PainReform

Investor Presentation

January 2021

Forward-Looking Statements

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PRF-110 Executive Summary

- **Post-operative pain treatment is a growing market (~$12B) with a need for better therapeutics[1]**
  - Local anesthetics provide pain relief for up to 6 hours and require augmentation with 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[1]
  - 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 PainReform[2]
- **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, 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

Management Team

Ehud Geller, PhD, MBA. Acting 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

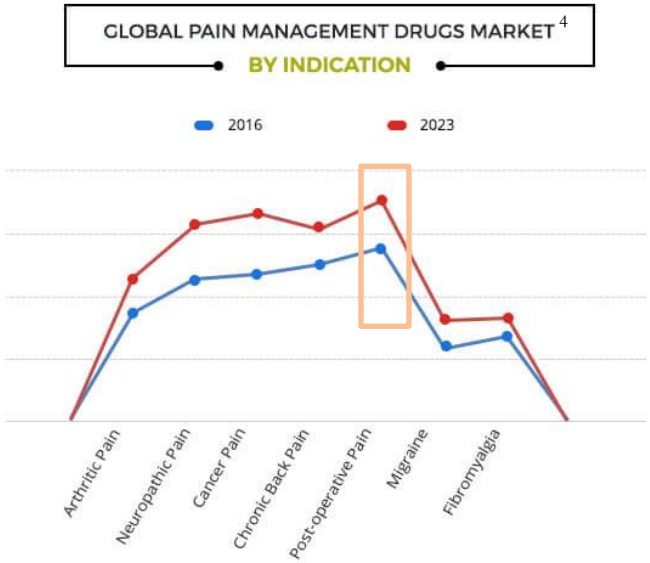
- Over 20 years of managerial experience in the Biotech industry.
- Former Chief R&D Officer at MediWound, a company specializing in deep burns and chronic wound care, where she was responsible for product development from early stages to final product approval by regulatory authorities.
- PhD in Immunology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

Post-Operative Pain Management Market Overview

- 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 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 40-45 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[3]
- 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. National Health Statistics Reports 2010 Surgery stats.pdf
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.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.

Problem: State of Opioid Crisis in America

11.4 Million

People misused opioids in 2019. 886K used heroin. 562K misused both pain relievers and heroin[3]

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 provider[3]

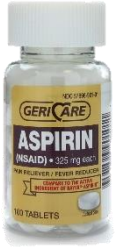
>$80.0 Billion

Per year US economic burden where 40,000 people a year die from opioid related issues[2]

- **99% of surgical patients** receive opioids to manage post-surgical pain[1]
- Opioids dependency can start within **3 days** of initial use
- 6% to 10% of surgical patients discharged with opiate prescription develop an opioid-dependency[5]
- **75% of patients** who undergo surgery experience acute post-operative pain, which is often medium-high in severity[4]
- 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.)

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

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

PainReform Solution: PRF-110 Post Operative Pain Management

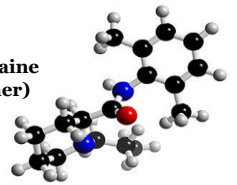
Pain Reduction Time
Studies have shown 48 hours of pain reduction in healthy volunteers and about 72 hours in a clinical setting

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



PRF-110: Timeline to NDA

Historical

- FDA agreed to PRF-110 product designation of 505(b)(2) accelerated regulatory pathway for NDA approval
- FDA determined the CMC data adequate to proceed to Phase I study
- Phase I study demonstrated PRF-110 to be well-tolerated in healthy volunteers. Also demonstrated extended anesthesia for the length of the study (48 hours)
- Positive Phase 2, proof-of-concept study in hernia repair: pain control up to 72 hours
- IND submitted to FDA and accepted for initiating Phase 3 clinical trials in hernia repair and bunionectomy

Future

- Initiate double blind, 3-arm (PRF-110: active comparator: placebo), placebo controlled Phase 3 studies in bunionectomy and hernia repair
- Study readouts ~9 months after dosing first patient
- NDA submission ~22 months following Phase 3 trial initiation

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 2022	
Valuation[3]	~$2.6 Billion	$1.9 Billion	~$40M	

[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.

