PainReform

Investor Presentation

March 2024

Forward-Looking Statements

This presentation contains forward-looking statements about our expectations, beliefs and intentions. Forward-looking statements can be identified by the use of forward-looking words such as "believe", "expect", "intend", "plan", "may", "should", "could", "might", "seek", "target", "will", "project", "forecast", "continue" or "anticipate" or their negatives or variations of these words or other comparable words or by the fact that these statements do not relate strictly to historical matters. These forward-looking statements are based on assumptions and assessments made in light of management's experience and perception of historical trends, current conditions, expected future developments and other factors believed to be appropriate. Because forward-looking statements relate to matters that have not yet occurred, these statements are inherently subject to risks and uncertainties that could cause our actual results to differ materially from any future results expressed or implied by the forward-looking statements. Many factors could cause our actual activities or results to differ materially from the activities and results anticipated in forward-looking statements, including, but not limited to, the following: our history of significant losses, our need to raise additional capital and our ability to obtain additional capital on acceptable terms, or at all; our dependence on the success of our initial product candidate, PRF-110; the outcomes of preclinical studies, clinical trials and other research regarding PRF-110 and future product candidates; the impact of the COVID-19 pandemic on our operations; our limited experience managing clinical trials; our ability to retain key personnel and recruit additional employees; our reliance on third parties for the conduct of clinical trials, product manufacturing and development; the impact of competition and new technologies; our ability to comply with regulatory requirements relating to the development and marketing of our product candidates; commercial success and market acceptance of our product candidates; our ability to establish sales and marketing capabilities or enter into agreements with third parties and our reliance on third party distributors and resellers; our ability to establish and maintain strategic partnerships and other corporate collaborations; the implementation of our business model and strategic plans for our business and product candidates; the scope of protection we are able to establish and maintain for intellectual property rights and our ability to operate our business without infringing the intellectual property rights of others; the overall global economic environment; our ability to develop an active trading market for our ordinary shares and whether the market price of our ordinary shares is volatile; and statements as to the impact of the political and security situation in Israel on our business. More detailed information about the risks and uncertainties affecting us is contained under the heading "Risk Factors" included in the Company's most recent Annual Report on Form 20-F and in other filings that we have made and may make with the Securities and Exchange Commission in the future.

These statements are only current predictions and are subject to known and unknown risks, uncertainties and other factors that may cause our or our industry's actual results, levels of activity, performance or achievements to be materially different from those anticipated by the forward-looking statements. Given these uncertainties, you should not rely upon forward-looking statements as predictions of future events.

All forward-looking statements attributable to us or persons acting on our behalf included in, but not limited to, this presentation speak only as of the date hereof and are expressly qualified in their entirety by the foregoing. We undertake no obligations to update or revise forward-looking statements to reflect events or circumstances that arise after the date made or to reflect the occurrence of unanticipated events. In evaluating forward-looking statements, you should consider these risks and uncertainties.

This presentation shall not constitute an offer to sell or the solicitation of an offer to buy, nor shall there be any sale of these securities in any state or other jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or other jurisdiction.

The presentation contains information about investigation-stage drug products under development, which have not yet been approved by the FDA for commercial distribution in the United States. All representations in this presentation are based upon investigations in certain clinical and other research, but which accordingly should not be construed as general claims for the safety or efficacy of the products when used by patients.

