Esketamine

Introduction

David Hough, MD

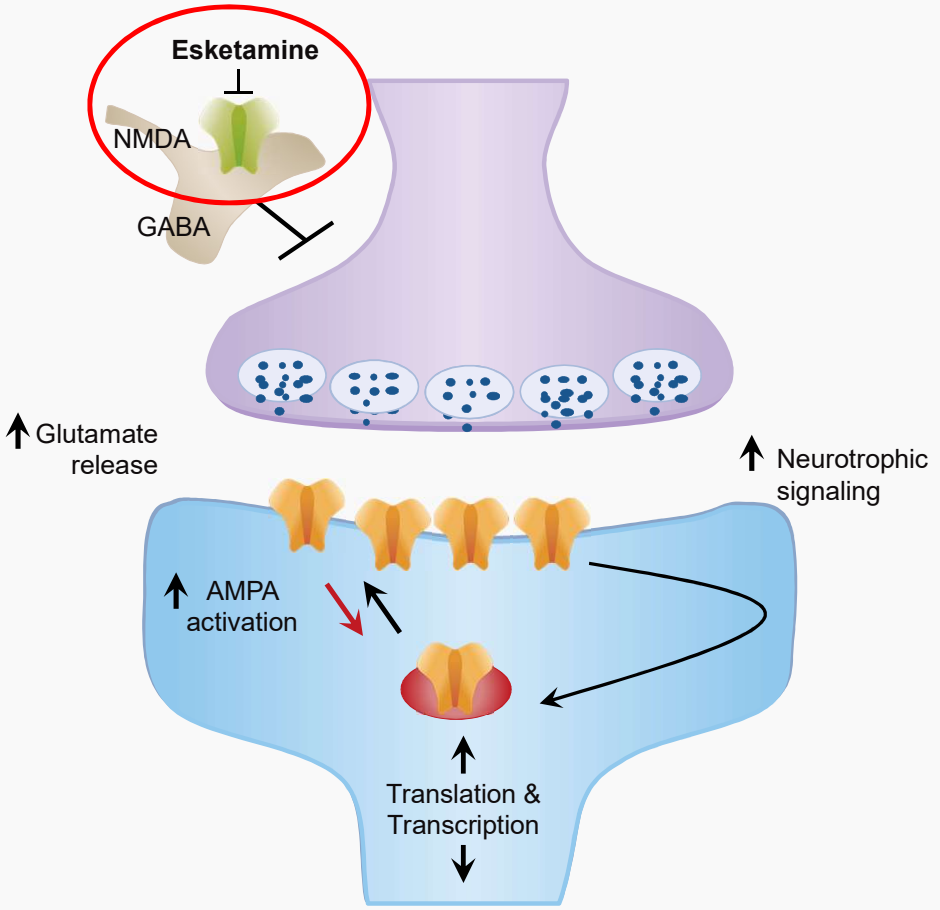
Janssen Research & Development, LLC
Esketamine Compound Development Team Leader

Sponsor Presentation Agenda

Introduction	**David Hough, MD**	Janssen Research & Development, LLC Esketamine Compound Development Team Leader
Unmet Medical Need	**A. John Rush, MD**	CEO Curbstone Consultant LLC Santa Fe, New Mexico Professor Emeritus Duke NUS
Clinical Development Program Efficacy	**Jaskaran Singh, MD**	Janssen Research & Development, LLC Senior Director, Clinical Development
Clinical Safety	**Vanina Popova, MD**	Janssen Research & Development, LLC Director, Clinical Development
Abuse Potential	**Andrew Krystal, MD**	Ray and Dagmar Dolby Distinguished Professor of Psychiatry, University of California San Francisco
Risk Mitigation	**David Hough, MD**	Janssen Research & Development, LLC Esketamine Compound Development Team Leader
Benefit-Risk Assessment	**David Hough, MD**	Janssen Research & Development, LLC Esketamine Compound Development Team Leader
Clinician's Perspective	**Madhukar Trivedi, MD**	Professor of Psychiatry at UT Southwestern Medical Center

Esketamine: Transformational Therapy with Novel Mechanism of Action

- **Esketamine works at the NMDA receptor**
- **NMDA antagonism (blocking) facilitates glutamate release -> AMPA receptor activation**
- **AMPA activation increases signaling of neurotrophic factors supporting both rapid onset and long term antidepressant effects**



Art adapted from Sanacora and Schatzberg, *Neuropsychopharmacology,* 2015

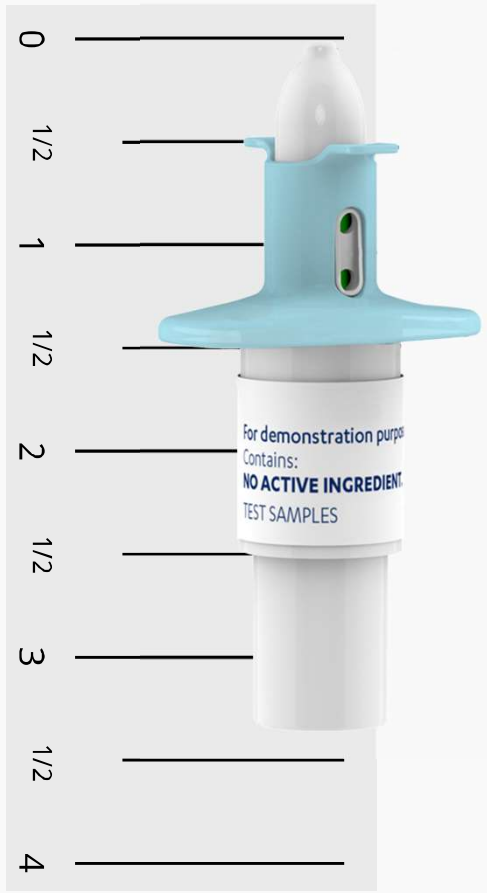
Esketamine Proposed Indication

Esketamine is indicated for treatment-resistant depression (Major Depressive Disorder in adults who have not responded adequately to at least two different antidepressants of adequate dose and duration to treat the current depressive episode)

Proposed Dosing and Administration

- **Should be given in conjunction with an oral antidepressant**
- **Intermittent dosing**
  - Induction
    - 2 times per week for 4 weeks
  - Maintenance
    - Once a week or once every two weeks
- **Flexible dosing**
  - Starting dose: 56 mg (2 devices)
  - Subsequent doses: 56 mg or 84 mg (3 devices)
  - Starting dose for patients ≥65 years is 28 mg (1 device)

Esketamine
Nasal Spray Device



Intranasal dosing is non-invasive and more convenient compared to IV infusion

Each device dispenses a total of 28 mg

Delivers 2 sprays

One spray for each nostril

Self-administered at site of care under medical supervision

Clinical Development Program

Nineteen Phase 1, Four Phase 2, and Seven Phase 3 Studies
Evaluated for Safety in >1700 Esketamine-treated Patients

Five Completed Phase 3 Studies with Intranasal Esketamine

3 Short Term

- TRANSFORM-1 (3001)
- TRANSFORM-2 (3002)
- TRANSFORM-3 (3005) (patients ≥65 years)

1 Maintenance of Effect

- SUSTAIN-1 (3003)

1 Long Term Open Label Safety

- SUSTAIN-2 (3004)

Ongoing Studies

- TRD3006 Short Term Study
- SUSTAIN-3 (3008) - Continuation Phase 3 Study

Clinical Development Program Results

	Statistically Positive Studies	2-sided p-value < 0.05
Phase 3	**TRANSFORM-2 (Pivotal)**	$p = 0.020$
Phase 3	**SUSTAIN-1 (Pivotal)**	$p = 0.003$
Phase 2	TRD2001	$p \leq 0.003$
Phase 2	TRD2002	$p < 0.001$
Phase 2	SYNAPSE (TRD)	$p = 0.043$ (28 mg) $p = 0.002$ (56 mg) $p < 0.001$ (84 mg)
Phase 2	PERSEVERE (Related population with major depression)	$p = 0.015$

	Not Statistically Positive Studies	2-sided p-value ≥ 0.05
Phase 3	TRANSFORM-1	$p = 0.088$
Phase 3	TRANSFORM-3	$p = 0.059$

Unmet Medical Need

A. John Rush, MD

Professor Emeritus, National University of Singapore, Duke-NUS

Adjunct Professor of Psychiatry and Behavioral Sciences
at Duke University School of Medicine

CEO, Curbstone Consultant LLC

MDD is a Serious Disease with Far-Reaching Impact

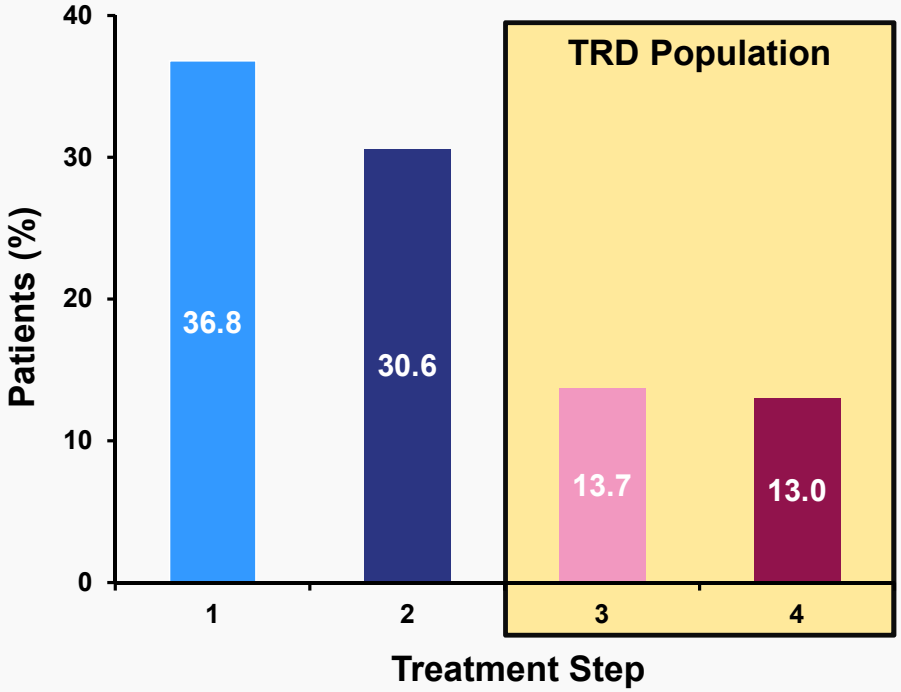
- **Global health problem, >300 million worldwide,[1] >17 million in US[2]**
  - Over 2 million US patients have treatment-resistant depression[3] (TRD: inadequate response to at least 2 antidepressants of adequate dose and duration)[4]
  - Affects core aspects of life–eating, sleeping, energy level, self-worth, intellect, and the desire to live[5]
  - Lowest self-rating of health and wellbeing among cancer, diabetes, or heart disease[6]
  - 65% report a significant inability to function in life[2]
  - Major cause of disability in US[2] and worldwide[7]

- **MDD increases the risk for other physical and psychiatric illnesses[8]**
  - MDD worsens the outcomes of other general medical and mental conditions
  - 10-year reduction in life-expectancy[9]

1. WHO News Release 30 Mar 2017; 2. NIMH Mental Health Website release November 2017; 3. Mazrek et al., *Psychiatr Serv*. 2014 Aug 1;65(8):977-87; 4. Agency for Healthcare Research and Quality. https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id105TA.pdf.; 5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*: DSM-5. Washington, DC: American Psychiatric Association, 2013; 6. Mitchell PM, et al. *PLoS ONE* 2015; 7. Global Burden of Disease 2010; 8. Taksler GB et al. *Am J Public Health*. 2017;107(10):1653–1659; 9. Walker ER, McGee RE, Druss BG. *JAMA Psychiatry*. 2015;72:334-341.

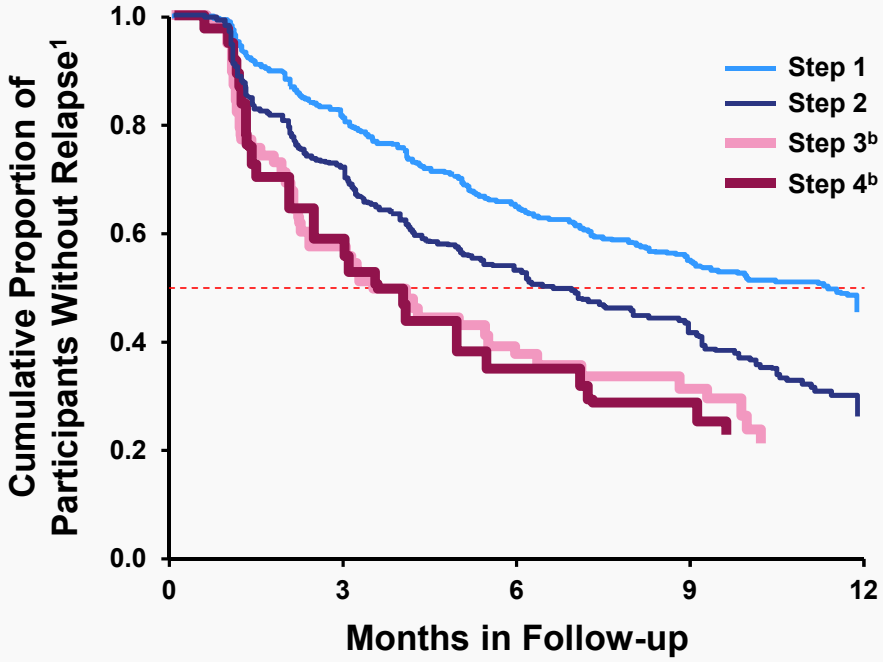
Challenges with TRD: Getting Well Staying Well

STAR*D Remission[a] Rates[1]



Time to remission: 5-7 weeks[1]

STAR*D Relapse Rates[1]



a. Remission definition: QIDS-SR16 ≤5; b. Treatment-Resistant Depression population

1. Rush AJ et al. *Am J Psychiatry*. 2006;163(11):1905-1917.

Consequences of TRD as Compared to MDD

More comorbidities

(e.g., hypertension, diabetes, heart failure)[1]

2x

Hospitalization rate [2]

36% longer

Mean hospital length of stay[2]

7-fold

Increase in suicide rate[3]

1. Amos T, Witt, EA, Alphs L, et al. Poster Presented at: 29th Annual US Psychiatric & Mental Health Congress, October 21-24, 2016; San Antonio, Texas;
2. Amos TB, Tandon N, Lefebvre P, et al. (2018). *J Clin Psychiatry*;
3. Feldman RL, Dunner DL, Muller JS, Stone DA (2012). *J Med Econ.*

Current Treatments Fail to Address Patient Needs

- **What do patients with TRD want and have themselves expressed to the FDA?[1]**
  - A **fast-acting treatmen**t to "jump start" recovery
  - A **durable treatment** that keeps them well over time
- **Current treatments do not address these needs**
  - **All current pharmacotherapies target the same mechanism of action**
    - MDD/TRD likely a heterogeneous disease that goes beyond monoamines
  - **Only 1 pharmacotherapy (olanzapine/fluoxetine combination) approved for TRD[2]**
    - Significant weight gain, movement disorder side effects[3]
  - **Only 1 somatic therapy (Transcranial Magnetic Stimulation) approved for TRD**
    - Limited data on efficacy[4] and long-term benefit[5]
  - **Other treatments do not meet patient needs (e.g., Electroconvulsive therapy)**
    - Anesthesia required, potential for severe side effects like memory loss

1. Moser G, Pink Sheet: Major Depressive Disorder Patients Emphasize Long-Term Nature of Disease In Feedback Meeting, 2018; 2. Sanacora G, et al. *Neuropharmacology*. 2012; 62(1):63-77; 3. Philip NS, et al. *Expert Opin Pharmacother*. 2010 Apr; 11(5): 709–722; 4. Work Group on Major Depressive Disorder, Gelenberg, AJ, Freeman, MP, et al. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd. Washington, DC: American Psychiatric Association; 2010; 5. Ont Health Technol Assess Ser. 2016; 16(5): 1–66.

Summary

- **TRD is chronic, recurrent, and difficult to treat**
  - TRD limits the health, productivity, quality of life, and longevity for 2 million Americans[1,2,3]
  - The scale of our need for new drugs: >200,000 US patients were hospitalized for depression in 2016[4]
- **Time is against our patients**
  - All current therapies target the monoamine pathway and have a slow onset of action[3]
  - We continue to offer drugs that essentially do the same thing, expecting a different outcome
  - Patients with TRD need an alternative treatment with a novel mechanism of action that acts rapidly, has a manageable profile, and keeps patients well

1. WHO News Release 30 Mar 2017; 2. NIMH Mental Health Website release November 2017; 3. Rush AJ et al. *Am J Psychiatry*. 2006;163(11):1905-1917;
4. H-CUP 2016 Survey: https://hcup-us.ahrq.gov/db/nation/nrd/stats/MaskedStats_NRD_2016_Severity.PDF

Program Design and Efficacy

Jaskaran Singh, MD

Clinical Leader, Esketamine-TRD
Janssen Research and Development

NIMH Proof of Concept Study with IV Ketamine

ORIGINAL ARTICLE

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

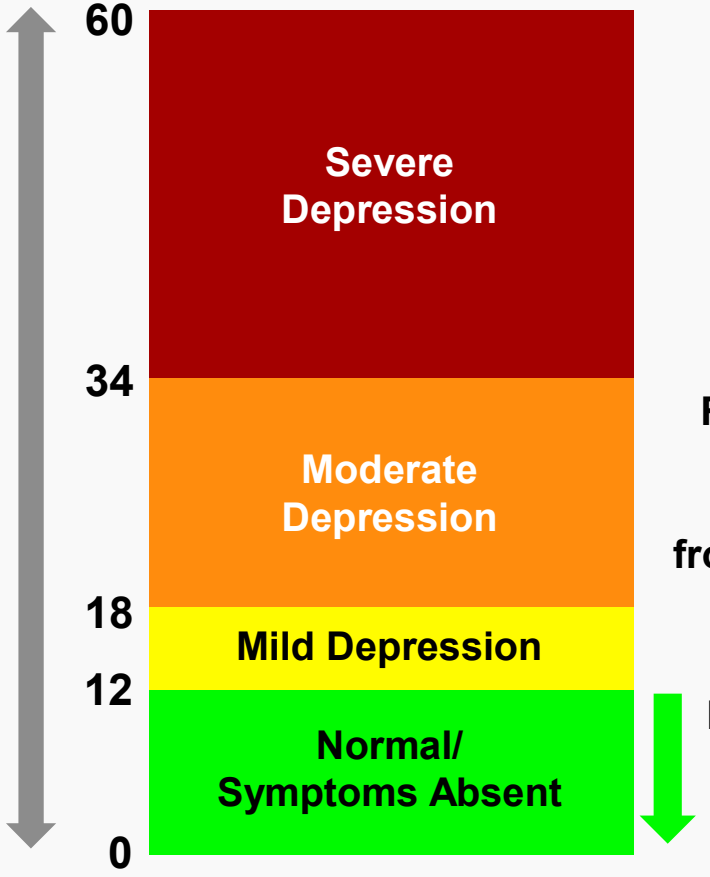
Carlos A. Zarate, Jr, MD; Jaskaran B. Singh, MD; Paul J. Carlson, MD; Nancy E. Brutsche, MSN; Rezvan Ameli, PhD; David A. Luckenbaugh, MA; Dennis S. Charney, MD; Husseini K. Manji, MD, FRCPC

Zarate CA Jr, Singh JB, Carlson PJ, et al. *Arch Gen Psychiatry* 2006; 63:856–864

Montgomery–Asberg Depression Rating Scale (MADRS)

- **MADRS: the primary outcome measure**
- **10 items, each scored 0-6**
  1. Apparent sadness
  2. Reported sadness
  3. Inner tension
  4. Reduced sleep
  5. Reduced appetite
  6. Concentration difficulties
  7. Lassitude
  8. Inability to feel
  9. Pessimistic thoughts
  10. Suicidal thoughts

