# PCRX PCRX INVESTOR DAY October 15, 2021



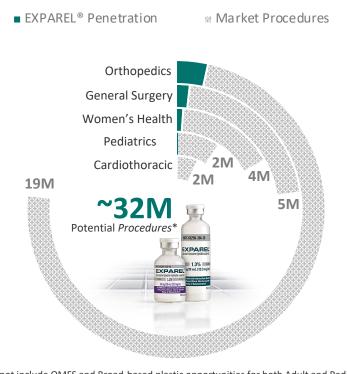
#### Forward-Looking Statements and Where to Find Additional Information

Any statements in this communication about Pacira BioSciences, Inc.'s ("Pacira") or Flexion Therapeutics, Inc.'s ("Flexion") future expectations, plans, trends, outlook, projections and prospects, and other statements containing the words "believes," "anticipates," "plans," "estimates," "intends," "intends," "would," "could," of The Private Securities Litigation Reform Act of 1995. These forward-looking statements include, without limitation, statements related to the anticipated consummation of the acquisition of Flexion and the timing and benefits thereof, Pacira's strategy, plans, objectives, expectations (financial or otherwise) and intentions, future financial results and growth potential, anticipated product portfolio, development programs, patent terms and other statements that are not historical facts. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including risks relating to, among others: risks related to Pacira's ability to complete the transaction on the proposed terms and schedule or at all; whether the tender offer conditions will be satisfied; whether sufficient stockholders of Flexion tender their shares in the transaction; the outcome of legal proceedings that may be instituted against Flexion and/or others relating to the transaction; the failure (or delay) to receive the required regulatory approvals relating to the transaction; the possibility that competing offers will be made; risks associated with acquisitions, such as the risk that the businesses will not be integrated successfully, that such integration may be more difficult, time-consuming or costly than expected or that the expected benefits of the proposed transaction will not occur; risks related to future opportunities and plans for Flexion and its products, including uncertainty of the expected financial performance of Flexion and its products, including whether the milestones will ever be achieved; disruption from the proposed transaction, making it more difficult to conduct business as usual or maintain relationships with customers, employees or suppliers; occurrence of any event, change or other circumstance that could give rise to the termination of the acquisition agreement; the possibility that if Pacira does not achieve the perceived benefits of the transaction as rapidly or to the extent anticipated by financial analysts or investors, the market price of Pacira's shares could decline; the impact of the worldwide COVID-19 (Coronavirus) pandemic and related global economic conditions on Pacira's and/or Flexion's business and results of operations; the success of Pacira's sales and manufacturing efforts in support of the commercialization of EXPAREL and iovera°; the rate and degree of market acceptance of EXPAREL and iovera°; the size and arowth of the potential markets for EXPAREL and iovera° and Pacira's ability to serve those markets; Pacira's plans to expand the use of EXPAREL and iovera° to additional indications and opportunities, and the timina and success of any related clinical trials for EXPAREL and iovera<sup>o</sup>; the ability to successfully integrate any future acquisitions into Pacira's existing business, including Flexion; and the recoverability of Pacira's deferred tax assets and other factors discussed in the "Risk Factors" of each of Pacira's and Flexion's most recent Annual Report on Form 10-K and in other filings that Pacira and Flexion periodically make with the Securities and Exchange Commission (the "SEC"). In addition, the forward-looking statements included in this communication represent Pacira's and/or Flexion's views, as applicable, as of the date of this communication. Important factors could cause actual results to differ materially from those indicated or implied by forward-looking statements, and as such each of Pacira and Flexion anticipates that subsequent events and developments will cause its respective views to change. However, while Pacira or Flexion may elect to update these forward-looking statements at some point in the future, each of Pacira or Flexion specifically disclaims any obligation to do so, except as required by law. These forward-looking statements should not be relied upon as representing either Pacira's or Flexion's views as of any date subsequent to the date of this communication.

#### Additional Information about the Transaction and Where to Find It

The tender offer (the "Offer") described in this communication has not yet commenced, and this communication is neither a recommendation, nor an offer to purchase nor a solicitation of an offer to sell any shares of the common stock of Flexion or any other securities. On the commencement date of the Offer, a tender offer statement on Schedule TO, including an offer to purchase, a letter of transmittal and related documents, will be filed with the SEC by Pacira and Oyster Acquisition Company Inc., a wholly owned subsidiary of Pacira, and a Solicitation/Recommendation Statement on Schedule 14D-9 will be filed with the SEC by Flexion. The Offer to purchase the outstanding shares of Flexion will only be made pursuant to the offer to purchase, the letter of transmittal and related documents filed as a part of the Schedule TO. **INVESTORS AND SECURITY HOLDERS ARE URGED TO READ THE TENDER OFFER MATERIALS (INCLUDING AN OFFER TO PURCHASE, A LETTER OF TRANSMITTAL AND RELATED DOCUMENTS) AND THE SOLICITATION/RECOMMENDATION STATEMENT ON SCHEDULE 14D-9 REGARDING THE OFFER, AS THEY MAY BE AMENDED OR SUPPLEMENTED FROM TIME TO TIME, WHEN THEY BECOME AVAILABLE BECAUSE THEY WILL CONTAIN IMPORTANT INFORMATION THAT INVESTORS AND SECURITY HOLDERS SHOULD CONSIDER BEFORE MAKING ANY DECISION REGARDING TENDERING THEIR SHARES, INCLUDING THE TERMS AND SECURITY HOLDERS and security holders may obtain a free copy of these statements (when available) and other documents filed with the SEC at the website maintained by the SEC at www.sec.gov or by directing such requests to the information agent for the Offer, which will be named in the tender offer statement. Investors and security holders may also obtain, at no charge, the documents filed or furnished to the SEC by Flexion under the "Investors" section of Flexion's website at investor.pacira.com.** 

#### Key Markets Expected to Propel EXPAREL Future Growth



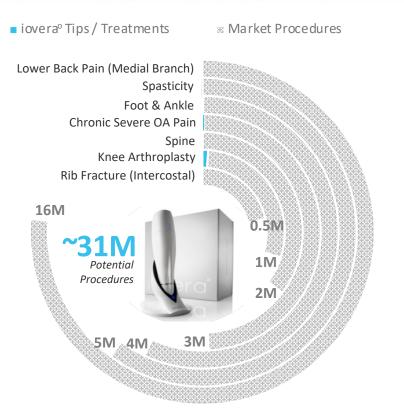
#### Market and Business Dynamics driving Growth

- Current Orthopedics and Soft Tissue each 50% of net sales
- The opioid epidemic is surging amidst the landscape of the COVID-19 pandemic
- Accelerating site of care shift: Patient, Provider, & Payer preferences increasingly driving procedures to 23-hr stay Enhanced Recovery After Surgery Protocols (ERAS) with effective, safe low or no opioid pain control
- Advanced Regional Anesthesia with non-opioid Intervention changing the face of surgical landscape
  - Regional approaches expected to grow from 20% to 75% of all techniques (vs general anesthesia) by 2025
- Adequately treating the growing community in recovery requires opioid-free protocols
- Rest of World expansion opportunities

\* TAM does not include OMFS and Broad-based plastic opportunities for both Adult and Pediatric Populations
 \* Pediatrics includes Ortho, Women's Health, General Surgery, Cardiothoracic, Otolaryngology, and Other

Source: IQVIA Market Procedural Data extrapolated for Post COVID market size estimated in 2022, OMFS from Friedman JW. The prophylactic extraction of third molars: a public health hazard. Am J Public Health. 2007;97(9):1554-1559. doi:10.2105/AJPH.2006.100271; Penetration is derived based on IQVIA EXPAREL® Utilization Data Triangulated With Pacira Internal Sales Data Through Jun'21 Forecasted based on internal assumptions

#### Key Markets Expected to Propel iovera<sup>o</sup> Future Growth



#### Market and Business Dynamics driving Growth

- COVID-19 pandemic delaying elective procedures, including TKA, creating unmet need for less invasive pain management alternatives
- Accelerate awareness and penetration into focused TKA & OA Knee markets expanding reach to ASC and Office based practices
- Expand opportunistically through life cycle mgmt. activities to provide innovative intervention in Spine, Chronic Lower Back Pain, Spasticity, Intercostal (Rib Fracture), Foot & Ankle
- Rest of World expansion opportunities
  - 2+ year backlog for TKA in UK

Source: IQVIA Market Procedural Data extrapolated for Post COVID market size estimated in 2022, Penetration is derived based on IQVIA iovera<sup>o</sup> Utilization Data Triangulated With Pacira Internal Sales Data Through Jun'21 Forecasted based on internal assumptions

## Every Hurdle Must be Cleared by ANDA Filer

#### Litigation/Patent Estate

#### **Orange Book Listed Patents**

- 9,585,838 product by process<sup>1</sup> expires December 24, 2021
- 11,033,495 product by process expires January 22, 2041
- Forthcoming product by process patent – expires January 22, 2041
- Forthcoming chemical composition patent – expires January 22, 2041

#### **Forthcoming Patents**

- Manufacturing Process
- Method of Use Patents
- QC Release Assay Patent

#### Regulatory

FDA guidance on bioequivalence established rigorous hurdles; generic liposomal bupivacaine must have equivalent <u>MVL</u> characteristics

- Liposome composition
- Amount of free and encapsulated drug
- Internal environment of liposome
- Liposomal particle structure and morphology
- Liposome size distribution
- Electrical surface potential or charge
- In vitro release rates



#### Manufacturing

#### **Clinical pK trial**

 Must use product produced by commercial scale cold-chain sterile manufacturing process

Liposome composition specifications and batch records have never been disclosed

 A generic manufacturer would have to speculate on processing and quality end points for bioequivalence and batch release

# IVRA QC Assay required by FDA for batch release

 Proprietary and requires reverseengineering/R&D in and of itself<sup>2</sup>

2. See redactions on publicly-available version of EXPAREL NDA at <a href="https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2011/022496Orig1s000TOC.cfm">https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2011/022496Orig1s000TOC.cfm</a>

Even though product-by-process claims are limited and defined by the process, the determination of patentability is based on the product its method of production. If the product in the product-by-process claim is the same or obvious, the claim will be unpatentable even if the prior product is made through a different process. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product does not depend on its method of production." In re Thorpe, 777 F.2d 695, 698 (Fed.Cir. 1985)(emphasis added)

## Proposed FLXN Transaction Makes Pacira Earnings Outlook Even <u>More</u> Compelling\*

Portfolio	<ul> <li>Innovative non-opioid portfolio highly complementary to EXPAREL and iovera<sup>o</sup>; 3 complementary commercial assets – each with strong growth potential</li> </ul>		
Expanding pain continuum	<ul> <li>ZILRETTA<sup>®</sup> is a non-opioid injection that will allow Pacira to offer a treatment to manage OA pain of the knee at an earlier stage of the patient's journey along the neural pain pathway</li> </ul>		
Immediate synergies	<ul> <li>Complementary drug/device portfolio and overlapping sales call points offers significant cost synergies across R&amp;D and Sales and Marketing organization</li> </ul>		
Robust milestones	<ul> <li>Adds multiple clinical milestones, including the initiation of P3 registration trial of ZILRETTA in shoulder osteoarthritis and advancement of P1 studies of FX201 and FX301</li> </ul>		
Financial impact	<ul> <li>Immediately revenue generating and expected to be accretive to full-year 2022 earnings and significantly accretive thereafter – Pacira estimates that it only needs to capture ~30% of potential synergies for breakeven in 2022</li> </ul>		
Lease diversification and growth to topline Meaningful synergies to drive substantial near- and long-term accretion management			

