Scilex Bio, a Controlling Interest of Joint Venture by Scilex Holding Company, Reports Phase 2 Trial for Obesity Currently Enrolling with U.S. Patient Cohort to be Added in 2025. Scilex Bio Reports Positive Results from the Recently Completed Phase 1 Trials Conducted by NeuroBiogen for KDS2010, a Novel Oral Tablet Recently Synthesized Potent, Selective, and Reversible Monoamine Oxidase B inhibitor

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- The ongoing obesity Phase 2 trial is a randomized, double-blind, placebo-controlled, dose finding, clinical trial to evaluate the safety and efficacy of KDS2010 in approximately 75 overweight or obese patients currently enrolling in South Korea with a cohort in U.S. to be added in 2025.
- KDS2010 has shown promising preclinical results with a novel mechanism of blocking MAO-B-dependent aberrant GABA (gamma-aminobutyric acid) production in reactive astrocytes and eliminates neuronal inhibition in Lateral Hypothalamic Area, stimulating metabolism and energy expenditure without affecting appetite.
- MAO-B controls tonic levels of GABA, a chief inhibitory neurotransmitter in the central nervous system. Selective inhibition of astrocytic GABA is a new molecular target for treating obesity.
- KDS2010 pharmacokinetics, lack of food effect, safety and dose selection have been characterized in Single Ascending Dose and Multiple Ascending Dose Phase 1 clinical trials with 88 healthy young adults and elderly subjects, demonstrating favorable safety and tolerability and adequate pharmacokinetics for once-daily dosing.
- Several important pharmacological attributes distinguish KDS2010 from molecules of this class.
    - Firstly, reversibility of the MAO-B inhibition is critical for long-lasting efficacy. Irreversible inhibitors such as selegiline covalently modify the MAO-B enzyme and destroy the enzyme itself to turn on the compensatory expression of enzyme diamine oxidase, which continues to produce GABA, whereas reversible inhibitor occupies the active site of MAO-B competitively, resulting in an intact MAO-B enzyme with no compensatory mechanism.
    - Secondly, only the selective inhibition of MAO-B shown to have selective inhibition of astrocytic GABA, important for anti-obesity effect.
    - Lastly, easy penetration of Blood-Brain Barrier by KDS2010 is very important for targeting astrocytes in Lateral Hypothalamic Area.

PALO ALTO, Calif., Dec. 11, 2024 (GLOBE NEWSWIRE) -- Scilex Bio, a controlling interest of joint venture by Scilex Holding Company (Nasdaq: SCLX, “Scilex” or “Company”) with IPMC Company, a representative company of the Bio Innovation Consortium (“IPMC”) which holds the exclusive rights to NeuroBiogen Company’s (“NB”) KDS2010 global license, announced ongoing Phase 2 trial for obesity currently enrolling with U.S. patient cohort to be added in 2025 and positive topline results from the recently completed Phase 1 trials for oral KDS2010, a novel oral tablet small molecule agent.

KDS2010 (Tisolagiline) is a potent, selective, and reversible Monoamine oxidase B (MAO-B) inhibitor of new generation, which overcomes the drawbacks of existing irreversible and reversible MAO-B inhibitors. Recently, a new important mechanism of action was discovered for this class of drugs. In contrast to the traditional belief, MAO-A and MAO-B have profoundly different roles: MAO-A regulates dopamine levels, whereas MAO-B controls tonic levels of GABA, gamma-aminobutyric acid, a chief inhibitory neurotransmitter in the central nervous system. Selective inhibition of astrocytic GABA is a molecular target for treating obesity. This discovery was published in Nature (Hyun-U Cho, et al. 2021).

“It is exciting to see a new oral medication in development for treatment of obesity with the potential of overcoming current limitations of obesity medications. Reducing obesity and related comorbidities, such as heart disease, hypertension, diabetes, fatty liver disease, and dyslipidemia is of paramount importance for health maintenance. A new oral centrally acting once-a-day medication that is safe and effective would be an exciting development,” said David J. Maron, MD, Chief of the Stanford Prevention Research Center, president-elect of the American Society for Preventive Cardiology, Professor at Stanford University School of Medicine.

