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Skye Announces Clinical Development Plan in Obesity for Differentiated Peripheral CB1 Inhibitor, Nimacimab

Skye files IND with FDA Division of Diabetes, Lipid Disorders and Obesity

Phase 2 study in patients with obesity and chronic kidney disease planned to initiate in first half of 2024

SAN DIEGO, Dec. 11, 2023 (GLOBE NEWSWIRE) -- Skye Bioscience, Inc. (OTCQB: SKYE) ("Skye"), a pharmaceutical company developing drugs targeting the endocannabinoid system, announced today that it plans to develop nimacimab, the Company's monoclonal antibody recently acquired from Bird Rock Bio, for weight loss and the treatment of obesity. The Company has filed an Investigational New Drug ("IND") application with the U.S. Food and Drug Administration ("FDA") for the initiation of a Phase 2 clinical study of nimacimab in patients with obesity and chronic kidney disease.

Nimacimab is a negative-allosteric modulating antibody targeting the cannabinoid 1 receptor ("CB1"), which has been implicated as an important target in multiple cardiometabolic diseases including obesity and renal complications. Obesity and kidney disease are highly correlated: 80% of patients who have kidney disease are also obese; 30% of obese patients have kidney disease. Moreover, the role of CB1 as an important regulator of appetite/satiety and diabetic renal complications has been demonstrated preclinically as well as clinically with a number of small molecule inverse agonists/antagonists. However, their efficacy has been hampered by mechanism-based safety issues related, in particular, to side effects of the central nervous system ("CNS"). Nimacimab effectively inhibits CB1 signaling and, based on preclinical and early clinical studies, is devoid of the CNS liabilities typically seen by small molecule drugs that target the CB1 receptor because it does not cross the blood-brain barrier. Skye owns the worldwide rights to nimacimab, with patents issued in the U.S. and other territories including claims to cannabinoid 1 receptor antibodies with inverse agonist function.

"The global overweight and obesity epidemic affects over a billion people worldwide and in the US is estimated to affect over 40% of the adult population. Even with the recent approvals of new drugs for the treatment of obesity, this number is only expected to grow," said Punit Dhillon, CEO and Chair of Skye. "GLP-1 and GIP receptor agonists have demonstrated that obesity can be treated therapeutically with safe and effective drugs, and have exposed a market opportunity that is just the tip of the iceberg. Despite the excitement and success around these drugs, a significant portion of the patient population cannot tolerate them and there is recognition of a need for differentiated therapeutic mechanisms. This need is underscored by recent activity of large pharmaceutical companies to acquire drugs with complementary mechanisms of action to treat obesity and highlights a trend toward combinations targeting two or even three mechanisms. As we look to a likely future where most major pharmas will have their own GLP-1 agonist, we see nimacimab as a key

potential component of future combination therapies."

The safety and tolerability assessments from the completed Phase 1b study of nimacimab in non-alcoholic fatty liver disease ("NAFLD") patients with diabetes or prediabetes demonstrated no serious adverse events ("SAEs"), no early terminations of treatment due to adverse events, and no adverse events of concern occurring in a dose-dependent manner. Encouraging trends were observed in exploratory biomarkers of cholesterol, liver enzymes and liver function in patients receiving nimacimab versus placebo after the three-week dosing period. Moreover, pharmacokinetic assessment of nimacimab highlighted a half-life of approximately three weeks, potentially allowing for monthly dosing. The drug is formulated in pre-filled syringes enabling convenient patient self-administration.

"The safety profile of nimacimab from preclinical and clinical studies is encouraging, and we believe it exceeds what others have demonstrated with small molecule drugs that also act to block the CB1 receptor. Because of the potential of this class of drug to treat a range of metabolic conditions, we believe a Phase 2 study to treat patients with obesity and comorbid chronic kidney disease offers the potential to evaluate multiple meaningful clinical endpoints beyond weight loss, such as changes in albuminuria to evaluate kidney function, that will guide the future development of nimacimab," said Tu Diep, Chief Development Officer of Skye. "The promising PK data from the Phase 1 study suggests that nimacimab can be dosed once-a-month subcutaneously, which we believe would be a significant competitive advantage over once-a-week subcutaneous dosing of the current peptidic GLP-1 receptor agonists or even orally dosed GLP-1 receptor agonists due to their less desirable tolerability profile."

