CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204803Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 204803	Submission Date: 4/12/13; 8/20/13
Submission Type; Code:	505(b)(2)
Brand/Code Name:	Posimir™
Generic Name:	Bupivacaine
Clinical Pharmacology Primary Reviewer:	David Lee, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology 2
OND Division:	Division of Anesthesia, Analgesia, and Addiction Products
Sponsor:	DURECT Corporation
Relevant NDA(s)	-
Relevant IND(s):	66086
Formulation; Strength(s):	Bupivacaine extended release sterile solution for *injection/infiltration/instillation* into the surgical site; 660 mg bupivacaine/5 mL (132 mg bupivacaine/mL), 13.2% (Proposed by the Applicant)
Proposed Indication:	For the post-surgical analgesia
Proposed Dosage Regimen:	Singe dose, 5 mL administered during surgery

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application for Posimir™*. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable, pending agreement on the labeling language.

*Note: Posimir formulation has also been referred to as Sucrose Acetate Isobutyrate Extended Release (SABER™)-Bupivacaine, Posidur, POSIDUR (SABER-Bupivacaine) 132 mg/mL, SABER-Bupivacaine 120 mg/g, SABER-Bupivacaine [BA] 12 wt%, SABER™-Bupivacaine-12 wt%, SAIB/BA-12 wt%, and Optesia™. Some of the referred terms were used to describe Posimir through out this review.

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of CP Findings

DURECT Corporation submitted a New Drug Application (NDA) for Posimir™ (notated as Posimir or 'SABER-Bupivacaine' throughout this study) under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The Applicant has developed (under IND 66086) Posimir for post-surgical analgesia as injection/infiltration/instillation into the wound before closure. Posimir (660 mg bupivacaine/5 mL (132 mg bupivacaine/mL; 13.2%)) is claimed by the Sponsor as bupivacaine extended-release (ER) sterile solution for injection/infiltration/instillation (e.g., as a trailing subcutaneous injection administered along each side of the incision; as a wound infiltration; or instillation directly into the wound) into the surgical site before closure for post-surgical analgesia. In the submission, the Sponsor claimed that Posimir will be administered once per surgery and deliver bupivacaine over, at least, 72 hours. As such, Posimir will be considered as single dose use only. The total Posimir dose will be 5 mL per surgery. Since

Posimir is administered at the local site(s) as a local acting product, the critical clinical pharmacology aspect of this NDA is to focus on the bupivacaine systemic exposure from the systemic safety purpose.

Several bupivacaine products have been commercially available for over 30 years for the production of local anesthesia or analgesia for surgery (it is noted that EXPAREL (bupivacaine liposome injectable suspension) was approved on 10/28/11 for single-dose infiltration into the surgical site to produce post-surgical analgesia). The Applicant proposed Marcain® (NDA 16964) as the listed drug and appropriately the Applicant conducted a relative bioavailability study between Posimir and Marcain (Study BU-001-IM).

The main focus of this application may be the fact that systemic bupivacaine exposure from the proposed Posimir formulation can be significantly influenced by the tissue properties at the site of administration, which may differ in their degree of vascularization and presence of different types of tissue at or near the wound. Bupivacaine exposure should be comparable for the same dose within studies of the same or similar surgical type. For example, similar bupivacaine exposure results are expected for the two shoulder subacromial studies, BU-002-IM and CLIN005-0006. If there are any differences observed between surgical sites, one may expect the rate of absorption (Cmax) be different due to the vasculature. However, regardless of the surgery or the vasculature, the bupivacaine extent of exposure (AUC values) should be comparable and independent of the type of surgery since Posimir is supposed to be completely retained at the surgery site after intra-wound administration and expected to be 100% absorbed systemically.

The mean plasma concentration-time profiles of bupivacaine after administration of Posimir show that bupivacaine was measurable at least up to 72 hours, with the majority of bupivacaine Tmax (median) occurring at 10 – 48 hours post Posimir administration. The profiles also suggest that there is no dose-dumping (see bupivacaine mean (SD and range) Cmax and AUC values in Table 2 below. Based on the observed bupivacaine systemic profile, Posimir exhibits the characteristics of delayed Tmax. However, Posimir is a locally administered drug and exerts its action locally. The bupivacaine systemic exposure from Posimir should only be used as supportive evidence to determine if Posimir can be categorized as an ER product. Whether Posimir can be categorized as an ER product should also rely on other aspects (e.g. *in vitro* release profile, especially whether Posimir could reduce the dosing frequency clinically compared to IR formulation of bupivacaine, etc.)

It is noted that an interesting observation was made from the results obtained from shoulder surgery studies. The Applicant submitted two arthroscopic shoulder surgery studies. Comparison of mean C_{max} and AUC values from Study BU-002-IM with Study CLIN005-0006, the results showed that Cmax and AUC values from Study BU-002-IM were about 50% lower than Study CLIN005-0006. However, Cmax and AUC values from Study CLIN005-0006 were comparable to all other studies. There were no clear explanations (by the Applicant) why Cmax and AUC values from Study BU-002-IM were approximately 50% less than CLIN005-0006 and all other studies. The plausible explanation provided by the Applicant was that Posimir leaked during the time of drug administration and wound closure.

The following table (Table 1) contains the studies provided by the Applicant. Except as indicated in the table below (SABER01-01), all of the studies submitted in the clinical pharmacology section were reviewed from the clinical pharmacology perspective. It is noted that BU-002-IM and CLIN803-006-0006 were identified as 'pivotal' efficacy trials. The majority of the bupivacaine exposure information came from the studies conducted with the final formulation.

Table 1 Studies submitted under Clinical pharmacology section

Study	P	Surgery	Study Drug (Dose)	Type of Administration	Clinical Pharmacology review
SABER01-01	I	Healthy Subjects	[redacted] (b) (4)		**No**; not a to-be-marketed formulation, and it is not in patients under surgery
CLIN005-0008	I	Healthy Subjects	SABER-Bup 5.0 mL Bupivacaine HCl IV Infusion (20 mL)	Two 2.5 mL Trailing SC Inj.[a]	Y; not an absolute BA study
CLIN004-0001	IIa	Hernia Repair Under general anesthetic	SABER-Bup (2.5, 5.0, 7.5 mL) Bup HCl (15 – 17.5 mL) SABER-Placebo	2 trailing SC inj.	Y
CLIN004-0009	IIa	Hernia Repair With local anesthetic (Marcain);	SABER-Bup (5.0, 7.5 mL) Bup HCl (5.0, 7.5 mL)	Infiltration + trailing inj.	Y; Use of local anesthetic.
CLIN005-0007	II	PILOT study Hernia Repair	SABER-Bup (5.0 mL)	Instillation	**Cursory review:** Posimir 'seeped' out from the wound.'
CLIN803-006-0006	II	Hernia Repair	SABER-Bup (2.5, 5.0 mL) SABER-Placebo	Instillation	Y; linearity information
CLIN005-0006 (06-07)	II	Subacromial Decompression	SABER-Bup (5.0 mL) SABER-Placebo	Subacromial Inj. + SC trailing inj. Subacromial Inj.	Y
BU-002-IM (09-2010)	II	Subacromial Decompression	SABER-Bup (5.0, 7.5 mL) SABER-Placebo Bup HCl 50 mg (20 mL)	Subacromial Inj.	Y; "SABER-bupi fluid leaked"
CLIN005-0002	II	Appendectomy	SABER-Bup (5.0 mL) SABER-Placebo	Trailing Inj.Only Infiltration + trailing inj.	Y
BU-001-IM	II	Hysterectomy	SABER-Bup (5.0 mL) SABER-Placebo Bup HCl 100 mg (40 mL)	Instillation /Infiltration	Y; relative BA
C803-025	III	Laparotomy procedures[b]	SABER-Bup (5.0 mL) SABER-Placebo Bup HCl 30 mL	Instillation /Infiltration	Y

a. Trailing inj. - advancing a needle into the SC space and inject continuously as the needle was withdrawn.

b. Laparotomy, Laparoscopic Cholecystectomy, Laparoscopically Assisted Colectomy

Exposure-Response Relationship

There is no exposure-response relationship for Posimir, since the systemic bupivacaine measured do not reflect the concentrations in the local surgical site(s).

Relative Bioavailability

Study BU-001-IM assessed the relative bioavailability of Posimir compared to Marcaine.
The individual curves from Posimir administration indicated that systemic bupivacaine concentrations may last until 72 hours post administration. Bupivacaine mean Cmax value from Posimir (660 mg bupivacaine) was 625 ng/mL compared to 342 ng/mL with Marcain (100 mg). Bupivacaine mean AUC value Posimir (660 mg bupivacaine) was 36830 ng.h/mL compared to 5740 ng.h/mL with Marcain (100 mg).

Dose linearity

Study CLIN-803-006-0006 provided bupivacaine Cmax and AUC values from 2.5 and 5 mL Posimir (330 mg and 660 mg bupivacaine, respectively). Bupivacaine Cmax and AUC values from the 2.5 and 5.0 mL Posimir exhibited linear pharmacokinetics.

Incision length

It appears that there is no correlation between bupivacaine Cmax or AUC and incision lengths. That is, increase in incision lengths does not increase bupivacaine Cmax or AUC. This observation is reasonable since the entire 5 mL-volume of Posimir was administered at the surgical site.

Pediatric population

Posimir has not been studied in pediatric population. The Applicant seeks waiver for children less than 3 years of age, due to reduced clearance of bupivacaine and benzyl alcohol in the formulation. For children and adolescent (3 to less than 18 years of age), the Applicant seeks deferral. (b) (4)

(b) (4)

Special population

No specific studies were conducted to evaluate the bupivacaine pharmacokinetics in special populations such as hepatic and renal impairments. In general, since bupivacaine is metabolized by the liver, Posimir should be used cautiously in patients with hepatic impairment.

With respect to renal impairment, bupivacaine is known to be excreted by the kidney. Accordingly, Posimir should be used cautiously in patients with renal impairment.

Age

Mean bupivacaine Cmax and AUC values from Trial C803-025 indicated that both Cmax and AUC values lower in younger patients (< 45 yr) than older patients (45 – 65 years and > 65

years), which appears reasonable since elderly may have lower renal function and bupivacaine is known to be excreted by the kidney. Tmax was earlier in younger patients than older patients in the study. Considering this is a local acting drug and the variability (values overlap between younger and older patients), the observed differences between younger and older patients do not warrant dose adjustments.

Gender

Mean bupivacaine Cmax and AUC values from Trial C803-025 indicated that male patients had lower Cmax and AUC values than compared to the female patients. However, considering this is a local acting drug and the variability (values overlap between male and female patients), the observed differences between male and female patients do not warrant dose adjustments.

Body Mass Index

Mean bupivacaine Cmax and AUC values from Trial C803-025 indicated that patients with BMI <18.5 kg/m had lower Cmax and AUC values than patients with BMI >18.5 kg/m. However, considering this is a local acting drug and the variability (values overlap between male and female patients), the observed differences between male and female patients do not warrant dose adjustments.

Drug Interaction

No drug interaction studies were submitted. This is a 505(b)(2) application and the Applicant will rely upon Marcain Label.

Bupivacaine exposure in various types of surgery

The following table (Table 2) contains mean (SD) bupivacaine Cmax and AUC values observed in various different surgical procedures. There were no extremely high Cmax values observed in all studies. The highest bupivacaine Cmax observed value was 2850 ng/mL (Phase 3 Trial C803-025).

Table 2 Mean bupivacaine Cmax and AUC (SD) [range] values from all clinical pharmacology studies

Study	P	Surgery	Study Drug (Dose)	Type of Administration	Cmax ng/mL	AUC ng.h/mL
CLIN005-0008	I	Healthy Subjects	Posimir 5.0 mL[c]	2 x 2.5 mL Trailing abdominal SC	638 ± 368 [238 – 1090]	42058.36 ± 17315.35[a] [26161 – 69230]

CLIN004-0001	IIa	Hernia Repair Under general anesthetic	Posimir 2.5 mL[d], and 5.0 mL	2 x 1.25 mL trailing SC 2 x 2.5 mL trailing SC	2.5 mL: 278 ± 109 [101 – 441] 5 mL: 470 ± 156 [317 – 695]	2.5 mL: 18173 ± 9610 [5792 – 28605] 5 mL: 37263 ± 17078[b] [19474 – 60964]
CLIN004-0009	IIa	Hernia Repair With **local anesthetic (Marcain);**	Posimir 5.0 mL	Infiltration + trailing injection	- values not reliable due to use of local anesthetic in the study	
CLIN803-006-0006	II	Hernia Repair	Posimir 2.5, 5.0 mL)	Instillation	2.5 mL: 467 ± 226 [190 – 854] 5 mL: 867 ± 427 [383 – 1650]	2.5 mL: 18543 ± 9865 [7555 – 37399] 5 mL: 41461 ± 20221[a] [18088 – 78909]
CLIN005-0006 (06-07)	II	Subacromial Decompression	Posimir 5.0 mL	2 x 2.5 mL SC trailing inj. 5 mL Subacromial Inj. N=4	SC: 965 ± 487 [172 – 1940] Subacr: 1146 ± 326 [813 – 1570]	SC: 45081 ± 21981 [7346 – 86448] Subac: 56635 ± 7797[a] [49420 – 66929]
BU-002-IM (09-2010)[e]	II	Subacromial Decompression	Posimir 5.0 mL "leaked"	Subacromial Inj.	593 ± 299 [70 – 1320]	19960 ± 12600[a] [1050 – 59200]
CLIN005-0002	II	Appendectomy	Posimir 5.0 mL	2 x 2.5 mL Trailing SC 2.5 mL Infiltration + 2.5 mL SC trailing inj.	SC 758.0 ± 320 [309 – 1260] Infiltration 1161.4 ± 595 [403 – 2170]	SC 51246.2 ± 22153 [26114 – 86241] Infiltration 69172.8 ± 25716[a] [33365 – 107651]
BU-001-IM	II	Hysterectomy	Posimir 5.0 mL	Instillation /Infiltration	625 ± 310 [119 – 1740]	36830 ± 21060[a] [4470 – 122170]
C803-025	III	Laparotomy procedures[b]	Posimir 5.0 mL	Instillation /Infiltration	laparotomy 956 ± 485 [133 – 1870] laparascopic cholecystectomy 752 ± 307 [357 – 1850] Laparoscopically-assisted colectomy 850 ± 478 [92 – 2850]	laparotomy 41942 ± 24344 [635 – 96625] laparascopic cholecystectomy 30997 ± 12680 [11100 – 68108] Laparoscopically-assisted colectomy 39602 ± 24049[b] [1626 – 136309]

A: AUC0-inf
B: AUC0-last
C: 5 mL Posimir: total 660 mg bupivacaine
D: 2.5 mL Posimir: total 330 mg bupivacaine
E: Comparison of mean Cmax and AUC values from Study BU-002-IM with Study CLIN005-0006, the results showed that Cmax and AUC values from Study BU-002-IM were about 50% lower than Study CLIN005-0006.

In all the following observations are made from the Posimir application:

1. The systemic bupivacaine concentrations were, at least, observed for 72 hours post administration when 5 mL Posimir was administered in all of the surgical procedures; additionally, no dose-dumping was observed;
2. Observed bupivacaine Cmax and AUC values were not too drastically different in abdominal, shoulder and hernia procedures for the same Posimir dose;

3. Observed bupivacaine Cmax and AUC values were not too drastically different when 5 mL Posimir was administered as subcutaneous, infiltration and instillation routes of administration;
4. No correlation was observed between bupivacaine Cmax and AUC and surgical incision lengths, as all 5 mL Posimir was administered in all surgical procedures;
5. No dosage adjustment may be warranted due to weight, age, gender, and race since it is a locally acting product.

