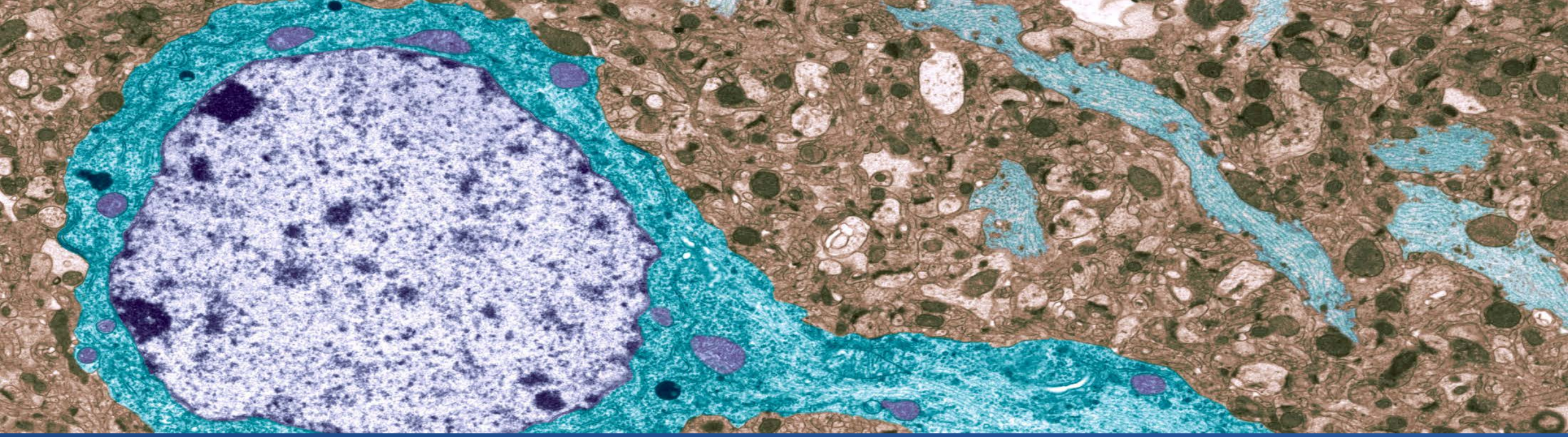

Esketamine Nasal Spray –CMS ICD 10 Procedure Code Meeting

H. Lynn Starr, MD

September 11, 2018

janssen Neuroscience

Esketamine Nasal Spray

- Esketamine Nasal Spray, a glutamate receptor modulator, is an **investigational** agent being studied by Janssen in clinical development programs for treatment-resistant depression, and major depressive disorder with imminent risk for suicide

  Both development programs are in phase 3 and have been granted a breakthrough therapy designation

- This product is not approved by the Food and Drug Administration (FDA). For information on ongoing clinical trials for esketamine, please visit www.clinicaltrials.gov

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Indication Sought for Treatment Resistant Depression

- 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)

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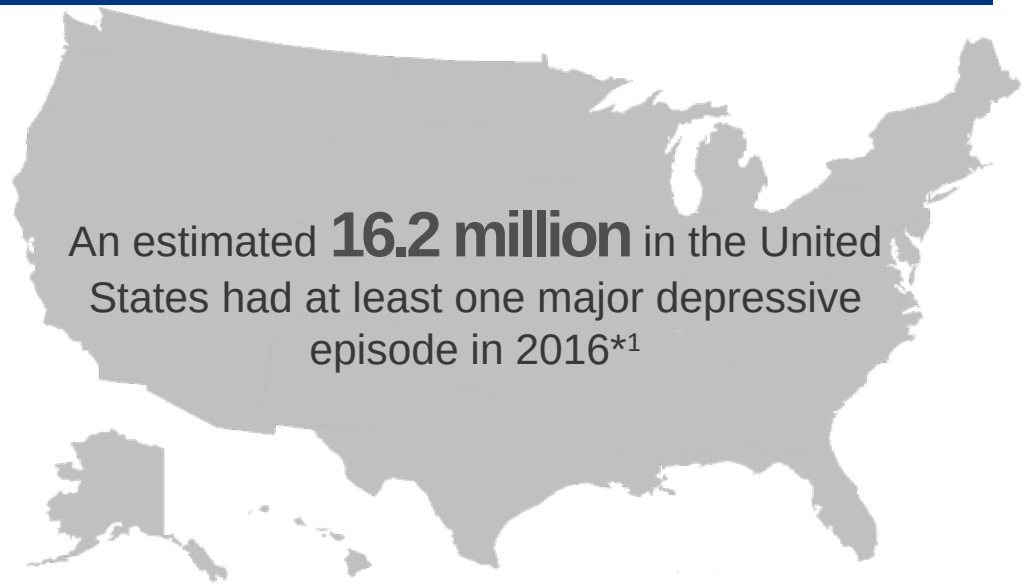
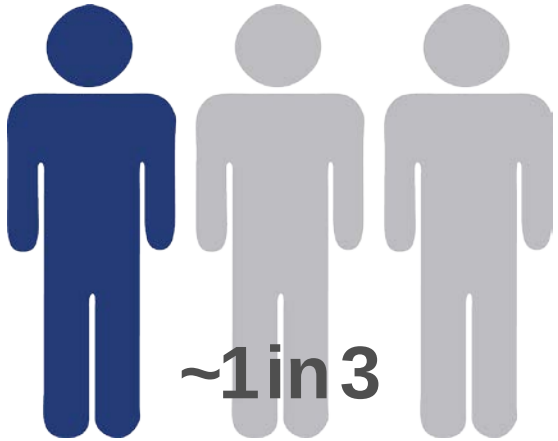
The Patient with Treatment Resistant Depression

