DIAMOND EQUITY RESEARCH

13 March 2025
Company Sponsored Research
Update Note | Sector: Healthcare

Ensysce Biosciences, Inc. – Annual Report Highlights Progress, Securing Strategic Partnership for Commercial Launch, Advancing PF614 and PF614-MPAR Clinical Programs, and Expanding Opioid Use Disorder Pipeline

Ensysce Biosciences, Inc. (NASDAQ: ENSC)

Share Price: $4.56

Valuation: $34.00

Key Statistics

52 Week Range	$2.11-$14.67
Avg. Volume (3 months)	12.49K
Shares Outstanding	1.4M
Market Capitalization	$6.41M
EV/Revenue	N/A
Cash Balance*	$3.50M
Analyst Coverage	2

***Cash balance as of December 2024**

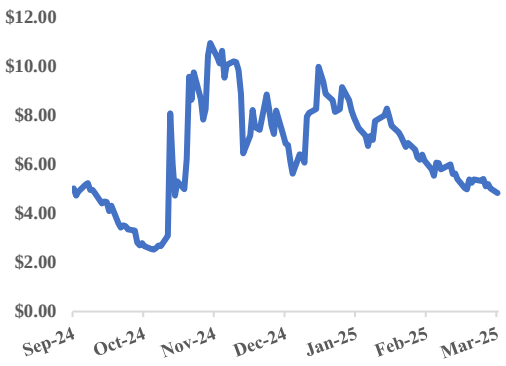
Revenue (in $mm)

Dec - FY	2024A	2025E	2026E
1Q	0.31	0.00	0.00
2Q	0.18	0.00	0.00
3Q	3.42	0.00	0.00
4Q	1.30	0.00	0.00
FY	5.21	0.00	0.00

EPS (in $)

Dec – FY	2024A	2025E	2026E
1Q	(8.21)	(1.53)	(0.82)
2Q	(3.35)	(1.61)	(0.43)
3Q	1.00	(0.97)	(0.35)
4Q	(2.90)	(0.61)	(0.59)
FY	(11.45)	(4.72)	(2.19)

Stock Price Chart



Investment Highlights

- **Ensysce Biosciences Advances Strategic Initiatives and Clinical Programs:** Ensysce Biosciences reported robust operational advancements for the fiscal year ended December 31, 2024. The company made substantial progress across several critical strategic and clinical fronts during the year:
  - **Strategic Partnership for Manufacturing and Commercialization:** During the fourth quarter of FY 2024, Ensysce secured a pivotal strategic partnership with a leading specialty drug manufacturer. This partnership will expedite the manufacture and targeted commercial launch of Ensysce's primary drug candidates, PF614 and PF614-MPAR. This collaboration emphasizes a joint commitment toward efficient regulatory approval and establishes readiness for commercial supply upon potential FDA approval, positioning Ensysce effectively in the highly competitive analgesic market.
  - **PF614 Clinical Program Update (TAAP™):** Ensysce's lead product candidate PF614, an extended-release oxycodone featuring the proprietary Trypsin-Activated Abuse Protection (TAAP™) technology, continued to achieve significant milestones. The TAAP™ technology ensures the opioid is inactive until orally ingested and activated by trypsin enzymes in the small intestine, thereby reducing the potential for abuse. Following constructive feedback from the FDA, Ensysce is actively preparing to initiate its pivotal Phase 3 clinical trial in the second quarter of 2025. This trial is expected to support a New Drug Application (NDA) submission targeted for 2026. Site selection and clinical team appointments are in the final stages, underscoring the company's dedication to swift and successful execution.
  - **PF614-MPAR Clinical Program Update (MPAR®):** The company also reported notable interim results from the ongoing PF614-MPAR-102 clinical trial. PF614-MPAR combines the TAAP™ prodrug PF614 with a trypsin inhibitor through its Multi-Pill Abuse Resistance (MPAR®) technology. Interim data revealed that the 100 mg dosage form of PF614-MPAR provided effective overdose protection when excessive doses were consumed. Supported by the National Institute on Drug Abuse, the study continues with higher dosage levels and additional safety evaluations. This innovative combination recently earned the FDA's Breakthrough Therapy designation in January 2024, reflecting its potential to significantly enhance opioid safety profiles. The study is advancing through parts two and three, examining food interactions and conducting ascending dose evaluations.
  - **Opioid Use Disorder (OUD) Pipeline Expansion:** Ensysce expanded its pipeline through its Opioid Use Disorder (OUD) program, selecting PF9001, a methadone analogue designed using TAAP™ technology. PF9001 aims to mitigate traditional methadone treatments' cardiovascular risks and abuse potential, facilitating safer and broader accessibility to effective OUD therapies. The program, funded through a multi-year Helping to End Addiction Long-Term (HEAL) award, is progressing through preclinical studies intended to pave the way for IND-enabling activities.