Individuals with obesity have an imbalance in food intake and energy expenditure, both of which are regulated by neural circuits that work inside the hypothalamus, in particular, in the lateral hypothalamic area (LHA). Astrocytes are glial cells known to be actively involved in the regulatory aspects of metabolic control, such as feeding and uptake of brain glucose. In addition to their physiological role, increasing lines of evidence point to the involvement of hypothalamic astrocytes in the pathogenesis of diet-induced obesity. Consumption of dietary fats induces metabolic damages in hypothalamic neurons. Genetic, pharmacological and electrophysiological evidence of existence of a distinct subpopulation of pacemaker-firing GABAergic neurons was recently discovered. It is a unique population of fat-burning neurons in LHA, regulating energy expenditure via astrocytic GABA without affecting food intake. Pharmacological inhibition of excessive astrocytic GABA synthesis may become a new effective therapeutic strategy for obesity. KDS2010 effectively and rapidly reduced obesity in mice, attenuated the elevated tonic inhibition in LHA, and reduced fats without suppressing appetite. These findings were published in Nature Metabolism (Moonsun Sa, et al. 2023).

Several important pharmacological attributes are distinguishing KDS2010 from other molecules of this class. Firstly, reversibility of the MAO-B inhibition is critical for long-lasting efficacy. Irreversible inhibitors such as selegiline covalently modify the MAO-B enzyme and destroy the enzyme itself to turn on the compensatory expression of enzyme diamine oxidase, which continues to produce GABA, whereas reversible inhibitor occupies the active site of MAO-B competitively, resulting in an intact MAO-B enzyme with no compensatory mechanism. Secondly, only the selective inhibition of MAO-B shown to have selective inhibition of astrocytic GABA, important for anti-obesity effect. And thirdly, easy penetration of Blood-Brain Barrier by KDS2010 is very important for targeting LHA astrocytes.

Several neuron-target obesity drugs were shown to be effective, but they suppress appetite and were withdrawn from the market or not used due serious safety risks, including cardiovascular and psychiatric complications. The current mainstay of obesity treatment, GLP-1 agonists, are associated with loss of appetite, gastrointestinal side effects, loss of muscle mass, depression, re-bound effect, and drug-resistance. KDS2010 has a potential to overcome these limitations and risks associated with GLP-1 agonists.

KDS2010 pharmacokinetics, lack of food effect, safety and dose selection has been characterized in Single Ascending Dose and Multiple Ascending Dose studies with approximately 90 patients, demonstrating favorable safety profile and tolerability. KDS2010 showed well tolerated and safe for single dose (30 to 960mg) and repeated dosing over 7 days (60 to 480mg) and has adequate pharmacokinetics for once-daily with dose-dependence in the range of 60 to 480mg for repeat dosing. KDS2010 also showed no significant differences in safety/tolerability and pharmacokinetics in healthy adults and the elderly, and between Korean and Western populations, with adequate pharmacokinetics for once-daily dosing.

A Randomized, Double-blind, Placebo-controlled, Dose Finding, Phase 2 Clinical Trial to Evaluate the Efficacy and Safety of KDS2010 in Overweight or Obese Patients is ongoing in South Korea and will be expanding to the USA in 2025. The trial investigates 12-week treatment in 75 patients with high BMI (Body Mass Index) and at least one of the weight-related comorbidities (hypertension, dyslipidaemia, or cardiovascular disease), assessing body weight change from the baseline, proportion of patients with reduction in body weight, and other parameters.

