



Investor Presentation

January 2021

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- **Post-operative pain treatment is a growing market (~\$12B) with a need for better therapeutics¹**
 - 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/yr¹
 - Exparel (Pacira), the only known marketed long-acting liposomal generic local anesthetic has >\$400M revenues: PCRX-market cap, at peak, over \$4.0B – an important benchmark for PainReform²
- **PainReform has developed PRF-110, a novel formulation extended release ropivacaine**
 - Robust **preclinical data package**
 - **Phase 1 data** in healthy volunteers suggest favorable PK profile and safety data
 - 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 design and IND approved; FDA confirmed 505(b)(2) designation**
 - Patent estate granted for PRF-110 and formulation platform through 2033 prior to extensions-for US, Canada, EU, IL, Australia, China, Japan, Russia and other countries
- **Clinical Development Plan**
 - Green light from **FDA to initiate two phase III trials** (soft and hard tissue) of ~400 patients each for NDA submission
 - 505(b)(2): A low risk barrier to approval

¹ White House [Report](#): Underestimated Cost of the Opioid Crisis
² Market Insider [Report](#): Pacira BioSciences Reports 2019 Results



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

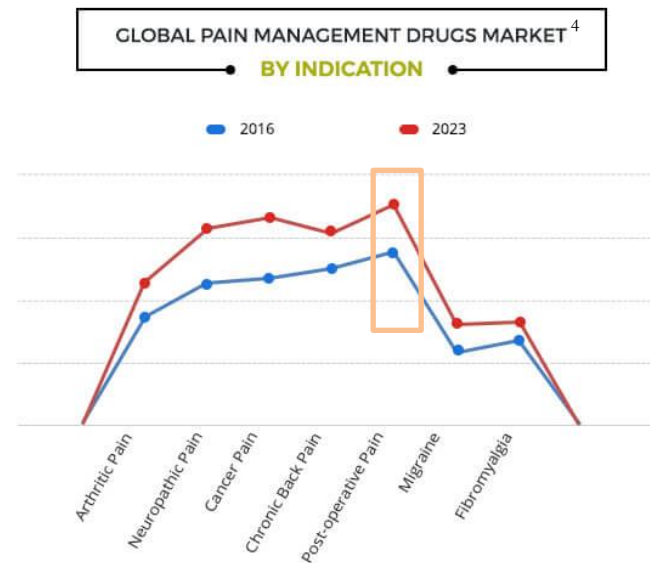
- Over 20 years of managerial experience in the Biotech industry.
- Former Chief R&D Officer at MediWound, a company specializing in deep burns and chronic wound care, where she was responsible for product development from early stages to final product approval by regulatory authorities.
- PhD in Immunology 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.

- The 2017 world-wide overall post-operative pain treatment market was estimated at US\$~12B and is expected to reach in excess of US\$45B by the end of 2026¹
- 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 year²
 - 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 surgery³
- 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. Source: Ask wonder

3. 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.

4. <https://www.medgadjet.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%20operative%20pain%20management,during%20forecasted%20period%202017%20to%202023.&text=Increasing%20number%20of%20surgic%20and,the%20growth%20of%20the%20market.>



11.4 Million

People misused opioids in 2019. 886K used heroin. 562K misused both pain relievers and heroin³



2.1 Million

People have an opioid use disorder. 1.7 million people with a prescription pain reliever have a use disorder.³



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 provider³



>\$80.0 Billion

Per year US economic burden where 40,000 people a year die from opioid related issues²

- **99% of surgical patients** receive opioids to manage post-surgical pain¹
- Opioids dependency can start within **3 days** of initial use
- 6% to 10% of surgical patients discharged with opiate prescription develop an opioid-dependency⁵
- **75% of patients** who undergo surgery experience acute post-operative pain, which is often medium-high in severity⁴
- A 2016 study which enrolled 799,449 patients, showed that reliance on opioid analgesics as the mainstay for **perioperative pain management is still widespread.**³

¹ NSDUH, 2017 Data; published Sept. 2018

² Med Care 2016 54 (10) 901-906, [Article](#)

³ Hollmann: Optimal postoperative pain management – redefining the role for opioids [Study](#)

⁴ NIH Horn; Kramer – Postoperative Pain Control [Study](#)

⁵ Lee, et al Clin Oncol. 2017;35(36):4042–9.



