Use of Clinical Global Impressions-Severity (CGI-S) to Assess Response to Antidepressant Treatment in Patients with Treatment-Resistant Depression

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BACKGROUND

- There is no objective measure for depression severity. Several validated subjective scales have been used to evaluate disease severity in major depressive disorder (MDD) that rely on information gathered from the patient either by clinician interview or self-report.[1,2]
- The Montgomery-Åsberg Depression Rating Scale (MADRS), a 10-item questionnaire (each item scored on a 7-point scale [0-6]) is a validated, clinician-rated measure of depression severity, also commonly used to determine clinical outcomes with antidepressant treatment in research and clinical trial settings.[3] It is a measure of symptoms that requires adequate rating knowledge and time to administer, therefore limiting its use in routine clinical practice.[3,4]
- The Clinical Global Impressions-Severity (CGI-S) scale is a more practical tool with one question assessing the patient's overall clinical status at the time of assessment and is scored on a 7-point response scale.[4,5]
- Unlike the structured questions in the MADRS, the CGI-S assessment reflects the overall clinical judgment on disease severity based on information gathered during routine psychiatric visits (symptoms, patient's history, impact of symptoms on the patient's functional ability etc.) and clinician experience.[4]
- Both MADRS and CGI-S have demonstrated comparable ability to measure treatment outcomes with a high correlation in population of patients with MDD.[1] However, to translate clinical trial results into clinical guidance it is important to evaluate rating agreement between MADRS-based and CGI-S-based outcomes using patient-level data.

OBJECTIVES

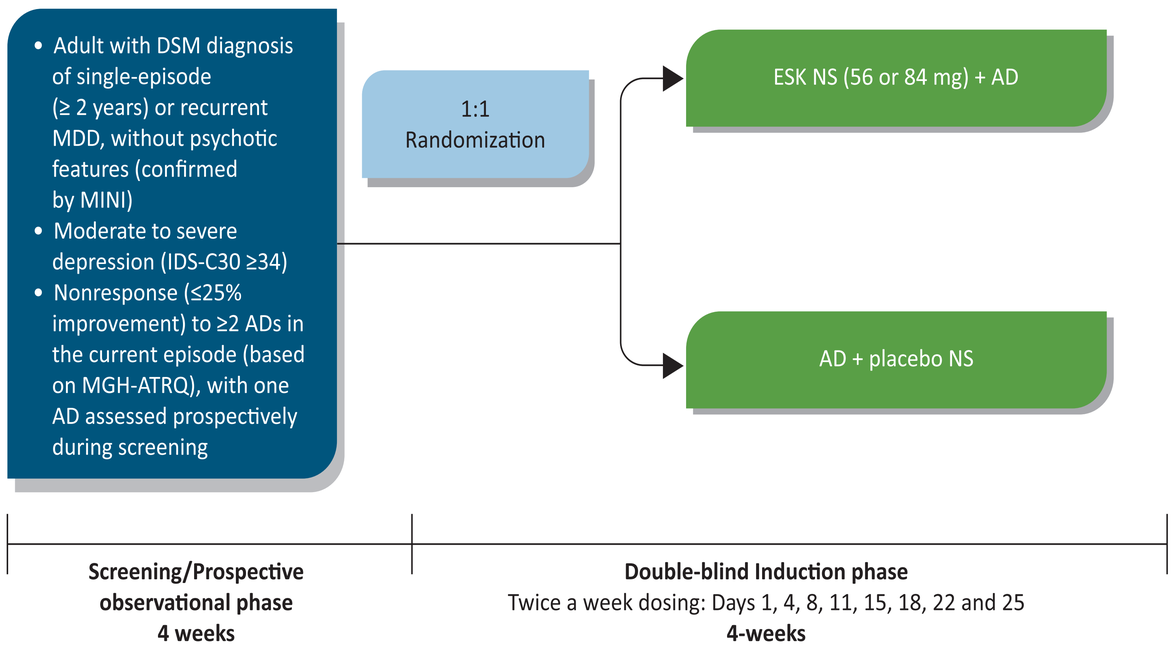
- To establish a CGI-S-based assessment of response to an acute antidepressant treatment and evaluate the agreement with the pre-specified MADRS-based assessment in patients with treatment-resistant depression (TRD).

METHODS

Study Overview

- Post hoc analysis of a phase 3 randomized, double-blind study (NCT02418585; TRANSFORM-2)[6] of flexible-dosing esketamine (or placebo) nasal spray plus a newly initiated oral antidepressant in patients withTRD.
- Eligible patients (aged 18-64 years) had DSM-5 diagnosis of MDD with moderate to severe depression (30-item Inventory of Depressive Symptoms-Clinician-rated total score ≥34).
- Patients also met the study definition of TRD: failed to respond to ≥2 antidepressant treatments of adequate dose and duration in the current episode, with one antidepressant treatment failure assessed prospectively at study entry.
- In the 4-week acute treatment phase, patients were randomly assigned to treatment with esketamine nasal spray (56 or 84 mg) twice a week plus a newly initiated oral antidepressant (ESK NS + AD) or antidepressant plus placebo nasal spray (AD + placebo NS).