As millions seek access to weight loss drugs, IQVIA experts at Institute for Data Science see a vast opportunity in weight loss drugs with annual global sales forecasts for the emerging obesity drug treatments to about $150 billion by the early 2030s. Global spending on obesity medication totaled $24 billion last year, IQVIA estimated in a 5-year outlook that sales could reach $131 billion by 2028.[1]

“We are very excited to acquire a New Chemical Entity molecule of known drug class, representing a new generation of MAO-B inhibitors, with a newly discovered central mechanism of action relevant for multiple neurological, analgesic and cardiometabolic indications. We are looking forward working with our partners to advance Tisolagiline development starting with adding a cohort of patients in the USA for the current obesity treatment trial,” said Dmitri Lissin, MD, Chief Medical Officer of Scilex Holding Company.

For more information on Scilex Holding Company, refer to www.scilexholding.com

For more information on Semnur Pharmaceuticals, refer to www.semnurpharma.com

For more information on Scilex Holding Company Sustainability Report, refer to www.scilexholding.com/investors/sustainability

For more information on ZTlido®, including Full Prescribing Information, refer to www.ztlido.com.

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info@scilexholding.com

About Scilex Holding Company

Scilex Holding Company is an innovative revenue-generating company focused on acquiring, developing and commercializing the treatment for neurodegenerative and cardiometabolic diseases, and non-opioid pain management products for the treatment of acute and chronic pain. Scilex targets indications with high unmet needs and large market opportunities with non-opioid therapies for the treatment of patients with acute and chronic pain and are dedicated to advancing and improving patient outcomes. Scilex’s commercial products include: (i) ZTlido® (lidocaine topical system) 1.8%, a prescription lidocaine topical product approved by the U.S. Food and Drug Administration (the “FDA”) for the relief of neuropathic pain associated with postherpetic neuralgia, which is a form of post-shingles nerve pain; (ii) ELYXYB®, a potential first-line treatment and the only FDA-approved, ready-to-use oral solution for the acute treatment of migraine, with or without aura, in adults; and (iii) Gloperba®, the first and only liquid oral version of the anti-gout medicine colchicine indicated for the prophylaxis of painful gout flares in adults.

In addition, Scilex has three product candidates: (i) SP-102 (10 mg, dexamethasone sodium phosphate viscous gel) (“SEMDEXA™” or “SP-102”), a novel, viscous gel formulation of a widely used corticosteroid for epidural injections to treat lumbosacral radicular pain, or sciatica, for which Scilex has completed a Phase 3 study and was granted Fast Track status from the FDA in 2017; (ii) SP-103 (lidocaine topical system) 5.4%, (“SP-103”), a next-generation, triple-strength formulation of ZTlido, for the treatment of acute pain and for which Scilex has recently completed a Phase 2 trial in acute low back pain. SP-103 has been granted Fast Track status from the FDA in low back pain; and (iii) SP-104 (4.5 mg, low-dose naltrexone

hydrochloride delayed-release capsules) (“SP-104”), a novel low-dose delayed-release naltrexone hydrochloride being developed for the treatment of fibromyalgia, for which Phase 1 trials were completed in the second quarter of 2022.

Scilex Holding Company is headquartered in Palo Alto, California.

For more information on Scilex Holding Company, refer to www.scilexholding.com

About Semnur Pharmaceuticals, Inc.

Semnur Pharmaceuticals, Inc. (“Semnur”) is a clinical-late stage specialty pharmaceutical company focused on the development and commercialization of novel non-opioid pain therapies. Semnur’s lead program, SP-102 (SEMDEXA™), is the first non-opioid novel gel formulation administered epidurally in development for patients with moderate to severe chronic radicular pain/sciatica.

Semnur Pharmaceuticals, Inc. is headquartered in Palo Alto, California.

For more information on Semnur Pharmaceuticals, refer to www.semnurpharma.com

About Scilex Bio

Scilex Holding Company and IPMC Company, a representative company of the Bio Innovation Consortium (“BOIC”), which holds the exclusive rights to NeuroBiogen Company’s (“NB”) KDS2010 global license, formed a joint venture, Scilex Bio, to develop and commercialize a next-generation reversible MAO-B Inhibitor, a novel inhibitor of aberrant GABA production in reactive astrocytes for the treatment of obesity and neurodegenerative diseases including Alzheimer’s disease.

