FDA Introductory Remarks

Anesthetic and Analgesic Drug Products
Advisory Committee Meeting
January 16, 2020

Rigoberto Roca, MD
Director (Acting), Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP)
Office of Neuroscience (ON), Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER), FDA

Discussion Point #1

Discuss whether the Applicant has provided sufficient information to support the proposed indication.

Discussion Point #2

Discuss whether there are issues with this Complete Response resubmission that warrant additional studies and, if so, should these studies be conducted before or after approval.

Discussion Point #3

Discuss whether the efficacy, safety, and overall risk-benefit profile of Posimir support the approval of this application.

Voting Question

Do you recommend approval of Posimir, bupivacaine extended-release solution, 660 mg/5 mL (132 mg/mL), for the proposed indication of single-dose instillation into the surgical site to produce post-surgical analgesia?

a. If you voted "Yes," please discuss the rationale for your vote and specify whether any post-approval studies should be required.

b. If you voted "No," please discuss the rationale for your vote and what additional data are needed for approval.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

NDA 204803

POSIMIR

Renee Petit-Scott, MD
Medical Officer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of New Drugs, Center for Drug Evaluation and Research, FDA
Anesthetic and Analgesic Drug Products Advisory Committee Meeting
January 16, 2020

Overview of Presentation

- Summary of current postsurgical analgesic treatment options
- Summary of clinical development program
- Statistical review of efficacy data – Katherine Meaker, M.S.
- Clinical implications of efficacy data
- Assessment of safety data from studies submitted in support of NDA
  - Concerns resulting in the Complete Response Action
    - Adverse events related to the shoulder joint
    - Wound-related adverse events
    - Benzyl alcohol systemic exposure
  - Applicant's response to CR deficiencies
- Conclusions

Current Postsurgical Analgesic Treatment Options

Renee Petit-Scott, MD

Current Postsurgical Analgesic Treatment Options

- Oral and IV analgesics
  - Opioids, NSAIDs, acetaminophen
- Unapproved adjuncts
  - Pre-op administration
    - Gabapentinoids
  - Intra-op administration
    - Lidocaine infusion
    - Ketamine infusion

Current Postsurgical Analgesic Treatment Options

- Local anesthetics
  - Administered via wound infiltration, and for peripheral nerve block (single injection and continuous infusion techniques) and neuraxial anesthesia
  - None currently labeled for extended-release
    - Extended-release pharmacokinetic profile does not imply prolonged postsurgical analgesia for locally-acting products
  - Commonly administered products
    - Lidocaine, bupivacaine, ropivacaine, mepivacaine, Exparel

NDA 204803

POSIMIR

Summary of Clinical Development Program

Renee Petit-Scott, MD

Proposed Indication

POSIMIR is an extended release solution of bupivacaine, an amide local anesthetic, indicated for single-dose instillation into the surgical site to produce post-surgical analgesia.

Clinical Development Program

- Original NDA submission (received April 12, 2013)
  - Seven efficacy studies evaluated
  - Division felt that the efficacy of SABER-bupivacaine over SABER-placebo had been demonstrated in arthroscopic shoulder surgery
- Discipline Review Letter issued (DRL; January 14, 2014)
  - Division concluded that efficacy was demonstrated for arthroscopic shoulder surgery only
  - Chondrolysis, and wound-related and neurological-related adverse events described
- Applicant's response to DRL (received February 3, 2014)
  - Division concluded that efficacy was demonstrated for inguinal hernia repair and the risk of chondrolysis was adequately addressed
  - Remaining safety concerns included in Complete Response Letter

Complete Response (CR) Letter (February 12, 2014)

Deficiency	Suggested Resolution
Adverse events related to the shoulder joint and surrounding tissues	Conduct a safety study in patients undergoing arthroscopic subacromial decompression.
Increased risk of wound-related adverse events (i.e., bruising, hematoma, pruritus, and dehiscence)	Conduct a safety study evaluating the occurrence of adverse reactions associated with skin and underlying tissues. The study must evaluate subjects undergoing each of the surgical procedures studied to date.
Increased risk of neurologically related adverse events (i.e., dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence)	Conduct a safety study evaluating the occurrence of adverse reactions associated with neurotoxicity. The study must evaluate subjects undergoing each of the surgical procedures studied to date.

Clinical Development Program

- End-of-Review-Cycle Meeting (September 23, 2014)
  - Study in second soft tissue model required for postsurgical analgesic indication
  - Applicant would no longer pursue post-arthroscopic shoulder indication

Clinical Development Program

- Formal Dispute Resolution Request (FDRR; received November 21, 2014)
  - Additional determination of safety *and* efficacy requested
  - Agency determined that modest efficacy was demonstrated in two surgical models and suggested two paths forward to address the identified safety concerns:
    - Conduct an additional study or
    - Submit all the information provided in the End-of-Review Cycle meeting background materials
- FDRR denied (January 15, 2015)

Clinical Development Program

- Phase 3 study protocol (PERSIST Study) submitted (August 31, 2015)
  - Patients undergoing laparoscopic cholecystectomy (lap chole)
  - Saline placebo control only
    - Advice letter (January 11, 2016) and teleconference (April 5, 2016) – strong recommendation to include a bupivacaine treatment group
    - Bupivacaine treatment group included in Protocol Amendment 3 (June 6, 2016)
- NDA resubmission (received June 27, 2019)
  - Supportive safety information discussed during End-of-Review-Cycle Meeting and lap chole study results submitted

Overview of Efficacy

- Arthroscopic shoulder surgery – three studies*
- Open inguinal hernia repair – two studies*
- Other soft tissue surgeries
  - Total abdominal hysterectomy, laparotomy†, lap chole†, laparoscopic-assisted (lap-assisted) colectomy†
- PERSIST Study† - laparoscopic cholecystectomy

*Phase 2 studies; †Phase 3 studies

NDA 204803
Posimir
Statistical Review of Efficacy Data

Katherine Meaker, MS
Statistics Reviewer
Division of Biometrics I, Office of Biostatistics
Office of Translational Sciences, Center for Drug Evaluation and Research, FDA

Posimir Clinical Studies

Surgical Model	Study	Conducted	Control
Arthroscopic shoulder	CLIN-005-0006	2006-07	SABER-Pbo
	C803-017	2008-09	SABER-Pbo
	BU-002-IM *	2009-11	Bupiv. 50mg SABER-Pbo
Inguinal Hernia	CLIN 005-0010	2006	SABER-Pbo
	CLIN-803-006-0006 *	2007	SABER-Pbo
Hysterectomy	BU-001-IM	2009-10	Bupiv. 100mg SABER-Pbo
Abdominal Laparoscopic Procedures	803-025 †	2009-11	Bupiv. 150mg SABER-Pbo
	PERSIST † (1 & 2)	2015-17	Part 1: Saline Pbo Part 2 Bupiv. 75mg

* Designated pivotal by Applicant † Planned as Phase 3 (otherwise planned as Phase 2)

Posimir Clinical Studies – Arthroscopic Shoulder Surgery

Study	Surgical Procedures	Treatment Arms (n)
CLIN-005-0006	Arthroscopic and open shoulder surgeries	Cohort 2: Posimir (n=21) SABER-Pbo (n=24)
C803-017	Arthroscopic and open shoulder surgeries	Posimir (n=40) SABER-Pbo (n=20)
BU-002-IM *	Arthroscopic only shoulder surgeries	Posimir (n=53) SABER-Pbo (n=25) Bupiv. 50mg (n=29)