Major Depressive Disorder (MDD)



Treatment Resistant Depression (TRD)



MDD patients are estimated to have TRD†[2]

A subset of Major Depressive Disorder patients are identified as treatment resistant and do not achieve remission despite multiple treatment steps.[2] Treatment Resistant Depression has been defined as a failure of treatment to produce response or remission for patients after 2 or more treatment attempts of adequate dose and duration[3]

***Prevalence rate of MDD in 2010 = 6.7% of all US adults.[1]**
†Based on the STAR*D trial.[2]

1. National Institute of Mental Health. Major depression among adults. https://www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed April 12, 2018. **2.** Rush AJ et al. Am J Psychiatry. 2006;163(11):1905-1917. **3.** Agency for Healthcare Research and Quality. Definition of treatment-resistant depression in the Medicare population. https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id105TA.pdf. Accessed April 12, 2018.

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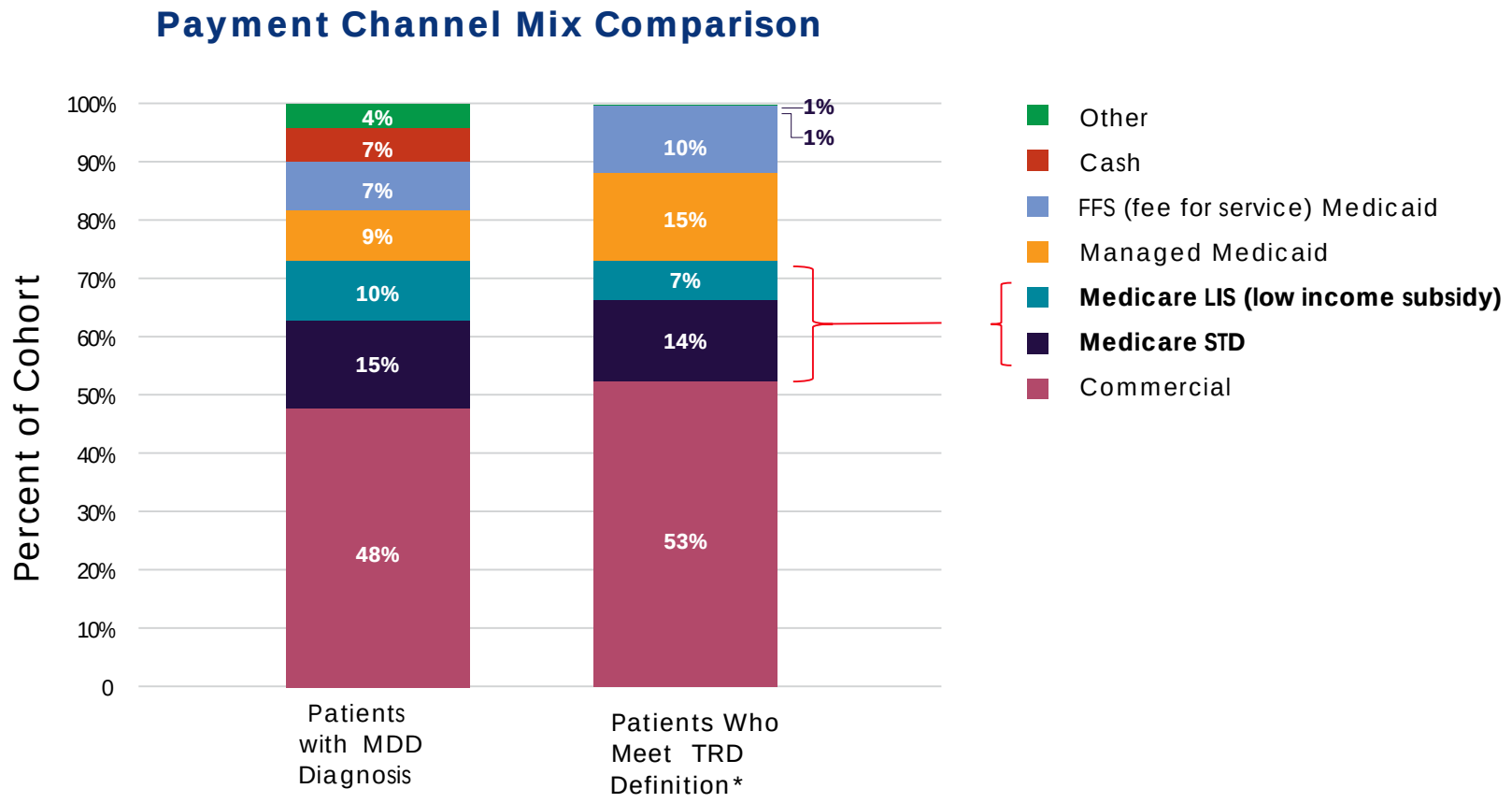
Medicare Beneficiaries account for over 21% of the TRD population