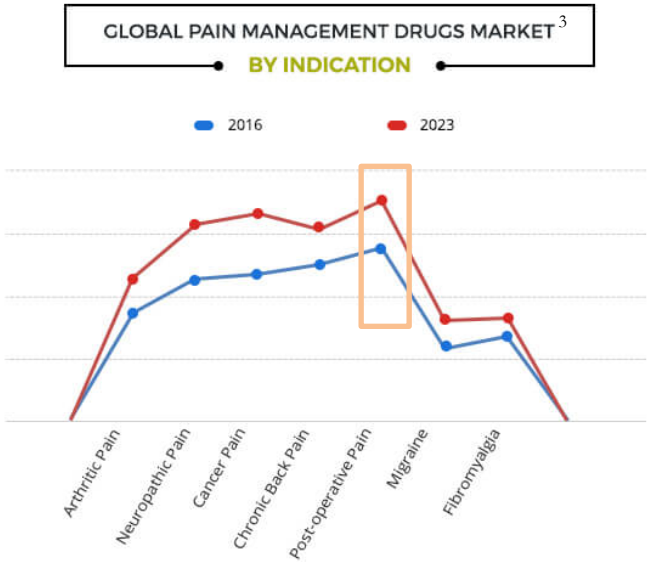
PRF-110 Executive Summary

- **Post-operative pain treatment is a growing market (~$12B) with a need for better therapeutics**
  - Local anesthetics provide pain relief for up to 6 hours and require augmentation with non-steroidal anti-inflammatory drugs (NSAIDs)
  - NSAIDs or opioids for moderate to severe pain, leading to side effects and dependence
  - Opiate abuse and addiction cause 70,000 death in the US & an economic burden of $80B/yr
  - Exparel (Pacira), a marketed long-acting liposomal generic local anesthetic has >$500M revenues: PCRX-market cap, at peak, over $4.0B – an important benchmark for PainReform
- **PainReform has developed PRF-110, a novel formulation extended release ropivacaine**
  - In a **Phase 2 clinical study** clinical study in 15 open hernia patients PRF-110 demonstrated pain relief of up to 72 hours
  - **Phase 3 study underway in the USA**
  - Patent estate granted for PRF-110 and formulation platform through 2033 prior to extensions-for US, Canada, EU, Israel, Australia, China, Japan, Russia, and other countries
  - Efficient manufacturing process for PRF-110 in the USA

- **Highly experienced board of directors and management team**
- **Inhouse clinical, manufacturing and QA know-how**

Post-Operative Pain Management Market Overview

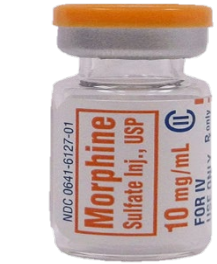
- The 2017 North America post-operative pain treatment market was estimated at ~$12B and is expected to reach ~$16B and $45B world-wide by the end of 2026[1]
- Significant unmet need for long-acting local anesthetic agents in order to spare opioids use, their side effects and reduce hospital length of stay due to complications
- Over 50 million procedures in the US per year
  - Just 10 % share provides over $500M in US revenues
- Despite the extensive use of opioids and NSAIDs, 74-86% of patients still experience moderate-to-extreme pain after surgery[2]
- Study of the global post-operative pain management market reveals a steady growth potential of **5.4% CAGR during the forecast period of 2017 to 2023**[4]



POST-OPERATIVE PAIN segment holds a dominant position in 2016 and would continue to maintain the lead over the forecast period.

1. https://www.persistencemarketresearch.com/market-research/postoperative-pain-management-market.asp
2 Gan, et al.,. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. CurrMed Res Opin. 2014;30(1):149–160.
3. https://www.medgadget.com/2018/06/post-operative-pain-management-market-2018-increasing-number-of-surgeries-has-led-to-grow-at-a-cagr-of-5-4-in-healthcare-industry-asserts-mrfr.html#:~:text=Global%20Post%2Doperative%20pain%20management,during%20forecasted%20period%202017%2D2023.&text=Increasing%20number%20of%20surgeries%20and,the%20growth%20of%20the%20market.

Current Approaches in Post-Operative Analgesia Are Lacking



Short-Acting Opioids

- Repeated dosing required
- Inconsistent pain control between doses
- Dependence risk increases with treatment duration

Long-Acting Opioids

- Poor efficacy in acute pain control
- Not intended for the treatment of post-operative pain

Significant adverse effects including respiratory depression, sedation and postoperative nausea and vomiting

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

- Moderate efficacy in acute pain control
- Repeated dosing required
- Inconsistent pain control between doses
- Significant safety issues, including bleeding, stroke, gastritis, renal toxicity

Exparel®

- Limited efficacy in acute pain control
- Liposomal bupivacaine
- Reduced postoperative opioid use
- Approved - revenues $500M
- Handling/delivery limitations

ZYNRELEF™
(bupivacaine and meloxicam)
extended-release solution
29.25 mg/mL and 0.88 mg/mL

Zynrelef®

- Complex, high production-price
- Bupivacaine and Meloxicam leading to a black box on the label
- Approved, launched July 2021
- 2022 revenues - $10.2M