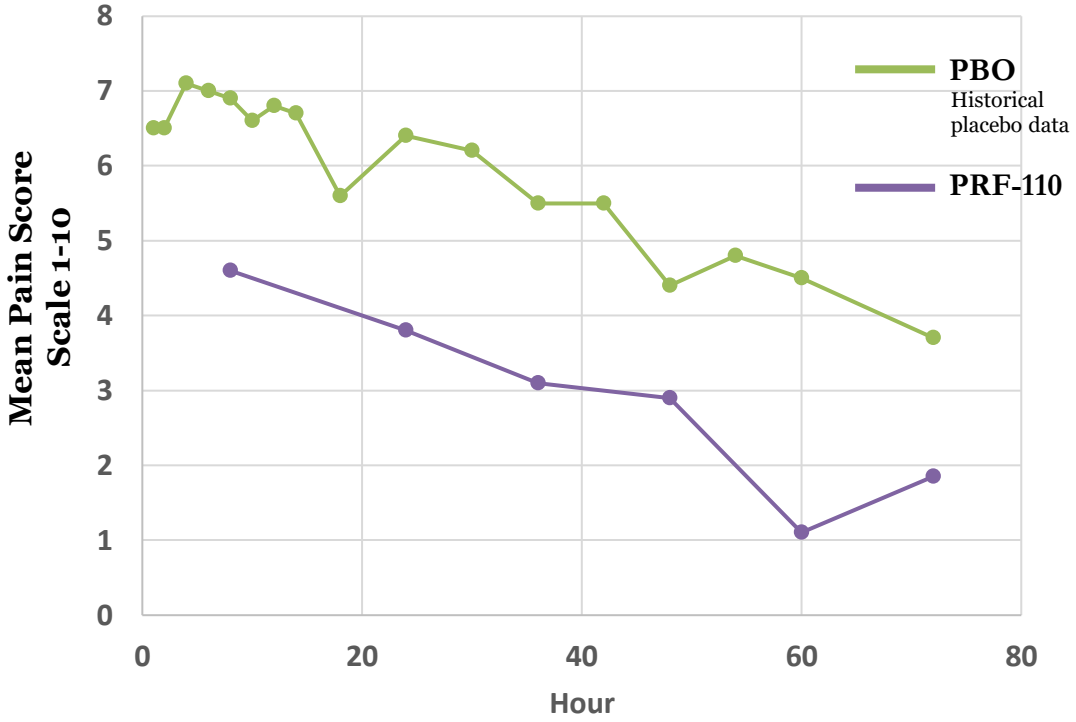
PRF-110 Safety

- 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** 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

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



PRF-110: Phase III Clinical Trial Protocol

- Two, **double blind, placebo control 72-hour treatment period**, studies planned (bunionectomy and hernia repair). For each study:
  - Three cohorts (n= ~400): 1. PRF-110; 2. Naropin® (ropivacaine); placebo; in a 2:2:1 ratio
  - Primary endpoint (Efficacy)
    - Mean pain scores over 72 hours (scale 0-10), compared to placebo
  - Secondary endpoints (Safety):
    - Incidence of TEAEs and Serious AEs (SAEs)
    - Physical examination
    - Wound Healing
  - Secondary endpoints (Efficacy)
    - Mean pain scores over 72 hours (scale 0-10), compared to placebo
    - Proportion of subjects who are opioid-free for PRF110 compared with active comparator Naropin® over 72 hours

PRF-110: Potential Best-In-Class

Efficacy

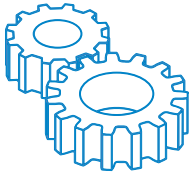
Cross study comparison of Phase II data, 72 hours pain AUC

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

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