* Methodology used reflects Major Depressive Disorder (MDD) patients failing on 2 or more oral antidepressant switches within a 24-month look-back period.

Study Methodology: Data sourced from IQVIA (IMS) patient claims database. MDD diagnosis was confirmed by using ICD-9 and ICD-10 codes. Patients defined as having treatment resistant depression required at least 1 MDD claim during a 2-year observation period. In addition, all patients must have progressed beyond the use of two antidepressants and initiated a third antidepressant, either an adjunct antipsychotic (Abilify, Seroquel, or Rexulti), or a procedure (ECT, TMS, or DBS). The analysis evaluated data across a 4-year time period (January 2013- September 2017).

1. IQVIA FIA. Jan 2013 – Sept 2017.

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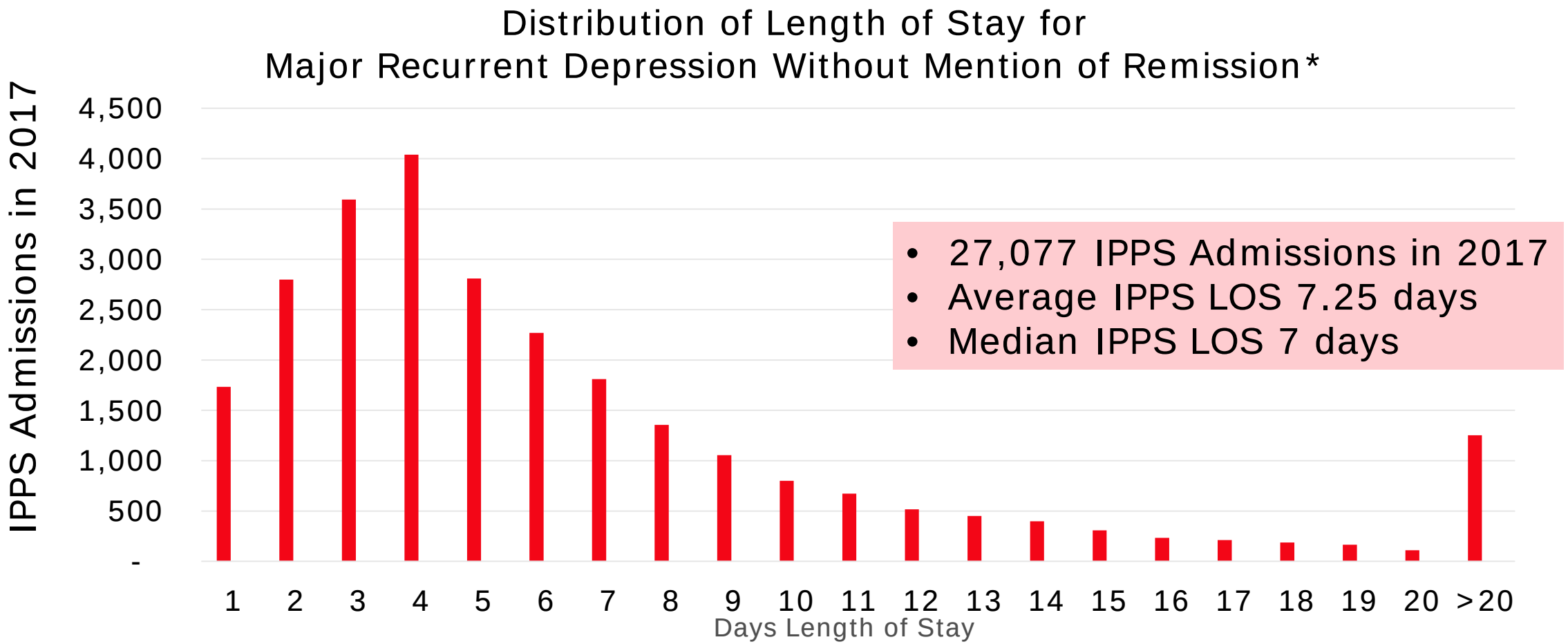
There Are About 27,000 IPPS Admissions Annually for Major Recurrent Depression Without Mention of Remission



