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Breaking the Pain-Safety Trade-Off: The Promise of Dual NOP/MOP Agonists

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As Tris Pharma advances cebranopadol toward a potential FDA submission, James Hackworth discusses a novel approach designed to separate effective pain relief from the neurobiological drivers of addiction.



The search for safer and more effective pain therapies remains one of medicine's most pressing challenges. Despite advances in pain management, clinicians and patients continue to face a difficult balance between adequate pain relief and the risks of addiction, overdose, and long-term dependence. **At BIO International Convention 2026 in San Diego, BioSpectrum Asia spoke with James Hackworth, President of the Brand Division at Tris Pharma,** about the science behind dual NOP/MOP receptor agonism, the company's lead investigational therapy cebranopadol, and how a novel approach to pain treatment could reshape the future of both acute and chronic pain management. As Tris Pharma prepares for a potential NDA submission, Hackworth outlines why the next generation of analgesics may finally challenge the long-standing trade-off between efficacy and safety.

The industry continues searching for safer pain therapies. Why is this challenge so difficult?

Pain is one of the most pervasive and consequential challenges in medicine and yet, despite decades of research, there remains a vast unmet need for safer therapies that still deliver meaningful relief. The complexity runs deep, beginning with the fundamental problem of measurement. Unlike many diseases, pain is entirely subjective. In the laboratory, we rely on animal models to explore new mechanisms and are limited to observation of behavior rather than communication, which can be misleading. An animal may cease a pain-related behavior for reasons that only partially have to do with analgesia and that ambiguity makes it difficult to translate preclinical findings into clinical success.

There are also pharmacological disconnects between species that have consequences for drug development. Certain adverse effects that limit dosing in humans, such as nausea and vomiting, for instance, do not appear in rodents. A rat can tolerate doses of an opioid that would be impossibly high in a person. That means a dose that looks therapeutically effective in an animal model may never be achievable in a patient.

Perhaps the most stubborn obstacle is neurobiological. Potent analgesia requires activity in the central nervous system, and the pathways that govern pain relief are, unfortunately, closely intertwined with the pathways that govern reward and pleasure. That is why many effective analgesics as well as non-analgesics that work in the brain (e.g., opioids, benzodiazepines, ketamine, stimulants) carry abuse liability. It is not a coincidence; it is a reflection of shared neurobiology. Breaking that link is the central challenge of pain drug development.

How does dual NOP/MOP agonism differ from traditional opioid approaches?

Dual-NMR agonists are designed to stimulate the Nociception/Orphanin FQ Peptide (NOP) and MOP (Mu) receptors to work together for the potential of a combined pain-relieving effect that is greater than either pathway alone while NOP attenuates many of the negative effects typically associated with MOP. This combined effect is not just two mechanisms running in parallel; it's the interplay between them that creates the potential for robust pain relief with improved safety.

Drugs like morphine, oxycodone, and fentanyl work primarily through selective activation of MOP. MOP stimulation is effective for pain, but it also drives the cascade of effects associated with the opioid crisis like euphoria, profound abuse liability, respiratory depression, dependence, tolerance, addiction, and overdose.

NOP receptors serve a dual role. They contribute to analgesia, while simultaneously counteracting MOP-related adverse effects. Together, the NOP and MOP receptors have the potential to provide effective analgesia with a novel, differentiated safety profile.

Notably, when compared to drugs like morphine or oxycodone, studies have demonstrated that our investigational, first-in-class dual NMR agonist, cebranopadol, may have lower abuse potential, less respiratory depression, a reduced risk of dependence and tolerance, and minimal MOP-related side effects.

What could a successful NDA submission mean for the pain management field?

We plan to submit a new drug application (NDA) for cebranopadol to the FDA this year. If accepted, the aim is to bring meaningful pain relief without the challenges patients and physicians have long faced.

In America alone, approximately 80 million people per year experience acute pain, many of whom require opioid level pain relief for effective management. However, the opioid addiction crisis has caused devastating loss of life and strained every part of the healthcare system. Due to fear of dependence and addiction, patients are forced to make an impossible choice: endure inadequate pain relief or accept risks that could lead to dependence, addiction or fatal overdose. Additionally, differences in state regulations, liability concerns, and DEA scrutiny have created an environment where prescribing opioids, even when medically appropriate, could jeopardize physicians' licenses.

A significant proportion of people who develop opioid use disorder began as legitimate pain patients. With treatment, they experienced not only relief but euphoria, and that experience opened a door to misuse that was difficult to close. If we can treat pain effectively without producing a euphoric signal, we can reduce new addiction cases and deliver meaningful and responsible care.

Once it is approved outside of the U.S., we hope that cebranopadol will allow access to a therapy designed to treat more severe pain with substantially lower risks of addiction and overdose in places that currently tightly restrict opioid use to minimize these risks.

How do you balance efficacy with abuse deterrence?

For a dual NOP/MOP receptor agonist, this balance is inherent to the mechanism.

Drugs like oxycodone are highly abusable because MOP stimulation triggers dopamine release in the brain's reward and pleasure centers. That dopaminergic signal is the physiological basis of euphoria, and euphoria is what drives misuse. NOP receptor activation, by contrast, inhibits dopamine release in those same regions.

In a dual NOP/MOP receptor agonist, those two effects are designed to work together with the goal of delivering responsible relief. MOP drives analgesia and would otherwise produce reward, but NOP simultaneously blunts this reward signal. The result is the potential for meaningful pain relief with a substantially reduced risk of abuse.

This stands in contrast to the current state of pain pharmacology, which presents clinicians with an inverse relationship between efficacy and safety. The most “effective” analgesics like fentanyl, for instance, carry the highest abuse potential. Reduce potency, and you get medications like tramadol with comparatively lower abuse risk but meaningfully reduced efficacy. Reduce potency further, and you reach NSAIDs and acetaminophen, which pose very limited abuse risk but can’t address severe pain. Patients and prescribers have always had to make these difficult trade-offs.

Dual NOP/MOP receptor agonists have the potential to break that equation. If approved, cebranopadol has the potential to unlock a new way of thinking about the risk-benefit calculus in pain management.

What is the next frontier in pain therapeutics?

Currently, cebranopadol is being evaluated in moderate-to-severe acute pain. Our next frontier is the transition to chronic pain.

Studies have demonstrated cebranopadol’s promise to deliver significant analgesia with substantially reduced risks compared to drugs like oxycodone, which represents a meaningful development in potential treatment options for moderate-to-severe acute pain. However, we recognize the burden of chronic pain is substantial and widespread as well. Patients living with chronic conditions often require sustained opioid therapy to function, and the risks associated with long-term opioid use can be even greater than with acute use, specifically, dependence and tolerance, the erosion of efficacy over time, and all of the associated social and psychological consequences.

Tolerance is a critical issue. Chronic opioid use frequently requires escalating doses to maintain the same level of pain control, which compounds both safety concerns and addiction risk. Early animal studies and preliminary human data suggest that dual NOP/MOP receptor agonists have a differentiated tolerance profile when compared to existing chronic pain treatments. If that signal holds in larger, pivotal chronic pain trials, it would be meaningful for the millions of patients whose quality of life depends on finding a sustainable solution to long-term pain.

The convergence of lower abuse potential, reduced dependence risk, and potentially sustained efficacy over time is precisely what the chronic pain space has needed, and we believe dual NOP/MOP receptor agonists are uniquely positioned to address this need.