Ensysce concluded 2024 well-positioned, having demonstrated substantial advancements in clinical development, strategic partnerships, and pipeline expansion, positioning itself as a potential disruptor in the opioid analgesic and OUD treatment markets.

Company Description

Ensysce Biosciences, Inc., a clinical-stage pharmaceutical company, engages in developing various prescription drugs for severe pain relief. The company's pipeline of drug candidates is developed on the back of its innovative technology platforms Trypsin Activated Abuse Protection (TAAP™), an abuse-resistant opioid prodrug technology; and Multi-Pill Abuse Resistance (MPAR™).

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Please see last page for important disclosures

- **Fourth Quarter and Full Year 2024 Financial Results Update:** For the year ended December 31, 2024, Ensysce Biosciences maintained a solid financial position, with cash and cash equivalents totaling $3.5 million, a decrease from $4.2 million as of September 30, 2024, but substantially higher than $1.1 million at the end of 2023. The company benefited significantly from federal grants, securing funding of $5.2 million for the full year, more than doubling the previous year's $2.2 million, driven primarily by a multi-year, $14 million grant from the National Institute on Drug Abuse (NIDA) supporting the MPAR clinical program. Ensysce's remaining MPAR grant funding stands at $1.6 million through May 31, 2025, with an additional $9.0 million available over the following two years. Research and development expenses in the fourth quarter of 2024 increased to $3.8 million from $2.2 million in the prior-year quarter due to intensified activity in MPAR and OUD programs. However, for the full year, R&D expenses declined modestly to $7.2 million from $7.6 million in 2023, primarily reflecting lower costs related to clinical activities for PF614 as efforts shifted towards preparation for its Phase 3 trial. General and administrative expenses for Q4 2024 were lower at $1.1 million compared to $1.4 million in Q4 2023, while annual G&A expenses dropped to $4.7 million from $5.4 million, mainly attributable to reduced stock-based compensation. The company expects these expenses to remain stable moving forward. Total other income for Q4 2024 was $12,054, reversing from an expense of $0.3 million in the prior-year quarter, while the full-year total other expenses were $1.3 million, compared to income of $0.1 million in 2023, driven largely by increased interest expenses related to debt issuance costs. Net loss attributable to common stockholders for Q4 2024 was $3.6 million, slightly up from $3.5 million in Q4 2023, though the full-year net loss narrowed significantly to $8.0 million from $10.6 million in 2023. We have updated our financial model to reflect the latest quarterly and annual results, accounting for the capital raise, resulting dilution, and the reverse stock split. Reassessing the comparable company analysis and incorporating these changes has resulted in a valuation of $34.00 per share, contingent upon successful execution by the company.

Company Overview

Based in La Jolla, California, Ensysce Biosciences, Inc. (NASDAQ: ENSC) is a clinical-stage pharmaceutical company developing innovative solutions for severe pain while minimizing the risk of both drug abuse and overdose. The company is dedicated to improving prescription drug safety and performance by applying sophisticated chemistry, combined with anti-abuse and anti-overdose technologies, to change the way drugs are activated during delivery to prevent the possibility of both abuse and overdose. Ensysce's products are primarily based on its two core technology platforms - Trypsin Activated Abuse Protection (TAAP™), an abuse-resistant opioid prodrug technology, and Multi-Pill Abuse Resistance (MPAR™) platform, an overdose protection opioid prodrug technology - which can be applied to prescription drugs with a wide variety of pharmaceutical applications, driving internal growth and external partnering opportunities.

