23 August 2024
Company Sponsored Research
Update Note | Sector: Healthcare

Ensysce Biosciences, Inc. – Significant Clinical Advancements, Strategic Partnerships, and Regulatory Achievements in H1 2024 Drive Ensysce's Mission to Enhance Pain Relief Therapies and Mitigate Opioid Abuse Risks

Ensysce Biosciences, Inc. (NASDAQ: ENSC)

Share Price: $0.41

Valuation: $8.00

Key Statistics

52 Week Range	$0.36-$2.06
Avg. Volume (3 months)	112.38K
Shares Outstanding	8.47M
Market Capitalization	$3.47M
EV/Revenue	NA
Cash Balance*	$1.04M
Analyst Coverage	3

***Cash balance as of June 2024**

Revenue (in $mm)

Dec - FY	2023A	2024E	2025E
1Q	0.79	0.31	0.00
2Q	0.49	0.18	0.00
3Q	0.44	0.36	0.00
4Q	0.51	0.35	0.00
FY	2.23	1.20	0.00

EPS (in $)

Dec – FY	2023A	2024E	2025E
1Q	(2.08)	(0.55)	(0.24)
2Q	(0.98)	(0.22)	(0.26)
3Q	(0.87)	(0.20)	(0.29)
4Q	(1.13)	(0.19)	(0.31)
FY	(4.69)	(1.16)	(1.10)

Stock Price Chart

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Investment Highlights

- **Pivotal Developments in Clinical Trials, Manufacturing Partnerships, and Regulatory Approvals in the First Half of 2024:** Ensysce Biosciences, Inc. has made notable advancements in the first half of 2024. The company provided a comprehensive mid-year update, highlighting significant progress in its key clinical programs. These advancements include preparations for the PF614 Phase 3 clinical trial, the receipt of Breakthrough Therapy designation for the PF614-MPAR program, and the identification of a lead clinical candidate for the opioid use disorder (OUD) program. Additionally, strategic manufacturing partnerships and non-dilutive funding applications underscore Ensysce's commitment to addressing the critical issues of opioid safety and access to pain care:

    - **PF614 Phase 3 Clinical Trial:** Ensysce Biosciences successfully completed an End of Phase 2 meeting with the FDA, receiving valuable guidance on the strategy and design of the upcoming Phase 3 clinical program. This pivotal meeting set the stage for the final phase of clinical trials, crucial for the approval and commercialization of PF614. Furthermore, the company published the bioequivalence results of PF614 to OxyContin, a significant milestone indicating that PF614 can potentially follow the shortened FDA 505(b)(2) regulatory pathway, expediting its development and market entry. To ensure readiness for commercial-scale production, Ensysce has established strategic manufacturing partnerships with Societal CDMO, Porton Pharma Solutions, and Purisys LLC, strengthening its manufacturing capabilities.

    - **Opioid Use Disorder (OUD) Program:** In its OUD program, Ensysce has identified PF9001, a TAAP methadone analogue, as the lead drug candidate. PF9001 demonstrates a lower potential for cardiovascular side effects compared to traditional methadone treatment, addressing a critical need in opioid use disorder therapies. This program continues to receive support from a $15 million multi-year NIDA HEAL award, underscoring the importance and potential impact of Ensysce's work in this area. Additionally, Ensysce has announced an agreement with Purisys LLC to scale the manufacture of PF9001.

- **Valuation**: Ensysce is progressively moving towards potential approval and commercialization of PF614. Additionally, the company has made advancements and achieved milestones across other pipeline candidates, including the recent progress and the breakthrough designation of PF614-MPAR, as well as the promising development of its opioid use disorder (OUD) program with the lead candidate PF9001. These achievements underscore Ensysce's commitment to innovation in pain management and opioid safety, potentially positioning it favorably for future growth and profitability. We have updated our financial model to reflect the latest quarterly results and updated share count. Re-assessing the comparable company analysis and accounting for these changes, we reiterate our valuation of $8.00 per share, contingent on successful execution by the company.

