Supplementary Online Content

Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. Published online December 27, 2017. doi:10.1001/jamapsychiatry.2017.3739

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Material and Methods

Inclusion/Exclusion Criteria

The study enrolled medically stable (based on physical examination, medical history, vital signs, and 12-lead ECG performed at screening) adults (20 to 64 years) with a diagnosis of MDD, according to the Diagnostic and Statistical Manual of Mental Disorders Fourth edition – Text revised (DSM-IV-TR). Participant's major depressive episode and treatment response were evaluated to confirm participant met criteria using the "State vs. Trait, Assessibility, Face Validity, Ecological Validity, Rule of Three P's" (SAFER) criteria interview [Targum et al., 2008], administered by remote, independent raters.

Key exclusion criteria included recent or current suicidal ideation with intent to act, suicidal behavior, or homicidal ideation/intent, diagnosis of bipolar or related disorders, intellectual disability, psychotic disorder, major depressive disorder (MDD)with psychosis, cluster B personality disorder (based on clinical assessment by the investigator), post-traumatic stress disorder, obsessive-compulsive disorder, history of non-response to electroconvulsive therapy. Individuals with substance or alcohol abuse or dependence during the past year were excluded, as well as those testing positive for cannabis at screening.

eReference.

Targum SD, Pollack MH, Fava M. Redefining affective disorders: relevance for drug development. CNS Neurosci Ther. 2008;14(1):2-9.

eTable 1. GAD-7: ANCOVA Analysis of Change from Baseline to Study End Point[a]

	Placebo	Esketamine 28 mg	Esketamine 56 mg	Esketamine 84 mg
Period 1				
N	33	11	11	12
LS mean (SE)	-1.7 (0.88)	-1.5 (1.34)	-3.1 (1.34)	-5.1(1.30)
LS mean difference from placebo (SE)		-0.21 (1.461)	-1.40 (1.478)	-3.44 (1.414)
p-value[b]		0.558	0.174	0.009
Period 2				
N	6	8	9	5
LS mean (SE)	0.4 (1.02)	-1.6 (0.87)	1.0 (0.98)	-0.9 (1.02)
LS mean difference from placebo (SE)		-2.02 (1.089)	0.60 (1.033)	-1.25 (1.205)
p-value[c]		0.039	0.718	0.156
Periods 1 and 2 Combined				
p-value		0.144	0.360	0.006

ANCOVA = analysis of covariance; GAD-7 = Generalized Anxiety Disorder 7-item; LS = least squares; SE = standard error

a. Change from first day to day 8 in each period.
b. Based on ANCOVA model with treatment, country, and Period 1 baseline value as a covariate.
c. Based on ANCOVA model with treatment, country, and Period 2 baseline Quick Inventory of Depressive Symptomatology-Self Report ($QIDS\text{-}SR_{16}$) score (moderate or severe), and Period 2 baseline value as a covariate.

eTable 2. CGI-S: ANCOVA Analysis of Change from Baseline to Study End Point[a]

	Placebo	Esketamine 28 mg	Esketamine 56 mg	Esketamine 84 mg
Period 1				
N	33	11	11	12
Median (Range)	5.0 (1, 6)	4.0 (3, 5)	4.0 (1, 5)	4.0 (1, 6)
Median Change (Range)	0.0 (-3, 2)	-1.0 (-2, 1)	-1.0 (-3, 0)	-0.5 (-4, 0)
p-value[b]		0.028	0.004	0.049
Period 2				
N	6	8	9	5
Median (Range)	5.0 (4, 5)	4.0 (3, 5)	5.0 (4, 6)	4.0 (3, 5)
Median Change (Range)	0.0 (0, 2)	-1.0 (-1, 0)	-1.0 (-2, 0)	-1.0 (-2, 0)
p-value[c]		0.009	0.050	0.022
Periods 1 and 2 Combined				
p-value		<0.001	<0.001	0.004

ANCOVA = analysis of covariance; CGI-S = Clinical Global Impression of Severity

a. Change from first day to day 8 in each period.

b. Based on ANCOVA model on ranks of change with treatment, country, and Period 1 baseline value (unranked) as a covariate.