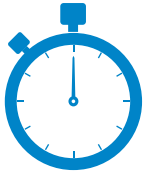
Prescription Opioids

- Prescription opioids can be used to treat moderate-to-severe pain and are often prescribed following surgery or injury
- In recent years, there has been a dramatic increase in the acceptance and use of prescription Opioids
- Opioid's dependency can start within 3 days of initial use
- More than 191 million opioid prescriptions were dispensed to American patients in 2017
- The most common drugs involved in prescription opioid overdose deaths include:
  - Methadone
  - Oxycodone (such as OxyContin®)
  - Hydrocodone (such as Vicodin®)
- Anyone who takes prescription opioids runs the risk of becoming addicted to them
- **99% of surgical patients** receive opioids to manage post-surgical pain and are released with opiate prescription
- 6% to 10% of surgical patients discharged with opiate prescriptions develop an opioid-dependency
- One in four patients receiving long-term opioid therapy in a primary care setting struggles with opioid addiction
- In 2016 and 2019, approximately 11.5 million Americans reported misusing prescription opioids in the past year
- Taking too many prescription opioids can stop a person's breathing—leading to death
- 62.6% Of people listed pain as their main reason for opioid misuse, where 36% of people with an opioid problem received a prescription from a healthcare provider

Source: CDC

PainReform Solution: PRF-110 Post Operative Pain Management

- PRF-110 has the potential to reduce the consumption of opioids to manage post-surgical pain
- In Phase III clinical study in the US
- Studies have shown 48 hours of pain reduction in healthy volunteers and about 72 hours in a clinical setting
- PainReform has developed a platform formulation for extended release of drugs
- Avoiding multiple injections reduces delivery time and complexity, reduces the risk of hematoma
- Reliable PK and low Cmax
- Physical attributes provide ease of surgeon use
- No injections, thereby avoiding the risk of inadvertent systemic administration
- Platform can be utilized for a wide range of APIs to generate a sustainable pipeline of new product applications
- Low variable costs allows for ease of manufacturing and production to meet high market demand
- Robust IP portfolio



PRF-110 Manufacturing

- Engaged Pharmaceutics International, Inc. (PII):
  - US-based contract manufacturing organization (CMO)
  - Well experienced in sterile manufacturing
  - PII is a premier, solutions-oriented, science-driven CMO with over 25 years of proven success in providing high-quality dosage form development
  - cGMP manufacturing services to the global biopharmaceutical industry
- Successfully developed a GMP manufacturing process for PRF-110
- PRF-110 is manufactured via a scalable and cost-effective process, is easy to commercialize, and contains excipients that are all FDA-approved as GRAS (generally regarded as safe)
- Low COGS compared to the current drug landscape