Ensysce Biosciences is a clinical-stage pharmaceutical company developing innovative solutions for severe pain while minimizing the risk of both drug abuse and overdose through its proprietary TAAP™ and MPAR™ technology platforms

Ensysce currently holds over 100 patents in 25 countries across North America, Europe, and Asia, ensuring the opportunity to address abuse globally. Leveraging its proprietary TAAP™ and MPAR™ platforms, which are well-protected by a suite of patents generated from over $100 million of research support, the company is expanding its pipeline with a primary focus on opioid pain products, including PF614, a TAAP abuse-deterrent oxycodone prodrug candidate that is in Phase II clinical trial for the treatment of acute or chronic pain and has been granted Fast Track designation by the FDA with 505(b)(2) regulatory development path; and PF614-MPAR, a combination product of PF614 and trypsin inhibitor nafamostat that is in Phase I clinical trial for overdose protection against excessive ingestion. In addition to these two lead product candidates, the company has other drugs in development for respiratory diseases and ADHD: an oral and inhalation drug product of nafamostat for use against coronaviral infections and other pulmonary diseases, such as cystic fibrosis; as well as PF8001 and PF8026, extended and immediate-release prodrugs of amphetamine for ADHD medication abuse.

Exhibit 1: Ensysce Product Pipeline. Source: Ensysce Investor Presentation

TAAP™ & MPAR™: Smart, Unique and Extensible Platforms Improving Drug Performance and Safety

Focusing on chemistry and innovation, the company has developed two novel molecular drug delivery platforms that aim to reduce the abuse of prescription drugs and inhibit overdose occurrences. The technology carries with it a wide variety of pharmaceutical applications, thus offering disruptive solutions to multiple drug abuse issues that often lead to health and humanitarian crises.

Ensysce's TAAP™ is designed to be highly resistant to tampering and abuse as compared to traditional Abuse-Deterrent Formulations (ADFs) of oxycodone

The Trypsin Activated Abuse Protection (TAAP™) is an abuse-resistant prodrug technology seeking to improve patient care while impeding prescription opioid drug abuse at the molecular level. The technology ensures that the drug consumed is released only when exposed to certain physiological conditions when taken orally (that is, when the drug is ingested and exposed to the digestive enzyme trypsin). The TAAP™ pro-drug delivery system follows a two-step mechanism of action (MoA) to deliver the API in a manner that restricts both oral and non-oral modes of abuse. The first step involves the separation and release of the amino acid chain from the drug formulation when exposed to trypsin, a proteolytic enzyme found in the lumen of the small intestine. The release is followed by a cyclization-release reaction separating the linker from the active drug to achieve ideal pharmacokinetic release and absorption of API.

The enzyme-mediated metabolic activation occurs only when the drug formulation is swallowed. The activating enzyme, in this case, Trypsin, are not present in the blood, saliva, or nasal passages; thus, there is no opportunity for activation if injected, chewed, or snorted. Further, a chemically designed release timing mechanism restricts the release of active drugs to achieve rapid, spiking blood levels and a euphoric rush.