* Designated pivotal by Applicant

Posimir Clinical Studies – Arthroscopic Shoulder Surgery

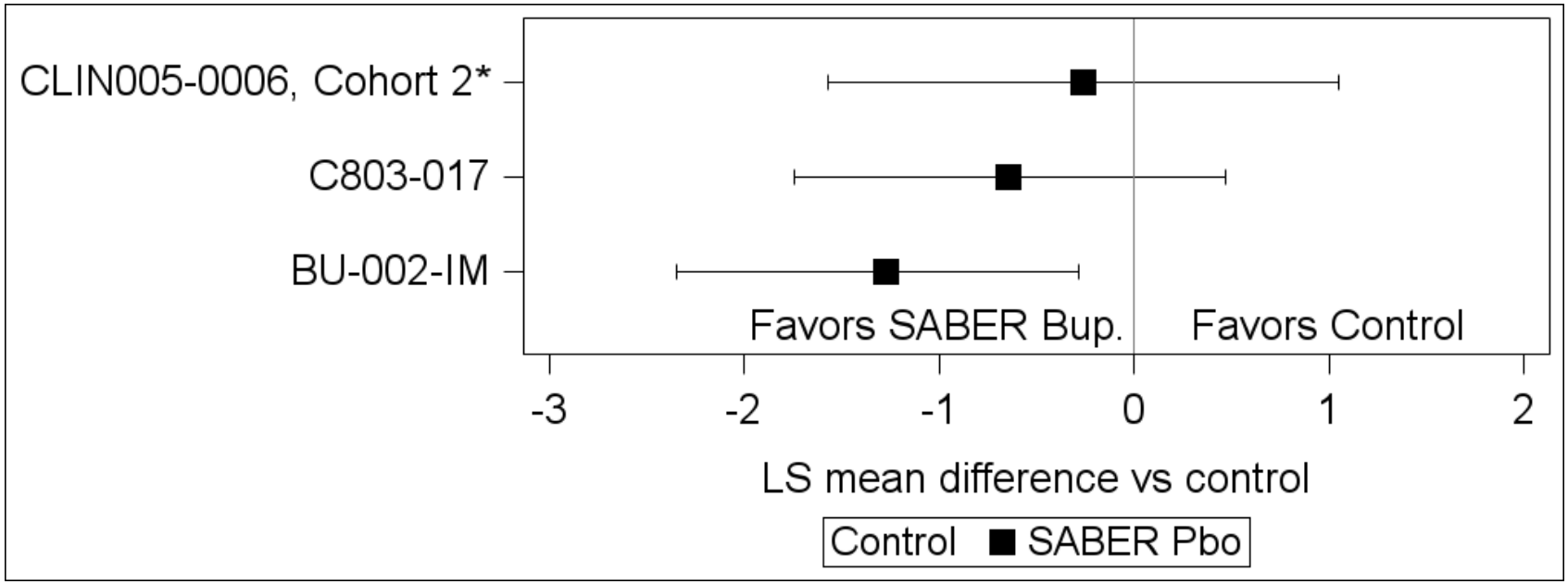
Pain on Movement (0-72 hrs)		Posimir	SABER-Placebo	Difference 95% CI	Conclusion
CLIN-005-0006 Cohort 2	N Mean (SE)	21 5.1 (0.7)	24 4.8 (0.7)	- 0.3 (-1.6, 1.1)	Not stat. signif.;
C803-017	N Mean (SE)	40 5.3 (0.3)	20 6.0 (0.5)	- 0.6 (-1.7, 0.5)	Not stat. signif.
BU-002-IM *	N Mean (SE)	53 5.2 (0.3)	25 6.4 (0.4)	- 1.3 (-2.3, -0.3)	p=0.012

SE – Standard Error of the Mean

* Designated pivotal by Applicant

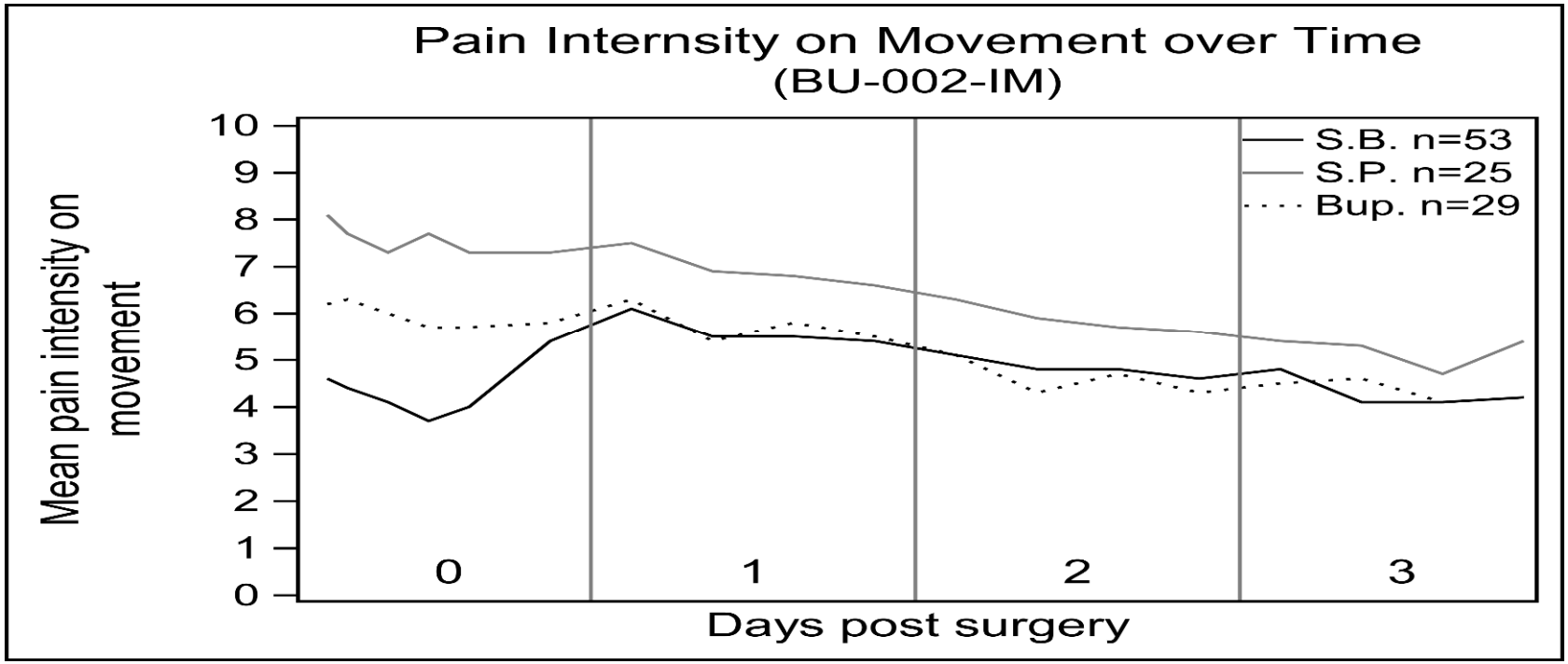
Posimir Clinical Studies – Arthroscopic Shoulder Surgery

Mean Pain on Movement for 0-72 Hours After Surgery



* Study CLIN005-0006 AUC 0-120 hrs

Posimir Clinical Studies – Arthroscopic Shoulder Surgery



Posimir Clinical Studies – Arthroscopic Shoulder Surgery

All three clinical studies were:

- Phase 2 studies
- Powered for comparison of Posimir to SABER-placebo
- Had appropriate statistical analysis plans

FDA considers CLIN-005-0006 Cohort 2 to be adequate and well-controlled (AWC).