2 QBR

2.1 General Attributes of the Drug and Drug Product

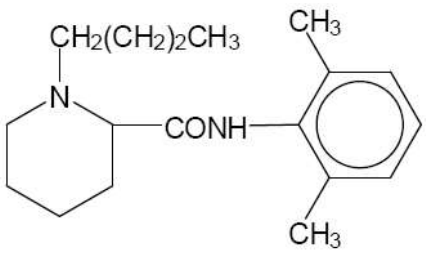
2.1.1 What is Posimir™ and what are the proposed dosage and route of administration?

Posimir (660 mg bupivacaine/5 mL (132 mg bupivacaine/mL; 13.2%)) is bupivacaine extended-release sterile solution for injection/infiltration/instillation (e.g., as a trailing subcutaneous injection administered along each side of the incision; as a wound infiltration; or instillation directly into the wound) into the surgical site before closure for post-surgical analgesia. Single-dose 5 mL volume is to be administered during surgery. Each mL of Posimir contains bupivacaine 132 mg, benzyl alcohol 242 mg, and sucrose acetate isobutyrate (SAIB) 726 mg, a fully esterified sugar derivative. As Posimir is administered, the Applicant stated that the benzyl alcohol diffuses away from the other components, resulting "in the in-situ formation of an extended release biodegradable matrix," a depot matrix formed by SAIB, which slowly releases the bupivacaine through diffusion over 72 hours.

2.1.2 What are some of the known properties of bupivacaine?

Bupivacaine is a locally acting, related chemically and pharmacologically to the amide-type anesthetic. It is a homologue of mepivacaine and is related chemically to lidocaine. Bupivacaine acts supposedly through inhibition of neuronal voltage-gated sodium channels. Local anesthetics primarily block the generation and the conduction of nerve impulses (by increasing the threshold for electrical excitation in the nerve) by slowing the propagation of the nerve impulse and by reducing the rate of rise of the action potential. Chemically, bupivacaine is 1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide with a molecular weight of 288.43 g/mole. Molecular Formula is $C_{18}H_{28}N_2O$. Bupivacaine has the following structural formula (Figure 1):

Figure 1 Bupivacaine structural formula



2.1.3 What is the to-be-marketed formulation?

During the development program, Posimir formulation has also been referred to as Sucrose Acetate Isobutyrate Extended Release (SABER™)-Bupivacaine, Posidur, POSIDUR (SABER-Bupivacaine) 132 mg/mL, SABER-Bupivacaine 120 mg/g, SABER-Bupivacaine [BA] 12 wt%, SABER™-Bupivacaine-12 wt%, SAIB/BA-12 wt%, and Optesia™. It is noted that through out this review, the some of the referred terms were used to describe Posimir. The target manufacturing fill volume of Posimir is (b) (4) and the Applicant stated that this will ensure that 5 mL can be withdrawn from the vial for administration. The to-be-marketed (TBM) formulation was used in most of the clinical studies. All relevant clinical pharmacology studies were conducted with the TBM formulation (Table 3).

Table 3 Composition and Ingredient Functions of Posimir

Ingredient	**Composition % w/w**	**Composition mg/mL[a]**	**Amount (mg) Administered in a 5 mL Dose**	**Function**	**Specification**
Bupivacaine	12	132	660	Active	In-House Specification
Sucrose acetate isobutyrate (SAIB)	66	726	3630	Extended release agent	In-House Specification
Benzyl alcohol	22	242	1210	Solvent	NF, EP
(b) (4)					
Total	**100**	**1100**	**5500**	**-**	**-**
[a] The density of SABER-Bupivacaine is 1.1 g/mL at 25°C, therefore the concentration expressed as 12% w/w is equivalent to 13.2% w/v					

It should be noted that there was one other early Phase 1 formulation (Table 4) which was used in Study SABER01-01; a cursory review was conducted for this healthy subject subcutaneous injection study (see Section 2.xxx).

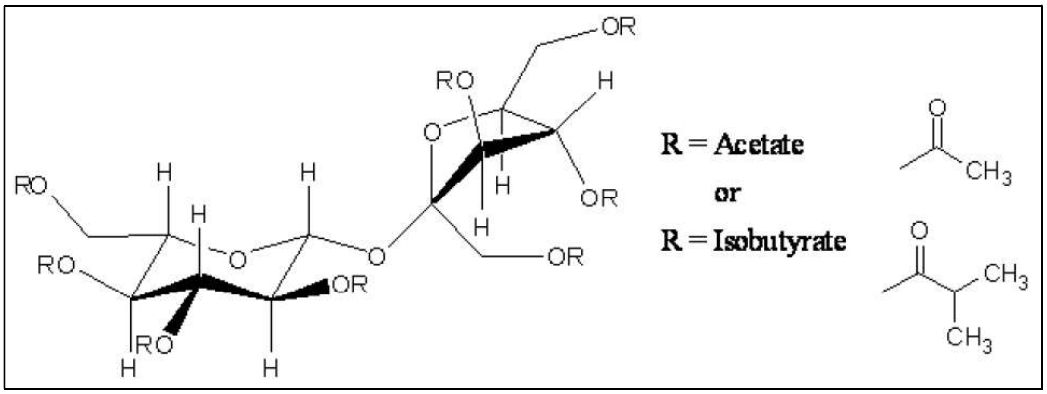
Table 4 Composition of SAIB (b) (4) Early Formulation used in Phase 1

(b) (4)

The SAIB/(b) (4) formulation of bupivacaine was used in Phase 1 study, SABER01-01.

The Applicant stated that they have selected SAIB (Figure 2 for inclusion in the Posimir formulation since it has high hydrophobicity and viscosity, which is the basis of the extended release feature of the product. SAIB is a hydrophobic, fully esterified sucrose derivative. As a mixed ester, SAIB is a non-crystalline, non-polymeric clear viscous liquid.

Figure 2 Structure of Sucrose Acetate Isobutyrate (SAIB)



2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials for Posimir?

The Applicant has chosen seven randomized trials for pooling the integrated summary of efficacy. Trials were based on double-blind, controlled (SABER-Placebo, and/or bupivacaine HCl), parallel design and used SABER-Bupivacaine 5 mL. The Applicant stated that five trials utilized SABER-Placebo (CLIN-803-006-0006, CLIN005-0010, CLIN005-0006, C803-017, and C803-025, Cohort 3). Two trials utilized both Posimir and bupivacaine HCl (BU-001-IM and BU-002-IM). All trials allowed the use of rescue medication for pain that was not controlled by the study drug. Generally post-treatment follow-up for the assessment of efficacy and safety was generally for 14 days. However, some trials had long-term follow-up visits or a telephone follow-up (30 days post administration: C803-025) to examine the surgical sites for healing (CLIN-803-006-0006, BU-002-IM, BU-001-IM, and C803-017e).

From seven trials, the Applicant stated that two trials were considered as primary adequate and well-controlled studies, CLIN-803-006-0006 and BU-002-IM. The two co-primary efficacy endpoints were measured in the trials were 1) mean pain intensity on movement AUC (time-normalized AUC) during the period 0 to 72 hours post-dose, and, 2) mean total morphine-equivalent opioid dose for supplemental analgesia. The Applicant stated that both trials showed statistically significant reductions in pain intensity on movement (AUC 1-72 h) and opioid use over 72 hours. Trials CLIN-803-006-0006 and BU-002-IM are briefly described below. It is noted that bupivacaine concentrations were collected from both trials.

CLIN-803-006-0006 was a randomized, double-blind, placebo-controlled hernia repair trial using the standard Lichtenstein tension-free surgical technique under general anesthesia (conducted in Australia and New Zealand). Patients received one of two doses of SABER-Bupivacaine (2.5 or 5 mL) or matching volumes of SABER-Placebo (2.5 or 5 mL). One-half of the drugs were instilled with a syringe (needle-free tip) into the floor of the inguinal canal after the reinforcing mesh was sutured in place. The external oblique aponeurosis was sutured and the other one-half of the drug was instilled into the subcutaneous space before final closure of the skin with sutures. The two co-primary efficacy endpoints were the mean pain intensity AIC on movement normalized over 1-72 hours post-surgery, and, the proportion of subjects who received opioid rescue medication 0-15 days post-surgery. The Applicant submitted following figure (Figure 3) and the summary of the results in below table (Table 5):

Figure 3 Mean Pain Intensity on Movement Normalized AUC (1-48 and 1-72 Hours)

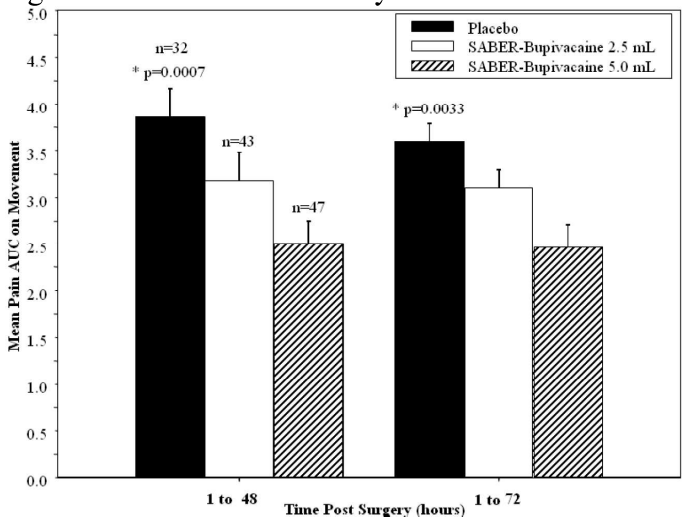


Table 5 Summary of Efficacy Results for Study CLIN-803-006-0006

	SABER-Bupivacaine 2.5 mL (N=43)	SABER-Bupivacaine 5 mL (N=47)	SABER-Placebo [1] (N=32)
Pain Intensity on Movement $AUCs_{1-72}$ Including Opioid Rescue Pain – ITT			
LS Mean (SE)	3.4 (0.26)	2.7 (0.25)	3.9 (0.29)
LS Mean difference from SABER-Placebo (SE)	-0.53 (0.359)	-1.14 (0.353)	
P-value [2]	0.2372	0.0031	
Exploratory Analysis - Pain Intensity on Movement AUC_{1-72}, Scheduled Pain Only – ITT			
LS Mean (SE)	3.2 (0.25)	2.6 (0.25)	3.7 (0.28)
LS Mean difference (SE)	-0.52 (0.349)	-1.11 (0.343)	
P-value [2]	0.2347	0.0029	
Pain Intensity on Movement $AUCs_{1-72}$: Sensitivity Analysis Using Half-Life Approach - ITT			
LS Mean (SE)	3.4 (0.27)	2.8 (0.26)	4.0 (0.30)
LS Mean difference (SE)	-0.57 (0.374)	-1.17 (0.368)	
P-value [2]	0.2223	0.0035	
Morphine Equivalent Use 0-72 Hours Using Non Parametric Approach - ITT			
Mean (SE)	11.2 (2.01)	7.9 (1.60)	23.5 (6.85)
Median	5	2.5	12.5
Median difference [3]	-5	-7.5	
P-value [4]	0.1333	0.0085	

Source: Study CLIN-803-006-0006 CSR Addendum, Table 6, Table 3, Table 2, and Table 12
[1] Aggregated group of SABER-Placebo 2.5 mL and SABER-Placebo 5 mL.
[2] Based on ANOVA model with study site and treatment group as factors, using Dunnett test to adjust for multiple comparisons.
[3] Hodges-Lehmann estimates for median difference.
[4] Wilcoxon rank-sum test.

The Applicant stated that the mean pain intensity on movement normalized AUC from 1 to 72 hours was significantly improved in the SABER-Bupivacaine 5.0-mL group versus the placebo group. However, no statistically significant differences were observed between the SABER-Bupivacaine 2.5-mL group and the placebo group.

BU-002-IM was a randomized, double-blind, placebo and active controlled study in arthroscopic subacromial decompression shoulder surgery (conducted in Europe). Patients received Posimir 5 mL, SABER-Placebo 5 mL, or bupivacaine HCL (20 ml, 0.25%, 50 mg). At the end of the surgery, the drug was instilled with a blunt tipped needle into the subacromial space through an arthroscopic portal. The two co-primary endpoints were pain intensity on movement AUC 1-72 post-surgery, and, total use of opioid rescue analgesia 0 to 72 hours after surgery (MED0-72). The pain intensity was compared between the Posimir and SABER-Placebo groups. The Applicant submitted the summary of the results in below table (Table 6):

Table 6 Summary of Efficacy Results for Study BU-002-IM

	SABER-Bupivacaine 5 mL (N=53)	SABER-Placebo 5 mL (N=25)	Bupivacaine HCl 20 mL (N=29)
Pain Intensity on movement AUC 1-72 hours - ITT Pre-specified Analysis			
LS Mean (SE)	5.0 (0.32)	6.3 (0.43)	5.0 (0.40)
LS Mean difference (SE)	-1.27 (0.497)		
P-value [1]	0.0122		
Sensitivity Analysis of pain on Movement AUC 1-72 hours - ITT			
LS Mean (SE)	5.0 (0.40)	6.1 (0.50)	4.9 (0.45)
LS Mean difference (SE)	-1.12 (0.508)		
P-value [1]	0.0305		
Morphine-Equivalent Use 0-72 Hours - ITT			
Mean (SE)	14.2 (4.00)	22.9 (5.03)	13.3 (3.47)
Median	4.0	12.0	8.0
Median difference [2]	-8.0		
P-value [3]	0.0130		

Source: BU-002-IM CSR Addendum, Table 5/Table 11 and ISE Table 7

Note: P-values are for the comparison between SABER-Bupivacaine and SABER-Placebo.

[1] From ANOVA with treatment and pooled sites as main effects.

[2] Hodges-Lehmann estimates for median difference.

[3] Wilcoxon rank-sum test.

With respect to overall safety findings, the Applicant stated that a total of 1075 patients or healthy subjects were included in the safety population. The volume of study drug administered ranged from 2.5 to 7.5 mL (trials using the 7.5 mL dose were completed prior to the Agency' clinical hold on the 7.5 mL dose) for Posimir. As stated above the proposed volume or the mg bupivacaine for Posimir is 5 mL or 660 mg bupivacaine per surgery. Of all patients who received Posimir, seventy one patients received 7.5 mL (990 mg bupivacaine) Posimir plus 50-75 mg of bupivacaine HCl injection, as the protocol design (two hernia trials, CLIN004-0001 and CLIN004-0009. Out of seventy one patients, thirty three patients had bupivacaine exposure information. In the CLIN004-0001 hernia trial, the mean C_{max} was 954 (range: 213 – 1960) ng/mL. In the CLIN004-0009 hernia trial, the mean C_{max} was 1479 (range: 826 – 2150) ng/mL. It is noted that as there was little evidence that the 7.5 mL dose of Posimir provided better analgesia than the 5 mL dose, subsequent trials conducted after hernia trials utilized 5 mL dose.

2.2.2 Is there a bupivacaine-concentration-response relationship for Posimir?

Posimir is a locally administered drug and exerts its action locally, thus, bupivacaine systemic exposure cannot be linked to its efficacy directly.

2.2.3 Is there any relationship between bupivacaine concentration and incision length?

Bupivacaine systemic concentrations may be significantly influenced by the tissue properties at the site of administration. Since Posimir was administered in several different surgical procedures. The procdures will dictate the lengths of the incision, e.g., incision lengths in Study CLIN005-0006 (rotator cuff surgery) were from 3 to 8 cm, whereas, in Study C803-025 (laparatomy related surgies) incision lengths were from 3 to 35 cm). The relationship between bupivacaine concentrations (Cmax and AUC) and incision lengths were explored.

Trial C803-025 was a multi-center, randomized, double-blind, active- and placebo-controlled trial in patients undergoing general surgical procedures: a) laparotomy: there were no restrictions on laparotomy incision length (typically with a single incision of 20 cm or more); b) laparoscopic cholecystectomy: there were no restrictions on the number of laparoscopic portals (typically with 4 laparoscopic ports inserted) which the larger port incisions received a larger volume of test drug; c) laparoscopically-assisted colectomy: incision lengths of up to 15 cm was allowed. Patients received Posimir 5.0 mL (660 mg bupivacaine – via instillation), Sensorcaine 30 mL 0.5% solution (150 mg – via infiltration with needle), or SABER- Placebo (instillation).

