GluRs as a Novel Molecular Target: Clinical Data on the Use Case of Ketamine and Esketamine

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Disclosures

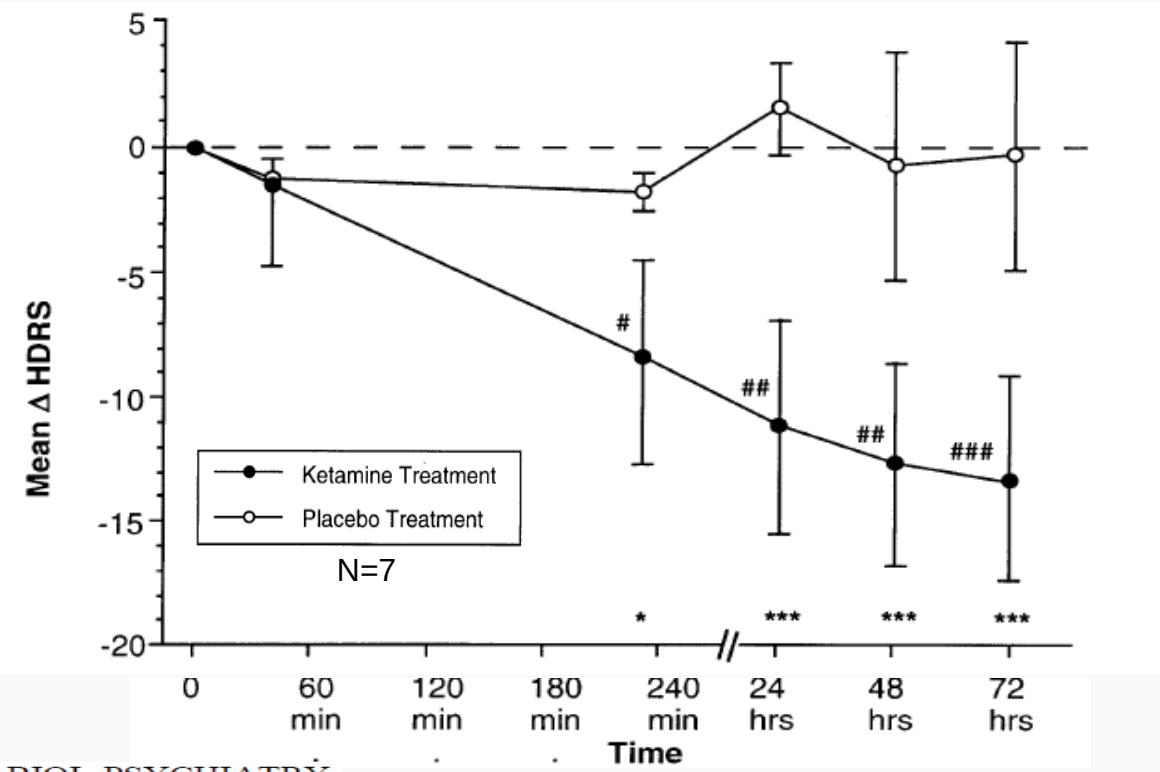
- **Employee of Janssen Research & Development**
- **Shareholder of Johnson & Johnson Stock**

Initial Proof of Concept Studies with IV Ketamine

BRIEF REPORTS

Antidepressant Effects of Ketamine in Depressed Patients

Robert M. Berman, Angela Cappiello, Amit Anand, Dan A. Oren, George R. Heninger, Dennis S. Charney, and John H. Krystal

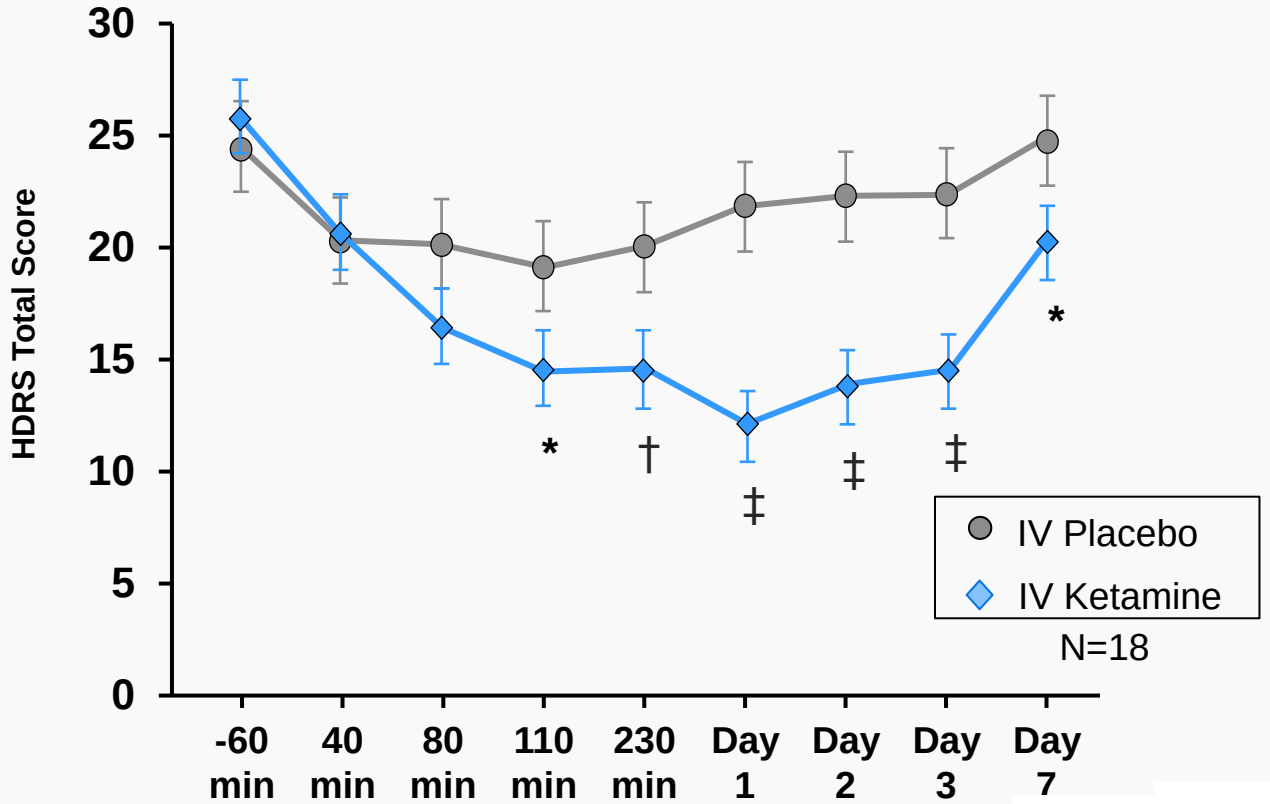


BIOL PSYCHIATRY
2000;47:351–354

ORIGINAL ARTICLE

A Randomized Trial of an *N*-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression

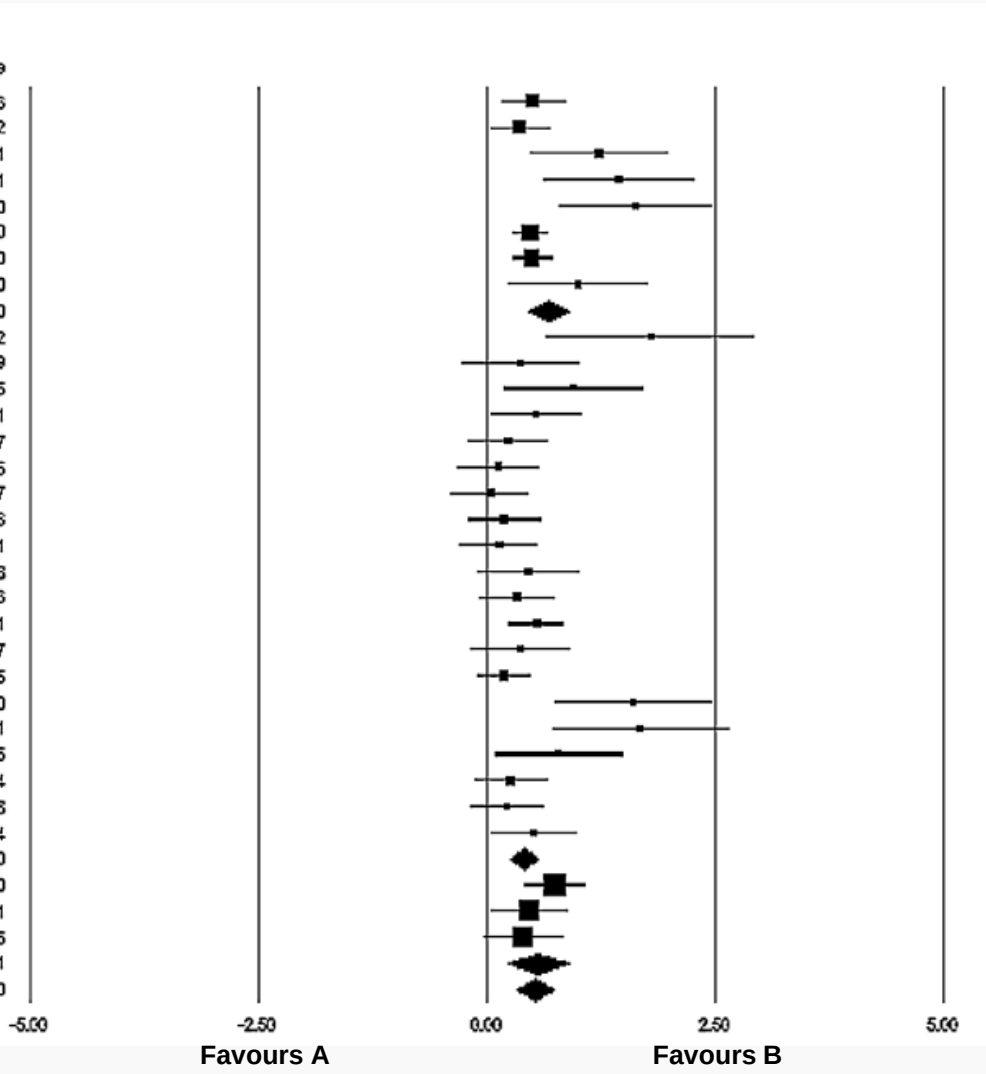
Carlos A. Zarate, Jr, MD; Jaskaran B. Singh, MD; Paul J. Carlson, MD; Nancy E. Brutsche, MSN; Rezvan Ameli, PhD; David A. Luckenbaugh, MA; Dennis S. Charney, MD; Husseini K. Manji, MD, FRCPC