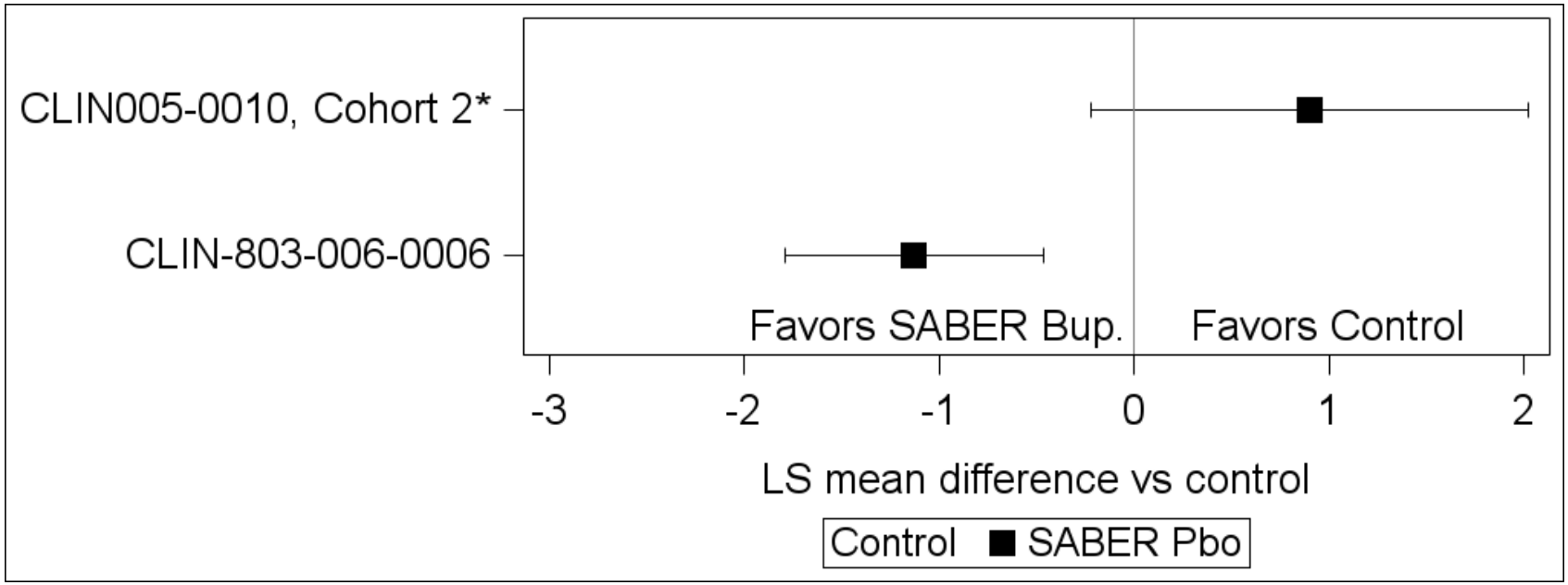
Posimir Clinical Studies – Inguinal Hernia

Pain on Movement (0-72 hrs)		Posimir	SABER-Placebo	Difference 95% CI	Conclusion
CLIN 005-0010 Cohort 2	N Mean (SE)	22 4.4 (0.4)	21 3.5 (0.4)	+ 0.9 (-0.2, 2.0)	Not stat. signif.; Direction favors SABER-Pbo.
CLIN-803-006-0006 *	N Mean (SE)	47 2.5 (0.2)	32 3.6 (0.3)	-1.1 (-1.8, -0.5)	p=.003

* Designated pivotal by Applicant

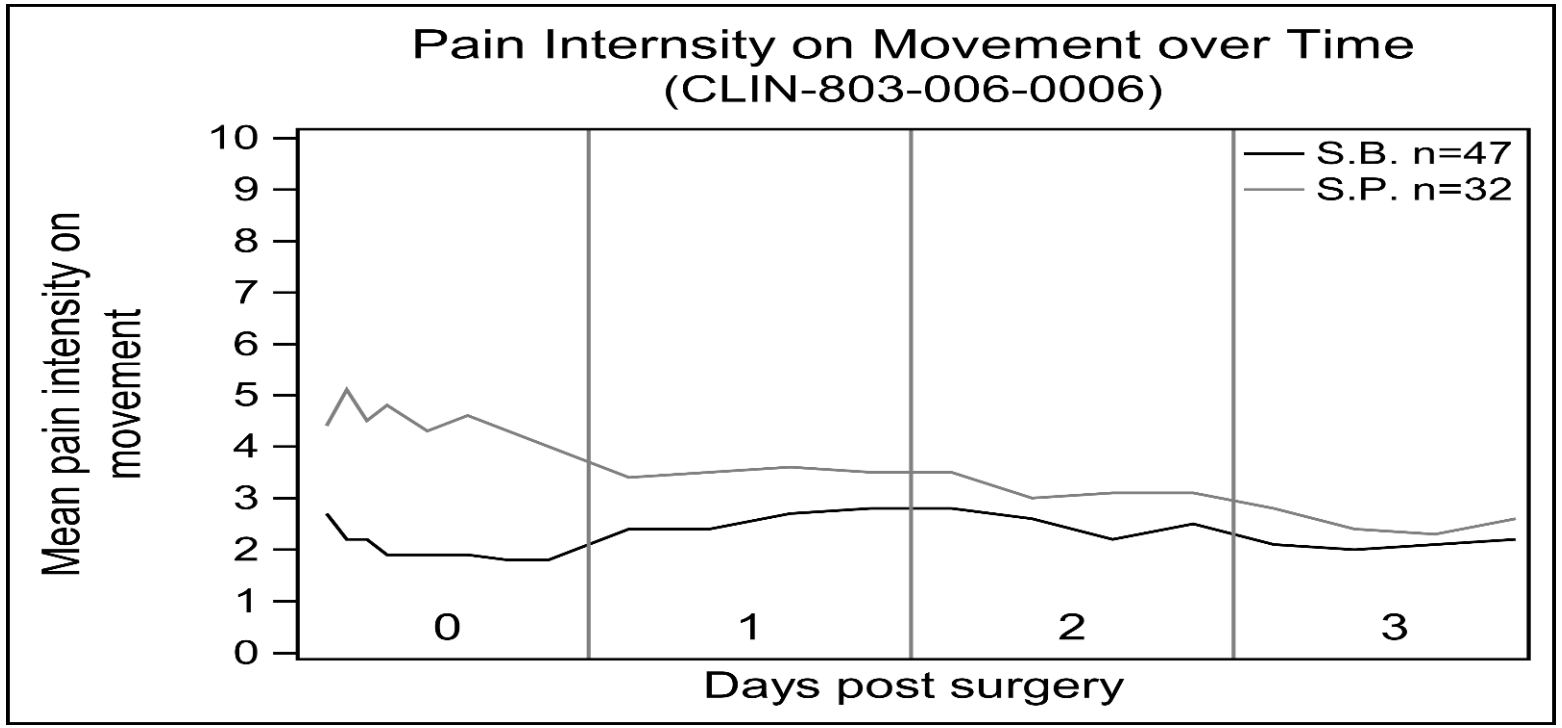
Posimir Clinical Studies – Inguinal Hernia

Mean Pain on Movement for 0-72 Hours After Surgery



* Study CLIN005-0010 AUC 0-120 hrs

Posimir Clinical Studies – Inguinal Hernia



Posimir Clinical Studies - Inguinal Hernia

Both clinical studies were:

- Phase 2 studies
- Powered for comparison of Posimir to SABER-placebo
- Had appropriate statistical analysis plans