Figure 1: Study Design



AD, antidepressant; DSM, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ESK, esketamine; IDS-C30, Inventory of Depressive Symptoms-Clinician-rated, 30-item; MDD, major depressive disorder; MGH-ATRQ, Massachusetts General Hospital Antidepressant Treatment Response Questionnaire MINI, Mini International Neuropsychiatric Interview; NS, nasal spray.

Assessment of Response

- Response was pre-specified as patients with ≥50% reduction in MADRS total score from baseline at the end of the 4-week acute treatment phase in the clinical trial.
- At baseline, all patients with moderate to severe TRD had a CGI-S score ranging from 4 to 7. For the alternative CGI-S-based assessment of response, patients with ≥2 points decrease from baseline or a CGI-S score of ≤3 (mildly depressed to normal) were considered responders, else non-responders. The proposed cut-off criterion was based on a best fit model of optimal definitions of response from the literature.

Table 1: CGI-S guideline

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

Total score	Scoring guideline
1	Normal—not at all ill, symptoms of disorder not present
2	Borderline mentally ill—subtle or suspected pathology
3	Mildly ill—clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function
4	Moderately ill—overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication
5	Markedly ill—intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress
6	Severely ill—disruptive pathology, behavior and function are frequently influenced by symptoms, may require assistance from others
7	Among the most extremely ill patients—pathology drastically interferes in many life functions; may be hospitalized

CGI-S, Clinical Global Impressions-Severity. Adapted from: Busner J & Targum SD. Psychiatry (Edgmont). 2007 Jul;4(7):28-37 and Guy W. In ECDEU Assessment Manual for Psychopharmacology Rockville, MD, USA: US Department of Health, Education, and Welfare; 1976:217-222.

- Transient dissociative and sedative effects of esketamine nasal spray could potentially bias the rater. To ensure unbiased evaluation, the MADRS assessment was conducted prior to dosing by remote independent raters.
- The CGI-S was conducted pre-dose by the site investigator at the site.

Statistical Methods

- Cohen's kappa coefficient was calculated to assess the level of agreement between MADRS- and CGI-S-based assessment of response.
- Sensitivity and specificity of the CGI-S-determined response was estimated, using MADRS-based classification as reference.

RESULTS

Patients

- Details of patient demographics, baseline characteristics and disposition are provided in the primary publication.[6]
- Efficacy analyses included 223 patients (ESK NS + AD: 114; AD + placebo NS: 109).
- Patients (n=223) had a mean (SD) age of 45.7 (11.89) years and were mostly women (61.9%) and White (93.3%).
- At baseline, the mean (SD) MADRS total score was 37.1 (5.67) and CGI-S total score was 5.1 (0.67).

Assessment of Response

- At the end of 4-week treatment, the proportion of responders among all patients (n=201) was similar when assessed using the MADRS (61%) and CGI-S (62%) methods.
- The Cohen's kappa was 0.76 (95% CI: 0.67-0.85), suggesting substantial agreement between the two methods.
- The CGI-S-based assessment demonstrated 92% sensitivity and 84% specificity vs the MADRS-based results.
- Similar results were observed in patients treated with ESK NS +AD. The proportion of responders was 69% using the MADRS scale and 68% using the CGI-S scale.
- Substantial agreement (Cohen's kappa=0.75, 95% CI: 0.61-0.89) was observed between the two scales and the CGI-S assessment showed 91% sensitivity and 84% specificity.

Table 2: Assessment of response using MADRS and CGI-S

	All patients[a] N=201		ESK NS + AD N=101	
	MADRS	CGI-S	MADRS	CGI-S
Responders, n (%)	122 (60.70)	125 (62.19)	70 (69.31)	69 (68.32)
Non-responders, n (%)	79 (39.30)	76 (37.81)	31 (30.69)	32 (31.68)
Sensitivity, %	92%		91%	
Specificity, %	84%		84%	
Cohen's kappa (95% CI)	0.76 (0.67-0.85)		0.75 (0.61-0.89)	

[a] Includes patients who received ESK NS + AD and patients who received AD + placebo NS
AD, antidepressant; CGI-S, Clinical Global Impression - Severity MADRS, Montgomery-Åsberg Depression Rating Scale; ESK, esketamine; NS, nasal spray.

CONCLUSIONS

- The results of response to an acute antidepressant treatment using the CGI-S-based definition were substantially consistent with the results using the pre-specified MADRS-based definition in patients with TRD in a phase 3 study of esketamine nasal spray.
- CGI-S is a practical and reliable alternative for MADRS to assess treatment response in patients with TRD.
- Thus, the clinicians can use the CGI-S-based definition to evaluate response to esketamine nasal spray treatment in patients with TRD in real-world practice to support informed treatment decisions.

References

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