*Source: 2017 MEDPAR Data, Direct Research, LLC

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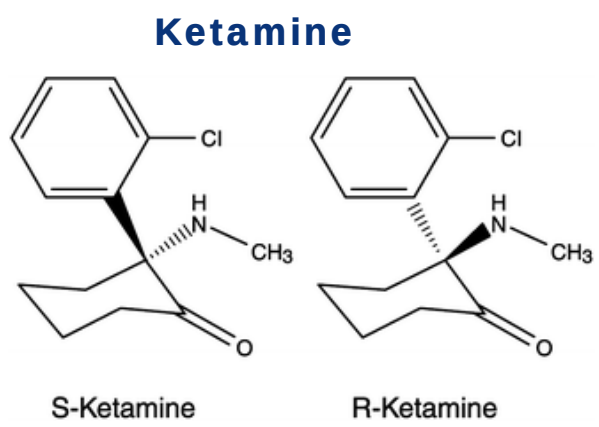
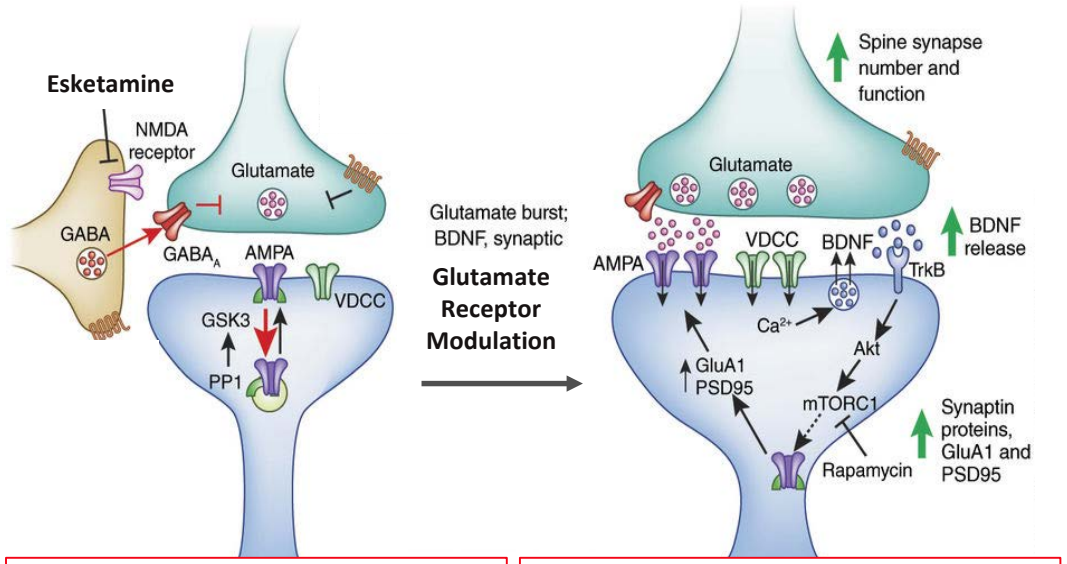
Esketamine Mechanism of Action