#### **PCRX** INVESTOR DAY

**The Regional Anesthesia Revolution:** *Transforming the standard of care with EXPAREL-based longacting blocks* 

Jeff Gadsden, MD



#### **Disruptive Technologies**

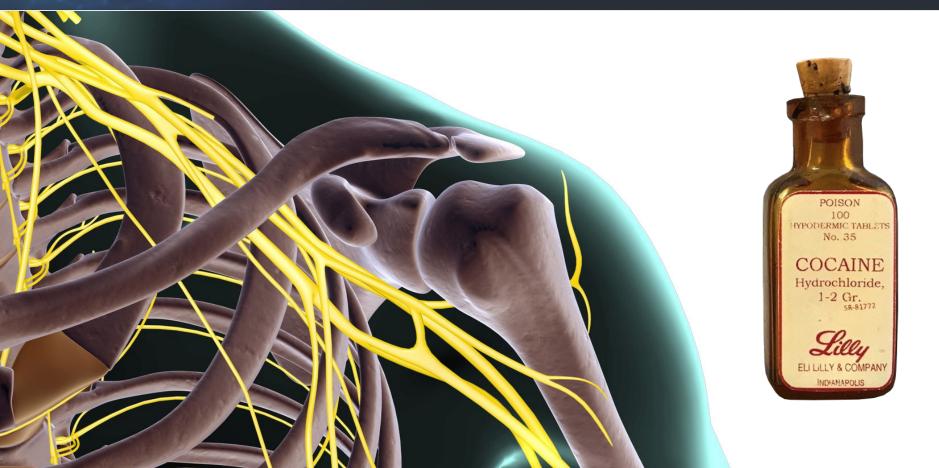


# Managing Pain in Ancient Times





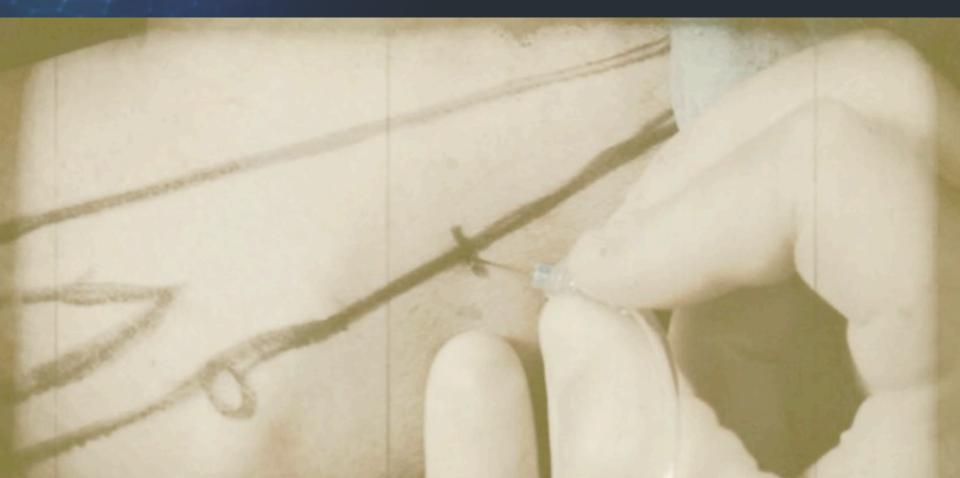
### The Birth of Regional Anesthesia



#### Flash Forward 100 Years



# Wizard-Like Skills



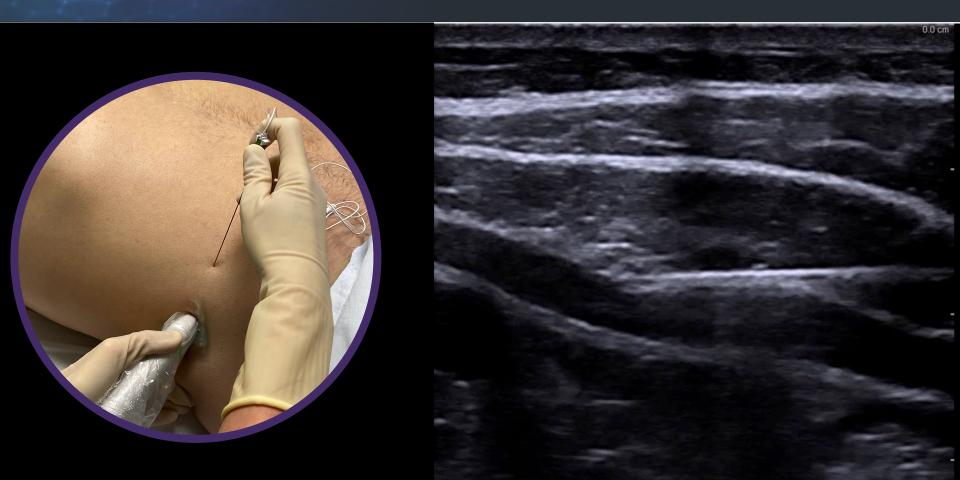
# Passing Down to the Next Generation



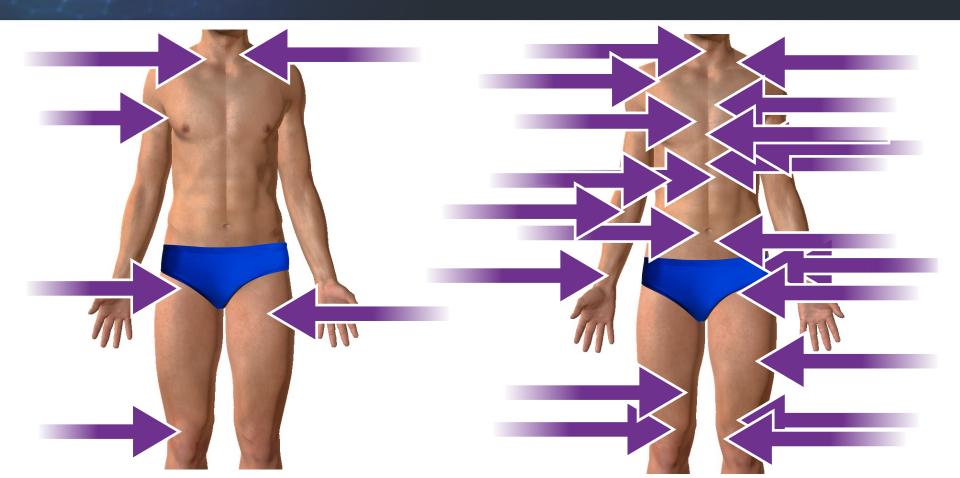
# Ultrasound: The First Disruptive Technology in Regional Anesthesia



# See the Target, Drive the Needle



## The Evolution of Regional Blocks from 1990 to 2021



#### But Wait...There's a Caveat...



# **12-24** hours.

#### The Desire for Patient Satisfaction Drove Opioid Prescribing



#### Enter EXPAREL | The BIGGEST Disruption Since Ultrasound

# **72** hours.



### Instant Gamechanger that Checks All the Boxes



# It's a Good Time to be a Regional Anesthesiologist, and it's an Amazing Time to be a Surgical Patient

# Standard of care.



#### **PCRX** INVESTOR DAY

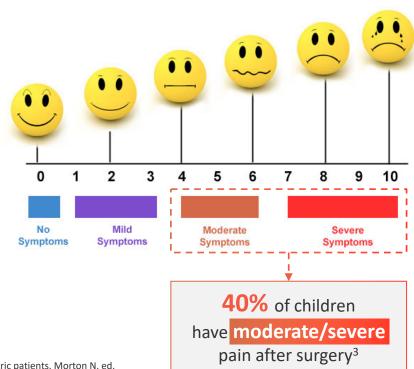
Changing the Face of Pediatric Pain Management: Providing our most vulnerable patient population with a long overdue non-opioid option

Sunny Tumber, DO



#### Pediatric Pain Management: Post-Surgical Experience

- Pediatric post-surgical pain management challenges continue despite advancements in surgical techniques, multimodal approaches & advanced pain management techniques
- Opioids are the "gold standard" for treatment of moderate/severe pain despite the significant side effects<sup>1</sup>
  - Persistent opioid use (between 3-6 months) was found in 5% of adolescents after surgery<sup>2</sup>



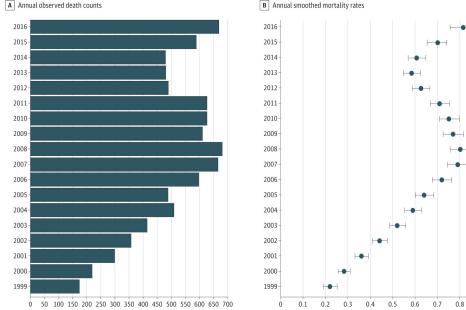
- 1. Jitpakdee T, Mandee S. Strategies for preventing side effects of systemic opioid in postoperative pediatric patients. Morton N, ed. *Paediatr Anaesth*. 2014;24(6):561-568.
- 2. Harbaugh CM, Lee JS, Hu HM, et al. Persistent opioid use among pediatric patients after surgery. Pediatrics. 2018;141(1):e20172439.
- 3. Walker SM. Pain after surgery in children: clinical recommendations. *Current Opinion in Anaesthesiology*. 2015;28(5):570-576.

#### **Opioids are NOT the Answer**

Children who legitimately use prescription opioids before the 12<sup>th</sup> grade have a **33% higher** risk of opioid misuse as an adult<sup>1</sup>

**2.3%** of children aged 12-17 years abused opioids in 2019<sup>2</sup>

**75%** of patients with an opioid use disorder were first exposed to opioids from a medical prescription<sup>3</sup>





#### Figure Legend:

0.9

Smoothed Mortality Rate per 100000 (95% CI)

US National Trends in Pediatric Deaths From Prescription and Illicit Opioids, 1999-2016<sup>4</sup>

- Number of Pediatric Opioid Deaths and Mortality Rates by Year
- Number of deaths (A) and mortality rates (B) for children and adolescents ages 0 to 19 years. Error bars indicate 95% CIs

**9,000** children/adolescents Overdose deaths 1999-2016

- 1. Miech R, Johnston L, O'Malley PM, Keyes KM, Heard K. Prescription opioids in adolescence and future opioid misuse. PEDIATRICS. 2015;136(5):e1169-e1177.
- 2. Substance Abuse and Mental Health Services Administration. (2019). Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH Series H-54). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.
- 3. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. JAMA Psychiatry. 2014;71(7):821-826.
- 4. Gaither JR, Shabanova V, Leventhal JM. US National Trends in Pediatric Deaths From Prescription and Illicit Opioids, 1999-2016. JAMA Netw Open. 2018;1(8):e186558. doi:10.1001/jamanetworkopen.2018.6558

#### Adolescent Brain Development

#### Areas of brain to develop in EARLY TEEN YEARS<sup>1</sup>:

Risk-taking and sensation-seeking

#### Areas of brain to develop LATER(early 20's):

- Regulates emotions
- Impulse control
- Considering consequences
- Judgement and decision-making





# Peripheral Nerve Blocks Can Block Pain Sensation and Decrease/Eliminate Opioid Use and Side Effects<sup>1</sup>

- The ideal regional anesthesia technique should provide long-acting analgesia to treat post op pain
  - Moderate/severe post operative pain after major surgery-> 24-72 hours<sup>2</sup>
  - Traditional local anesthetics in nerve blocks offer **12-16** hours of pain relief
- Ideal regional anesthesia technique should be:
  - ✓ Safe and effective
  - ✓ Efficient to place
  - Palatable to patients, parents, and surgeons

- 1. This presentation references off-label use of EXPAREL in pediatrics and is intended solely for the purpose of financial analysis and equity-based trading decisions.
- 2. Suresh S, Ecoffey C, Bosenberg A, et al. The european society of regional anaesthesia and pain therapy/american society of regional anesthesia and pain medicine recommendations on local anesthetics and adjuvants dosage in pediatric regional anesthesia: *Regional Anesthesia and Pain Medicine*. Published online January 2018:1.

### **Continuous Nerve Block Catheters**

#### **PROS:**

✓ Can provide long duration of analgesia, titratable

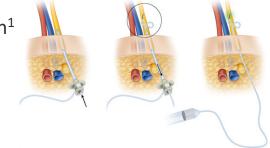
#### CONS:

- Costly, resource intensive, and difficult to accept for some children/parents-> not all surgery warrants placement
- × Issues can include infection, dislodgement, kinking, and malfunction<sup>1</sup>
- × Continuous catheters can have up to a 50% failure rate<sup>2</sup>

#### 1. Walker BJ, Long JB, De Oliveira GS, et al. Peripheral nerve catheters in children: an analysis of safety and practice patterns from the pediatric regional anesthesia network (Pran). British Journal of Anaesthesia. 2015;115(3):457-462.