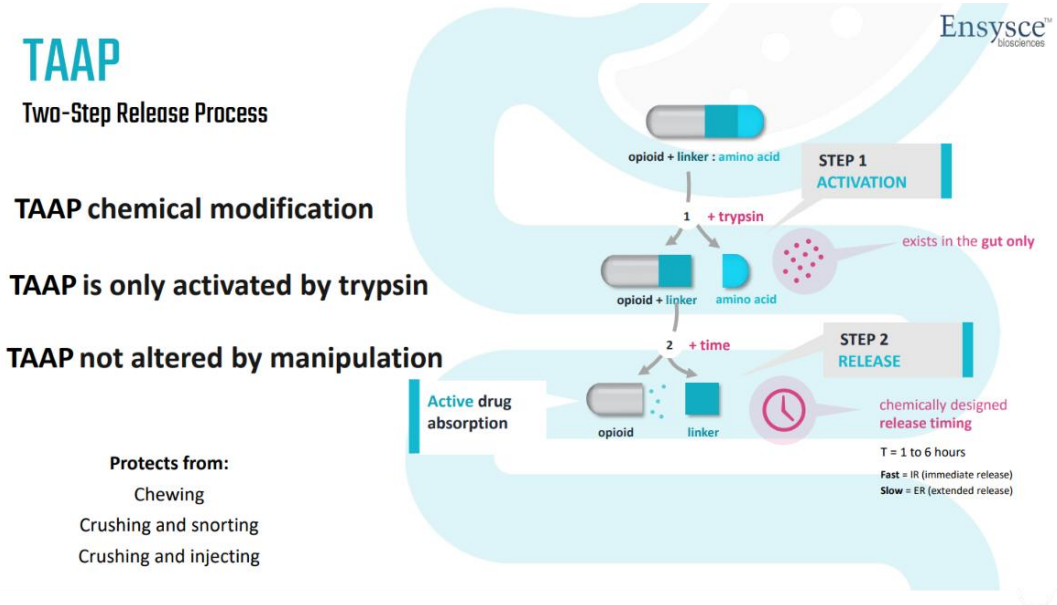

Exhibit 2: TAAP™ Mechanism of Action (MoA). Source: Company Filings

The Multi-Pill Abuse Resistant (MPAR™) platform, when combined with TAAP™ products, not only inhibits drug abuse but also protects against drug overdose. The technology leverages trypsin inhibitor, nafamostat, which is co-formulated with a TAAP™-enabled drug to provide

protection against drug overdose. Nafamostat is a small molecule, highly potent protease inhibitor (trypsin inhibitor) with a steep dose-response curve. The combination drug formulation, when administered at prescribed dosage levels, would not be affected by the drug's mechanism of action or release and absorption of API. If the TAAP™ prodrug nafamostat combination (MPAR™) is administered in larger quantities than prescribed levels, the trypsin inhibitor, Nafamostat, blocks the activation process (refer to exhibit 3) and prevents the release and absorption of the API itself, thus protecting against the drug overdose.

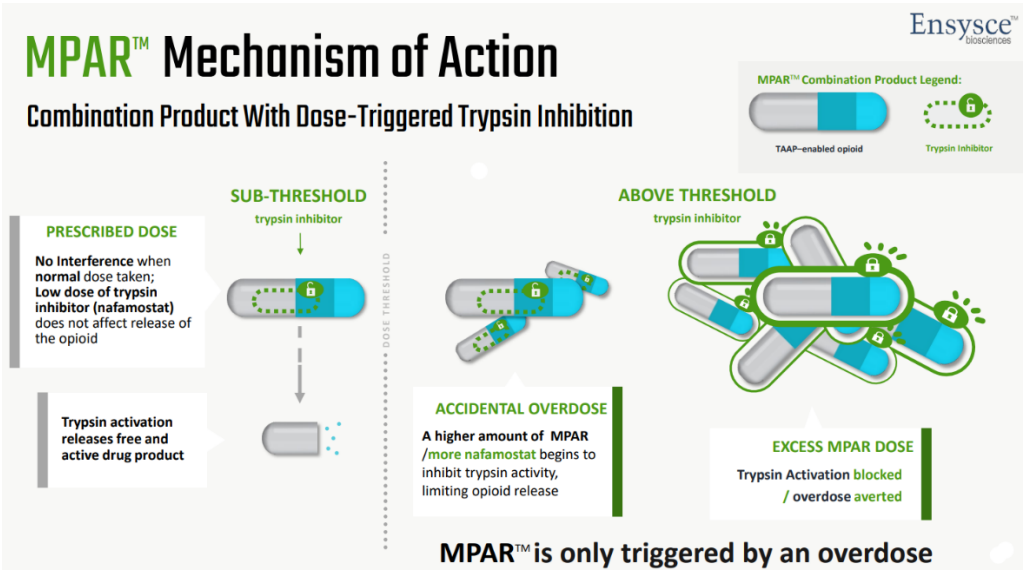

Exhibit 3: MPAR™ Mechanism of Action (MoA). Source: Company Filings

MPAR™ provides another layer of protection and safety to Ensysce's TAAP prodrugs and holds the promise of eliminating accidental or deliberate overdose

TAAP™ and MPAR™ technology platforms, when applied to numerous drug cases, hold the potential to enhance bioavailability, controlled duration of action, improved safety, and eliminate accidental or deliberate overdose. The company's diversified product pipeline targeting severe pain and CNS disorders is backed by these two technology platforms.