Arch Gen Psychiatry. 2006;63:856-864

Numerous RTCs of Ketamine and Esketamine Demonstrate Short-term Efficacy in Depression

Hedges's g	Standard error	Group by Administration	Study name	Variance	Lower Limit	Upper Limit	Z-Value	p-Value
0.516	0.176	Intranasal	Canuso, Singh, Fedgchin, et al 2018	0.031	0.170	0.861	2.924	0.003
0.368	0.172	Intranasal	Canuso, Singh, Fedgchin, et al 2018	0.030	0.031	0.705	2.142	0.032
1.237	0.387	Intranasal	Daly, Singh, et al 2017 (28mg)	0.149	0.479	1.995	3.199	0.001
1.446	0.417	Intranasal	Daly, Singh, et al 2017 (56mg)	0.174	0.630	2.263	3.472	0.001
1.637	0.429	Intranasal	Daly, Singh, et al 2017 (84mg)	0.184	0.796	2.477	3.818	0.000
0.481	0.100	Intranasal	Fedgchin, Trivedi, Daly, et al 2019 (56mg)	0.010	0.285	0.676	4.828	0.000
0.501	0.106	Intranasal	Fedgchin, Trivedi, Daly, et al 2019 (84mg)	0.011	0.293	0.710	4.711	0.000
1.001	0.389	Intranasal	Lapidus, Levitch, et al 2015	0.152	0.237	1.764	2.570	0.010
0.667	0.110	Intranasal		0.012	0.451	0.882	6.064	0.000
1.793	0.583	Intravenous	Berman, Cappiello, Anand, et al 2000	0.340	0.651	2.935	3.077	0.002
0.361	0.327	Intravenous	Chen, Li, Lin, et al 2018 (0.2mg)	0.107	-0.280	1.002	1.104	0.269
0.952	0.394	Intravenous	Chen, Li, Lin, et al 2018 (0.5mg)	0.155	0.180	1.725	2.416	0.016
0.542	0.252	Intravenous	Diazgranados, Ibrahim, Brutsche, et al 2010	0.063	0.049	1.035	2.154	0.031
0.237	0.218	Intravenous	Fan, Yang, Sun, et al 2017	0.048	-0.190	0.665	1.087	0.277
0.130	0.226	Intravenous	Fava, Freeman, Flynn, et al 2018 (0.1mg)	0.051	-0.314	0.573	0.573	0.566
0.036	0.215	Intravenous	Fava, Freeman, Flynn, et al 2018 (0.2mg)	0.045	-0.385	0.457	0.167	0.867
0.197	0.206	Intravenous	Fava, Freeman, Flynn, et al 2018 (0.5mg)	0.043	-0.210	0.604	0.948	0.343
0.132	0.215	Intravenous	Fava, Freeman, Flynn, et al 2018 (1mg)	0.047	-0.291	0.555	0.611	0.541
0.455	0.283	Intravenous	Hu, Xiang, Fang, et al 2015	0.080	-0.100	1.011	1.608	0.108
0.333	0.215	Intravenous	Ibrahim, Diazgranados, et al 2012	0.047	-0.091	0.757	1.541	0.123
0.544	0.158	Intravenous	Murrough, Iosifescu, Chang, et al 2013	0.025	0.235	0.853	3.448	0.001
0.377	0.279	Intravenous	Murrough, Soleiman, DeWilde, et al 2015	0.078	-0.170	0.925	1.350	0.177
0.183	0.151	Intravenous	Phillips, Norris, Talbot, et al 2019	0.023	-0.113	0.479	1.214	0.225
1.598	0.440	Intravenous	Singh, Fedgchin, Daly, 2016 (0.4mg)	0.194	0.736	2.461	3.633	0.000
1.686	0.499	Intravenous	Singh, Fedgchin, Daly, et al 2016 (0.2mg)	0.249	0.709	2.663	3.382	0.001
0.794	0.354	Intravenous	Sos, Kilrova, Novak, et al 2013	0.125	0.099	1.488	2.239	0.025
0.267	0.201	Intravenous	Su, Chen, Li et al 2017 0.5mg	0.040	-0.127	0.662	1.328	0.184
0.226	0.204	Intravenous	Su, Chen, Li, et al 2017 0.2mg	0.042	-0.174	0.625	1.108	0.268
0.514	0.242	Intravenous	Zarate, 2006	0.059	0.039	0.989	2.120	0.034
0.406	0.074	Intravenous		0.005	0.261	0.552	5.482	0.000
0.749	0.174	Oral	Arabzadeh et al 2016	0.030	0.407	1.091	4.294	0.000
0.471	0.216	Oral	Domany, Bleich-Cohen, et al 2019	0.047	0.044	0.898	2.162	0.031
0.398	0.224	Oral	Jaterinia et al 2016	0.050	-0.040	0.837	1.781	0.075
0.556	0.169	Oral		0.029	0.224	0.887	3.285	0.001
0.529	0.102	Overall		0.010	0.328	0.729	5.169	0.000



■ Effect size of individual studies

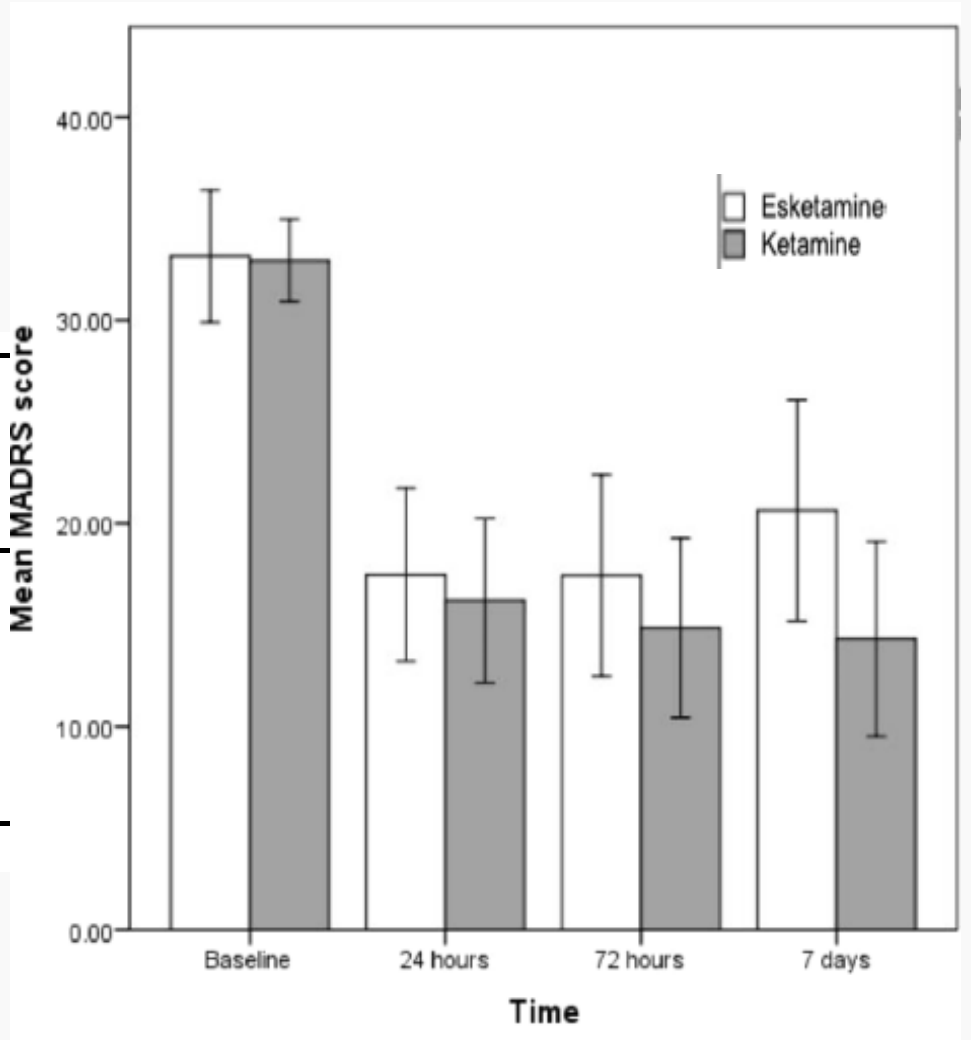
◆ Summary measures of each formulation and overall findings

McIntyre R.S et al. *J Affective Disorders* 276 (2020) 576-544

Are Ketamine and Esketamine Equally Effective?