About IPMC

IPMC is a private biopharmaceutical company focused on the development of new medicines for the treatment of cardiometabolic and neurodegenerative diseases.

Forward-Looking Statements

This press release and any statements made for and during any presentation or meeting concerning the matters discussed in this press release contain forward-looking statements related to Scilex and its subsidiaries and are subject to risks and uncertainties that could cause actual results to differ materially from those projected. Forward-looking statements include statements regarding the Scilex and its subsidiaries, including but not limited to, statements regarding the terms of the potential licensing transaction, statements regarding KDS2010 and the potential efficacy and preclinical results, the potential for KDS2010 to be an innovative new treatment for obesity and Alzheimer’s disease benefitting people living with neurodegenerative and cardiometabolic diseases, the potential market size and growth opportunity for the weight loss and Alzheimer’s global drug market, the Company’s outlook, goals and expectations for 2024, and the Company’s development and commercialization plans. Although each of Scilex and its subsidiaries believes that it has a reasonable basis for each forward-looking statement contained in this press release, each of Scilex and its subsidiaries caution you that these statements are based on a combination of facts and factors currently known and projections of the future, which are inherently uncertain.

Risks and uncertainties that could cause actual results of Scilex to differ materially and adversely from those expressed in our forward-looking statements, include, but are not limited to: the inability of the parties to consummate the licensing transaction for any reason, including any failure to satisfy or waive any closing conditions; changes in the structure, timing and completion of the proposed transaction between Scilex and NeuroBiogen; the ability of the parties to achieve the benefits of the proposed licensing transaction, risks related to the outcome of any legal proceedings that may be instituted against the parties following the announcement of the proposed licensing transaction; risks associated with the unpredictability of trading markets; general economic, political and business conditions; the risk that the potential product candidates that Scilex or Scilex Bio develops may not progress through clinical development or receive required regulatory approvals within expected timelines or at all; risks relating to uncertainty regarding the regulatory pathway for Scilex’s and Scilex Bio’s product candidates; the risk that Scilex and Scilex Bio will be unable to successfully market or gain market acceptance of its product candidates; the risk that Scilex’s product candidates may not be beneficial to patients or successfully commercialized; the risk that Scilex has overestimated the size of the target patient population, their willingness to try new therapies and the willingness of physicians to prescribe these therapies; risks that the outcome of the trials and studies for SP-102, SP-103 or SP-104 may not be successful or reflect positive outcomes; risks that the prior results of the clinical and investigator-initiated trials of SP-102 (SEMDEXA™), SP-103 or SP-104 may not be replicated; regulatory and intellectual property risks; and other risks and uncertainties indicated from time to time and other risks described in Scilex’s most recent periodic reports filed with the SEC, including its Annual Reports on Form 10-K for the year ended December 31, 2023 and subsequent Quarterly Reports on Form 10-Q that the Company has filed or may file, including the risk factors set forth in those filings. Investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this release, and Scilex undertakes no obligation to update any forward-looking statement in this press release except as may be required by law.

Contacts:

Investors and Media
Scilex Holding Company
960 San Antonio Road
Palo Alto, CA 94303
Office: (650) 516-4310

Email: investorrelations@scilexholding.com

Website: www.scilexholding.com

Investors and Media
Denali Capital Acquisition Corp.
437 Madison Avenue, 27th Floor
New York, NY 10022

References

1. www.reuters.com/business/healthcare-pharmaceuticals/weight-loss-drug-forecasts-jump-150-billion-supply-grows-2024-05-28/

SEMDEXA™ (SP-102) is a trademark owned by Semnur Pharmaceuticals, Inc., a wholly-owned subsidiary of Scilex Holding Company. A proprietary name review by the FDA is planned.

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