, day 1 and day 8. Predictive value was defined as the number of correctly matched response or remission outcomes (responder or non-responder status) made by the blinded, site-independent raters divided by all 14 outcomes.

3. Results

The overall study results have been reported elsewhere (Daly et al., 2017). Sixty-seven patients were randomized into Period 1 of Panel A: 33 patients were randomly assigned to placebo and 34 to one of 3 doses of esketamine. The change from baseline of the total MADRS score was statistically significantly greater in all 3 esketamine-assigned treatment groups compared to the placebo group after 1 week of treatment (day 8, the primary endpoint) and revealed a significant ascending dose-response relationship. Further, the treatment response was rapid in onset and appeared to increase over time with repeated dosing.

This pilot study focused on the 2-h post dose treatment response following the initial esketamine nasal spray administration in Period 1. Esketamine at all 3 doses revealed a rapid treatment response at 2 h in the ITT set. As noted in Table 1, 50.0% of the combined esketamine-assigned patients in the ITT set achieved a treatment response and 23.5% achieved remission within 2 h in contrast to 18.2% response and 3.0% remission in the placebo-assigned patients.

3.1. Comparison of pilot group response with the overall ITT set at 2 h post-dose

Seven of the 14 patients in the pilot group were randomly assigned to placebo, 2 patients to esketamine 28 mg, 3 patients to 56 mg, and 2 patients to 84 mg in Period 1. None of the 7 placebo-assigned patients achieved a treatment response or remission at the 2-h post-dose assessment. Four of the 7 esketamine-assigned patients (57.1%) achieved a treatment response at 2-h post-dose, and 3 patients (42.9%) achieved remission based upon a MADRS score ≤10. Two of these 4 patients received esketamine 28 mg and 2 patients received 84 mg.

As shown in Table 1, the pilot group revealed similar mean MADRS score changes, treatment response, and remission rates between the pre-dose baseline and the 2-h post dose assessment as the overall ITT set of 67 patients. Hence, the pilot group of 14 patients appears to be representative of the ITT set.

3.2. Treatment emergent adverse events

Table 2 lists the frequently reported TEAEs that occurred during the double-blind phase in the overall safety analysis set (n = 89) and TEAEs that occurred on day 1 in the pilot group (n = 14). The most common TEAEs reported across all patient groups in the safety analysis set were dizziness (23.6%), transient dissociation (21.3%), and headaches (16.9%), with the majority of these TEAEs associated with esketamine.

Table 2
Summary of frequently reported* treatment emergent adverse events.

Preferred Term	Double-Blind Safety Analysis Set (Double-Blind Phase)					Pilot Study set (Day 1 only)	
	Placebo	Esketamine					
		28 mg	56 mg	84 mg	All Esk	Placebo	All Esk[a]
n	33	19	20	17	56	7	7
	Number (% participants)					**Number**	
Dizziness	1 (3)	4 (21)	8 (40)	8 (47)	20 (36)	0	3
Dissociation[b]	1 (3)	2 (11)	8 (40)	8 (47)	18 (32)	0	3
Headache	3 (9)	6 (32)	3 (15)	3 (18)	12 (21)	0	1
Dysgeusia	7 (21)	2 (11)	3 (15)	5 (29)	10 (18)	0	1
Nausea	3 (9)	2 (11)	4 (20)	4 (24)	10 (18)	1	1
Hypoesthesia oral	0	1 (5)	4 (20)	2 (12)	7 (13)	0	1
Vertigo	0	2 (11)	1 (5)	1 (6)	4 (7)	0	0
Sedation	0	1 (5)	2 (10)	1 (6)	4 (7)	0	0
Feeling abnormal	0	2 (11)	1 (5)	1 (6)	4 (7)	1	1
Hypoesthesia	0	1 (5)	1 (5)	1 (6)	3 (5)	0	1
Nasal discomfort	3 (9)	0	2 (10)	1 (6)	3 (5)	0	0
Hypertension	2 (6)	0	2 (10)	1 (6)	3 (5)	0	0
Oropharyngeal pain	2 (6)	0	1 (5)	2 (12)	3 (5)	0	0
Throat irritation	0	1 (5)	0	2 (12)	3 (5)	0	0
Vision blurred	0	0	0	2 (12)	2 (4)	0	0
Insomnia	1 (3)	0	2 (10)	0	2 (4)	0	0
Tunnel vision	0	0	0	2 (12)	2 (4)	0	0
Hypersomnia	0	2 (11)	0	0	2 (4)	0	0
Polyuria	0	0	2 (10)	0	2 (4)	0	1
Decreased appetite	0	0	1 (5)	0	1 (2)	0	1
Peripheral coldness	0	0	1 (5)	0	1 (2)	0	1
Sluggishness	0	0	1 (5)	0	1 (2)	0	1
Muscle tightness	0	0	1 (5)	0	1 (2)	0	1

*Defined as ≥10% of participants in any esketamine does group. Events presented in descending order in the totals esketamine (combined doses) group.
[a] Includes patients randomly assigned to esketamine 28 mg (2), 56 mg, (3) and 84 mg. (2).
[b] Includes reports of either dissociative reactions or dissociative symptoms.