c. Based on ANCOVA model on ranks of change with treatment, country, Period 2 baseline Quick Inventory of Depressive Symptomatology-Self Report ($QIDS\text{-}SR_{16}$) score (moderate or severe), and Period 2 baseline value (unranked) as a covariate.

eTable 3. Demographics and Baseline Characteristics

Parameter	Placebo N = 33	Esketamine 28 mg N = 11	Esketamine 56 mg N = 11	Esketamine 84 mg N = 12	Total N = 67
Age, years					
Mean (SD)	44.4 (9.60)	42.1 (10.31)	42.7 (11.23)	49.8 (9.29)	44.7 (10.04)
Range	21 – 57	21 – 53	20 – 57	32 – 63	20 – 63
Sex, n (%)					
Female	18 (54.5)	5 (45.5)	9 (81.8)	6 (50.0)	38 (56.7)
Male	15 (45.5)	6 (54.5)	2 (18.2)	6 (50.0)	29 (43.3)
Race, n (%)					
White	24 (72.7)	7 (63.6)	6 (54.5)	11 (91.7)	48 (71.6)
Black or African American	9 (27.3)	4 (36.4)	4 (36.4)	1 (8.3)	18 (26.9)
American Indian or Alaska native	0	0	1 (9.1)	0	1 (1.5)
BMI, kg/m^2					
Mean (SD)	29.7 (6.00)	29.0 (6.18)	30.1 (8.30)	30.4 (8.47)	29.8 (6.77)
Range	17 – 49	23 – 44	19 – 45	21 – 49	17 – 49
MADRS Total Score					
Mean (SD)	35.0 (5.18)	31.3 (3.80)	33.2 (6.26)	35.0 (4.22)	34.1 (5.11)
Range	25 – 45	26 – 37	23 – 46	27 – 41	23 – 46
IDS-C_{30} Total Score					
Category, n (%)					
Moderate (34-39)	10 (30.3)	4 (36.4)	3 (27.3)	3 (25.5)	20 (29.9)
Severe (40 – 48)	15 (45.5)	7 (63.6)	6 (54.5)	9 (75.0)	37 (55.2)
Very severe (≥49)	8 (24.2)	0	2 (18.2)	0	10 (14.9)
Mean (SD)	43.9 (6.81)	41.1 (4.25)	42.3 (6.72)	42.5 (4.23)	42.9 (6.02)
Range	35 – 59	35 – 48	34 – 57	34 – 48	34 – 59
Duration of Current Episode (wks)					
Mean (SD)	65.2 (79.93)	56.1 (39.28)	39.9 (21.82)	66.6 (51.54)	59.8 (63.5)
Range	12 – 302	14 – 122	10 – 75	18 – 162	10 – 302

Number of Major Depressive Episodes					
< 3	4 (12.1)	3 (33.3)	2 (20.0)	2 (18.2)	11 (17.5)
≥ 3	29 (87.9)	6 (66.7)	8 (80.0)	9 (81.8)	52 (82.5)
Number of Antidepressants in Current Episode of Major Depression					
1	21 (63.6)	6 (54.5)	8 (72.7)	8 (66.7)	43 (64.2)
2	7 (21.2)	4 (36.4)	2 (18.2)	2 (16.7)	15 (22.4)
≥ 3	5 (15.2)	1 (9.1)	1 (9.1)	2 (16.7)	9 (13.4)