No significant difference on antidepressant and dissociation measures after single IV infusion of ketamine and esketamine at their approximate equipotent doses (0.5 mg/kg and 0.25 mg/kg)

Variable (MADRS) Remission	Esketamine Group ($n = 34$) N	%	Ketamine Group ($n = 29$) N	%	Difference
24 h	10	29.4	7	24.1	5.27 (95% CI_{LB} −13.6)
72 h	11	35.5	11	39.3	−3.8 (95% CI_{LB} −24.6)
7 days	9	28.1	12	41.4	−13.2 (95% CI_{LB} −33.2)



Correia-Melo FS, et al Journal of Affective Disorders Volume 264, 1 March 2020, 527-534

Esketamine Nasal Spray FDA Approved Indications

Esketamine is indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Limitations of Use:

- The effectiveness of esketamine in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of eketamine does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of esketamine
- Esketamine is not approved as an anesthetic agent. The safety and effectiveness of as an anesthetic agent have not been established.

Clinical Populations Studied & Strength of Evidence

+++++: ≥ 2 RTCs, acute & maintenance

++++: ≥ 2 RTCs, single & repeated dosing

+++: ≥ 2 RTCs single dosing or < 2 RTCs single & repeated dosing

++: < 2 RTCs, single dosing

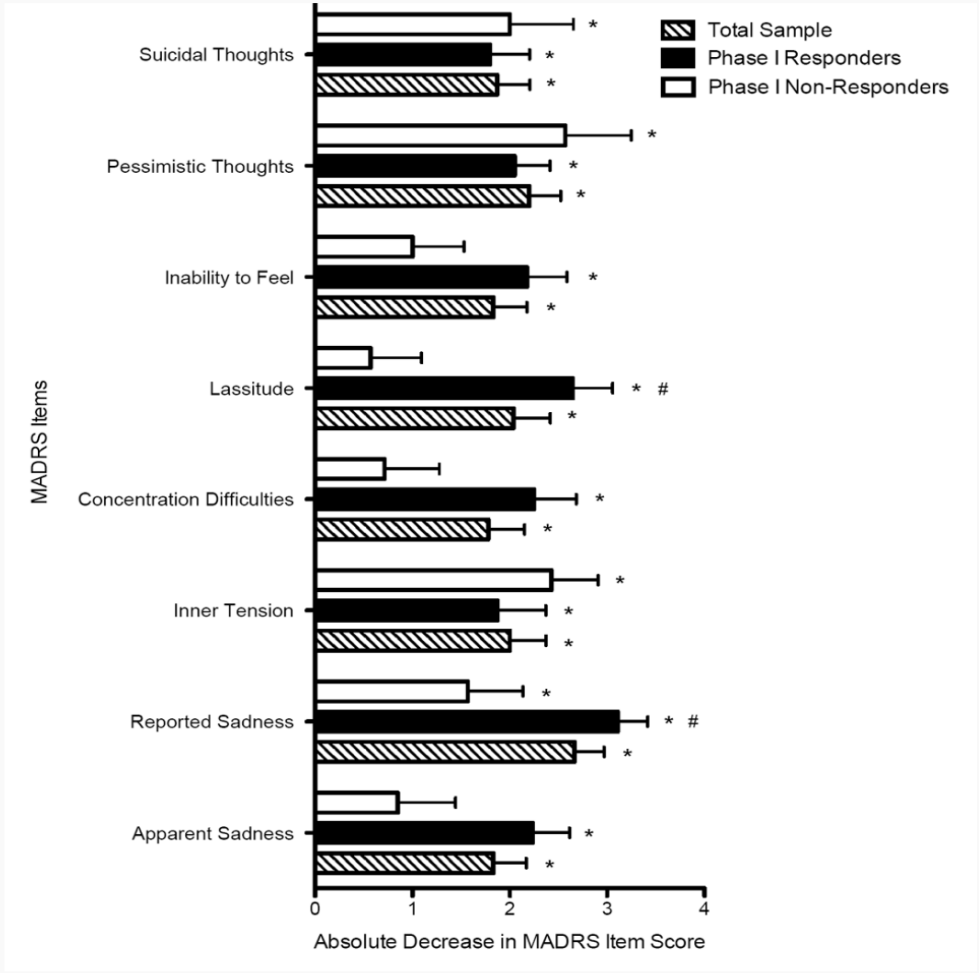
+: Open-label /case report

	IV Ketamine	IN Esketamine	Outcome Measure(s)
Treatment-Resistant Depression	++++	+++++	HDRS, MADRS
Major Depression w/ Suicidal Ideation or Behavior	+++	++++	HDRS, MADRS, BSI/SSI, CGI-ss-r
Bipolar Depression	+++		MADRS
Post-Traumatic Stress Disorder	+++		Impact-of-Event Scale, CAPS
Obsessive Compulsive Disorder	++		OCD-VAS, Y-BOCS
Borderline Personality Disorder	+		N/A
ETOH/Substance Use Disorders	++		Various
Anhedonia	++		SHAPS
Cancer w/ MDD and SI	++		MADRS, BSI
Geriatric		+++	MADRS
Pediatric	+	ongoing	CDRS-R, MADRS

References in back-up slides

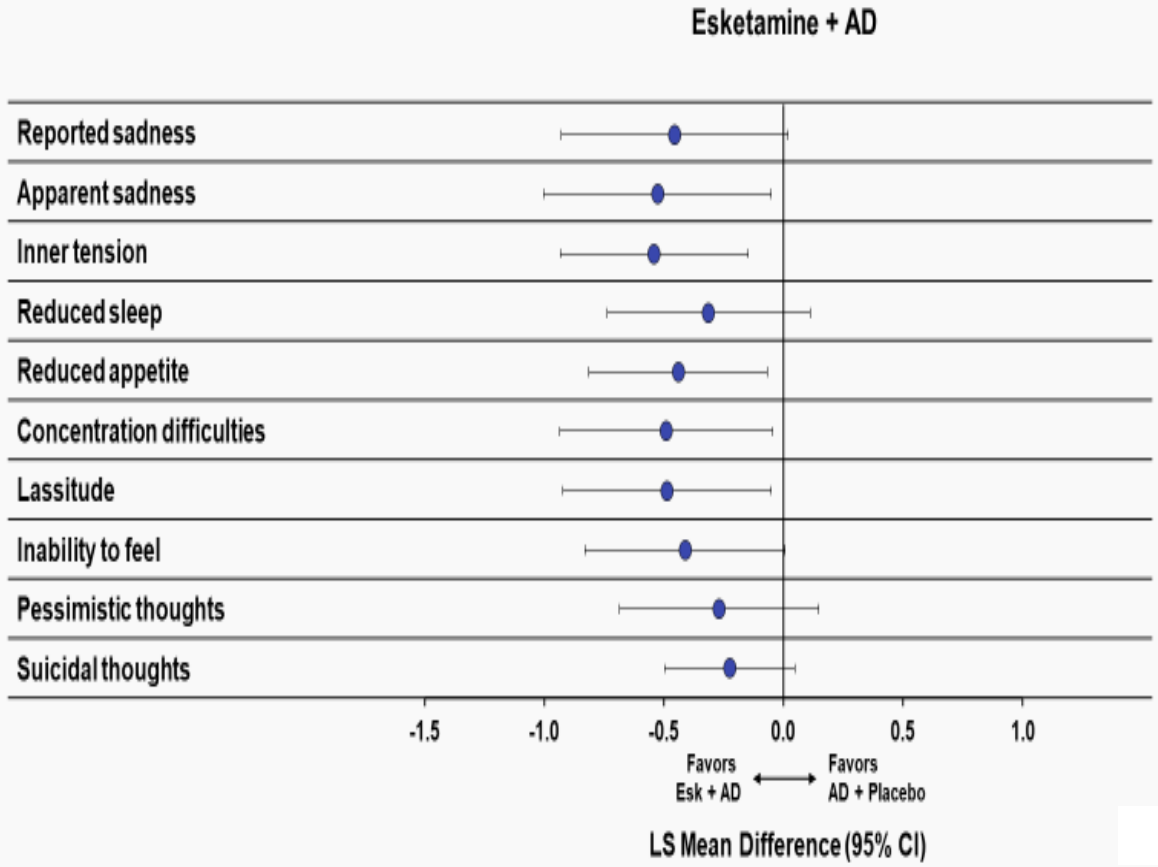
How Do Individual Symptoms Respond in TRD?