PF614: 'TAAP™' Oxycodone

The company's lead drug candidate, PF614, is a novel abuse-resistant TAAP™ prodrug of oxycodone currently being studied as an acute or chronic pain analgesic in phase 2 clinical trials. This innovative therapy remains the need of the hour, considering the extent of opioid abuse and opioid use disorder, particularly in North American countries. PF614 is developed on the back of the company's proprietary TAAP™ technology and uses an advantageous prodrug approach instead of the conventional active form. The drug is an extended-release prodrug of oxycodone utilizing a unique bioactivation mechanism. PF614 is pharmacologically and chemically inert until activation by pancreatic trypsin, which is followed by a second non-enzymatic cyclization producing free oxycodone with extended-release characteristics. It has been found to resist ex vivo extraction with household chemicals and is pharmacologically inactive when administered by non-oral routes (nasal and parenteral), thereby substantially reducing its intravenous and intranasal abuse potential.

PF614-MPAR™: TAAP™ Oxycodone with Overdose Protection

PF614-MPAR™ is a novel opioid combination product in phase 1 clinical trials for a potentially safer treatment for acute or chronic pain. The drug is a combination product of PF614 and nafamostat (a trypsin inhibitor). This combination adds another layer of protection of overdose inhibition in addition to TAAP™'s abuse deterrence. The MPAR™ platform is designed in a way that prevents overdose by inhibiting the TAAP™ activation, the first in the release mechanism of PF614. The combination product is expected to prevent all major methods of drug abuse, including oral abuse, chewing, intravenous, and intranasal.

The company was awarded a grant to develop its MPAR™ platform by NIH through NIDA in September 2018. The total funding from this grant amounted to $10.8 million and has been awarded in different phases supporting the clinical development of PF614-MPAR™.

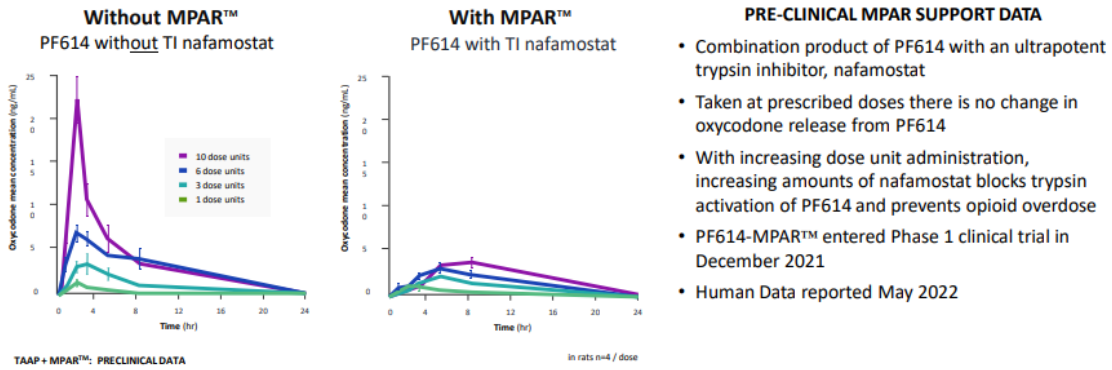

Exhibit 4: PF614-MPAR™ Pre-Clinical Data. Source: ENSC Investor Presentation

Initial pharmacokinetic data for PF614-MPAR™ demonstrates that MPAR™ can provide overdose protection by blocking the activation of PF614 and oxycodone release if overdosed

The preclinical data indicated the novel combination product limited oxycodone exposure and prevented overdose. Without MPAR™, oxycodone exposure increases substantially as the dosage level is increased, while the variability and exposure in oxycodone absorption at multiple dosage levels is significantly reduced, with MPAR™ indicating abuse inhibition properties. The Cmax at higher dosage levels in treatment without MPAR™ was significantly larger when compared to PF614 treatment with MPAR™.