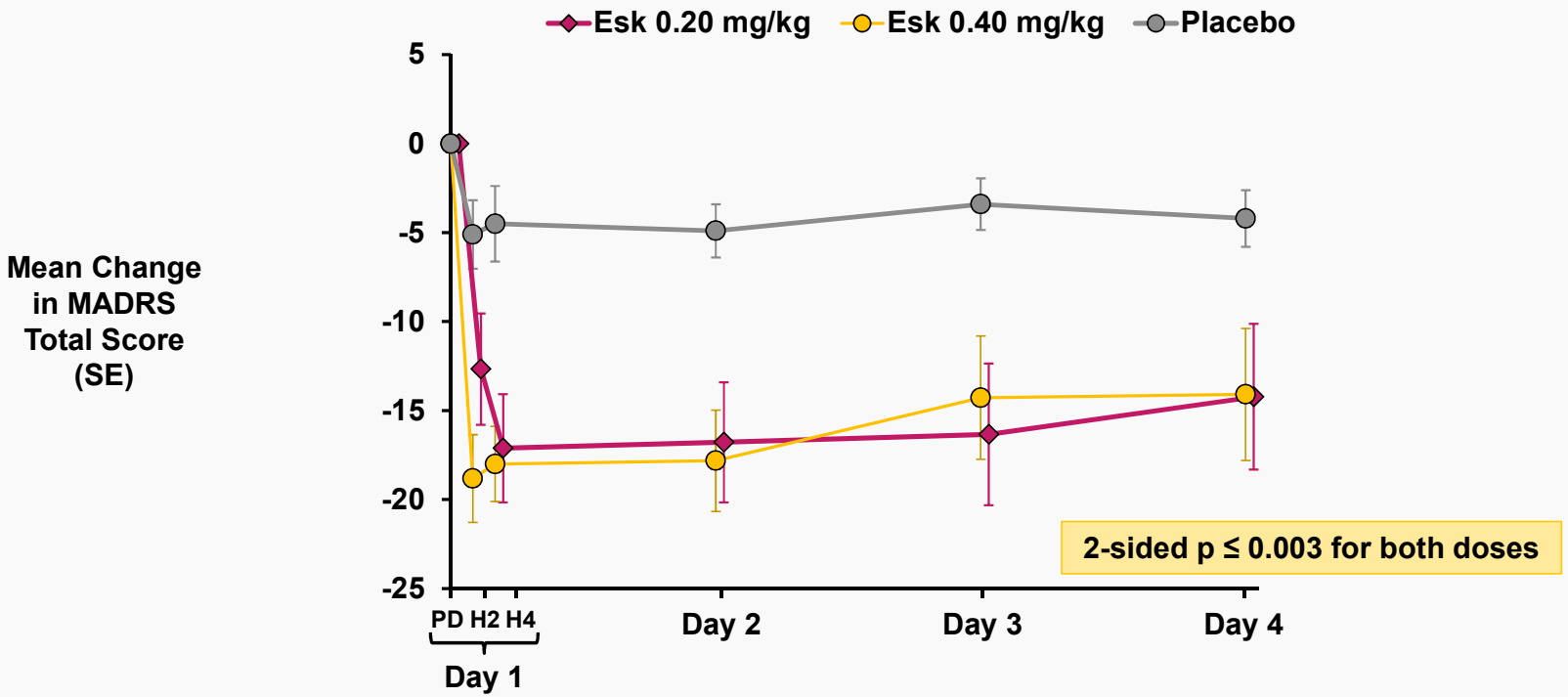
Overall Score Range from 0 to 60



Response: 50% reduction from baseline

Remission Criteria of ≤12

Phase 2 Study IV Esketamine
Study 2001

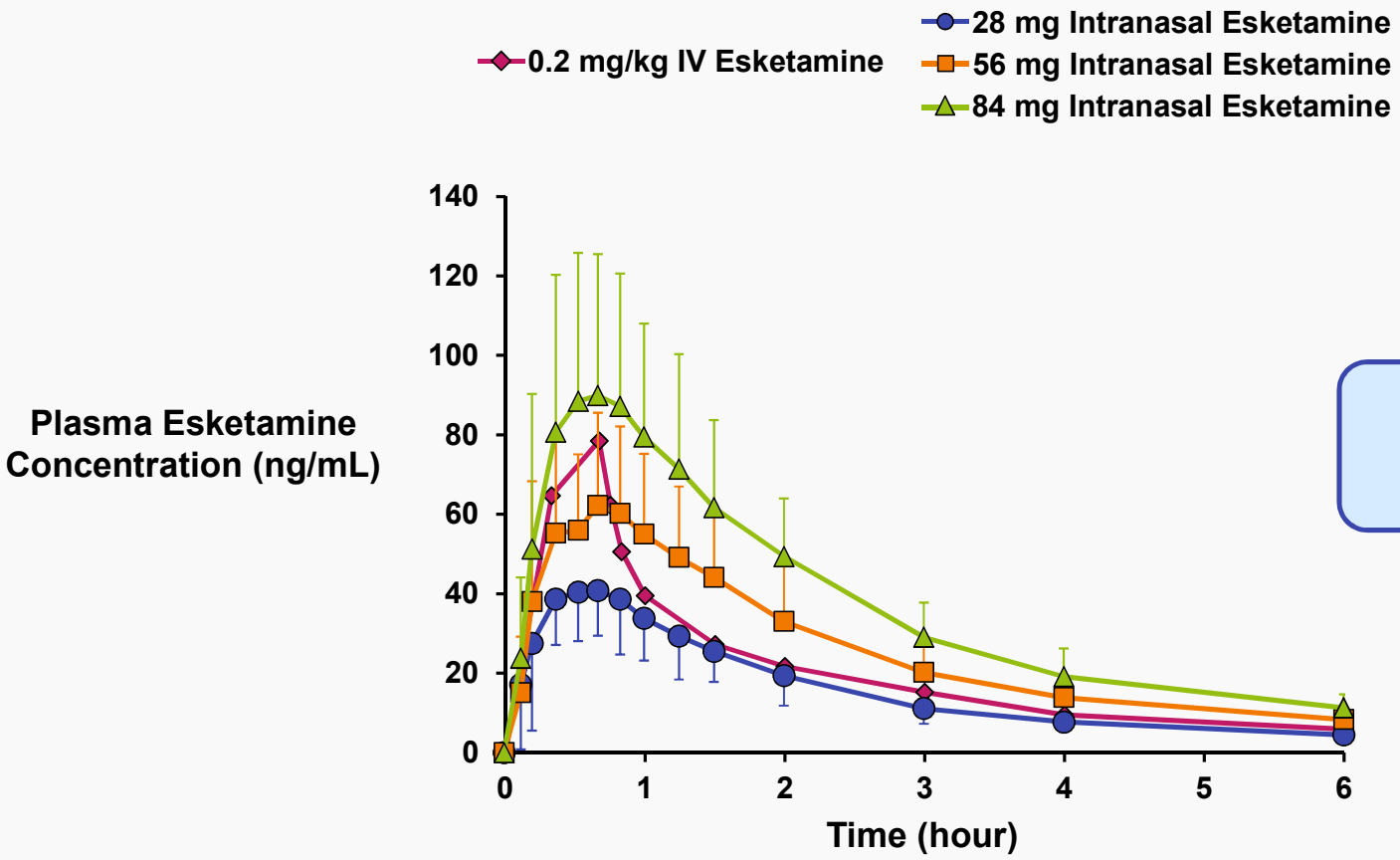


No. of Patients						
Placebo	10	10	10	10	10	10
Esk 0.20 mg/kg	9	9	9	9	9	9
Esk 0.40 mg/kg	11	11	11	11	11	11

Singh JB, Fedgchin M, Daly E, et al. *Biol Psychiatry*. 2016 Sep 15;80(6):424-431.

Pharmacokinetics of Intranasal Esketamine

Study 2001 and Study 1002



Rapidly absorbed (Tmax ~40 minutes), readily bioavailable

Pharmacokinetics of Intranasal Esketamine

- **No dose adjustment needed for:**
  - Body weight
  - Sex
  - Renal impairment
  - Hepatic impairment
  - Nasal congestion

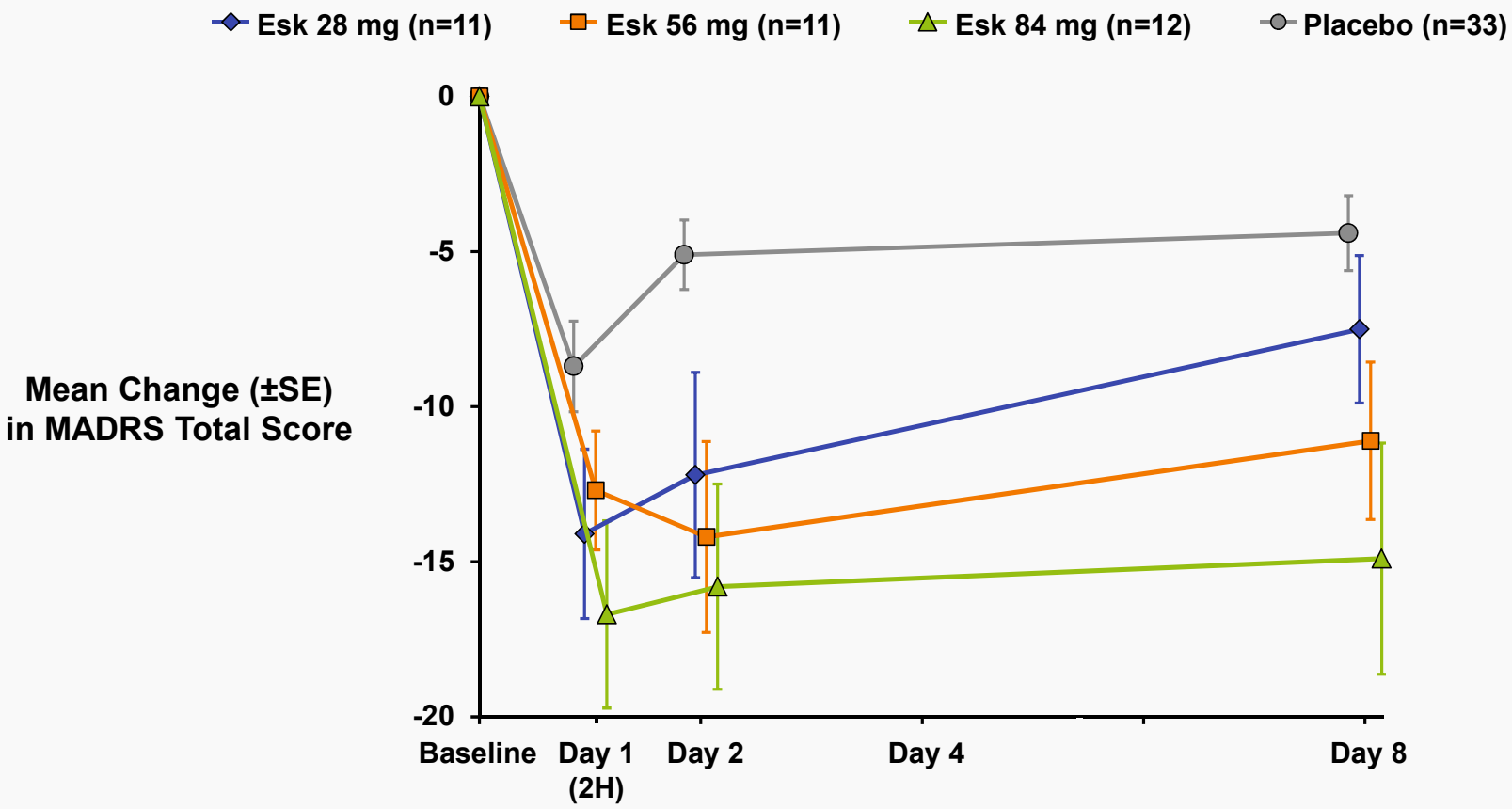
- **No clinically relevant pharmacokinetic drug-drug interactions with CYP450 inhibitors and inducers**

Phase 2 Study Dose Frequency
Study 2002

- **Published data showed that the antidepressant effect from a single 0.5 mg/kg IV dose of ketamine lasts about 5 days**
- **In Study 2002[1], we assessed efficacy of IV ketamine 2 and 3 times per week**
- **Both dosing frequencies had positive and similar results**
- **Therefore, the lower frequency of twice weekly was selected**

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

Phase 2 Dose Response Intranasal Esketamine
SYNAPSE (Study 2003): Period 1, Panel A



Daly EJ, Singh JB, Fedgchin M, et al. *JAMA Psychiatry*. 2018 Feb 1;75(2):139-148

Short-Term Clinical Studies
TRANSFORM-1 (3001), -2 (3002), and -3 (3005)

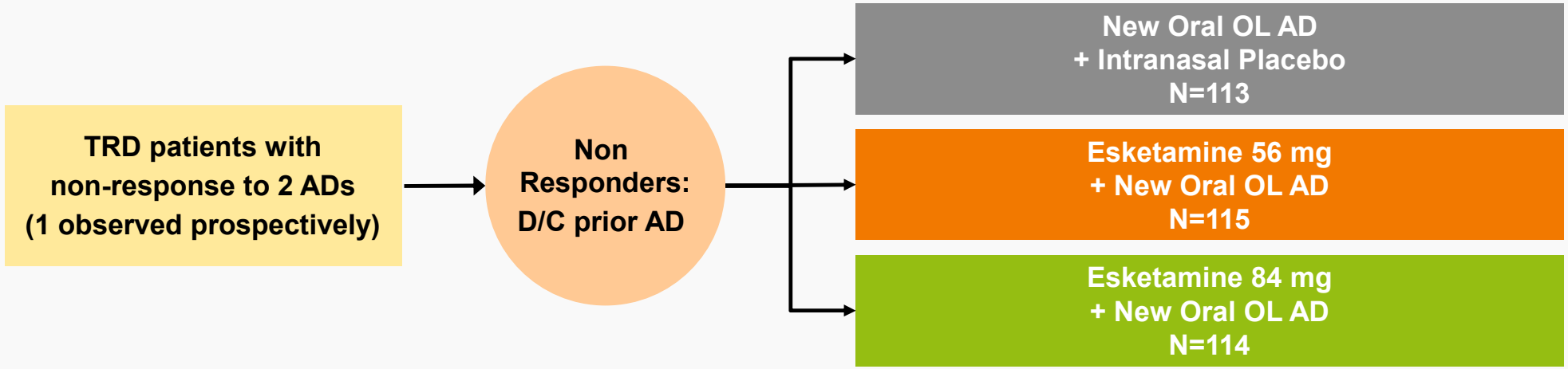
Important Characteristic of Study Design

- **Switch to *new* oral antidepressant (4 choices) in all arms**
  - Consistent with treatment guidelines
  - Evaluate maintenance of effect with oral antidepressant alone

Important Characteristics of Study Design

- **Twice weekly visits, high interaction with clinician**
- **Blinding**
  - Independent, blinded, remote telephone MADRS predose assessments
  - Bittering agent in placebo nasal spray

Fixed Dose Short-Term Study Design
TRANSFORM-1 (3001)



Screening

4 weeks

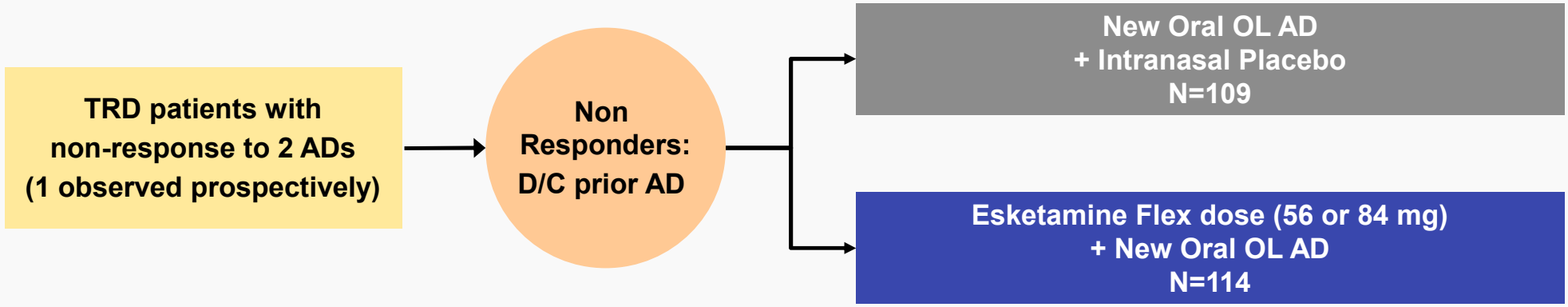
Double-blind Induction Phase
Nasal Spray Dose Frequency: 2x per week

4 weeks

Included interim analysis for sample size re-estimation

AD=antidepressant; D/C=discontinued; OL=open label

Flexible Dose Short-Term Study Design
TRANSFORM-2 (3002)

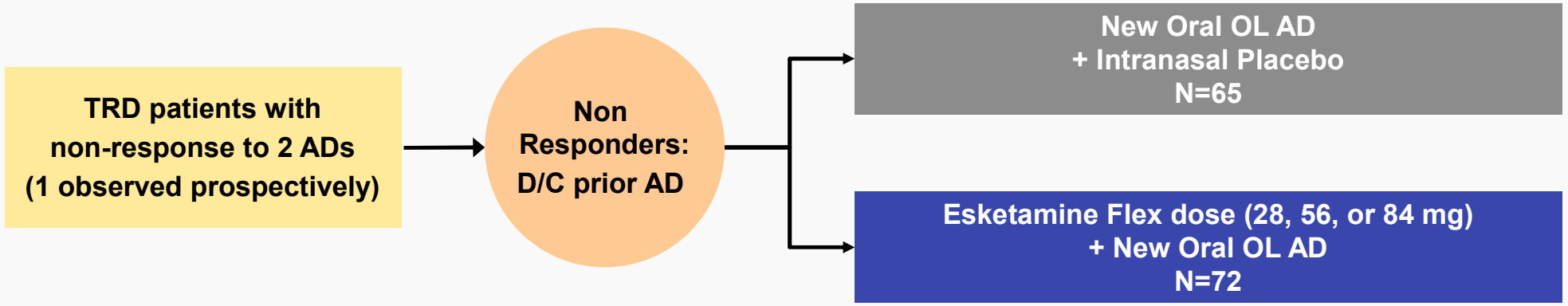


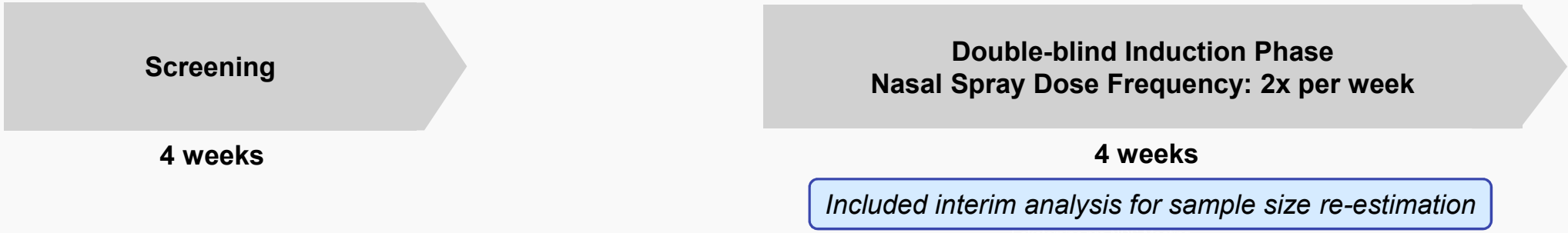
4 weeks

4 weeks

AD=antidepressant; D/C=discontinued; OL=open label

Flexible Dose Short-Term Study Design – Age ≥65 Years
TRANSFORM-3 (3005)





AD=antidepressant; D/C=discontinued; OL=open label

Study Objectives

- **Primary Objective**
  - Efficacy of esketamine + new AD vs. new AD + placebo as measured by change in MADRS Total Score from baseline to Day 28

- **Key Secondary Objectives (TRANSFORM-1 and -2 only)**
  - Onset of clinical response by Day 2 AND sustained through Day 28
  - Change in functioning and disability (SDS)
  - Change in patient-reported depressive symptoms (PHQ-9)

Short-term Studies: Demographics

	TRANSFORM-1 N=342	TRANSFORM-2 N=223	TRANSFORM-3 N=137
Sex, %			
Female	**70.5**	**61.9**	**62.0**
Age, years			
Mean (SD)	**46.3 (11.19)**	**45.7 (11.89)**	**70.0 (4.52)**
Age when diagnosed with MDD, years			
Mean (SD)	**31.4 (12.54)**	**33.7 (12.86)**	**43.1 (16.18)**