Change in Individual Symptoms 2 Hrs After 1st Ketamine Dose



Murrough, J et al *Biol Psychiatry*. 2013 August 15; 74(4): 250–256. doi:10.1016/j.biopsych.20

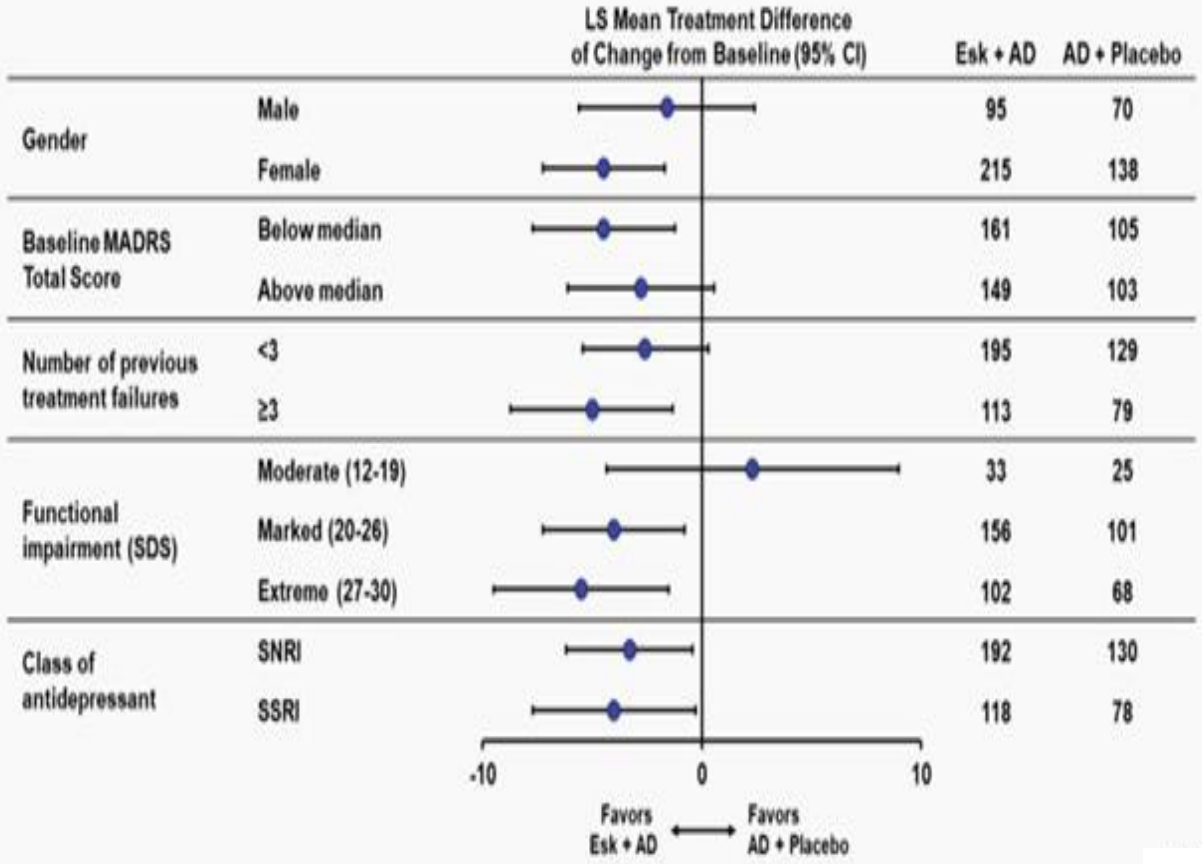
MADRS Items – LS Mean Differences from Placebo (95% CI) for Change from Baseline at Day 28 (MMRM) TRANSFORM-2 (3002)



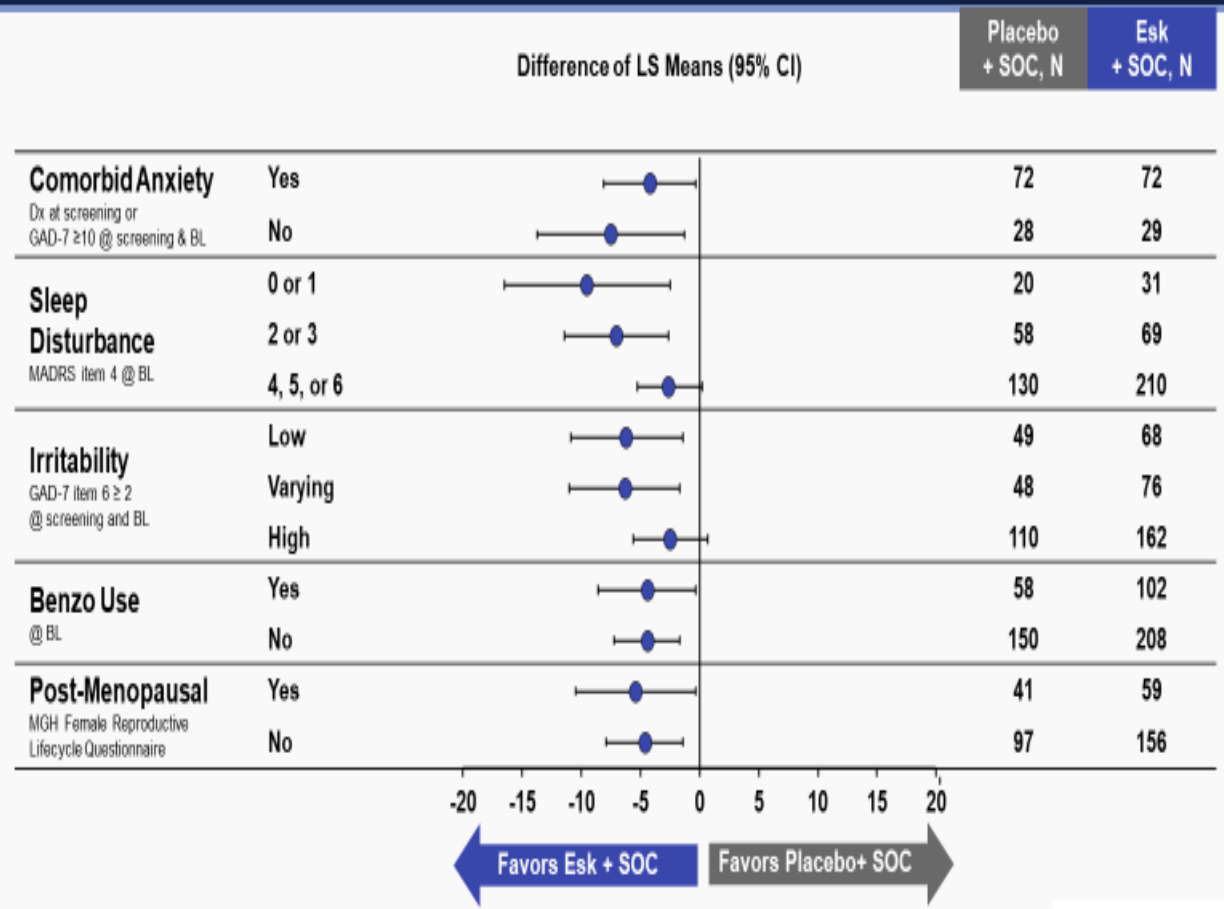
Popova, V et al., Janssen Data on File

How Do Patient Sub-groups Respond in TRD?

MADRS Total Score: LS Mean Treatment Difference of Change from Baseline to Day 28 MMRM Across Subgroups
Pooled TRANSFORM-1 (3001) and 2 (3002)



Post-Hoc Subgroups Analyses from TRANSFORM 1 (3001) and Transform 2 (3002)

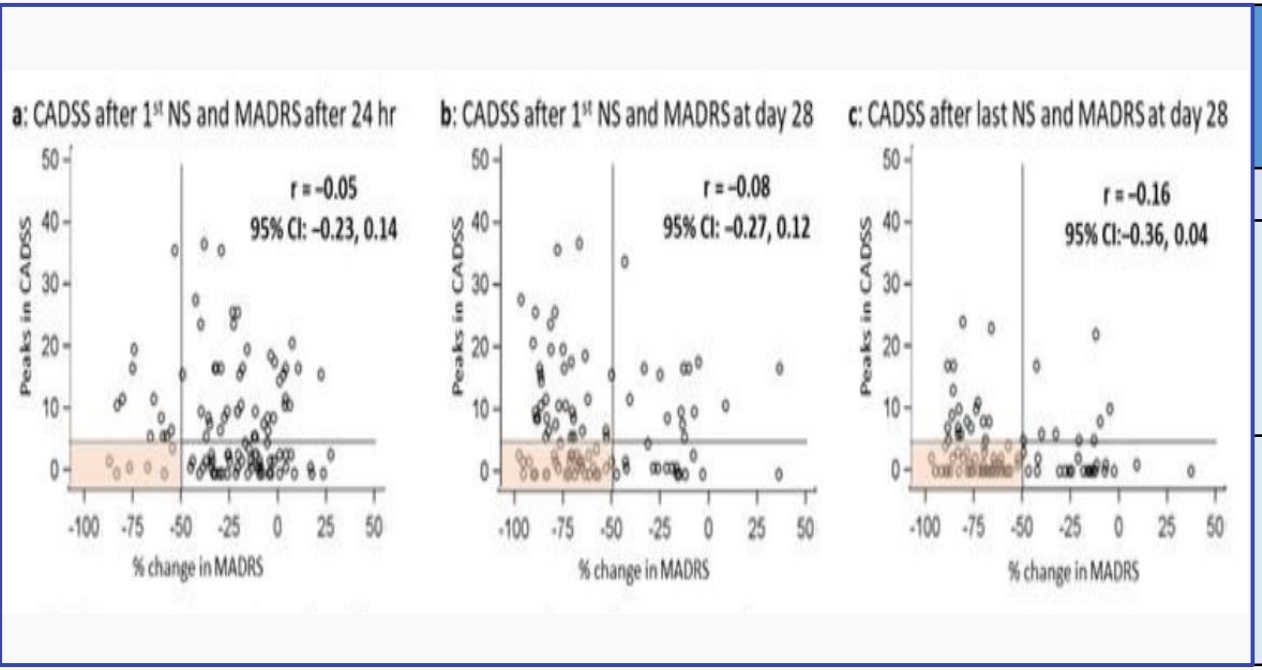


Janssen Data on File

Is Dissociation Necessary for Response?

