TSND-201 (Methylone) for the Treatment for PTSD: Functional and Global Improvements from the Open- Label Portion of the IMPACT-1 Study

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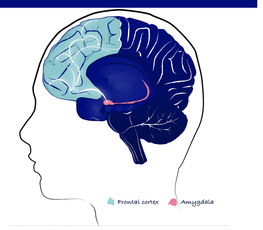
Introduction

- Post-traumatic stress disorder (PTSD) is a serious debilitating disorder impacting approximately 13M Americans each year.[1]
- A diagnosis of PTSD requires symptoms to cause significant distress or impairment in social, occupational, or other important areas of functioning.[2]
- Approved pharmacotherapies for the treatment of PTSD (sertraline and paroxetine) have limited effectiveness. Less than 30% of patients treated with first-line pharmacotherapy achieve remission, which often takes many weeks to achieve.[3]
- TSND-201 has demonstrated rapid, robust, and durable improvements on PTSD and depressive symptoms.[4]
- Functional impairment is common with PTSD, often resulting in significantly reduced quality of life.[5]
- There is an urgent need for rapid-acting, non-hallucinogenic treatments for PTSD.

About TSND-201 (Methylone)

- **Methylone is a rapid-acting neuroplastogen**
  - Rapidly induces neuroplasticity gene expression (e.g., BDNF) in brain areas underlying pathophysiology of PTSD, depression, and anxiety[6]
- **Well-characterized primary pharmacology**
  - Monoamine transporters are primary site of action
  - No binding at 5HT2A receptor, not hallucinogenic
  - Rapid, robust serotonin and norepinephrine release in the frontal cortex



IMPACT-1 Study Design

Overview

Currently enrolling

Part A Open-label — N = 14 → **Part B** Placebo-controlled — N = ~64

Study Design (Part A and B)

Patients with severe PTSD (CAPS-5 ≥ 35) → 4 Week Treatment Period: Dose, Dose, Dose, Dose → 6 Week Follow-up Period → End of Study

ClinicalTrials.gov: NCT05741710

Key Inclusion	Key Exclusion
• Age 18-65	• Concurrent substance abuse disorder
• DSM-5 diagnosis of PTSD	• Use of MDMA or psychedelic <12 months
• CAPS-5 ≥ 35	• History of schizophrenia, psychotic disorder, bipolar, personality disorder, etc.
• Failed 1 prior PTSD treatment	

- TSND-201 was administered once a week for 4 weeks. Each dose given as an initial dose, followed by a second dose 90 minutes later.
- Participants were accompanied by a trained Mentor during the dosing session who provided non-directive support.
- After the 4-week treatment period, participants attended follow-up visits at 1, 2, 3, and 6 weeks following the last dose.
- Safety was assessed via standard measures including adverse events.
- Functioning was assessed via the 3 domains of the Sheehan Disability Scale (school/work, family life, social life). The overall SDS is presented as the mean of the 3 domains.
- Global improvement was measured by the Clinician Global Impression of Improvement (CGI-I) scale.

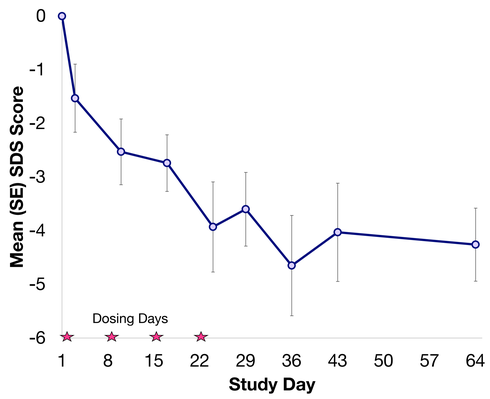
Results

Baseline and End of Study SDS Scores

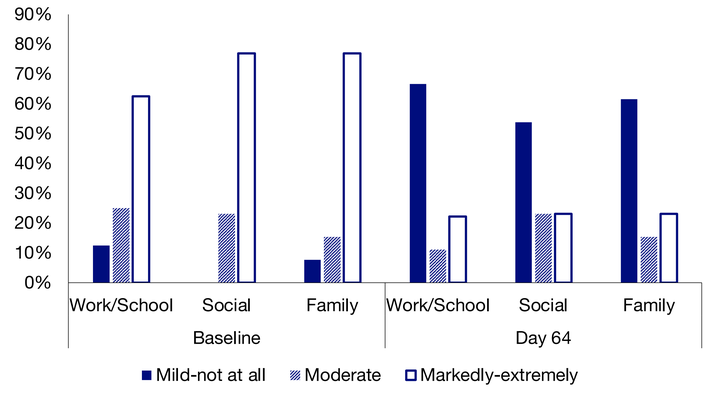
SDS Domain	Baseline	Day 64
Mean Overall	7.3 (1.72)	3.1 (3.12)
Work/School	6. 4 (2.50)	3.3 (3.78)
Social Life	7.8 (1.54)	3.2 (3.39)
Family Life	7.1 (2.67)	3.1 (3.45)