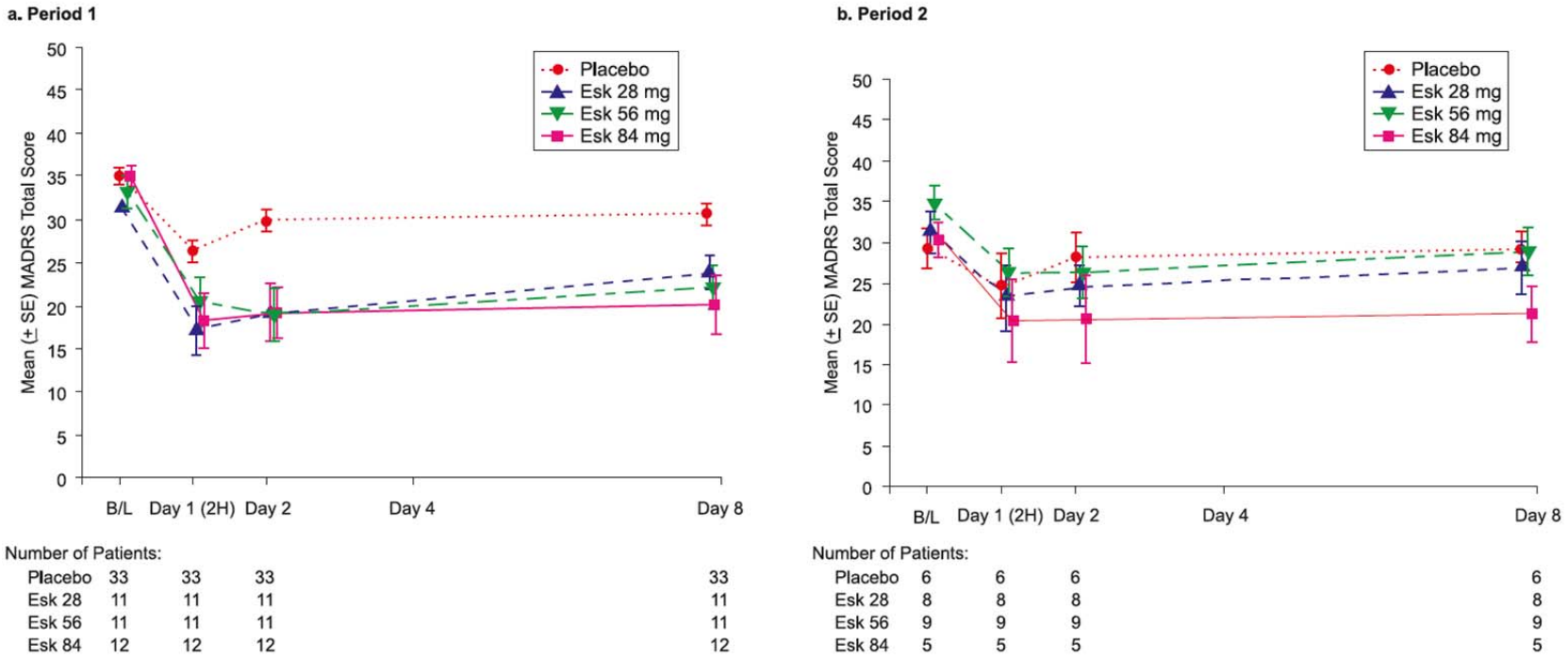
BMI = body mass index; IDS-C_{30} = Inventory of Depressive Symptomatology-Clinician rated, 30 item; MADRS = Montgomery-Asberg Depression Rating Scale; SD = standard deviation

eTable 4. Summary of Most Frequently Reported[a] Treatment-Emergent Adverse Events (Double-Blind Safety Analysis Data Set)

		Number (%) of Participants			
		Esketamine			
Preferred Term	Placebo N = 33	28 mg N = 19	56 mg N = 20	84 mg N = 17	Total N = 56
Total with events	18 (55)	11 (58)	16 (80)	15 (88)	42 (75)
Dizziness	1 (3)	4 (21)	8 (40)	8 (47)	20 (36)
Headache	3 (9)	6 (32)	3 (15)	3 (18)	12 (21)
Dissociation[b,c]	1 (3)	0	7 (35)	4 (24)	11 (20)
Dysgeusia	7 (21)	2 (11)	3 (15)	5 (29)	10 (18)
Nausea	3 (9)	2 (11)	4 (20)	4 (24)	10 (18)
Dissociative disorder[b,c]	0	2 (11)	1 (5)	4 (24)	7 (13)
Hypoesthesia oral	0	1 (5)	4 (20)	2 (12)	7 (13)
Vertigo	0	2 (11)	1 (5)	1 (6)	4 (7)
Sedation	0	1 (5)	2 (10)	1 (6)	4 (7)
Feeling abnormal	0	2 (11)	1 (5)	1 (6)	4 (7)
Nasal discomfort	3 (9)	0	2 (10)	1 (6)	3 (5)
Hypertension	2 (6)	0	2 (10)	1 (6)	3 (5)
Oropharyngeal pain	2 (6)	0	1 (5)	2 (12)	3 (5)
Throat irritation	0	1 (5)	0	2 (12)	3 (5)
Vision blurred	0	0	0	2 (12)	2 (4)
Insomnia	1 (3)	0	2 (10)	0	2 (4)
Tunnel vision	0	0	0	2 (12)	2 (4)
Hypersomnia	0	2 (11)	0	0	2 (4)
Polyuria	0	0	2 (10)	0	2 (4)