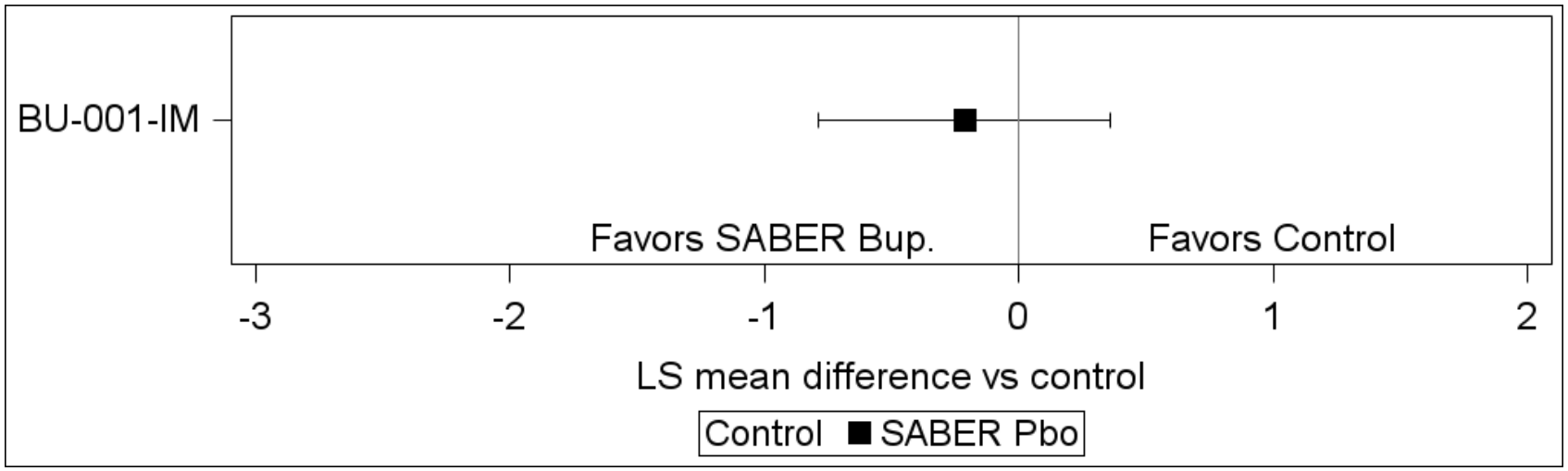
FDA considers CLIN-005-0010 Cohort 2 to be adequate and well-controlled.

Posimir Clinical Studies – Open Hysterectomy

Pain on Movement (0-72 hrs)		Posimir	Control	Difference 95% CI	Conclusion
BU-001-IM	n Mean (SE)	60 4.2 (0.2)	27 4.5 (0.3) SABER-Pbo	-0.2 (-0.8, 0.4)	Not stat. signif.
	n Mean (SE)	60 4.2 (0.2)	27 4.3 (0.3) Bupiv. 100mg	-0.1 (-0.7, 0.5)	Exploratory

Posimir Clinical Studies – Open Hysterectomy

Mean Pain on Movement for 0-72 Hours After Surgery



Posimir Clinical Studies – Open Hysterectomy

A single clinical study was:

- Phase 2
- Powered for comparison of Posimir to SABER-placebo
- Had appropriate statistical analysis plans
- Not powered for comparison of Posimir to Bupivacaine 100mg active-control arm.

Posimir Clinical Studies – Abdominal Procedures

Study	Surgical Procedure	Control
803-025 †	Cohort 1: Laparotomy Cohort 2: Laparoscopic Cholecystectomy (Lap. Chole.) Cohort 3: Laparoscopic Colectomy	Bupiv. 150 mg (Cohorts 1 and 2) SABER-Pbo (Cohort 3)
PERSIST (Part 1) †	Lap. Chole.	Part 1: saline
PERSIST (Part 2) †	Lap. Chole.	Part 2 Bupiv. 75 mg

† Planned as Phase 3 (otherwise planned as Phase 2)

Posimir Clinical Studies – Abdominal Procedures

Pain on Movement (0-72 hrs)		Posimir	Control	Difference 95% CI	Conclusion
803-025 Cohort 1	N Mean (SE)	26 4.9 (0.4)	17 5.8 (0.5) Bupiv. 150 mg	-0.9 (-2.1, 0.3)	Exploratory
803-025 Cohort 2	N Mean (SE)	30 2.8 (0.4)	20 3.9 (0.5) Bupiv. 150 mg	-1.1 (-2.2, 0.1)	Exploratory
803-025 † Cohort 3	N Mean (SE)	126 4.8 (0.2)	77 5.1 (0.2) SABER-Pbo	-0.3 (-0.8, 0.1)	Not stat. signif.

† Planned as Phase 3 (otherwise planned as Phase 2)

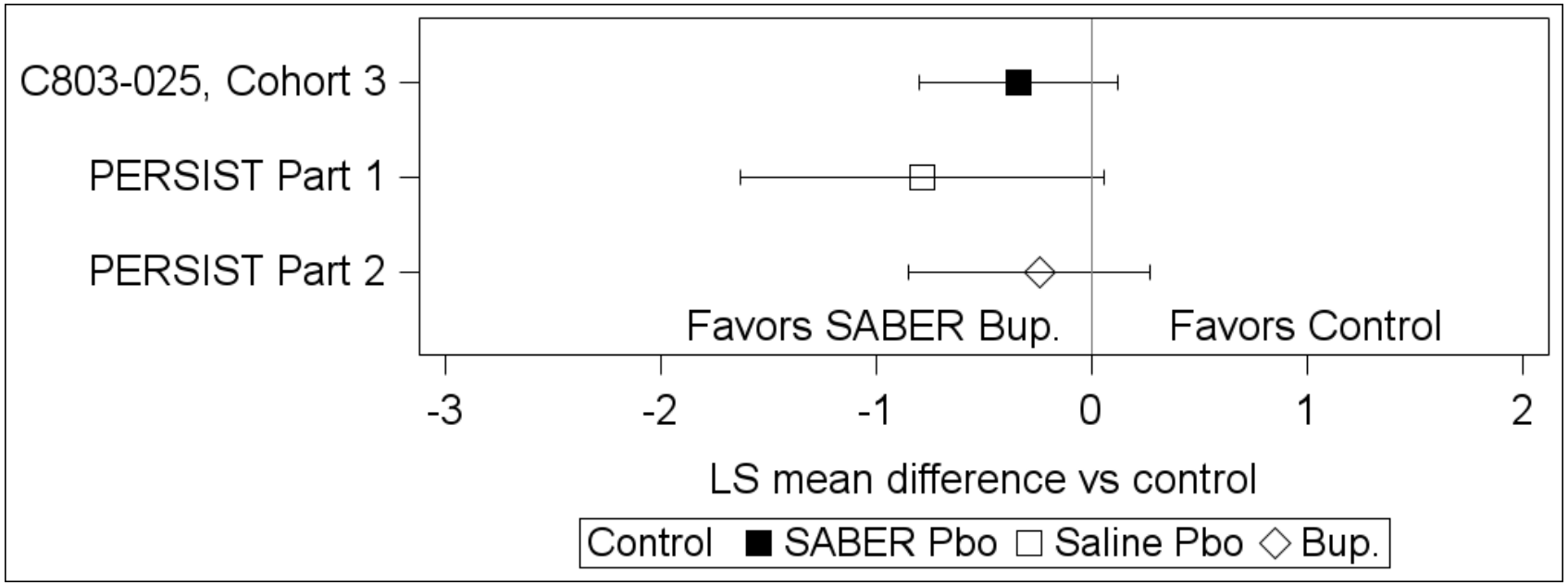
Posimir Clinical Studies – Abdominal Procedures

Pain on Movement (0-72 hrs)		Posimir	Control	Difference 95% CI	Conclusion
PERSIST (Part 1) †	N Mean (SE)	46 4.4 (0.1)	46 5.2 (0.1) saline	-0.8 (-1.6, 0.1)	Not stat. signif.
PERSIST (Part 2) †	N Mean (SE)	148 5.1 (0.1)	148 5.4 (0.1) Bupiv. 75mg	-0.3 (-0.9, 0.3)	Not stat. signif.