The results indicated that that there were little or no differences in bupivacaine exposure with increased incision lengths [see scatter plots (Cmax - Figures 4, 5, 6 and AUC - Figures 7, 8, 9, respectively, for laparotomy, laparoscopic Cholecystectomy, and Laparoscopically Assisted Colectomy procedures)]. The findings suggest that bupivacaine exposure is not correlated to the lengths of incision made during the surgery, which indicated that bupivacaine exposure depends on the total amount of bupivacaine administered at the surgery site. This observation is reasonable since the entire 5 mL-volume of Posimir was administered at the surgical site.

Bupivacaine Cmax:

Figure 4 Laparotomy procedure. Scatter Plot of bupivacaine Cmax versus incision length

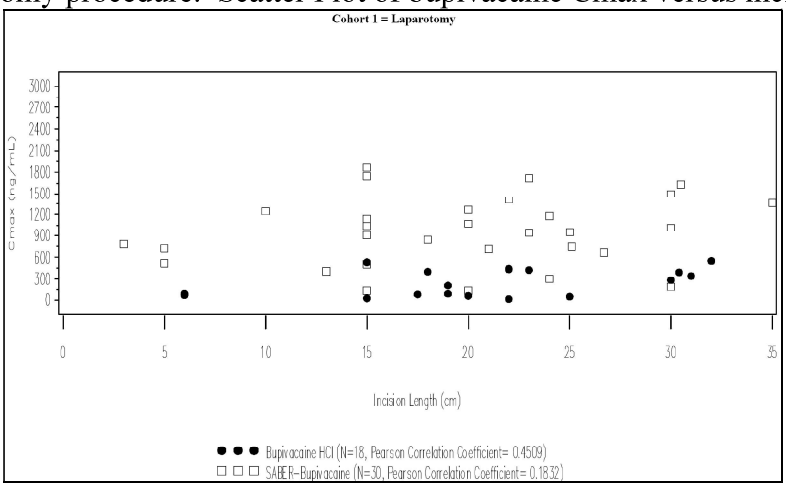


Figure 5 Laparoscopic Cholecystectomy procedure. Scatter plot of bupivacaine Cmax versus incision length

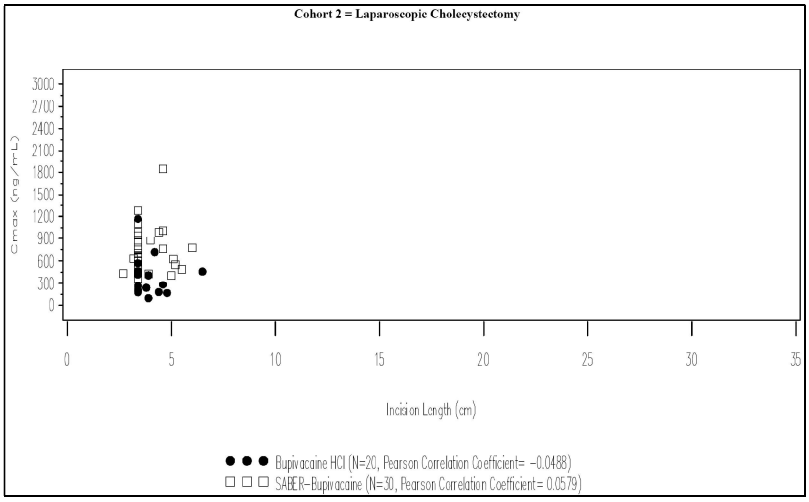
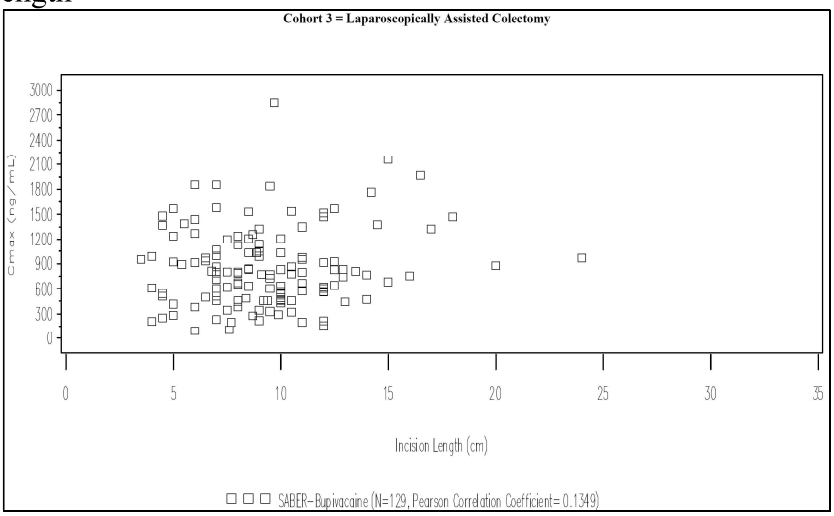


Figure 6 Laparoscopically Assisted Colectomy procedure. Scatter plot of bupivacaine Cmax versus incision length



Bupivacaine AUC:

Figure 7 Laparotomy procedure. Scatter plot of AUC0-last versus incision length

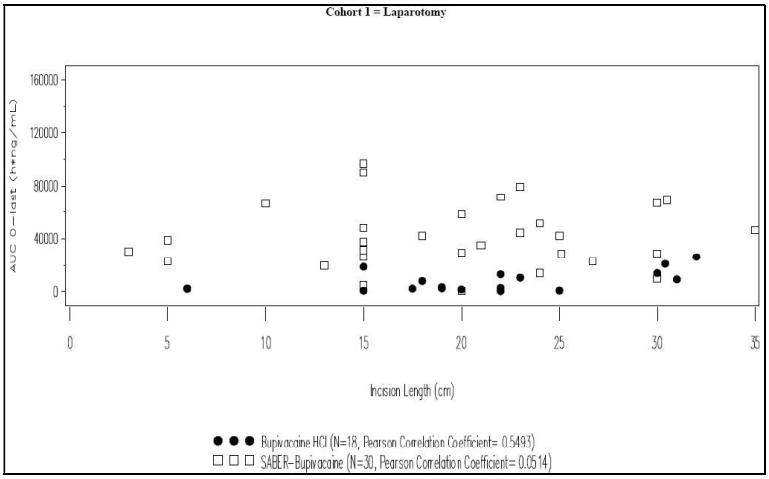


Figure 8 Laparoscopic Cholecystectomy procedure. Scatter plot of AUC0-last versus incision length

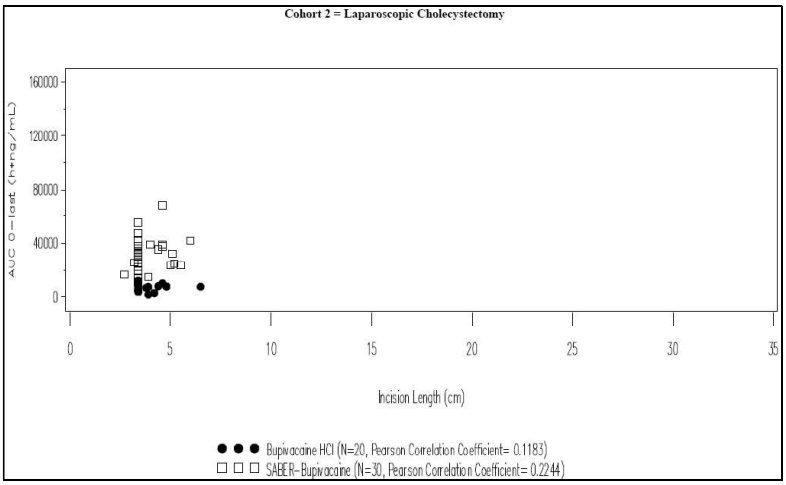
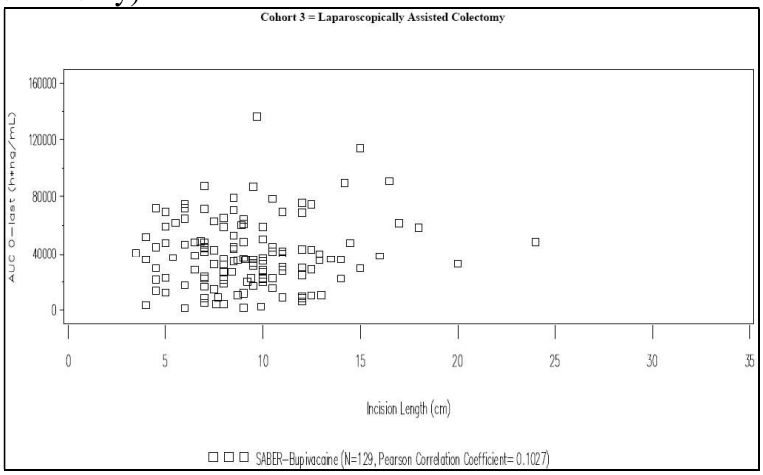


Figure 9 Laparoscopically Assisted Colectomy procedure. Scatter plot of AUC0-last versus incision length (Posimir only)



As with Trial C803-025, the results from Study CLIN005-0006 (rotator cuff surgery; Figures 10, 11 and 12) and Study BU-001-IM (hysterectomy surgery; Figure 13), it appears that there is no correlation between bupivacaine concentration (Cmax and AUC) and incision lengths.

Figure 10 All subjects in CLIN005-0006: Cmax (top) and AUC (bottom) versus incision lengths. Treatment 1 (subcutaneous and subacromial injections)

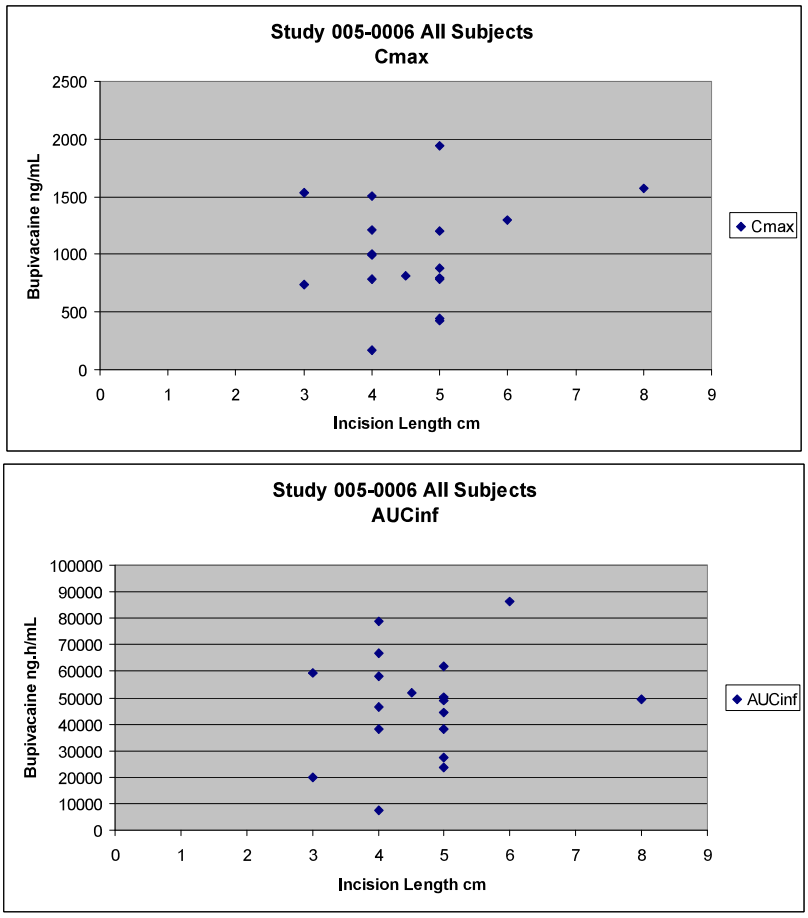
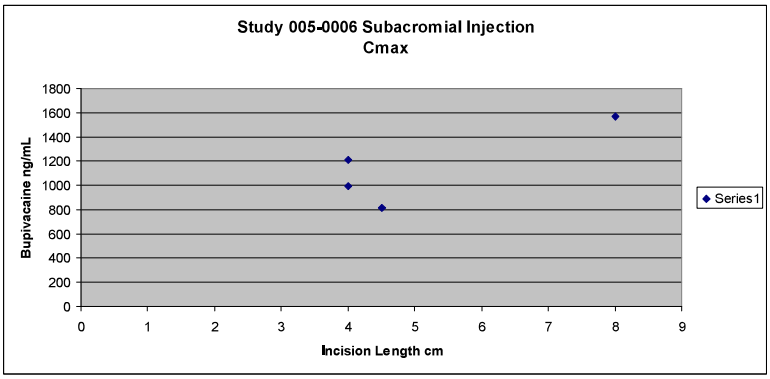


Figure 11 CLIN005-0006: Cmax (top) and AUC (bottom) versus incision lengths. Treatment 5 (5.0 mL subacromial space injection during wound closure)



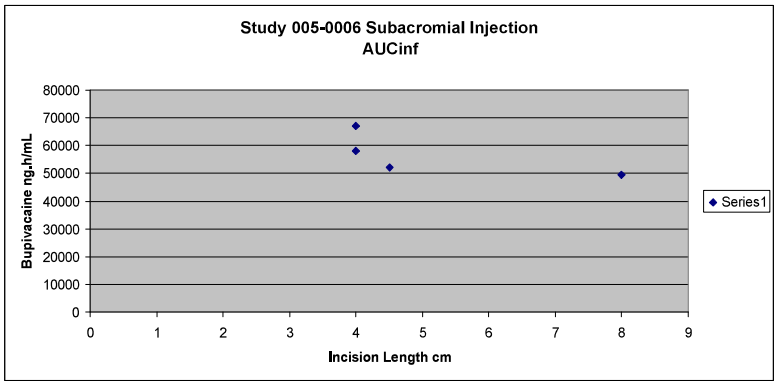
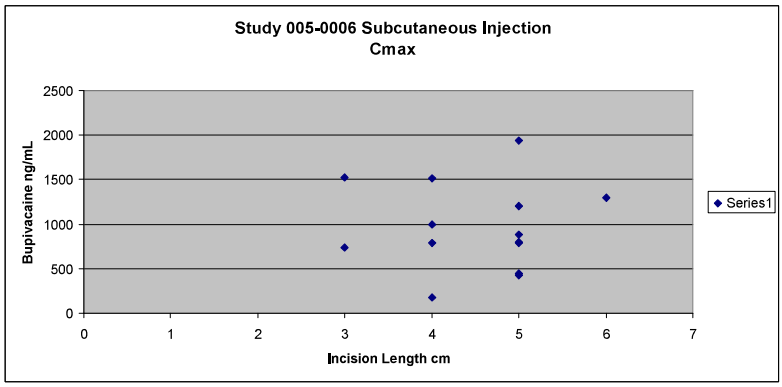


Figure 12 CLIN005-0006: Cmax (top) and AUC (bottom) versus incision lengths. Treatment 1 (5.0 mL 2 trailing SC injection along side of the incision line after wound closure)