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™).

Please see last page for important disclosures

- **Q2 and H1 2024 Financial Results Update:** The company ended H1 of 2024 with cash reserves of $1.04 million compared to $1.1 million at the end of 2023. Total operating cash burn for the first half of 2024 was $5.7 million compared to $6.7 million for the same period in the previous year. In line with the decline in operating burn, total operating expenses decreased to $2.14 million in Q2 2024 compared to $2.78 million in Q2 2023. This decline has been majorly attributed to a decrease in research and development expenditure offset by a slight increase in general and administrative expenses. Net losses for Q2 2024 decreased to $1.97 million compared to $2.23 million for Q2 2023.

- **PF614-MPAR Breakthrough Therapy Designation:** The PF614-MPAR program achieved a significant milestone by receiving Breakthrough Therapy designation from the FDA, recognizing the innovative potential of the MPAR® overdose protection technology. This elite designation will expedite the development and review process, highlighting the substantial improvement PF614-MPAR could offer over existing therapies. Ensysce has applied for $15 million in non-dilutive grant funding from NIH and NIDA to support three years of continued development, with a potential start date in Q3 2024. The company presented compelling clinical data at the NIH annual HEAL meeting and the AAPM annual meeting, where the PF614-MPAR platform was acknowledged in the Trailblazer Session. Additionally, Ensysce received FDA guidance aimed at potentially reducing the costs associated with the non-clinical program. The company is advancing its collaboration with Quotient Sciences to undertake the second clinical trial, PF614-MPAR-102, expected to commence in Q4 2024.

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.

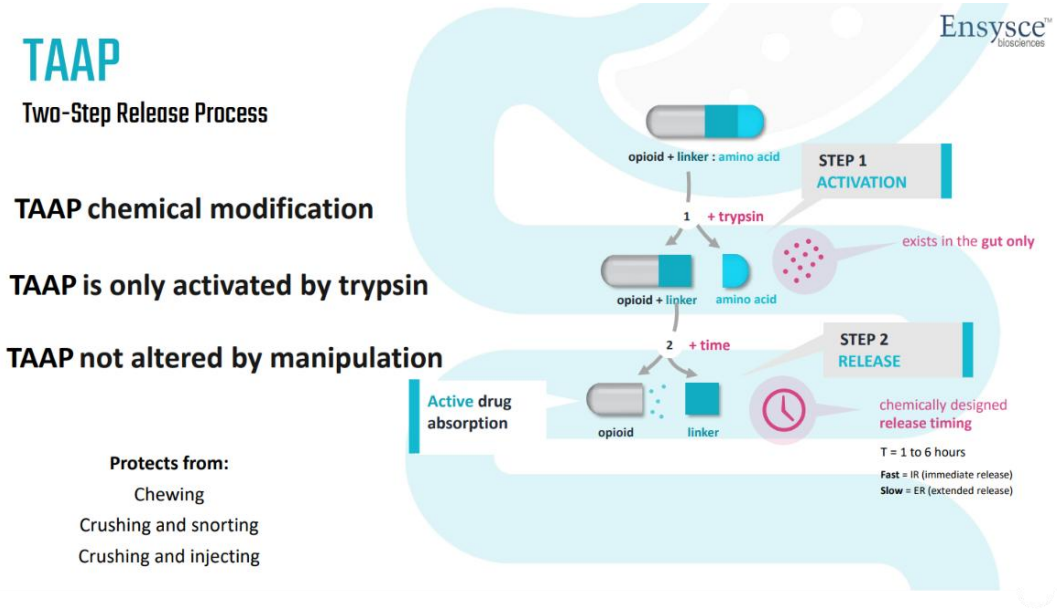

Exhibit 2: TAAP™ Mechanism of Action (MoA). Source: Company Filings

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.