Average duration of current episode >1 year

35-50% across studies had non-response to ≥3 ADs

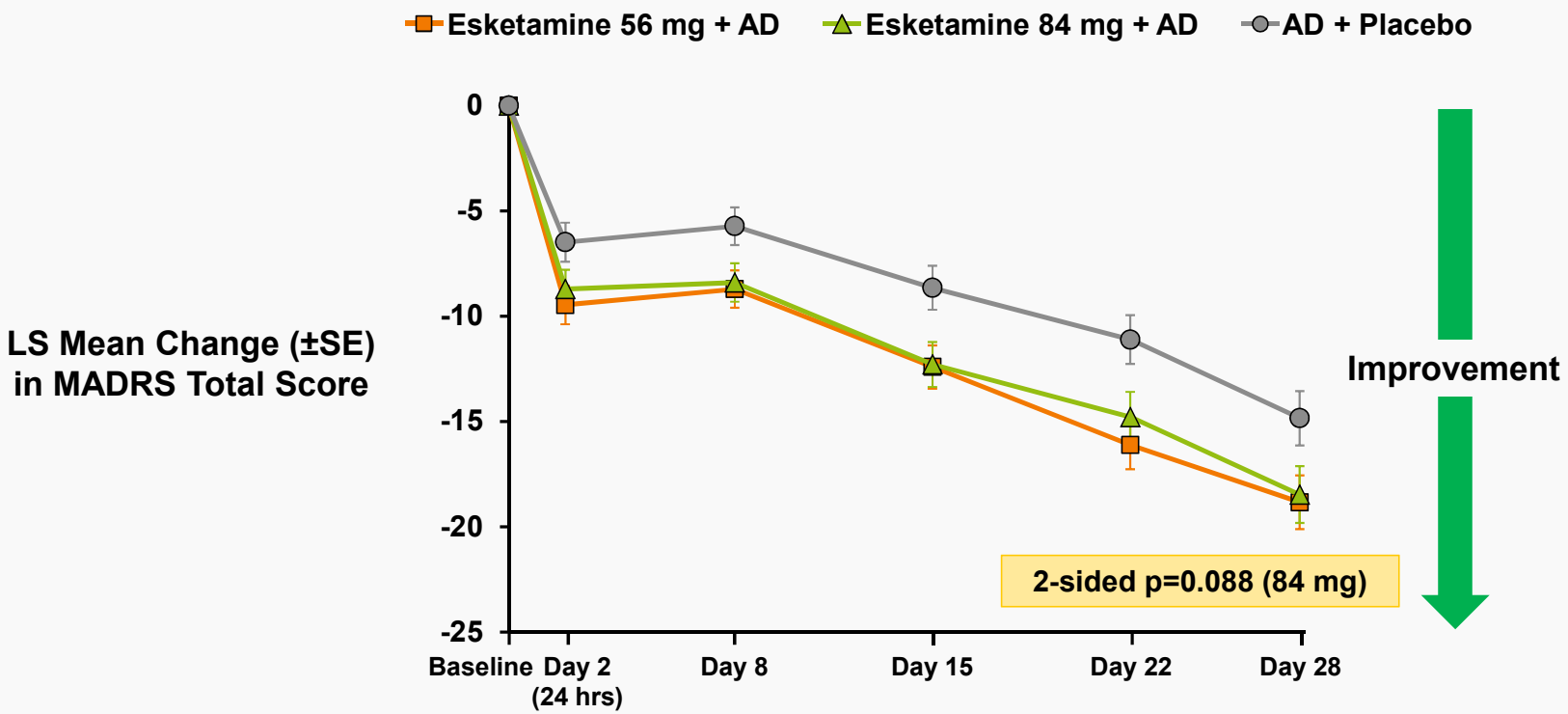
Based on Full Analysis Set
MDD=Major Depressive Disorder

Depression Severity at Baseline

	TRANSFORM-1 N=342	TRANSFORM-2 N=223	TRANSFORM-3 N=137
Baseline MADRS total score			
Mean (SD)	37.6 (5.51)	37.1 (5.67)	35.2 (6.16)
Median (range)	37 (18; 53)	37 (21; 52)	36 (19; 51)
Severe (%)	72.5	66.4	56.2
Baseline SDS[a]			
Mean (SD)	24.4 (4.19)	24.1 (4.22)	22.3 (5.36)
Median (range)	25.0 (6; 30)	25.0 (11; 30)	24.0 (8; 30)
Health Status Index[b]			
Mean (SD)	0.52 (0.21)	0.52 (0.21)	0.61 (0.23)
Median (range)	0.54 (-0.06; 0.93)	0.50 (0.04; 0.93)	0.63 (0.07; 0.95)

Full Analysis Set
a. SDS total score ranges from 0 to 30; N = 215 (TRANSFORM-2), N = 320 (TRANSFORM-1), N = 89 (TRANSFORM-3)
b. Health Status Index ranges from -0.148 to 0.949 and is anchored at 0 (health state valued equal to dead) and 1 (full health)

Primary Endpoint: Least Squares Mean Changes in MADRS Total Score Over Time MMRM
TRANSFORM-1 (3001)



No. of Patients						
Esk 56 mg + AD	115	105	114	110	107	111
Esk 84 mg + AD	114	104	107	99	96	98
AD + Placebo	113	101	111	106	105	108

MADRS Total Score: Change from Baseline to Day 28
TRANSFORM-1 (3001)

	Intranasal Esk 56 mg + AD	Intranasal Esk 84 mg + AD	AD + Intranasal Placebo
Baseline, N	115	114	113
Mean (SD)	37.4 (4.76)	37.8 (5.58)	37.5 (6.16)
Day 28, N	111	98	108
Mean (SD)	18.5 (13.25)	19.4 (13.89)	22.8 (13.68)
Change from Baseline to Day 28			
Mean (SD)	-19.0 (13.86)	-18.8 (14.12)	-14.8 (15.07)
MMRM Analysis			
Diff. of LS means (Esk+AD minus AD + Placebo)	-4.1	-3.2	
95% confidence interval on diff.	-7.67; -0.49	-6.88; 0.45	
2-sided p-value	0.027*	0.088	

*Nominal

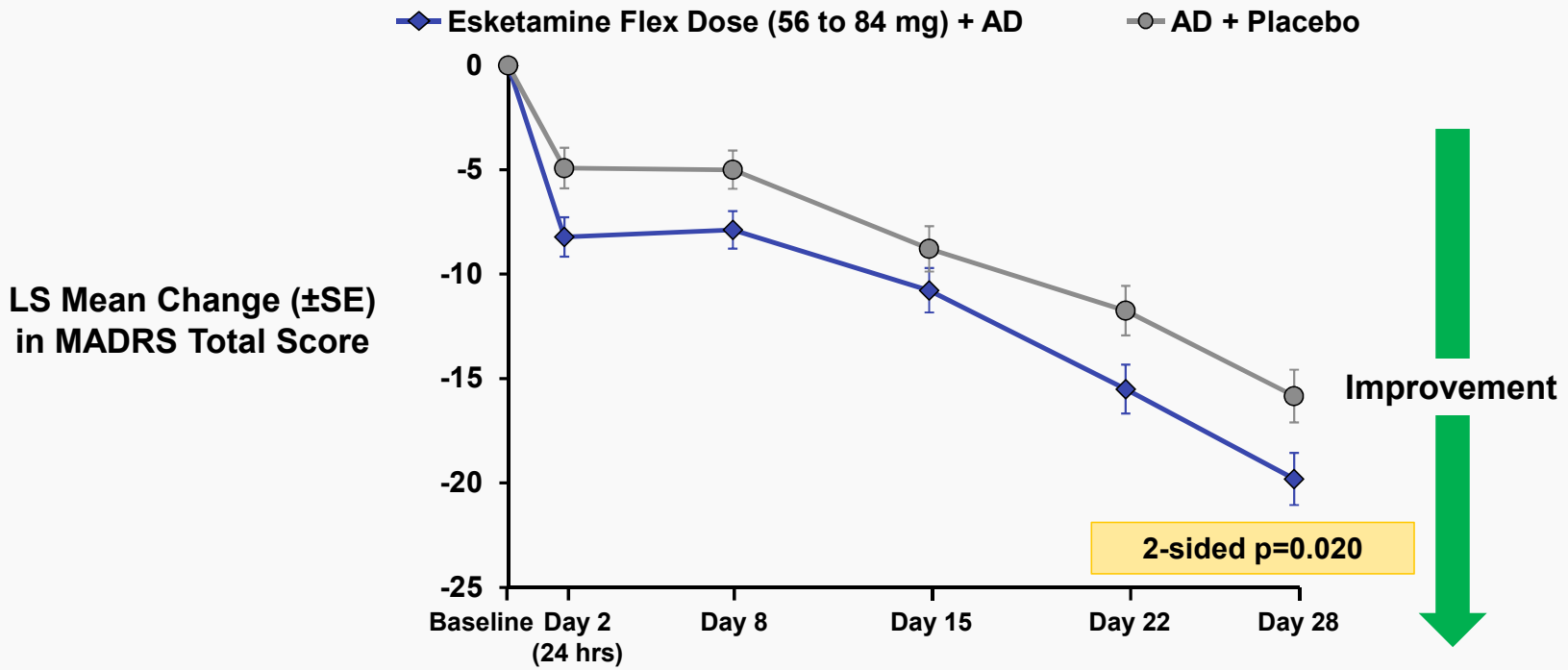
Completion and Withdrawal Information (All Randomized Patients)
TRANSFORM-1 (3001)

Double-Blind Induction Phase	Intranasal Esk 56 mg + AD N=117 n (%)	Intranasal Esk 84 mg + AD N=116 n (%)	AD + Intranasal Placebo N=113 n (%)
Completed	111 (94.9)	97 (83.6)	107 (94.7)
Withdrawn	6 (5.1)	19 (16.4)	6 (5.3)
Adverse event	1 (0.9)	7 (6.0)	2 (1.8)
Lack of efficacy	1 (0.9)	1 (0.9)	0
Lost to follow-up	0	1 (0.9)	0
Protocol violation	2 (1.7)	1 (0.9)	1 (0.9)
Withdrawal by patient	1 (0.9)	5 (4.3)	1 (0.9)
Other	1 (0.9)	4 (3.4)	2 (1.8)

11 of 19 patients who withdrew only received the 56 mg dose

Primary Endpoint: Least Squares Mean Changes in MADRS Total Score Over Time MMRM

TRANSFORM-2 (3002)

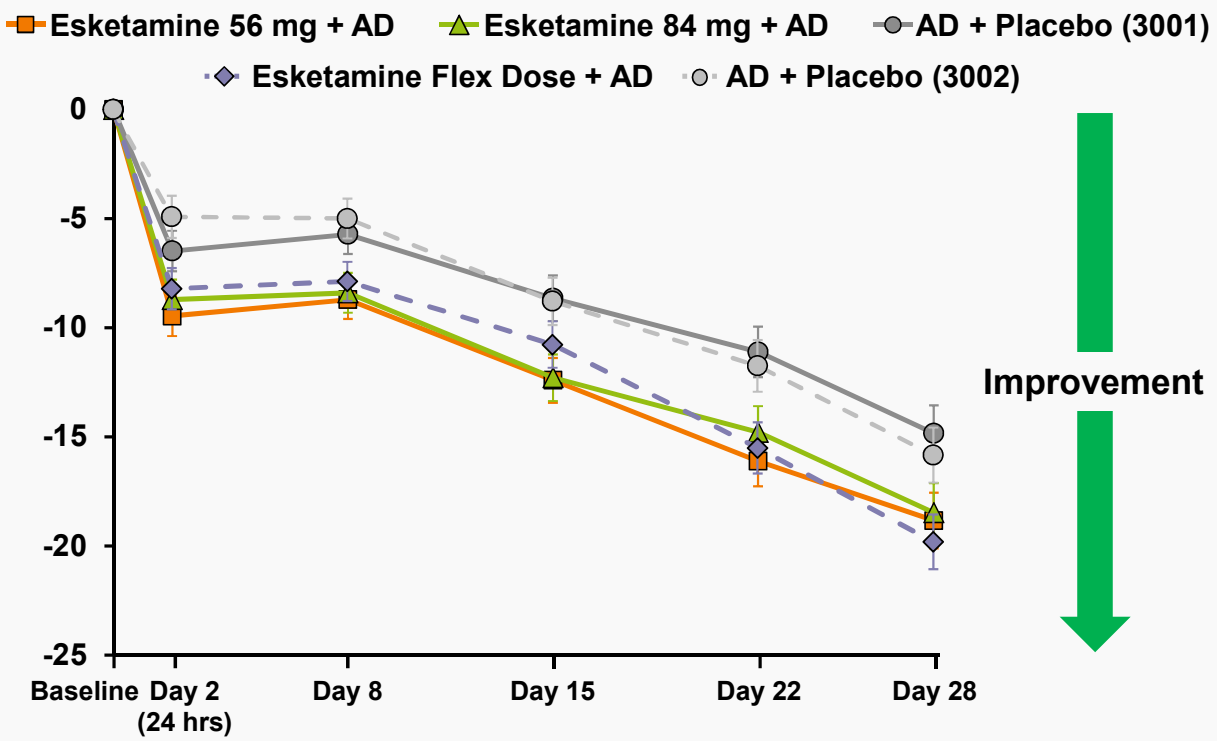


No. of Patients						
Esketamine + AD	114	109	109	107	103	101
AD + Placebo	109	102	105	102	104	100

MADRS Total Score: Change from Baseline to Day 28 (MMRM)
TRANSFORM-2 (3002)

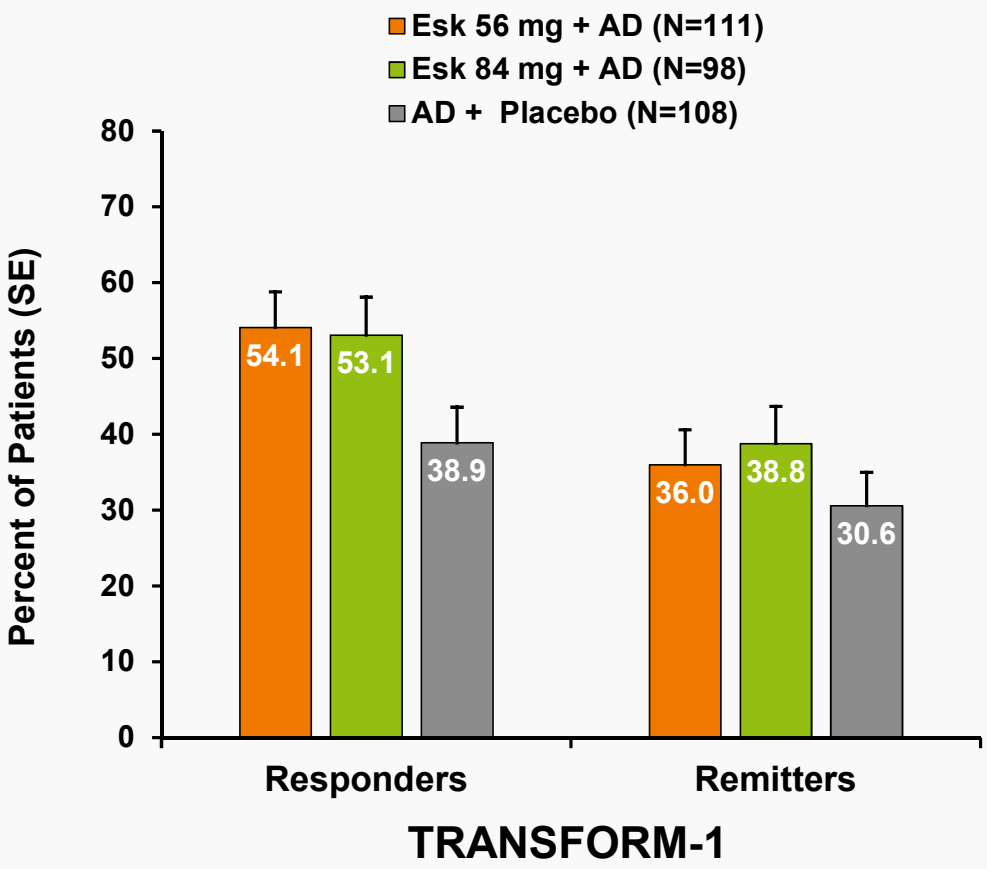
	Esketamine + AD	AD + Placebo
Baseline, N	114	109
Mean (SD)	37.0 (5.69)	37.3 (5.66)
Day 28, N	101	100
Mean (SD)	15.5 (10.67)	20.6 (12.70)
Change from baseline to Day 28		
Mean (SD)	-21.4 (12.32)	-17.0 (13.88)
MMRM analysis		
Diff. of LS means (SE) (Esk + AD minus AD + placebo)	-4.0 (1.69)	
95% confidence interval on difference	-7.31; -0.64	
2-sided p-value	0.020	

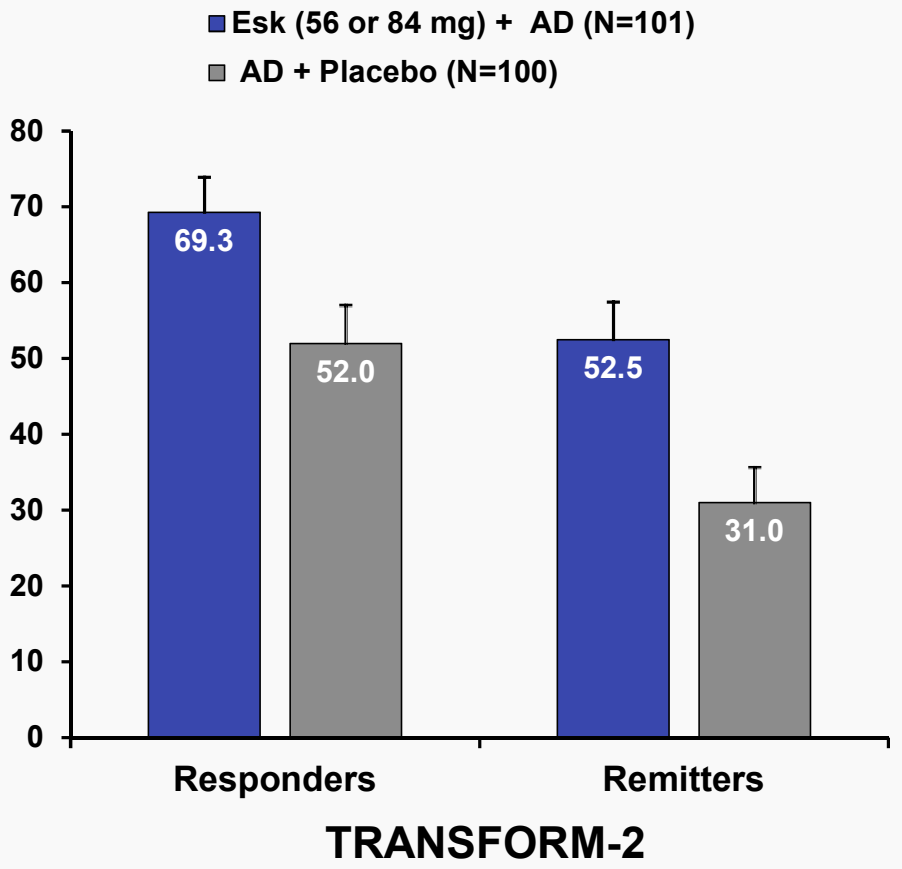
Primary Endpoint: Least Squares Mean Changes in MADRS Total Score Over Time MMRM
TRANSFORM-1 (3001) and -2 (3002)



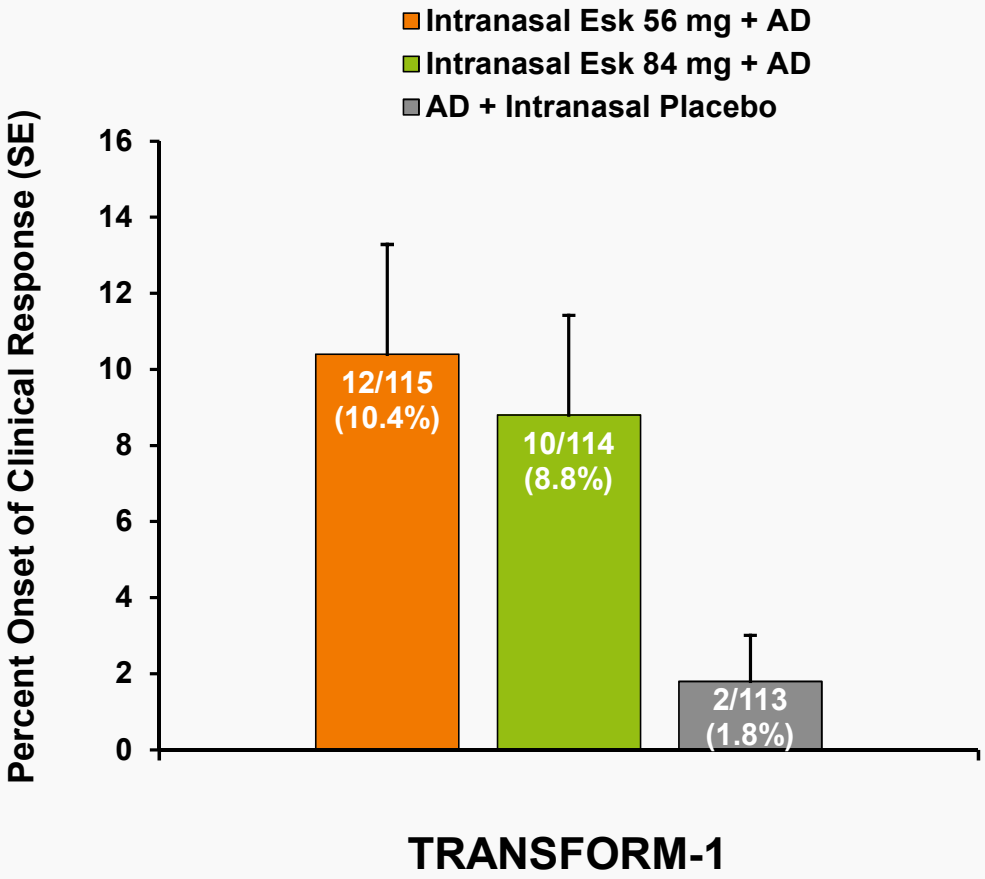
Two-thirds of patients in TRANSFORM-2 were on 84 mg at Day 28

