October 6, 2025

Skye Bioscience Reports Topline CBeyond™ Phase 2a Data from Nimacimab Monotherapy and Combination Clinical Trial

- *Nimacimab monotherapy did not meet its primary endpoint for weight loss; preliminary pharmacokinetic analysis showed lower than expected drug exposure, potentially indicating the need for higher dosing as a monotherapy.*
- *Clinically meaningful additional weight loss observed with combination of nimacimab, a peripheral CB1 inhibitor, and semaglutide compared to semaglutide alone.*
- *Nimacimab alone and in combination demonstrated a clean safety profile, with no added gastrointestinal adverse events and no nimacimab-associated neuropsychiatric adverse events reported.*
- *Company to host conference call today at 8:00 a.m. ET.*

SAN DIEGO, Oct. 06, 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, today announced the topline data from its 26-week Phase 2a CBeyond™ proof-of-concept study of nimacimab, its peripherally-restricted CB1 inhibitor antibody.

In CBeyond™, the nimacimab monotherapy arm did not achieve the primary endpoint of weight loss compared to placebo (-1.52% vs. -0.26 for placebo, mITT[1]). Preliminary pharmacokinetic analysis showed an association between exposure and response, suggesting that the 200 mg, subcutaneous weekly dose was suboptimal as a monotherapy.

In the combination cohort, nimacimab 200 mg (subcutaneous, weekly) plus semaglutide demonstrated a clinically meaningful magnitude of weight loss compared to semaglutide alone (-13.2% vs -10.25%, p=0.0372, mITT), with no plateau being observed through Week 26. This finding supports potential further studies to evaluate combinations of nimacimab and incretin-based therapies.

At the tested dose and exposure levels, nimacimab 200 mg demonstrated a favorable safety profile with placebo-like tolerability. In combination with semaglutide, there was no increase in gastrointestinal (GI) adverse events. Importantly, there were no increases in neuropsychiatric adverse events reported resulting from treatment with nimacimab.

"The 200 mg monotherapy arm provided important pharmacokinetic insight, showing that lower-than-expected drug exposure may have limited the observed effect and informing the dose-ranging strategy we are developing," said Puneet Arora, MD, FACE, Chief Medical Officer of Skye Bioscience. "At the same time, the combination of nimacimab with semaglutide produced a clinically meaningful additional weight loss that exceeded

semaglutide alone, with a favorable tolerability profile even in patients who achieved the highest exposure levels. With our preclinical data, toxicology safety margins, and PK modeling, we believe we have a path to support higher dosing, and we are evaluating the next stage of development to optimize dosing in potential future clinical trials."

“This is the first clinical study to show that the combination of a CB1 inhibitor and a GLP-1 therapeutic can drive clinically meaningful additional weight loss beyond a GLP-1 drug alone,” said Louis Aronne, MD, past President, The Obesity Society; past Chairman, American Board of Obesity Medicine; and clinical advisor to Skye. “Equally important, although the sample size is small, nimacimab achieved this without neuropsychiatric or additive gastrointestinal adverse events. I believe these results warrant further evaluation of the therapeutic potential of this novel CB1 inhibitor.”

“Gastrointestinal side effects remain a leading cause of discontinuation with obesity therapies,” said Sean Wharton, MD, Director, Wharton Medical Clinic and clinical advisor to Skye. “It was notable that nimacimab did not increase GI adverse events while adding clinically meaningful weight loss in combination with semaglutide. In my view, a next study with higher nimacimab dosing is the logical step to fully define its role in clinical practice.”

CBeyond™ Phase 2a Topline Results at 26 Weeks

- **Monotherapy dosed at 200 mg demonstrated lower than expected drug exposure.** In the monotherapy arm, nimacimab 200 mg did not achieve the primary endpoint, with placebo-subtracted weight loss of -1.26% at week 26 (p=0.2699, mITT). Preliminary pharmacokinetic analysis showed lower than expected drug exposure of nimacimab, supporting evaluation of higher dosing.

- **Clinically meaningful add-on efficacy with semaglutide.** -13.2% weight loss in the nimacimab plus semaglutide combination arm at Week 26 compared to -10.25% in the semaglutide-alone arm (-2.95%, p=0.0372, mITT). Notably, no plateau was observed at 26 weeks, which indicates potential for future weight loss.
- **High frequency of responders in the combination arm** In the per protocol analysis, 100% achieved >5% weight loss (vs. 85% with semaglutide) and 67% achieved >10% weight loss (vs. 50% with semaglutide).
- **Body composition.** An improvement in lean mass to fat mass ratio was observed at Week 26 comparing the nimacimab plus semaglutide combination arm to the placebo arm (0.26 vs. 0.02, p <0.0001), and the combination arm compared to semaglutide alone (0.26 vs. 0.13, p = 0.0126).