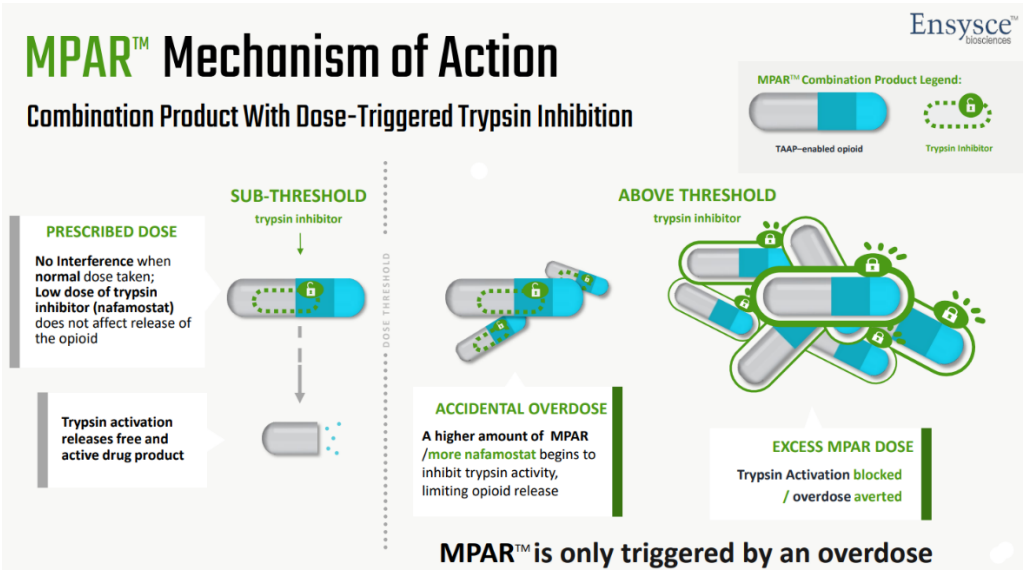

Exhibit 3: MPAR™ Mechanism of Action (MoA). Source: Company Filings

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™.