Presently, the literature does not support the conclusion that dissociation is necessary for antidepressant response to ketamine. However, further work is needed to explore the relationship between dissociation and antidepressant response at the molecular, biomarker, and psychological levels.

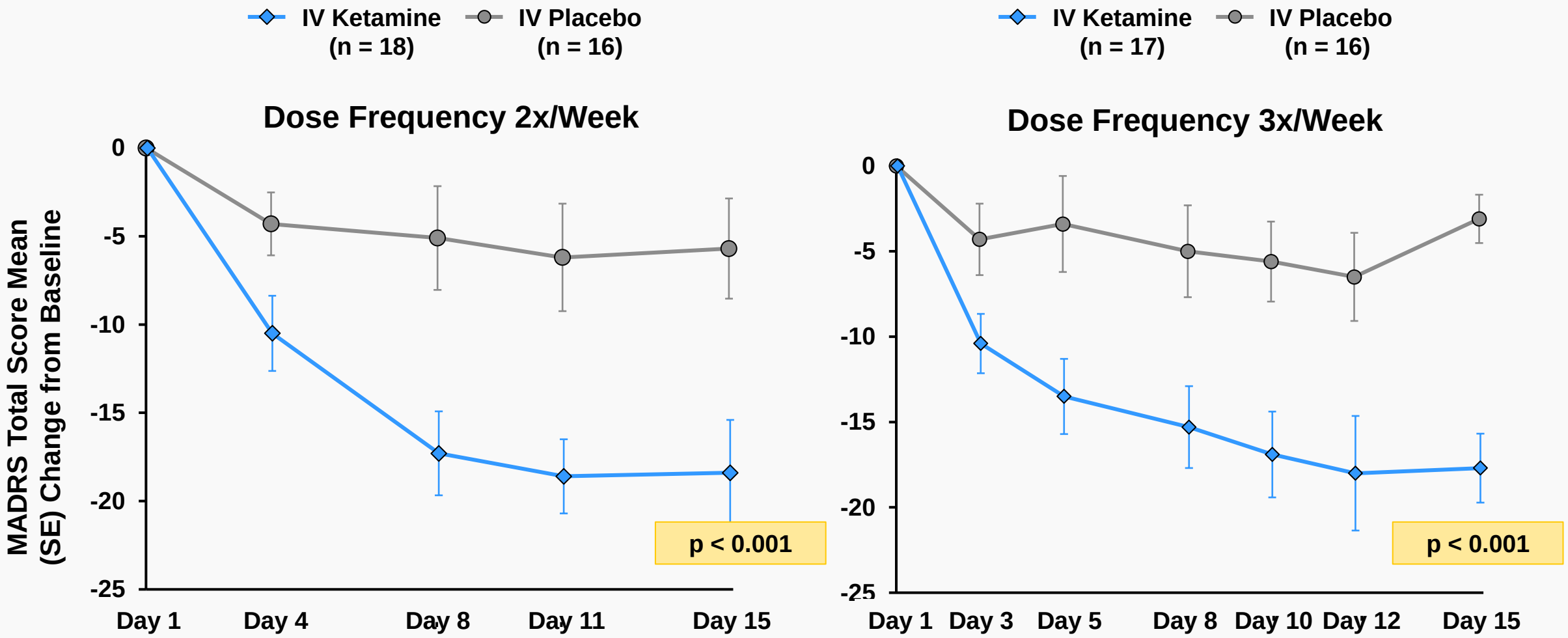
Ballard and Zarate *Nature Communications* | https://doi.org/10.1038/s41467-020-20190-4



Mediator	Outcome	Direct effect LS mean (95% CI)	Indirect effect LS mean (95% CI)	% mediated
TRANSFORM-2				
Change in **CADSS** total score at 40 min post-dose (day 1)	Decrease from BL in **MADRS** total score (day 2)	−3.62 (−6.62, −0.74)	−0.45 (−1.85, 0.85)	11%
Change in **CADSS** total score at 40 min post-dose (day 25)	Decrease from BL in **MADRS** total score (day 28)	−4.83 (−8.37, −1.28)	−0.42 (−1.95, 0.94)	8%

Chen et al., Janssen Data on File

How Frequently Should a Patient be Dosed?

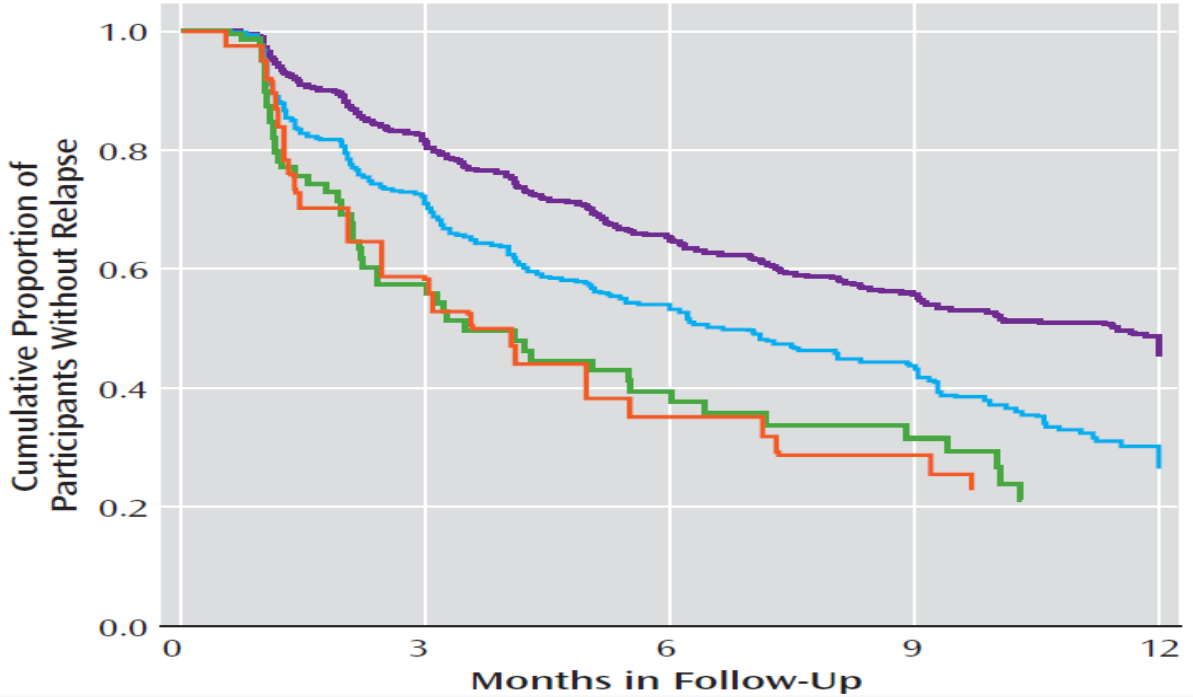


The recommended initial dose frequency of IN esketamine is 2 times/week for 4 weeks

Singh JB, Fedgchin M, Daly EJ, et al. *Am J Psychiatry*. 2016 Aug 1;173(8):816-26.

Can Relapse be Prevented with Continued, Intermittent Dosing?