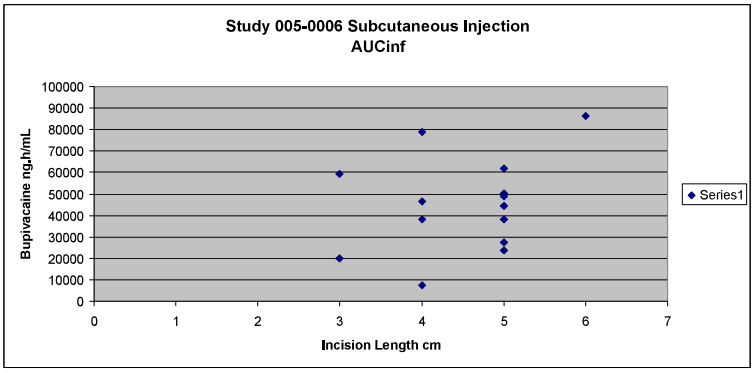
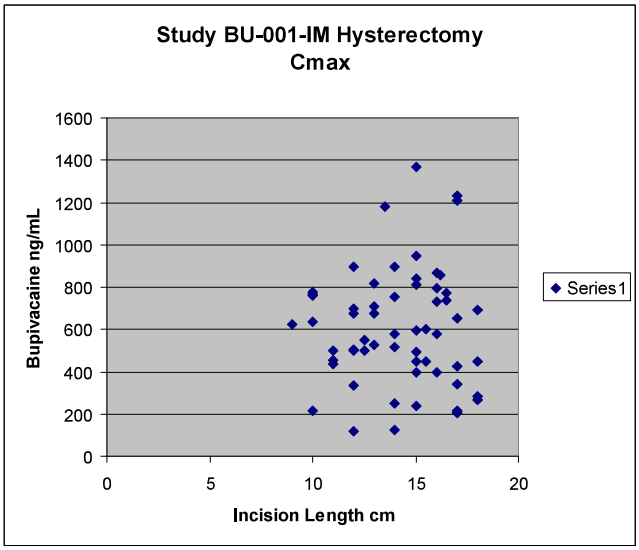
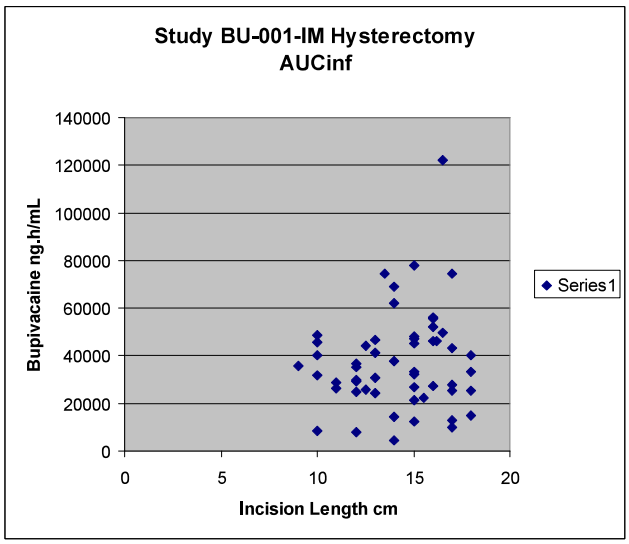


Figure 13 BU-001-IM (Hysterectormy): Cmax (top) and AUC (bottom) versus incision lengths





2.2.4 What are known bupivacaine clinical pharmacology information?

The following Clinical Pharmacology information was obtained from Marcaine (N16964) Label:

> CLINICAL PHARMACOLOGY
> Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.
> Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with

normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine. Therefore, incremental dosing is necessary. Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

Pharmacokinetics:
(Distribution) The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 mcg/mL) usually reduces the rate of absorption and peak plasma concentration of MARCAINE, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.
The onset of action with MARCAINE is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with MARCAINE than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced. The onset of action following dental injections is usually 2 to 10 minutes and anesthesia may last two or three times longer than lidocaine and mepivacaine for dental use, in many patients up to 7 hours. The duration of anesthetic effect is prolonged by the addition of epinephrine 1:200,000.

Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug the higher the percentage of drug bound to plasma proteins.

Local anesthetics appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/ maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. MARCAINE with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal

circulation. Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Pharmacokinetic studies on the plasma profile of MARCAINE after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

After injection of MARCAINE for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours. Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of MARCAINE in adults is 2.7 hours and in neonates 8.1 hours.

In clinical studies, elderly patients reached the maximal spread of analgesia and maximal motor blockade more rapidly than younger patients. Elderly patients also exhibited higher peak plasma concentrations following administration of this product. The total plasma clearance was decreased in these patients.

Amide-type local anesthetics such as MARCAINE are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecoloxylidine is the major metabolite of MARCAINE.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine. When administered in recommended doses and concentrations, MARCAINE does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

Additionally, the literature information (Clinical Pharmacology Online) indicates that:

- Bupivacaine is excreted renally; approximately 6% is excreted as unchanged drug.
- Bupivacaine half-life is 3.5 +/- 2 hours in adults.
- Metabolism is primarily in the liver via conjugation.

- Formation of major metabolite pipecolylxylidine appears to be mediated by the CYP3A subfamily (N-dealkylation) - a cDNA expressed form of human CYP3A4 catalyzed the biotransformation of bupivacaine into pipecolylxylidine; however, formation of pipecolylxylidine by N-dealkylation of bupivacaine does not appear to account for a large percentage of the drug's metabolism, and the clinical significance of concurrent use of CYP3A4 inhibitors and bupivacaine is unknown.
- CYP2C19 and CYP2D6 may also metabolized bupivacaine into pipecolylxylidine slightly
- Major metabolite pipecoloxylidine is hydroxylated followed by glucuronidation.

2.2.5 What are the PK characteristics of the bupivacaine from Posimir?

2.2.5.1 What are the single dose PK parameters in healthy subjects after a subcutaneous injection?

Study CLIN005-0008 (subcutaneous) in lower abdomen in healthy subjects 5 mL SABER™ – Bupivacaine

Study CLIN005-0008 was an open-label, crossover, Phase 1 study to assess the safety and performance of Bupivacaine Transdermal Therapeutic System (TTS)(as a comparator; a transdermal 140-cm^2 delivery system containing 3% bupivacaine (140-cm^2 Bupivacaine TTS contains 40.8 mg of bupivacaine base)), an intravenous bupivacaine infusion (8 mg bupivacaine as 4-h infusion, 2 mg/hr), and SABER™–Bupivacaine in healthy male and female volunteers. SABER™ – Bupivacaine (12.0 wt%) 5 mL was administered as 2 trailing injections of 2.5 mL each into abdominal subcutaneous space (location was not specified). The trailing injections were accomplished by advancing a needle into the subcutaneous space and injecting SABER™ – Bupivacaine continuously as the needle was withdrawn**.** Following figures (Figures 14 and 15) are individual and mean bupivacaine plasma concentration-time profiles following SABER-bupi two trailing abdominal subcutaneous injections administrations, respectively. Profiles from other parts (Parts 1 and 2) are not presented.

Figure 14 Plot of individual Subject Bupivacaine Plasma Concentration-Time Profiles Following 5 mL SABER-Bupivacaine as two 2.5 mL trailing abdominal subcutaneous injections

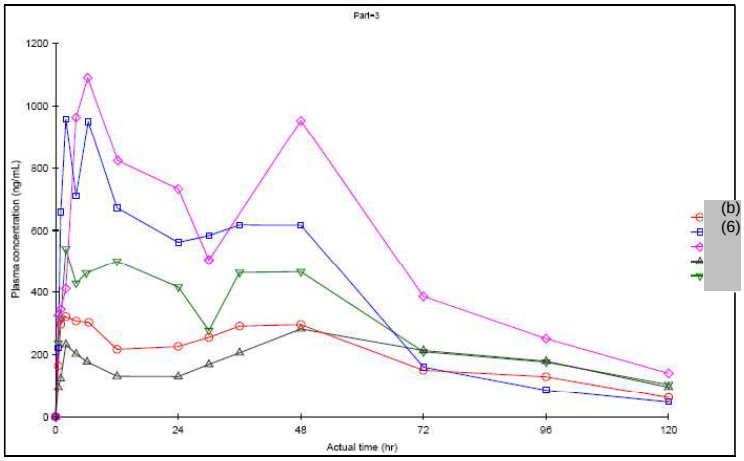
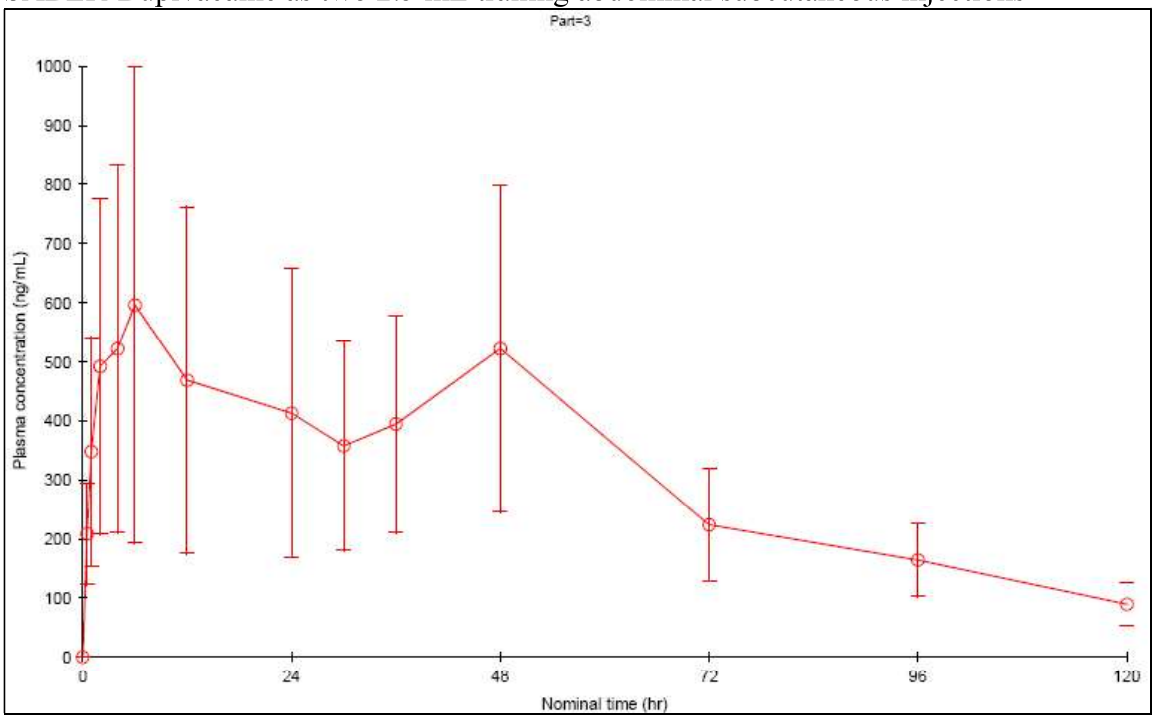


Figure 15 Mean (SD) Bupivacaine Plasma Concentration-Time Profiles Following 5 mL SABER-Bupivacaine as two 2.5 mL trailing abdominal subcutaneous injections



The following table (Table 7) contains bupivacaine pharmacokinetic parameters from 2 trailing SC injections in healthy subjects.

Table 7 Bupivacaine Plasma Pharmacokinetics Parameters from 5 mL SABER-Bupivacaine as two 2.5 mL trailing abdominal subcutaneous injections

Subject	AUC0-∞ ng h/mL	AUC0-t ng.h/mL	Cmax ng/mL	λz	t1/2 h	Tmax h
(b) (6)	26161.15	23198.44	321	0.02	33.89	2
	45329.4	43523.17	957	0.03	26.92	2
	69230.29	62604.35	1090	0.02	32.81	6.28
	28011.97	22297.45	282	0.02	41.48	48
	41559	36207.68	540	0.02	35.67	2
N	5	5	5	5	5	5
Mean	**42058.36**	**37566.22**	**638**	**0.021**	**34.152**	**12.056**
SD	**17315.35**	**16611.8**	**368.407**	**0.003**	**5.246**	**20.179**
Min	26161.15	22297.45	282	0.02	26.92	2
Median	41559	36207.68	540	0.02	33.89	2
Max	69230.29	62604.35	1090	0.03	41.48	48
CV%	41.2	44.2	57.7	15.9	15.4	167.4

Mean bupivacaine concentration-time profile appears to show that bupivacaine was measurable at least up to 72 hours. Bupivacaine Cmax and AUC values after two trailing abdominal subcutaneous injections were 638 ng/mL and 42058 ng.h/mL, respectively, in healthy subjects.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Pharmacokinetics of bupivacaine from Posimir administration in various surgical procedures was evaluated. The bupivacaine pharmacokinetic information is presented according to the surgical procedures, namely, inguinal hernia repair, orthopedic (rotator cuff repair/shoulder surgery), and abdominal surgeries.

2.2.5.2.1 Inguinal hernia repair surgeries

There were 4 hernia studies: CLIN004-0001, CLIN004-0009, CLIN005-0007, and CLIN803-006-0006. CLIN005-0007 was considered as a 'pilot' study and a comprehensive review was not conducted for this study.

Study CLIN004-0001 inguinal hernia repair single dose 2.5, 5 and 7.5 mL SABER-bupivacaine (subcutaneous) under general anesthesia (Note: 7.5 mL SABER-Bupivacaine dose was administered with Sensorcaine)

Study title: A pharmacokinetic/pharmacodynamic dose escalation study with subcutaneously administered SABER-Bupivacaine and/or Bupivacaine HCl following open inguinal hernia repair

Study CLIN004-0001 was a single-blind, active-controlled, Phase IIa study to assess the pharmacokinetics/pharmacodynamics, safety and tolerability of 12.0wt% SABER-Bupivacaine (subcutaneous injection) in open inguinal hernia repair patients (under general anesthesia). This

study was conducted as three-part studies, Cohorts 1, 2 and 3. Some groups received 0.5% bupivacaine (Sensorcaine®) as a comparison purpose. Of note, Cohort 2, treatment group 2 and Cohort 3, treatment group 2 received both SABER-Bupivacaine and 0.5% bupivacaine (Sensorcaine®; it is noted that Sensorcaine was infiltrated into the wound). SABER-Bupivacaine was administered as two trailing subcutaneous injections along each side of the incision (an incision total length of 5 cm; e.g., for 5 mL dose: 0.50mL/cm administered along each side of the incision, 2.5 mL per side). Treatment groups are as follows (Table 8).

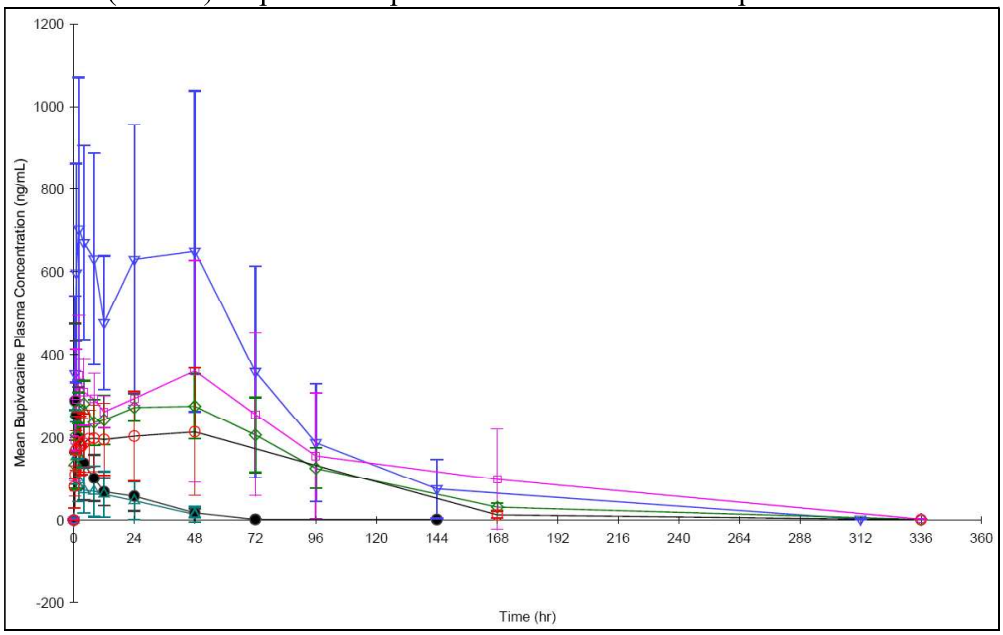
Table 8 Treatment groups for Study CLIN004-0001

Study Cohort	**SABER-Bupivacaine**	**Sensorcaine® 0.5% Bupivacaine (5 mg/mL)**	**Total Bupivacaine Dose**
Cohort 1	2.5 mL	0	330 mg
Cohort 2	-	-	-
Trt. Group 1	5 mL	0	660 mg
Trt. Group 2	5 mL	10 mL	710 mg
Trt. Group 3	-	5 mL+ 10 mL	75 mg
Cohort 3			
Trt. Group 2	7.5 mL	10 mL	1040 mg
Trt. Group 3	-	7.5 mL + 10 mL	87.5 mg

For a comparison purpose, bupivacaine pharmacokinetic information from Cohort 1 and Cohort 2, treatment group 1 are compared, that is, 2.5 mL and 5 mL SABER-Bupivacaine. Additionally, Cohort 2, treatment group 2 and Cohort 3 treatment group 2 are compared, that is, SABER-Bupivacaine (5 and 7.5 mL) plus Sensorcaine (10 mL) treatment groups.

