January 8, 2025

Ensysce Biosciences Issues Annual Shareholder Letter

~ FDA Breakthrough Therapy designation received for PF614-MPAR ~
~ PF614-MPAR second clinical trial initiated ~
~ Lead clinical candidate identified for OUD program ~
~ PF614 Phase 3 trial poised to commence 1H 2025 ~

SAN DIEGO, CA / ACCESSWIRE / January 8, 2025 /Ensysce Biosciences, Inc. (NASDAQ:ENSC) ("Ensysce" or "Company"), a clinical-stage pharmaceutical company developing innovative solutions for severe pain relief while reducing the potential for opioid abuse and overdose, today issued a letter to shareholders from Chief Executive Officer, Dr. Lynn Kirkpatrick.

Dear Fellow Shareholders,

2024 was underscored by outstanding progress for our two clinical programs, and I would like to thank you and all of our committed shareholders for their support over the last year. We have achieved several key milestones in our efforts to develop our highly novel approach to providing opioid pain relief while reducing abuse and prescription drug overdose, an approach that we believe will save many lives. I welcome this opportunity to summarize last year's events and milestones achieved and to present a look ahead to what we believe will be another exceptional year in 2025.

Our focus in 2024 was to continue the advancement of our two clinical programs built around our TAAP™ and MPAR® platforms. Our lead product PF614, a Trypsin-Activated Abuse Protection (TAAP^{TM}) extended-release oxycodone, will spearhead our "next generation" analgesic portfolio. The TAAP^{TM} chemical modification is designed to control the rate of release of a known prescription drug and to be highly resistant to tampering for recreational use, thereby reducing abuse via non-oral routes of administration including snorting, chewing or injecting. Our second drug candidate PF614-MPAR, built on the platform of PF614, has added oral-overdose protection, and is a combination product of PF614 with a trypsin inhibitor. MPAR® (Multi-Pill Abuse Resistance) is designed to deliver powerful pain relief yet "switches off" the release of the opioid in an overdose situation, providing an additional layer of protection to Ensysce's TAAP™ medications. This represents an industry first and a major breakthrough for Ensysce that was recognized by the U.S. Food & Drug Administration (FDA) with Breakthrough Therapy designation in January 2024.

These two programs are positioned to be approved at a vital time, with the safety of opioids and limited access to pain medication being some of the most critical healthcare issues in the U.S. today. We believe our TAAP™ and MPAR® opioids can act as a solution by providing relief to the millions of people in the U.S. suffering from severe and chronic pain

who are now struggling to gain access to drugs that provide them with an improved quality of life.

In 2024, we made significant progress toward our development milestones for PF614. Early in 2024, we completed a regulatory End of Phase 2 meeting with the FDA, an important discussion about our program which provided feedback and guidance on the design of our Phase 3 clinical program, ultimately reducing the regulatory risks for our commercialization plan.

We also announced the peer reviewed online publication of our manuscript reporting the results of our second clinical study of PF614 entitled, "Clinical evaluation of PF614, a novel TAAP™ prodrug of oxycodone, versus OxyContin® in a multi-ascending dose study with a bioequivalence arm in healthy volunteers" in *Clinical and Translational Science* (CTS), a journal of the American Society of Clinical Pharmacology and Therapeutics (ASCPT). The results from the two-part PF614-102 study demonstrated a clear dose relationship between PF614 and oxycodone release. Importantly, the study established the bioequivalence between PF614 and OxyContin, which can potentially lead to using the streamlined 505(b)(2) path to registration.

Mid-year, we submitted the Phase 3 study protocol and statistical analysis plan for regulatory review by the FDA. This PF614-301 study, entitled "A Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Study to Evaluate the Efficacy and Safety of PF614 for the Treatment of Moderate to Severe Pain after Abdominoplasty", intends to evaluate PF614 versus placebo for pain relief in subjects undergoing abdominoplasty surgery. Feedback on the Phase 3 design was received in December, and we are now reviewing Contract Research Organizations (CROs) to select an experienced team to work with to successfully execute this important study which we expect to start enrolling in the second quarter of 2025. We enter this Phase 3 study having support that PF614 delivers a known and effective analgesic and we look forward to being able to provide an update in our next annual letter.

