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Skye Bioscience Comments on Monlunabant Phase 2 Top-line Data and Reiterates Confidence in Nimacimab Clinical Development Plan

16-week top-line weight loss data validates mechanism of action targeting peripheral CB1 receptors

Skye highlights safety advantages of large-molecule CB1 inhibition compared to small-molecule approach

SAN DIEGO, Sept. 23, 2024 (GLOBE NEWSWIRE) -- Skye Bioscience, Inc. (Nasdaq: SKYE) ("Skye"), a clinical-stage biopharmaceutical company focused on developing new therapeutics for metabolic health, is providing a statement regarding a recent announcement by Novo Nordisk on Phase 2a top-line data with monlunabant, Novo's small-molecule oral cannabinoid receptor (CB1) inverse agonist.

"We are encouraged to see that monlunabant met its primary endpoint and demonstrated at least a 6% placebo-adjusted weight loss at 16 weeks, which we see as broadly supportive of the mechanism of action for inhibition of peripheral CB1 receptors and its role in weight loss," said Punit Dhillon, Skye's Chief Executive Officer and Chairman of the Board. "The observation of dose-dependent neuropsychiatric side effects in this study was unfortunate, however, this highlights a key distinction between our large-molecule CB1 inhibitor and known small-molecule CB1 inhibitors currently in development. Nimacimab, a monoclonal antibody being developed by Skye, has demonstrated minimal accumulation of drug in the brain in preclinical non-human primate studies, and in our limited data set from the Phase 1 MAD study in non-alcoholic fatty liver disease (NAFLD), importantly, no neuropsychiatric adverse events (N=62) were observed."

"In pharmacodynamic models, the key advantages of nimacimab's peripheral restriction from the brain have been underscored," said Chris Twitty, Skye's Chief Scientific Officer. "Modeling of Phase 1 pharmacokinetic and preclinical biodistribution data demonstrate* that both nimacimab and monlunabant have sufficient peripheral exposure to exceed their respective IC_{90} thresholds to inhibit CB1 signaling. However, as expected for a small molecule, monlunabant has reported notable leakage into the brain, leading to central exposure exceeding the IC_{75} concentration at all doses tested in the Phase 2a study. We believe these data demonstrate a critical challenge faced by current CB1 small molecules in development, which lack adequate restriction from the brain and an increased potential for neuropsychiatric side effects."

Mr. Dhillon added, "It is clear that with increased restriction from the brain, nimacimab provides a potential clear safety advantage over a small molecule approach. In addition, nonclinical studies have shown the predominant role of peripherally-driven CB1 inhibition in

achieving weight loss and metabolic gains versus centrally-driven CB1 inhibition. To support our hypothesis, Skye has developed a murine mouse model expressing the human variant of the CB1 receptor, which will allow us to evaluate the effects on weight loss with nimacimab in a diet-induced obesity murine model. We expect to share results from these studies in the near future."

Skye launched its Phase 2 trial of nimacimab in obesity in August 2024. This trial, which is the first to also assess a GLP-1/CB1 inhibitor combination, is expected to report interim weight loss data in Q2 2025 and top-line data in Q4 2025.

Following is a summary of Skye data and perspectives on the prospects for CB1 inhibition and nimacimab.

Potency and Pharmacokinetics

- **Nimacimab**: Using both Skye's Phase 1 clinical PK data and non-human primate biodistribution studies, a robust model was developed to predict both peripheral and central exposure of nimacimab at the current Phase 2 clinical dose (200 mg administered subcutaneously once-weekly). This model demonstrates* that the concentration of drug in the periphery greatly exceeds the dose required to inhibit CB1 receptor signaling (IC_{90}), with highly limited exposure in the brain at a level 100-fold less than the IC_{50} and 600-fold less than the IC_{90}, potentially mitigating the risk of promoting neuropsychiatric side effects.

- **Monlunabant**: Published Phase 1 clinical data as well as preclinical biodistribution and potency data for monlunabant has been used to establish a model that predicts both peripheral and central exposure at all Phase 2 clinical doses. This model underscores that while sufficient peripheral inhibition has been achieved at all doses, notable brain exposure* in this chronic setting exceeds the IC_{75} concentration at all doses, with the highest dose exceeding IC_{90} levels. This model is consistent with the dose-dependent increase in neuropsychiatric AEs reported in monlunabant's Phase 2 trial.

- **Nimacimab Wider Therapeutic Index:** These models highlight that in contrast to the small-molecule-based CB1 inhibitors, nimacimab has a potentially wider therapeutic index that may lead to greater flexibility to dose considerably higher while still maintaining central levels well below the IC_{50}. Of note, nimacimab's Phase 1 clinical data has also demonstrated favorable tolerability, providing further support for a potential broader therapeutic index.

Efficacy

- Monlunabant achieved approximately 6% weight loss at 16 weeks, which aligns with historical benchmarks achieved by rimonabant and is similar to oral semaglutide at similar time points (approximately 6% placebo-adjusted).

- This data is in line with and validates the trend for CB1 inhibitors, and is highly supportive of the 8% placebo-adjusted weight loss target at 26 weeks in Skye's current Phase 2 obesity study of nimacimab.

Neuropsychiatric Safety Concerns

- Monlunabant previously showed accumulation in the brain, preclinical and Phase 1 neuropsychiatric side effects were observed, and Phase 2 dose-dependent neuropsychiatric side effects were observed, reflecting the CNS exposure also seen with other small-molecule CB1 inhibitors.

- Nimacimab has had no known CNS safety concerns, showing no neurological toxicity in preclinical studies and zero neuropsychiatric side effects in its Phase 1 trial (with a larger N than the monlunabant Phase 1).

Nimacimab Differentiation

- **Monlunabant Dose Limitation:** Limited weight loss at higher doses suggests a potential plateau in efficacy and reinforces potential PK/PD limitations that may compress the therapeutic index. While brain exposure is a critical hurdle that may require a lower clinical dose, these small molecules also have the disadvantage of targeting the orthosteric site of CB1, which necessitates competition with often high concentrations of peripheral endocannabinoids.

- **Non-Competitive Inhibition of CB1 Signaling:** Antibody-based CB1 inhibition not only drives its heightened peripheral restriction but also allows nimacimab to bind to the CB1 receptor away from the endocannabinoid binding pocket at the allosteric site. This binding still allows nimacimab to inhibit CB1 signaling as both an inverse agonist and an antagonist while avoiding competition with natural ligands (2-AG and AEA), ensuring a better PK/PD relationship even with higher endocannabinoid levels.

  *** Graphs reflecting statements in this release are included in Skye's investor deck**

About Nimacimab

Nimacimab is a first-in-class humanized negative allosteric monoclonal antibody that inhibits CB1 signaling in the periphery as an inverse agonist and antagonist. Inhibition of CB1 has shown anti-fibrotic, anti-inflammatory, and metabolic mechanisms of action with potential to address a broad range of diseases with unmet medical needs such as obesity, chronic kidney disease, and metabolic dysfunction-associated steatohepatitis (MASH).

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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FORWARD LOOKING STATEMENTS

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Source: Skye Bioscience, Inc.