Hauritz RW, Hannig KE, Balocco AL, et al. Peripheral nerve catheters: A critical review of the efficacy. Best Practice & Research Clinical Anaesthesiology. 2019;33(3):325-339.
 Image source: Butterworth JF, Mackay DC, Wasnick JD: Morgan & Mikhail's Clinical Anesthesiology, 5<sup>th</sup> edition: www.accessmedicine.com. Images are property of their respective owners.



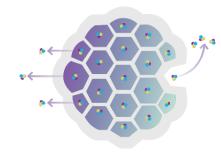


## A Shift in the Standard of Care



#### FDA Approval of EXPAREL in Children 6 Years and Older for Single-Dose Infiltration

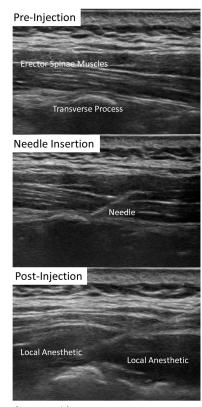
*First and only* FDA approved long-acting local anesthetic for the pediatric population as young as age six.



EXPAREL DepoFoam Technology Sustained Release of Local Anesthesia Over 72 Hours

### **EXPAREL** and Scoliosis Surgery

#### Erector Spinae Plane Block (ESP) with EXPAREL

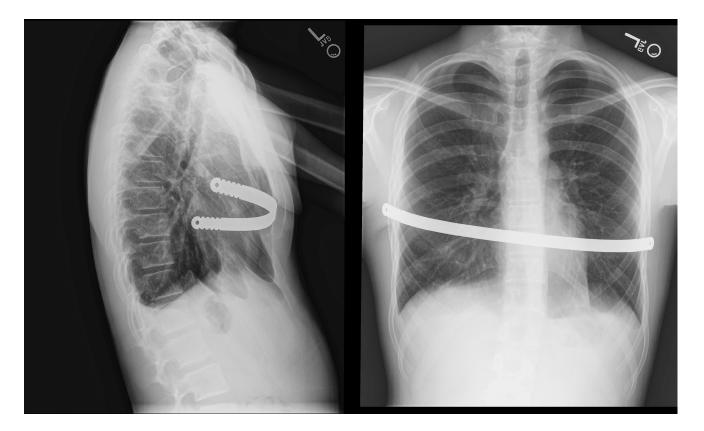






\*Images with consent

## **EXPAREL** and Nuss Bar Placement



#### **EXPAREL** and Colorectal Surgery

#### Journal of Pediatric Surgery Case Reports 74 (2021) 102059



Contents lists available at ScienceDirect
Journal of Pediatric Surgery Case Reports

journal homepage: www.elsevier.com/locate/epsc

Opioid-free recovery after laparoscopic-assisted redo pull-through and loop ileostomy via sacral and thoracic erector spinae plane blocks

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#### ARTICLE INFO

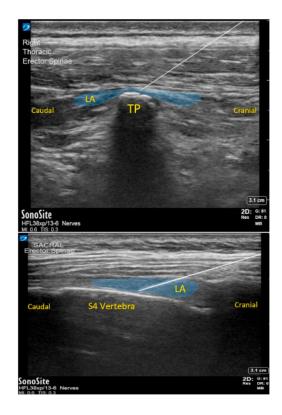
#### Keywordz: Sacrał erector spinae plane block Sacrał multifidus plane block Pediatric regional nerve block Liposomal bupivacaine Exparel Multimodal analgesia Hirscheprung disease Pull-through

#### ABSTRACT

Multi-modal analgesia with a reduction in perioperative opioid use has been a goal for many institutions due to the ongoing opioid epidemic. A reduction in opioid use can also limit undesirable side effects such as nausea, respiratory depression, and ileus in the perioperative and postoperative periods. In this case report, we describe a child who had excellent pain control for colorectal surgery after receiving a novel sacral erector spinae plane block (ESPB) along with bilateral thoracic ESPB's with sustained-release liposomal bupivacaine (Exparel). While there is ample literature describing the efficacy of thoracic and lumbar ESPB's for sot-operative analgesia, there is a paucity of information regarding the sacral approach to the ESPB when combined with liposomal bupivacaine and its application to perineal, perinal, and colorectal surgery.







\*Images with consent

#### Pediatric Pain Management: Future Direction

- Pediatric regional anesthesia today is one of the **fastest growing** and *exciting aspects* of pediatric anesthesia
- Pediatric QI registries (*PRAN-Pediatric Regional Anesthesia Network*) support the use and safety of pediatric nerve blocks
- Regional techniques provide excellent pain relief and <u>decrease the use</u> of opioids

• EXPAREL offers unique advantages in pediatric regional anesthesia
• Growth potential of EXPAREL in regional anesthesia is significant

#### **PCRX** INVESTOR DAY

Resetting Expectations in Spine Surgery: Advancing an opioid-sparing multimodal approach in particularly complicated procedures

Mike Wang, MD



# **2014** Awake Spinal Fusion



#### Awake Spinal Fusion Options



**Awake Anesthesia** 



**Percutaneous Fixation** 



#### Endoscopic Visualization



**Osteobiologics for Fusion** 

Awake Spinal Fusion Version 1.0



#### Long-Acting Na+ Blockers



**Expandable Interbody** 



## 15 Minutes After a Spinal Fusion Surgery

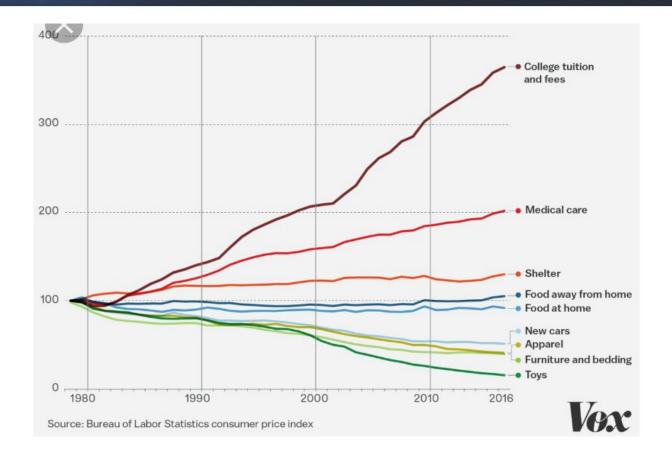


## 86-year-old Cardiac Ejection Fraction of 11%



# **2018** ERAS and Economics

#### Changes in Prices of Goods and Services Relative to Overall Price Level



### 2018 ERAS and Economics

#### CONCEPTS, INNOVATIONS AND TECHNIQUES

Reduced Acute Care Costs With the ERAS<sup>®</sup> Minimally Invasive Transforaminal Lumbar Interbody Fusion Compared With Conventional Minimally Invasive Transforaminal Lumbar Interbody Fusion

BACKGROUND: Enhancing Recovery After Surgery (ERAS<sup>®</sup>) programs have been widely

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adopted throughout the world, but not in spinal surgery. In this report, we review the implementation of a "fast track" surgery for lumbar fusion and its effect on acute care hospi- talization costs. OBJECTIVE: To determine if a "fast track" surgery methodology results in acute care cost	
savings.	
<b>METHODS:</b> Thirty-eight consecutive ERAS patients were compared with patients under- going conventional minimally invasive transforaminal lumbar interbody fusion. Differ- ences between these groups included the use of endoscopic decompression, injections of liposomal bupivacaine, and performing the surgery under sedation in the ERAS <sup>®</sup> group. <b>RESULTS:</b> Patients had similar medical comorbidities (2.02 vs 2 for ERAS <sup>®</sup> ) and comparator groups, respectively; <i>P</i> = .458). Body mass index was similar (26.5 vs 27.0; <i>P</i> = .329). ERAS <sup>®</sup> patients were older (65 vs 59 yr, <i>P</i> = .031). Both groups had excellent clinical results with an improvement of 23% and 24%, respectively. Intraoperative blood loss was less (68 ± 31 cc vs 231 ± 73, <i>P</i> < 0.001). Length of stay was also less with ERAS <sup>®</sup> surgery, at amean of 1.23 ± 0.8 d vs 3.9 ± 1.1 d ( <i>P</i> = 0.009). When comparing ERAS <sup>®</sup> surgery to standard minimally invasive transforaminal lumbar interbody fusion, the total cost for the acute care hospitalization was 519 212 vs 522 656, respectively ( <i>P</i> < 0.001). This reflected an average of \$3444 in savings, which was a 15.2% reduction.	
<b>CONCLUSION:</b> ERAS <sup>®</sup> programs for spinal fusion surgery have the potential to reduce the costs of acute care. This is made possible by leveraging less invasive interventions to minimize soft tissue damage.	
KEY WORDS: Minimally invasive, Cost, Economic, Spine, QALY, Anesthesia, Pedicle screw, Percutaneous, ERAS, Enhancing recovery, Exparel	

Enhancing recovery, Exparel
Neurosurgery 0:1-7, 2017 DDI:00.1093/neuros/myx400 www.neurosurgery-online.com

JI:10.1093/neuros/nyx400 WWW.neurosu

	ERAS <sup>®</sup> spinal fusion	Standard MIS fusion
Cost center		
Med/Surg unit	773	1597
ICU	-	1174
Surgery unit	2669	4253
Recovery unit	466	326
Pharmacy	475	777
Surgical implants	12 833	13 208
Medical services	1141	413
Anesthesia unit	89	165
CT scan	33	36
Radiology	268	238
Pathology	39	30
Magnetic resonance imaging	126	-
Laboratory	49	40
Blood bank	86	64
Physical therapy	90	219
Occupational therapy	75	116
Total	$19212\pm1754$	22 656 ± 3218

## Time Saved Using Awake TLIF

## **GETA TLIF**

#### Case Tracking Events

Event	Time In
In Facility	0512
Prep on Floor	
In Pre-Procedure	0551
Pre-Procedure Complete	0630
Anesthesia Start	0722
Setup Start	
Setup Complete	
Room Ready - Anesthesia	0708
Room Ready - Nursing	0709
In Room	0725
Induction	
Anesthesia Ready	0736
Prep Start	0749
Procedure Prep Complete	0753
Procedure Start	0800
Procedure Closing	1031
PACU Request	
Procedure Finish	1056
Out of Room	1106
Cleanup Start	
Cleanup Complete	
In Recovery Phase I	1107
Anesthesia Finish	1114
Recovery Phase I Care Complete	
Out of Recovery Phase I	1300

## Awake TLIF

#### **Case Tracking Events**

Se macking Events	
Event	Time In
In Facility	0535
Prep on Floor	
In Pre-Procedure	0553
Pre-Procedure Complete	0645
Anesthesia Start	0726
Setup Start	
Setup Complete	
Room Ready - Anesthesia	0712
Room Ready - Nursing	0715
In Room	0725
Induction	
Anesthesia Ready	0733
Prep Start	0732
Procedure Prep Complete	0735
Procedure Start	0738
Procedure Closing	0823
PACU Request	
Procedure Finish	0830
Out of Room	0835
Cleanup Start	
Cleanup Complete	
In Recovery Phase I	0835
Anesthesia Finish	0843
Recovery Phase I Care Complete	
Out of Recovery Phase I	1130

Minutes saved T- 17 T- 22 T- 126 T- 151

# 151 minutes saved per case

If you perform 100 cases/year

You save 15,100 minutes

Which is 251 hours Adding up to 10.5 days

## Enhanced Recovery After Surgery (ERAS)

Preoperative Phase	<ul> <li>Patient/family education</li> <li>Shortened fasting</li> <li>Fluid &amp; carbohydrate loading</li> <li>No bowel preparation</li> <li>Antibiotic prophylaxis</li> <li>Thromboprophylaxis</li> <li>No premedication</li> </ul>	<ul><li>Key features:</li><li>Patient focus</li><li>Team approach</li></ul>
Intraoperative Phase	<ul> <li>Epidural/regional blocks</li> <li>Laparoscopic/minimally invasive surgery</li> <li>Normothermia</li> <li>Preoperative fluid management</li> <li>Avoidance of tubes, drains and lines</li> </ul>	<ul> <li>Multi-modal</li> <li>Surgical journey</li> </ul>
Intraoperative Phase	<ul> <li>Early removal of urinary catheter</li> <li>No nasogastric tube</li> <li>Avoidance of salt and water overload</li> <li>Prevention of PONV</li> <li>Non-opioid oral analgesia</li> <li>Early oral nutrition</li> <li>Early mobilization</li> <li>Defined discharge criteria and patient education</li> <li>Gum chewing</li> </ul>	<ul><li> "Fast tracking"</li><li> Iterative improvement</li></ul>

