ELYSIUM
THERAPEUTICS

January 2, 2024

Dear Investor:

This is a very special update as we achieved two key milestones for our O2P (Oral Overdose Protection) hydrocodone program.

- **Completed Phase 1 study:** Based on the demonstrated safety of our O2P hydrocodone prodrugs (e.g. ETR028 and ETR029) we were able to complete the initial evaluation and multi-fold dose escalations of ETR028, ETR029, and several [ETR028 + ETR029] blends. Dosing concluded with one of the final cohorts receiving an 80mg hydrocodone equivalent dose of a blend of ETR028/029 (i.e., sixteen 5mg tablets) and a comparator cohort receiving 80mg of hydrocodone bitartrate.
- **Demonstrated human Proof-of-Concept (hPOC):** We reported safety and pharmacokinetic data from all cohorts to our Board of Directors last week, and we are blessed and honored to report that we have demonstrated hPOC for our lead program, O2P hydrocodone. Congratulations to Dr. Tom Jenkins, co-founder of Elysium and inventor of our O2P technology, and thank you, investors for your support and encouragement. Data supporting hPOC are detailed below.

O2P™ (Oral Overdose Protection) Program

We dosed 75 healthy volunteers with ETR028 and/or ETR029 up to an 80mg dose (i.e., equivalent to an overdose of sixteen 5mg tablets). To achieve hPOC, we needed to demonstrate three key attributes: (1) Safety; (2) Hydrocodone exposure at levels known to provide analgesia within the prescribed dose range; and (3) Meaningful reduction in the maximum exposure of hydrocodone in overdose scenarios (i.e., Oral Overdose Protection). This new human data in combination with previous data from an outside lab demonstrating a high level of tamper resistance, and in vivo data demonstrating that hydrocodone will not be released when abused by non-oral routes of administration render our product profile highly attractive.

Safety

In all treatment periods ETR028 and ETR029 alone or blended were generally well tolerated in all subjects with no serious adverse events. The onsite principal investigator has described ETR028 and ETR029 as “benign,” which may be the most positive descriptor for safety of a new drug.

Prescribed Dose Range

From an efficacy perspective, when 1 or 2 doses of ETR028/ETR029 are ingested orally, the resulting maximum plasma hydrocodone exposures were similar to that demonstrated by a 5 mg and 10 mg hydrocodone comparator, respectively. Thus, at the prescribed doses hydrocodone exposures (i.e., analgesic potency) can be titrated to the desired effect.

Importantly, therapeutic doses of our O2P prodrugs also demonstrated a unique pharmacokinetic (PK) profile, producing known analgesic levels of hydrocodone that could allow for once-a-day dosing. This is a significant finding as O2P would allow for a significant reduction in the number of pills prescribed, adding yet another layer of overdose protection. For example, many states now limit opioid prescribing to no more than seven days. With O2P, only 7-14 tablets would be prescribed compared to 28-84 generic tablets to provide seven days of effective analgesia. That is a significant reduction in tablets available for abuse/diversion without even considering the game-changing oral overdose protection.

Oral Overdose Protection

The plasma exposures of hydrocodone following administration of a defined blend of our O2P prodrugs (e.g., a 50/50 blend of ETR028 and ETR029) demonstrated non-linear dose proportionality, as designed.

- When supratherapeutic doses (i.e., 8-fold and 16-fold oral overdoses) were ingested, substantial (~60%) reductions in plasma hydrocodone exposures vs. hydrocodone exposures expected from dose-proportional exposures were observed. This data closely parallels what we observed preclinically in dogs.
- At the 8-fold and 16-fold doses of our O2P prodrugs, hydrocodone exposures were 43-44% below hydrocodone exposures demonstrated with a hydrocodone comparator.
- Importantly, the hydrocodone exposures from ETR028/ETR029 even at the highest 16-fold dose studied were below the potentially lethal exposure level, whereas this same dose of hydrocodone bitartrate comparator resulted in a potentially lethal exposure level.[1]

These data represent the first demonstration of oral overdose protection for an acute-use opioid in humans.

Next Steps

As recommended by the FDA during our O2P pre-IND meeting, we will apply for Breakthrough Therapy Designation with the completion of the final clinical report in 1Q2024. Once filed, the FDA has 60 days to review and decide on the request. Breakthrough Therapy Designation would expedite O2P development and approval. Thus, this designation would be valuable in our parallel pursuit of a potential commercial licensing deal and/or additional financing.

Now that we have O2P hPOC data, we will execute a strategy to garner support for our technology with stakeholders (e.g., patients, physicians, policymakers, potential partners, payors). This is critical as we work to overcome the headwinds caused by opiophobia sparked by the opioid crisis, driven by the many bad actors that led to billion-dollar opioid settlements paid by opioid pharma companies and distributors. The current environment has limited the number of players in the opioid market, stifled safer opioid innovation, and, sadly, rewarded the manufacturers of the most unprotected, unsafe, highly abusable prescription opioids on the market.