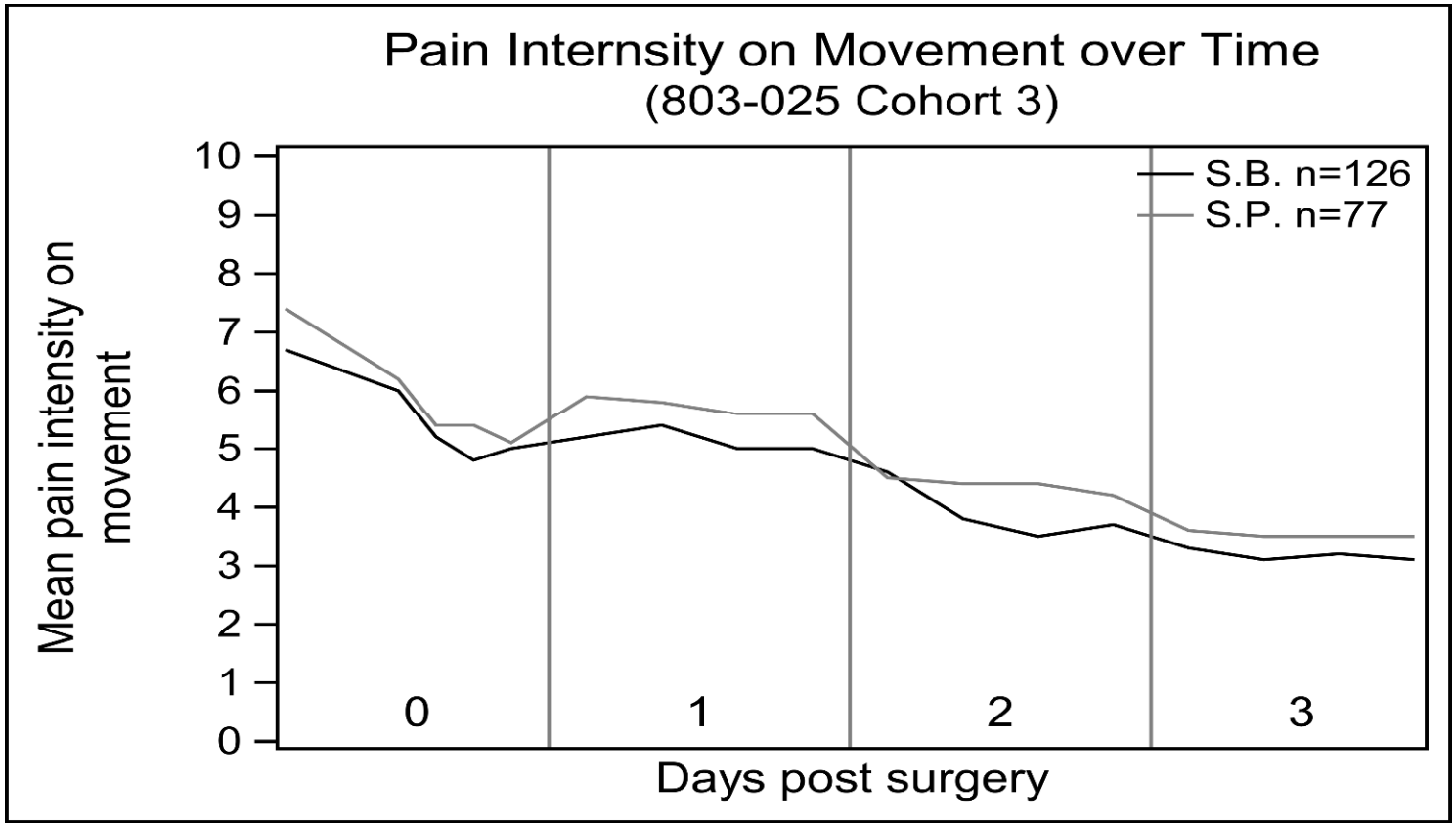
† Planned as Phase 3 (otherwise planned as Phase 2)

Posimir Clinical Studies – Abdominal Procedures

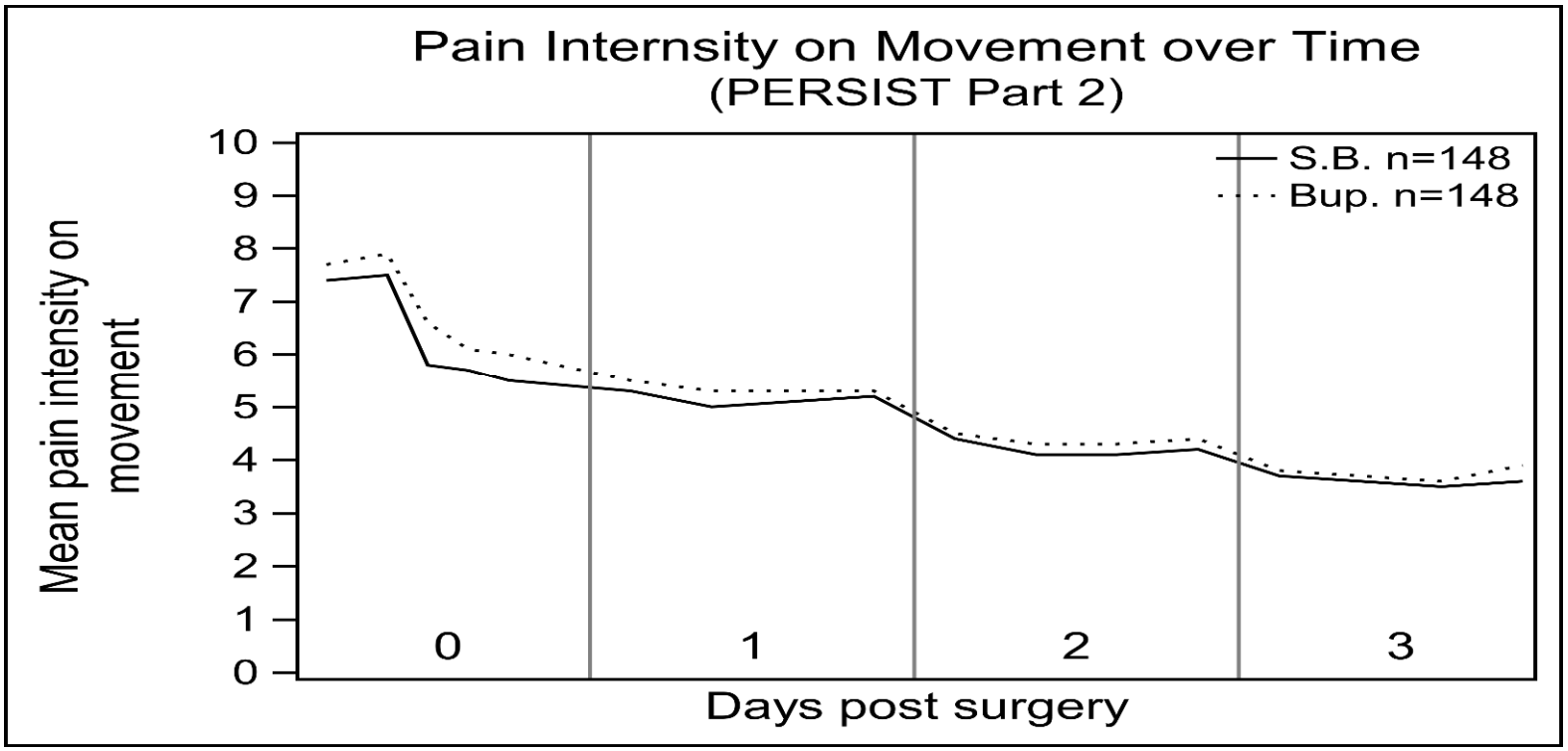
Mean Pain on Movement for 0-72 Hours After Surgery



Posimir Clinical Studies – Abdominal Procedures



Posimir Clinical Studies – Abdominal Procedures



Posimir Clinical Studies – Abdominal Procedures

Both clinical studies were Phase 3 studies:

- 803-205 (Cohort 3): Powered for comparison of Posimir to SABER-placebo
- PERSIST (Part 2): Powered for comparison of Posimir to Bupivacaine 75mg

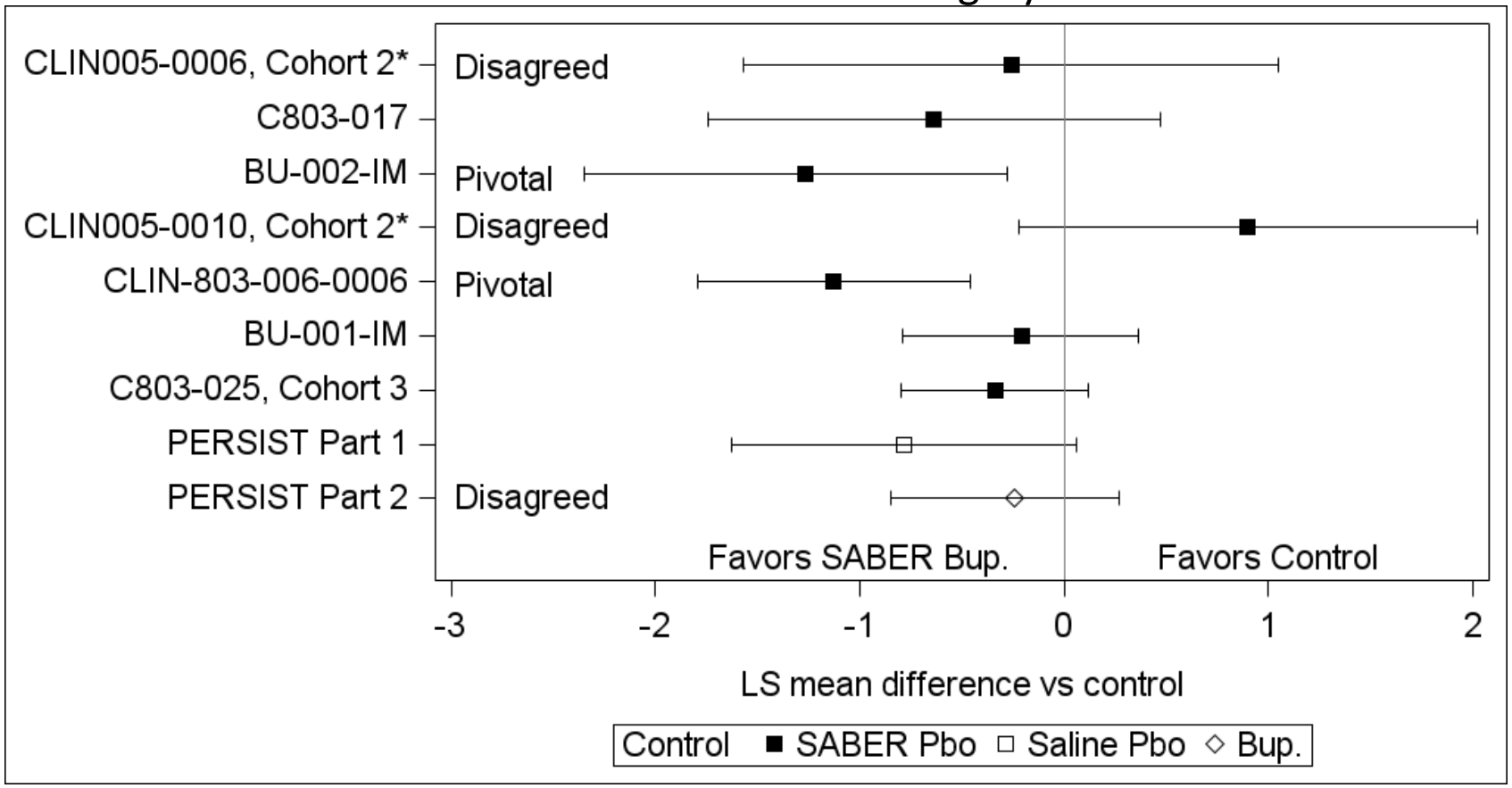
FDA considers PERSIST Part 2 to be adequate and well-controlled.

Surgical Procedure	Study	Control	Designation	
			Applicant	Disagreed
Arthroscopic shoulder	CLIN-005-0006	SABER-Pbo	Non-AWC	X
	C803-017	SABER-Pbo	AWC	
	BU-002-IM *	Bupiv. 50mg SABER-Pbo	AWC	
Inguinal Hernia	CLIN 005-0010	SABER-Pbo	Non-AWC	X
	CLIN-803-006-0006 *	SABER-Pbo	AWC	
Hysterectomy	BU-001-IM	Bupiv. 100mg SABER-Pbo	AWC	
Abdominal	803-025 †	Bupiv. 150mg SABER-Pbo	Cohorts 1&2 Non-AWC Cohort 3: AWC	
	PERSIST †	Part 1: Saline Pbo Part 2 Bupiv. 75mg	Part 1 AWC Part 2 non-AWC	X

* Designated pivotal by Applicant † Planned as Phase 3 (otherwise planned as Phase 2)

Summary of Efficacy Evidence

Mean Pain on Movement for 0-72 Hours After Surgery



* Studies CLIN005-0006 and CLIN005-0010 AUC 0-120 hrs

Conclusions

After dispute resolution of the original submission FDA concluded evidence of efficacy was “modest and inconsistent.”

PERSIST Part 2 was designed and powered to test superiority of Posimir to Bupivacaine 75mg and was not able to determine a statistically significant difference.

Conclusions (cont.)

The results from the clinical studies:

- are inconsistent within the surgical procedures the applicant planned to demonstrate efficacy
- do not consistently show superiority of Posimir to SABER-placebo

When a statistically significant treatment effect is detected for pain on movement for 0-72 hours after surgery, the majority of the treatment effect is observed in the first 24 hours after treatment.

NDA 204803
Posimir
Clinical Implications of Efficacy Data

Renee Petit-Scott, MD

Shoulder Procedures Evaluated

Study Number (Dates, Location)	Procedures Performed	Route of SABER-bupivacaine Administration
CLIN005-0006 (2006-2007; U.S. and New Zealand)	arthroscopic subacromial decompression; rotator cuff repair, glenoid labrum repair or debridement, and biceps tendon repair	subacromial instillation + sub-Q trailing injections or subacromial instillation
C803-017 (2008-2009; Australia and New Zealand)	arthroscopic subacromial decompression, open Mumford procedure (distal clavicle excision) after protocol amendment	subacromial instillation
BU-002-IM* (2009-2011; Europe)	arthroscopic subacromial decompression, distal clavicle excision, bursectomy, synovectomy, removal of loose body, resection of coracoacromial ligament and subacromial spurs, and minor debridement of articular cartilage	subacromial instillation

*Designated pivotal by Applicant

Open Inguinal Hernia Repair Studies

- CLIN005-0010 (2006-2007; U.S. and New Zealand)
  - Primary efficacy endpoint was mean pain intensity on movement through 120 hours (AUC_{120M})
  - Exploratory analysis of AUC_{72M} favored SABER-placebo treatment
- CLIN803-006-0006* (2007; Australia and New Zealand)
  - Efficacy of SABER-bupivacaine demonstrated over SABER-placebo (AUC_{72M})

*Designated pivotal by Applicant

Other Soft Tissue Studies

- BU-001-IM - total abdominal hysterectomy
- C803-025 (Phase 3)
  - Cohort 1 - laparotomy
  - Cohort 2 - lap chole
  - Cohort 3 - laparoscopic-assisted colectomy
- C803-028 (PERSIST; Phase 3) – lap chole

PERSIST Study

- Part 1 was terminated early due to change in comparator treatment. If full enrollment had been reached, statistical significance favoring SABER-bupivacaine over saline placebo would likely have been achieved (AUC_{72M})
- Part 2 is considered an adequate and well-controlled study that was unable to demonstrate an improvement in post-operative pain when compared to bupivacaine HCl (75 mg) over *48 hours* (AUC_{48M})

Efficacy Summary

- Efficacy was demonstrated in one of five soft tissue studies and one of three orthopedic studies conducted by the Applicant
- The studies that the Applicant has chosen to remove from the overall assessment of efficacy *were* adequate and well-controlled to evaluate the stated endpoints
- Early versus extended analgesic benefit based on pain curves for the 'pivotal' studies

Efficacy Summary (cont'd)

- Efficacy was demonstrated only above SABER-placebo treatment
  - Statistically significant difference between treatment groups is not clinically meaningful; i.e., 1.1 to 1.3 difference above placebo treatment on 11-point pain scale does not offer any benefit to the patient
- Based on PK data for SABER-bupivacaine, additional local anesthetic administration through 96 hours is contraindicated, suggesting that for patients in whom SABER-bupivacaine is not efficacious, alternate pain management is limited to oral and IV analgesics, including opioids.