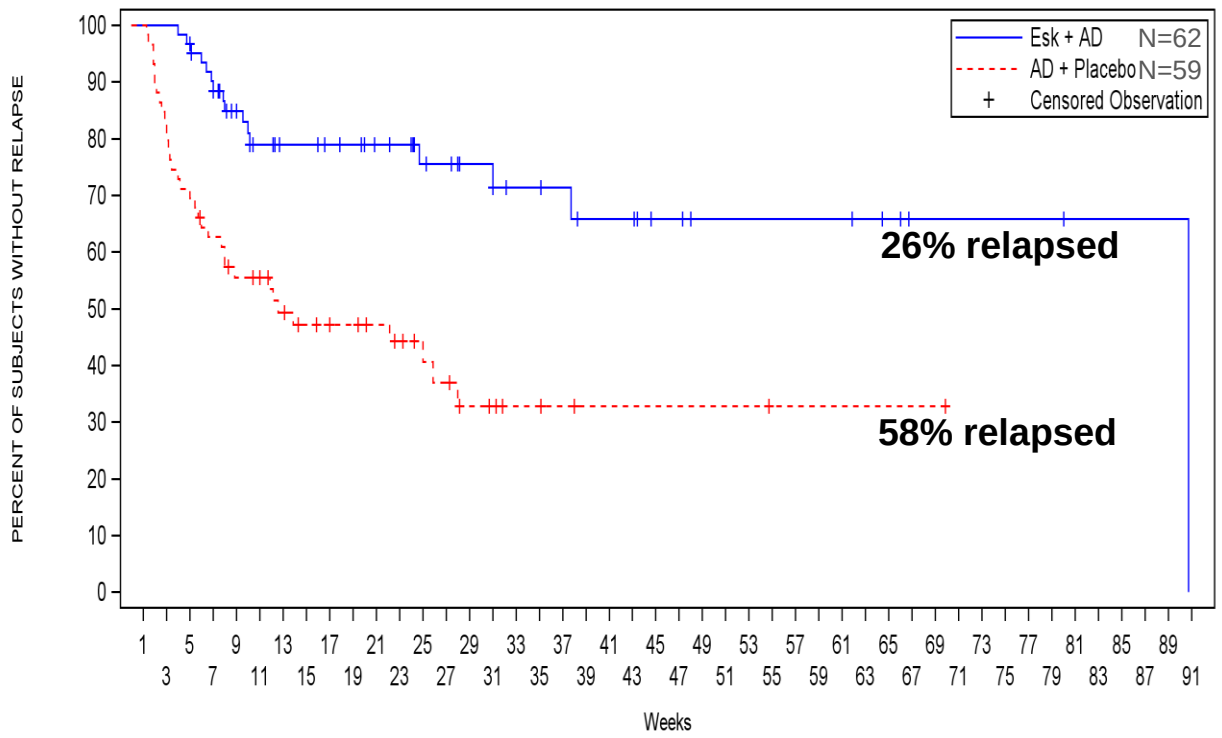
STAR-D Relapse Analysis



> 70 % relapse over 1 year

Rush, AJ et al *Am J Psychiatry 163:11, November 2006*

Relapse Rates Among Stable Responders



69% of stable remitters mostly received treatment every other week

55% of stable responders mostly received treatment once weekly

Daly E, et al *JAMA Psychiatry* September 2019 76 (9)

What is the Safety Profile of Long-term, Intermittent Dosing?

IN Esketamine Risk Evaluation and Mitigation Strategy (REMS)
To mitigate risks related to sedation, dissociation, and abuse and misuse, IN Esketamine is only available through a restricted REMS program

SUSTAIN-3
Ongoing Long-term, OL, Safety Study of IN Esketamine
N=1148
Median (range) Exposure: 31.7 (0-50) months

No New or Unexpected Safety Findings

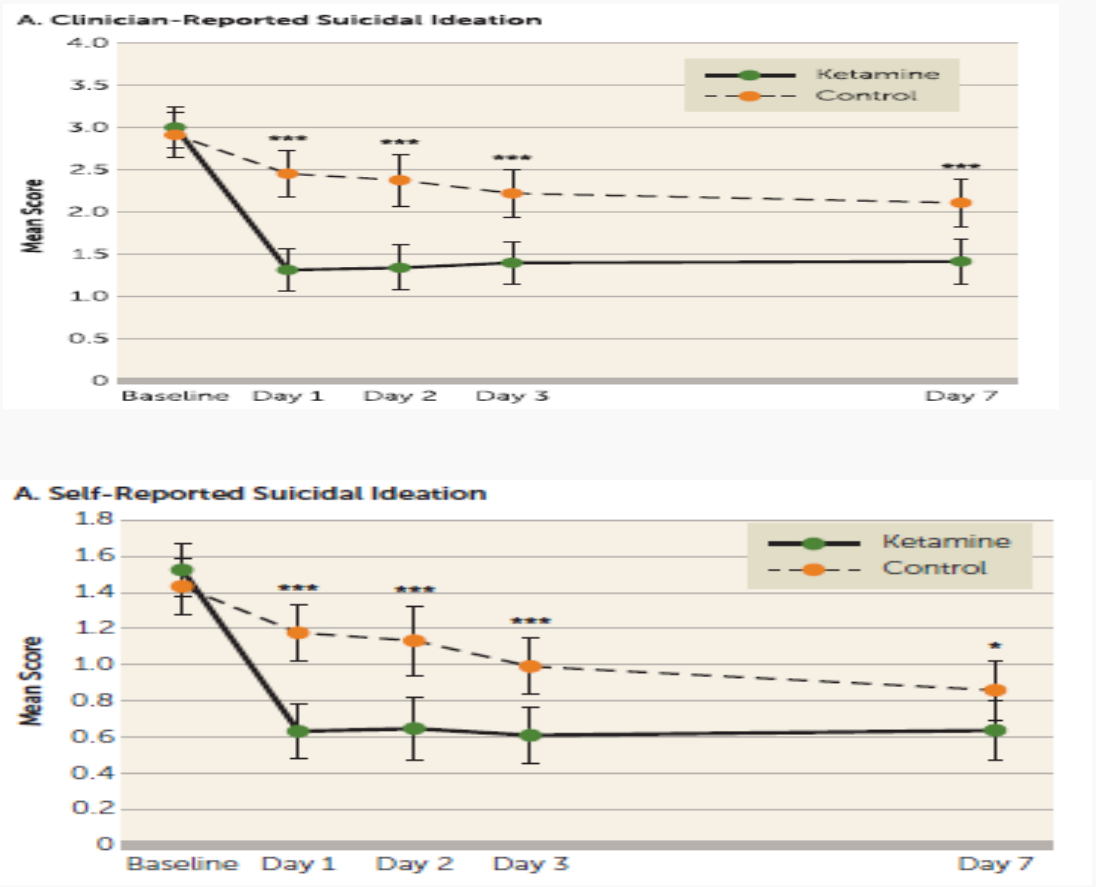
Cognition remained stable among patients, except for a slight slowing of reaction times in those ≥65 years, consistent with results of another longitudinal trial

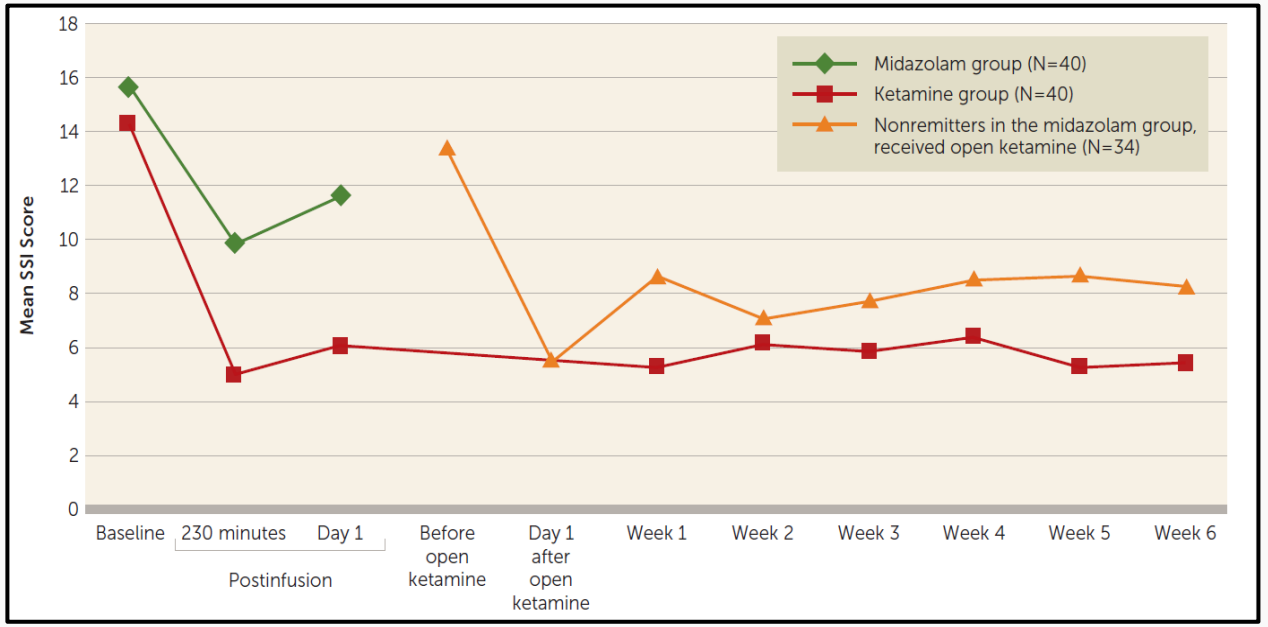
No evidence of abuse, dependence or withdrawal