Response and Remission Rates at Day 28
TRANSFORM-1 (3001) and -2 (3002)

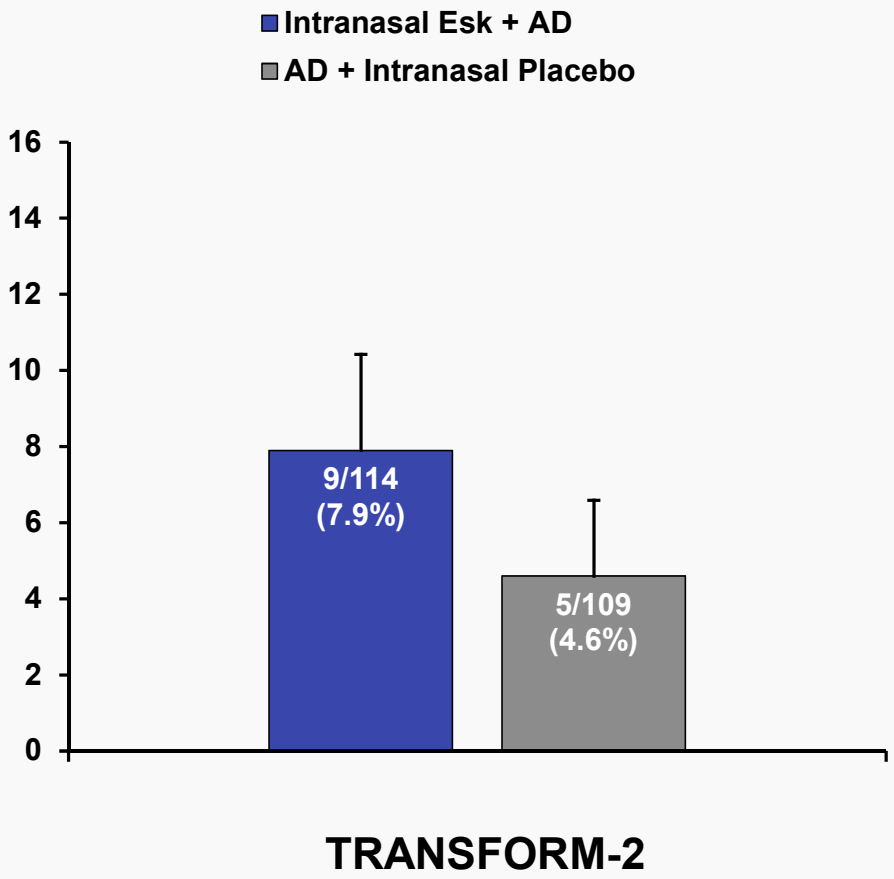




Key Secondary Endpoint: Onset of Clinical Response – ≥50% Improvement by Day 2 and Sustained Through Day 28



TRANSFORM-1



TRANSFORM-2

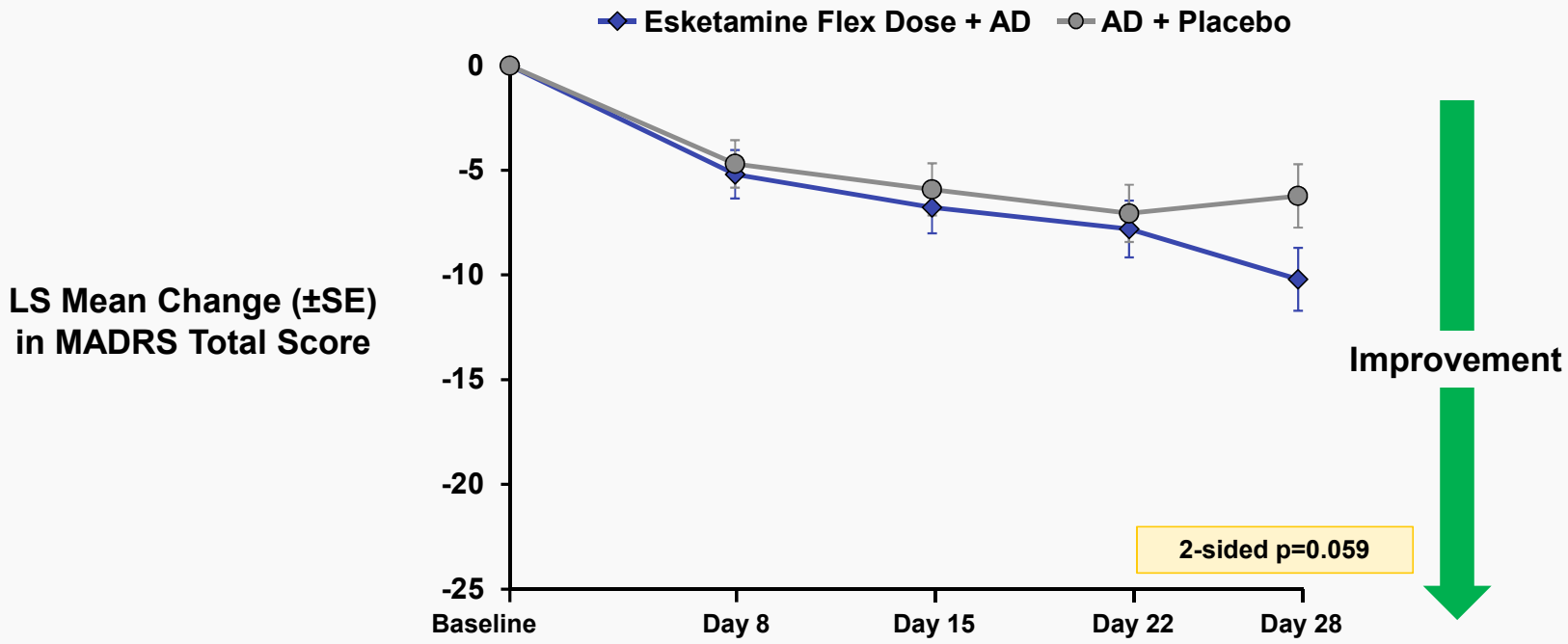
CC-40

MADRS Total Score: Change from Baseline to Day 28
TRANSFORM-3 (3005) (Age ≥65)

	Intranasal Esk + AD	AD + Intranasal Placebo
Baseline, N	72	65
Mean (SD)	35.5 (5.91)	34.8 (6.44)
Day 28, N	63	60
Mean (SD)	25.4 (12.70)	28.7 (10.11)
Change from baseline to Day 28		
N	63	60
Mean (SD)	-10.0 (12.74)	-6.3 (8.86)
MMRM analysis		
Diff. of LS means (Esk + AD minus AD + placebo)	-3.6	
95% confidence interval on diff.	-7.20; 0.07	
2-sided p-value	0.059	

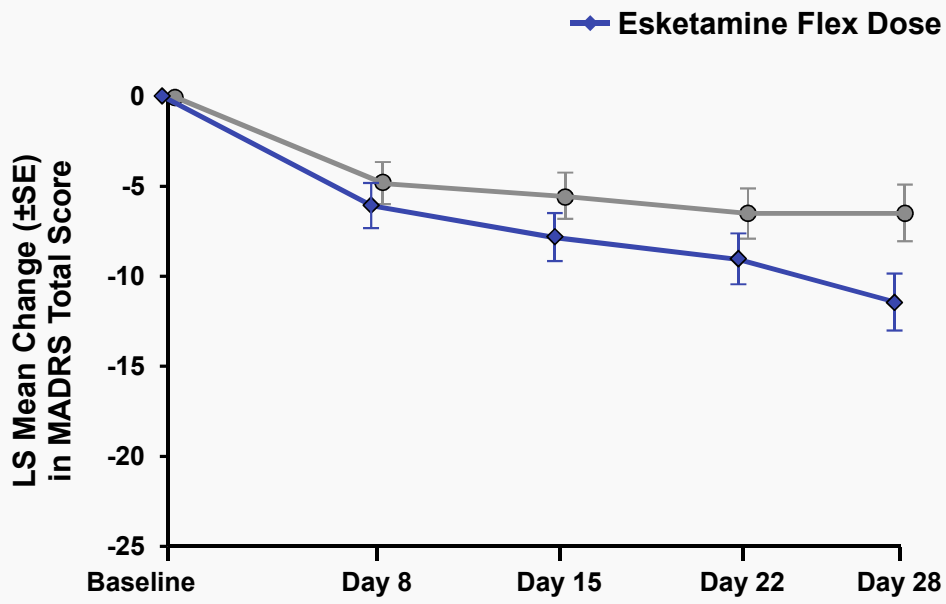
Primary Endpoint: Least Squares Mean Changes in MADRS Total Score Over Time MMRM

TRANSFORM-3 (3005)



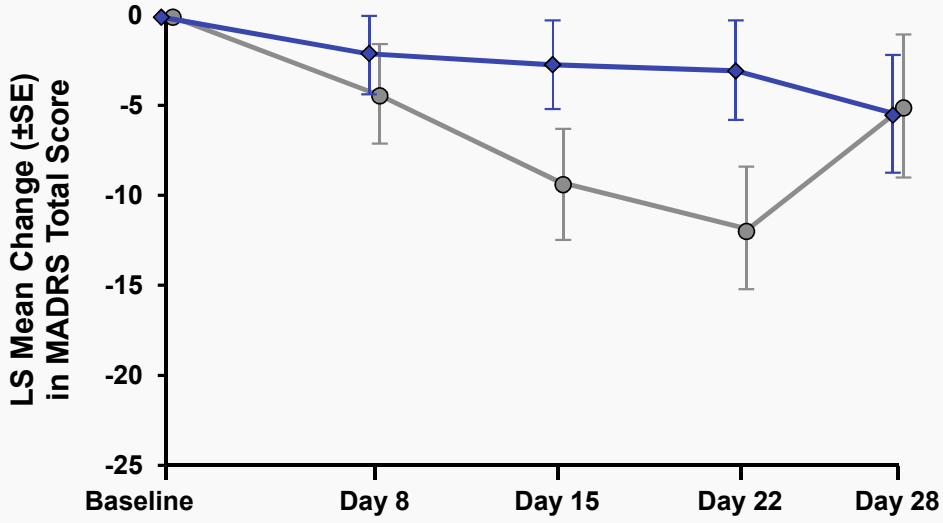
No. of Patients					
Esketamine + AD	72	66	68	60	63
AD + Placebo	65	63	62	56	60

Least Squares Mean Changes in MADRS Total Score Over Time by Age Group (MMRM)
TRANSFORM-3 (3005)



No. of Patients					
Esketamine + AD	59	54	57	50	53
AD + Placebo	57	56	54	49	53

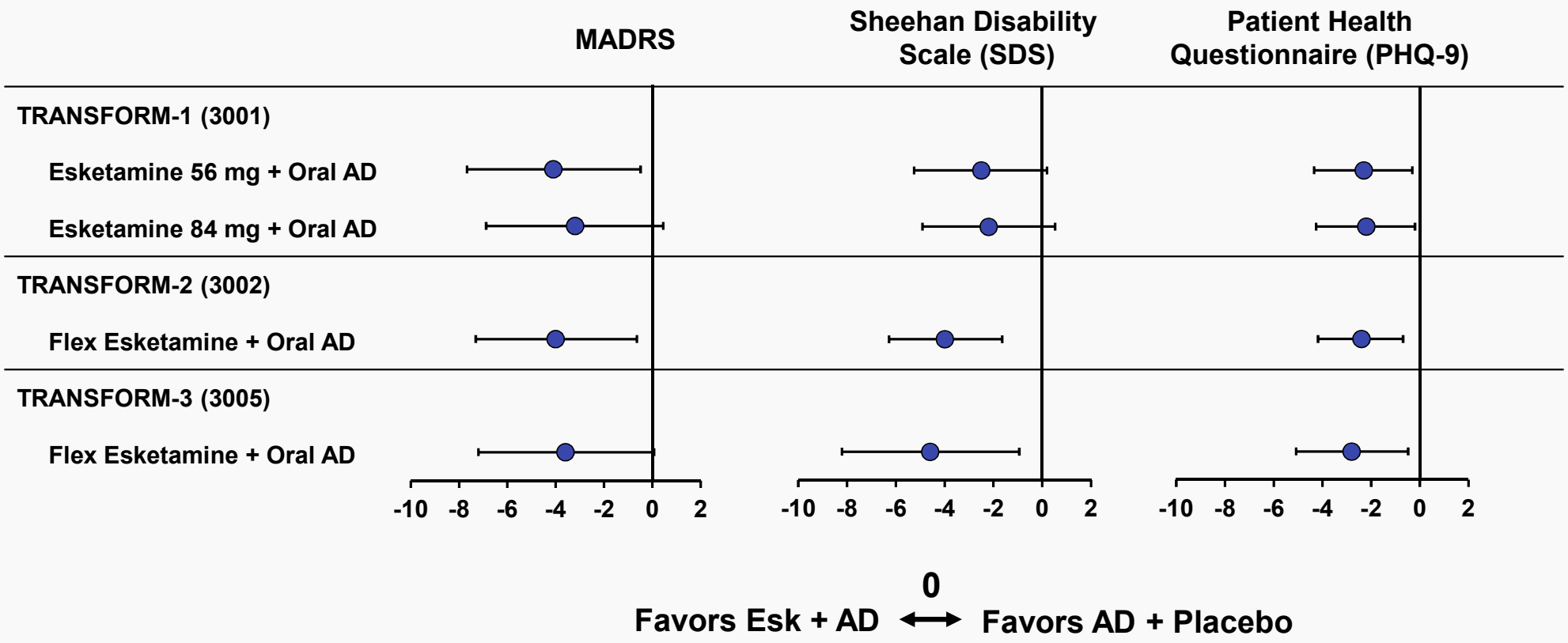
65-74 Years Old



13	12	11	10	10
8	7	8	7	7

≥75 Years Old

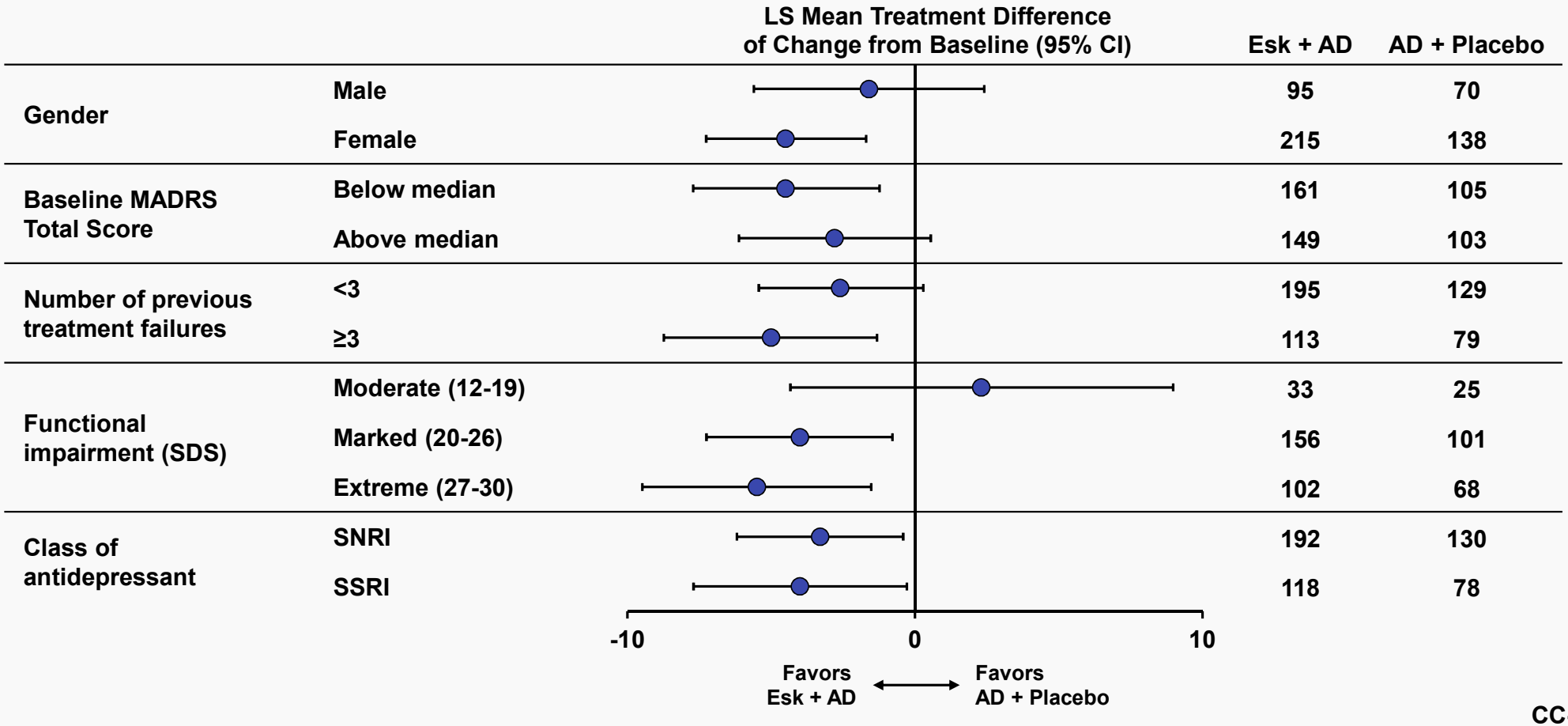
Primary and Key Secondary Endpoints: LS Mean Difference in Change from Baseline



Left and right of 0: better than AD + placebo, worse than AD + placebo, respectively

MADRS Total Score: LS Mean Treatment Difference of Change from Baseline to Day 28 MMRM Across Subgroups

Pooled TRANSFORM-1 (3001) and 2 (3002)



Long-Term Maintenance Study
SUSTAIN-1 (3003)

Study Objectives
SUSTAIN-1 (3003)

- **Primary Objective**
  - Efficacy of esketamine plus AD in delaying relapse of depressive symptoms in stable remitters

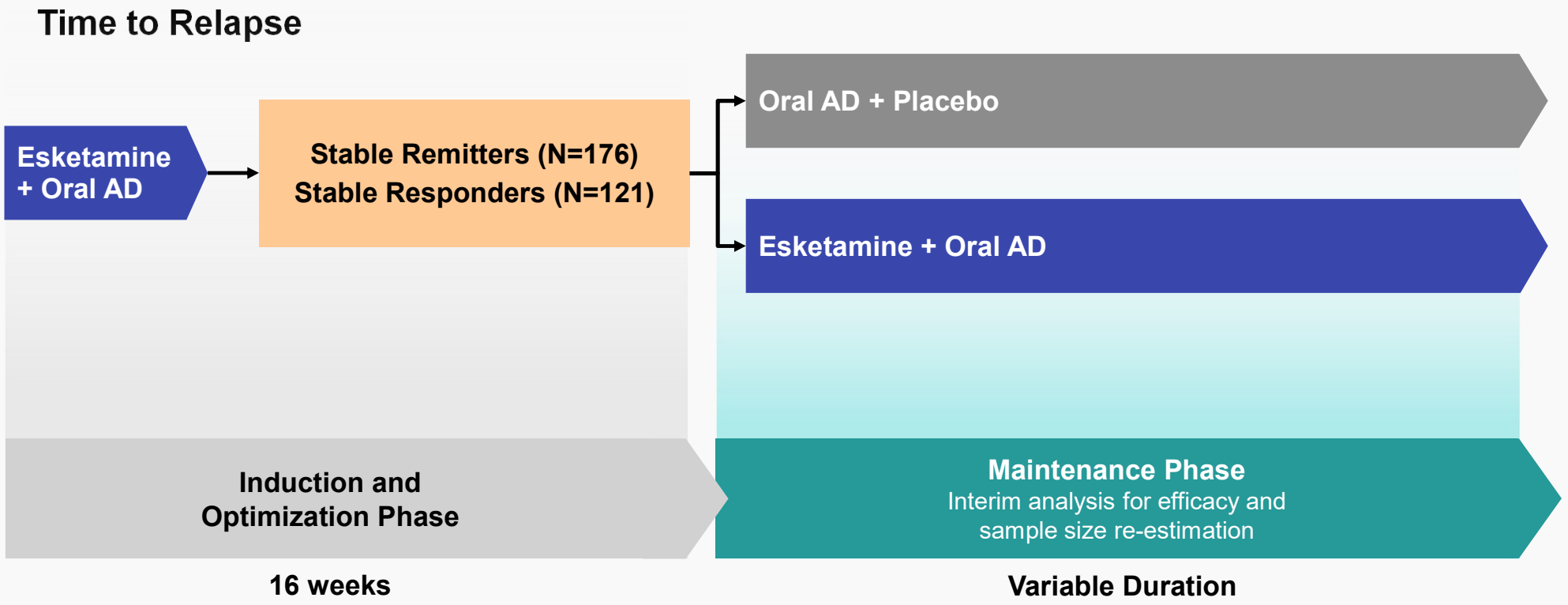
- **Secondary Objectives**
  - Efficacy of esketamine plus AD in delaying relapse of depressive symptoms in stable responders (but not remitters)