NDA 204803

POSIMIR

Assessment of Safety Data From Studies Submitted in Support of NDA

Renee Petit-Scott, MD

Safety Concerns Identified in CR Letter

1. Adverse events related to the shoulder joint and surrounding tissues
2. Increased risk of wound-related adverse events (i.e., bruising, hematoma, pruritus, and dehiscence)
3. Increased risk of neurologically related adverse events (i.e., dizziness, dysgeusia, headache, hypoesthesia, paresthesia, and somnolence)

Applicant's Response to CR Letter Deficiencies

Shoulder study follow-up:

- Study CLIN005-0006 (14-day follow-up)
  - Review of long-term follow-up data
- Study C803-017 (18-month follow-up, reported as C803-107e)
  - Blinded orthopedic surgeons re-reading baseline and 18-month follow-up MRIs for the three patients with findings suggestive of post-arthroscopic glenohumeral chondrolysis
  - Blinded radiologist re-reading available baseline and 18-month follow-up MRIs
  - Evaluated 18-month follow-up physical exams conducted by blinded investigators
- Study BU-002-IM (6-month follow-up)
  - Review of long-term follow-up data

Applicant's Response to CR Letter Deficiencies

Shoulder study follow-up conclusions:

- CLIN005-0006
  - No clinically significant differences in physical exam findings between treatment groups (no non-SABER comparator)
- C803-017
  - No true cases of chondrolysis identified
  - No MRI-confirmed loss of articular cartilage
  - No clinically significant differences in physical exam findings between treatment groups (no non-SABER comparator)

Applicant's Response to CR Letter Deficiencies

Shoulder study follow-up conclusions (cont'd):

- Study BU-002-IM
  - only study to use non-SABER comparator (bupivacaine)
  - least supportive of safety
    - 6-month MRI findings
    - least improvement in mean Constant-Murley (C-M) scores
    - 7 patients with worsening C-M scores all treated with SABER-bupivacaine or SABER-placebo (MRIs reportedly unchanged)

Applicant's Response to CR Letter Deficiencies

PERSIST study

- 6 prespecified wound-related adverse events
  - Peri-incisional bruising, wound hematoma, wound dehiscence, surgical site infection, surgical site bleeding, and drainage from the surgical site
  - Incisions were evaluated on study days 4, 8, 15, and 30 (additional visit on study day 60 after Protocol Amendment 5)

PERSIST Study

Incidence of 6 prespecified wound-related adverse events

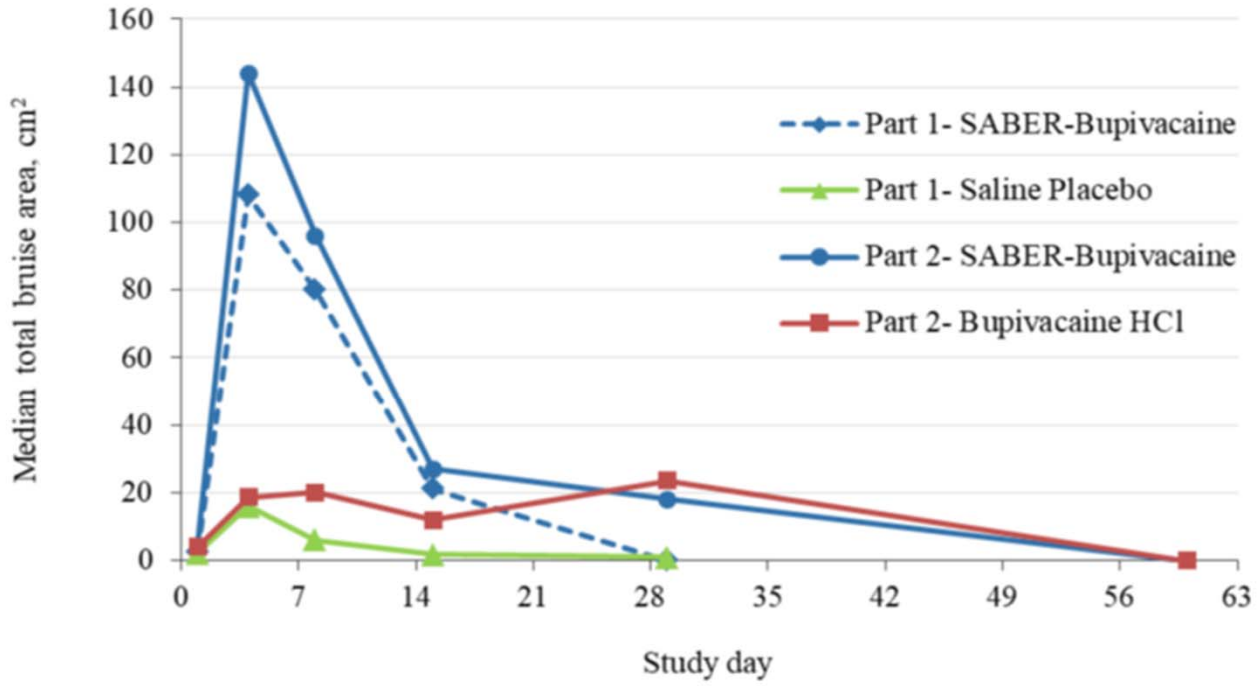
Pre-Specified Surgical Site Complication, n (%)	Part 1		Part 2		Combined Parts 1 & 2	Risk Ratio [1] (95% CI)
	SABER-Bupivacaine (N=45)	Saline Placebo (N=47)	SABER-Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER-Bupivacaine (N=193)	
Visible bruising	41 (91.1%)	33 (70.2%)	142 (95.9%)	105 (70.9%)	183 (94.8%)	1.336 (1.199, 1.489)
Surgical site bleeding	22 (48.9%)	20 (42.6%)	19 (12.8%)	24 (16.2%)	41 (21.2%)	1.310 (0.830, 2.067)
Drainage from surgical incision(s)	2 (4.4%)	3 (6.4%)	11 (7.4%)	6 (4.1%)	13 (6.7%)	1.661 (0.647, 4.268)
Wound hematoma	0 (0.0%)	0 (0.0%)	6 (4.1%)	2 (1.4%)	6 (3.1%)	2.301 (0.471, 11.235)
Wound dehiscence	0 (0.0%)	0 (0.0%)	2 (1.4%)	3 (2.0%)	2 (1.0%)	0.511 (0.087, 3.020)
Surgical site infection	0 (0.0%)	0 (0.0%)	2 (1.4%)	1 (0.7%)	2 (1.0%)	1.534 (0.140, 16.753)

[1] (Combined Parts 1 & 2 SABER-Bupivacaine) / (bupivacaine HCl)

Source: C803-028 PERSIST Report Body, p. 129, Applicant's submission.