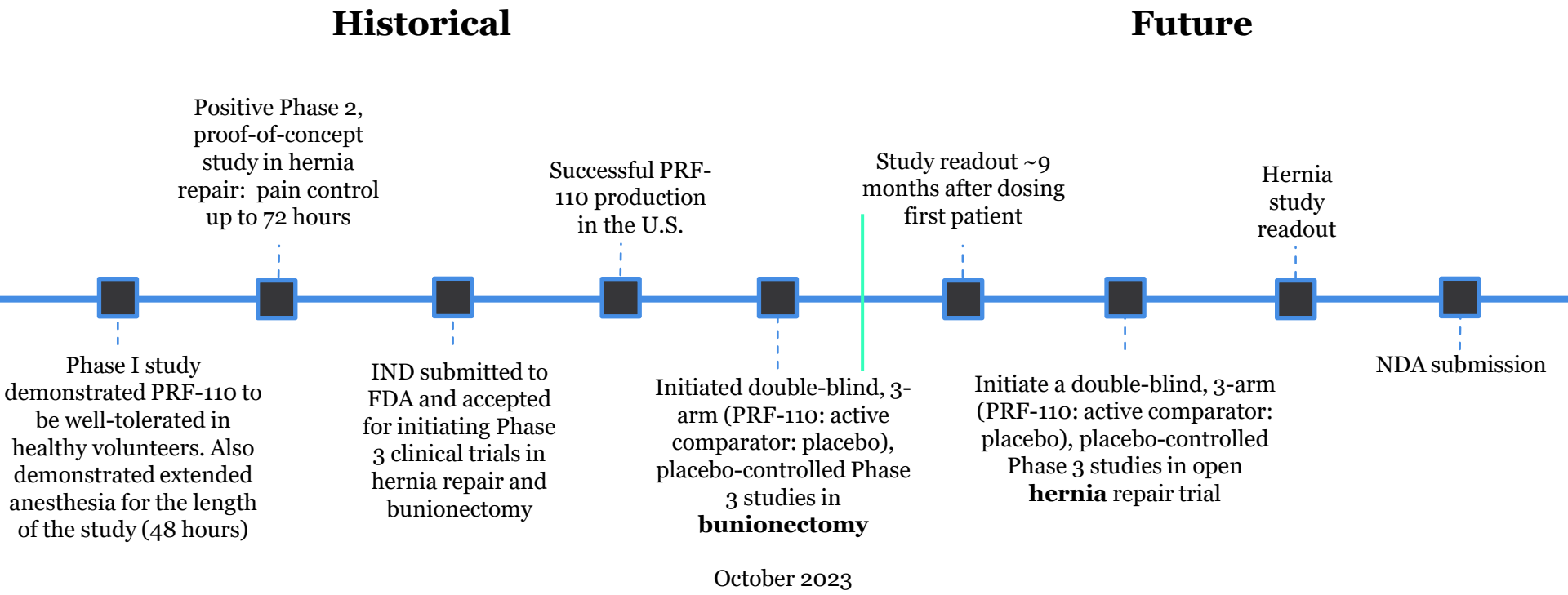
PRF-110 Safety

- PainReform carried out extensive FDA-requested wound healing and related animal studies that showed:
  - ✓ PRF-110 **allows for normal wound healing of surgical incisions** equal to both Naropin® and saline without any untoward histological or radiologic (microCT) effects observed in soft or bony tissue
  - ✓ Tensile strength of healed surgical skin following exposure to PRF-110 is equal to that of incisions exposed to either Naropin® or saline
  - ✓ Integrity of surgical sutures and surgical meshes is not affected by PRF-110 (compared to saline)
  - ✓ **No systemic side effects were** observed in any models
- PRF-110 safety in human trials showed **no systemic, wound healing or scarring abnormalities**. Wound healing in all patients was complete and similar to that expected in surgery without PRF-110

Comparison of PRF-110 Versus Market Leading Product

- Critically required for post-surgical topical applications
- During in vitro tests that were designed to mimic the spreadability attributes of PRF-110:
  - PRF-110 demonstrated superior formulation properties with respect to surface-tissue spreading
  - Lower viscosity, PRF-110 1,500 cP vs. about 10,000 cP for the commercial competitor
  - Superior surface interaction with surgical tissue based on a slide test, which demonstrated that the sliding of PRF-110 was twice that of the competitor.
- These results demonstrate that PRF-110 provides unique and significant benefits for local administration in postoperative pain management
- PRF-110 excelled in surface/tissue spreading and staying in place—a key advantage in achieving effective post-surgical pain relief—as it is critical to have even distribution inside the surgical wound.

PRF-110: Timeline to NDA



PRF-110: Phase III Clinical Trial Protocol

- Two, **double-blind, placebo control 72-hour treatment period**, studies planned (bunionectomy and hernia surgery). For each study:
  - Three cohorts (target = 400): PRF-110; Naropin® (ropivacaine); placebo; in a 2:2:1 ratio
- First patient, part II, initiated October 2023

<u>Primary endpoint (Efficacy)</u>

- Compare the analgesic efficacy of PRF-110 to placebo during the first 72 hours after completion of the surgery