## Miami ERAS Version 1.0

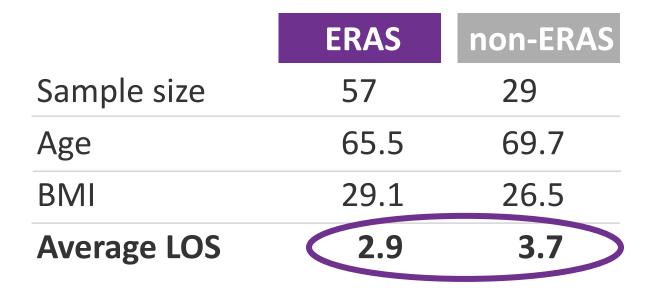




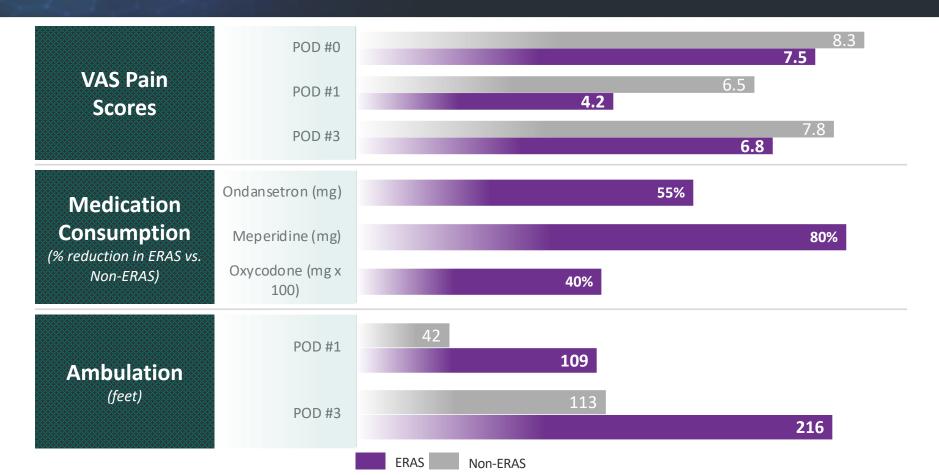




### Patient Demographics



## Establishing the Standard of Care Using ERAS Protocols



#### Cost Savings Over the First Six Months

# \$290,753

# \$5,101 per patient

# **2020** Coping with COVID-19

# Now is when doing minimally invasive surgery will <u>really</u> matter



## New York Times | April 6, 2020

#### During a Pandemic, an Unanticipated Problem: Out-of-Work Health Workers

Across the country, plunging revenues from canceled nonemergency medical appointments have forced hospitals to furlough or cut the pay of doctors, nurses and other staff.



Scott Weavil, a lawyer in California who counsels physicians and other health care workers on employment contracts, said he was hearing from doctors across the country who were being asked to take pay cuts of 20 to 70 percent.

#### RASED ON HD.TO.DATE DATA AND READINESS

P	NG UP AMERICA
P	
A	
	-

OPENING UP AMERICA AGAIN

Phase One

SPECIFIC TYPES OF EMPLOYERS

AGAIN

SCHOOLS AND ORGANIZED YOUTH ACTIVITIES (e.g., daycare, camp) that are currently closed should remain closed.

VISITS TO SENIOR LIVING FACILITIES AND HOSPITALS should be prohibited. Those who do interact with residents and patients must adhere to strict protocols regarding hygiene.

LARGE VENUES (e.g., sit-down dining, movie theaters, sporting venues, places of worship) can operate under strict physical distancing protocols.

ELECTIVE SURGERIES can resume, as clinically appropriate, on an outpatient basis at factures that appretto CMS gaugetimes.

GYMS can open if they adhere to strict physical distancing and sanitation protocols.

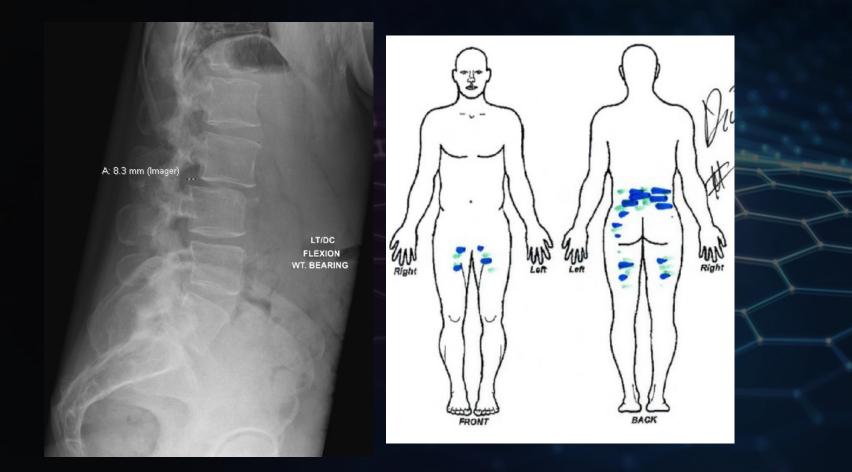
BARS should remain closed.

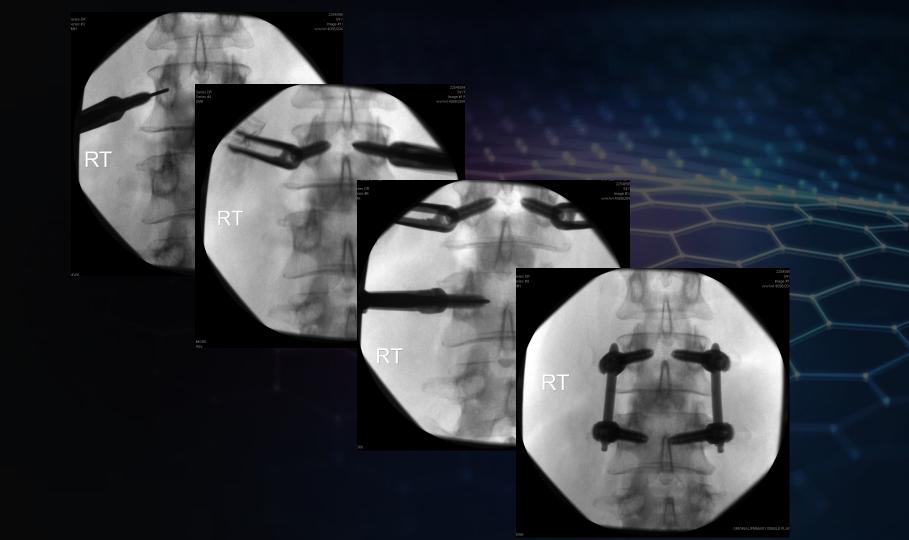
EACH PHASE OF THIS GUIDANCE ADDRESSES THOSE ASPECTS OF DAILY LIFE FOR WHICH RESTRICTIONS REMAIN APPROPRIATE DUE TO COVID.

### So Many Potential Issues

- Patients are afraid of coming to the hospital
- The economy may collapse in a protracted recession
- There will be a bigger push for "single payor" (Medicare for all)
- •The number of privately insured patients is shrinking
- Insurance companies will have carte blanche to deny surgery
- Tremendous economic pressure on hospitals & health systems

Will some of these effects be long-lasting?







•Spine surgery service lines are highly profitable with robust growth anticipated for at least the next decade

•Surgeons searching for strategies to improve outcomes and adapt to existing/future challenges will find **EXPAREL** a powerful adjunct

•Pacira provides a unique and differentiating product that will see increased clinical usage

#### **PCRX** INVESTOR DAY

Catalyzing the Site of Care Shift: Providing the non-opioid foundation for opioid-free, outpatient shoulder surgeries

Paul Sethi, MD



## Evolution of Controlling Pain in Shoulder Surgery

#### Circa 2005: The Challenge



- No evidence-based guidelines
- Limitations of NSAIDs
- Rebound pain after short-acting block wore off

Difficult surgery with poor pain control Accounted for most patient phone calls





Rotator Cuff Repair had the highest oral morphine equivalents (OME) among shoulder surgeries

Over-prescription, diversion, dependence, addiction

## Simultaneously Fighting Two Battles





#### Reduce pain

- Minimize (eliminate) opiates
- Create reproducible (scalable) protocols
- Outpatient replacements



## **Current Recommendations RCR**

Washington State's Agency Medical Directors Group (AMDG) released "evidence-based" guidelines in 2018:

Rotator Cuff Repair	42 Pills 315 OMEs		
"Consensus-based" guidelines by Stepan et. al. (2019, JBJS) recommend:			
Rotator Cuff Repair	60 Pills 300 - 480 OMEs		
Shoulder Arthroplasty	40 Pills 200 - 320 OMEs		

### Liposomal bupivacaine reduces opiate consumption after rotator cuff repair in a randomized controlled trial

Paul M. Sethi, MD<sup>a,b,\*</sup>, Devon T. Brameier, BS<sup>b</sup>, Nikhil K. Mandava, BA<sup>b</sup>, Seth R. Miller, MD<sup>b</sup>

<sup>a</sup>Orthopaedic & Neurosurgery Specialists, Greenwich, CT, USA <sup>b</sup>The ONS Foundation for Clinical Research and Education, Greenwich, CT, USA

#### Liposomal Bupivacaine for Pain Control After Rotator Cuff Repair: Results

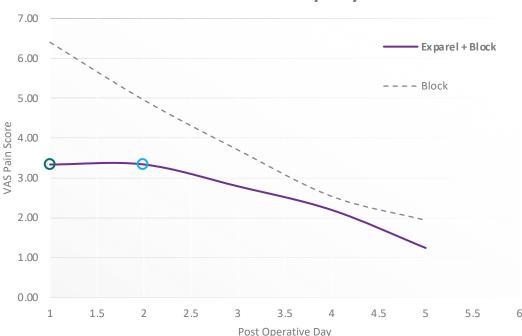
• Clinically and Statistically Significant different VAS Scores on Post Operative Day 1

- 6.4 vs 3.33 (P < .005)

• Clinically Significant different VAS Pain Scores on Post Operative Day 2

- 4.95 vs 3.33 (MCID 1.4)

• VAS Pain Scores were not clinically or statistically different for POD 3, 4 and 5



VAS Pain Scores by Day



## **Progression of Pain Management: Anesthesia Partnership**

#### Goal of the Interscalene Brachial Plexus Nerve Block (ISBPNB)

- Local anesthetic spread around superior and middle trunks of brachial plexus
- Inject between the anterior and middle scalene muscles

#### Distribution

- Anesthesia of shoulder and upper arm
- Supraclavicular branches of the cervical plexus
  - Supplying the skin over the acromion and clavicle
  - May also be blocked due to the proximal and superficial spread of local anesthetic



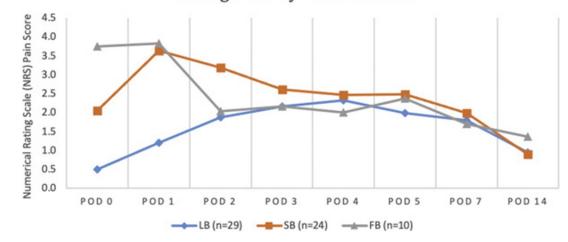
distribution of the interscalene brachial plexus block (in red)

### The Second Study

# Narcotic requirements after shoulder arthroplasty are low using a multimodal approach to pain

Paul M. Sethi, MD<sup>a,\*</sup>, Nikhil K. Mandava, BA<sup>a</sup>, Nicole Liddy, BS, MS<sup>a</sup>, Patrick J. Denard, MD<sup>b</sup>, Georges Haidamous, MD<sup>b</sup>, Charles D. Reimers, BS<sup>b</sup>