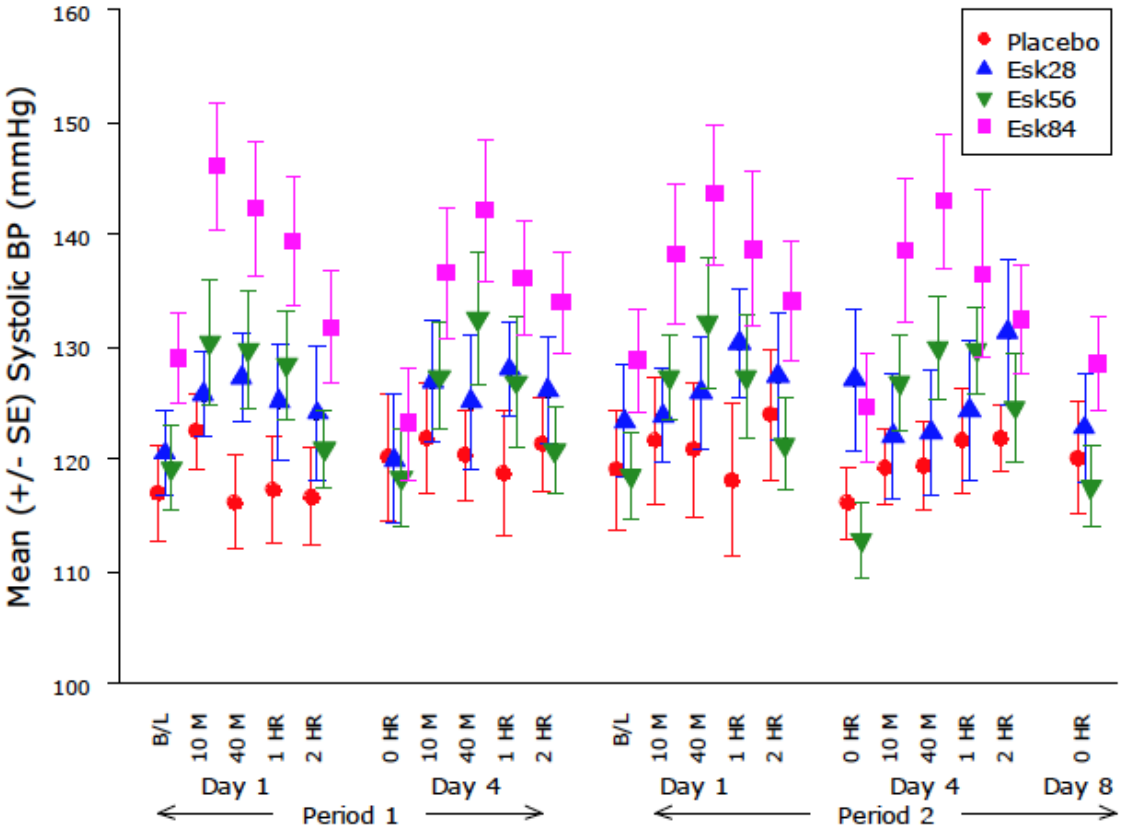
a. Defined as ≥10% of participants in any esketamine dose group. Events presented in descending order in the total esketamine (combined doses) group.
b. Participants reported either dissociative reaction or dissociative symptoms and, depending on the verbatim term used these events were coded as dissociative disorder or dissociative symptoms, respectively.
c. All adverse events coded to dissociation or dissociative disorder resolved on the same day as dosing.