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

Extended release, Local, Non-Opioid Analgesic (Exparel®)

- Limited efficacy in acute pain control
- Liposomal bupivacaine
- Reduced postoperative opioid use
- Approved - revenues \$400M
- Complex production-price
- Handling/delivery limitations



Pain Reduction Time

Studies have shown 48 hours of pain reduction in healthy volunteers and about 72 hours in a clinical setting



Scalable and Cost Effective

Low variable costs allows for ease of manufacturing and production to meet high market demand



Easy Application

Avoiding multiple injection reduces delivery time and complexity, reduces the risk of hematoma

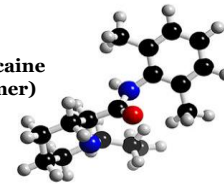


Core Platform

Platform can be utilized for a wide-range of APIs to generate sustainable pipeline of new product applications

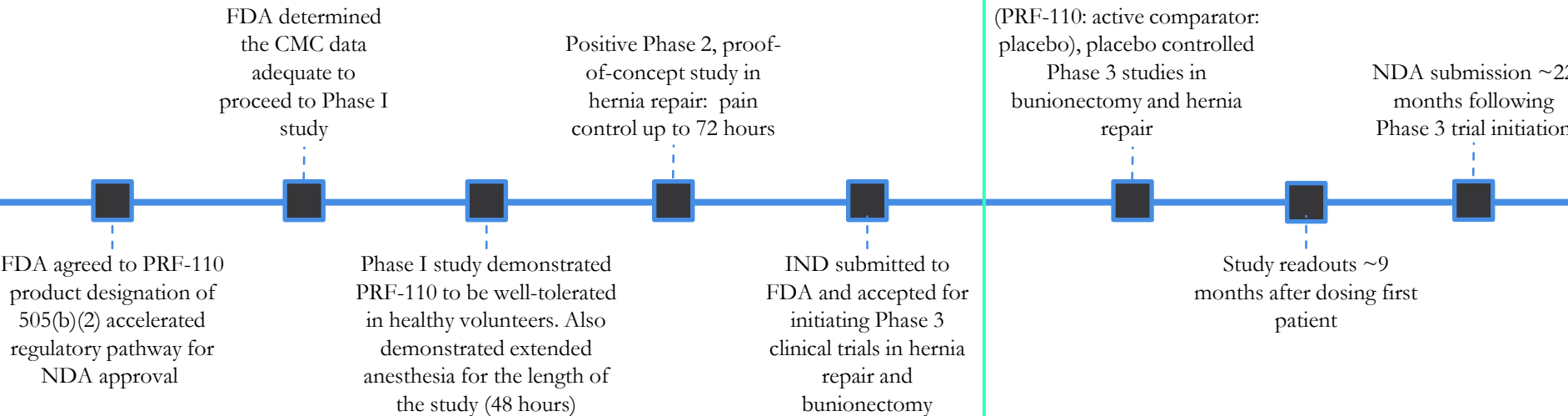
- PainReform has developed a platform formulation for extended release of drugs
- Low COGS compared to current drug landscape
- Reliable PK and low Cmax
- No free API
- Physical attributes provide ease of surgeon use
- No injections, thereby avoiding risk of inadvertent systemic administration
- Robust IP portfolio

Ropivacaine
(s-isomer)