Stable Remission and Stable Response Definitions
SUSTAIN-1 (3003)

- **Stable Remission**
  - MADRS total score ≤12 for at least 3 of the last 4 weeks prior to randomization

- **Stable Response**
  - ≥50% reduction in the MADRS total score from baseline in each of the last 2 weeks prior to randomization, but does not meet criteria for stable remission

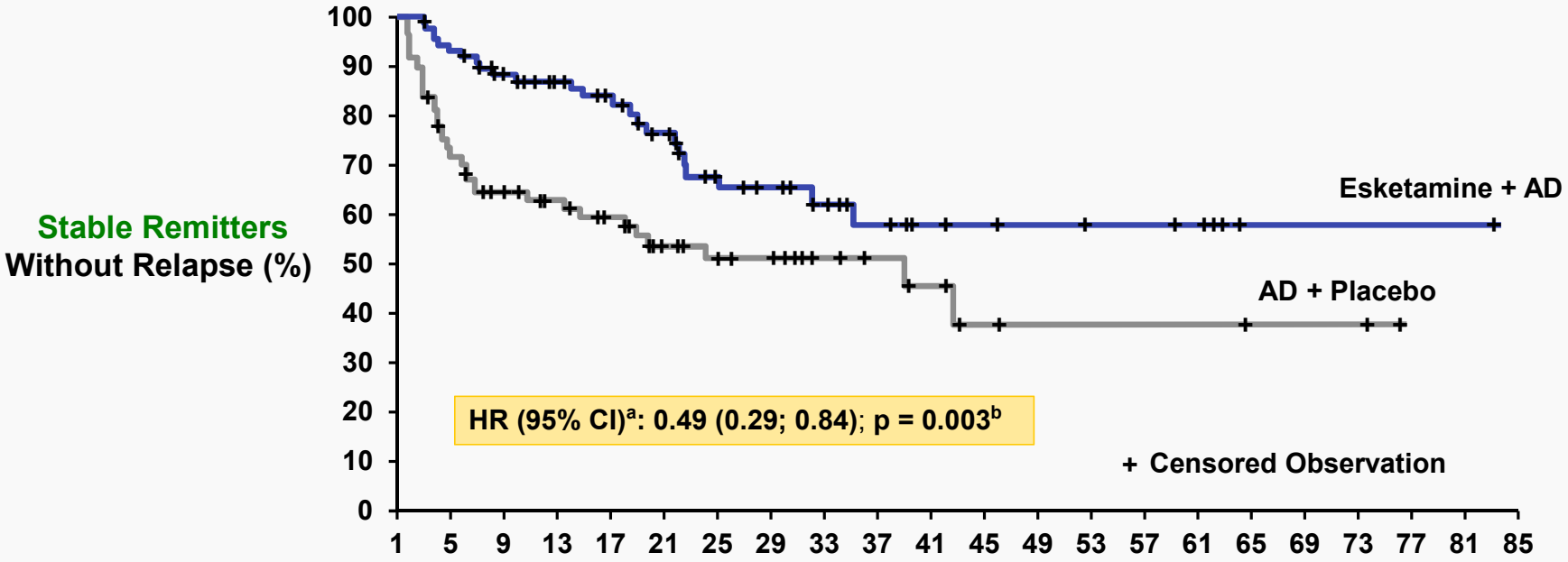
Study Design – Maintenance Phase
SUSTAIN-1 (3003)



Definition of Relapse

- **MADRS total score ≥22 for 2 consecutive weeks**
- **Clinically relevant events**
  - Hospitalization for worsening depression or suicide prevention
  - Attempted or completed suicide
  - Other clinically relevant event suggestive of a relapse
    - Reviewed by independent blinded adjudication committee

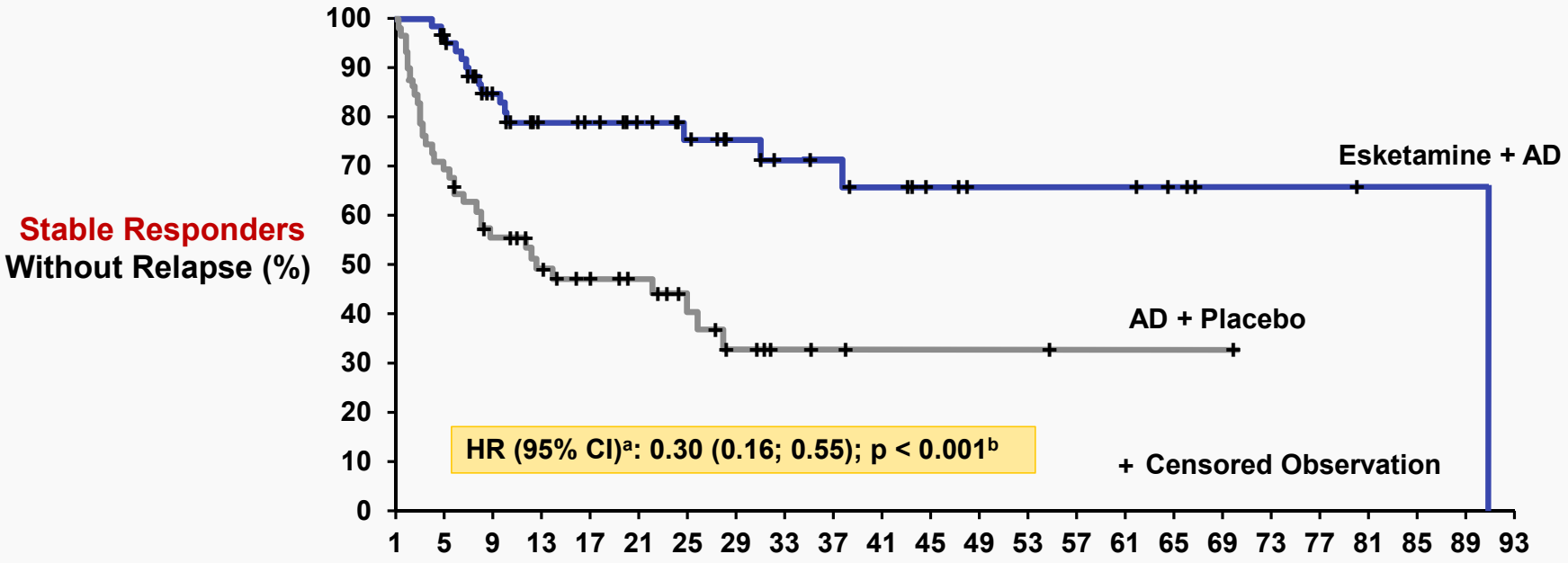
Stable Remitters who Remained Relapse Free
SUSTAIN-1 (3003)



Patients at risk																					
Esketamine + AD	89	83	68	56	47	38	28	23	18	14	10	8	7	6	6	5	1	1	1	1	1	0
AD + Placebo	86	62	47	39	32	24	21	19	11	9	7	4	3	3	3	3	2	2	2	0	0	0

a. Hazard ratio and CI are weighted estimates based on Wassmer (2006) and calculated using R
b. Two-sided P-value is based on the final test statistic, which is a weighted combination of the log-rank test statistics calculated on the interim full analysis set and on the full analysis set in stable remitters

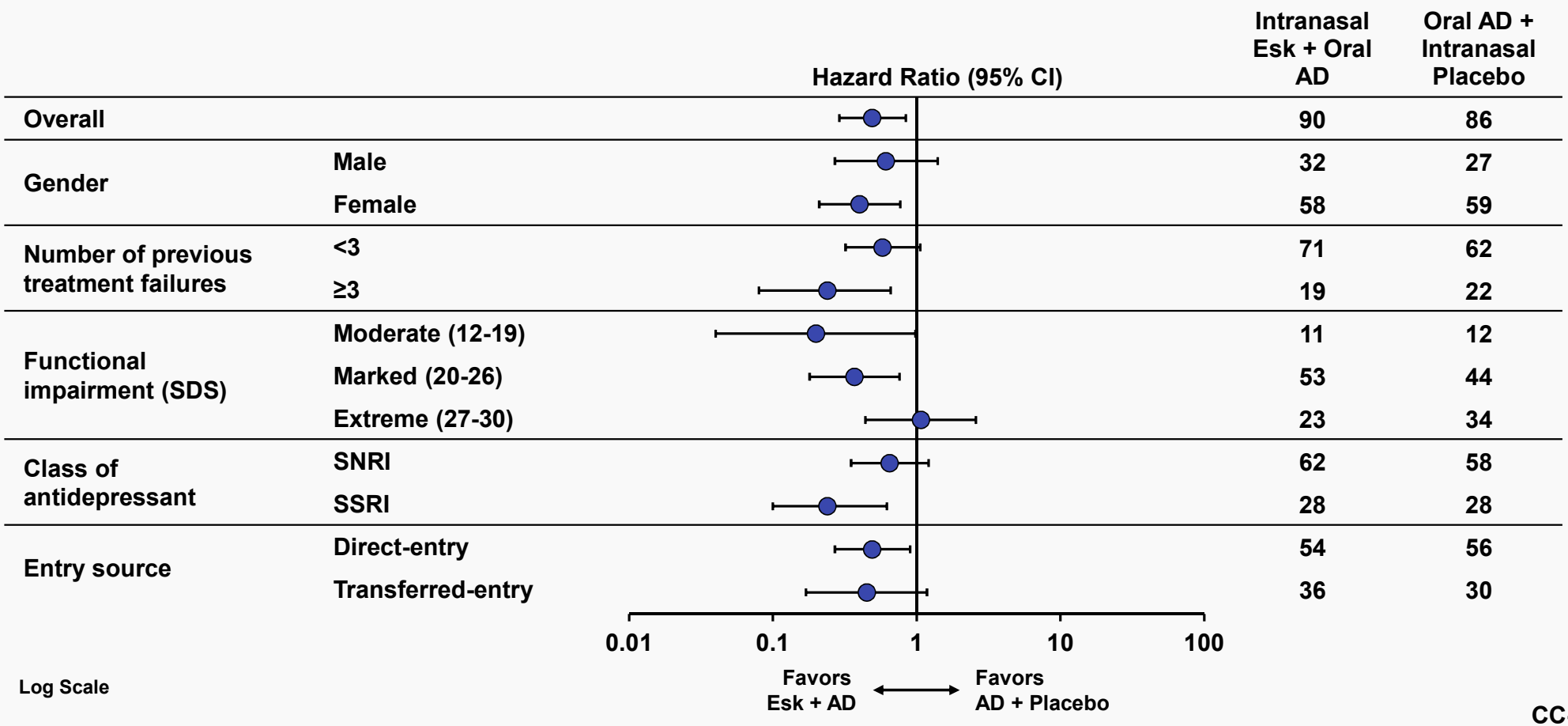
Stable Responders who Remained Relapse Free
SUSTAIN-1 (3003)



Patients at risk																							
Esketamine + AD	62	60	44	35	33	29	22	18	14	13	11	8	6	6	6	6	4	2	2	2	1	1	1	0
AD + Placebo	59	42	30	24	19	16	12	7	4	3	2	2	2	2	1	1	1	1	0	0	0	0	0	0

a. Regression analysis of survival data based on Cox proportional hazards model with treatment as a factor
b. Log-rank test

Risk of Relapse Across Subgroups in Stable Remitters
SUSTAIN-1 (3003)



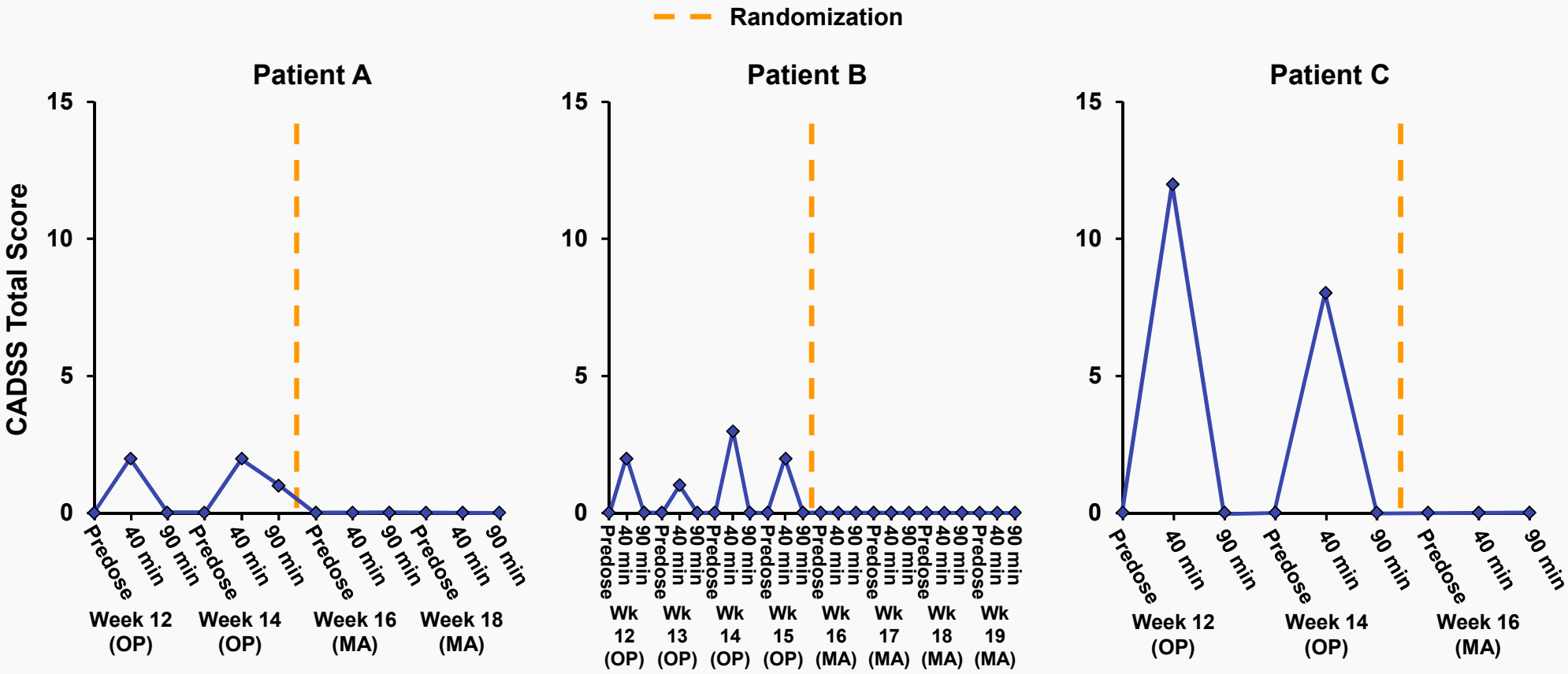
Potential Impact of Functional Unblinding Related to Dissociation
SUSTAIN-1 (3003)

- **Measures taken to ensure blinding**
  - Remote, independent, blinded assessment of MADRS performed pre-dose
  - Bittering agent in placebo nasal spray
- **Analyses to assess potential impact of dissociation on treatment effect**
  - Sensitivity analysis
  - Mediation analysis

Potential Impact of Functional Unblinding Related to Dissociation
SUSTAIN-1 (3003)

- **Clinician-Administered Dissociative States Scale (CADSS) was used to assess the severity of dissociation at every dosing visit**
  - The total score ranges from 0 to 92
  - Score of 4 or less is considered in the normal range
- **If a patient is experiencing dissociation while on esketamine, and then does not experience any dissociative symptoms upon discontinuing esketamine, functional unblinding may occur**
- **If functional unblinding led to a relapse, it would be expected to occur shortly after discontinuing esketamine**

Identifying Potentially Unblinded Oral AD + Placebo Patients Based on Pattern of Dissociative Symptoms (CADSS)
SUSTAIN-1 (3003)

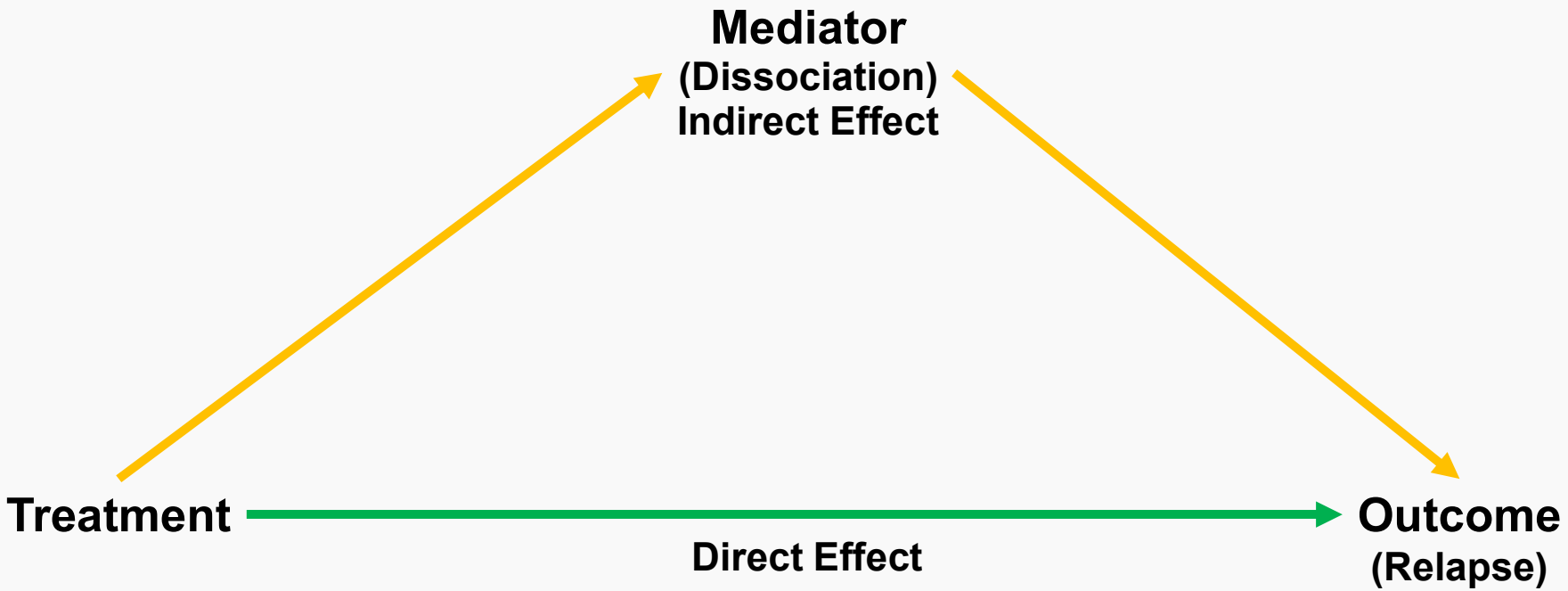


Early Relapse Events Censored for These 3 Stable Remitter Patients (A, B and C)
SUSTAIN-1 (3003)

	Esketamine + AD	AD + Placebo
Time to relapse (days)[a]		
Number assessed	**90**	**86**
Number censored (%)	**66 (73.3)**	**50 (58.1)**
Number of relapses (%)	**24 (26.7)**	**36 (41.9)**
Median (95% CI)	**NE**	**273.0 (126.0; NE)**
Hazard ratio (95% CI)[b]	**0.50 (0.30; 0.84)**	
Two-sided p-value[c]	**0.008**	

a. Based on Kaplan-Meier product limit estimates
b. Regression analysis of survival data based on Cox proportional hazards model with treatment as a factor
c. Log-rank test
NE=not estimable