Figure 16 represents mean bupivacaine plasma concentration profile of all cohorts.

Figure 16 Mean (+/- SD) Bupivacaine plasma concentration-time profiles from all treatments



○ Cohort 1, Treatment 1. SABER+Saline (330.0 mg)
◇ Cohort 2, Treatment 2. SABER+0.5% bupiv (710.0 mg)
▽ Cohort 3, Treatment 2. SABER+0.5% bupiv (1040.0 mg)
□ Cohort 2, Treatment 1. SABER+Saline (660.0 mg)
△ Cohort 2, Treatment 3. 0.5% bipiv+0.5% bupiv (75 mg)
● Cohort 3, Treatment 3. 0.5% bipiv+0.5% bupiv (87.5 mg)

The following figures (Figures 17 and 18, respectively) represent individual and mean bupivacaine profiles from SABER-Bupivacaine treatments for 2.5 and 5 mL only (Cohort 1 and Cohort 2, treatment group 2).

Figure 17 Individual bupivacaine plasma concentration-time profiles from Cohort 1 and Cohort 2, treatment group 1, respectively (330 mg (top); 660 mg (bottom))

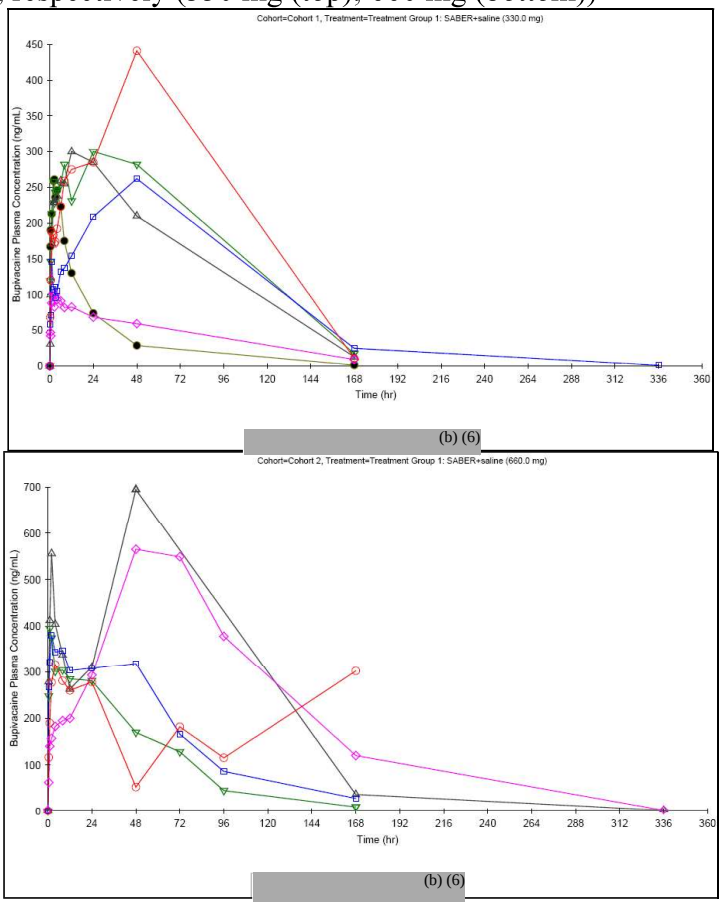
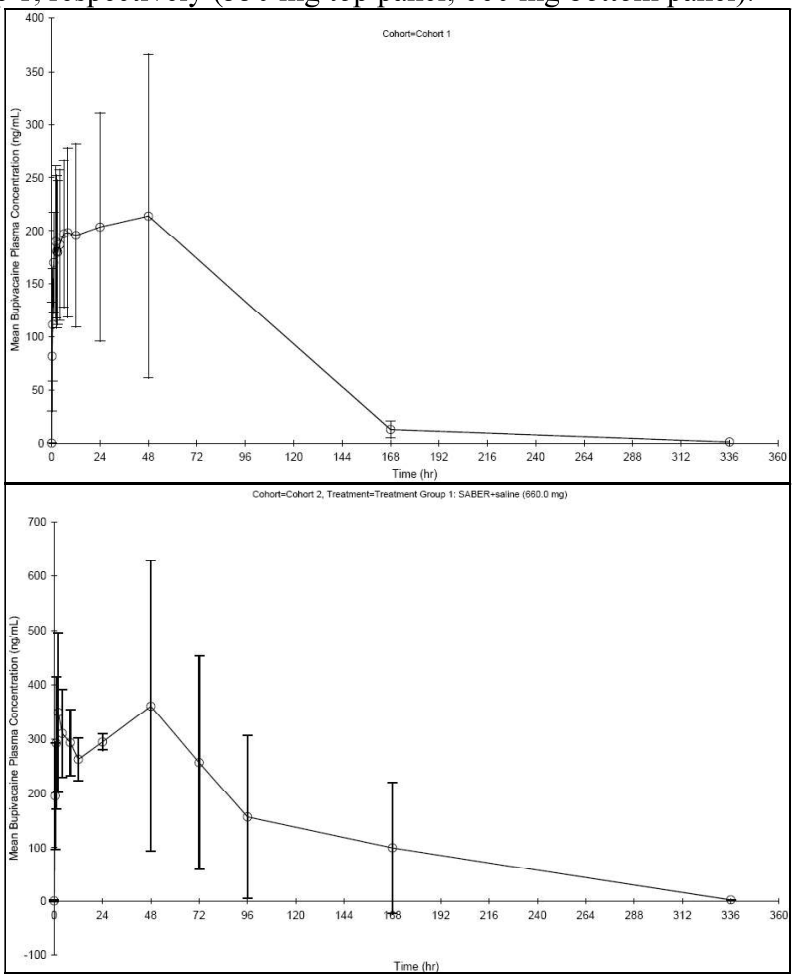


Figure 18 Mean (+/- SD) Bupivacaine plasma concentration-time profiles Cohort 1 and Cohort 2, treatment group 1, respectively (330 mg top panel; 660 mg bottom panel).



The following table (Table 9) represents pharmacokinetic parameters from Cohort 1 and Cohort 2, treatment group 1.

Table 9 Pharmacokinetic parameters from Cohort 1 and Cohort 2, treatment group 1

Cohort	**Treatment**	**Subject**	**λ_z (1/hr)**	**$t_{1/2}$ (hr)**	**T_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{last} (hr*ng/mL)**	**AUC_{144hr} (hr*ng/mL)**
Cohort 1	Treatment Group 1: SABER+saline Total Bupivacaine: 330.0 mg							
		N	3	3	6	6	6	6
		Mean	0.0211	35.1	22.8	278	18173	17554
		SD	0.0062	11.5	21.1	109	9610	9337
		Min	0.0145	25.8	2.0	101	5792	5746
		Median	0.0221	31.4	18.0	281	21723	20496
		Max	0.0268	47.9	48.0	441	28605	28221
		CV%	29.6	32.8	92.9	39.3	52.9	53.2
Cohort 2	Treatment Group 1: SABER+saline Total Bupivacaine: 660.0 mg							

		N	3	3	5	5	5	5
		Mean	0.0217	32.7	20.6	470	37263	33430
		SD	0.0039	5.9	25.0	156	17078	14629
		Min	0.0179	27.0	1.0	317	19474	19172
		Median	0.0215	32.3	4.0	395	29631	26613
		Max	0.0257	38.8	48.0	695	60964	52400
		CV%	18.0	18.0	121.5	33.1	45.8	43.8

The following table (Table 10) represents pharmacokinetic parameters from Cohort 2, treatment group 2 and Cohort 3 treatment group 2.

Table 10 Pharmacokinetic parameters from Cohort 2, treatment group 2 and Cohort 3 treatment group 2

Cohort	**Treatment**	**Subject**	**λ_z (1/hr)**	**$t_{1/2}$ (hr)**	**T_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{last} (hr*ng/mL)**	**AUC_{144hr} (hr*ng/mL)**
Cohort 2	Treatment Group 2: SABER+0.5% Bupivacaine Total Bupivacaine: 710.0 mg							
		N	5	5	5	5	5	5
		Mean	0.0180	39.2	25.2	311	27893	25477
		SD	0.0025	5.5	22.5	61	7370	6672
		Min	0.0150	33.0	2.0	232	21977	19532
		Median	0.0172	40.4	24.0	342	23979	23272
		Max	0.0210	46.1	48.0	371	37782	34386
		CV%	14.1	14.0	89.4	19.6	26.4	26.2
Cohort 3	Treatment Group 2: SABER+0.5% Bupivacaine Total Bupivacaine: 1040.0 mg							
		N	24	24	44	44	44	43
		Mean	0.0220	33.1	21.0	954	55347	55358
		SD	0.0052	7.8	20.3	402	27102	26652
		Min	0.0143	19.6	1.0	213	15480	15480
		Median	0.0213	32.5	16.0	873	49595	49242
		Max	0.0353	48.6	48.0	1960	152058	152058
		CV%	23.5	23.5	96.6	42.2	49.0	48

Mean bupivacaine concentration-time profile appears to show that bupivacaine was measurable at least up to 72 hours. Bupivacaine Cmax and AUClast values after 2.5 and 5 mL SABER-Bupivacaine as two trailing abdominal subcutaneous injections were 278 ng/mL and 18173 ng.h/mL and 470 ng/mL and 37263 ng.h/mL, respectively, in inguinal hernia repair patients.

Compared to bupivacaine Cmax values in healthy subjects (638 ng/mL for Cmax), the bupivacaine exposure in inguinal hernia repair patients had somewhat lower bupivacaine concentrations.

==========

Study CLIN004-0009 inguinal hernia repair single dose 5 mL SABER-bupivacaine (subcutaneous and as a wound infiltrate) under local anesthesia (Marcain)

Title: A pharmacodynamic/pharmacokinetic study of SABER-bupivacaine and/or bupivacaine HCl administered Intra-operatively during open inguinal hernia repair Under local anesthesia

Study CLIN004-0009 was a Phase IIa study to compare the efficacy of SABER-Bupivacaine administered subcutaneously (Group 1) and as a wound infiltrate to Bupivacaine HCl (Marcain® 0.25%) administered subcutaneously (Group 2) and as a wound infiltrate in open inguinal hernia repair patients (suggested incision total length was 5 cm) under local anesthesia (30 mL of Bupivacaine HCl (Marcain® 0.25%, 75 mg of Bupivacaine HCl). The following table (Table 11) depicts the treatment groups:

Table 11 Treatment groups for Study CLIN004-0009

Group	Local anesthetic for inguinal hernia procedure	SABER-Bupivacaine	Bupivacaine HCl (Marcain® 0.25%)	Note
1	75 mg bupivacaine	2.5 mL SABER-Bupi administered into the deeper wound tissues after hernia repair and prior to wound closure. Then, 5.0 mL SABER-Bupi administered up to 0.5 mL/cm as 2 trailing SC injections, 2.5 mL in each side of the incision. The total delivered volume of SABER-Bupi was 7.5 mL (990 mg bupivacaine).		For the first 6 patients only administered SC 2.5 mL in each side of the incision; total delivered volume SABER-Bupi 5.0 mL
2	75 mg bupivacaine		2.5 mL Bupivacaine HCl (Marcain® 0.25%) administered into the deeper wound tissues after hernia repair and prior to wound closure. Then, 5.0 mL Bupi HCl 0.25% Administered up to 0.5 mL/cm as 2 trailing SC injections, 2.5 mL Bupivacaine HCl 0.25% in each side of the incision; Total delivered 7.5 mL (18.75 mg of Bupi HCl)	For the first 2 patients only administered SC 2.5 mL in each side of the incision; total delivered volume Bupivacaine HCl 0.25% 5.0 mL.

The following table (Table 12) represents pharmacokinetic parameters from 5 and 7.5 mL SABER-Bupivacaine administration.

Table 12 Mean (SEM) [Range] Pharmacokinetic Parameters of Bupivacaine

Pharmacokinetic Parameter	**SABER-Bupivacaine**		**Marcain**	
	5.0 mL (N=6)[a]	**7.5 mL (N=9)**	**5.0 mL (N=2)[b]**	**7.5 mL (N=1)**
Tmax	18.0 (7.26)	3.06 (0.81)	1.25 (0.75)	0.5

(hr)	[2.0 – 48.0]	[0.5 – 8.0]	[0.5 – 2.0]	-
Cmax (ng/mL)	674.7 (58.01)	1479 (126.5)	477 (307.9)	452
	[550 – 891]	[826 – 2150]	[170 – 784]	-
AUC (ng*hr/mL)	49192 (2551)	68135 (5652)	5154 (1373)	6344
	[40301 – 57632]	[45866 – 101596]	[3784 – 6523]	-

a: For the first 6 patients only administered SC 2.5 mL in each side of the incision; total delivered volume SABER-Bupi 5.0 mL
b. For the first 2 patients only administered SC 2.5 mL in each side of the incision; total delivered volume Bupivacaine HCl 0.25% 5.0 mL.

It is noted that the bupivacaine Cmax and AUC values observed after each study treatment are confounded by the use of local anesthetic, Marcain.

The range of maximum plasma bupivaciane concentration after 5.0 mL and 7.5 mL dose of SABER-Bupivacaine was 550 – 891 ng/ mL and 826 – 2150 ng/mL, respectively. The overall exposure (AUC) appeared to be somewhat proportional to the administered dose of SABERBupivacaine.

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Study Clin005-0007 'pilot' study (instillation) inguinal hernia repair single dose 5 mL SABER-bupivacaine (Note: cursory review due to 'pilot' study and Posimir 'leaking from the wound')

Title: A pilot study of the pharmacokinetics and safety of SABER-Bupivacaine instilled into the wound in patients undergoing Open inguinal hernia repair

Study CLIN005-0007 was a pilot, patient-blinded, Phase II study to assess the pharmacokinetics, safety, tolerability and efficacy of SABER™-Bupivacaine as a delivery system in open inguinal hernia repair patients. The study investigated instillation of 12.0 wt% SABER™-Bupivacaine directly into the wound, with patients being enrolled into two treatment groups: 1) Treatment Group 1 – During wound closure 2.5 mL of SABER™-Bupivacaine was placed topically, in approximately equal volumes, into the superior, medial and inferior subaponeurotic spaces. After closure of the external oblique aponeurosis (and prior to skin closure) another 2.5 mL of SABER™-Bupivacaine was placed topically along the length of the sutured external oblique aponeurosis. The total delivered volume of SABER™-Bupivacaine was 5.0 mL; 2) Treatment Group 2 – After closure of the external oblique aponeurosis (and prior to skin closure) 5.0 mL of SABER™-Bupivacaine was placed topically along the length of the sutured external oblique aponeurosis. The total delivered volume of SABER™-Bupivacaine instilled into the wound was 5.0 mL.

Mean (SD) bupivacaine PK parameters from Groups 1 and 2 are presented in table below (Table 13).