Percent Change in Body Weight from Baseline at Week 26 (mITT Analysis)**

	Placebo *N = 44*	**Nimacimab 200 mg** *N = 40*	**Placebo + Semaglutide** *N = 24*	**Nimacimab 200 mg + Semaglutide** *N = 28*

Least-squares mean percent reduction *(SE)* (95% CI)*	-0.26 *(0.881)* *(-2.0, 1.5)*	-1.52 *(0.889)* *(-3.3, 0.2)*	-10.25 *(1.092)* *(-12.4, -8.1)*	-13.2 *(1.016)* *(-15.2, -11.2)*
Placebo-subtracted weight loss (SE) *(95% CI), P-value*		-1.26 *(1.136)* *(-3.5,1.0), 0.2699*	-9.99 *(1.286)* *(-12.5, -7.4), <0.0001*	-12.94 *(1.244)* *(-15.4, -10.5), <0.0001*
Semaglutide-subtracted weight loss (SE) *(95% CI), P-value*				-2.95 *(1.405)* *(-5.7, -0.2), 0.0372*

Percent Change in Body Weight from Baseline at Week 26 (Per Protocol Analysis*)**

	Placebo *N = 32*	**Nimacimab 200 mg** *N = 31*	**Placebo + Semaglutide** *N = 20*	**Nimacimab 200 mg + Semaglutide** *N = 21*
Least-squares mean percent reduction *(SE)* (95% CI)*	0.81 *(1.013)* *(-1.2, 2.8)*	-0.52 *(0.936)* *(-2.4,1.3)*	-9.97 *(1.143)* *(-12.2, -7.7)*	-13.47 *(1.087)* *(-15.6,-11.3)*
Placebo-subtracted weight loss (SE) *(95% CI), P-value*		-1.33 *(1.246)* *(-3.8,1.1), 0.2878*	-10.78 *(1.365)* *(-13.5, -8.1), <0.0001*	-14.29 *(1.334)* *(-16.9, -11.6), <0.0001*
Semaglutide-subtracted weight loss (SE) *(95% CI), P-value*				-3.51 *(1.460)* *(-6.4, -0.6), 0.0178*

*Analyzed based on the primary efficacy estimand using a mixed model for repeated measures (MMRM).
** Modified intent to treat analysis (mITT) includes all randomized, treated participants
*** Per Protocol analysis excludes major protocol deviations and non-adherent subjects

- **Favorable tolerability results.** Nimacimab 200 mg demonstrated a clean safety profile as a monotherapy with placebo-like tolerability. When combined with semaglutide, no increase in gastrointestinal (GI) adverse events were observed. In the safety analysis population, rates of GI adverse events were 27% with nimacimab alone versus 29.5% with placebo, and 57.1% in combination with semaglutide versus 66.7% with semaglutide alone.

Incidence of Selected Gastrointestinal Adverse Events

	Placebo *N = 44*	**Nimacimab** *N = 40*	**Nimacimab 200 mg + Semaglutide** *N = 28*	**Placebo + Semaglutide** *N = 24*
Nausea, n (%)	4 (9.1)	5 (12.5)	9 (32.1)	7 (29.2)

Constipation, n (%)	1 (2.3)	4 (10.0)	2 (7.1)	6 (25.0)
Vomiting, n (%)	1 (2.3)	1 (2.5)	6 (21.4)	1 (4.2)
Diarrhea, n (%)	5 (11.4)	0 (0.0)	2 (7.1)	1 (4.2)

- **Neuropsychiatric safety.** No neuropsychiatric concerns were observed, with no increase in anxiety, insomnia, or depression resulting from treatment with nimacimab 200 mg as a monotherapy or in combination with semaglutide.

Incidence of Selected Neuropsychiatric Adverse Events (mITT Analysis)

	Placebo *N = 44*	**Nimacimab 200 mg** *N = 40*	**Nimacimab 200 mg + Semaglutide** *N = 28*	**Placebo + Semaglutide** *N = 24*
Insomnia	1 (2.3)	1 (2.5)	0 (0.0)	1 (4.2)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)

- **Patient discontinuation.** The CBeyond™ study had an overall discontinuation rate of 27%; 3.7% discontinuations across the study were due to adverse events, with the placebo group contributing to 60% of these discontinuations.

Patient Discontinuations During 26 Week Treatment Period

	Placebo *N = 44*	**Nimacimab 200 mg** *N = 40*	**Nimacimab 200 mg + Semaglutide** *N = 28*	**Placebo + Semaglutide** *N = 24*	**Overall** ***N = 136***
Primary Study Period Withdrawal (%)	14 (30.4)	13 (28.9)	6 (26.1)	4 (18.2)	37 (27.2)
Withdrawal Due to Adverse Event	3 (6.5)	1 (2.2)	1 (4.4)	0 (0.0)	5 (3.7)

Skye believes multiple factors support evaluation of nimacimab at higher doses, including the combination of preclinical toxicology margins and modeling; preclinical data showing dose-dependent increases in weight loss with nimacimab monotherapy and GLP-1 combinations; and the notable safety profile in this Phase 2a study. Skye is continuing to evaluate the data to determine next steps, including a potential follow-on Phase 2 study beyond the ongoing Phase 2a extension study.

The next set of detailed results from the 26-week treatment period of the CBeyond™ trial will be presented at ObesityWeek in November.