Mediation Analysis Framework



Mediation Analyses of Change in Dissociation (CADSS Total Score) on Time to Relapse
SUSTAIN-1 (3003)

Mediator	Outcome	Direct Effect* (95% CI)	Indirect Effect* (95% CI)	Proportion of Treatment Effect Accounted for by Dissociation
Change in CADSS at 40 min, Day 1 (MA)	Time to Relapse	-2.44 (-4.04, -0.84) $x10^{-3}$	0.12 (-3.22, 3.45) $x10^{-3}$	~ 0

Results suggest that the absence or presence of dissociation does *not* account for the Esketamine treatment effect

*Effect expressed as change in number of relapses per day per 1000 people

Efficacy Conclusions

- **Totality of evidence supports efficacy of esketamine 56 and 84 mg for TRD**
- **Rapid reduction of symptoms as early as 24 hours post-dose**
- **Robust efficacy with high rates of response and remission after induction**
- **Demonstrated maintenance of effect with individualized, reduced dosing frequency**

Safety

Vanina Popova, MD

Study Responsible Physician Esketamine TRD
Janssen Research and Development

Extent of Exposure

	Number Exposed to Esketamine
Total unique exposures (≥1 dose of esketamine)	**1,708**
≥6 months	**479**
≥12 months	**178**
≥65 years of age	**194**

611 patient-years of esketamine exposure
(100 patient-years of antidepressant + placebo exposure)

Comprehensive Safety Evaluation

- **Esketamine clinical program included a safety assessment incorporating multiple components, including AEs; clinical laboratory and ECG**
- **Vital signs included pulse oximetry, respiratory rate, heart rate, etc.**
- **Numerous rating scales to systematically assess topics of special interest:**

Topic of Interest	Ratings Scale
Suicidal ideation/behavior	Columbia-Suicide Severity Rating Scale (C-SSRS)
Dissociation	Clinician-Administered Dissociative States Scale (CADSS)
Psychosis	Brief Psychiatric Rating Scale Positive Symptoms Subscale (BPRS+)
Sedation	Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)
Cognition	Cogstate Battery, HVLT-R
Nasal tolerability	Nasal Symptom Questionnaire (NSQ)
Sense of smell	University of Pennsylvania Smell Identification Test (UPSIT)
Withdrawal symptoms	Physician Withdrawal Checklist (PWC-20)
Interstitial cystitis	Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS)

Key Features of Esketamine Safety and Tolerability Profile

- **Majority of AEs occurred on the dosing day**
  - **Onset:** shortly after dosing
  - **Transient nature:** generally resolved by 1.5 hours on the same day of dosing
- **Similar safety profile across:**
  - Doses (56 and 84 mg)
  - Subgroups, including age
  - Long-term exposure

Agenda for Esketamine Safety Presentation

- **Overall adverse events**
  - Safety pooling strategy: TRANSFORM-1/2 (18-64 yo)
- **Topics of special interest:**
  - Suicidal ideation and behavior
  - Blood pressure
  - Dissociative/perceptual effects
  - Sedation
- **Ketamine Class topics of interest**
  - Cognition
  - Interstitial cystitis
  - Liver function

Most Common Adverse Events (≥5%)
Short-term Phase 3 Studies

	Pooled TRANSFORM-1/2 (Age 18-64)	
	Esk + AD N=346 %	AD + Placebo N=222 %
Total percent of patients with TEAE	87.0	64.4
Nausea	28.3	8.6
Dissociation	26.6	3.6
Dizziness	23.7	6.8
Vertigo	22.5	2.3
Headache	20.2	17.1
Dysgeusia	18.8	13.5
Somnolence	17.3	9.0
Paresthesia	12.4	1.8
Hypoesthesia	11.0	1.4
Hypoesthesia oral	10.7	1.4
Vomiting	9.2	1.8
Vision blurred	9.0	1.4
Anxiety	9.0	5.4
Blood pressure increased	8.7	2.3
Insomnia	8.4	7.2
Fatigue	7.2	5.0

Most Common Adverse Events (≥5%)
Short-term Phase 3 Studies

	Pooled TRANSFORM-1/2 (Age 18-64)		TRANSFORM-3 (Age ≥65)	
	Esk + AD N=346 %	AD + Placebo N=222 %	Esk + AD N=72 %	AD + Placebo N=65 %
Total percent of patients with TEAE	87.0	64.4	70.8	60.0
Nausea	28.3	8.6	18.1	4.6
Dissociation	26.6	3.6	12.5	1.5
Dizziness	23.7	6.8	20.8	7.7
Vertigo	22.5	2.3	11.1	3.1
Headache	20.2	17.1	12.5	3.1
Dysgeusia	18.8	13.5	5.6	4.6
Somnolence	17.3	9.0	1.4	4.6
Paresthesia	12.4	1.8	5.6	3.1
Hypoesthesia	11.0	1.4	5.6	1.5
Hypoesthesia oral	10.7	1.4	6.9	0
Vomiting	9.2	1.8	6.9	1.5
Vision blurred	9.0	1.4	2.8	0
Anxiety	9.0	5.4	2.8	7.7
Blood pressure increased	8.7	2.3	12.5	4.6
Insomnia	8.4	7.2	5.6	4.6
Fatigue	7.2	5.0	12.5	7.7

Most Common Adverse Events (≥10%) by Dose (56 mg and 84 mg)
TRANSFORM-1

	Onset On or After Second Dose	
	Esk 56 mg + Oral AD N=115 %	Esk 84 mg + Oral AD N=105 %
Dizziness	20.9	19.0
Dissociation	17.4	23.8
Nausea	20.0	21.0
Headache	13.9	15.2
Vertigo	18.3	16.2
Dysgeusia	13.0	14.3
Somnolence	15.7	16.2
Hypoesthesia oral	12.2	9.5
Paresthesia	13.0	10.5
Hypoesthesia	10.4	12.4

Severe Adverse Events (≥1%)
Completed Phase 3 Studies

	All Randomized, Blinded Trials Population		All Clinical Trials Population
	Esk + Oral AD N=571 %	Oral AD+ Placebo N=486 %	Esk+Oral AD N=1708 %
Total patients with a TEAE, n (%)	69 (12.1)	18 (3.7)	252 (14.8)
Dissociation	2.3	0	2.2
Vertigo	2.3	0	1.6
Dizziness	1.4	0.2	1.5
Dysgeusia	1.2	0	1.1
Nausea	1.1	0	1.3
Headache	0.9	0.8	1.2
Anxiety	0.9	0.4	1.2

Occurrence and Resolution of TEAEs
Completed Phase 3 Studies

- **Over 90% (pooled TRANSFORM-1/2) and over 85% (TRANSFORM-3) of esketamine adverse events occurred and resolved on same dosing day**

- **Esketamine associated events reported as not resolving on dosing day (>15% of events in at least one Phase 3 study):**
  - Headache, nausea and anxiety
- **Pattern of same day resolution was similar in the long-term studies (SUSTAIN-1 and -2), including severe AEs**

Discontinuations Due to Adverse Events
Completed Phase 3 Studies

	Esk + AD		AD + Placebo	
	N	n (%)	N	n (%)
Pooled TRANSFORM-1/2	346	16 (4.6)	222	3 (1.4)
TRANSFORM-3	72	4 (5.6)	65	2 (3.1)
SUSTAIN-1				
Induction Phase	437	22 (5.0)		
Optimization Phase	455	5 (1.1)		
Maintenance Phase	152	4 (2.6)	145	3 (2.1)
SUSTAIN-2	802	76 (9.5)		

Adverse events leading to esketamine discontinuation in more than 2 patients (>0.1%) (in order of frequency):

- Anxiety, depression, blood pressure increased, dizziness, suicidal ideation, dissociation, nausea, vomiting, headache, muscular weakness, vertigo, hypertension, panic attack, and sedation

Serious Adverse Events Considered Related to Esketamine by Investigator Completed Phase 3 TRD Studies (601 patient years of exposure)

Study	SAE n (%)	SAE (includes 1 patient each with):
Pooled TRANSFORM-1/2	2 (0.6)	Depression, headache
TRANSFORM-3	2 (2.8)	Blood pressure increased, anxiety disorder
SUSTAIN-1	6 (1.4)	Disorientation, suicidal ideation, sedation, autonomic nervous system imbalance and simple partial seizures[a], lacunar stroke[a], hypothermia
SUSTAIN-2	4 (0.5)	Delirium, anxiety and delusion, suicidal ideation, suicide attempt[a]

a. Sponsor causality assessment considered not related

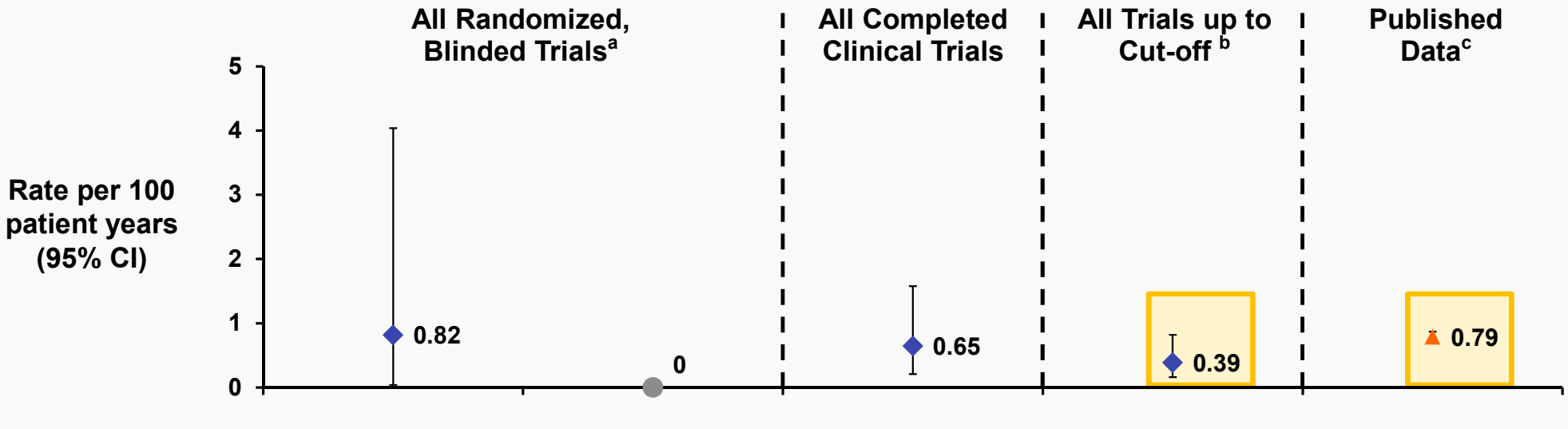
Deaths

Study Phase	Event	Last Esketamine Dose
Completed Double Blind Studies	**Multiple injuries from road traffic accident**	**28 hours after (84 mg)**
Completed and Ongoing Open-Label Studies/Study Phases	Acute cardiac and respiratory failure	5 days after (56 mg)
	Myocardial Infarction	6 days after (84 mg)
	Completed suicide	21 days after (56 mg) (Follow-up Phase)
	Completed suicide	12 days after (84 mg)
	Completed suicide	4 days after (84 mg)

Blue text indicates one death which occurred in one of the short term controlled studies.

All-cause Mortality Rates
Phase 2 and 3 Studies in TRD

Mortality Rates in Phase 2/3 Esketamine TRD Trials



	Esk + AD	AD + Placebo	Esk + AD	Esk + AD	TRD
N	571	486	1708	1861	15,013
Patient years	122	100	611	1520	54,697
Number of events	1	0	4	6	432

a. Exposure calculated for the DB portion only
b. Cut off – 4th September, 2018
c. J. Reutfors et al. *Journal of Affective Disorders 238 (2018) 674–679* Mortality in treatment-resistant unipolar depression: A register-based cohort study in Sweden

Topics of Special Interest

- **Suicidal Ideation and Behavior**
- Blood Pressure
- Dissociative/Perceptual Effects
- Sedation
- Cognition
- Interstitial Cystitis
- Liver Function

Suicidal Ideation and Behavior

- **Columbia-Suicide Severity Rating Scale (C-SSRS) used to assess potential suicidal ideation and behavior**
- **Patients with suicidal ideation were not excluded**
  - However, suicidal behavior in the past year and suicidal ideation with some intent to act in the previous 6 months were excluded
- **Across all Phase 2 and 3 studies, suicidal ideation, assessed by C-SSRS, showed a decrease from baseline to the endpoint in the esketamine treatment groups**
- **No evidence of association between esketamine and increased risk of treatment-emergent suicidal ideation and behavior**

Postbaseline Reported Treatment Emergent Suicidal Ideation (C-SSRS) in Patients with No Ideation at Baseline

Completed Phase 3 Studies

	Esk 56 mg + AD n (%)	Esk 84 mg + AD n (%)	Esk 28, 56 or 84 + AD n (%)	AD + Placebo n (%)
TRANSFORM-1/2			**26 (10.2)**	**20 (12.3)**
TRANSFORM-3			**8 (13.8)**	**9 (16.7)**
SUSTAIN-1				
Induction (IND)			**41 (11.3)**	
Optimization (OP)			**22 (5.7)**	
Maintenance (MA)			**3 (2.4)**	**6 (4.5)**
SUSTAIN-2				
IND			**71 (11.1)**	
OP/MA			**59 (11.6)**	

C-SSRS category Suicidal ideation = 1, 2, 3, 4, 5.
Each patient is counted only once, based on the most severe postbaseline C-SSRS category

Postbaseline Reported Treatment Emergent Suicidal Behavior (C-SSRS)
Completed Phase 3 Studies

Study Phase	Treatment (+ Oral AD)	Patients with No Suicidal Ideation or Behavior (No Event) at Baseline		Patients with Suicidal Ideation at Baseline	
		N	n (%) with Suicidal Behavior at Any Time Postbaseline	N	n (%) with Suicidal Behavior at Any Time Postbaseline
TRANSFORM-1/2					
	Esk	254	0	86	1 (1.2)
	Placebo	162	0	60	0
TRANSFORM-3					
	Esk	58	0	12	0
	Placebo	54	0	11	0
SUSTAIN-1					
IND	Esk	362	1 (0.3)	62	0
OP	Esk	387	0	64	0
MA	Esk	126	0	25	0
	Placebo	133	0	12	0
SUSTAIN-2					
IND	Esk	637	2 (0.3)	124	2 (1.6)
OP/MA	Esk	509	2 (0.4)	93	2 (2.2)

C-SSRS category Suicidal behavior = 6, 7, 8, 9, 10.

Each patient is counted only once, based on the most severe postbaseline C-SSRS category

Topics of Special Interest

- Suicidal Ideation and Behavior
- **Blood Pressure**
- Dissociative/Perceptual Effects
- Sedation
- Cognition
- Interstitial Cystitis
- Liver Function

Blood Pressure Guidelines on Dosing Days

- **Pre-dose blood pressure**
  - Systolic blood pressure (SBP) ≤140 mmHg (≤150 mmHg age 65 and above) and/or diastolic blood pressure (DBP) ≤90 mmHg
- **Post-dose blood pressure**
  - SBP ≥180 or DBP ≥110 (acute hypertension) –> dosing interrupted:
    - Treatment continued following evaluation by specialist
  - SBP ≥200 mmHg (≥ 190 – age 65 and above) or the DBP ≥120 mmHg (≥110 age 65 and above) –> did not receive any additional doses of esketamine

Blood Pressure

- Generally peak around 40 minutes of dosing and return to, or near to predose levels by 1.5 - 2 hours post dose
- Blood pressure increases were not associated with adverse clinical outcomes (e.g. cardiovascular/cerebrovascular accidents)

Blood Pressure – Magnitude of Change

Completed Phase 3 Studies

	Mean (SD) Maximum Elevations Compared to Pre-dose			
	Esk 56 mg + AD	Esk 84 mg + AD	Esk 28, 56 or 84 mg + AD	AD + Placebo
TRANSFORM-1/2 (age 18-64)				
SBP, mmHg			13.3 (12.49)	6.1 (9.99)
DBP, mmHg			8.7 (7.40)	4.9 (6.66)
TRANSFORM-1 (age 18-64)				
SBP, mmHg	14.3 (13.26)	15.0 (14.00)		7.2 (11.41)
DBP, mmHg	8.9 (8.15)	9.4 (8.51)		5.3 (7.54)
TRANSFORM-3 (age ≥65)				
SBP, mmHg			16.0 (15.59)	11.1 (9.73)
DBP, mmHg			9.5 (8.17)	6.8 (5.90)
SUSTAIN-2			Week 4 / Week 48	
SBP, mmHg			7.6 (11.04) / 8.4 (10.28)	
DBP, mmHg			4.7 (7.75) / 4.5 (7.02)	

Incidence of Patients with SBP ≥180 or DBP ≥110

Completed Phase 3 Studies

	Esk 56 mg + AD % (n/N)	Esk 84 mg + AD % (n/N)	Esk 28, 56 or 84 mg + AD % (n/N)	AD + Placebo % (n/N)
TRANSFORM-1/2			4.9 (17/346)	0.9 (2/222)
TRANSFORM-1	7.0 (8/115)	4.3 (5/116)		1.8 (2/113)
TRANSFORM-2			3.5 (4/115)	0 (0/109)
TRANSFORM-3			11.1 (8/72)	6.2 (4/65)
SUSTAIN-1			4.4 (27/619)	1.2 (1/86)
SUSTAIN-2			4.1 (33/802)	

68% of patients had a single occurrence of acute hypertension

Visits with Highest Blood Pressure Measured at 1.5 Hour and SBP Increase ≥10 or DBP >105 and Increase ≥5
Completed Phase 3 Studies

	Esk 28, 56 or 84 mg + AD N (%)	AD + Placebo N (%)
TRANSFORM-1		
SBP	177 (10.4)	83 (9.6)
DBP	3 (0.2)	1 (0.1)
TRANSFORM-2		
SBP	79 (9.4)	62 (7.5)
DBP	0	0
TRANSFORM-3		
SBP	79 (14.9)	102 (20.5)
DBP	0	1 (0.2)
SUSTAIN-1		
SBP	659 (6.9)	203 (6.0)
DBP	10 (0.1)	2 (0.1)
SUSTAIN-2		
SBP	1423 (7.3)	
DBP	4 (0.02)	

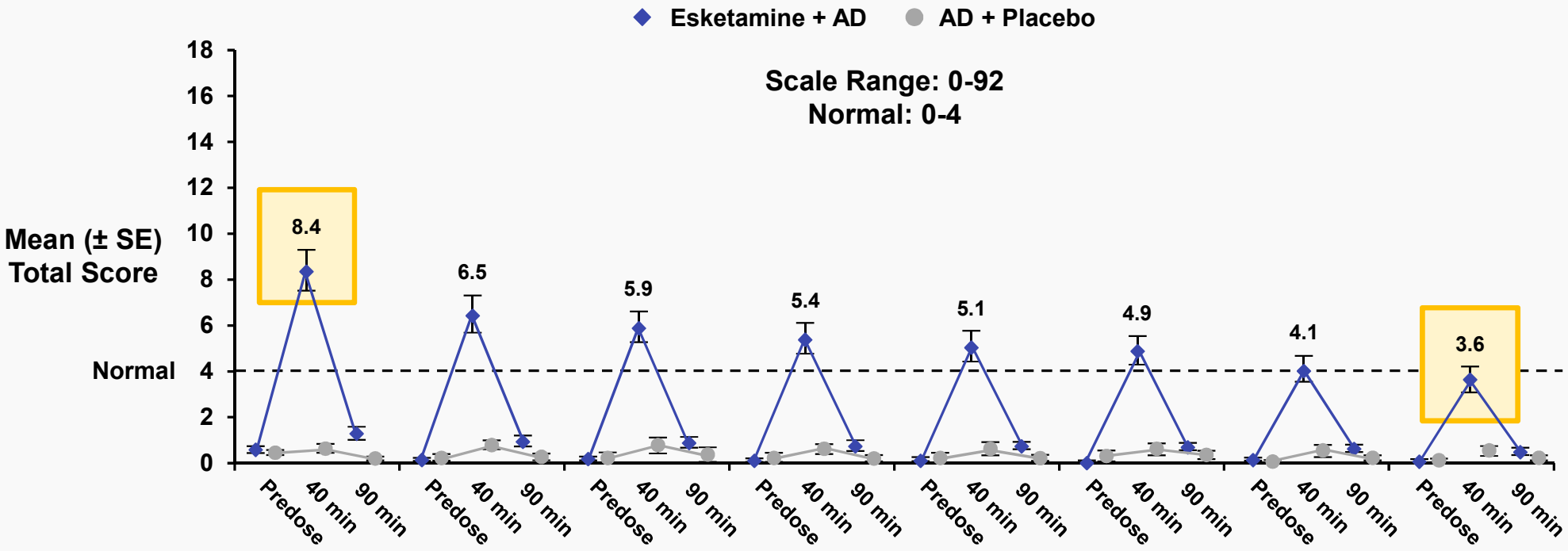
Blood Pressure-Risk Mitigation: Proposed Label