Three of the 14 pilot-group patients (21.4%) experienced transient dissociation or perceptual symptoms during day 1. The transient dissociation occurred in one patient assigned to esketamine 56 mg and in 2 patients assigned to esketamine 84 mg. Therefore, the potential functional unblinding of site-based raters by virtue of the emergence of dissociative symptoms was possible at the 2-h post-dose assessment in the pilot group.

3.3. CADSS scores following the initial esketamine administration

Following the initial esketamine administration, there was an increase in dissociative symptoms as measured by the CADSS amongst the 7 patients assigned to esketamine nasal spray at the 40-min post-dose assessment that generally resolved by the 2- hour post-dose assessment (Fig. 1).

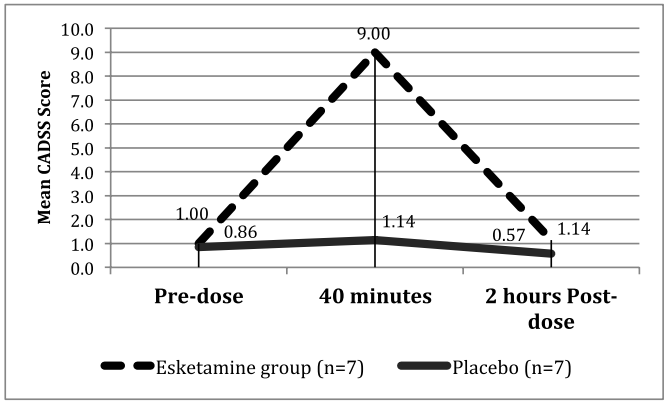

Fig. 1. Mean CADSS Scores following initial dose of esketamine spray.

3.4. Site-based MADRS scores and paired blinded, remote ratings

Table 3 compares the treatment outcomes at 2 h post-dose for the paired site-based and site-independent remote ratings in the pilot group. The site-independent raters listened to audio recordings of the site-based MADRS interviews but were blinded to the site location, subject visit, and any adverse event information. The blinded site-independent raters essentially replicated the site-based MADRS scores. The paired MADRS scores between the 14 site-based and 14 remote, site-independent ratings were highly correlated at the pre-dose and 2 h time points (pre-dose ICC: $r = 0.775$, $F = 7.9$, $p = 0.0002$; post-dose ICC: $r = 0.902$, $F = 19.5$, $p < 0.0001$).

In this sub-group of 14 paired MADRS ratings, the 2-h site-based MADRS change score yielded an effect size (ES) favoring esketamine (all doses) of −0.97 with a 57.1% response rate, 42.9% remission rate, and 100% specificity. The blinded, site-independent raters MADRS scores yielded an ES of −0.58 favoring esketamine, and matched the response and remission outcomes on 13 of the 14 paired site-based MADRS ratings (predictive value = 92.9%).

4. Discussion

Placebo is used as a control in double-blind studies to mask the efficacy and adverse effects of the candidate drug in order to demonstrate a genuine drug effect if is exists (Thase et al., 2011). Functional unblinding due to distinct TEAEs represents an inherent challenge for many clinical trials. In this pilot study of esketamine nasal spray or placebo nasal spray in TRD, 3 of 14 patients (21.4%) experienced transient dissociation following the first administration of esketamine that might have functionally unblinded a live rating at 2-h post-dose. Further, the CADSS score revealed a marked increase in dissociative or perceptual symptoms in 4 of the 7 esketamine-assigned patients at the 40-min post-dose assessment that might have influenced a site-based

Table 3
Comparison of Paired MADRS scores at baseline and 2 Hours post-dose.