PERSIST Study

Bruising



Note: Bruise area calculated as a rectangle (length × width) based on length and width recorded in the CRF.
Source: Table 14.3.1.10.2

Source: C803-028 PERSIST Report Body, p. 131, Applicant's submission.

PERSIST Study

Surgical Site Bleeding*

External bleeding at ≥ 1 incision, n (%)	Part 1		Part 2	
	SABER-bupiv (N=45)	Saline placebo (N=47)	SABER-bupiv (N=148)	Bupiv (75 mg) (N=148)
Day of surgery	21 (47%)	18 (38%)	18 (12%)	23 (16%)
Day 4	6 (13%)	5 (11%)	1 (1%)	2 (1%)
Day 8	2 (4%)	1 (2%)	2 (1%)	0
Day 15	0	1 (2%)	1 (1%)	0
Day 29	0	0	0	0
Day 60	-	-	0	0

*Spotting of the dressing, soaking of the dressing, or continuous bleeding
SABER-bupiv = SABER-bupivacaine; bupiv = bupivacaine HCl
Source: Adapted from C803-028 PERSIST Report Body, p. 134, Applicant's submission.

PERSIST Study

Hematoma

Treatment Group	Study Day	Affected Incision	Treatment
SABER-bupiv	4	Umbilical	None
SABER-bupiv	8	Mid-axillary & mid-clavicular	None
SABER-bupiv	4	Umbilical	None
SABER-bupiv	4	Umbilical	None
SABER-bupiv	3 (unscheduled) & 8	Umbilical & epigastric	Ice
SABER-bupiv	4	Umbilical	None
Bupiv HCl	4, 8, & 16	Epigastric & umbilical	Percutaneous drainage (umbilical)
Bupiv HCl	8	Umbilical	None

PERSIST Study

Surgical Site Infection

Study Part	Treatment Group	Infection Description	Day Start, End	Treatment
2	Bupiv HCl	Superficial incisional (umbilical and midaxillary)	54, 78	Bactrim DS
2	Bupiv HCl	Post-procedure cellulitis	3, 26	Bactrim DS
2	SABER-bupiv	Incision site	11, 16	Augmentin
1	SABER-bupiv	Stitch abscess	21, 26	Keflex
2	SABER-bupiv	Superficial incisional (umbilical)	11, 24	Bactrim DS
2	SABER-bupiv	Incision site	32, 60	Keflex, augmentin
2	SABER-bupiv	Superficial incisional (umbilical)	15, 29	Topical Neosporin, Bactrim DS, Keflex

Source: Adapted from C803-028 PERSIST Report Body, Applicant's submission

PERSIST Study

White Blood Cell Count

	Part 1		Part 2	
	SABER-bupiv (N=45)	Saline placebo (N=47)	SABER-bupiv (N=148)	Bupiv HCl (N=148)
Day 4				
Leukocyte increase ≥ 30%	11 (24%)	5 (11%)	28 (19%)	22 (15%)
Neutrophil increase ≥ 30%	14 (31%)	14 (30%)	53 (36%)	41 (28%)
Day 29				
Leukocyte increase ≥ 30%	1 (2%)	2 (4%)	11 (7%)	9 (6%)
Neutrophil increase ≥ 30%	4 (9%)	6 (13%)	19 (13%)	13 (9%)

PERSIST Study

Creatine Kinase (CK)

Creatine Kinase (units/L)	Part 1		Part 2	
	SABER-bupiv (N=45)	Saline placebo (N=47)	SABER-bupiv (N=148)	Bupiv (75 mg) (N=148)
Change from normal to high*+	4 (9%)	2 (4%)	18 (12%)	8 (5%)

*It appears two different reference ranges were used for CK measurement: 33 – 211 units/L and 32 – 294 units/L

+7 patients had elevations > 2x upper limit of normal, six treated with SABER-bupivacaine, one treated with bupivacaine HCl. Single patient treated with SABER-bupivacaine with elevation > 7x ULN and a peri-incisional umbilical bruise surface area 294 cm^2

PERSIST Study

Central Nervous System-Related Adverse Events

Dictionary-Derived Term (Verbatim LogPad Term)	Part 1		Part 2		Parts 1 & 2	Study Total (N=388)
	SABER-Bupivacaine (N=45)	Saline Placebo (N=47)	SABER-Bupivacaine (N=148)	Bupivacaine HCl (N=148)	SABER-Bupivacaine (N=193)	
Subjects reporting at least one solicited adverse event [1], n (%)	25 (55.6%)	29 (61.7%)	103 (69.6%)	97 (65.5%)	128 (66.3%)	254 (65.5%)
Somnolence (Drowsiness)	18 (40.0%)	16 (34.0%)	60 (40.5%)	48 (32.4%)	78 (40.4%)	142 (36.6%)
Nausea (Nausea)	9 (20.0%)	13 (27.7%)	48 (32.4%)	57 (38.5%)	57 (29.5%)	127 (32.7%)
Dizziness (Dizziness)	3 (6.7%)	3 (6.4%)	28 (18.9%)	31 (20.9%)	31 (16.1%)	65 (16.8%)
Headache (Headache)	5 (11.1%)	4 (8.5%)	23 (15.5%)	18 (12.2%)	28 (14.5%)	50 (12.9%)
Vomiting (Vomiting)	2 (4.4%)	3 (6.4%)	10 (6.8%)	15 (10.1%)	12 (6.2%)	30 (7.7%)
Constipation (Constipation)	0 (0.0%)	4 (8.5%)	9 (6.1%)	10 (6.8%)	9 (4.7%)	23 (5.9%)
Pruritus (Itching)	1 (2.2%)	1 (2.1%)	6 (4.1%)	5 (3.4%)	7 (3.6%)	13 (3.4%)
Events Added with Amendment 2, n (%)	**(N=23)**	**(N=22)**	**(N=148)**	**(N=148)**	**(N=171)**	**(N=341)**
Dysgeusia (Metallic Taste in Mouth)	3 (13.0%)	2 (9.1%)	26 (17.6%)	22 (14.9%)	29 (17.0%)	53 (15.5%)
Paraesthesia (Tingling)	0 (0.0%)	0 (0.0%)	2 (1.4%)	6 (4.1%)	2 (1.2%)	8 (2.3%)
Hypoaesthesia (Numbness)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.6%)	2 (0.6%)

Source: Response to Information Request, October 11, 2019, Applicant's submission.

Applicant's Response to CR Letter Deficiencies

Wound-Related Adverse Events

Follow-up from previously completed studies:

- Peri-incisional bruising incidence and size are increased in SABER-treated patients compared to non-SABER control-treated patients
- Less of a difference in the incidence of wound dehiscence between SABER-treated patients and bupivacaine HCl-treated patients
- No consistently identified abnormal wound healing in SABER-treated patients
- No long-term, wound-related complications in SABER-treated patients

Applicant's Response to CR Letter Deficiencies

Central Nervous System-Related Adverse Events

Follow-up from previously completed studies:

- Clinically relevant differences in incidence between SABER-treated patients and bupivacaine HCl-treated patients may have been due to solicited versus spontaneous adverse event reporting across studies
- Headache appeared to be observed more frequently in patients treated with SABER-bupivacaine compared to patients treated with bupivacaine HCl

Safety Summary

Post hoc analyses of data submitted in the initial NDA submission is more supportive of the safety profile of SABER-bupivacaine

Safety Summary (cont'd)

PERSIST Study Results:

There was an increased incidence in bruising, surgical site bleeding on study day 8, and surgical site infection in both Part 1 and 2 of the study and hematoma in Part 2 of the study.

There was an increased incidence in somnolence, headache, pruritus, and dysgeusia in both Part 1 and 2 of the study and dizziness in Part 1 of the study.

Questions?


FDA
U.S. FOOD & DRUG
ADMINISTRATION