Our MPAR program also continued to advance in 2024. The Breakthrough Therapy designation for PF614-MPAR, received in January, is provided to expedite the development and review of drugs that are intended to treat a serious condition where the drug may demonstrate substantial improvement over available therapies. This rare designation from the FDA speaks to the innovation of our MPAR® overdose protection platform. Additional regulatory guidance from the FDA was received in February for the PF614-MPAR non-clinical program, aiding its progression toward a new drug application (NDA) submission and accelerating its pace to market.

To progress the clinical development of PF614-MPAR, we renewed our collaboration with Quotient Sciences and received approval from the Investigational Review Board (IRB) to undertake the Phase 1b study, PF614-MPAR-102, "A Single and Multiple Dose Study to Evaluate the Pharmacokinetics of Oxycodone and PF614 when PF614 capsule is Co-Administered with Nafamostat as a combination Immediate Release solution and Extended-Release Capsule Formulation in Healthy Subjects". This study will examine the full commercial dose range of the PF614-MPAR drug product to verify both overdose protection and effective delivery of oxycodone. The study is applying the Quotient Sciences Translational Pharmaceutics® platform to manufacture and test the PF614-MPAR drug

product, expediting the clinical study process. Following receipt in September of a $14 million dollar award from the NIH, described below, the study was quickly implemented, and in November, the first group of subjects were enrolled and successfully dosed. We look forward to completing this three-part trial in 2025. The data generated will provide the basis to undertake additional productive discussions with the FDA regarding the development path to registration of this combination product, the first overdose-protected opioid.

2024 also saw a critical milestone achieved for our Opioid Use Disorder (OUD) program. Based on the data package that had been built over the last few years, we were able to select PF9001 as the lead drug candidate. PF9001 is designed using our TAAP™ and MPAR® technology to provide a safer treatment for the millions of Americans who are suffering from opioid overuse and addiction. A critical benefit of PF9001 is its lower potential for cardiovascular side effects compared with traditional methadone OUD treatments.

As we position our analgesic portfolio for commercial-scale production, we have established several strategic partnerships to strengthen our manufacturing capabilities. Today, PF614 drug substance is being produced for clinical trial use and will see commercial scale-up in 2025 through Purisys LLC. Most recently we initiated a strategic partnership with a leading specialty drug product manufacturer for the development and commercial launch of both PF614 and PF614-MPAR. This partnership will provide us with clinical trial material, drug products for regulatory submissions, and initial commercial batches of PF614 and PF614-MPAR. Additional services encompass the complete manufacturing process, including packaging, labeling, and shipment of the products, ensuring a seamless transition from regulatory approval to market entry.

To reinforce the innovative science and positive results of our programs, we presented the continued development progress of our programs at the following global events:

- Annual National Institutes of Health (NIH) "Helping to End Addiction Long-term" (HEAL) Initiative Scientific Meeting, Bethesda, MD.
- 2024 American Association of Pain Medicine (AAPM) Meeting, Los Angeles, CA.
- European Pharmaceutical Market Research Association (EPHMRA) Annual Conference, London, UK.
- International Association for the Study of Pain (IASP) 2024 World Congress on Pain, Amsterdam, NL.
- Society for Neuroscience Meeting, Chicago IL.
- Formulation & Delivery US 2024, San Diego, CA.
- 18th Annual Pain Therapeutics Summit, Boston, MA.

Company led financing activities in 2024 that supported the significant milestones of our three programs included a warrant inducement transaction in February that provided $4.7 million in gross proceeds and a financing transaction in August which raised $5 million in gross proceeds.