The reality is that:

- Prescription opioids continue to be needed:

  - For millions of people suffering from moderate to severe pain, currently available non-opioid analgesics do not provide adequate pain relief.
  - Although numerous novel non-opioid targets have been/are being explored within academia and the pharmaceutical industry with the hope that they might lead to new analgesics that provide the same level of safe and effective pain relief to patients as opioids. Despite these ongoing efforts, no products are on the imminent horizon to help address the ongoing opioid crisis and undertreated pain.
  - Thus, now and for the foreseeable future, prescription opioids will continue to have a critical role in healthcare.
- When misused, prescription opioids can serve as a gateway to illicit opioids. Despite a recent campaign to significantly reduce the number of prescribed opioids, fatal overdoses from prescription opioids remains relatively flat. Thus, safer opioids with meaningful safety features are an important component of what is needed to address the opioid crisis:
  - Shifting the prescription opioid supply from easily manipulated and abusable products to safer opioids, like O2P, is necessary to fully realize the enormous public health benefits of such safer opioids.

We believe that pharmaceutical companies that manufacture and sell opioids should be required to increase the safety of their products to be introduced or continue to be marketed the same way that automobile manufacturers are required to improve the safety standards of their products. We will be meeting with policymakers and other key stakeholders to support our vision. O2P will set a new, significantly higher standard of safety for prescription opioids. We can reduce the number of opioid tablets prescribed, protect against overdose via all routes of administration, and, hopefully, reduce the next generation of OUD sufferers, while providing patients in need of effective moderate to severe pain management with proven effective analgesia.

Series Seed IV October 2020 Warrant-holders

In accordance with the terms of the October 2020 Series Seed IV Warrants, holders of such warrants have 60 days following the date the Company first provides human proof-of-concept data, as approved by the Board on January 2, 2024, to exercise these warrants. After 60 days, these warrants shall expire and shall no longer be exercisable.

SOOPR™ (Synthetic Opioid Overdose Prevention and Rescue) Program

The tragic rise in synthetic opioid (e.g., fentanyl) deaths is clear evidence that existing short-acting rescue agents (e.g., Narcan® and Opvee®) are no match for these potent opioids. Despite the availability of these rescue agents, fentanyl has become the leading cause of death for Americans aged 18-45 – more than car accidents, suicide, COVID-19, and cancer. In 2022, over 73,000 people died of fentanyl overdose in the US, more than double the number of deaths in 2019.

The onset of fentanyl overdose occurs rapidly, and the duration is significantly longer than that of other opioids, especially when taken orally. While Narcan and Opvee have rapid onset to effect an emergency

rescue of a fentanyl overdose patient, they do not have the necessary long duration of action required to fully overcome a fentanyl overdose. Consequently, this leads to re-narcotization (return of overdose symptoms), which increases the risk of traumatic brain injury (caused by lack of oxygen to the brain) and death.

To be effective, rescue from a fentanyl overdose often requires multiple doses of Narcan (usually 4-6 doses to get a patient to the ER according to first responders), which are not typically available to friends and family. Further, overdose patients often refuse transport to the ER. In these situations, the risk of fatality or toxic brain injury is unacceptably high due to the short duration of action of existing rescue agents. Further, existing rescue agents do not provide a meaningful intervention window in which friends and family could get their loved one on a road to recovery.

SOOPR was engineered to provide loved ones of OUD (opioid use disorder) sufferers and brave first responders with the peace of mind that comes from knowing they are equipped to save a life and help someone on the road to recovery.

- One easily administered dose of SOOPR will be effective against fentanyl and other potent synthetic opioids
- SOOPR will block opioid receptors ~5 times longer than existing rescue agents, reducing the risk of renarcotization, and, thus, reducing the risk of death or toxic brain injury.
- Friends and family will have the time to help their loved one on the road to recovery while SOOPR provides a bridge to medically-assisted therapy, providing OUD sufferers the best chance at recovery.

We are pleased that we have recently demonstrated in vivo proof of concept in animal models for (i) rapid onset of action suitable for an emergency intervention, and (ii) a superior duration of action vs. Narcan and Opvee.

With funds from the recent financing, we have:

- Identified a potential delivery device partner that has an existing autoinjector that has been previously approved by the FDA for emergency use and appears capable of delivering SOOPR at targeted doses;
- Completed additional in vivo studies to demonstrate SOOPR's rapid onset and longer duration of action; and,
- Begun to prepare a pre-IND package for the FDA, which will enable agreement upon the development path for SOOPR based on the recent (May 2023) approval of Opvee.

With the above data, and agreement with the FDA on the development path for SOOPR, we plan to pursue a potential commercial licensing deal in 2024 to accelerate development of this much needed, life-saving product.

Financing

We are grateful to all our investors and granting agencies (i.e., NIH and Ohio Third Frontier) for funding

our mission to disrupt the prescription opioid market by developing a new generation opioid pain relievers with unprecedented safety, and an opioid overdose rescue agent designed specifically to combat the devastating rise in fatalities from highly potent synthetic opioids. We expect to raise additional funds in 2024 to advance our programs toward commercialization. Additional funding could be from one or a combination of equity financing, non-dilutive grant funding or licensing deals.

We are also grateful for the extraordinary virtual team that enabled Elysium to achieve O2P human Proof-of-Concept and SOOPR in vivo proof-of-concept. While we will take a moment to celebrate truly historic results, we have much work to do to realize our mission and vision. Thank you again for your support.

If you have questions, please feel free to contact me.

Thank you and best regards,

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[1] Molina DK, Hargrove VM. What is the lethal concentration of hydrocodone?: a comparison of postmortem hydrocodone concentrations in lethal and incidental intoxications. Am J Forensic Med Pathol. 2011 Jun;32(2):108-11. doi: 10.1097/PAF.0b013e3181dd5a75. PMID: 20407360.