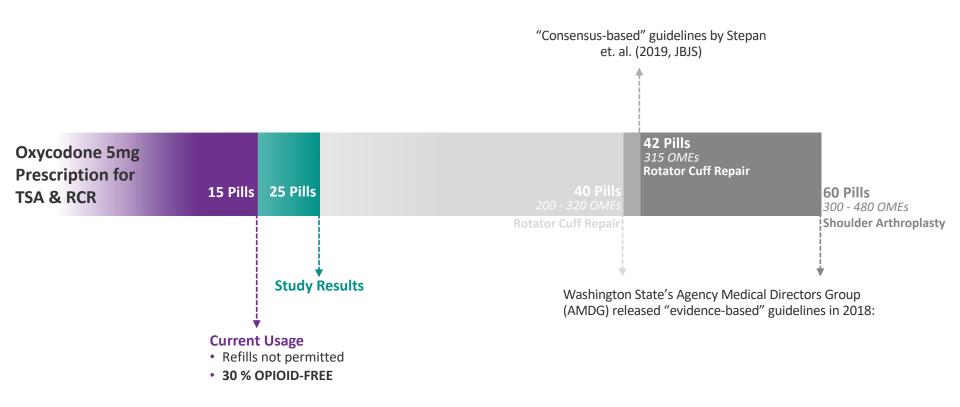
<sup>a</sup> Orthopedic and Neurosurgery Specilaists Foundation, Greenwich, CT, USA <sup>b</sup> Southern Oregon Orthopaedics, Medford, OR, USA



#### Average Daily Pain Scores

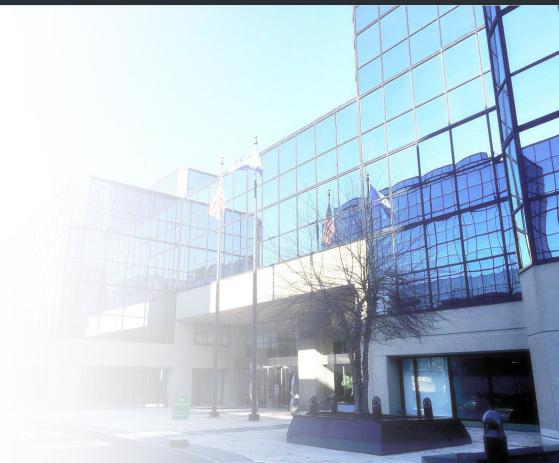
LB=liposomal bupivacaine nerve block; SB=standard bupivacaine nerve block; FB=standard bupivacaine field block. Sethi PM et. al. *JSES Int.* 2021; 5(4): 722-728.

### **Evidence Based Guidelines**



## These Outcomes have Facilitated the Shift to the Outpatient Environment





## One Week After Replacement Surgery



## One Week After Replacement Surgery



## **PCRX** INVESTOR DAY

Redefining Recovery for New Mothers: Accelerating recovery and improving outcomes after childbirth

Stephen Garber, MD



## EXPAREL is Improving C-section Outcomes | So Good. So Good. So Good.

**EXPAREL** is successfully transforming the postsurgical experience for C-section mothers at Saddleback



- Patients love it for the duration of *pain control* with <u>little</u> or no opioids so mothers can be more engaged with baby and family
- Nursing staff excited for the same reason <u>less opioids</u> and opioid-related adverse effects
- Doctors benefit from positive patient referrals/word of mouth
- Pharmacy dispensing less opioids for pain and medications to treat opioid-related nausea, vomiting and constipation

## EXPAREL Consistently Delivering Positive Results for the "4<sup>th</sup> Trimester"



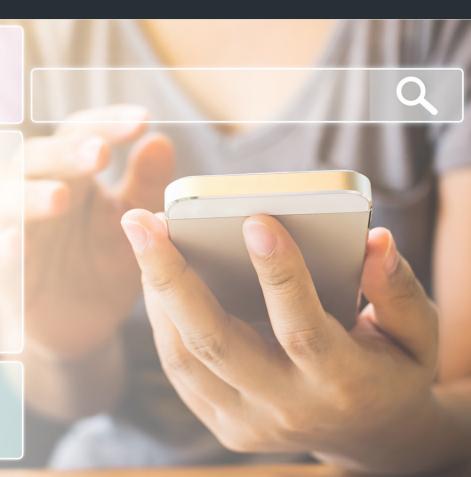
- Extremely low incidence of nausea/vomiting
- ✓ Extremely low incidence of pruritis
- ✓ No post-op opioids is typical
- ✓ Increased early activity
- ✓ Reduced length-of-stay
- ✓ Increased patient satisfaction
- ✓ Decreased nursing acuity
- ✓ Decreased use of antiemetics

## Over 1.2 Million C-sections Performed Annually in the U.S.

<u>**C-section**</u> is the most common major surgery performed in the world; EXPAREL has the potential to make a huge difference for C-section mothers

- 9 in 10 Mothers have concerns about taking opioids during and after childbirth
- **74%** of C-section mothers think a non-opioid option is appealing
- 50% of C-section mothers are prescribed an opioid
- **44%** of C-section mothers were not satisfied with pain management following childbirth

**EXPAREL** is addressing these concerns and helping C-section mothers recover faster to spend time with their babies



# Women are 40% More Likely than Men to Use Opioids Persistently After Surgery



**1-2%** of C-section mothers who receive opioids progress to persistent opioid use<sup>1,2</sup>

- Every year **13,000+** C-section mothers in the U.S. at risk of persistent opioid use after surgery<sup>2</sup>
- Multimodal analgesia while minimizing opioids can mitigate risks
- Saddleback has reduced the number of opioids prescribed at discharge by 70% using an EXPARELbased multimodal protocol for pain management

• **EXPAREL-based** opioid-sparing protocol can eliminate discharge prescriptions that can lead to abuse of leftover pills

<sup>1.</sup> Peahl AF, Morgan DM, Dalton VK, Zivin K, Lai YL, Hu HM, Langer E, Low L, Brummett CM, Waljee JF, Bauer ME. New Persistent Opioid Use After Acute Opioid Prescribing in Pregnancy: A Nationwide Analysis. Obstetric Anesthesia Digest. Volume 41, Number 3, September 2021

Peahl AF, Dalton VK, Montgomery JR, Lai Y, Hu HM, Waljee JF. Rates of New Persistent Opioid Use After Vaginal or Cesarean Birth Among US Women. JAMA Netw Open. 2019;2(7):e197863.doi:10.1001/jamanetworkopen.2019.7863. Assumes 50% of C-section mothers receive an opioid prescription at discharge and 2.2% progress to persistent use.

## Transforming the Post Operative Course in Women's Health



• Women make over **80%** of healthcare decisions in the U.S.<sup>1</sup> (for their families, themselves, parents, etc.)

• Positive outcomes in C-section has allowed Saddleback to retain entire families for care

1. Matoff-Stepp S, Applebaum B, Pooler J, Kavanagh E. Women as health care decision-makers: implications for health care coverage in the United States. J Health Care Poor Underserved. 2014 Nov;25(4):1507-13. doi: 10.1353/hpu.2014.0154. PMID: 25418222.

# EXPAREL-Based Multimodal Protocol has Redefined the Standard of Care for C-Sections at Saddleback



- Safe, proven and straightforward protocol that can be easily rolled out at any institution
- Started with **10** repeat C-Section patients
  - Patients experienced the benefits of an
     EXPAREL-based multimodal regimen versus
     prior opioid-based regimen
  - Results were dramatic
  - Result-driven method triggered broad formulary access

# Patient Experience: Meet Ashley



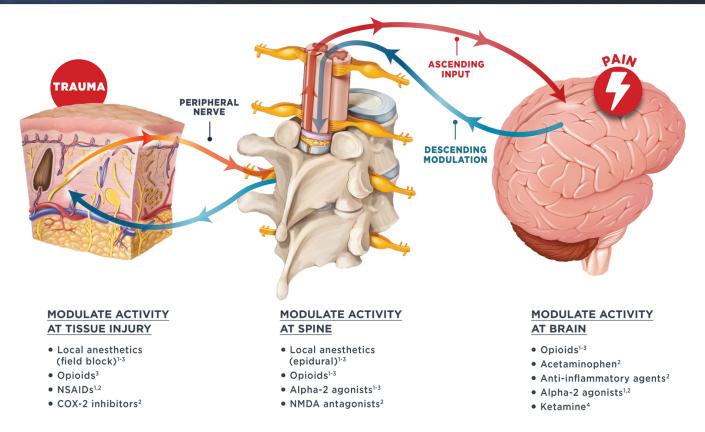
## PCRX INVESTOR DAY

**The Total Procedural Solution:** *Combining EXPAREL and iovera*<sup>o</sup> *to reduce opioids, pain, and length of stay after TKA* 

Josh A. Urban, MD



A Multimodal Approach Aims to Address Pain Across the Nervous System With a Variety of Therapeutic Agents



COX-2=cyclooxygenase 2; NMDA=N-Methyl-D-aspartate; NSAID=non-steroidal anti-inflammatory drug; ORAE=opioid-related adverse event.

1. Gottschalk A, Smith DS. Am Fam Physician. 2001;63(10):1979-1984; 2. Gandhi K, Viscusi E. The Journal of NYSORA. 2009;13:1-10; 3. Kehlet H, Dahl JB. Anesth Analg. 1993;77(5):1048-1056; 4. Joshi GP, et al. Best Pract Res Clin Anaesthesiol. 2014;28(2):191-201.

## Multimodal Approach to Orthopedic Surgical Pain

#### Pros

- Multiple drugs = many mechanisms of action
  - Diminishes reliance on one drug/pathway (opioids)
  - Alternatives in case of allergies/intolerance

### Cons

- Most are systemically given (po or IV)
  - Fraction of administered dose to desired location
  - Increased chance of systemic side effects

Most effective modality is nerve blockade

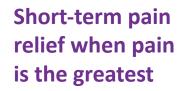
- Blocks the message of pain
- No conscious appreciation of pain

All other modalities mitigate pain but do not block or eliminate it

# The Most Effective Tool in our Multimodal Pain Modality Toolbox is the Nerve Blockade

- Disadvantage
  - Short-lived (hours)
  - Pain will still have to be addressed when nerve block wears off

### We need modalities that block nerves longer

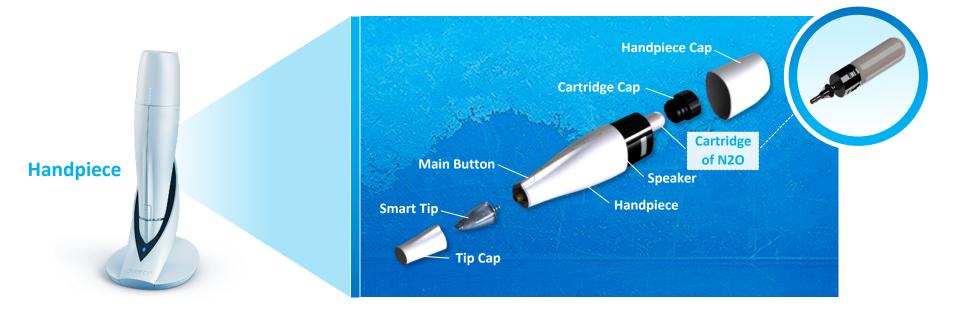




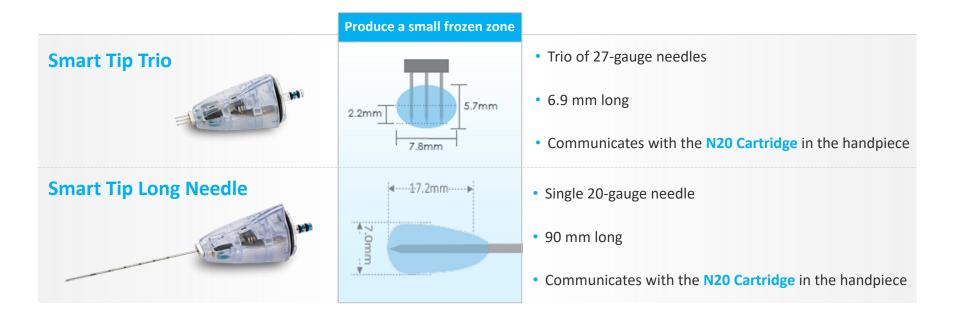
Intermediate to long duration for weeks and months