	Mean MADRS Score ± SD				
	Pre-dose Baseline	2-HR post dose	Difference (%)	Responders	Remitters
Placebo (n = 7)					
Site-based ratings	38.4 ± 4.7	30.3 ± 5.2	−8.1 (21.2%)	0	0
Independent ratings	38.1 ± 6.9	26.0 ± 5.1	−12.1 (31.8%)	0	0
All Esketamine (n = 7) [a]					
Site-based ratings	35.9 ± 5.2	18.3 ± 12.8	−17.6 (49.0%)	4	3
Independent ratings	33.0 ± 6.9	16.4 ± 13.8	−16.6 (50.2%)	5	4
Paired Comparison of Treatment Responders					
	MADRS Baseline	2-HR post dose	Difference (%)	Treatment Emergent Adverse Events	
Subj 101 (esk 28 mg)					
Site-based rating	35	9	−26 (74.3%)	None	
Independent rating	33	9	−24 (72.7%)		
Subj 109 (esk 28 mg)					
Site-based rating	31	7	−24 (77.4%)	Headaches	
Independent rating	26	7	−19 (73.1%)		
Subj 104 (esk 84 mg)					
Site-based rating	39	9	−30 (76.9%)	Dissociation	
Independent rating	32	9	−23 (71.9%)		
Subj 117 (esk 84 mg)					
Site-based rating	34	11	−23 (67.6%)	Dissociation, dizziness	
Independent rating	28	9	−19 (67.9%)		

[a] Includes patients randomly assigned to esketamine 28 mg (2), 56 mg, (3) and 84 mg. (2).

MADRS rater at the 2-h assessment. It has been reported that the early, transient emergence of dissociative symptoms as measured by the CADSS is commonly seen following the initial administration of esketamine nasal spray, improves within 2-h, and attenuates at subsequent, repeated administrations (Daly et al., 2017).

In this pilot study, the site-independent raters who were blinded to any TEAEs replicated the site-based findings from audio-digital recordings of the site-based MADRS interviews. The blinded, site-independent ratings affirmed the rapid efficacy of esketamine nasal spray within 2 h of dosing in contrast to placebo nasal spray and matched the site-based response and remission outcomes with a 92.9% predictive value. These findings are consistent with two previous TRD studies that replicated site-based MADRS scores using site-independent ratings of recorded site-based MADRS interviews (Targum et al., 2014; Leigh-Pemberton et al., 2014).

The central ratings in this study were obtained by listening to audio-recorded MADRS interviews. Therefore, the reliability of the central scores was dependent on the competency of the live site-based interviewer as well as the cooperation of the patient. The inter-rater reliability between the site-based and independent raters listening to these recorded site-based MADRS interviews was highly correlated but does not mean that either score is truly valid and any more accurate than patient-rated scores.

The findings from this pilot study are limited by its small size and must be interpreted with caution. Further, although blinded to treatment assignments, the 3 participating clinical trial sites were aware of the rationale for conducting the site-independent assessments and were particularly motivated to conduct good interviews given the audio recording surveillance component. In fact, the ICC between site-based and site-independent ratings was 0.94. It is noteworthy that despite the high ICC, there was some discordance between a few site-based and site-independent ratings that may have been due to interview quality, patient response, or merely differences in clinical interpretation.

It is possible that some patients might have been a bit disconnected from their thoughts or feelings during the site-based MADRS interviews at 2 hours because of the transient dissociative effects that are associated with esketamine administration. Of course, this was the objective of using blinded, central raters to minimize the likelihood of functional unblinding. The possibility that the central raters might be unintentionally unblinded was managed because the site-based raters were instructed to focus their interview on the semi-structured probe queries of the SIGMA that does not assess adverse events.

This small pilot study affirms the utility of remote, site-independent ratings to monitor and assure site-based rater quality. This study also demonstrated that blinded remote ratings (without the possibility of functional unblinding) are comparable to site-based ratings of efficacy of esketamine nasal spray. This audio-digital recording method offers a reasonable strategy for other studies that may also be vulnerable to functional unblinding due to distinctive TEAEs.

5. Contributors

Dr.'s Targum, Daly, Fedgchin, and Singh, as well as Ms. Cooper all participated in the design, implementation, and analysis of the original study and conceived, analyzed, and wrote the current post-hoc analysis reported in this manuscript.

Conflict of interest disclosures

Dr. Targum is an employee of Bracket LLC and has received vendor grants from Janssen Research & Development, LLC as well as grants, retainers, or honoraria from Acadia Pharmaceuticals, Alkermes Inc., Functional Neuromodulation Inc., Intracellular Therapeutics, Karuna, Methylation Sciences Inc., Navitor Pharmaceuticals, Neurim Pharmaceuticals, Pfizer Inc., Prana Biotechnology Ltd., Resilience Therapeutics, and Sunovion.

Dr.'s Daly, Singh, and Fedgchin, and Ms. Cooper are employees of Janssen Research & Development, LLC and hold company stock/stock options.

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received study grants from the sponsor to conduct the registered study at their sites. These investigators were not involved in the design or analysis of the study data and received no additional compensation for their participation in this recorded independent paired ratings pilot sub-study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.01.017.

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