Esketamine is a First-in-Class Glutamate Receptor Modulator





Esketamine is the S-enantiomer of Ketamine

- Intranasal route was selected to avoid the first-pass metabolism of oral delivery.
- Esketamine formulation requires less volume than ketamine, making it more suitable for nasal spray administration

Impaired Synaptic Plasticity[1]

Restored Synaptic Connectivity[1]

- Unlike existing approved antidepressant pharmacotherapies, esketamine's putative antidepressant activity does not primarily modulate monoamine systems (norepinephrine, serotonin, dopamine).[2]
- Increased synaptic protein synthesis and spine synapse number detected within 24h post-treatment[3]

1. DoF. **2.** Duman RS, et al. *Nat Med.* 2016 Mar;22(3):238-49. **3.** Li N, et al. *Science.* 2010; 329;959-964.

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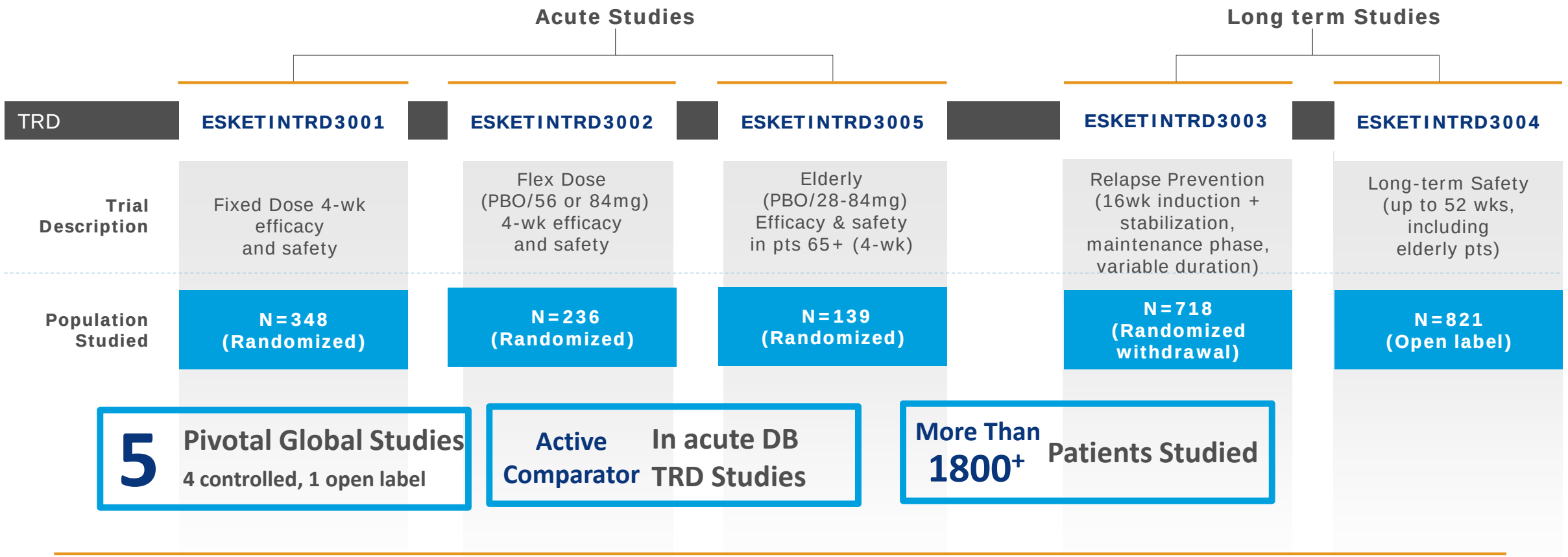
Esketamine Nasal Spray TRD Phase III Clinical Trial Program[1-7]



1. Janssen, Inc. Available from: https://clinicaltrials.gov/ct2/show/NCT02417064 . NLM identifier: NCT02417064. Accessed April 12, 2018. **2.** Janssen, Inc. Available from: https://clinicaltrials.gov/ct2/show/NCT02418585. NLM identifier: NCT02418585. Accessed April 12, 2018. **3.** Janssen, Inc. Available from: https://clinicaltrials.gov/ct2/show/NCT02493868. NLM identifier: NCT02493868. Accessed April 12, 2018. **4.** Janssen, Inc. Available from: https://clinicaltrials.gov/ct2/show/NCT02422186. NLM identifier: NCT02422186. Accessed April 12, 2018. **5.** Janssen, Inc. Available from: https://clinicaltrials.gov/ct2/show/NCT02497287. NLM identifier: NCT02497287. Accessed April 12, 2018. **6.** Janssen, Inc. Available from: https://clinicaltrials.gov/ct2/show/NCT02782104. NLM identifier: NCT02782104. Accessed April 12, 2018. **7.** Janssen, Inc. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03097133. NLM identifier: NCT03097133. Accessed April 12, 2018.

