Ensysce Biosciences, Inc. – Receives $14 Million NIH and NIDA Grant and IRB Approval for PF614-MPAR, Advancing Clinical Trials to Potentially Revolutionize Pain Management with Overdose Protection

Ensysce Biosciences, Inc. (NASDAQ: ENSC)

Share Price: $0.63

Valuation: $8.00

Key Statistics

52 Week Range	$0.36-$2.06
Avg. Volume (3 months)	1.61M
Shares Outstanding	8.47M
Market Capitalization	$5.46M
EV/Revenue	NA
Cash Balance*	$1.04M
Analyst Coverage	3

***Cash balance as of June 2024 (Excluding Recent Federal Grants)**

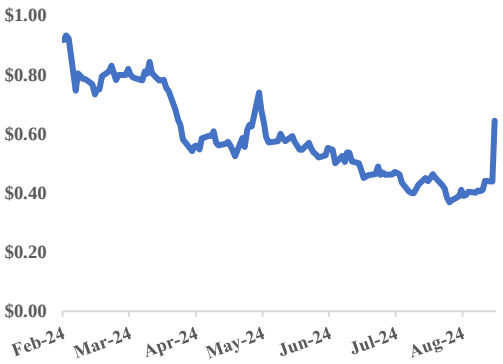
Revenue (in $mm)

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



Investment Highlights

- **NIH and NIDA Award $14 Million Grant to Ensysce Biosciences for Opioid Development with Overdose Protection:** Ensysce Biosciences has received a $14 million grant from the National Institutes of Health (NIH) and the National Institute on Drug Abuse (NIDA) to support the clinical development of PF614-MPAR, an innovative opioid designed to reduce the potential for abuse and prevent overdose. This grant, part of a three-year funding initiative, will facilitate the Phase 1b clinical trial, PF614-MPAR-102, which aims to further develop the product based on outcomes from the initial PF614-MPAR-101 study that confirmed its overdose protection capabilities. The funding, which brings the total federal support for this project to $40 million, follows the FDA's Breakthrough Therapy designation received in January 2024. This designation facilitates frequent interactions with the FDA, ensuring a streamlined path to a potential approval. PF614-MPAR (Multi-Pill Abuse Resistance) is engineered to potentially deliver effective pain relief at therapeutic doses while automatically limiting opioid release when excessive amounts are consumed, thereby addressing severe pain management needs without the common risks associated with traditional opioids. Importantly, the MPAR® technology also holds the potential for broadening safety applications beyond opioids, suggesting possible enhancements in drug safety for various pharmaceuticals. This grant emphasizes a significant federal commitment to combating the public health crisis of opioid overdose, which claims nearly two lives per hour, according to the Centers for Disease Control (CDC).

- **Secures IRB Approval to Advance MPAR Study with Federal Support:** Ensysce Biosciences, Inc. has received Investigational Review Board (IRB) approval for its next critical study of PF614-MPAR, a novel opioid designed to combat abuse and prevent overdose. The approved protocol, PF614-MPAR-102, involves a detailed pharmacokinetic evaluation of oxycodone and PF614 when co-administered with Nafamostat in both immediate-release solutions and extended-release capsule formulations. This study, conducted in collaboration with Quotient Sciences using their Translational Pharmaceutics® platform, is a continuation of Ensysce's efforts to develop safer opioid alternatives, supported by a $14 million federal grant from the National Institutes of Health (NIH) and the National Institute on Drug Abuse (NIDA). The trial is scheduled to commence immediately, with initial data expected by mid-2025. The federal backing signifies strong government support for Ensysce's innovative approach, reflecting confidence in the company's potential to bring safer therapeutic solutions to market.

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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™).

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.

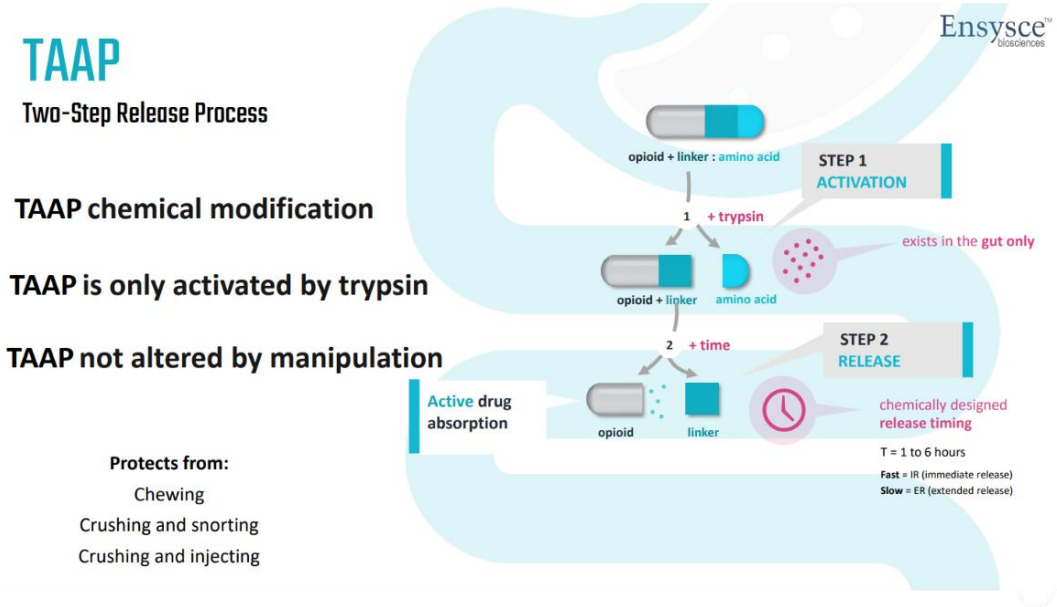

Exhibit 2: TAAP™ Mechanism of Action (MoA). Source: Company Filings

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.