Opioid Analgesics Market and Abuse-Deterrent Opioid Analgesics

Opioids are natural, synthetic, or semi-synthetic chemical substances that act on opioid receptors in the cells to provide pain-relieving effects. Major prescription opioids include Codeine, Fentanyl, Hydrocodone, Oxycodone, and Morphine, to name a few. Opioids function by mimicking natural endorphins that dampen the perception of pain and also cause euphoria. Repeated use of the drug affects brain processes and chemistry that often leads to drug liking, tolerance, dependence, and addiction. An estimated 50.2 million U.S. adults are affected by chronic pain, while 24.4 million suffer high-impact chronic pain with work limitations.[1] Furthermore, the total estimated value of lost productivity at approximately $300 billion.[2]

[1] Yong, R. Jason et al., PAIN: February 2022 - Volume 163 - Issue 2 - p e328-e332
[2] Brigham and Women's Hospital. (2021, April 20).

Opioid medications remain one of the common treatment modalities for chronic or acute pain sufferers, with 20% of patients with pain-related diagnoses receiving an opioid prescription. The U.S opioid market is currently valued at $16.28 billion and is expected to grow at 5.5% for the next eight years, reaching a value of $24.94 billion.[3] A total of 142.81 million prescriptions of opioids were dispensed in the United States in 2020.[4] The past two decades saw a considerable rise in opioid prescriptions for pain management in the United States. Given the addictive nature of the drug, there has been a significant increase in drug abuse cases and drug overdose mortality driven by illicit and prescription opioids. The prevalence of opioid misuse within chronic pain populations is estimated to be as high as 29%.[5] Additionally, 187 people die every day from opioid overdose (Rx and illicit).[4] Even though the total opioid prescriptions have declined substantially in the past 5-7 years, opioid overdose mortality remained high, aided by the increasing manufacturing of illicit opioids such as fentanyl.

The chronic pain market is currently served by pharmaceutical agents that can be potentially abused. There is an urgent need for much safer alternatives with similar efficacy profile for the underlying growing market

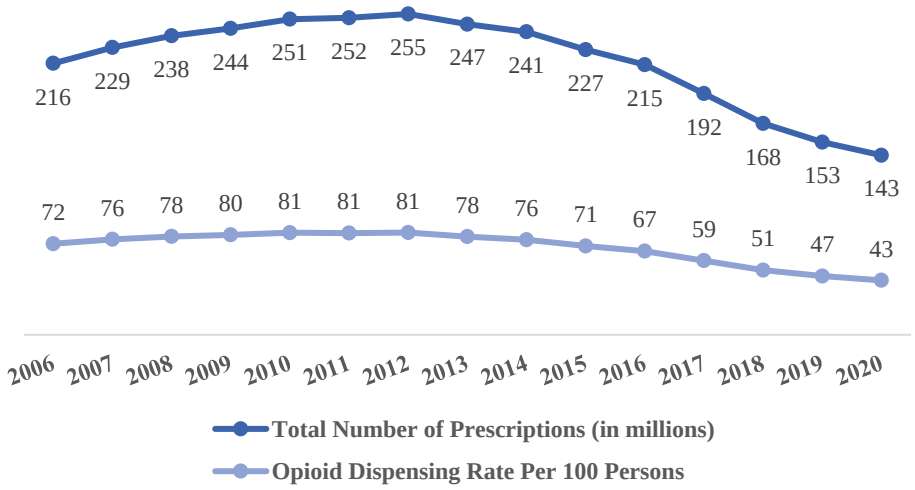

Exhibit 5: Total Opioid Prescriptions Dispensed and Opioid Dispensing Rate per 100 People. Source: CDC

[3] Coherent Market Insights
[4] The Centers for Disease Control and Prevention (CDC)
[5] Vowles KE et al., Pain. 2015 Apr;156(4):569-576.

