

# KOR antagonists struggle to address anhedonia in late-phase studies in MDD

Market Event Summary

# Aticaprant and navacaprant encounter hurdles addressing anhedonia in late-phase MDD trials

## Background

**Kappa opioid receptors (KORs)** are heavily implicated in mediating negative stress responses such as anxiety and aversion, and KOR activation promotes depression-like behaviors. Because KOR inhibition avoids many consequences of stress, it represents a novel therapeutic target for MDD and anhedonia.

## KOR antagonism, a setback in MDD

KOR antagonism is believed to be a promising mechanism for inadequately responding adult MDD patients with moderate to severe anhedonia. **Aticaprant**, developed by J&J Innovative Medicine, is a selective KOR antagonist that was investigated as an adjunctive therapy for inadequately responding MDD patients to current ADTs and with moderate to severe anhedonia. On March 6, 2025, J&J decided to discontinue its Phase 3 development program (VENTURA) because of unfavorable efficacy results, although the drug was found to be safe and well tolerated.

**Navacaprant**, developed by Neumora Therapeutics, also faced hurdles in its late-phase trials. Unlike aticaprant, navacaprant is in development as a monotherapy for MDD. The Phase 3 KOASTAL-1 trial, which included 383 participants with moderate to severe MDD, failed to show significant improvements in depressive symptoms (measured by MADRS) or anhedonia (measured by SHAPS) compared with placebo. Both the navacaprant and placebo groups exhibited similar improvements in depressive symptoms, with no significant differences noted between them. Interestingly, there was an efficacy signal in female participants, suggesting potential gender differences in response. Neumora is analyzing these results to better understand the underlying factors and determine the next steps for navacaprant's development.

## Market impact

### Clarivate's takeaways

- **Key opinion leaders interviewed by Clarivate** find anhedonia (the loss of pleasure or diminished interest in almost all activities) as a key foundational symptom in MDD and find it difficult to treat. Approximately 20% to 30% of MDD patients experience residual anhedonia, and bupropion is a key drug used to manage the condition.
- **Better therapeutic options for managing anhedonia in MDD remains an unmet need:** Anhedonia remains a challenge in MDD as the potential KOR antagonists fail to demonstrate significant efficacy.
- **Impact:** The presence of anhedonia has been shown to be associated with more-severe MDD, as well as worse long-term prognosis and high suicidal rates.
- **The road ahead:** Addressing anhedonia is challenging because it involves complex neurobiological mechanisms that are not fully understood. The setbacks faced by aticaprant and navacaprant highlight the necessity for further research to develop effective treatments for this debilitating symptom.

# About the author



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MS. Kaur has substantial experience in market research and competitive intelligence. On Clarivate's CNS/Ophthalmology team she is mainly involved in market research and forecasting for depression. She holds an M.B.A. in pharmaceutical management from Jamia Hamdard University.

### Clarivate coverage of Major depressive disorder

- Disease Landscape & Forecast: Major depressive disorder (G7), providing comprehensive market intelligence insights
- Epidemiology: diagnosed incidence and prevalence data of MDD across the G7 and emerging markets.
- Current Treatment: physician insights (EU5 and the United States), exploring prescribing trends among surveyed psychiatrists and primary care physicians.
- Current Treatment: Treatment Algorithms | MDD (US), exploring prescribing trends via claims data analysis
- Unmet Need: Treatment-resistant depression (US / EU), including an Excel-based target product profile simulator
- Access & Reimbursement: MDD (US), providing insights on the impact of payer policy on prescribing behavior in MDD.



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