- Blood pressure should be assessed prior to esketamine dosing
- Elevated blood pressure should be controlled prior to dosing
- Blood pressure should be monitored after dose administration until blood pressure returns to acceptable levels

Topics of Special Interest

- Suicidal Ideation and Behavior
- Blood Pressure
- **Dissociative and Perceptual Effects**
- Sedation
- Cognition
- Interstitial Cystitis
- Liver Function

CADSS Total Score Over Time
TRANSFORM-2 (3002)



Number of Patients	Day 1 Dose 1			Day 4 Dose 2			Day 8 Dose 3			Day 11 Dose 4			Day 15 Dose 5			Day 18 Dose 6			Day 22 Dose 7			Day 25 Dose 8		
Esk + AD	115	114	111	106	106	106	107	107	107	104	104	103	104	104	103	96	96	96	101	100	100	93	93	93
AD + Placebo	103	105	103	102	102	102	100	100	100	97	97	97	100	100	100	96	96	95	100	100	98	95	95	94

Topics of Special Interest

- Suicidal Ideation and Behavior
- Blood Pressure
- Dissociative/Perceptual Effects
- **Sedation**
- Cognition
- Interstitial Cystitis
- Liver Function

MOAA/S Score	ASA Continuum	Description
5	**Minimal sedation**	Responds readily to name spoken in normal tone (awake)
4	**Moderate sedation**	Lethargic response to name spoken in normal tone
3	**Moderate sedation**	Responds after name called loudly or repeatedly
2	**Moderate sedation**	Purposeful response to mild prodding or mild shaking
1	**Deep sedation**	Responds to trapezius squeeze (includes purposeful and reflexive withdrawal)
0	**General anesthesia**	No response to painful stimulus (trapezius squeeze)

MOAA/S=Modified Observer's Assessment of Alertness/Sedation Scale
ASA= American Society of Anesthesiologists

Sedation

- **40-50% of esketamine patients did not experience sedation**
- **Generally, for patients that experienced sedation**
  - Onset around 15 minutes into dosing
  - Peaked at 30 to 45 minutes post-dose
  - Spontaneous resolution by 1 to 1.5 hours post-dose
- **Sedation was not associated with hypoxemia**

Incidences of Sedation (MOAA/S[a] Score ≤4)

	Esk 56 mg + AD % (n/N)	Esk 84 mg + AD % (n/N)	Esk 28, 56 or 84 mg + AD % (n/N)	AD + Placebo % (n/N)
TRANSFORM-1	50.4 (58/115)	59.5 (69/116)		13.3 (15/113)
TRANSFORM-2			57.4 (66/115)	11.0 (12/109)
TRANSFORM-3			48.6 (35/72)	21.5 (14/65)
SUSTAIN-1				
IND			50.9 (222/436)	
OP			38.1 (172/451)	
MA			41.4 (63/152)	9.7 (14/145)
SUSTAIN-2				
IND			52.1 (405/777)	
OP/MA			54.2 (327/603)	

a. MOAA/S (Modified Observer's Assessment of Alertness and Sedation)

Onset of Sedation (MOAA/S= 0,1)

Age/Gender	Dosing Day(s)	Esk Dose	MOAA/S	Onset Time (Min)	Potential Confounding Factors
57y/F	277	84 mg	1	122	**1 h post dose**: 5 mg IV Midazolam (TEAE- Anxiety)
34y/M	4	56 mg	1	90	Data entry error
55y/F	22	56 mg	0	45	
48y/F	8	28 mg	0	45	Concomitant Use of Lorazepam
50y/F	4	56 mg	1	40	
40y/F	96	56 mg	1	40	
60y/M	15	84 mg	0	30	
53y/M	11	84 mg	1	30	
47y/F	1	56 mg	1	25	Concomitant medication: Alprazolam XR
53y/M	4,8,12,22,25	56 mg	0	15-20	
35y/F	4	84 mg	1	15	Concomitant medication: Alprazolam XR

11 events across 31,563 dosing days

Topics of Special Interest

- Suicidal Ideation and Behavior
- Blood Pressure
- Dissociative/Perceptual Effects
- Sedation
- **Cognition**
- Interstitial Cystitis
- Liver Function

Cogstate Computerized Test Battery + HVLT-R

- Simple reaction time (SRT)
- Choice reaction time (CRT)
- Visual learning and recall
- Working memory (1 back)
- Executive function / visuospatial memory and sequencing (Groton Maze)
- Hopkins Verbal Learning Test - Revised (HVLT-R)

Cognition: Summary

- **Controlled Studies**
  - No differences between esketamine groups and placebo groups in Studies TRANSFORM-1,2,3 and SUSTAIN-1

- **Open label long-term safety, SUSTAIN-2**
  - Some slowing of reaction time (RT) in patients 65 years and above
    - High intra-individual variability observed, making it difficult to distinguish drug effects from other factors
    - More complex aspects of cognition, e.g. learning and memory, and planning and decision-making were not influenced at all by 12 months treatment

Topics of Special Interest

- Suicidal Ideation and Behavior
- Blood Pressure
- Dissociative/Perceptual Effects
- Sedation
- Cognition
- **Interstitial Cystitis**
- Liver Function

Interstitial Cystitis

- Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) was used systematically in all Phase 3 studies for assessment
- No cases of interstitial cystitis or ulcerative cystitis

Topics of Special Interest

- Suicidal Ideation and Behavior
- Blood Pressure
- Dissociative/Perceptual Effects
- Sedation
- Cognition
- Interstitial Cystitis
- **Liver Function**

Liver Function

- No persistent increases in liver enzymes were observed
- No cases across all studies met the criteria for severe drug-induced hepatocellular injury as defined by Hy's law
- In patients with elevated baseline liver enzymes, no elevated total serum bilirubin >2xULN and/or ≥2x baseline values were observed

Safety Conclusion

- **Well-characterized safety profile within the proposed therapeutic dose range for use in a TRD population**
- **Transient adverse events**
  - Predictable based on mechanism of action
  - Onset and resolution generally by 1.5 hours post-dose
- **No new safety findings with long term use**
  - No cases of respiratory depression, no patient required cardiopulmonary resuscitation or other medical interventions
  - No interstitial cystitis or cognitive impairment observed
  - No evidence of severe liver toxicity

Additional Key Post Marketing Data Sources

Source	Evidence contribution
Long Term Clinical Studies	Structured data with consistent capture during active phase, longer follow-up in a well defined population
Observational Databases (EHR, Claims)*	Larger population, characterize real world users, comparator cohorts, predictive models
Explore linking EHR and enhanced data collection	In some centers, explore the ability to follow patient longer, collect additional data, link to EHR for more complete clinical history, possible selection of comparator population from same site, predictive models

*Selected based on patient exposures and contribution of evidence

Abuse Potential

Andrew Krystal, MD

Ray and Dagmar Dolby Distinguished Professor of Psychiatry
Director of the Dolby Center for Mood Disorders

Vice-Chair for Research at University of California San Francisco

Professor Emeritus at Duke School of Medicine

Esketamine Clinical Trial Data

1. No reports of drug seeking, abuse/misuse, or overdose

- >1700 patients treated

2. No evidence of a withdrawal syndrome

- Physicians Withdrawal Checklist (PWC-20)
- Adverse event profile after drug discontinuation

3. No respiratory depression

- >30,000 pulse oximetry and respiration rate measurements

Ketamine and Esketamine Risks are Comparable

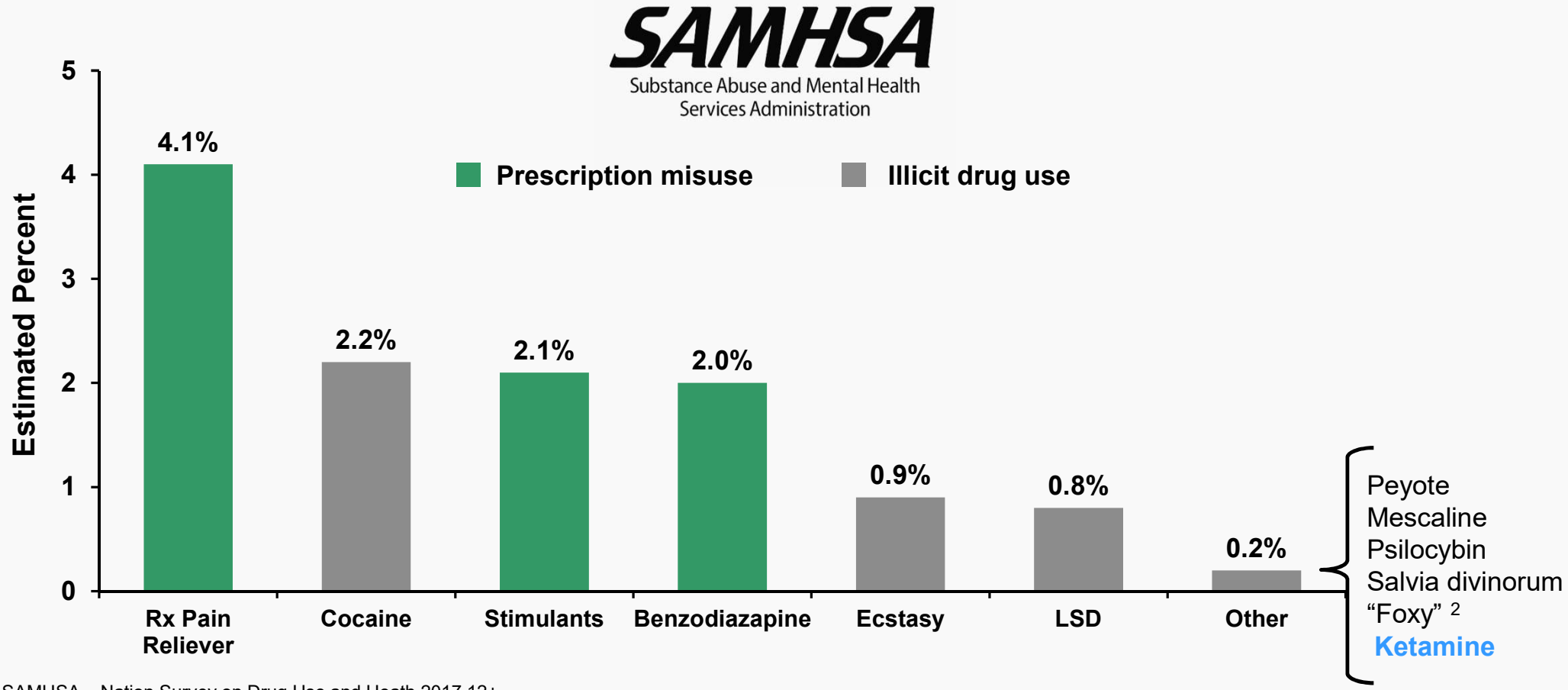
- **Ketamine consists of esketamine and arketamine (50:50 mixture)**
- **Ketamine is administered by healthcare professionals in the structure of medical settings as will be the case for esketamine**
- **Human Abuse Potential study - Phase 1**
  - In recreational drug users ketamine and esketamine have similar abuse potential

Ketamine

- **Rapid-acting general anesthetic with favorable safety profile**
  - Lack of respiratory depression and hypotension risks
- **World Health Organization (WHO) essential medicine**
  - *Ketamine's high level of safety also makes it unique amongst other anesthetics, as it does not require reliable electricity supply, oxygen, highly trained staff or monitoring systems to administer*[1]
- **Widely available in clinical settings (ER, hospitals, veterinary clinics) and administered by healthcare professionals**
- **Used off label in a growing number of pain and depression clinics**

1. https://www.who.int/medicines/news/20160309_FactFile_Ketamine.pdf

2017 Prevalence Estimate Abuse/Misuse



1. SAMHSA – Nation Survey on Drug Use and Heath 2017 12+
2. Foxy – 5-Methoxy-N,N-diisopropyltryptamine

CC-105

2016 Drug Overdose Death

Top 15 Drugs Most Frequently Involved in Drug Overdose Deaths

Referent Drug	Number of Deaths	Percent of Deaths
Fentanyl	18,335	28.8
Heroin	15,961	25.1
Cocaine	11,316	17.8
Methamphetamine	6,762	10.6
Alprazolam	6,209	9.8
Oxycodone	6,199	9.7
Morphine	5,014	7.9
Methadone	3,493	5.5
Hydrocodone	3,199	5.0
Diazepam	2,022	3.2
Diphenhydramine	2,008	3.2
Clonazepam	1,656	2.6
Gabapentin	1,546	2.4
Tramadol	1,250	2.0
Amphetamine	1,193	1.9

2016 World Health Organization:

"The risk of fatal intoxication associated with ketamine is very low"

1. National Vital Statistics Reports, 2016 – Drugs Most Frequently Involved in Drug Overdose Deaths, n=63,632

Deaths with Toxicology Report Indicating Presence of Ketamine

	Poly-drug use Including Ketamine	Ketamine
US/EU [1] 1987-2000	9	3
UK [2] 1993-2006	19	4
Total Deaths	**28**	**7**

1. A European Monitoring Centre for Drugs and Drug Addiction report
2. Schifano F, Corkery J, Oyefeso A, Tonia T, Ghodse AH.. *J Clin Psychopharmacol*. 2008;28:1146.

Summary of Esketamine Abuse/Misuse Profile

- **Esketamine clinical trials**
  - No evidence of abuse or misuse
  - No withdrawal symptoms
  - No overdose deaths or respiratory depression
- **Ketamine and esketamine have similar likability in recreational drug users**
- **Ketamine real world evidence**
  - Abuse rate less than 0.2%
  - Deaths due to ketamine are exceedingly rare

Summary

- **Unlike ketamine, esketamine will have an FDA approved label for TRD and associated education and monitoring program**
- **The abuse/misuse risk of esketamine will be mitigated with a comprehensive REMS program**

Risk Mitigation

David Hough, MD

Janssen Research & Development, LLC
Esketamine Compound Development Team Leader

Risk Mitigation Measures

- Proposed Risk Evaluation and Mitigation Strategy (REMS)
- Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS)
- Device design features to deter misuse or abuse
- Suspicious order monitoring
- Labeling and legal status (Schedule CIII)
- Enhanced Pharmacovigilance

Risk Evaluation and Mitigation Strategy (REMS) Goals

- **The Sponsor and FDA are aligned on the REMS Goals**
- **To mitigate the risks of misuse, abuse and serious adverse outcomes from dissociation, sedation, and blood pressure changes as a result of esketamine administration by:**
  - Ensuring that esketamine is only dispensed and administered in medically supervised healthcare settings that can provide patient monitoring
  - Enrollment of patients in a REMS to further characterize the risks and safe use of esketamine

REMS: Controlled Medication Distribution System

- **Wholesalers and distributers will only ship esketamine to REMS certified pharmacies and certified healthcare settings**
  - Patients will not receive esketamine directly
- **Patients will self-administer esketamine only under direct supervision of a HCP at the site of care**
- **Used devices will be disposed of as medical waste per local and federal regulations**

REMS: Healthcare Setting Requirements

- **REMS enrollment and certification required for ALL healthcare settings**
- **Only DEA licensed sites authorized to handle controlled substances**
- **Have necessary infrastructure to support dosing and monitoring**
- **Each setting must have an authorized representative who will attest there are appropriate processes and procedures**
  - e.g. patients are supervised during and post-dosing; all appropriate personnel are trained, etc.
- **Janssen will audit sites for compliance with the REMS requirements and perform knowledge and behavior surveys**

REMS: Patient Enrollment and Post Dose Monitoring

- **All patients will be enrolled in the REMS to further characterize the safe use of esketamine**
  - Onset: All patients will be monitored for a minimum of 1.5 hours to capture the onset of the events of interest
  - Monitoring: Events of interest will be recorded on the Patient Monitoring Form (PMF), including onset and time of resolution
  - Resolution & Discharge: Patients will be monitored until clinically stable and ready for discharge based on clinical judgement, but no earlier than 1.5 hours, and discharge readiness will be captured on the PMF
- **In the phase 3 program, 90% of patients were ready for discharge in 1.5 hours**

RADARS (The Researched Abuse, Diversion and Addiction-Related Surveillance System) Monitoring

- **RADARS collects product-and geographically-specific data on abuse, misuse, and diversion of prescription drugs**
- **Mosaic approach with expert analysis across data sources**
  - Global Toxico-surveillance Network (GTNet)
  - Surveys of patients in drug treatment centers
  - Web monitoring for early signals
  - StreetRX – website for buyers/users
  - General Adult Surveys of non-medical use of prescription drugs
- **Will prospectively collect data for ketamine and esketamine**

Device Design Features

- Single-use, disposable nasal spray device which delivers 28 mg dose (two sprays)
- Limited pack size for specific dose: 1, 2, or 3 devices
- Small residual volume ~30uL, difficult to extract
- Used devices disposed of as medical waste
- Unused devices returned to pharmacy or disposed of according to local or institutional SOP

Suspicious Order Monitoring

- Janssen currently has a SOM program to monitor approved controlled products
- Esketamine will be added to this program
- Suspicious activity will be reported to DEA and state agencies per local/federal regulations

Risk Mitigation Summary

- Risk Evaluation and Mitigation Strategy (REMS)
- Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS)
- Device design features to deter misuse or abuse
- Suspicious order monitoring
- Labeling and legal status (Schedule CIII)
- Enhanced Pharmacovigilance

Benefit-Risk Assessment

David Hough, MD

Janssen Research & Development, LLC
Esketamine Compound Development Team Leader

Benefit-Risk Summary: Disease, Unmet Need and Clinical Benefits

Analysis of Condition	• MDD is a serious and life-threatening condition • Burden of TRD is substantially greater than MDD
Unmet Medical Need	• Higher rates of hospitalization, suicidal ideation/behavior, and medical complications compared to MDD • Current treatment options are limited • Urgent need for rapid acting, more efficacious treatments
Clinical Benefits	• Rapid onset of therapeutic effect • High rates of response and remission • Prolonged duration of benefit with intermittent dosing • Low rate of relapse • High rates of retention and engagement with treatment

Benefit-Risk Summary: Risks and Risk Management

Clinical Risks	Risk Management

• **Transient dissociation, sedation and blood pressure changes**	• **Labelling**
	• **Proposed REMS:**
	  ▸ Administration in certified healthcare settings
	  ▸ Direct supervision of patients during and post-dosing by HCP
	  ▸ Patient enrollment in REMS and data collection at the time of each dose

• **Potential long term consequences of blood pressure changes**	• **Observational study (retrospective comparative cohort study)**

Benefit-Risk Summary: Risks and Risk Management

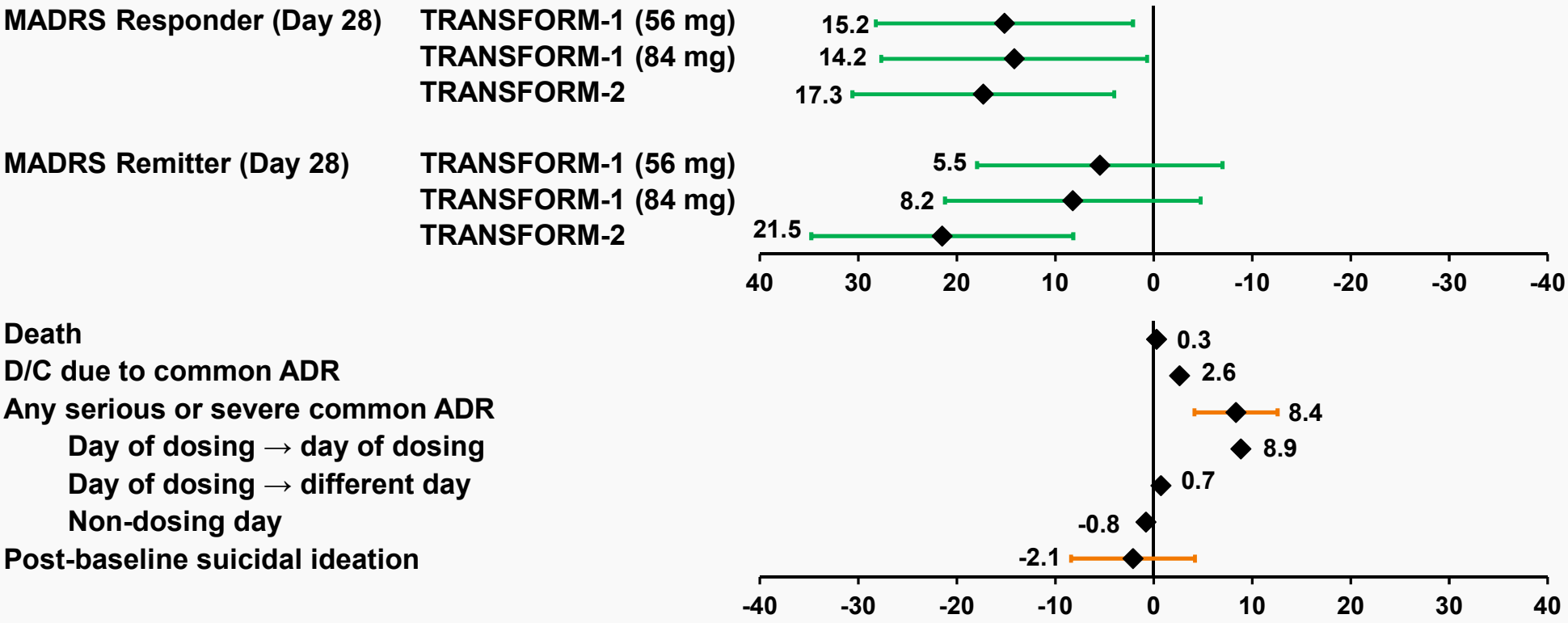
Clinical Risks

- **Abuse potential**

Risk Management

- **Proposed REMS**
  - Controlled medication distribution program
  - REMS certified pharmacies and sites of care
  - Administration under supervision of HCP
- **Suspicious order monitoring**
- **RADARS monitoring**
- **Enhanced Pharmacovigilance**