CBeyond™ Trial Design

The randomized, placebo- and active-controlled, double-blind CBeyond™ Phase 2a trial enrolled 136 adults with overweight or obesity, including individuals with a BMI ≥27 kg/m²

with at least one comorbidity. Patients were randomized across four arms, 2:2:1:1 to arms with weekly nimacimab 200 mg subcutaneously, placebo, nimacimab 200 mg plus semaglutide (Wegovy®), or placebo plus semaglutide, and were dosed weekly for 26 weeks. Patients not participating in a 26-week extension were monitored for 13 weeks post-treatment.

Patients who completed 26 weeks of treatment in the primary phase of the study were eligible to enroll in a 26-week extension for a potential full treatment duration of 52 weeks with a 13-week follow-up period. In the combination arms, patients will continue with blinded treatment with nimacimab or placebo and will continue receiving semaglutide (Wegovy®). Patients in the monotherapy arm will receive nimacimab 300 mg during the extension. Enrollment for the extension is complete. Skye expects to report data from the extension study in Q1 2026.

The 26 week treatment period was designed to evaluate efficacy, safety, and pharmacokinetics and exploratory endpoints, with the extension ongoing to further assess these endpoints, and follow-up to assess durability and weight regain. The trial population was broadly representative of adults living with obesity, with a mean BMI of ~36.84 kg/m^2 and majority female participants.

Conference Call and Webcast Information

Skye Bioscience will host a conference call and webcast to discuss these results at today at 8:00 a.m. ET. The webcast will be accessible at this link. (Please allow time for registration.) A replay will be available on the company's Investor Relations website for 30 days following the live event.

About Nimacimab

Nimacimab is a potential first-in-class, peripherally-restricted monoclonal antibody inhibitor of the CB1 receptor. Unlike previous CB1-targeting drugs, nimacimab is designed to avoid central nervous system penetration, potentially limiting neuropsychiatric side effects seen with small-molecule antagonists. As a non-incretin, non-peptide agent, nimacimab acts independently of the GLP-1 pathway and has also demonstrated additive or complementary effects in combination with incretin-based therapies in preclinical and clinical studies.

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 2a 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

This press release includes “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release other than statements of historical fact should be considered forward-looking statements, including, without limitation, statements relating to the preliminary pharmacokinetic analysis and dose-exposure response analysis and the potential for higher dosing of nimacimab to achieve greater drug exposure and increased efficacy; the potential for future weight loss beyond 26 weeks; plans to advance nimacimab into the next stage of development to optimize dosing; future clinical development of nimacimab, including the initiation and design of any future clinical trials; the expected timing for reporting data from the Phase 2a extension study; the ability of nimacimab to drive weight loss without neuropsychiatric adverse events; the potential for nimacimab to be a first-in-class drug. When used herein, words including “anticipate,” “believe,” “can,” “continue,” “could,” “designed,” “estimate,” “expect,” “forecast,” “goal,” “intend,” “may,” “might,” “plan,” “planning,” “possible,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, though not all forward-looking statements use these words or expressions. All forward-looking statements are based upon the Company’s current expectations and various assumptions. The Company believes there is a reasonable basis for its expectations and beliefs, but they are inherently uncertain. The Company may not realize its expectations, and its beliefs may not prove correct. Actual results could differ materially from those described or implied by such forward-looking statements as a result of various important risks and uncertainties, including, without limitation, the initiation and design of any future clinical trials will be impacted by the Company’s capital resources, the Company’s ability to obtain additional sources of capital needed to run an additional Phase 2 clinical trial, program considerations and potentially other factors outside the Company’s control; the Company's preliminary pharmacokinetic and dose-exposure analysis is not complete, and such analysis may change following receipt of the full pharmacokinetic modeling and dose-exposure response analysis; the potential for additional weight loss after 26 weeks may not ultimately be observed; there is no guarantee that higher dosing of nimacimab will achieve increased efficacy, and likewise it is possible that higher dosing will produce adversely different safety and tolerability results than those observed to date; the Company’s dependence on third parties in connection with product manufacturing; research and preclinical and clinical testing; the Company’s ability to advance, obtain regulatory approval of and ultimately commercialize nimacimab, competitive products or approaches

limiting the commercial value of nimacimab; the timing and results of preclinical and clinical trials; the Company's ability to fund development activities and achieve development goals; the impact of any global pandemics, inflation, supply chain issues, government shutdowns, high interest rates, adverse regulatory changes; the Company's ability to protect its intellectual property; risks associated with the Company's common stock and the other important factors discussed under the caption "Risk Factors" in the Company's filings with the Securities and Exchange Commission, including in its Annual Report on Form 10-K for the year ended December 31, 2024, which are accessible on the SEC's website at www.sec.gov and the Investors section of the Company's website. Any such forward-looking statements represent management's estimates as of the date of this press release. While the Company may elect to update such forward-looking statements at some point in the future, except as required by law, it disclaims any obligation to do so, even if subsequent events cause the Company's views to change. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date of this press release.

[1] Modified intention to treat analysis (mITT): All participants who were randomized and received any amount of study medication (IP, active or placebo comparator), regardless of adherence to the treatment plan. Participants were included in the treatment group corresponding to the study treatment they actually received.

Source: Skye Bioscience, Inc.