- At baseline, participants were markedly impaired, as evidenced by the mean SDS score.
- Treatment with TSND-201 rapidly and durably improved functioning.
- By 6 weeks after the last dose, the mean SDS score had improved by 4.26 points.
- Improvements were consistent across each domain.
  - By the end of study, >50% of participants having mild or no impairment, compared to >85% reporting markedly or extreme impairment at baseline.

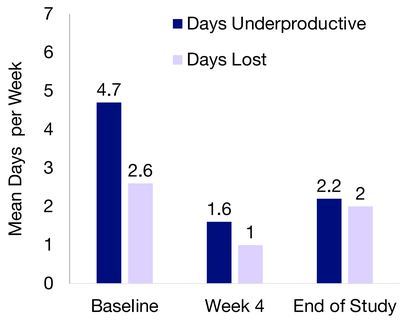
Change from Baseline in Mean SDS Score



Percent of Patients with Mild, Moderate, or Marked Severity by SDS Domain

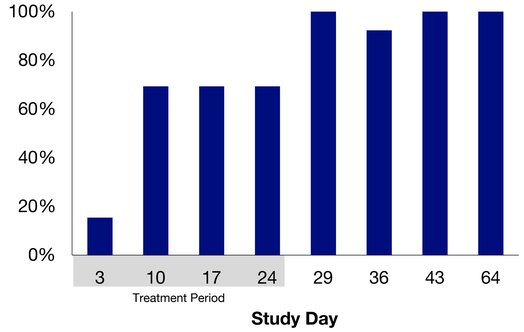


Days per Week Lost and Underproductive



- Treatment with TSND-201 provided improvements in the number of days underproductive and days lost.
- At baseline, the mean number of days underproductive and lost were 4.7 and 2.6, respectively.
- At the end of the 4-week treatment period, TSND-201 had reduced the number of days underproductive and lost by -3.3 and -2.0, respectively.

Percent of Patients who were Much or Very Much Improved on the CGI-Improvement Over Time



- At baseline, the mean CGI-severity was 4.8, representing a moderate to markedly severe PTSD population.
- By Day 10, two days after the 2nd dose, nearly 70% of participants were “much” (38.5%) or “very much” (30.8%) improved.
- At the end of the study, all participants were considered “much” (15.4%) or “very much” (84.6%) improved.

Treatment-Emergent Adverse Events in > 1 Participant

Adverse Event	TSND-201 (N=14)
Any AE	**78.6%**
Headache	42.9%
Decreased appetite	28.6%
Non-cardiac chest pain	21.4%
Fatigue	21.4%
Bruxism	14.3%
Dizziness	14.3%
Hyperhidrosis	14.3%
Influenza-like illness	14.3%
Insomnia	14.3%
Nasopharyngitis	14.3%

Conclusions

- TSND-201 demonstrated rapid, robust, and durable improvements in functioning. Functional improvements were consistent across all domains (school/work, family life, social life).
- Productivity was improved after treatment with TSND-201, as noted by a reduction in the days lost and underproductive.
- TSND-201 has previously shown robust efficacy on PTSD, depression, and sleep-related symptoms. These improvements are consistent with the high rates of improvement on global measures of overall improvement.
- TSND-201 was generally safe and well tolerated, the most common AE was headache.
- Limitations of this study include an open-label design and small sample size.
- This study supports further development of TSND-201 as a treatment for PTSD. Part B of IMPACT-1, a randomized, placebo-controlled study, is currently enrolling.

References

1. NIMH, 2023. 2. APA, 2013. 3. Kelmendi et al., *European Journal of Psychotraumatology,* 2016. 4. Jones et al., *ACNP annual meeting*, 2023. 5. Seedat, *Pharmacoeconomics,* 2006. 6. Warner-Schmidt et al., *Frontiers in Neuroscience*, 2024.

Disclosures

AJ, JW-S, MS, BM, HK are full-time employees with equity in Transcend Therapeutics. BK has equity in Transcend Therapeutics. THWC is a consultant to Transcend Therapeutics.