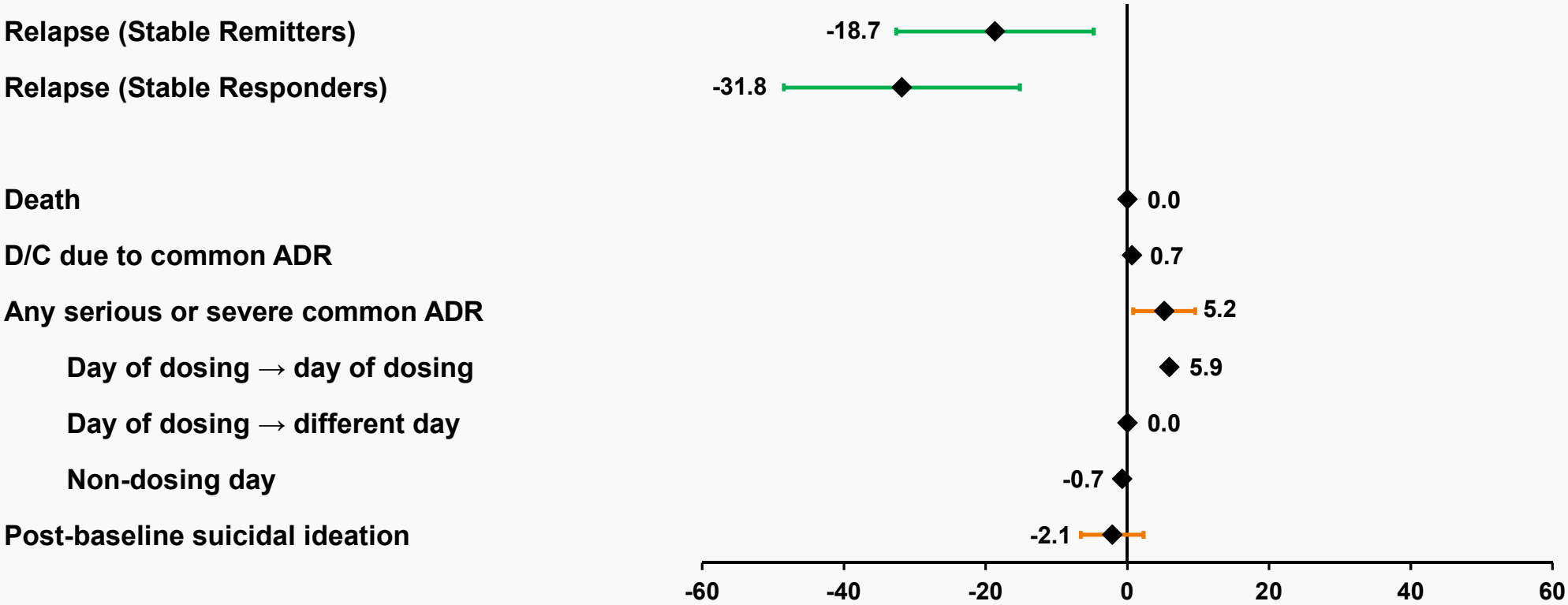
Benefit-Risk Assessment for Short Term Treatment
Risk Differences: TRANSFORM - 1 and 2 (3001, 3002)



Common adverse drug reactions (ADR) have an incidence of ≥10% in subjects treated with intranasal esketamine + oral AD and greater than oral AD + placebo and include dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoesthesia, blood pressure increased, anxiety and vomiting
No 95% confidence interval provided if data is 0 or 1 events in either group

CC-124

Benefit-Risk Assessment for Maintenance Treatment
Risk Differences: Stable Remitters & Responders SUSTAIN-1 (3003)



Common adverse drug reactions (ADR) have an incidence of ≥10% in subjects treated with intranasal esketamine + oral AD and greater than oral AD + placebo and include dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoesthesia, blood pressure increased, anxiety and vomiting
No 95% confidence interval provided if data is 0 or 1 events in either group

CC-125

Patient Preference Study*

- We assessed the TRD patient perspective on benefit-risk tradeoffs
- Patients highly value treatments that significantly improve depression symptoms
- Transient adverse events and dosing issues were of low importance
- Patients willing to accept risks observed in ketamine substance abuse to obtain better efficacy

*Discrete-choice survey developed with Duke Clinical Research Institute
Sample size: Clinical Trial (n=159) and Panel (n=297)

Clinical Perspective

Madhukar Trivedi, MD

Professor, Department of Psychiatry, UT Southwestern Medical Center
Chief of the Division of Mood Disorders

Founding Director of the Center for Depression Research and Clinical Care
Betty Jo Hay Distinguished Chair in Mental Health

Julie K. Hersh Chair for Depression Research and Clinical Care

Clinician's Perspective

- **Lessons learned from STAR*D**
  - Current treatments fall short for TRD patients
  - Limited options after multiple treatment failures
- **Need for Novel Antidepressants that can act rapidly and also accomplish sustained benefit for patients with TRD**
- **Esketamine as Novel Choice that meets patient needs**

External Responders Available for Q&A

Eric Lenze, MD	**Professor of Psychiatry** **Geriatric Psychiatry Rotation Director** **Washington University at St. Louis**
Paul Maruff, Ph.D	**Chief Scientific Officer** **Cogstate HealthCare** **Melbourne, Australia**
Michael Weber, MD	**Professor of Medicine** **SUNY College of Medicine Downstate Medical Center**

Backups Shown

Frequency Distribution of Esketamine Daily Dose Over Time
TRANSFORM-3 (3005)

	Esk 28 mg + AD n (%)	Esk 56 mg + AD n (%)	Esk 84 mg + AD n (%)
Day 1, N=72	72 (100.0)	–	–
Day 4, N=71	21 (29.6)	50 (70.4)	–
Day 11, N=66	9 (13.6)	20 (30.3)	37 (56.1)
Day 15, N=65	8 (12.3)	9 (13.8)	48 (73.8)
Day 18, N=65	8 (12.3)	9 (13.8)	48 (73.8)
Day 22, N=62	7 (11.3)	12 (19.4)	43 (69.4)
Day 25, N=62	6 (9.7)	16 (25.8)	40 (64.5)

Key Exclusion Criteria
TRANSFORM-1 and 2 (3001 and 3002)

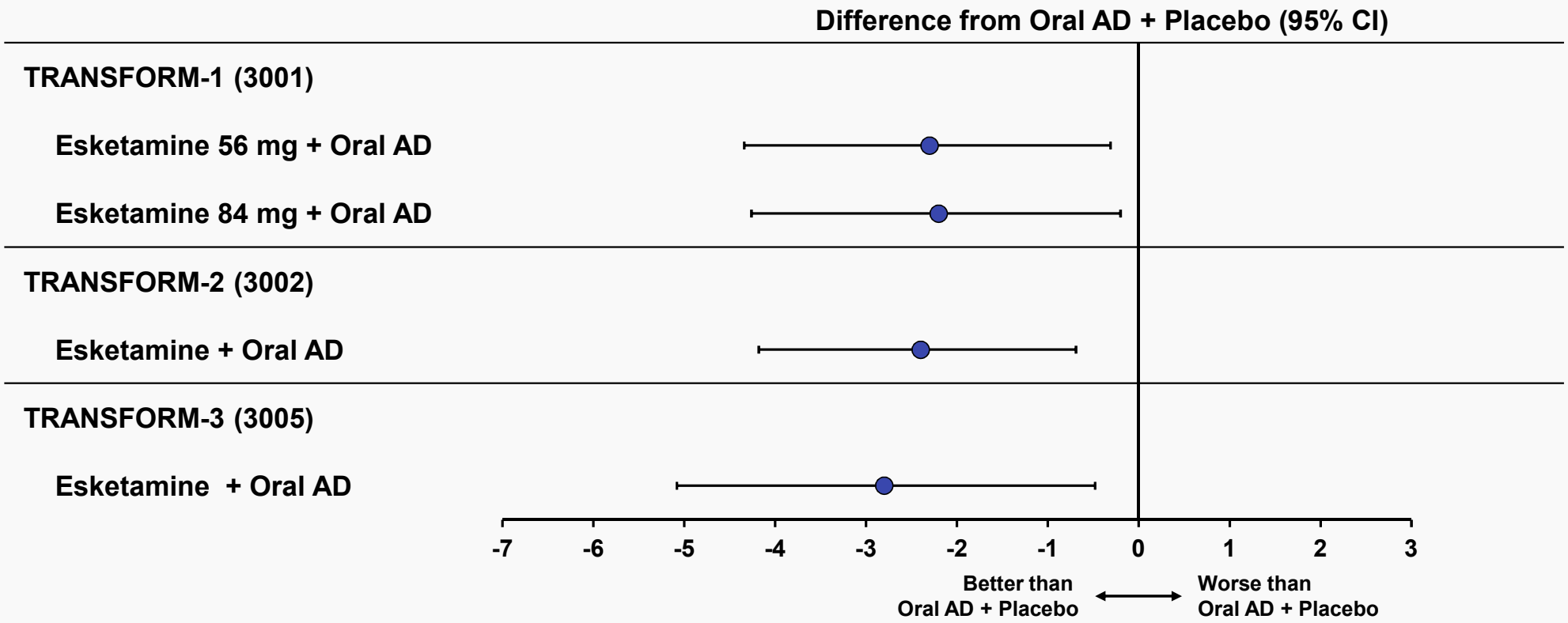
- **Suicidal ideation w/ intent to act within past 6 months; behavior within past 1 year**
- **History of moderate or severe substance or alcohol use disorder within 6 months**
- **Current/prior DSM diagnosis:**
  - Psychotic disorder or MDD with psychotic features
  - Bipolar or related disorders (confirmed by the MINI)
  - Obsessive compulsive disorder (current diagnosis only)
- **Liver cirrhosis**
- **Uncontrolled diabetes mellitus**
- **Severe renal impairment**
- **Uncontrolled Hypertension at study start and/or at Day 1 >140 SBP and/ or DBP >90**

Early Relapse Events Censored for 5 Patients with Pre- but not Post-randomization Dissociation or Pre-randomization Sedation AE who Discontinued Esketamine (Stable Remitters)

	Esketamine + AD	AD + Placebo
Time to relapse (days)[a]		
Number assessed	**90**	**86**
Number censored (%)	**66 (73.3)**	**51 (59.3)**
Number of relapses (%)	**24 (26.7)**	**35 (40.7)**
Median (95% CI)	**NE**	**273.0 (126.0; NE)**
Hazard ratio (95% CI)[b]	**0.52 (0.31; 0.87)**	
Two-sided p-value[c]	**0.011**	

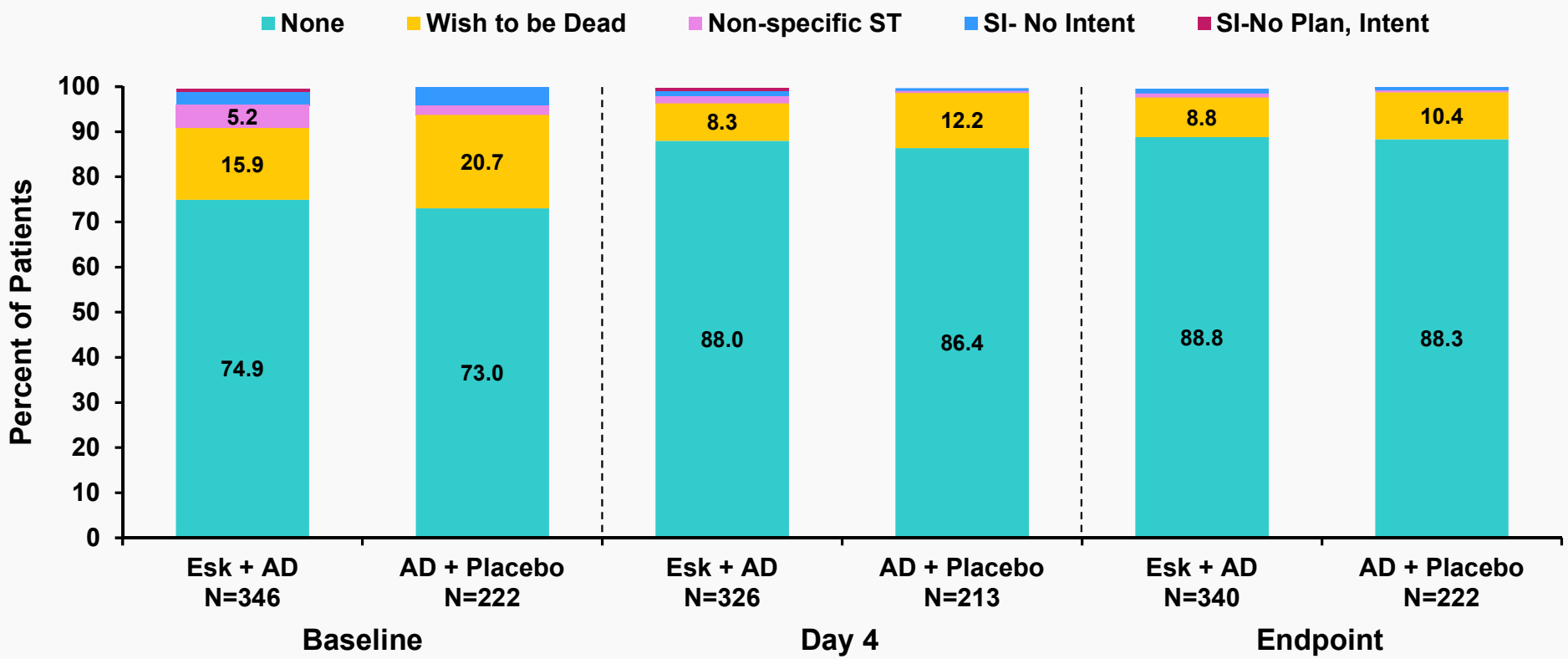
a. Based on Kaplan-Meier product limit estimates
b. Regression analysis of survival data based on Cox proportional hazards model with treatment as a factor
c. Log-rank test
NE=not estimable

Key Secondary Endpoint: LS Mean Difference in Change from Baseline in Patient Health Questionnaire (PHQ-9) Total Score at Day 28



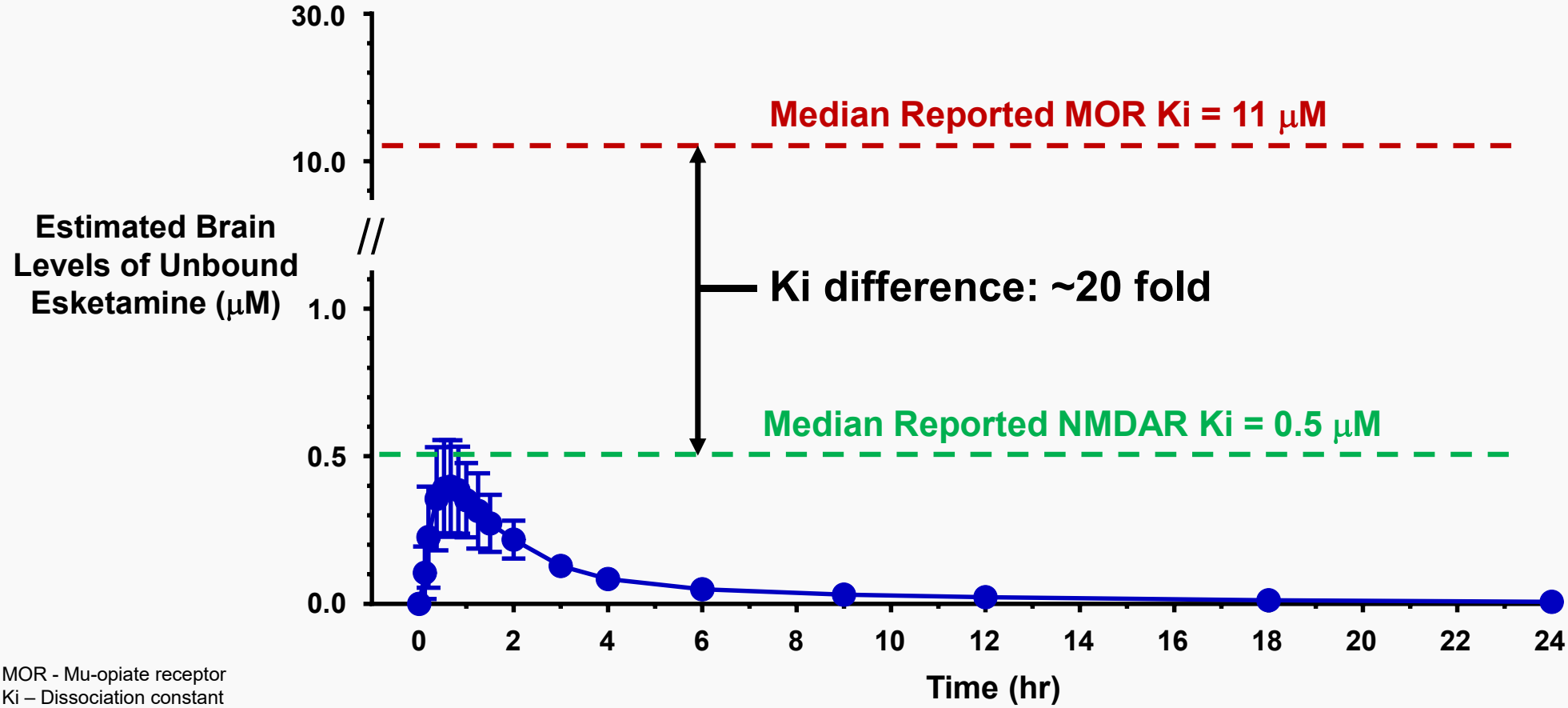
Suicidal Ideation Category (CSSRS) Changes from Baseline

Pooled 3001 and 3002 Studies



SA-364

Lack of Evidence for MOR Stimulation at Highest Recommended Dose of Esketamine Nasal Spray



MOR - Mu-opiate receptor
Ki – Dissociation constant
Blue line indicates estimated brain free esketamine levels in patients receiving 84mg

NC-334

No Evidence of Neurotoxicity with Esketamine in Adult Animals

Grouping	Study	Esketamine Top Dose (Route)
Brain histopathology	Rat single-dose neurotoxicity[1]	9 mg (intranasal)
	Rat single-dose neurotoxicity[2]	72 mg (intranasal)
	Rat 2-week neurotoxicity[3]	54 mg (intranasal)
	Rat 3-month toxicology[4]	9 mg/day (intranasal)
	Rat 2-year carcinogenicity[5]	9 mg/day (intranasal)
	Dog 3-month toxicology[6]	72 mg/day (intranasal)
	Transgenic mouse 6-month carcinogenicity[7]	75/40 mg/kg (subcutaneous)
	Rat pre- and postnatal development (dams)[8]	9 mg/day (intranasal)
Brain histopathology/ neurobehavioral testing	Rat 6-month toxicology[9]	9 mg/day (intranasal)
Brain histopathology/ neurology testing	Dog 9-month toxicology[10]	72 mg/day (intranasal)

1. TOX10415; 2. TOX11374; 3. TOX10950; 4. TOX10517; 5. TOX10702; 6. TOX10524; 7. TOX11233; 8. TOX10766; 9. TOX10768; 10. TOX10701