Additionally, in August, we received a non-dilutive $14 million multi-year grant from the NIH and National Institute on Drug Abuse (NIDA) for the continued development of PF614-MPAR. Funding from this award will complete the Phase 1b clinical trial, PF614-MPAR-102, as well as non-clinical studies required for our NDA submission for both PF614 and PF614-MPAR. This grant brings the total non-dilutive funding awarded since 2018 to $40 million.

Looking ahead, we are focused on the continued rapid execution of our clinical development milestones for PF614 and PF614-MPAR. With the selection of a CRO, we intend to initiate activities in Q1 of 2025 to allow us to complete the PF614 Phase 3 study in 2025. Our current plans have us on track to submit our PF614 New Drug Application in 2026 with commercialization to follow. We are advancing our MPAR® program with our second clinical study underway. This safety and pharmacokinetic study will generate data for an interim review in the first quarter of 2025, which we will use to build the balance of the study dosing plan.

Our non-clinical OUD program is continuing, and following discussions with NIDA in early 2025, we expect to advance to Investigational New Drug (IND) enabling studies, with ambitions to initiate a Phase 1 study in 2026.

Altogether, we are incredibly proud of our accomplishments in 2024, completed with tightly managed resources. We believe 2025 will be another strong year for Ensysce, with pivotal data anticipated by year end. We are grateful to our committed shareholders in helping us achieve our goals. We remain confident in our potential to play a key role in providing safer pain medication for those suffering with severe pain, whether short-term or chronic, while we also provide options to address the prescription drug abuse crisis in the U.S. I look forward to sharing additional exciting milestones in the year to come.

Sincerely,
Dr. Lynn Kirkpatrick
Chief Executive Officer

About Ensysce Biosciences

Ensysce Biosciences is a clinical-stage pharmaceutical company using its proprietary technology platforms to develop safer prescription drugs. Leveraging its Trypsin-Activated Abuse Protection (TAAP™) and Multi-Pill Abuse Resistance (MPAR®) platforms, the Company is developing unique, tamper-proof treatment options for pain that minimize the risk of both drug abuse and overdose. Ensysce's products are anticipated to provide safer options to treat patients suffering from severe pain and assist in preventing deaths caused by medication abuse. The platforms are covered by an extensive worldwide intellectual property portfolio for a wide array of prescription drug compositions. For more information, please visit www.ensysce.com.

Forward-Looking Statements

Statements contained in this press release that are not purely historical may be deemed to be forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995 and other federal securities laws. Without limiting the foregoing, the use of words such as "may," "intends," "can," "might," "will," "expect," "plan," "possible," "believe" and other similar expressions are intended to identify

forward-looking statements. The product candidates discussed are in clinic and not approved and there can be no assurance that the clinical programs will be successful in demonstrating safety and/or efficacy, that Ensysce will not encounter problems or delays in clinical development, or that any product candidate will ever receive regulatory approval or be successfully commercialized. All forward-looking statements are based on estimates and assumptions by Ensysce's management that, although Ensysce believes to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that Ensysce expected. In addition, Ensysce's business is subject to additional risks and uncertainties, including among others, the initiation and conduct of preclinical studies and clinical trials; the timing and availability of data from preclinical studies and clinical trials; expectations for regulatory submissions and approvals; potential safety concerns related to, or efficacy of, Ensysce's product candidates; the availability or commercial potential of product candidates; the ability of Ensysce to fund its continued operations, including its planned clinical trials; the dilutive effect of stock issuances from our fundraising; and Ensysce's and its partners' ability to perform under their license, collaboration and manufacturing arrangements. These statements are also subject to a number of material risks and uncertainties that are described in Ensysce's most recent quarterly report on Form 10-Q and current reports on Form 8-K, which are available, free of charge, at the SEC's website at www.sec.gov. Any forward-looking statement speaks only as of the date on which it was made. Ensysce undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required under applicable law.

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