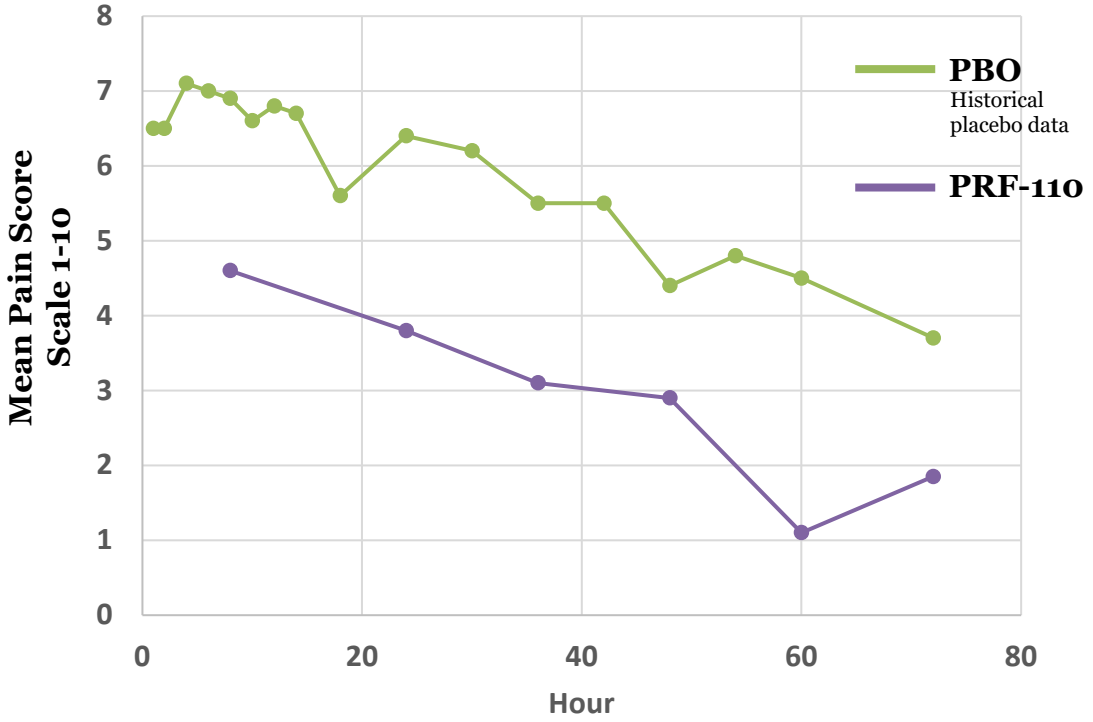
<u>Secondary endpoints Objectives:</u>

- Efficacy:
  - Compare the mean analgesic efficacy of PRF-110 to that of plain Naropin® during the first 72 hours after completion of bunionectomy or hernia surgery
  - Compare post-surgery opioid consumption through 72 hours for PRF-110 to that of ropivacaine injection
  - Compare post-surgery opioid consumption (in morphine milligram equivalents) over 72 hours for PRF-110 to that of placebo
  - Compare the proportion of subjects who were opioid-free through 72 hours for PRF-110 to that of plain ropivacaine
- Safety Objective:
  - Evaluate the safety and tolerability of PRF-110 in subjects undergoing bunionectomy or hernia surgery
- **As of Feb. 29, 2024, we enrolled over 140 patients in the trial, out of our target**

PRF-110 Phase 2 Results in Hernia

- **Efficacy**
  - PRF-110 provided post-operative pain control for up to 72 hours after a single application
- **Safety**
  - PRF-110 was well tolerated
- **Ease of use**
  - Easy to use and compliant with standard surgical techniques

PRF-110 Pain Reduction Up to 72-Hours After a Single Application



Product differentiation PRF-110 vs. Competition

	Pacira– Exparel™	Heron - Zynrelef®	PRF-110	PRF-110 Advantages
Formulation	Watery, complex liposomal suspension	Biochronomer technology: **Non-dilutable (Limited market)**	Waterless, viscous, oil-based solution (GRAS)	Uniformity, **viscosity, & retention**
Pain intensity reduction time	12-24 hours in surgical setting. **Not significantly better than Bupivacaine alone**	Pain control up to 72 hours. Nerve block-problematic. AEs: Site inflammation, necrosis, bradycardia and impaired wound healing (Pacira citizen petition)	Approx. 72 hours pain control in clinical setting	**Potentially longer duration of clinical activity, well-tolerated, no injection-related inflammation, infection or accidental systemic exposure**
Manufacturing & Market	Special equipment & complex methodology resulting in high COGS	Complex chemistry and methodology	Simple, short standard process and formulation.	**Scalable and cost effective. WW market**
Status	Product launched in 2012, sales $500M in 2022 Loss of exclusivity expected during 2024	FDA approval received for soft tissue or periarticular instillation for bunionectomy, open inguinal herniorrhaphy and total knee arthroplasty **Prescribing information includes a black box warning**	In Phase III clinical in the U.S.	
Valuation	~$1.3 Billion	~$392 Million	~$5M	

