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Skye Bioscience Clinical Model Demonstrating Necessity of Peripheral CB1 Inhibition for Weight Loss Presented at European Congress on Obesity

• This model demonstrates that central inhibition of CB1 is not required for weight loss

• Anti-CB1 inhibiting antibody, nimacimab, showed greatest peripheral restriction compared with monlunabant and rimonabant, small molecule-based CB1 inhibitors, which both exhibited increasing dose-dependent brain penetration

• This model predicts nimacimab's potentially superior therapeutic index, which is dependent on minimal brain exposure while maintaining sufficient peripheral inhibition

SAN DIEGO, May 13, 2025 (GLOBE NEWSWIRE) -- Skye Bioscience, Inc. (Nasdaq: SKYE) ("Skye"), a clinical-stage biotechnology company focused on unlocking new therapeutic pathways for obesity and other metabolic health disorders, presented a clinical pharmacokinetic ("PK") and pharmacodynamic ("PD") model that underscores the fundamental relationship between biodistribution and efficacy of CB1 inhibitors at the annual European Congress on Obesity meeting. This model demonstrated that achieving strong peripheral CB1 inhibition is sufficient to achieve efficacy, including weight loss. In contrast, blocking CB1 in the brain (central inhibition), which is associated with neuropsychiatric side effects, is not enough on its own to achieve weight loss.

Published clinical PK and potency data coupled with Phase 2 ("P2") and Phase 3 efficacy data from Novo Nordisk's monlunabant and Sanofi's rimonabant, respectively, as well as Phase 1 data from nimacimab were used to develop a model to determine whether peripheral CB1 inhibition alone is sufficient for weight loss, or if central inhibition is also required for optimal efficacy. The results showed that central inhibition of CB1 alone was not sufficient for weight loss with P2 data for monlunabant, and demonstrated that increasing drug levels in the brain did not improve efficacy. Relatedly, monlunabant's Ph2 dose range established that all doses achieved significant peripheral inhibition, resulting in significant but similar weight loss. The model also showed that a 5 mg dose of rimonabant that had significant levels in the brain but not peripherally was not effective, leading to only minimal weight loss.

"This model meaningfully advances our understanding of how CB1 inhibitors work, demonstrating that peripheral and not central target engagement is foundational to achieving efficacy including weight loss. Moreover, it clarifies how the therapeutic index of CB1 inhibitors is tied to the relationship between receptor inhibition in the brain, or centrally, versus peripherally--and the widest therapeutic index is associated with the greatest

peripheral restriction," said Punit Dhillon, CEO. "Our clinical model, together with Skye's recent mouse diet-induced obesity studies, highlights that nimacimab can potentially achieve significant weight loss with a molecule uniquely restricted to tissues outside the brain. We believe nimacimab's highly favorable therapeutic index sets our antibody-based drug apart from small-molecule CB1 inhibitors."

Beyond the relationship with weight loss, using reported safety data from the same clinical trials allowed the model to provide further insight into the therapeutic index of different CB1 inhibitors. Unlike weight loss, neuropsychiatric adverse events such as anxiety and mood changes became present and escalated as CB1 inhibition in the brain increased. While nimacimab has been shown to be virtually undetectable in the brain, penetration into the brain is a challenge small molecule CB1 inhibitors such as rimonabant and monulunabant continue to face.

Dr. Chris Twitty, Chief Scientific Officer added, "While the sufficiency of peripheral CB1 inhibition, as it relates to metabolic gains including weight loss, has been demonstrated preclinically in tissue-specific knock-out systems, our modeling provides a clinical lens that demonstrates parallel findings. Our data show that nimacimab's Phase 2 dose achieves peripheral CB1 engagement at more than seven times the inhibition threshold, while remaining over 600 times below this threshold in the brain. We remain confident in our belief that the Phase 2 dose of nimacimab will be safe and effective, with potent inhibition and a favorable PK profile in the periphery with very little presence in the brain."

The poster can be accessed on Skye's Spotlight page.

About Skye Bioscience

Skye is focused on unlocking new therapeutic pathways for metabolic health through the development of next-generation molecules that modulate G-protein coupled receptors. Skye's strategy leverages biologic targets with substantial human proof of mechanism for the development of first-in-class therapeutics with clinical and commercial differentiation. Skye is conducting a Phase 2 clinical trial (ClinicalTrials.gov: NCT06577090) in obesity for nimacimab, a negative allosteric modulating antibody that peripherally inhibits CB1. This study is also assessing the combination of nimacimab and a GLP-1R agonist (Wegovy®). For more information, please visit: www.skyebioscience.com. Connect with us on X and LinkedIn.

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Source: Skye Bioscience, Inc.