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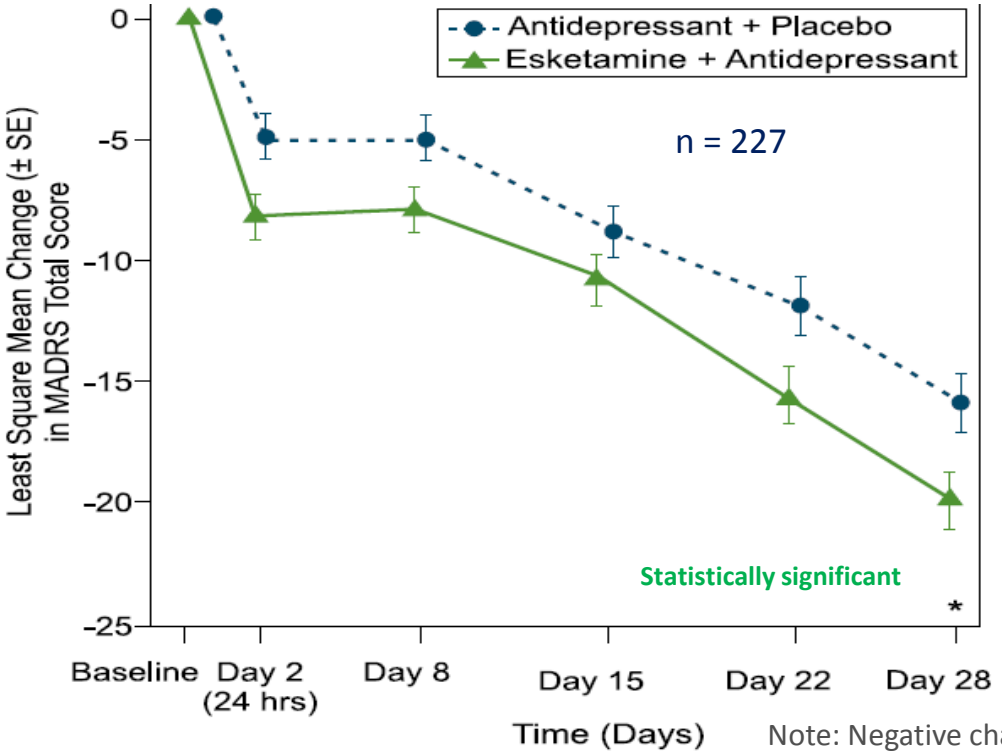
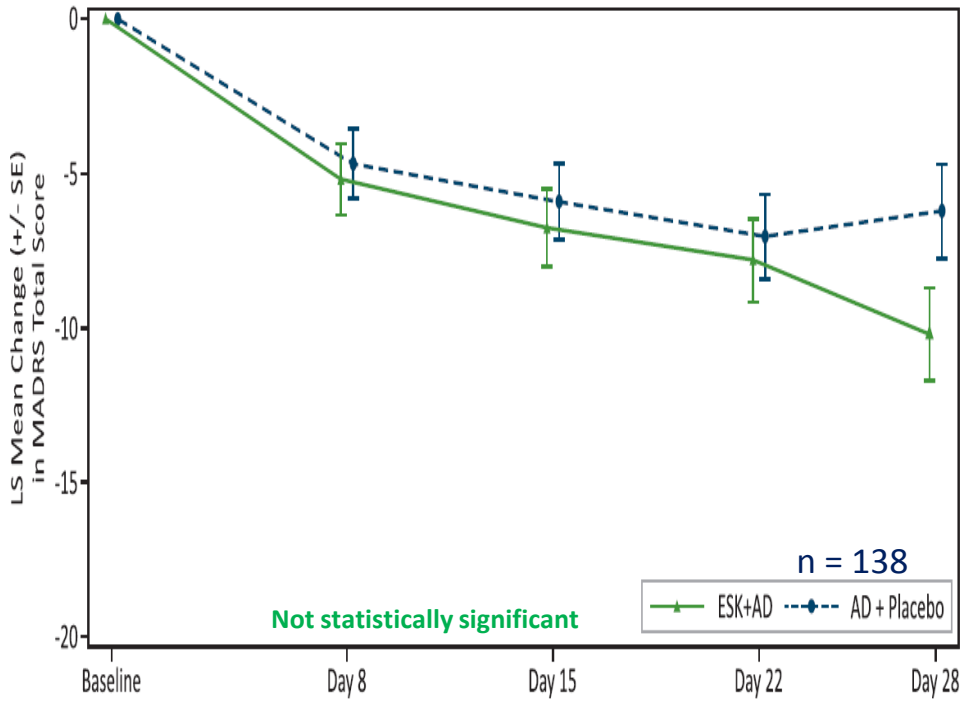
Primary TRD Endpoint: Least Square Mean Change (± SE) in MADRS* Total Score Over Time in Double-Blind Phase