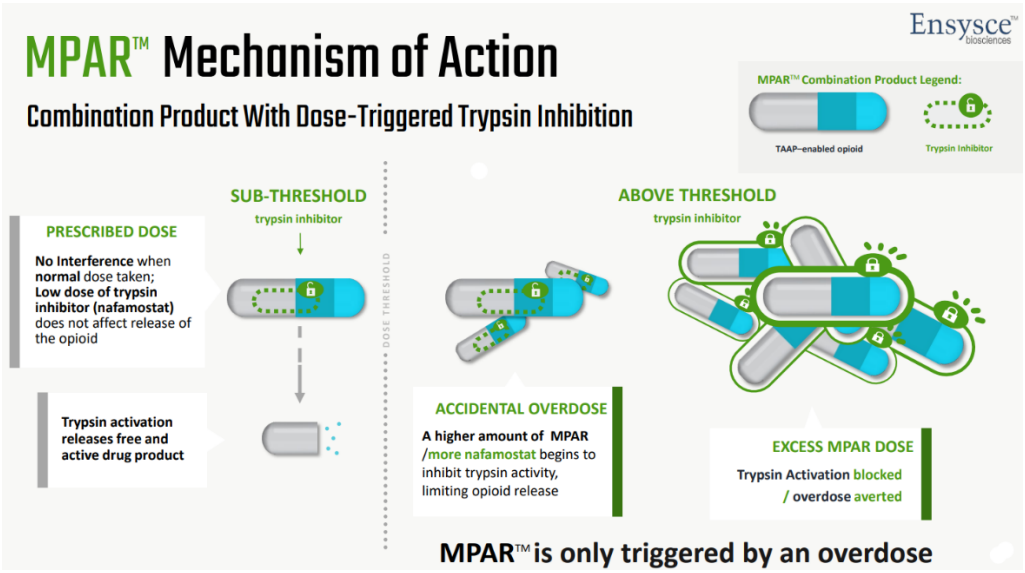

Exhibit 3: MPAR™ Mechanism of Action (MoA). Source: Company Filings

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™.

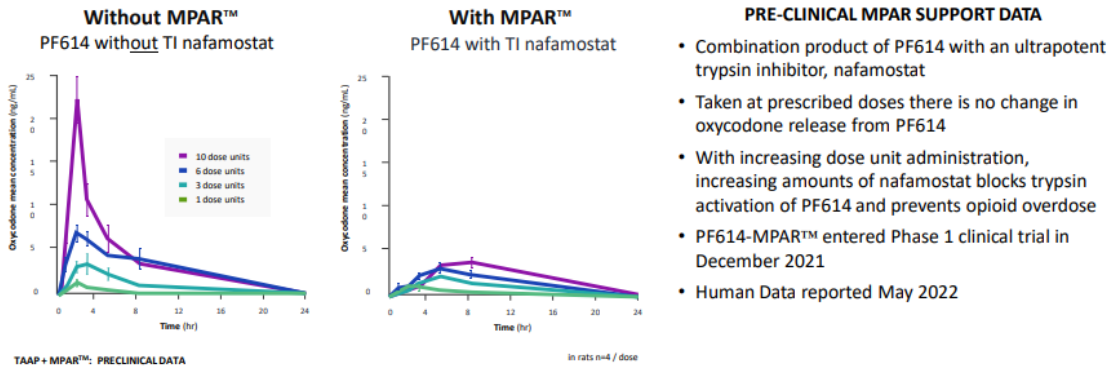

Exhibit 4: PF614-MPAR™ Pre-Clinical Data. Source: ENSC Investor Presentation

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

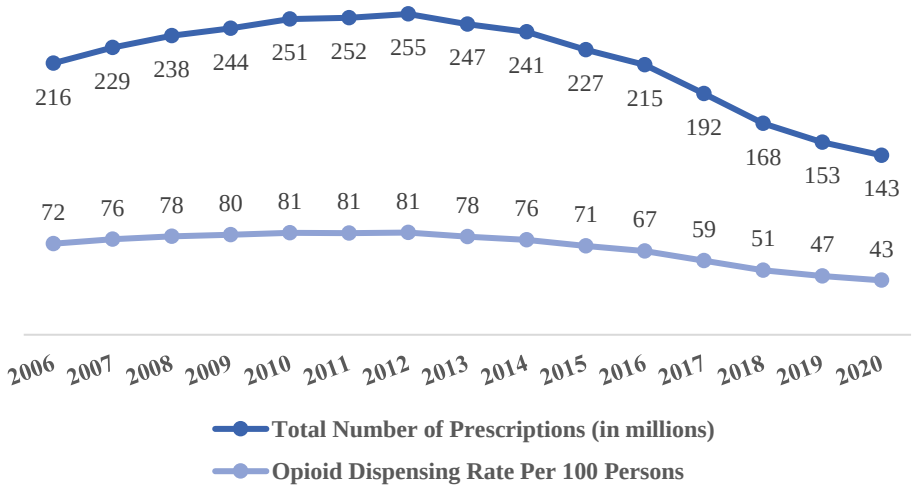

Exhibit 5: Total Opioid Prescriptions Dispensed and Opioid Dispensing Rate per 100 People. Source: CDC

[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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