Historical

Future



Product differentiation PRF-110 vs. Competition

	Pacira ¹ – Exparel™	Heron ² -HTX 011	PRF-110	PRF-110 Advantages
Formulation	Watery, complex liposomal suspension	Biochronomer technology ⁽⁴⁾ : 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; US only	Complex chemistry and methodology	Simple, short standard process and formulation.	Scalable and cost effective. WW market
Status	Product launched in 2012, sales \$400M in 2019	FDA (3/4/19) requested additional CMC and pre-clinical information, NDA resubmitted Nov. 2020	Preparing for Phase III, expected launch in 2023	
Valuation³	~\$2.6 Billion	\$1.9 Billion	~\$55M	

Additional competing products (approved and in development):

- Posimir by Durect (“DRRX”), held up at phase III due to safety profile of the matrix (synthetic polymer), FDA approval for only arthroscopic subacromial decompression (niche market).
- Innocoll, completed 2 hernia phase III trials (XARACOLL, a surgically implantable and bioresorbable bupivacaine-collagen matrix) - FDA Refusal letter 12/2016-Drug/Device combination. Acquired by Gurnet Point Capital for \$209M in July 2017. August 2020, FDA approval for only open inguinal hernia repair.
- Taiwan Liposome Company (TLC) – Liposomal Ropivacaine – Phase II.

¹ Pacira published data, news, presentation

² Heron published data, news, presentation

³ As of 1/5/2021

⁴ The Biochronomer® polymer is a semi-solid, highly viscous polyorthoester polymer & alpha-hydroxy (e.g., lactic & glycolic) acids are incorporated into the polymer backbone to promote degradation. Hydrolysis releases drugs while creating acidic environment.

- 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** 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

- **Efficacy**

- PRF-110 provided post-operative pain control for up to 72 hours after a single application

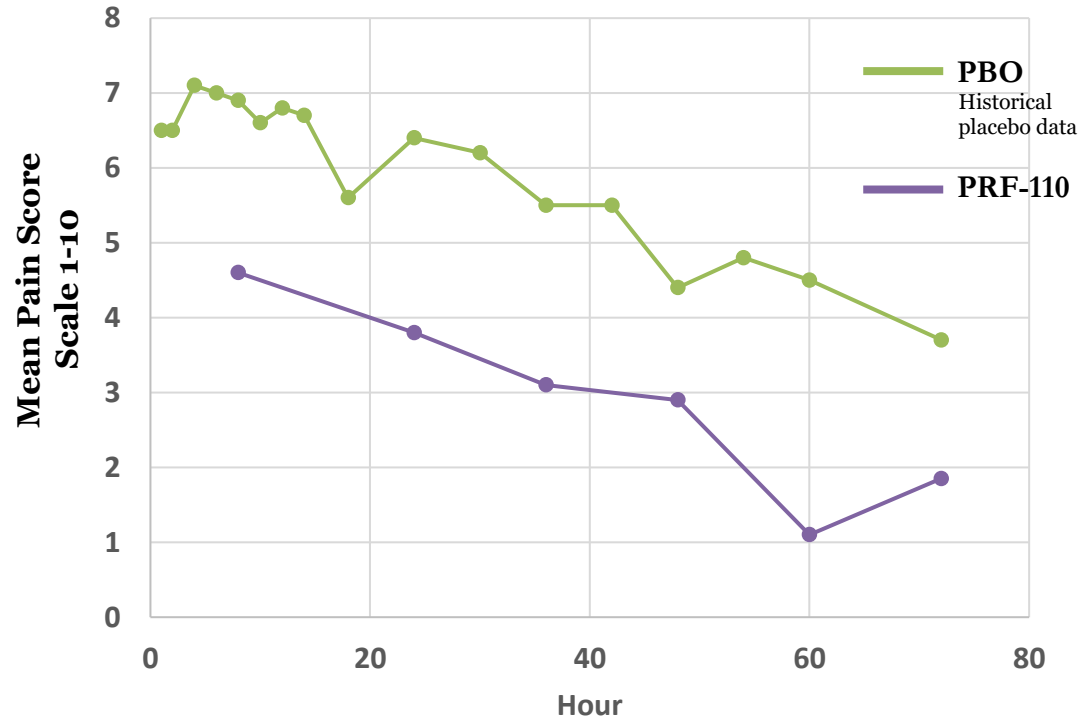
- **Safety**

- 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



- **Two, double blind, placebo control 72-hour treatment period**, studies planned (bunionectomy and hernia surgery). For each study:
 - Three cohorts (n= ~400): PRF-110; Naropin[®] (ropivacaine); placebo; in a 2:2:1 ratio