Table 13 Mean (SD) Pharmacokinetic Parameters of Bupivacaine

PK Parameter	Subaponeurotic Spaces + Oblique Aponeurosis (Group 1) (N=6)	Oblique Aponeurosis Alone (Group 2) (N=6)
Cmax (ng/mL)	717.3 (279.3)	506.8 (248.5)
Tmax (hr)	24.06 (8.07 - 24.18)	18.03 (8.03 - 24.07)
AUClast (ng*hr/mL)	33233.7 (7148.3)	23851.3 (15859.6)
AUCinf (ng*hr/mL)	33393.5 (7079.3)	24085.1 (16070.4)

The mean (SD) Cmax in Groups 1 and 2 were 717.3 (279.3) and 506.83 (248.52) ng/mL, respectively. The median (range) Tmax in Groups 1 and 2 were 24.06 (8.07 - 24.18) and 18.03 (8.03 - 24.07) hours, respectively. The mean (SD) AUC0-t for Groups 1 and 2 were 33233.7 (7148.3) and 23851.3 (15859.6) ng*hr/mL, respectively.

The Applicant stated that a certain amount of SABER-bupivacaine fluid was seeping out from the wound (Group 2). Therefore the information derived from this study should be interpreted with caution.

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Study Clin-803-006-0006 inguinal hernia repair single dose 2.5 and 5 mL SABER-bupivacaine (instillation) (Note: 'Pivotal' efficacy study; linearity assessment)

Title: A double-blind, placebo-controlled, pharmacodynamic and pharmacokinetic dose response study of SABER-Bupivacaine instilled into the wound in patients undergoing open inguinal hernia repair

Study CLIN-803-006-0006 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response, Phase II study to examine the efficacy, pharmacokinetics, and safety of SABER-Bupivacaine instilled directly into the wound in patients undergoing elective open unilateral tension-free inguinal hernia repair. Patients (95% men and 5% women; 95% White) received one of the following 4 treatments: SABER-Bupivacaine (12.0 wt%, 132 mg/mL bupivacaine) 5.0 mL (660 mg), SABER-Bupivacaine 2.5 mL (330 mg), SABER-Placebo 5.0 mL, or SABER-Placebo 2.5 mL.

The following figures (Figures 19 and 20, respectively) depict bupivacaine plasma concentration profiles obtained from 2.5 mL [n=14] and 5.0 mL SABER-Bupivacaine [n=14]).

Figure 19 Individual plasma concentrations of bupivacaine following instillation of 2.5 mL SABER-Bupivacaine (330 mg bupivacaine)

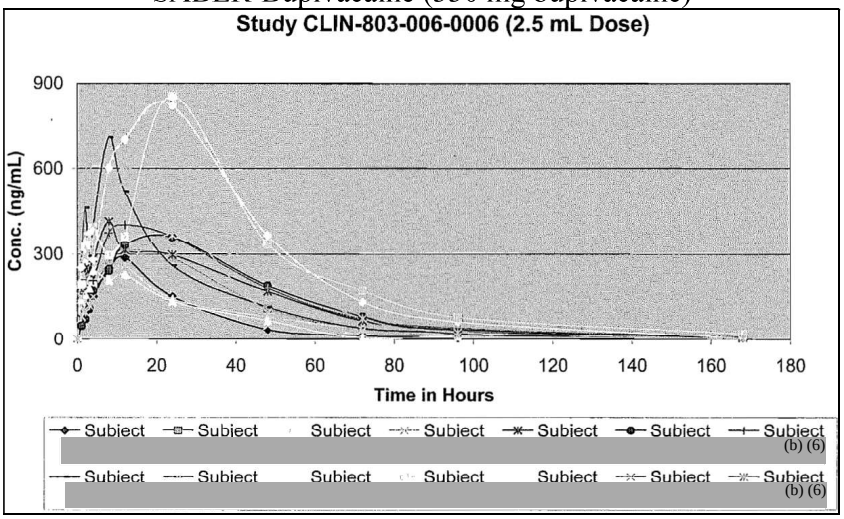
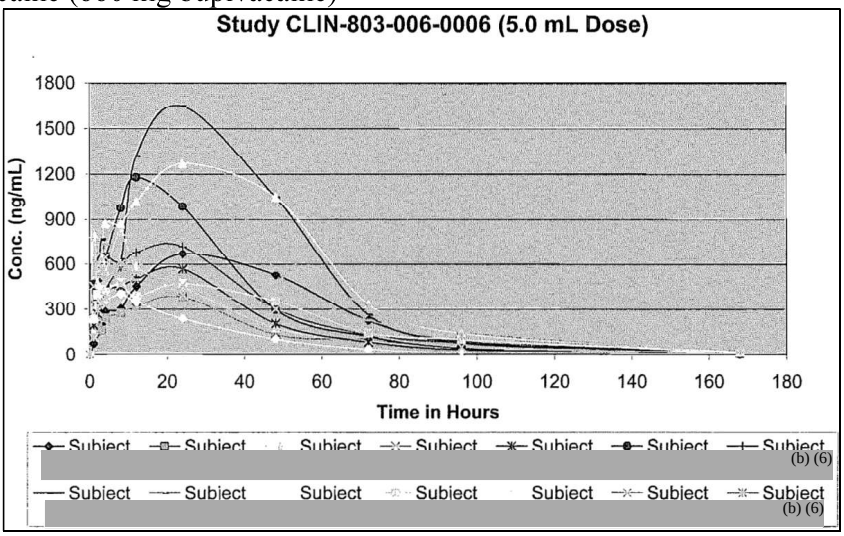
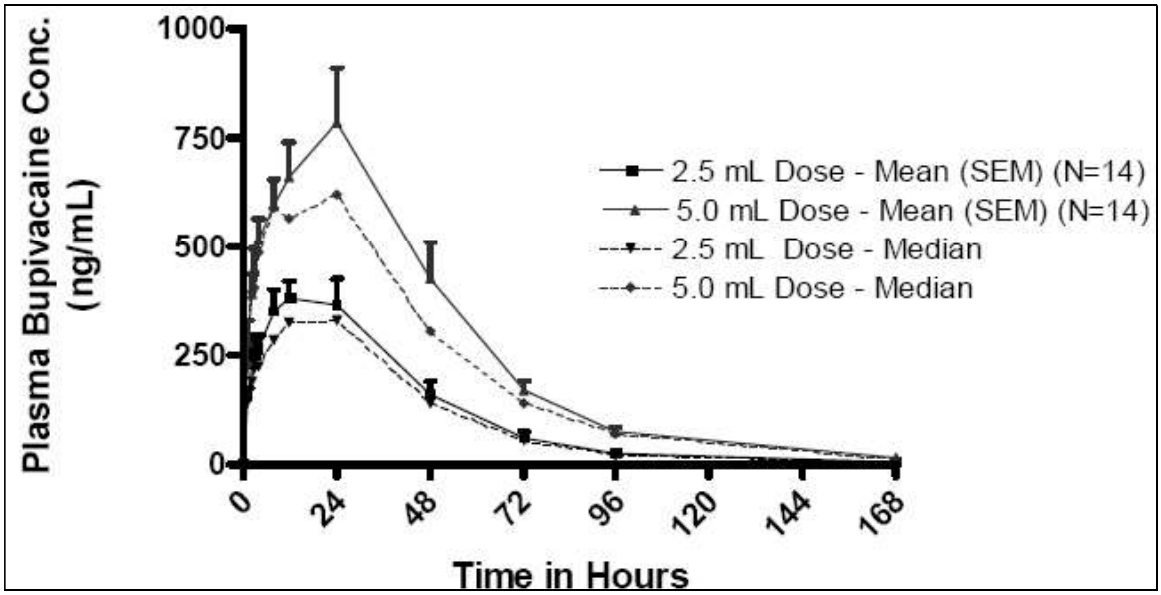


Figure 20 Individual plasma concentrations of bupivacaine following instillation of 5.0 mL SABER-Bupivacaine (660 mg bupivacaine)



Mean bupivacaine plasma concentration profiles from 2.5 mL and 5.0 mL SABER-Bupivacaine shown below (Figure 21).

Figure 21 Mean plasma Bupivacaine Concentrations Following 2.5 mL and 5.0 mL Dose of SABER-Bupivacaine



Pharmacokinetic results obtained from a total of 28 patients (receiving 2.5 mL SABER-Bupivacaine [n=14] and 5.0 mL SABER-Bupivacaine [n=14]) are shown below (Table 14).

Table 14 Individual and mean bupivacaine pharmacokinetic parameters from the 2.5 (top) and 5.0 (bottom) mL SABER-Bupivacaine

Patient #	Tmax (hr)	Cmax (ng/mL)	Half-life (hr)	Tlast (hr)	Clast (ng/mL)	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)
(b) (6)	12.00	288.00	13.47	96.10	3.06	7512.06	7571.53
	12.00	315.00	13.02	96.20	8.50	12853.93	13013.64
	12.00	257.00	22.16	168.30	1.95	9957.24	10019.59
	12.20	190.00	46.50	168.20	4.14	7277.07	7554.82
	8.00	414.00	28.66	168.00	6.30	17696.39	17956.86
	24.00	360.00	19.98	168.30	2.40	17518.35	17587.52
	12.10	403.00	24.01	167.80	4.72	19570.95	19734.41
	8.10	712.00	31.97	168.60	5.09	18048.75	18283.50
	2.90	707.00	30.32	168.20	10.40	27689.16	28144.15
	24.10	820.00	17.57	168.00	3.16	37279.31	37359.41
	24.10	854.00	32.99	168.40	21.00	36399.34	37398.75
	4.00	242.00	27.30	167.90	1.29	7749.35	7800.16
	12.00	605.00	23.00	168.10	1.65	19203.67	19258.41
	24.00	368.00	20.64	167.50	2.78	17833.76	17916.55
Mean	**13.68**	**466.79**	**25.11**	**157.83**	**5.46**	**18327.81**	**18542.81**
SD	**7.44**	**226.31**	**8.82**	**26.13**	**5.19**	**9719.51**	**9865.13**
SEM	**1.99**	**60.48**	**2.36**	**6.98**	**1.39**	**2597.65**	**2636.57**
Minimum	**2.90**	**190.00**	**13.02**	**96.10**	**1.29**	**7277.07**	**7554.82**
Maximum	**24.10**	**854.00**	**46.50**	**168.60**	**21.00**	**37279.31**	**37398.75**
%CV	**54.39**	**48.48**	**35.10**	**16.56**	**95.04**	**53.03**	**53.20**
Median	**12.00**	**ND**	**23.50**	**168.05**	**ND**	**ND**	**ND**

Patient #	Tmax (hr)	Cmax (ng/mL)	Half-life (hr)	Tlast (hr)	Clast (ng/mL)	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)
(b) (6)	24.00	671.00	22.28	168.00	10.50	38790.43	39127.89
	24.00	383.00	24.27	168.00	6.09	18380.22	18593.47
	8.00	820.00	22.17	168.60	4.56	27065.32	27211.14
	12.00	623.00	33.77	168.80	17.80	28710.63	29577.89
	23.90	570.00	26.80	167.50	6.87	25758.13	26023.78
	12.00	1180.00	21.32	168.20	5.17	44433.50	44592.54
	24.00	719.00	26.80	168.10	11.60	35747.58	36196.05
	24.00	1650.00	20.87	167.60	10.20	78602.04	78909.23
	24.10	1630.00	26.55	168.30	19.50	62501.74	63248.55
	8.00	402.00	73.33	168.10	26.00	15337.89	18088.47
	8.00	479.00	27.45	167.80	13.90	31617.88	32168.31
	24.10	1270.00	23.80	168.10	19.40	75277.93	75943.97
	4.00	645.00	21.80	169.10	6.27	30403.66	30600.82
	24.00	1090.00	29.54	167.80	30.10	58894.76	60177.41
Mean	**17.44**	**866.57**	**28.62**	**168.14**	**13.43**	**40822.98**	**41461.39**
SD	**8.10**	**426.61**	**13.37**	**0.44**	**8.06**	**20311.58**	**20220.87**
SEM	**2.16**	**114.02**	**3.57**	**0.12**	**2.15**	**5428.50**	**5404.26**
Minimum	**4.00**	**383.00**	**20.87**	**167.50**	**4.56**	**15337.89**	**18088.47**
Maximum	**24.10**	**1650.00**	**73.33**	**169.10**	**30.10**	**78602.04**	**78909.23**
%CV	**46.45**	**49.23**	**46.70**	**0.26**	**60.06**	**49.76**	**48.77**
Median	**23.95**	**ND**	**25.41**	**168.10**	**ND**	**ND**	**ND**

The pharmacokinetic parameters from 2.5 and 5 mL dose are compared and presented in Table 15.

Table 15 Mean (SD) [range] Pharmacokinetic Parameters of Bupivacaine Following the 2.5 and 5.0 mL Dose of SABER-Bupivacaine

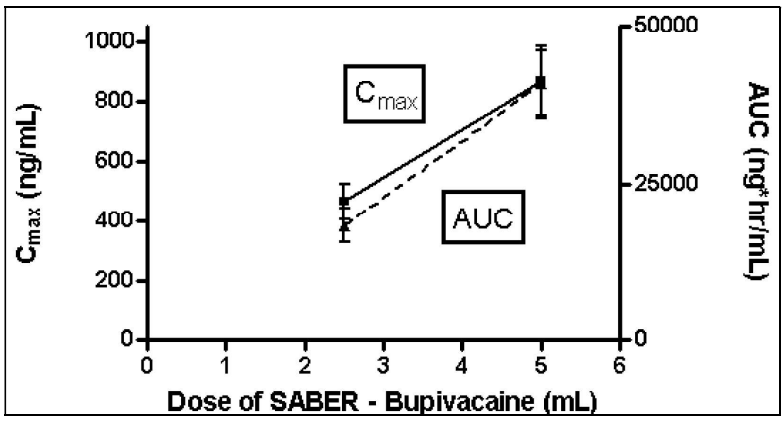
Pharmacokinetic Parameter	SABER-Bupivacaine 2.5 mL (N=14)	SABER-Bupivacaine 5.0 mL (N=14)
Cmax (ng/mL)	467 (226) [190 – 854]	867 (427) [383 – 1650]
Tmax (h) *	12.0 (2.9 – 24.10)	23.95 (4.0 – 24.10)
T1/2 (h)	25.11 (8.82) [13.02 – 46.5]	28.62 (13.37) [20.87 – 73.33]
AUC(0-t) (ng•hr/mL)	18328 (9720) [7277 – 37279]	40823 (20312) [15338 – 78602]
AUC(0-inf) (ng•hr/mL)	18543 (9865) [7555 – 37399]	41461 (20221) [18088 – 78909]

* Tmax data presented as median (range); t=168 h

The mean (range) C_{max} of bupivacaine observed following the 2.5 mL and the 5.0 mL dose of SABER-Bupivacaine were 466.8 ng/mL (190.0-854.0 ng/mL) and 866.6 ng/mL (383.0- 1650.0 ng/mL), respectively. Similarly, the mean $AUC_{(0-t)}$ for the 2.5 mL and the 5.0 mL dose of SABER-Bupivacaine was 18327.8 and 40822.9 ng•hr/mL and the mean $AUC_{(0-inf)}$ was 18542.8 and 41461.4 ng•hr/mL, respectively.

Bupivacaine C_{max} and AUC values from the 2.5 and 5.0 mL dose of SABER-Bupivacaine exhibited linear pharmacokinetics (Figure 22).

Figure 22 Bupivacaine Cmax and AUC linearity plot of 2.5 and 5.0 mL SABER-Bupivacaine



2.2.5.2.2 Orthopedic surgeries – arthroscopic shoulder surgeries

There were 2 arthroscopic studies: CLIN005-0006 (rotator cuff repair) and BU-002-IM (arthroscopic shoulder surgery).

