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## 2025 Neuroscience:

# A Look into Key Events

**Following our 2024 Neuroscience Recap, we highlight several key events to anticipate this year. We have included major clinical events as well as thoughts on the biopharmaceutical industry's response to the new administration's impact on the neuroscience market.**

**Lumanity offers extensive experience-based strategic guidance and insights in the field of neuroscience. Our goal is to provide our clients with actionable solutions that de-risk and optimize the development and commercialization of therapies, ultimately improving the lives of patients who are impacted across a range of conditions.**

## Carolina Lahmann, PhD

### Narcolepsy Type 1 (NT1): A new era of treatment

Narcolepsy Type 1 (NT1) is a rare yet profoundly impactful disorder, characterized by debilitating symptoms that disrupt daily life, affecting everything from work productivity and school performance to social interactions and relationships. The root cause of NT1 is the selective loss of orexin neurons, leading to a deficiency in orexin (also known as hypocretin), a crucial neuropeptide that regulates wakefulness and other physiological processes. Given this clear etiology, there is significant interest in the potential of orexin receptor agonists to restore orexin signaling and directly address the disorder's underlying cause.

In a groundbreaking development, Takeda announced in 2024 the promising results of their Phase IIB trial for NT1. Their innovative Orexin Receptor 2 (OX2R) agonist, oveporexton, demonstrated the ability to normalize wakefulness, as measured by the maintenance of wakefulness test (MWT), and demonstrated improvements in cognitive symptoms —a first for any NT1 treatment. As the anticipation builds, Phase III trials are ongoing, with results expected in the second half of 2025. Adding to the excitement, Alkermes and Centessa are also in Phase II clinical development of additional OX2R agonists for NT1, with key data readouts also anticipated in late 2025.

A pivotal question remains: Will orexin agonists prove effective in treating other sleep disorders beyond NT1, such as Narcolepsy Type 2 (NT2) and Idiopathic Hypersomnia (IH), where the role of orexin is less defined? Both Alkermes and Centessa are actively pursuing Phase II trials in NT2 and IH, while Takeda is advancing another OX2R agonist (TAK-360) in these conditions. The results from these trials will be crucial, guiding strategic decisions on the indication selection and prioritization of orexin agonists not only in sleep disorders but potentially in other neurological conditions as well.

The future of NT1 treatment is bright, with the potential for orexin receptor agonists to revolutionize care. As we await the results of these pivotal trials, there is hope on the horizon for those affected by this challenging disorder.

## Ginger Johnson, PhD

### GLP-1 agonists make inroads in neuroscience

Glucagon-like peptide-1 (GLP-1) receptor agonists, known for their effectiveness in diabetes and weight loss, are now showing promise in Alzheimer's disease (AD). The link between diabetes and AD suggests that improved insulin signaling could help mitigate neurodegeneration. GLP-1 agonists may offer neuroprotective benefits in AD through various mechanisms including neuroinflammatory, vascular, and other AD-related processes, but more large-scale trials are needed to confirm their efficacy and safety.

Semaglutide (Ozempic, Wegovy) and liraglutide (Saxenda, Victoza) have been noted for their potential in this area. A study in Alzheimer's and Dementia found that semaglutide reduced the risk of Alzheimer's diagnosis by 40% to 70% in patients with type 2 diabetes. Additionally, a Phase II trial showed liraglutide slowed cognitive decline by 18% compared to a placebo.

I, with the rest of the AD community, am eagerly anticipating Novo Nordisk's Phase III evoke and evoke+ trials – the first large-scale trials to investigate the disease-modifying potential of semaglutide in participants with early-stage symptomatic AD, including exploration of effects on AD biomarkers and neuroinflammation. Completion of the trials' main phase is expected in September 2025, and the 52-week extension will continue to October 2026.

Beyond AD, GLP-1 agonists are being explored for their potential in treating Parkinson's disease, ALS, and mood disorders, highlighting their versatility in advancing neuroscience. Strategic choices in pursuing these indications will be crucial to fully realizing the potential of GLP-1 agonists in various neurological conditions.

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## Jumaah Goldberg, DPT, MBA

### Anti-PACAP therapies emerge as a major player in migraine and beyond

The pituitary adenylate cyclase-activating polypeptide (PACAP) pathway has emerged as a significant target in migraine and broader neurological research, with key Phase IIb results for Lu AG09222 expected in the second half of 2025. PACAP, a neuropeptide involved in vasodilation, neuroinflammation, and pain signaling, has been shown to trigger migraine attacks in susceptible individuals. Recent clinical data indicate that blocking PACAP with monoclonal antibodies significantly reduces migraine frequency, including in patients unresponsive to CGRP-based treatments. Additionally, PACAP inhibition is being explored in post-traumatic headache (PTH), with studies showing that PACAP-38 infusion can induce migraine-like headaches in individuals with persistent PTH.

Beyond headache disorders, PACAP's role in neurodegeneration has gained attention. Preclinical research suggests that PACAP modulation may enhance non-amyloidogenic processing of amyloid precursor protein (APP), reducing amyloid-beta accumulation and potentially slowing cognitive decline in Alzheimer's disease. Furthermore, PACAP exhibits neuroprotective properties in models of Parkinson's and Huntington's diseases, where it promotes neuronal survival and modulates inflammatory responses.

While anti-PACAP therapies present a promising frontier, challenges remain in refining selectivity, optimizing patient stratification, and ensuring long-term safety. The strategic selection of indications and continued investment in clinical validation will be crucial in determining whether anti-PACAP approaches redefine treatment paradigms across multiple neurological conditions.

## Bobby Moy

### The biopharmaceutical industry's response to the new administration's impact on the neuroscience market

Given a new administration which has been working to radically reshape the FDA and HHS, I'll be watching for how decisions in these institutions affect the procurement of care, what gets covered, and what gets approved.

Many neuroscience agents have concentrated populations on Medicare or Medicaid. Age-related neurodegenerative disorders such as Alzheimer's and Parkinson's primarily affect those on Medicare, while mental health conditions are more commonly treated under Medicaid programs. Shifts in policy and budgeting could substantially impact the delivery of care for neurological disorders, potentially altering the landscape of commercial opportunities in these fields. Drug developers must closely monitor national and state-level changes to understand how these developments may influence the future market.

Furthermore, changes to the FDA may significantly change the timing and content of FDA reviews, potentially exposing them to political influence. Modifications to FDA recommendations concerning diversity could also hinder the ability to gather data that accurately reflects the diverse US population. This might result in inadequate data collection for specific groups, such as the transgender community.

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