Appendix

Income Statement	FY2023 A	FY2024 A	FY2025 E	FY2026 E	FY2027 E
Net sales	2,230,520.0	5,210,031.0	-	-	35,120,376.0
Cost of sales	-	-	-	-	(10,536,112.8)
Gross profit	**2,230,520.0**	**5,210,031.0**	-	-	**24,584,263.2**
Operating expenses					
General and Administrative Expenses	(5,361,234.0)	(4,720,728.0)	(5,192,800.8)	(5,712,080.9)	(12,292,131.6)
Marketing Expense	-	-	-	-	(4,214,445.1)
Research and Development	(7,587,473.0)	(7,219,437.0)	(7,941,380.7)	(9,529,656.8)	(8,780,094.0)
EBITDA	**(10,718,187.0)**	**(6,730,134.0)**	**(13,134,181.5)**	**(15,241,737.7)**	**(702,407.5)**
Depreciation and amortization expenses	-	-	-	-	(52,695.7)
Other income/ (expense)					
License Agreement Payments	-	-	-	-	-
EBIT	**(10,718,187.0)**	**(6,730,134.0)**	**(13,134,181.5)**	**(15,241,737.7)**	**(755,103.2)**
Interest Income	-	-	-	-	-
Interest Expense	(353,945.0)	(1,290,444.0)	(36,199.2)	(36,199.2)	(36,199.2)
Profit before exceptional items, extraordinary items and tax	**(11,072,132.0)**	**(8,020,578.0)**	**(13,170,380.7)**	**(15,277,936.9)**	**(791,302.4)**
Issuance cost for convertible notes	-	-	-	-	-
Change in fair value of derivative liabilities	-	-	-	-	-
Loss on issuance of convertible notes	-				
Change in fair value of convertible notes	146,479.0	-	-	-	-
Issuance of liability classified warrants	-	16,292.0	-	-	-
Change in fair value of liability classified warrants	283,958.0	-	-	-	-
Loss on debt conversion	-				
Other income and expense, net	15,420.0	17,277.0	-	-	-
Profit before tax from continuing operations	**(10,626,275.0)**	**(7,987,009.0)**	**(13,170,380.7)**	**(15,277,936.9)**	**(791,302.4)**
Income tax (expense) benefit	-	-	-	-	-
Net earnings including noncontrolling interests	**(10,626,275.0)**	**(7,987,009.0)**	**(13,170,380.7)**	**(15,277,936.9)**	**(791,302.4)**

Exhibit 6: Income Statement. Source: Diamond Equity Research

Risks

- **Clinical Development Risk -** ENSC is a pharmaceutical company in a clinical stage. The emergence of any undesirable side effects in test subjects could hinder approvals. Their success hinges on PF614 and PF614 product candidates, both of which are in the trial stages.

- **Regulatory Risk -** As a pharmaceutical company, ENSC has to obtain approvals from multiple authorities under various legislations and compliance. The regulatory processes are also lengthy, and approval is uncertain. There is also a risk of regulatory bodies disagreeing with their product regulatory plans. The FDA fast-track designation might not provide the intended ease if products fall short in compliance. They are also subject to lawsuits from future collaborators and any infringements on intellectual property.

- **Finance and Dilution Risk -** ENSC has a limited operating history and incurred significant losses. This risk is exacerbated by the possibility of encountering unforeseen losses in their trials. Furthermore, there is the risk involved in the listing and volatility of their common stock. With their requirement for substantial funding, raising capital by issue of common stock under market value would adversely affect dilution, their market price, their operations, and their control over their technologies and product candidates. There is also a risk of their stocks being delisted from NASDAQ or their warrants' trading being discontinued in the OTC Pink Open Market.

- **Strategic/Competitive Risk -** Growth depends on the product candidates' success in commercialization, discovery, and development. Failure to do so would significantly hinder growth. Furthermore, competitive products could diminish or eliminate commercialization potential. Reliance on third parties for trials, manufacturing, and development also poses a significant risk. Lastly, even if product candidates receive regulatory approval, the possibility of failing in market acceptance poses a risk to successful commercialization.

- **Intellectual Property Risk -** It is important to note risks related to securing, protecting, and updating of intellectual property since any failures would deter operational success and could have major competitive implications. There are also Litigation risks related to the infringement of intellectual parties' intellectual property rights when they challenge the validity of ENSC patents or other intellectual property. ENSC could also be involved in litigation to protect their own intellectual property and other risks related to protection, like the lack of protection under the Hatch-Waxman Amendments through the extension of the patent term.

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