TRANSFORM-2 (3002)
Total Study Population
(18 – 64 years of age)



TRANSFORM-3 (3005)
Total Study Population
(65 – 86 years of age)



Note: Negative change in MADRS score indicates improvement.

Statistical Superiority demonstrated for esketamine nasal spray +antidepressant vs antidepressant+placebo LS Mean Difference at Day 28:
Total Study Population: -4.0 (*1-sided *P*<0.010)

Popova V, et al. Poster presented at the 2018 Annual Meeting of the American Psychiatric Association (APA), May 8, 2018, New York, NY..

Median unbiased LS difference estimate between esketamine nasal spray + antidepressant vs placebo nasal spray + antidepressant at Day 28:
Total Study Population: -3.6 (1-sided P<0.029), favored ESK + AD

Ochs-Ross R, et al. Poster presented at the 2018 Annual Meeting of the American Psychiatric Association (APA), May 8, 2018, New York, NY..

*Montgomery-Asberg Depression Rating Scale (MADRS)

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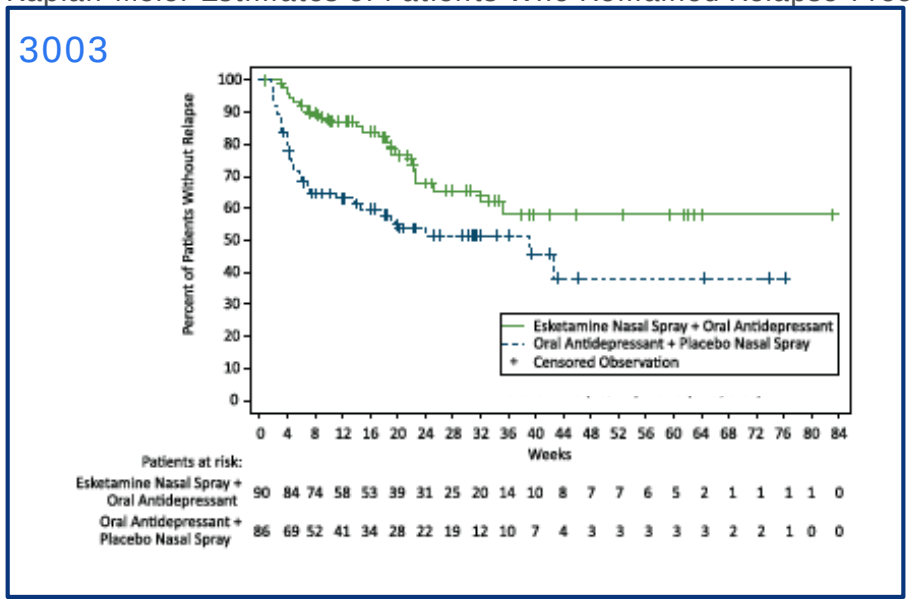
Esketamine Plus an Antidepressant Significantly Delayed Relapse in The Long-term Relapse Prevention Study[1]

LONG TERM STUDY RESULTS

Primary Endpoint: Cumulative Distribution of Time-to-Relapse During the Maintenance Phase Among Stable Remitters

Kaplan-Meier Estimates of Patients Who Remained Relapse-Free



- Patients in stable remission*, after 16 weeks of treatment with ESK+AD, who continued treatment with ESK + AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on AD + PBO; 2-sided p=0.003
- Treatment with ESK + AD decreased the risk of relapse by 51% among patients in stable remission, as compared to AD + PBO

*Stable remission was defined as MADRS total score 12 at least 3 of the last 4 weeks of the optimization phase.
ESK=esketamine nasal spray; AD=antidepressant; PBO=placebo.