## iovera<sup>o</sup>: Non-Pharmacologic Long-Acting Nerve Block



## iovera<sup>o</sup>: Non-Pharmacologic Long-Acting Nerve Block



## Why Nitrous Oxide?

**Nitrous Oxide** 

Liquid Nitrogen

#### Reversible

#### 1<sup>st</sup> Degree

Neuropraxia – Interruption of conduction; Short recovery +10 to -20°C time

#### 2<sup>nd</sup> Degree

Axonotmesis – Loss of continuity of the axon; Wallerian degeneration; Preservation of endo- peri- and epineurium

### Non-Reversible

3<sup>rd</sup>/4<sup>th</sup> Degree

Neurotmesis – Loss of continuity; Some loss of continuity of epineurium and perineurium

5<sup>th</sup> Degree

Transection (Severe Neurotmesis) - Gross loss of continuity

-140°C and colder Not possible with FCT

-20°C

to -100°C

FCT

Falls in this range

Not possible with FCT

## Comparison of Neurolytic Treatments<sup>1,2</sup>



Irreversible nerve Degeneration 2<sup>nd</sup> Degree(-100° to -20°C) Sunderland Classification<sup>4</sup> Temporary nerve degeneration<sup>4</sup>

Risk of bruising, numbness, redness, tenderness upon palpitation and swelling at the treatment site<sup>6</sup> Risk of neuroma formation post denervation, neuritis, and injury to nearby tissue and vessels<sup>1</sup>

## iovera<sup>o</sup> Nerve Regeneration

## Treatment

A cold zone is created, lowering the temperature to below -20°C

#### Degeneration

Cold zone causes degeneration of the axon and myelin sheath, temporarily blocking nerve signals

#### Regeneration

Post-treatment, the axon regenerates at the rate of about 1 to 2 mm per day<sup>1</sup>

### Reinnervation

The axon and myelin sheath are fully regenerated and nerve signaling is restored

## Where iovera<sup>o</sup> is Making a Meaningful Difference Today

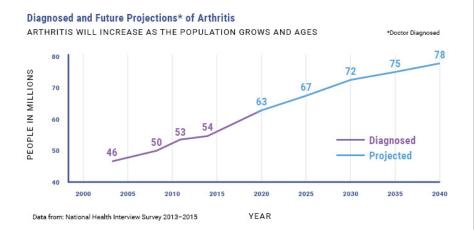


## Knee Osteoarthritis (OA)

## **Total Knee Arthroplasty (TKA)**

- Common conditions
- Highly painful
- Patients at risk of chronic opioid use/misuse

## The Economic and Disease Burdens of Osteoarthritis of the Knee



## Total societal cost of lifetime opioid use in patients with symptomatic knee osteoarthritis:



# <sup>\$14</sup> billion

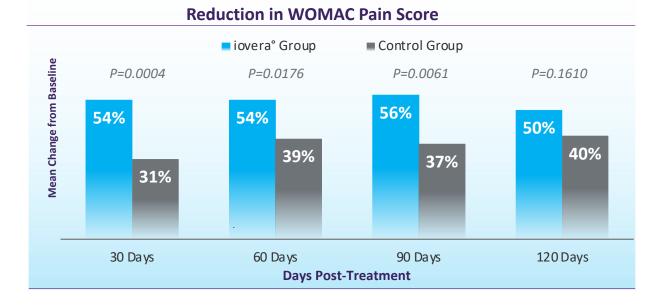
Nearly half - \$6.52 billion - of these costs were attributable to lost productivity, criminal justice and diversion costs. The annual societal cost of opioid use in the population is approaching \$500 million



## Knee Osteoarthritis and iovera<sup>o</sup>

### **Literature Review**

- Radnovich et al. 2017
  - Prospective, double-blind
  - Improvement in pain scores up to 90 days

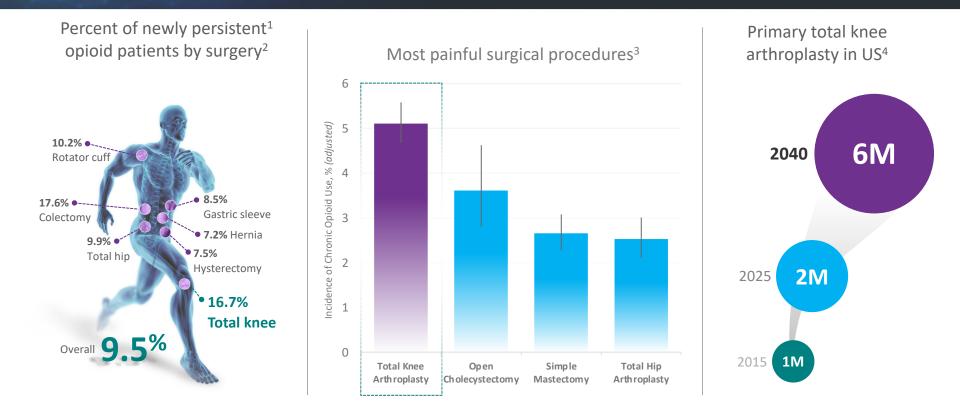


## Total Knee Arthroplasty (TKA)

- Perfect for iovera<sup>o</sup> cryoneurolysis
  - Common
  - Painful
  - Long recovery
  - High dissatisfaction rate (20%)



## TKA: Painful and Long Recovery Resulting in Opioid Misuse



1. Pacira. United States for Non-Dependence: An Analysis of the Impact of Opioid Overprescribing in America. September 2017. [Analysis in the report was based on research conducted by the Quintiles IMS Institute].

2. Newly persistent defined as patients using an opioid 3-6 months beyond the postsurgical recovery period.

3. Sun EC, Darnall BD, Baker LC, et al. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA Intern Med. September 1 2016;176(9):1286–1293.

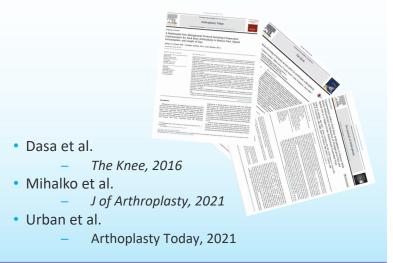
4. Jasvinder A. Singh, Shaohua Yu, Lang Chen and John D. Cleveland, The Journal of Rheumatology September 2019, 46 (9) 1134-1140; DOI: https://doi.org/10.3899/jrheum.170990

## Why iovera<sup>o</sup> for TKA Patients?

- Challenges in TKA
  - Pain Control
  - Minimizing Opioid use
  - Regaining function and range of motion

## TKA and iovera<sup>o</sup> – literature review

- Statistically significant improvements in:
  - Pain scores
  - Opioid use
  - Length of stay
  - Recovery time



## John's Story

- 61-year-old male
- Left TKA 11/2019 with pre-op iovera<sup>o</sup>
- Right TKA 12/2020 without iovera<sup>o</sup>
  - Insurance would not cover



## Future Direction of iovera<sup>o</sup> in the Knee

- OA patients
  - Determine the role of <u>deep</u> genicular nerves in OA pain
    - Should we be treating them in conjunction with the <u>superficial</u> nerves?
  - Establish criteria for appropriate patient selection
- TKA patients
  - Role of deep nerves?
  - Post-TKA treatment for chronic pain
  - Post-TKA neuromas

## iovera<sup>o</sup> – Areas of Research Internationally

- Occipital Neuralgia
- Knee
  - OA
  - ТКА
  - Chronic pain (post-TKA, etc.)
  - Post-op neuromas
- Shoulder
  - Suprascapular nerve
- Spine
  - Medial dorsal branch

- Intercostals
  - Rib fractures
- Foot/ankle
  - Morton's neuroma
- Spasticity
  - Cerebral palsy
  - Post-CVA
- Restless Legs Syndrome (RLS)

## **Restless Legs Syndrome**

- Nomenclature is deceptive
  - Symptoms can be severe
  - Quality of life threatening
- Etiology is unknown



## Restless Legs Syndrome and iovera<sup>o</sup>

## Serendipitous discovery

- Several patients with knee OA and RLS
  - Improvement in RLS symptoms too
- JAU cadaver study research student
  - Treated with iovera<sup>o</sup> 1/2019 specifically for RLS
  - Symptoms
    - 1. Intolerance of tight pants
    - 2. Intolerance of long car rides
    - 3. Difficulty sleeping
    - 4. Alcohol intolerance
    - 5. Intolerance to touch



# Carmen's Story



## Carmen's RLS Treatment with iovera<sup>o</sup>

- 50-80% improvement in 4 of 5 RLS symptoms that outlasted the nerve regeneration x 2 years
  - ✓ Tight clothing
  - ✓ Intolerance of long car rides
  - ✓ Difficulty sleeping
  - ✓ Alcohol intolerance
  - Intolerance to touch
- Restless Legs Syndrome Study
  - Pacira agreed to fund a pilot study
  - Design
    - 30-40 patients
    - Dr. Pam Santamaria (neurologist at the Nebraska Medical Center)
      - Local expert in RLS

# Symptom improvement far outlasts return of sensory nerve function

## Ramifications of iovera<sup>o</sup> Success in RLS

- Etiology of RLS better understood
  - Possibly multifactorial
- Societal impact great
  - 10% prevalence globally
- Why the prolonged improvement in symptoms?
  - Did a pathologic nerve regrow back to a normal nerve??
- Extrapolate to other neuropathic conditions
  - 100 peripheral neuropathies
  - Spasticity

## PCRX INVESTOR DAY

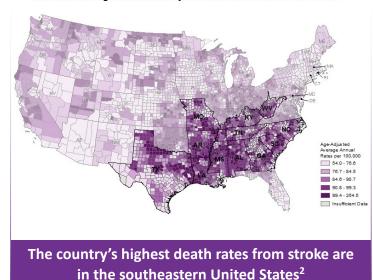
The Promise of iovera<sup>o</sup> as an Innovative Approach to Meeting the Unmet Needs of Individuals with Spasticity

Paul Winston, MD



## Stroke Facts

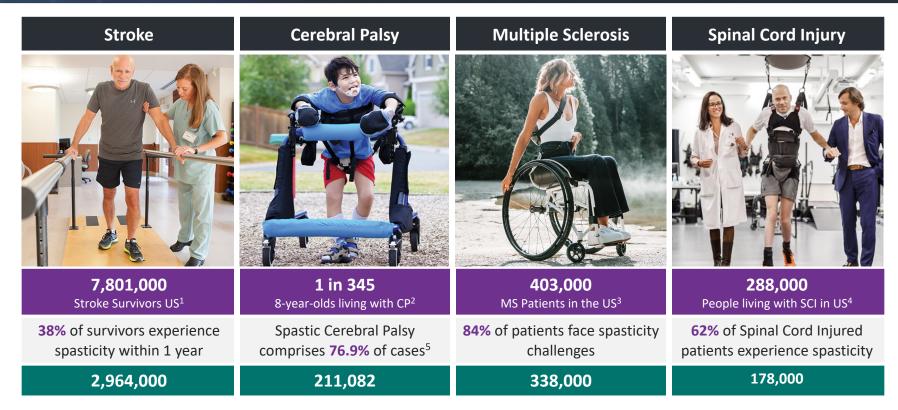
- Someone in the United States has a stroke every 40 seconds, every 4 minutes, someone dies of stroke<sup>1</sup>
- Every year, more than 795,000 people in the United States have a stroke, about 610,000 of these are first or new strokes<sup>1</sup>
- Stroke-related costs in the United States came to nearly \$46 billion a year
- Stroke is a leading cause of serious long-term disability<sup>1</sup>, stroke reduces mobility in more than half of stroke survivors age 65 and over<sup>1</sup>



Counties with High Stroke Mortality Rates are Concentrated in the South<sup>2</sup>

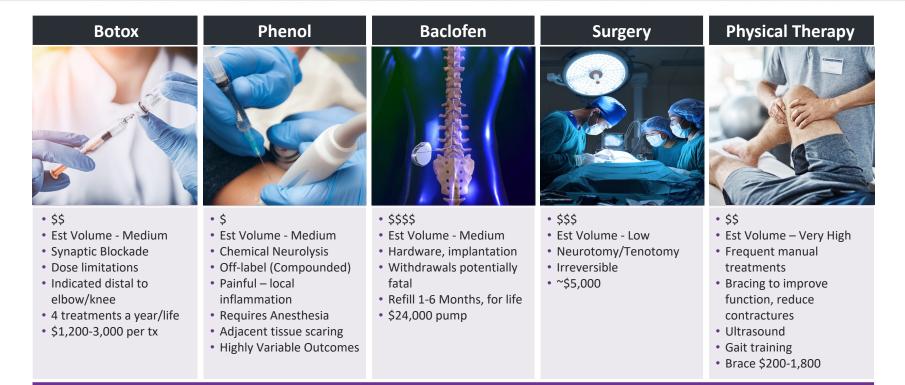
2. Data Source: National Vital Statistics System, National Center for Health Statistics.