About the Endocannabinoid System and Peripheral CB1 Inhibition for Weight Loss

The endocannabinoid system ("ECS") has emerged as one of the most relevant regulators of energy balance. The ECS acts through two cannabinoid receptors: types 1 and 2 (CB1 and CB2). CB1 is widely expressed in the CNS and brain, but is also expressed in peripheral tissues such as adipose tissue, skeletal muscle, and in the liver, kidney, gut, and pancreas. In obese states, CB1 agonists such as anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG), the body's naturally-produced endocannabinoids, are increased and may exert unfavorable effects on insulin-sensitive tissues. Peripheral inhibition of CB1 has been shown to cause a reduction in food intake and a sustained weight loss through multiple mechanisms, including increasing incretin expression in the gut and reducing ghrelin expression. The ECS also contributes to the control of lipid and glucose metabolism, and it is well established that blockade of CB1 receptors enhances insulin sensitivity in both humans and rodents.

Clinically, early development of small molecule drugs that blocked the CB1 appeared encouraging with the approval of rimonabant (Sanofi) in Europe for weight loss and obesity. However, it was soon removed from the market because of side effects related to the high exposure of the drug to the CNS and brain, which resulted in safety issues such as depression, anxiety and suicidal ideations. A new class of drugs are now designed to only target the CB1 in the periphery, while avoiding the CNS.

About Nimacimab

Nimacimab is a first-in-class humanized monoclonal antibody that acts as a negative

allosteric modulator to inhibit CB1 signaling in the periphery. Inhibition of CB1 has shown anti-fibrotic, anti-inflammatory, and metabolic mechanisms of action with significant potential to address a broad range of diseases with notable unmet medical needs such as chronic kidney disease, obesity, and non-alcoholic steatohepatitis (NASH). Nonclinical studies over 26 weeks showed that nimacimab does not accumulate in the brain. A Phase 1 study showed PK of approximately 21 days with no safety concerns after four weeks of dosing, suggesting a favorable potential dosing regimen. Collectively, this data highlights nimacimab's potential as a new class of CB1 inhibitor.

About Skye Bioscience

Skye is focused on unlocking the pharmaceutical potential of the endocannabinoid system to treat diseases with inflammatory, fibrotic, and metabolic processes. Backed by leading life science venture investors, Skye's strategy leverages biologic targets with substantial human proof of mechanism for the development of first-in-class therapeutics with significant clinical and commercial differentiation. Nimacimab, a negative allosteric modulating antibody that inhibits peripheral CB1, showed a favorable safety and tolerability profile in a Phase 1 study. Skye plans to start a Phase 2 study in obesity and chronic kidney disease for nimacimab in H1 2024. SBI-100 Ophthalmic Emulsion, a CB1 agonist, is currently being studied in a Phase 2 study of patients with glaucoma and ocular hypertension. For more information, please visit: https://www.skyebioscience.com.

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FORWARD-LOOKING STATEMENTS

This press release contains forward-looking statements, including statements regarding our product development, business strategy, timing of clinical trials and commercialization of cannabinoid-derived therapeutics. Such statements and other statements in this press release that are not descriptions of historical facts are forward-looking statements that are based on management's current expectations and assumptions and are subject to risks and uncertainties. If such risks or uncertainties materialize or such assumptions prove incorrect, our business, operating results, financial condition, and stock price could be materially negatively affected. In some cases, forward-looking statements can be identified by terminology including "anticipated," "plans," "goal," "focus," "aims," "intends," "believes," "can," "could," "challenge," "predictable," "will," "would," "may" or the negative of these terms or other comparable terminology. We operate in a rapidly changing environment and new risks emerge from time to time. As a result, it is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements the Company may make. Risks and uncertainties that may cause actual results to differ materially include, among others, our capital resources, uncertainty regarding the results of future testing and development efforts

and other risks that are described in the Risk Factors section of Skye's most recent annual or quarterly report filed with the Securities and Exchange Commission. Except as expressly required by law, Skye disclaims any intent or obligation to update these forward-looking statements.

Source: Skye Bioscience, Inc.