1. Daly E et al. Poster presented at: American Society of Clinical Pharmacology 2018; May 29 – June 1; Miami Beach, Florida.

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Esketamine Nasal Spray Safety Information from the Long-Term Open-Label Trial (3004)[1]

The safety of esketamine nasal spray has not been reviewed by the FDA

- Most adverse events were mild to moderate, observed post-dose on dosing days, and generally resolved in the same day

Most common AEs reported (≥10% of subjects) (%)
Dizziness (32.9%)
Dissociation (27.6%)
Nausea (25.1%)
Headache (24.9%)
Somnolence (16.7%)
Dysgeusia (11.8%)
Hypoaesthesia (11.8%)
Vertigo (11.0%)
Vomiting (10.8%)
Viral upper respiratory tract infection (10.2%)

SAEs=serious adverse events; TEAEs=treatment emergent adverse events.

- AEs led to withdrawal of ESK in 9.5% of subjects (6.8% in the induction phase and 3.8% in the subsequent 48-week treatment phase)
- SAEs were reported by 55 subjects (6.9%).
- 2 deaths reported, neither considered related to intranasal medication

- Dissociative symptoms as measured by the Clinician Administered Dissociative States Scale (CADSS) generally began shortly after the start of esketamine nasal spray dosing, peaked at 40 minutes, and generally resolved by 1.5 hours

- Increases in mean systolic and diastolic blood pressure were reported at the 40-minute post-dose timepoint and generally returned, or were close to, pre-dose values by 1.5 hours post-dose

1. Wajs E, Aluisio L, Morrison R, et al. Long-Term Safety of Esketamine Nasal Spray Plus Oral Antidepressant in Patients with Treatment Resistant Depression: Phase 3, Open-Label, Safety and Efficacy Study (SUSTAIN-2). Poster presented at: American Society of Clinical Psychopharmacology (ASCP); May 29 - June 1, 2018; Miami, FL

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Esketamine Nasal Spray Anticipated Dosing and Administration Considerations

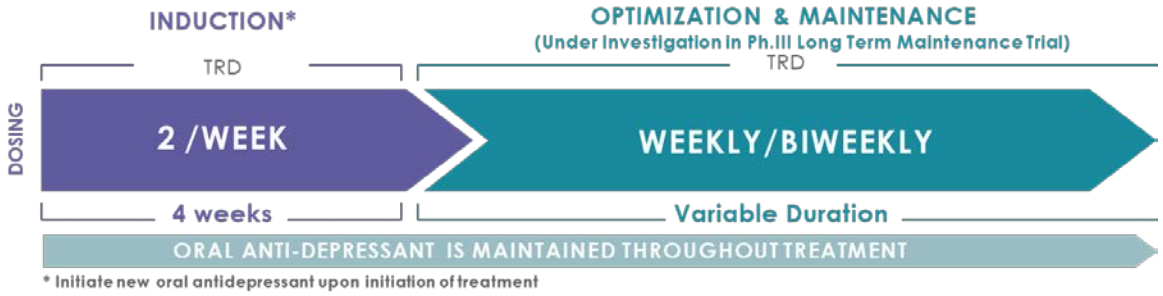
Currently under investigation in a phase III clinical program and subject to FDA approval of final labeling.

Product Formulation

Up to 3 devices may be needed for each session

Delivered via nasal spray from a single-use device

Course of Therapy



A newly initiated daily oral antidepressant is required throughout course of therapy

Induction & Maintenance course of therapy

Administration & Monitoring

Periodic monitoring will be required up to 2 hours.

Self-Administration with HCP observation

Each session will require HCP oversight of administration & monitoring

1. Janssen Inc. Esketamine Receives Breakthrough Therapy Designation from U.S. Food and Drug Administration for Major Depressive Disorder with Imminent Risk for Suicide. Available from: https://www.jnj.com/media-center/press-releases/esketamine-recieves-breakthrough-therapy-designation-from-us-food-and-drug-administration-for-major-depressive-disorder-with-imminent-risk-of-suicide. Accessed April 12, 2018.

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Questions