## The Many Faces of Spasticity



- 1. National Health Interview Survey, 2018. US Dept of H/H
- 2. Paediatric Perinatology Epidemiology, 2016. Durkin
- 3. Neurology, March 2016. Dilothornsakul
- 4. National Spinal Cord Injury Statistical Center, 2018
- 5. Cerebralpalsy.org, 2002

# Current Standard of Care "Not Sufficient and Expensive" – Estimated >4M Treatments/Year



Direct costs for 12-month stroke survivors are **4 times higher** than direct costs for patients with stroke without spasticity during the first year after the event<sup>1</sup>

# Satisfaction with botulinum toxin treatment in post-stroke spasticity: results from two crosssectional surveys (patients and physicians)

Djamel Bensmail, Angelika Hanschmann & Jörg Wissel

To cite this article: Djamel Bensmail, Angelika Hanschmann & Jörg Wissel (2014) Satisfaction with botulinum toxin treatment in post-stroke spasticity: results from two cross-sectional surveys (patients and physicians), Journal of Medical Economics, 17:9, 618-625, DOI: <u>10.3111/13696998.2014.925462</u>



# Past and Current Research

CRYONEUROTOMY AS A PERCUTANEOUS MINI-INVASIVE THERAPY FOR THE TREATMENT OF THE SPASTIC Limb: case presentation, review of the literature and proposed approach for use

### AUTHORS

Paul Winston, Patricia Branco Mills, Rajiv Reebye, Daniel Vincent



frontiers in Rehabilitation CASE REPORT published: 06 September 2021 doi: 10.3389/freec.2021.719054

Carefular

### Case Report: Perspective of a Caregiver on Functional Outcomes Following Bilateral Lateral Pectoral Nerve Cryoneurotomy to Treat Spasticity in a Pediatric Patient With Cerebral Palsy

Jack Scobie<sup>1†</sup> and Paul Winston<sup>2,3\*†</sup>

<sup>1</sup>Island Madeal Program, University of British Columbia, Victoria, BC, Canada, <sup>2</sup>Division of Physical Modeline and Rehabilitation, University of British Columbia, Victoria, BC, Canada, <sup>2</sup>Canadian Advances in Neuro-Orthopodics for Spasticity Congress, Victoria, BC, Canada

OPEN ACCESS

# Ultrasound with e-stimulation diagnostic nerve blocks for targeted muscle selection in spasticity

Winston, Paul MD<sup>1,2</sup>; Hashemi, Mahdis MD<sup>2</sup>; Vincent, Daniel MD<sup>2,3</sup>

Author Information 😔

American Journal of Physical Medicine & Rehabilitation: July 13, 2021 - Volume - Issue - doi: 10.1097/PHM.00000000001801

**Cryoneurotomy** to reduce spasticity and improve range of motion in spastic flexed elbow. A visual vignette

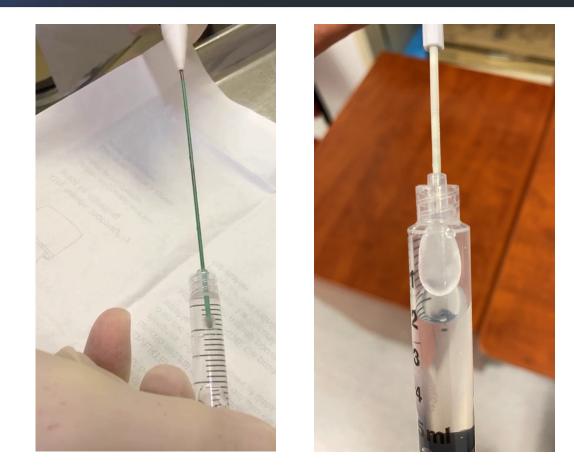
Rubenstein, Jonathan<sup>1</sup>; Harvey, Alexandra W.<sup>1</sup>; Vincent, Daniel MD<sup>1,2</sup>; *Winston*, Paul<sup>1,3</sup> Journal of Physical Medicine & Rehabilitation: <u>October 23, 2020 - Volume Publish Ahead of Print - Issue -</u>

# Antiquated Cumbersome Devices Versus Modern Innovation

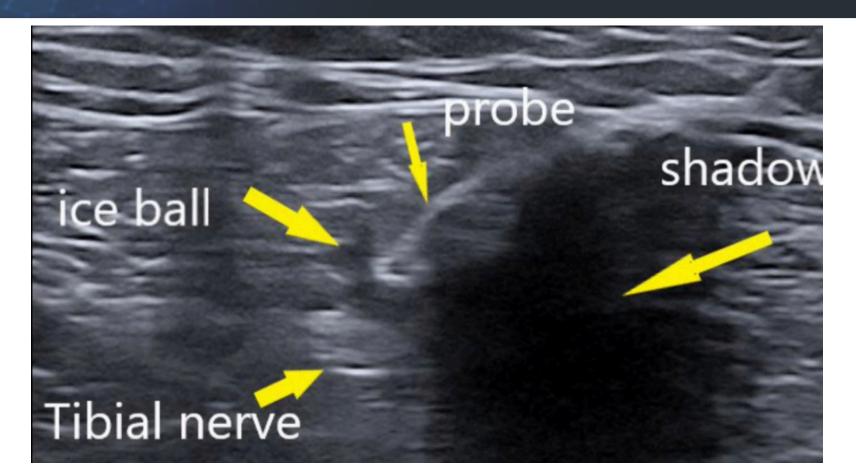


EpiMed PainBlocker<sup>™</sup>

# Late Model Epimed Versus iovera<sup>o</sup>



# Then We Discovered the Potential of iovera<sup>o</sup> Treatment

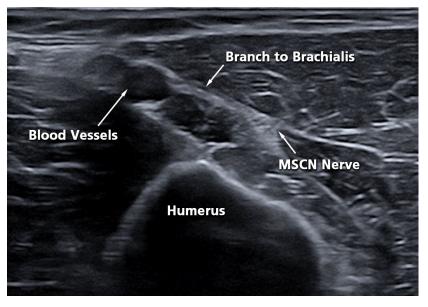


# **Treatment Pathway**

# **Nerve block**

# ioveraº Treatment





# The iovera<sup>o</sup> Treatment Results



# Before iovera<sup>o</sup>

# 7.5 months post iovera<sup>o</sup>

# Treatment on Multiple Sclerosis Pregnant Patient

# **Post-treatment Pre-treatment**

# Treatment on Multiple Sclerosis Pregnant Patient

# Pre-treatment 4 Weeks Post-treatment



10 Months Post-treatment | Multiple Sclerosis Pregnant Patient Still Doing Great

# With brace

# Walking has improved



# Quadriplegia Spinal Cord Injury

# **Pre-treatment**



# 9 Days Post-treatment



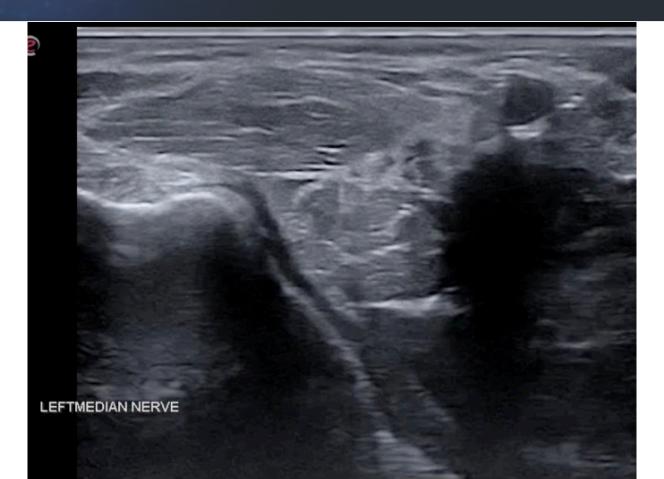
# **Increase in Function**



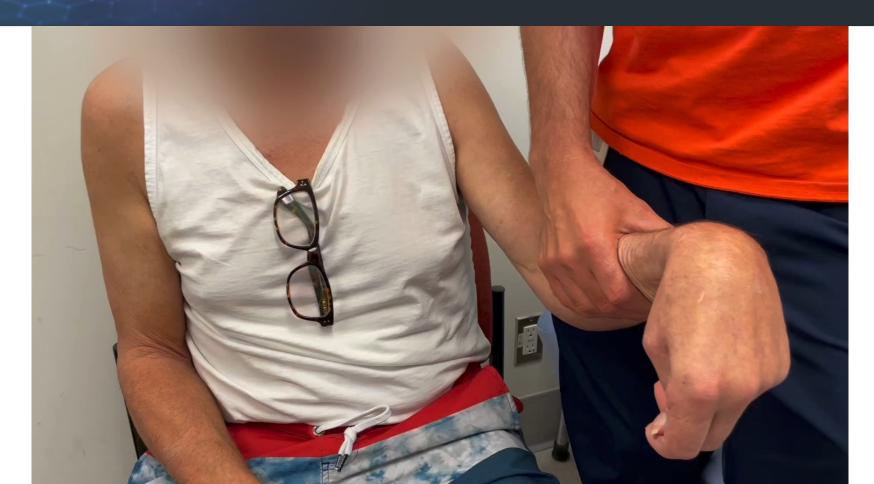
# Increase in Mobility



# Median Nerve iovera<sup>o</sup> Treatment



# Stroke Patient



# For this Stroke Patient's Disease, Botox is Contra-Indicated

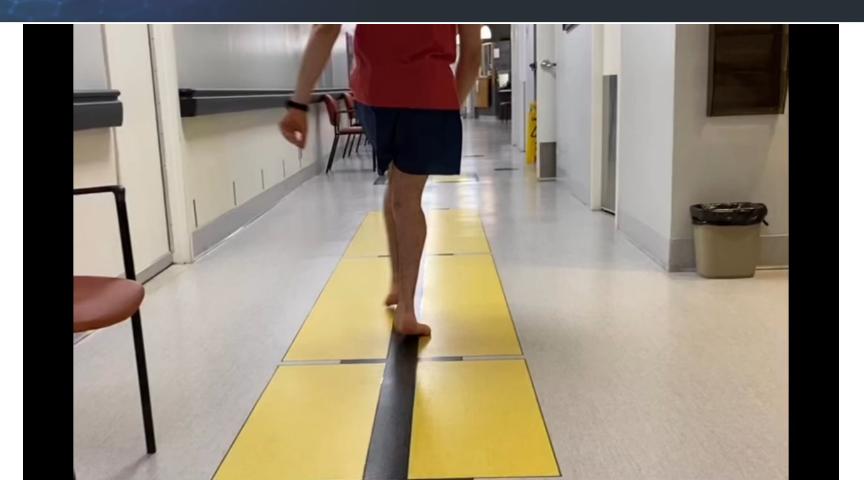


# Obturator Nerve Block in Cerebral Palsy





# Before and After iovera<sup>o</sup> Treatment in Cerebral Palsy



# iovera<sup>o</sup> Investigator-Initiated Trial



### H-reflex in Spastic Lower Limb Cryoneurotomy

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has
 been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04907201

Recruitment Status ① : Recruiting First Posted ① : May 28, 2021 Last Update Posted ① : June 3, 2021

