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Skye Bioscience Receives Australian Ethics Committee Approval to Start First-in-Human Phase 1 Study of SBI-100 Ophthalmic Emulsion

Lead drug candidate has shown superior and longer-lasting lowering of intraocular pressure, a risk factor associated with glaucoma, in preclinical studies

San Diego, California--(Newsfile Corp. - June 30, 2022) - Skye Bioscience, Inc. (OTCQB: SKYE) ("Skye" or the "Company"), a pharmaceutical company developing a proprietary, synthetic cannabinoid derivative to treat glaucoma, has received regulatory approval to begin its first-in-human Phase 1 clinical study of SBI-100 Ophthalmic Emulsion ("SBI-100 OE") from the Australian Human Research Ethics Committee ("HREC"). SBI-100 OE is a patented drug representing a new class of therapeutics to potentially treat glaucoma.

The primary endpoints for this randomized, double-masked, placebo-controlled Phase 1 study of SBI-100 OE are an assessment of safety and tolerability of the drug in healthy volunteers. The secondary endpoint is an assessment of pharmacokinetics. The study will also measure changes to intraocular pressure. A total of 48 subjects will be administered SBI-100 OE or placebo in single ascending dose (SAD) and multiple ascending dose (MAD) arms. Preliminary top-line data is expected in Q4 and final data in Q1 of 2023.

In the study, each arm will consist of three cohorts of eight subjects, six receiving SBI-100 OE and two receiving placebo. In the SAD arm, each subject will be administered a single 35uL drop to one study eye of placebo or SBI-100 OE at concentrations of 0.5%, 1.0% and 2.0% of active drug in cohorts one, two, and three, respectively. In the MAD arm, each subject will receive two drops per day over five days using the respective dose levels of the SAD arm. A Safety Review Committee will monitor the study and review safety data before approving escalation to the next cohort.

"After submitting our clinical trial protocol to HREC in March, we are pleased to receive their approval and look forward to assessing SBI-100 Ophthalmic Emulsion for the first time in humans," said Tu Diep, Chief Development Officer of Skye. "Decades of research have established the role of cannabinoid receptor type 1 (CB1R) in lowering IOP, however, there has been no CB1R agonist therapeutic agent approved by a regulatory agency to treat glaucoma. No other company has methodically created a patented molecule and proprietary formulation - representing a new class of therapeutic drug - to improve the inherent positive attributes of natural cannabinoids while limiting potentially negative systemic effects, and with the goal of enhancing the treatment of glaucoma beyond today's approved drugs.

"Achieving these goals is Skye's focus. We have not only created a drug with this ambition but we have also navigated the complexities of synthetic manufacturing and conducted extensive preclinical assessments, and now we are embracing the rigors of the clinical and

regulatory processes to validate our drug."

The Phase 1 study will be conducted in the clinical trial facility of CMAX Clinical Research in Adelaide, Australia ("CMAX"). Conducting the Phase 1 clinical study in Australia qualifies Skye to receive a tax credit of up to 43.5%.

Next Steps

- *Submission of Clinical Trial Notification to Australian Therapeutic Goods Administration*. This submission is prepared and will be filed now that HREC approval has been obtained.

- *Site visit and training.* Skye will train the study investigators and CMAX's clinical study staff on the clinical protocol and procedures and ensure that the pharmacy understands how to appropriately handle the drug formulation.

- *Clinical trial material (CTM) production.* The manufacturing process of SBI-100 OE requires very specific and specialized equipment, consumables and excipients that cannot be easily substituted. Global supply chain constraints delayed or limited access to certain components of the manufacturing process and delayed CTM production, which was originally scheduled to be completed in early June. We are working with our contract manufacturer, Pharmaceutics International Inc., to finalize logistical and scheduling details. We expect to complete Phase 1 CTM production in July.

- *Secure DEA export license and deliver CTM to Australia.* Skye has secured the import license required for a controlled substance from the Australian Department of Health. We require an export license from the U.S. Drug Enforcement Agency but must complete CTM production before submitting our application. There can be variability in the timing of the DEA's review and issue of an export license. We do not expect to receive this license earlier than August, after which delivery of drug product to Australia will be expedited.

- *Subject screening, enrollment, and first dosing.* Recruitment of study participants will begin after the prior listed steps are substantially completed, since subjects must be administered drug within 28 days of enrollment. Taking into account the listed variables, Skye is aiming to dose the first subject in August.

- *Reporting of study data.* Skye expects to report preliminary topline data in Q4 2022, with final data to be reported in Q1 2023.

"Glaucoma is still an inadequately treated disease that has lacked pharmacological innovation for decades. There is a need for new classes of therapeutics with differentiated mechanisms of action and we have strong conviction in the potential of our novel drug based on relevant independent research and our preclinical data," said Punit Dhillon, CEO and Chair of Skye. "This study will be the first time a novel cannabinoid prodrug will be topically delivered into human's eyes using a nanoemulsion formulation, and marks an important step in the development of SBI-100 Ophthalmic Emulsion to demonstrate the safety of this approach. Importantly, this study may also provide initial insights into this drug's effect on IOP.

"In parallel, we aim to submit an investigational new drug (IND) application, which is not dependent upon Phase 1 data, with the FDA by year-end for our planned US-based Phase 2 in 2023 to assess efficacy and safety in patients with glaucoma."

About SBI-100 Ophthalmic Emulsion
Increased intraocular pressure (IOP) is a key risk factor in the progression of glaucoma. The first observations that consuming cannabis lowered IOP in humans took place in the early 1970s, which led to a significant amount of research on the effects of cannabinoids in the eye. Independent studies demonstrated that activation of the cannabinoid receptor-type 1 (CB1R) in ocular tissue mediates IOP-lowering. However, no cannabinoid-related drug has been approved for clinical use in the eye due primarily to the shortcomings of current delivery methods of CB1R agonists to the eye in a therapeutically beneficial dose. When cannabinoids are administered systemically they can lower IOP but also result in undesirable psychotropic effects. Alternatively, extracted natural cannabinoids delivered topically as an eye drop do not penetrate ocular tissue well enough to effectively lower IOP due to the lipophilic, or oily, properties of natural cannabinoids and the aqueous, or watery, surface of the eye.

To address these challenges, Skye developed SBI-100 OE, a proprietary, synthetic cannabinoid derivative possessing a novel molecular structure and formulation that was rationally designed to enable better penetration of ocular tissue and effective topical delivery of a CB1R agonist. In preclinical studies involving three different species, a nanoemulsion formulation of the drug applied topically to the eye resulted in enhanced therapeutic efficacy and duration of response in lowering IOP. Importantly these studies also demonstrated advantages compared to today's standard of care and, if clinically validated in subsequent efficacy studies, may provide a suitable therapeutic window to be a new class of medicine for glaucoma.

About Skye Bioscience
Skye Bioscience is a pharmaceutical company unlocking the potential of cannabinoids through the development of its proprietary cannabinoid derivatives to treat diseases with significant unmet needs. The company's lead program, SBI-100 OE, is focused on developing a treatment for glaucoma, the world's leading cause of irreversible blindness. For more information, please visit: www.skyebioscience.com.

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FORWARD-LOOKING STATEMENTS
This letter contains forward-looking statements, including statements regarding our product development, business strategy, the 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.

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