No new blood pressure, bladder, renal or hepatic findings

Janssen Data on File

Ketamine in MDD with Suicidal Ideation or Behavior





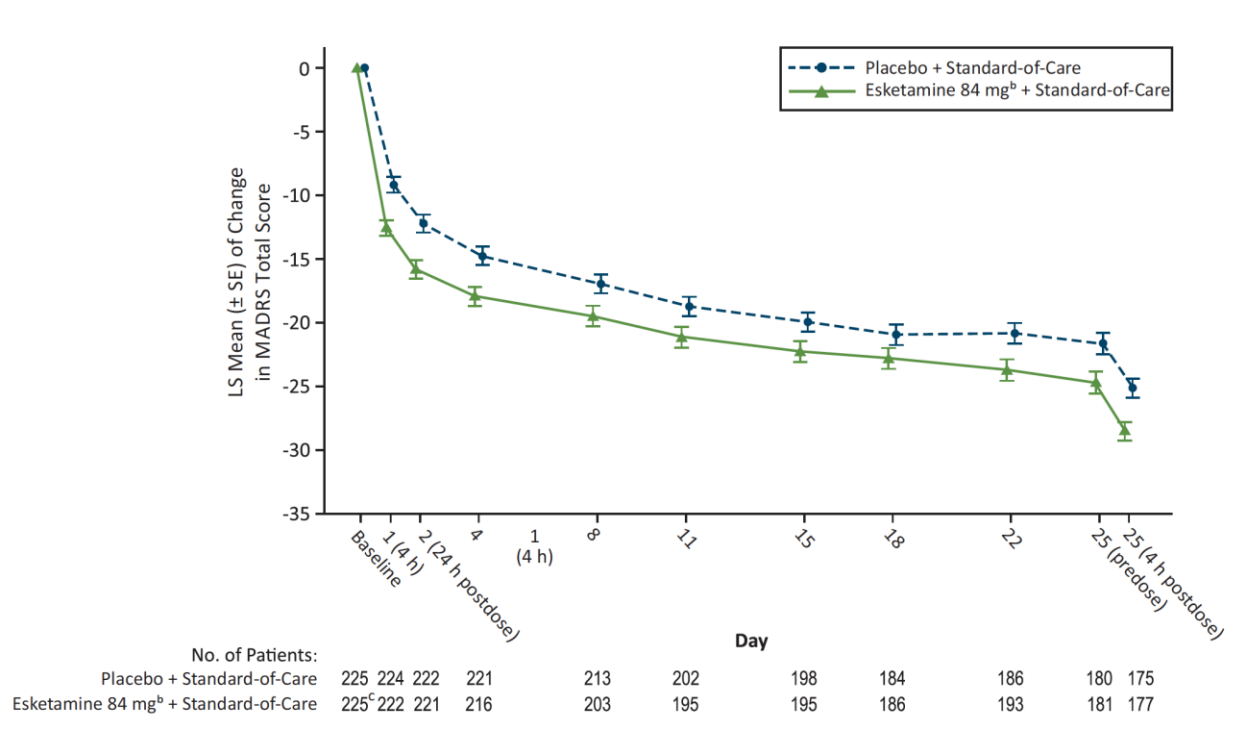
Improvement in depression mediated 33.6% of the effect on suicidal ideation score

Wilkinson S et al *Am J Psychiatry 175:2, February 2018*

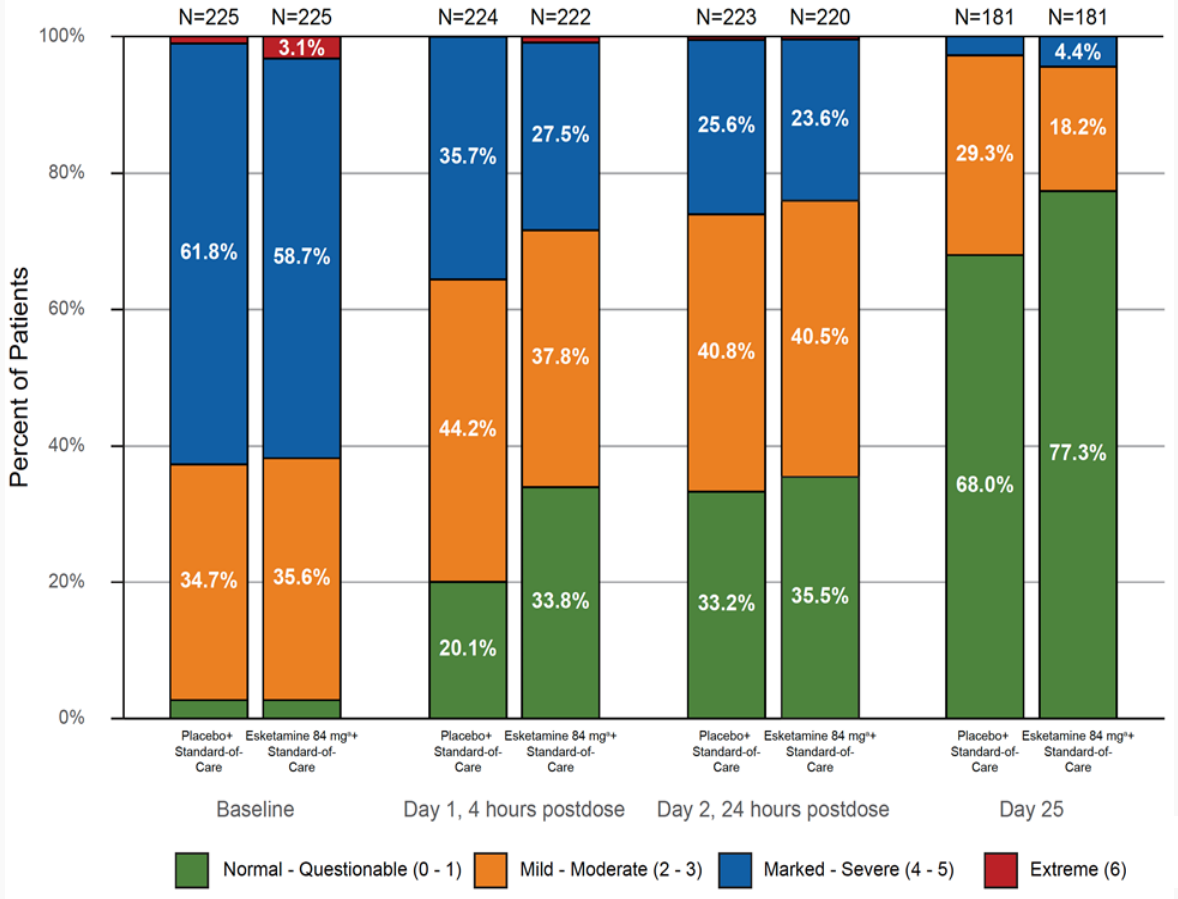
Grunebaum M et al *Am J Psychiatry 175:4, April 2018*

Esketamine in MDD with Suicidal Ideation or Behavior

Least-Squares Mean (± SE) Changes in MADRS Total Score From Baseline During the Double-Blind Treatment Phase[a]



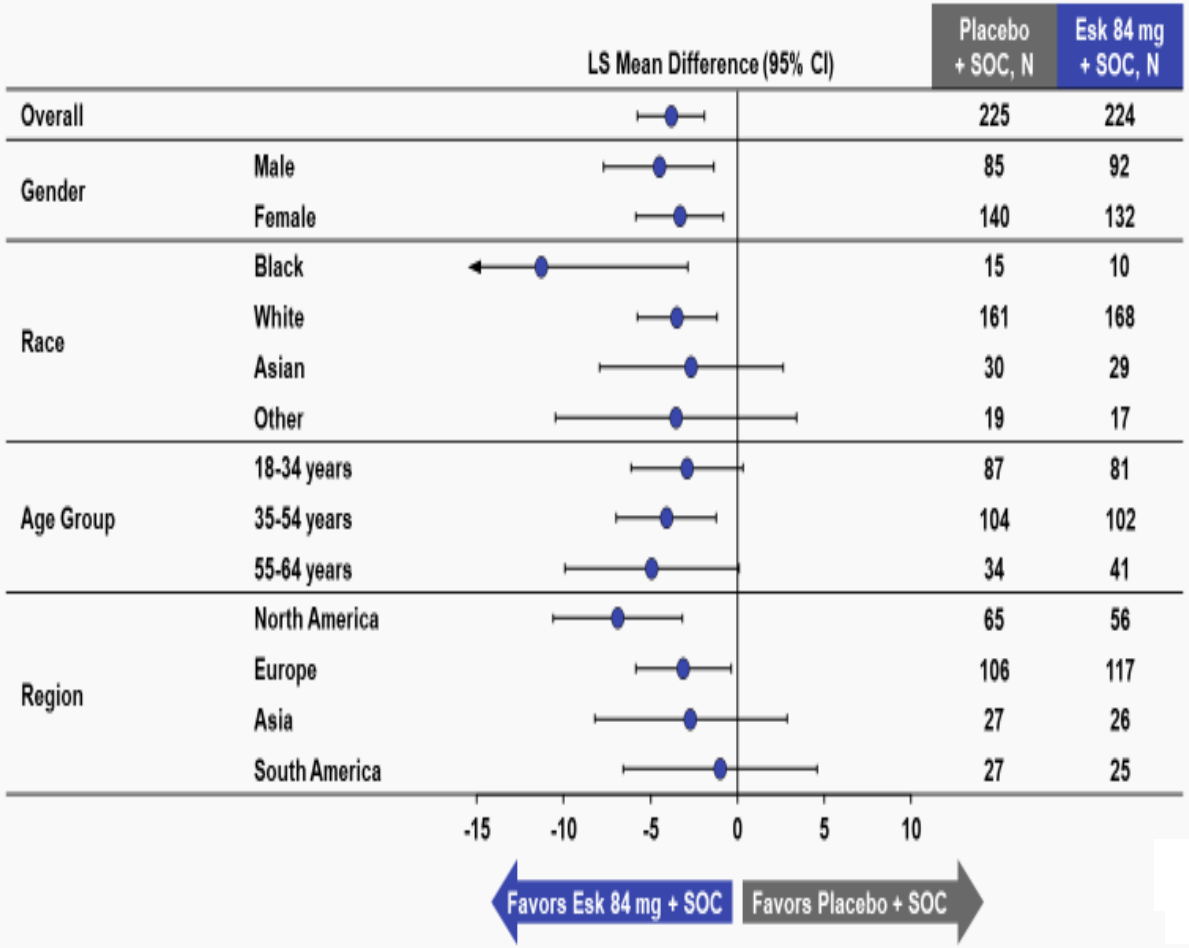
Frequency Distribution of CGI-SS-r Score at Baseline, 4 and 24 Hours Post-First Dose, and Day 25 (Observed Cases)