See Contacts and Locations

# The Human Factor Cannot be Underestimated



# PCRX INVESTOR DAY

**Product Pipeline:** *EXPAREL, iovera<sup>o</sup> and DepoFoam clinical initiatives and upcoming milestones* 

Roy Winston, MD



# EXPAREL

# • Lower Extremity Nerve Block

- Popliteal Block (sciatic nerve) for bunionectomy
- Adductor Canal Block (saphenous nerve) for TKA
- Target Joint sNDA submission 3Q22

# • Pediatric Label Expansion 0 to <6 years

- Safety/Efficacy 0 to <6</li>
- Include an EU site to satisfy both FDA and EMA requirements

# • Development:

- Stellate Ganglion – EXPAREL chronic pain application/dysrhythmia storm

# • Post-Marketing EXPAREL:

- Shriners/Cleveland Clinic Erector Spinae for Pediatric Scoliosis Correction
- Henry Ford Opioid Free C-Section

# ioverao

- PREPARE TKA Interim results 4Q21, 200 pts, Interim @60 pts
- Painful OA ioveraº vs. Steroid, 220 pts with 6-month follow-up
- **iGOR** (Innovations in Genicular Outcomes Registry)
  - Accommodates many clinical scenarios (e.g., repeat treatments, variety of treatments, variations in PT)
  - 100% electronic data capture primarily direct from patients
- Lower back pain and spine surgery Pilot
- Rib Fracture/Intercostal block 2 Pilot studies Dallas Methodist/Penn
- Ankle OA Awaiting final report
- Upper and Lower Limb Spasticity
  - 2 pilot IITs underway, (Dr. Paul Winston, Vancouver)
  - Educational grant also provided for Dr. Winston's session on cryoneurolysis at the Canadian Advances in Neuro-Orthopedics for Spasticity Congress

# **Depofoam Pipeline**

# Intrathecal EXPAREL

- Phase 1 study part A completed, Part B to be completed 1Q22
- Phase 2-3 studies 4Q22

# • DepoDexamethasone treatment of radicular low back pain

- Toxicology studies currently underway
- Phase 2 4Q22

# • Depo20: 20mg/ml, 5–6-day bupivacaine formulation

- Toxicology studies currently underway
- Phase 2 4Q22

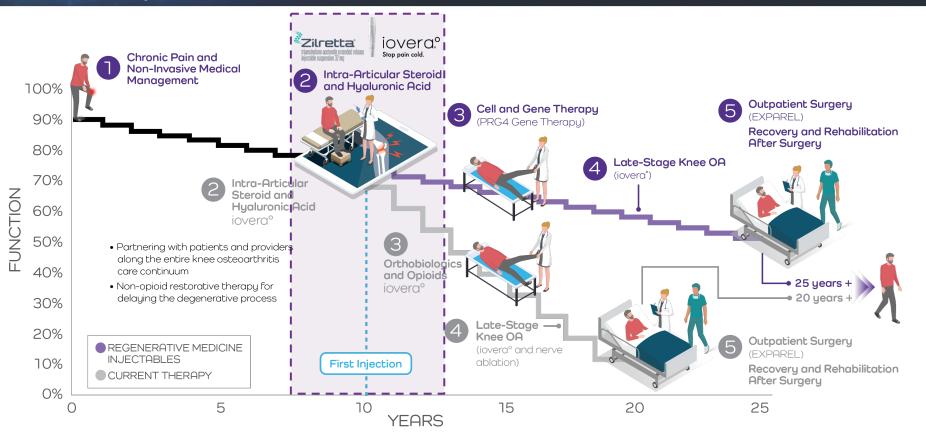
# **PCRX** INVESTOR DAY

Improving the Patient Journey: Taking an innovative approach to managing pain along the neural pain pathway

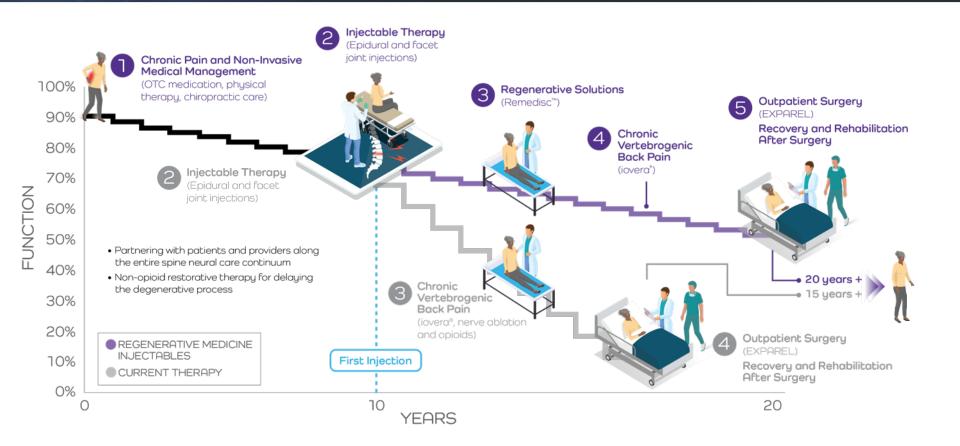
Ron Ellis, DO



# Pacira is Focused on Improving OA Patient Journey Every Step of the Way...



# Improving the Patient Journey: Chronic Vertebrogenic Back Pain



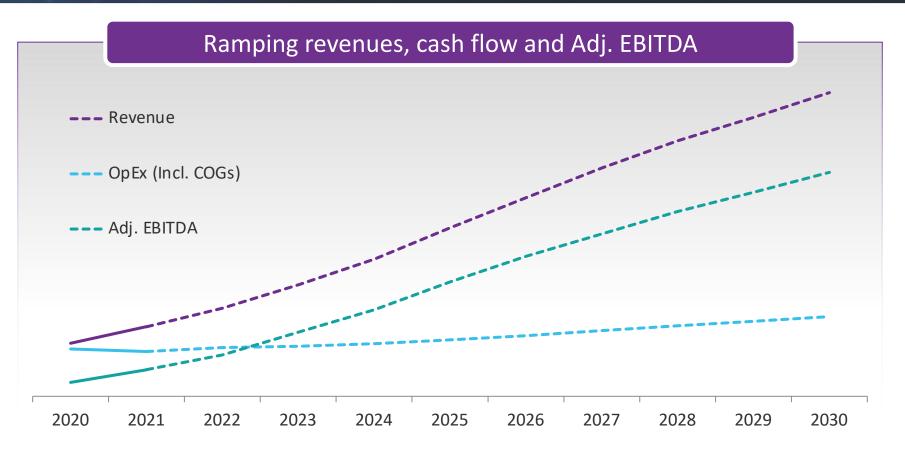
# **PCRX** INVESTOR DAY

# **Closing Remarks**

Dave Stack, CEO & Chairman



# Current EXPAREL & iovera<sup>o</sup> Base Business Places Pacira in a Position of Strength with a Best-in-Class Revenue and Adj. EBITDA Ramp



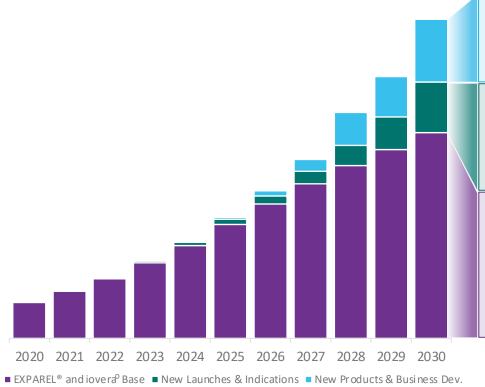
# Robust Organic and Acquired Opportunities Provide Significant Upside to Long-term Value Proposition

	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	
	Orthopedics, General Surgery, Women's Health (i.e., C-Section), and Cardiothoracic											<ul> <li>Expandin</li> <li>C-section</li> </ul>
	Pediatrics											4+M proc • LENB con
	Lower Extremity Nerve Block (LENB)											Stellate
	Cardiac Dysrhythmia (Stellate Ganglion Block)										lock)	2M proce PTSD, Pla
iovera°	TKA & Osteoarthritis Knee markets											• Expandin
	Spine (New Smart Tips for Specific Procedures)											osteoart
	Lower Back Pain (Medial Branch Block with New Smart Tips)											New iove 27M pro- back pair
	Rib Fracture (Intercostal Block)											
	Approval 4022 Spasticity (Breakthrough Designation Assumed)									•		
New Products & Business Dev					Phase 2, 3Q24			DepoDexamethasone			ne	<ul><li>DepoDex</li><li>DepoBup</li></ul>
								Depol	Bupivacai	ne (high-	dose)	Intratheo     application
		Phase 2, 4Q22				Intrathecal EXPAREL (low-dose)						Non-opio
	Business Development Opportunities											journey p
	EXPAREL & iovera <sup>o</sup> base business New Launches and Indications New Products & Business Dev								isiness Dev.	Rest-of-V		

- Expanding penetration in existing label;
   C-section and pediatrics combined
   4+M procedures/year
- LENB combined ~5M procedures/year
- Stellate Ganglion Block: Dysrhythmia 2M procedures/year; potential in PTSD, Plastic Surgery, Scleroderma
- Expanding penetration in TKA and osteoarthritis markets
- New iovera<sup>o</sup> indications and launches 27M procedures per year (spine, lower back pain, rib fracture, and spasticity)
- DepoDexamethasone; low back pain
- DepoBupivacaine; 20mg dose ~5+ days
- Intrathecal delivery; low dose/broad applications
- Non-opioid targets along the patient journey pain continuum
- Rest-of-World Market Expansion

# Building Robust Top-line Ramp through Penetration of Core Targeted Procedures, Organic Growth, and Acquired Innovation

**Projected Revenue Potential** 



- Business Development: Orthopedics & Regenerative Medicine
- Organic Pipeline: DepoDexamethasone for lumbar radiculopathy (inflammation); High Potency DepoBupivacaine extended release via epidural, intrathecal, chronic pain; Intrathecal EXPAREL®
- *Stellate Ganglion* for treatment of post operative dysrhythmia; other opportunities include PTSD, Plastic Surgery, Scleroderma
- *Spasticity* (with current 190 tip); *Lower Back Pain* (with new 167 tip), *Spine Surgery* (with new tips)
- Rib fracture (intercostal)
- EXPAREL<sup>®</sup> penetration within Ortho, General Surgery; Women's Health; Cardiothoracic; new adoption across C-Section, Pediatrics, and Lower Extremity Nerve Block populations
- iovera<sup>o</sup> penetration in TKA and OA collectively presenting a revenue realization opportunity of >\$200M
- Global expansion in Europe, Canada, and LATAM markets

# Multiple Market Dynamics Leave Pacira Uniquely Positioned for Long-Term Leadership in Opioid-sparing Pain Management

Colliding COVID and opioid crises intensifying need for opioid alternatives

Unprecedented **93,331** Americans died from drug overdose in 2020

75% involved opioids;40% increase over 2019

**20+M** Americans in recovery <u>require</u> opioid-free protocols

- EXPAREL<sup>®</sup>-based regional blocks becoming cornerstone of care
- iovera<sup>o</sup> significant advancement over opioids through immediate, drug-free, long-acting pain control

Accelerating site-of-care shift to 23-hour stay environment

### Patients, providers and payers <u>overwhelmingly</u> prefer outpatient environment

- Preservation of hospital beds
- Significant economic benefits fueling shift of complex, painful procedures
- Favorable reimbursement for EXPAREL<sup>®</sup> and iovera<sup>o</sup> provide additional incentive for migration

Case migration <u>only possible</u> with effective, durable, safe and replicable non-opioid pain control

Redefining surgical care using advanced regional techniques coupled with ERAS protocols

Regional block growth vs. general anesthesia

### Rapidity of shift being driven by:

- Procedure-based Enhanced Recovery After Surgery (ERAS) protocols
- Advanced regional field blocks and nerve blocks (e.g. ESP, TAP, PENG)
- Long-acting locals like EXPAREL<sup>®</sup>
- Improved ultrasound technology
- Mounting demand for outpatient sites-of-care

Protocols being *institutionalized* and embedded in clinical practice