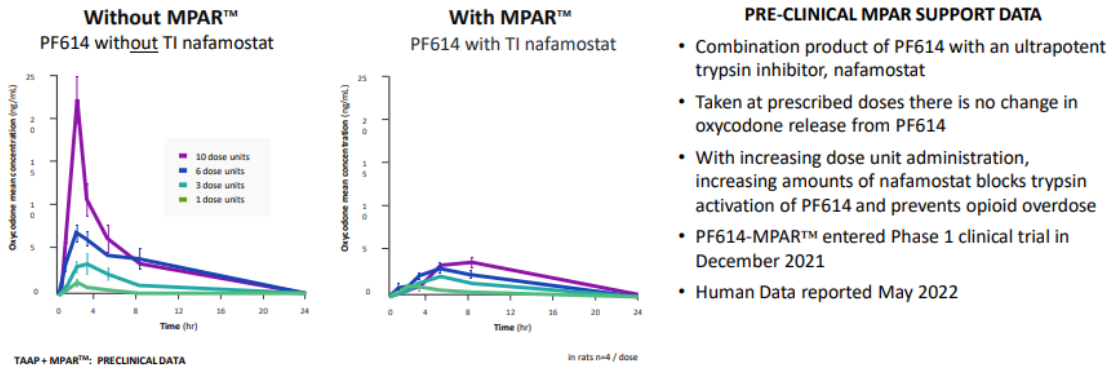

Exhibit 4: PF614-MPAR™ Pre-Clinical Data. Source: ENSC Investor Presentation

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

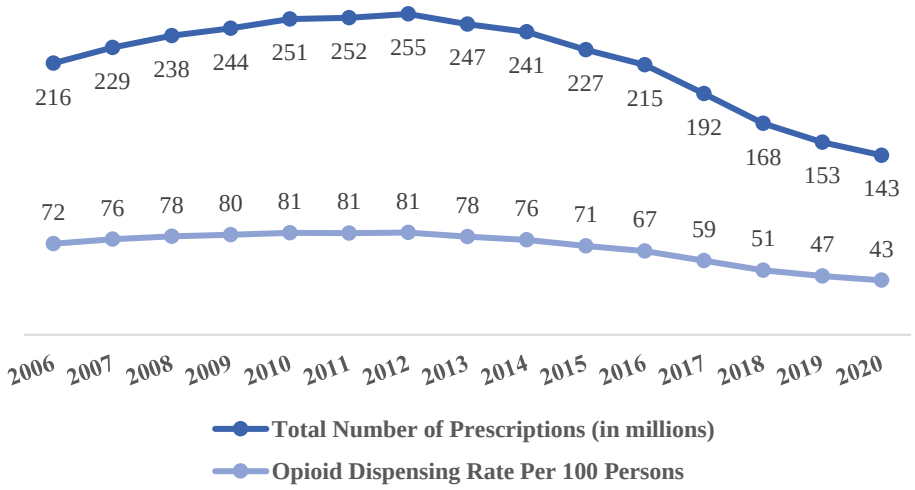

Exhibit 5: Total Opioid Prescriptions Dispensed and Opioid Dispensing Rate per 100 People. Source: CDC

[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	FY2022 A	FY2023 A	FY2024 E	FY2025 E	FY2026 E
Net sales	2,523,383.0	2,230,520.0	1,200,000.0	-	13,651,896.0
Cost of sales	-	-	-	-	(4,095,568.8)
Gross profit	**2,523,383.0**	**2,230,520.0**	**1,200,000.0**	**-**	**9,556,327.2**
Operating expenses					
General and Administrative Expenses	(6,909,603.0)	(5,361,234.0)	(6,433,480.8)	(7,076,828.9)	(10,238,922.0)
Marketing Expense	-	-	-	-	(2,730,379.2)
Research and Development	(19,835,875.0)	(7,587,473.0)	(6,449,352.1)	(9,674,028.1)	(8,191,137.6)
EBITDA	**(24,222,095.0)**	**(10,718,187.0)**	**(11,682,832.9)**	**(16,750,857.0)**	**(11,604,111.6)**
Depreciation and amortization expenses	-	-	-	-	(34,144.8)
Other income/ (expense)					
License Agreement Payments	-	-	-	-	-
EBIT	**(24,222,095.0)**	**(10,718,187.0)**	**(11,682,832.9)**	**(16,750,857.0)**	**(11,638,256.4)**
Interest Income	-	-	-	-	-
Interest Expense	(109,525.0)	(353,945.0)	(102,563.6)	(102,563.6)	(102,563.6)
Profit before exceptional items, extraordinary items and tax	**(24,331,620.0)**	**(11,072,132.0)**	**(11,785,396.5)**	**(16,853,420.6)**	**(11,740,820.1)**
Issuance cost for convertible notes	(1,137,740.0)	-	-	-	-
Change in fair value of derivative liabilities	(3,609,944.0)	-	-	-	-
Loss on issuance of convertible notes	-	-			
Change in fair value of convertible notes	5,756,787.0	146,479.0	-	-	-
Issuance of liability classified warrants	(3,737,371.0)	-	-	-	-
Change in fair value of liability classified warrants	6,730,613.0	283,958.0	-	-	-
Loss on debt conversion	(3,964,633.0)	-			
Other income and expense, net	86,223.0	15,420.0	-	-	-
Profit before tax from continuing operations	**(24,207,685.0)**	**(10,626,275.0)**	**(11,785,396.5)**	**(16,853,420.6)**	**(11,740,820.1)**
Income tax (expense) benefit	-	-	-	-	-
Net earnings including noncontrolling interests	**(24,207,685.0)**	**(10,626,275.0)**	**(11,785,396.5)**	**(16,853,420.6)**	**(11,740,820.1)**

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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