Additional competing products (approved and in development):

- Posimir® by Durect ("DRRX") - FDA approval for only arthroscopic subacromial decompression (niche market)
- XARACOLL® by Innocoll, a surgically implantable and bioresorbable bupivacaine-collagen matrix - FDA approval for only open inguinal hernia repair, launched Sep. 2023
- Allay Therapeutics ATX-101, product based on bupivacaine going into phase 2b, development status unknown
- Taiwan Liposome Company (TLC) – Liposomal Ropivacaine – Phase II clinical trial completed
- Cali Biosciences Co,. Ltd. – In phase III of Long-Acting Ropivacaine (CPL-01)

PRF-110: Potential Best-In-Class

Efficacy

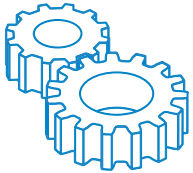
Cross study comparison of Phase II data, 72 hours pain AUC

Safety

Met FDA required extensive pre-clinical studies to demonstrate no wound healing issues

Administration

PRF-110 viscosity and uniformity are highly suitable for standard surgical site administration.



COGS

Low cost of good sold allows a highly strategic pricing plan and considerations

Highly experienced management Team

Ehud Geller, PhD, MBA. Executive Chairman

- Former President & CEO of Interpharm Laboratories and EVP of Teva Group
- Former head of the Israeli Pharmaceutical Manufacturers Association and board member of the Tel Aviv Stock Exchange
- National Industry award for contribution to biotech industry and management leadership, Samuel Johnson Medal – Columbia
- Columbia University, Drexel Institute – Chemical Engineering (bio-chemical technology), MBA, PhD

Ilan Hadar, MBA, Chief Executive Officer

- Former Country Manger and CFO of Foamix Pharmaceuticals Ltd. (now Nasdaq: VYNE)
- Over 20 years of multinational managerial and corporate experience with pharmaceutical and high-tech companies
- Has been instrumental in building companies from start-ups to hundreds of millions of dollars in operations
- Successfully took part in the development, approval, and launch of new pharmaceutical products in the U.S. and Israel
- Received his MBA in Finance and Business Entrepreneurship and B.A. degree at The Hebrew University in Jerusalem

Eli Hazum, PhD, MBA, Chief Technical Officer

- Spent 5 years at Glaxo Inc. as Head of Department of Receptor Research and Metabolic Diseases
- Over last 25 years Eli has taken leadership roles within Medica portfolio companies including interim CEO for Collgard Biopharmaceuticals and Ester Neurosciences, where he was responsible for executing Ester's acquisition by Amarin Pharmaceuticals.
- Received Ph.D. from the Weizmann Institute of Science in the field of hormone biochemistry, and has an executive MBA from Humberside University in the UK

Sigal Aviel, PhD, MBA, Chief Operating Officer

- Over 20 years of managerial experience in the Biotech industry.
- Former chief R&D officer at MediWound, a company specializing in deep burns and chronic wound care, where she was responsible for product development from early stages to final product approval by regulatory authorities.
- PhD in Immunology and Microbiology from Duke University Medical School as well as an executive MBA degree from the Kellogg school of business at NW University

Rita Keynan, V.P. Pharma Operations

- Over 25 years of managerial experience in the pharmaceutical industry.
- Former executive director of drug development at VYNE Therapeutics Ltd., formerly Foamix Pharmaceuticals, where she managed the drug development department
- Mrs. Keynan is the co-inventor of over two dozen patents
- Mrs. Keynan holds a B.Sc. in Chemistry and a M.Sc. in Pharm from the Hebrew University in Jerusalem.

Summary

1. **Innovative Formulation / Delivery System**
2. **Opioid Epidemic Presents Significant Commercial Opportunity**
3. **Seasoned Management Team with Decades of Experience**
4. **Robust US and International IP Portfolio**
5. **Core platform can be utilized for wide-range of APIs to generate sustainable pipeline**

Large Unmet Need in Non-Opioid Postoperative Pain Management[1]

[1]Market Watch Post-Operative Pain Management Market Size Analysis 2019 Report

PainReform

Thank You