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Study CLIN005-0006 rotator cuff repair surgery single dose 5 mL SABER-Bupivacaine (subacromial injection and SC injection) (Note: no leakage from the wound) under local or general anesthesia (according to standard local practice)

Title: A randomized, double-blind, placebo-controlled study of the efficacy and safety of subcutaneous or subacromial SABER-Bupivacaine in patients undergoing rotator cuff repair

Study CLIN005-0006 was a randomized, double-blind, placebo-controlled, Phase 2 study to examine the efficacy and safety of SABER-Bupivacaine administered subcutaneously or into the subacromial space in subjects undergoing elective arthroscopic shoulder surgery. Surgical procedures were performed under local or general anesthesia according to standard local practice. The study was conducted in 2 separate and sequential cohorts (Cohort 1 and Cohort 2). For all treatment groups if the procedure was performed arthroscopically, the subcutaneous doses of study drug were administered evenly around all arthroscopic portals. (It is noted that the protocol was amended to changed the amount of drug to be administered in Cohort 2 from 7.5 mL to 5.0 mL (the Agency recommendation that additional safety data be collected on the 7.5-mL dose before its use in clinical trials); however, 3 subjects were administered with 7.5 mL SABER-Bupivacaine before this amendment was put into effect. However, it is noted that there was no information from 3 patients who received 7.5 mL SABER-Bupivacaine. As a part of pharmacokinetic assessment, patients in Cohort 1, treatment 1 and Cohort 2, treatment 5 were analyzed. The following table (Table 16) describes the treatments:

Table 16 Treatment groups for Study CLIN005-0006

		Prior to wound closure	After wound closure	During wound closure	Total mg bup	Comments
Cohort 1	TRT 1[a]	5 mL SABER-PL subacromial space injection	5 mL SABER-Bup as 2 trailing SC injections along each side of the	-	660 mg	For all treatment groups if the procedure was

			incision line (suggested incision total length to be 3 to 6 cm)			performed arthroscopically, the subcutaneous doses of study drug were administered evenly around all arthroscopic portals.
	TRT 2	5 mL SABER-Bup subacromial space injection	5 mL SABER-PL as 2 trailing SC injections along each side of the incision line	-	660 mg	
	TRT 3	5 mL SABER-PL subacromial space injection	5 mL SABER-PL as 2 trailing SC injections along each side of the incision line	-	-	
Cohort 2	TRT 4			5.0 mL of SABER-PL subacromial space injection	-	
	TRT 4a			7.5 mL of SABER-PL subacromial space injection	-	
	TRT 5[a]			5.0 mL of SABER-Bup subacromial space injection	660 mg	
	TRT 5a			7.5 mL of SABER-Bup subacromial space injection	990 mg[b]	

a: Pharmacokinetic information
b: no bupivacaine exposure information in Treatment 5a

Individual and mean bupivacaine plasma concentration profiles are shown below from Cohort 1, treatment 1 and Cohort 2, treatment 5, with 5.0 mL SABER-Bupivacaine (Figures 23 and 24, respectively).

Figure 23 Individual plots of bupivacaine concentrations in Cohort 1, treatment 1 and Cohort 2, treatment 5, following rotator cuff repair surgery with 5.0 mL SABER-Bupivacaine

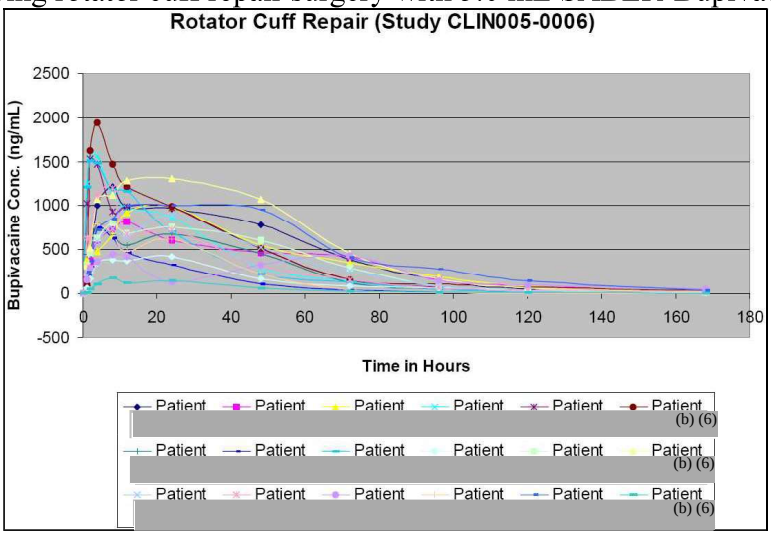
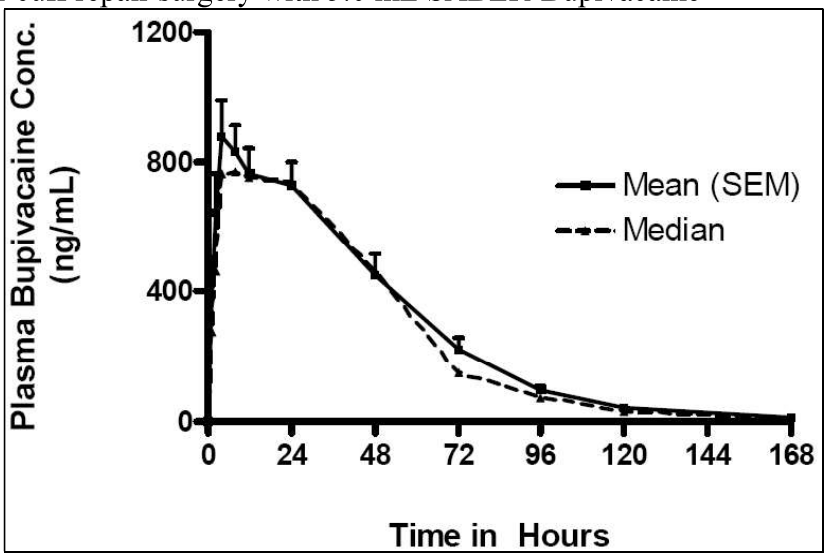


Figure 24 Mean bupivacaine concentrations in Cohort 1, treatment 1 and Cohort 2, treatment 5, following rotator cuff repair surgery with 5.0 mL SABER-Bupivacaine



The following tables (Table 17 for all patients, Table 18 and 19 for subcutaneous and subacromial injections, respectively) contain pharmacokinetic parameters from patients in pharmacokinetic assessment.

Table 17 Mean (SD) Pharmacokinetic Parameters of Bupivacaine Following 5.0 mL SABER™- Bupivacaine in rotator cuff surgery

	Cmax ng/mL	Tmax h	AUCinf ng.h/mL	T1/2 h
Mean	1006	10.56	47649	26.1
SD	453.6	8.51	20116	5.22
Min	172	2.08	7346	16.64
Max	1940	26.85	86448	50.84

Table 18 Treatment 1 (5.0 mL 2 trailing **subcutaneous injection** along side of the incision line after wound closure)

Subj.	Cmax ng/mL	Tmax h	AUCinf ng h/mL	T1/2 h
Mean	965	10.21	45081	27.63
SD	487	8.86	21981	8.71
Min	172	2.08	7346	16.64
Max	1940	26.85	86448	50.84

Table 19 Treatment 5 (5.0 mL **subacromial space injection** during wound closure);

Subj.	Cmax ng/mL	Tmax h	AUCinf ng h/mL	T1/2 h

Mean	1146	11.78	56635	20.75
SD	326	8.18	7797	2.32
Min	813	7.9	49420	18.58
Max	1570	23.13	66929	22.96

The mean bupivacaine Cmax was 1006 ng/mL, with 965 and 1146 ng/mL for subcutaneous and subacromial injections, respectively.

The mean AUC (0-inf) was 47649 ng.h/mL, with 45081 and 56635 ng.h/mL for subcutaneous and subacromial injections, respectively.

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Study BU-002-IM arthroscopic shoulder surgery 5 mL SABER-Bupivacaine ('administered into the subacromial space') (Note: Applicant stated 'leakage' from the surgical site; 'Pivotal' efficacy study)

Title: An international, randomized, double-blinded, multi-centre, active- and placebo-controlled dose response trial to evaluate the efficacy and safety of SABER-Bupivacaine for post-operative pain control in patients following arthroscopic shoulder surgery

Study BU-002-IM was a parallel group, randomized, double-blinded, active- and placebo-controlled, dose response trial of SABER-Bupivacaine with post-operative assessments of pain intensity, PK, safety, and health economics in patients undergoing elective arthroscopic shoulder surgery. The objective of this clinical trial was to identify the optimal dose of SABER-Bupivacaine for post-operative pain control administered into the subacromial space through one of the portals in patients undergoing elective arthroscopic shoulder surgery on the basis of PK, efficacy, and safety evaluations. Patients were administered with one of the following treatments: a) 5 mL or 7.5 mL SABER-Bupivacaine (660 mg or 990 mg bupivacaine, respectively) subacromial administration; b) 5 mL or 7.5 mL SABER-placebo subacromial administration; and c) 20 mL standard bupivacaine hydrochloride (HCl) (50 mg bupivacaine; Marcain®). It is noted that the Applicant suspected leakage of SABER-Bupivacaine from the administration site when bupivacaine Cmax and AUC values were compared with CLIN005-0006. No incision lengths information was provided for this study. It is also noted that the protocol was amended not to increase to the 7.5 mL dose (Data Review Committee recommendation).

Individual bupivacaine plasma concentrations profiles are shown in Figures 25 and 26 from 5 mL SABER-Bupivacaine and Marcain, Cohort 1a and 1c, respectively.

Figure 25 Individual bupivacaine plasma concentration profiles following 5 mL SABER-Bupivacaine (cohort 1a) administered into the subacromial space

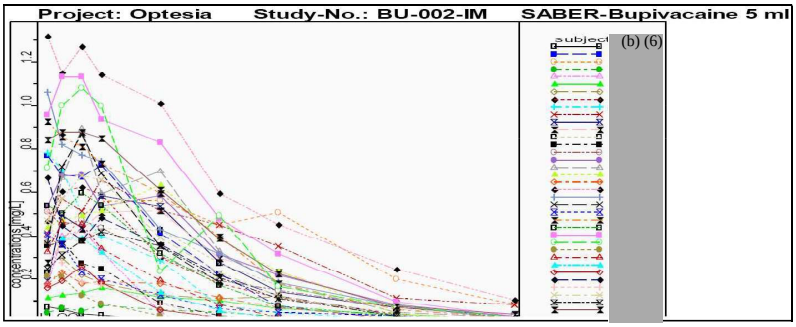
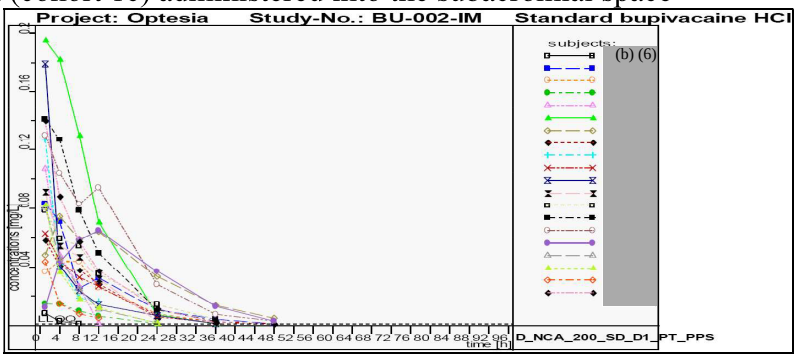


Figure 26 Individual bupivacaine plasma concentration profiles following 20 mL Marcain (bupivacaine HCl (cohort 1c) administered into the subacromial space



Mean bupivacaine (total and free) plasma concentrations profiles are shown in Figures 27 SABER-Bupivacaine and Marcain, Cohort 1a and 1c, respectively.

Figure 27 Total and free bupivacaine plasma concentrations following administration of 5 mL SABER-Bupivacaine (cohort 1a) or 20 mL standard bupivacaine HCl (Marcain, cohort 1c)

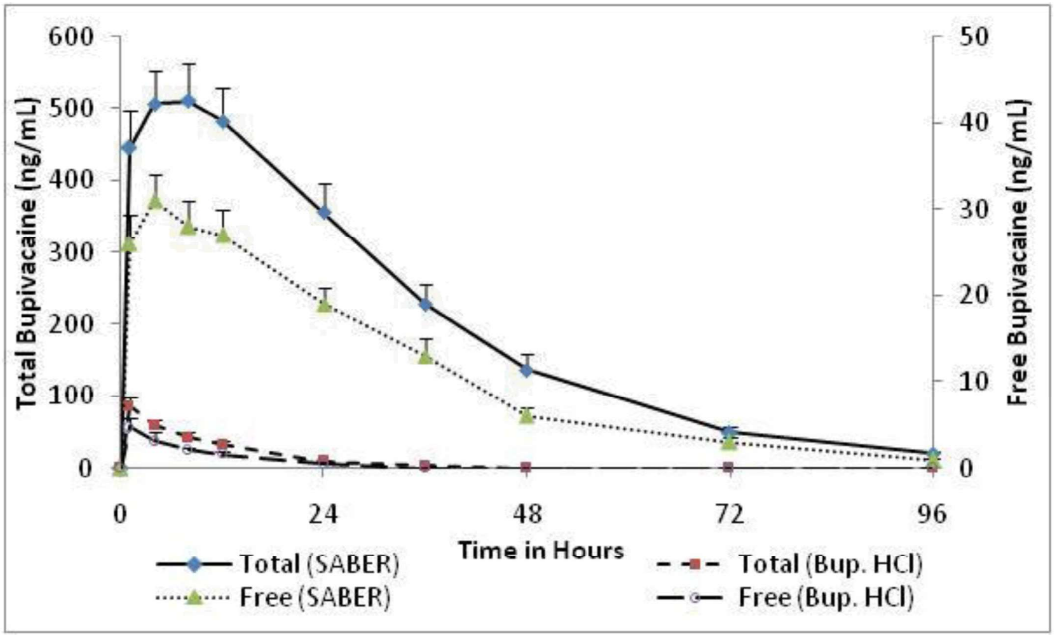


Table 20 contains mean (SD) bupivacaine pharmacokinetic parameters obtained from patients undergoing shoulder arthroscopic surgery.

Table 20 Mean (SD) and [range] Plasma Pharmacokinetic Parameters of Bupivacaine Following Administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine) or 20 mL Bupivacaine HCl (50 mg bupivacaine)

Pharmacokinetic Parameter	**SABER-Bupivacaine**	**Marcain (Bupivacaine HCl)**
	Total (N=36)	**Total (N=20)**
Cmax (ng/mL)	593 (299) [70 – 1320]	90 (50) [8 – 195]
Tmax (h) (median)	5.9 [0 – 24]	1.0 [0.9 – 12.0]
t½ (h)	16.4 (5.08) [8.4 – 28.87]	5.93 (1.72) [2.57 – 9.64]
AUCt (ng*h/mL)	19390 (12060) [1030 – 55370]	940 (620) [30 – 221]
AUCinf (ng*h/mL)	19960 (12600) [1050 – 59200]	960 (630) [30 – 222]

The highest individual bupivacaine Cmax-value from SABER-Bupivacaine was 1320 ng/mL.

The Applicant stated that the mean bupivacaine Cmax and AUC values obtained from the current study in both the SABER-Bupivacaine and standard bupivacaine HCl groups, were considerably lower (approximately 50%) than previously observed (CLIN005-0006).

This is assumed to have occurred by seepage of variable volumes of the administered dose from the wound between the time of drug administration and closure of the wound (arthroscopic portals).

The following table (Table 21) provides bupivacaine Cmax and AUC comparison between CLIN005-006 and current study.

