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<tr><td>Study/Reference</td><td colspan="2">Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II)</td></tr>
<tr><td>Purpose/Background</td><td colspan="2">

Until the approval of esketamine for this indication, there was no approved medication for the emergency treatment of patients with major depressive disorder (MDD) who were in need of rapid symptom control.
Between 10-20% of patients with MDD attempt suicide over the course of their lifetime.
The current standard of care for MDD is includes initiation or optimization of oral antidepressants and frequently, a short hospital stay.
Standard antidepressants take roughly 4 weeks to get the therapeutic effect.
Esketamine nasal spray was approved in 2019 in the United States and European Union for treatment-resistant depression in adults
This study aimed to determine if treatment with esketamine nasal spray plus standard of care would significantly improve MDD symptoms in patients with suicidal ideation more than a placebo plus standard of care.

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<tr><td>Study Design</td><td colspan="2">
Phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted between June of 2017 through April of 2019 at 47 research sites in Argentina, Austria, Belgium, Brazil, Canada, Czech Republic, France, Lithuania, Poland, Spain, Turkey and the United States.

The study had 3 phases:

Screening phase /visit performed 48 hours before the first dose of study drug to assess patients' eligibility for enrollment
25-day, double-blind treatment phase
9-week follow-up phase

Total duration of the study was 90 days
To maintain blinding, a bittering agent was added to the placebo solution.
Intranasal study drug was administered by the patient at the study site and was supervised by a healthcare professional at the site.
The first dose was administered in an emergency department or inpatient psychiatric unit where the patient would stay for at least 5 days.
After the first dose, a protocol-permitted one-time dose reduction of esketamine (or placebo) from 84mg to 56mg was allowed for patients who experienced intolerance.

Patients were randomly assigned in a 1:1 fashion

Treatment group (n=115): Esketamine nasal spray 84 mg plus standard of care

Esketamine nasal spray administered twice weekly for 4 weeks
Initiated or optimized oral antidepressant medications
5 day hospitalization (some countries required longer)

Control group (n=115): Identical placebo plus standard of care

Placebo nasal spray administered twice weekly for 4 weeks
Initiated or optimized oral antidepressant medications
5-day hospitalization (some countries required longer)

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<tr><td>Inclusion/Exclusion Criteria</td><td>Inclusion:

18 – 64 years old
Met DSM-5 criteria for MDD
Had a MADRS total score > 28 at baseline
Had to present with suicidal ideation with intent
Had to undergo comprehensive standard of care treatment including hospitalization
Women had to be of non-childbearing age or using strict contraception methods
</td><td>Exclusion:

Concurrent psychiatric disorders
Moderate to severe substance or alcohol use disorder within 6 months prior to screening
Diagnosis of psychotic disorder
Positive urine drug screen for phencyclidine, cocaine, or amphetamines unless patient had a prescription.
Pregnant or breast-feeding women
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<tr><td>Outcomes</td><td colspan="2"><u>Primary:</u>

Change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline (day 1 pre-dose) to 24 hours after the first dose
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	Secondary: • Change in Clinical Global Impression–Severity of Suicidality–revised (CGI-SS-r) from baseline to 24 hours after the first dose o The secondary efficacy endpoint was only to be tested only after the null hypothesis for the primary endpoint was rejected.	
Stats	• The full efficacy analysis set included all randomized patients who received at least one dose of study drug and had baseline and at least one post-baseline evaluation for MADRS or CGI-SS-r. • Statistical analyses were conducted at a 2-sided, 0.05 level of significance. • Randomization of approximately 112 patients to each treatment group would give a 90% power. • Endpoints were analyzed using Last Observation Carried Forward (LOCF) data using ANCOVA.	

Results	• Of 273 patients screened, only 230 were randomized.
	  o 115 patients to each arm, but 3 patients were excluded from all analyses because they did not get a dose of the study drug. (placebo group n=113 & esketamine group n=114)
	  o 90/115 patients in the esketamine group finished the 4-week treatment phase
	  o 94/115 patients in the placebo group finished the 4-week treatment phase
	  o 89 patients in the esketamine entered the follow-up phase but only 81 finished
	  o 94 patients in the placebo group entered the follow-up period but only 85 finshed.
	• MADRS total score decreased from baseline to 24 hours after first dose in both the esketamine and placebo groups. (primary endpoint)
	  o Esketamine group – (Mean [SD]: -15.7 [11.56])
	  o Placebo group – (Mean [SD]: -12.4 [10.43])
	  o Significantly greater improvement with esketamine - (LS mean difference [SE]: -3.9 [1.39], 95% CI: -6.38 to -1.11; p=0.006)
	• The percentage of patients who achieved remission (MADRS score <12) was numerically greater for the esketamine group than the placebo group. The treatment difference (95% CI):
	  o 11.3% (1.83-20.8) 24 hours post-dose
	  o 10.2% (-2.58-22.98) 4 hours post-dose on day 25
	• Patients in both treatment groups experienced rapid reduction in CGI-SS-r scores (secondary endpoint)
	  o The between group comparison was not statistically significant; p=0.379	

Conclusions	Author Conclusions: • The findings of this study confirm those of the ASPIRE I trial with both showing that esketamine nasal spray reduced depressive symptoms in patients with suicidal ideation with intent. • the rapid reduction in suicidality observed in both treatment groups may have been attributed to the enhanced clinical contact and use of benzodiazepines. My Conclusions: • Esketamine nasal spray plus standard of care showed that it was significantly better at managing MDD symptoms in patients with intent than placebo plus standard of care. • This drug could be beneficial in the acute setting of suicidal ideation with intent, it is uclear how long the drug should be continued after the first dose. Duration may be dependent on patient specific characteristics and severity of symptoms. • Studying this drug in regard to duration of therapy after the acute event of suicidal ideation with intent may be necessary.	
Strengths/Weaknesses	Strengths: • Adequate sample size • Administration of drug was monitored so adherence was confirmed • Adequate length of trial period	Weaknesses: • Good number of patients were lost to follow-up • Psychotherapy was permitted during the study phase • Did not report p values for most data

Reference:
Ionescu DF, Fu DJ, Qiu X, Lane R, Lim P, Kasper S, Hough D, Drevets WC, Manji H, Canuso CM. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). Int J Neuropsychopharmacol. 2020 Aug 29:pyaa068. doi: 10.1093/ijnp/pyaa068. Epub ahead of print. PMID: 32861217.

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