Primary endpoint (Efficacy)

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

Secondary endpoints Objectives:

- **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 (in morphine milligram equivalents) over 72 hours for PRF-110 to that of placebo
 - Compare post-surgery opioid consumption through 72 hours for PRF-110 to that of plain ropivacaine
 - 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



Efficacy

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



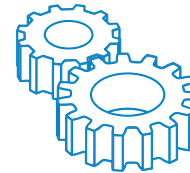
Safety

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



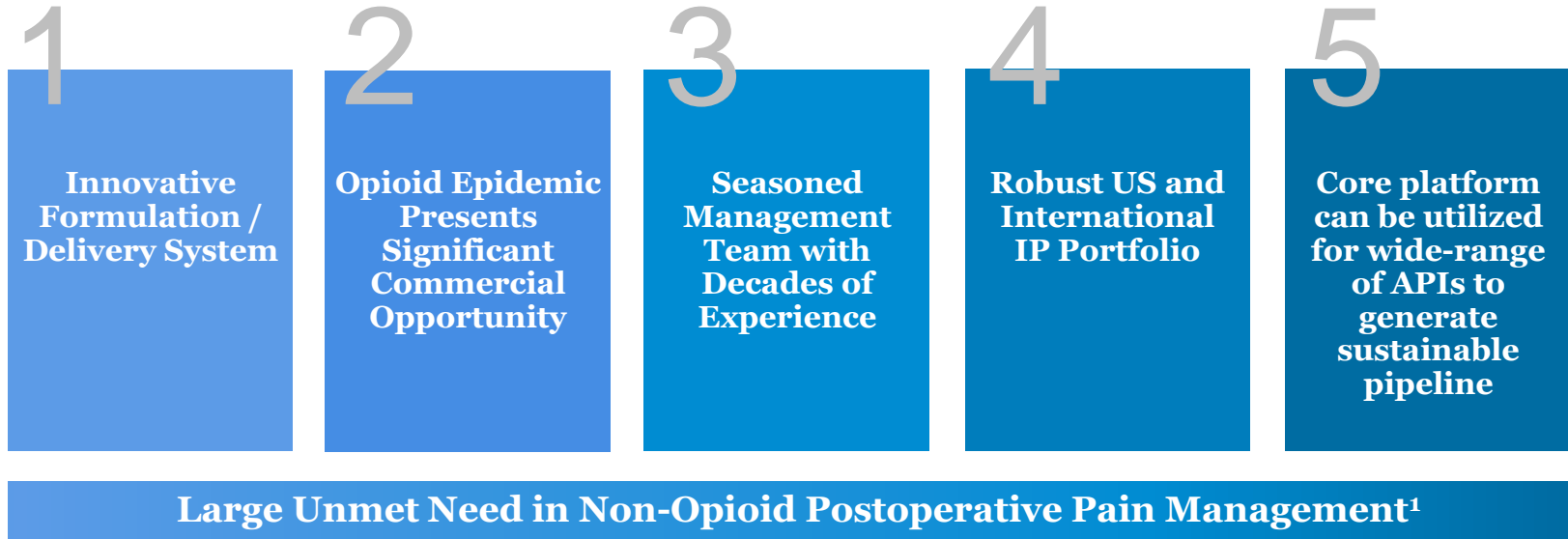
Administration

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



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

The logo for PainReform features the word "PainReform" in a serif font. The word "Pain" is colored green, and "Reform" is colored blue. A blue swoosh underline starts under the "P", loops around the "R", and ends under the "m".

PainReform

A solid blue horizontal banner with the text "Thank You" centered in a white serif font. The banner is flanked by thin green lines above and below it.

Thank You