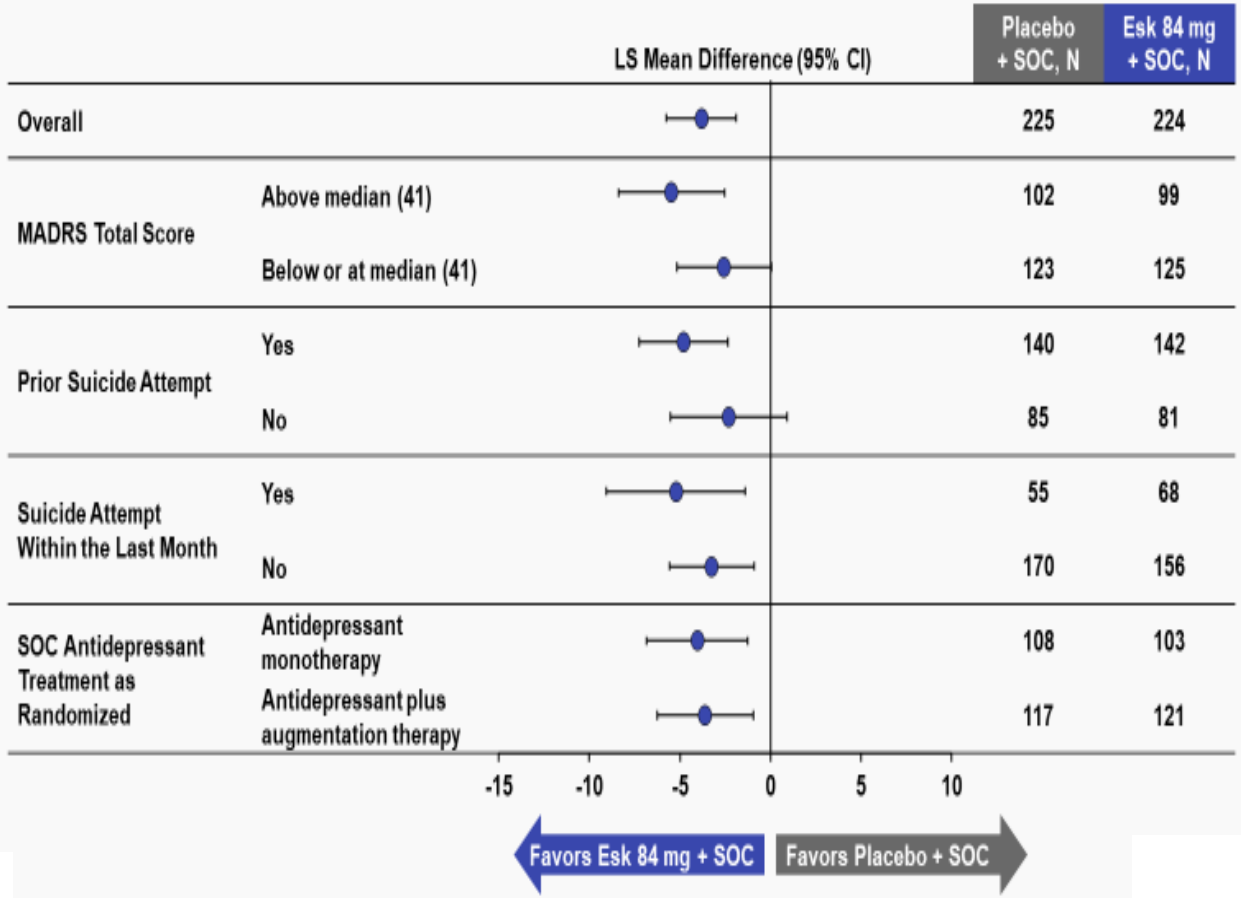
Canuso, C. et al ACNP 58th Annual Meeting, 2019

How Do Patient Sub-groups Respond in MDD with SI/B? Depression

Phase 3 Pooled MADRS Total Score: Treatment Effect at 24 Hours by Demographic Subgroups



Phase 3 Pooled MADRS Total Score: Treatment Effect at 24 Hours by Baseline Clinical Characteristics



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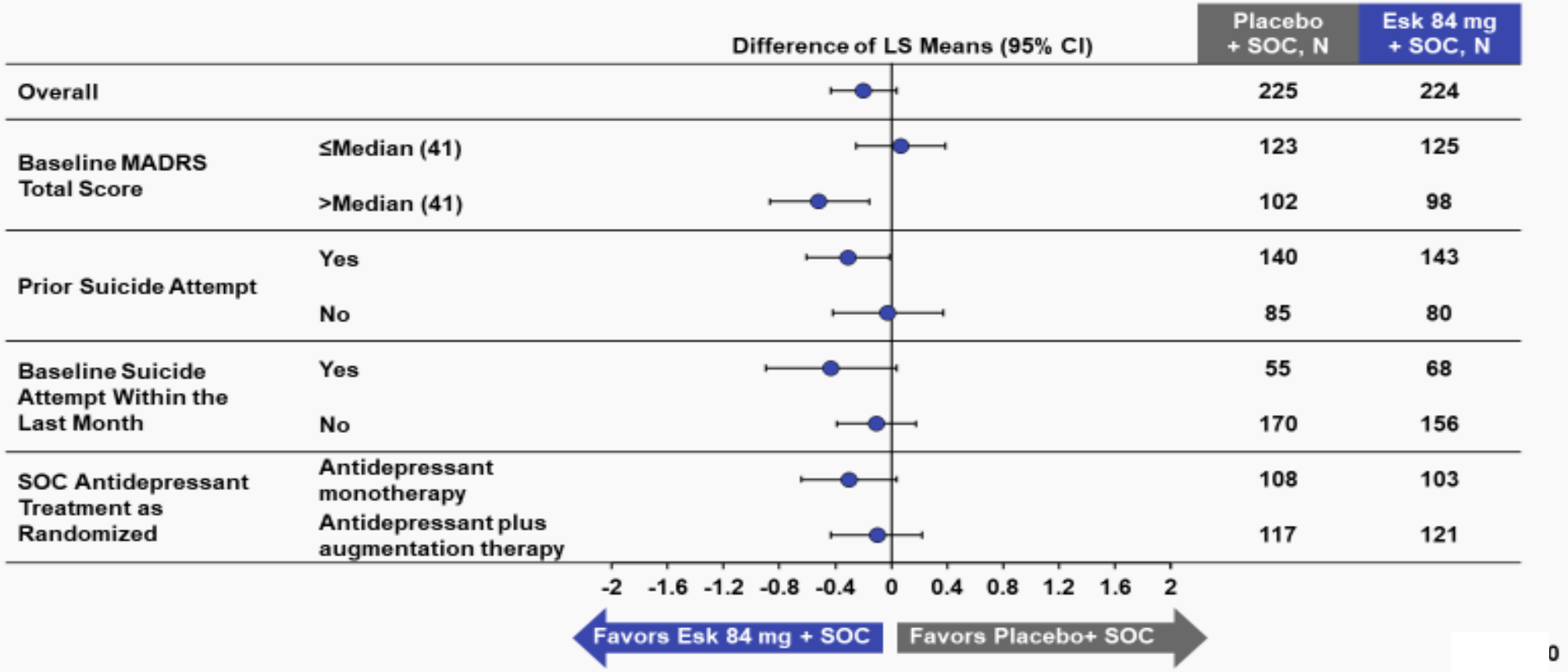
How Do Patient Sub-groups Respond in MDD with SI/B ? Suicidality

Phase 3 Pooled CGI-SS-r: Treatment Effect at 24 Hours by Baseline Clinical Characteristics



Canuso, C. et al ACNP 58th Annual Meeting, 2019

Summary

- **Unequivocal evidence for IV ketamine and IN esketamine in rapid and robust efficacy in treatment of depressive symptoms**
  - Direct comparison of ketamine and esketamine is limited but suggests similar efficacy
  - Broad-spectrum efficacy seen across symptoms, sub-groups and sub-types
  - Antidepressant efficacy appears independent of dissociation
  - Long-term efficacy and safety, and dosing regimen established for IN esketamine
- **Mixed results for effect on suicidality**
  - Methodologic issues may account for differences in outcomes across studies
- **More research is needed in other diagnoses/dimensions, special populations and with arketamine**
- **More comparative research is needed across racemic, S- and R-ketamine as well as across various routes of administration**

Back-Up

Slide #7 References

Dakwar E, et al. Am J Psychiatry https://doi.org/10.1176/appi.ajp.2019.19070684

Fan W et al Oncotarget. 2017 Jan 10; 8(2): 2356–2360

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McIntyre R.S, et al. J Affective Disorders 276 (2020) 576-544

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Peyrovian B, et al J Psychiatr Res. 2020 Aug;127:1-12

Rodriguez C, et al Neuropsychopharmacology 38 (2013); 2475–2483

Wilkinson ST, et al. Am J Psychiatry https://doi.org/10.1176/appi.ajp.2017.17040472