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2025 Stockholder Letter

To the Stockholders' of Skye Bioscience, Inc.:

In the past twelve months, we have taken decisive steps to build what we believe can be the most compelling CB1-targeted therapeutic program in obesity. With urgency and precision, we have been executing our clinical development plan around nimacimab—a first-in-class, peripherally restricted CB1 inhibitor antibody—designed to solve what we believe to be one of the most persistent challenges in the obesity epidemic: achieving long-term, tolerable, and metabolically effective weight loss.

We know what is expected of us. Investors do not want grand narratives; they want strategic clarity, execution, and data. That's why we have delivered—on time and ahead of plan—milestones that underscore the seriousness of our intent and the caliber of our team. This letter outlines what we have done, why CB1 matters, and how we intend to move forward with focus and discipline.

Bird Rock Acquisition and Reset: August 2023

Our August 2023 acquisition of Bird Rock Bio, Inc. ("Bird Rock Bio") was strategic and singular in purpose—its only asset, nimacimab, represented a unique chance to revive the CB1 inhibition class with an antibody engineered for peripheral selectivity without CNS penetration and with strong preclinical and early clinical proof of metabolic benefit. Within 90 days of closing the acquisition of Bird Rock Bio, we submitted an IND with the Division of Diabetes, Lipid Disorders and Obesity and had secured clearance from the agency to proceed with our planned clinical protocol by January 2024. We subsequently raised gross proceeds of $90 million in financing from top-tier healthcare investors.

Adding to our leadership team and changing our board of directors, we adopted a complete focus on one goal: proving that peripherally restricted CB1 inhibition could drive durable weight loss, avoid central side effects, and offer a differentiated mechanism to the crowded incretin-centric space of anti-obesity drugs.

Execution in 2024: Delivering on the CBeyond™ Trial

We launched our Phase 2a clinical trial for nimacimab, CBeyond™, in August 2024. Our goals were clear: initiate a multi-center, placebo-controlled, randomized study evaluating nimacimab with and without semaglutide, evaluate for a meaningful weight loss difference, and generate top-line data in under 15 months.

Enrollment was completed in February 2025, four months ahead of schedule. The trial randomized 136 patients, exceeding our 120-patient plan. We are now positioned to deliver 26-week top-line results in late Q3 or early Q4 2025—without requiring interim analysis. This performance reflects both strong patient demand and our team's clinical operations discipline.

The study now also includes a 26-week extension, enabling 52-week long-term efficacy and safety readouts in 2026, and will provide us with further insight to design future clinical trials.

Why Nimacimab, Why Now?

We believe obesity requires chronic therapy. But today's leading treatments—GLP-1 receptor agonists—face challenges with tolerability, accessibility, lean mass loss, and discontinuation rates exceeding 50% within one year. CB1 inhibition has the potential to address these issues from a different mechanistic angle: emphasizing fat metabolism, not appetite suppression alone.

The CB1 pathway is central to energy storage and adipocyte signaling, and it is CB1 receptors in peripheral tissue that plays a critical role in these functions. To our knowledge, nimacimab is the only antibody in development that selectively targets peripheral CB1 for inhibition. Preclinical studies showed significant reductions in fat mass, improved glycemic markers, and preservation of lean mass. We also demonstrated superior exclusion from the brain—with nimacimab being 600-fold below the concentration to inhibit signaling in the brain (IC_{90})—and have seen no neuropsychiatric adverse events in studies to date.

In short: nimacimab can potentially be used chronically, and complement GLP-1s or stand alone. We believe nimacimab can enable the next wave of safe, sustainable anti-obesity medicines.

The Road Ahead: Data, Differentiation, and Development

We look forward to the forthcoming data in 2025. We expect to deliver additional preclinical data that further validates nimacimab's mechanism of action—specifically its role in weight loss, promoting fat metabolism, preserving lean mass, and improving metabolic parameters in diet-induced obesity models, without the need for inhibition of centrally located CB1 receptors. Reported findings already have reinforced, and we believe additional data will further support, the foundation of our clinical hypothesis and continue to support our regulatory strategy.

By late Q3 or early Q4 2025, we expect to deliver top-line results from the CBeyond™ study. If our hypothesis holds—demonstrating durable weight loss with a clean safety profile—we intend to proceed directly to Phase 2b planning. Preparations are already underway: CRO engagement, regulatory planning, protocol development, and manufacturing scale-up are in progress.

We believe our balance sheet is strong, with our cash runway projected through at least Q1 2027. We intend to remain disciplined in capital allocation, focusing on programs that build our pipeline with a clear path to registration and commercial value.

Positioned to Lead

The obesity space is crowded if you look at it through a lens focused on GLP-1 drugs commercialized or under development. Fundamentally, however, the obesity market is very large, is growing, and has heterogeneous segments of patients with distinct and unmet needs. We believe there is an important role for complementary therapies that are mechanistically distinct from incretin approaches. And nimacimab—if successful—has the potential to become the benchmark CB1 therapeutic: effective in metabolically important tissue in the periphery, safe, durable, and combinable.

We are operating with urgency and clarity because we understand the magnitude of the opportunity. Our team and board are aligned behind a singular goal: to establish Skye as the category-defining leader in metabolic therapeutics. Every resource is directed toward executing this plan with discipline and precision. We're focused on the fundamentals—delivering data, scaling thoughtfully, and staying ahead of the science.

Thank you for your continued support. We look forward to sharing more in the coming months.

Sincerely,

/s/ Punit Dhillon

Chief Executive Officer

This proxy statement, including the letter from our CEO, contains forward-looking statements based upon current expectations that involve risks, uncertainties and assumptions. For more information, see the section entitled "Forward-Looking Statements."