eFigure 1. Mean (± SE) MADRS Total Score Over Time in Double-Blind Phase



ESK = esketamine; MADRS = Montgomery-Asberg Depression Rating Scale; SE = standard error
Note: Period 2 consists only of those participants who had been on placebo in Period 1 and had moderate-to-severe symptoms (n=28). At the 2-hour time point, modified MADRS was used, with baseline scores for sleep and appetite items carried forward.

eFigure 2. Mean Systolic Blood Pressure Over Time by Period for Participants who Received the Same Treatment for Both Periods During the Double-Blind Phase

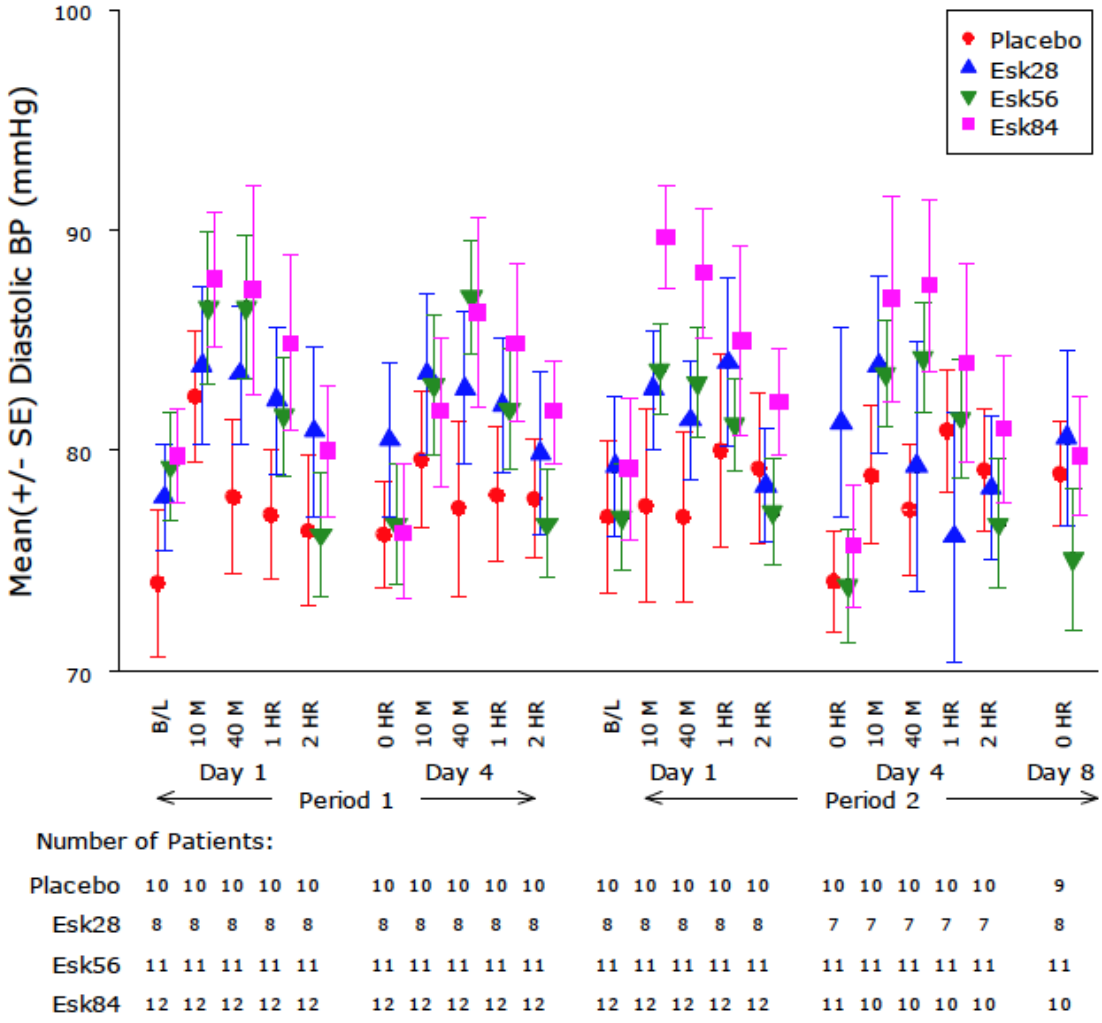


Number of Patients:

Placebo	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9
Esk28	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	7	7	7	7	8
Esk56	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Esk84	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	10	10	10	10

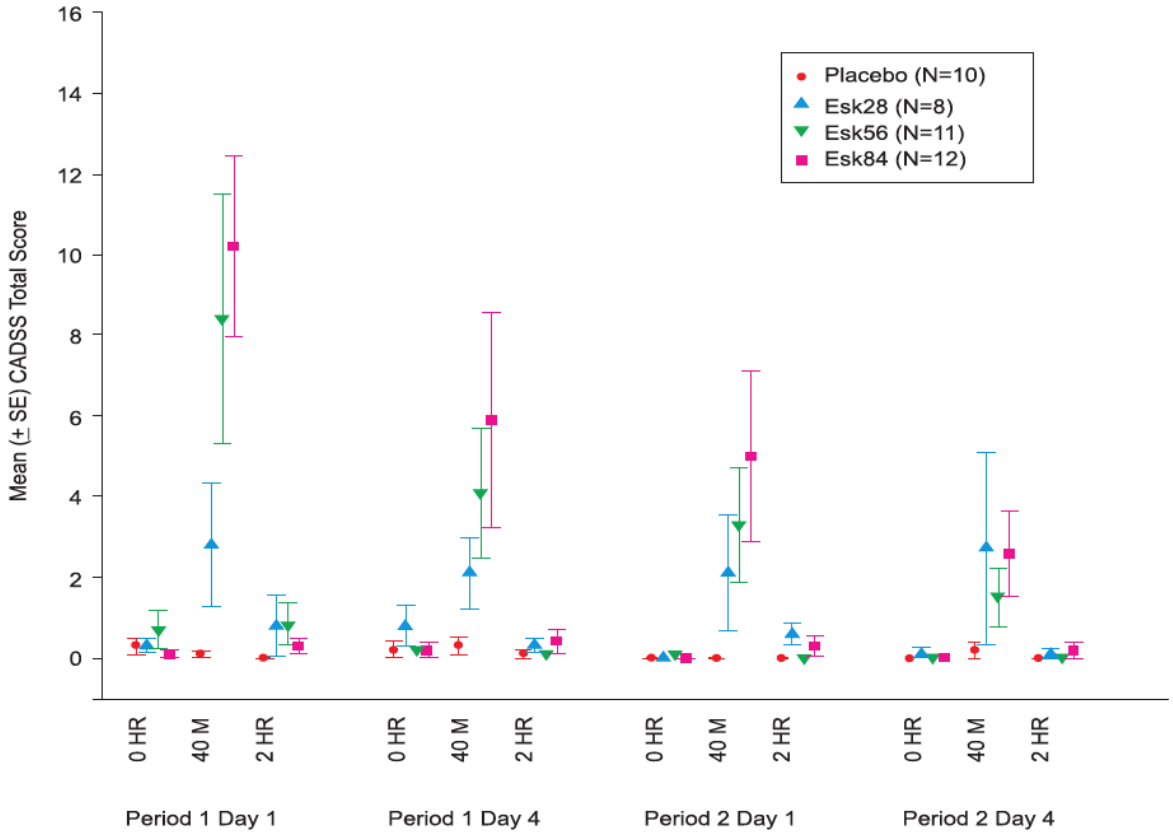
B/L = baseline; BP = blood pressure; ESK = esketamine; HR = hours; M = minutes; SE = standard error

eFigure 3. Mean Diastolic Blood Pressure Over Time by Period for Participants who Received the Same Treatment for Both Periods During the Double-Blind Phase



B/L = baseline; BP = blood pressure; ESK = esketamine; HR = hours; M = minutes; SE = standard error

eFigure 4. Mean CADSS Total Score Over Time for Participants who Received the Same Treatment for Both Periods



CADSS = Clinician Assessed Dissociative Symptom Scale; HR = hours; M = minutes; SE = standard error