Table 21 Comparison of bupivacaine Cmax and AUC between trials CLIN005-0006 and BU-002-IM

	Cmax (SD) ng/mL	AUC (SD) ng.h/mL
BU-002-IM Subacromial administration	593 (299) [Range 70 – 1320]	19960 (12600) [Range 1050 – 59200]
CLIN005-0006 Subacromial injection	1146 (326) [Range 813 – 1570]	56635 (7797) [Range 49420 – 66929]
CLIN005-0006 Subcutaneous injection	965 (487) [Range 172 – 1940]	45081 (21981) [Range 7346 – 86448]

Looking at the individual Cmax and AUC values between CLIN005-0006 and BU-002-IM, bupivacaine Cmax and AUC values were in fact smaller than the Study CLIN005-0006.

However, interestingly, according to the statistical reviewer, the current study showed that SABER-Bupivacaine was efficacious in shoulder surgery.

2.2.5.2.3 Abdominal surgeries

There were 3 abdominal studies: CLIN005-0002 (appendectomy), BU-001-IM (abdominal hysterectomy) and C803-025 (Surgeries included Laparotomy, Laparoscopic Cholecystectomy, Laparoscopically Assisted Colectomy).

==========

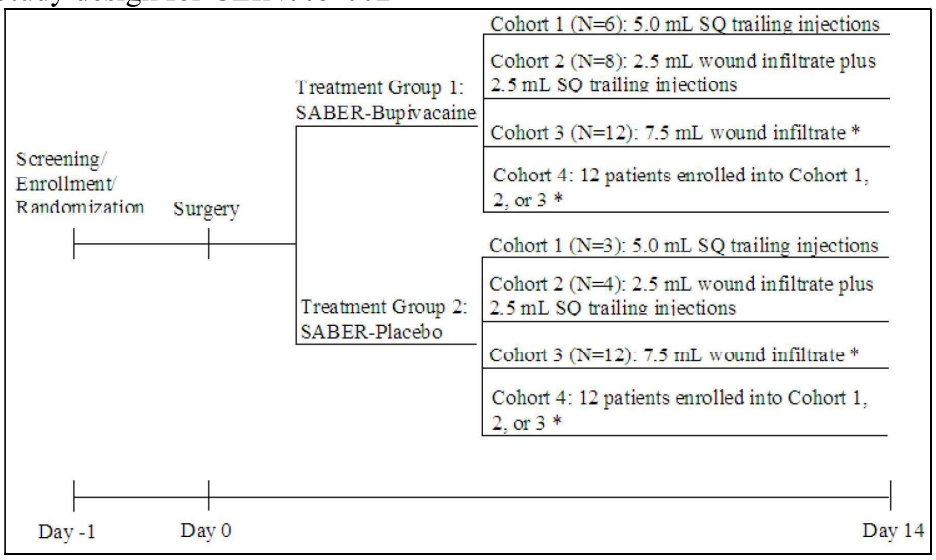
Study CLIN005-002 appendectomy single dose 5 mL SABER-bupivacaine ('wound infiltrate')

Title: A double-blind, placebo-controlled, pharmacodynamic and Pharmacokinetic pilot study with SABER-bupivacaine Administered as a wound infiltrate following semi-elective Open appendectomy

Study CLIN005-002 was a Phase II, single-center, randomized, double-blind, placebo-controlled, parallel-group study. Patients received SABER-Bupivacaine 5 mL (660 mg bupivacaine) (Treatment Group 1; Cohort 1 - 5 mL administered subcutaneously equally divided trailing injections 0.5 cm on each side of the length of the incision; Cohort 2 – 2.5 mL as wound infiltrate into deeper tissues prior to wound closure and 2.5 mL subcutaneous trailing injections, equally divided between trailing injections 0.5 cm on each side of the incision), or SABER-

Placebo (Treatment Group 2) administered as a wound infiltrate. The incision length was set to approximately 5 cm. The planned study design is depicted in Figure 28:

Figure 28 Study design for CLIN005-002



*Cohorts 3 and 4: The study was terminated early because of sponsor changes in the clinical development plan. No patients were enrolled into Cohorts 3 and 4.

Individual bupivacaine plasma concentrations profiles are shown in Figures 29 and 30 for Treatment 1, Cohorts 1 and 2, respectively.

Figure 29 Individual bupivacaine concentration time profiles of Treatment 1, Cohort 1: 5 mL administered subcutaneously equally divided trailing injections 0.5 cm on each side of the length of the incision

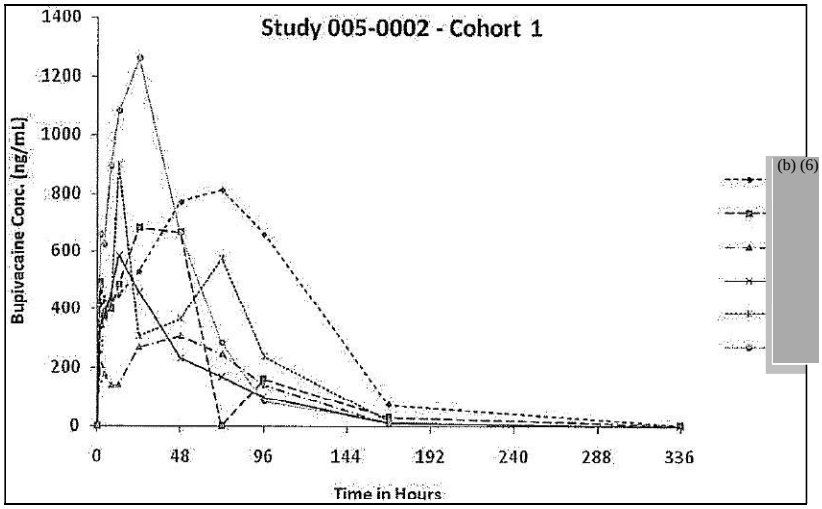
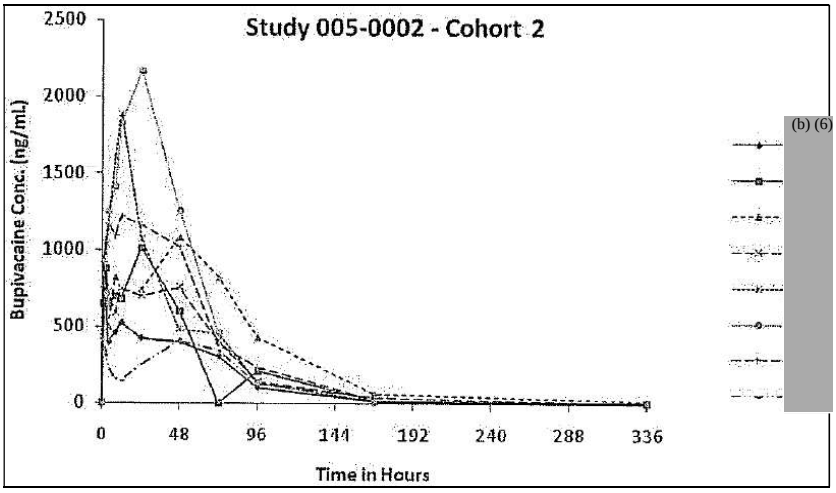


Figure 30 Individual bupivacaine concentration time profiles of Treatment 1 Cohort 2: 2.5 mL as wound infiltrate into deeper tissues prior to wound closure and 2.5 mL subcutaneous trailing injections, equally divided between trailing injections 0.5 cm on each side of the incision



Mean bupivacaine plasma concentrations profiles from Treatment 1, Cohort 1 and Treatment 1 Cohort 2 are shown in Figures 31.

Figure 31 Mean (SEM) Plasma Bupivacaine Concentrations for Treatment 1 Cohorts 1 and 2

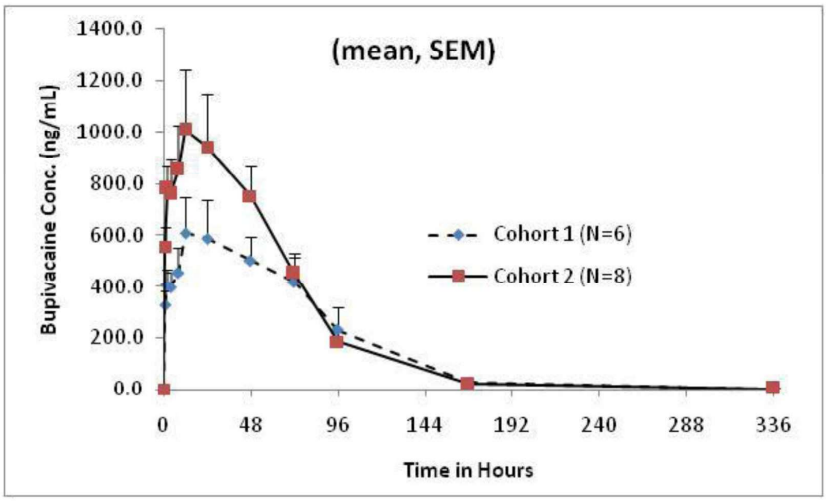


Table 22 contains mean (SD) bupivacaine pharmacokinetic parameters obtained from patients undergoing appendectomy surgery.

Table 22 Mean (SD) and [range] bupivacaine Pharmacokinetic Parameters of Bupivacaine Following Administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine) from Treatment 1 Cohorts 1 and 2

PK Parameter	**Cohort 1 (N=6)**	**Cohort 2 (N=8)**
T_{max} (hr) [a]	24.0 [12.0 - 72.0]	24.0 [2.0 - 48.0]

C_{max} (ng/mL)	758.0 (320) [309 – 1260]	1161.4 (595) [403 – 2170]
$T_{1/2}$ (hr) [a]	24.18 (10.89) [18.61-47.50]	33.42 (14.29) [17.82 - 54.59]
AUC_{last} (ng*hr/mL)	50874 (22176) [25907 – 86018]	68623.1 (25873) [31734 – 107394]
AUC_{inf} (ng*hr/mL)	51246.2 (22153) [26114 – 86241]	69172.8 (25716) [33365 – 107651]
a Median [range].		

Comparing Cohorts 1 and 2, bupivacaine Cmax and AUC values for Cohort 2 were larger than Cohort 1. Bupivacaine concentrations were observed over the 72 hours from SABER-Bupivacaine in appendectomy patients.

==========

Study BU-001-IM abdominal hysterectomy 5 mL SABER-Bupivacaine compared to Marcain (Note: relative bioavailability information)

Title: An international, randomized, double-blinded, multi-centre, active- and placebo-controlled dose response trial to evaluate the efficacy and safety of SABER-Bupivacaine for post-operative pain control in patients undergoing primary, elective, open, abdominal hysterectomy

Study BU-001-IM was a Phase 2, randomized, multi-center, double-blind, parallel group, placebo- and active-controlled study in women undergoing primary elective open non-malignant abdominal hysterectomy. The treatment groups were a) 5.0 mL SABER-Bupivacaine via instillation; b) 5.0 mL SABER-placebo instillation; or c) 40 mL standard bupivacaine hydrochloride (HCl) (100 mg bupivacaine) infiltration (Marcain®). The realtive bioavailability result in this study was used to establish the "link" between the proposed product and Marcain.

Individual plasma concentrations of bupivacaine following instillation of 5.0 mL SABER-Bupivacaine (660 mg bupivacaine) and Marcain® are shown below (Figures 32 and 33, respectively.

Figure 32 Individual bupivacaine plasma concentrations following administration of SABER-Bupivacaine (Cohort a)

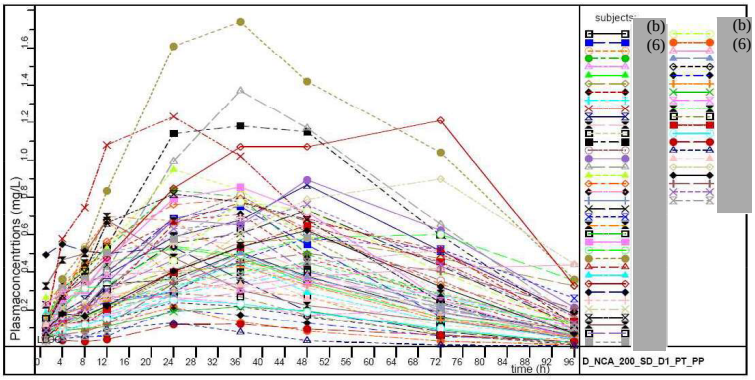
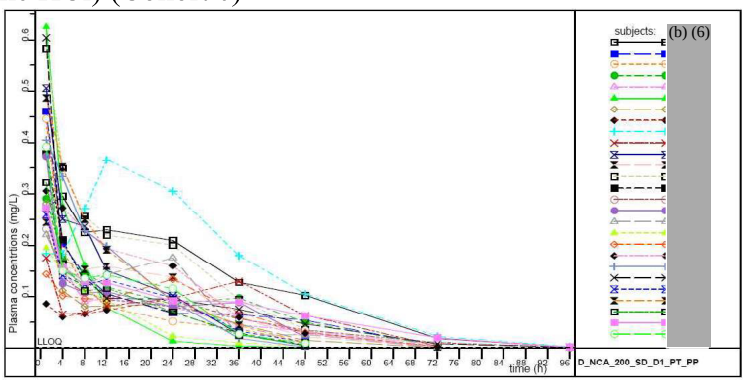
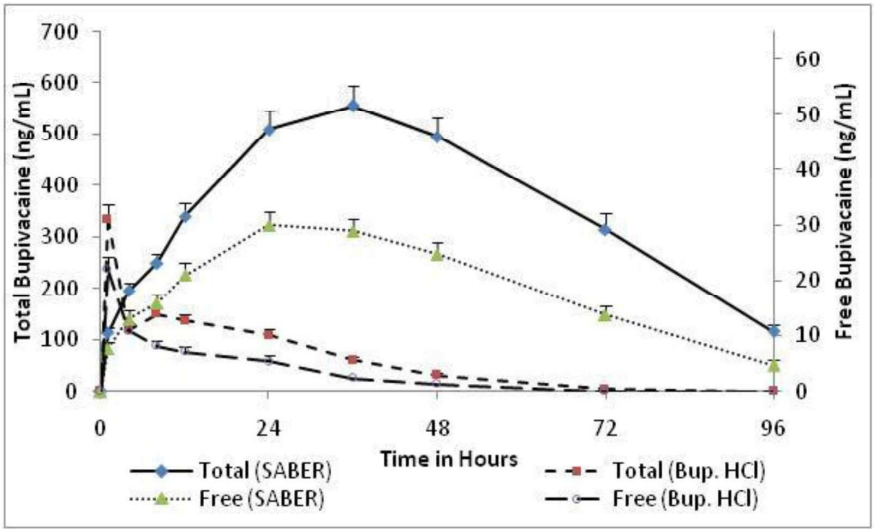


Figure 33: Individual bupivacaine plasma concentrations following administration of Marcain (standard bupivacaine HCl) (Cohort c)



Mean bupivacaine concentration profiles following instillation of 5.0 mL SABER-Bupivacaine (660 mg bupivacaine) and Marcain® are shown below (Figures 34).

Figure 34 Mean total and free bupivacaine and benzyl alcohol plasma concentrations following administration of SABER-Bupivacaine (660 mg bupivacaine; Cohort 1a) or Marcain (100 mg bupivacaine; standard bupivacaine HCl) (Cohort 1c)



Tables 23 and 24 contain mean (SD) bupivacaine pharmacokinetic parameters obtained from Cohort 1 and 2, respectively, in patients undergoing abdominal hysterectomy.

Table 23 Plasma parameters of bupivacaine following administration of 5 mL SABER-Bupivacaine (660 mg bupivacaine) (Cohort a)

	T_{max} [h]	C_{max} [ng/mL]	AUC_t [ng·h/mL]	AUC_{inf} [ng.h/mL]	$t_{1/2}$ [h]
N	59	59	59	54	54
mean	37.32	625	35230	36830	19.5
SD	16.47	310	18720	21060	4.67
median	36.00	595	33020	33150	18.48
min	4.00	119	4420	4470	11.27
max	95.92	1740	105320	122170	29.18

Table 24 Plasma parameters bupivacaine following administration of 40 mL Marcain (100 mg bupivacaine; standard bupivacaine HCl) (Cohort c)

	T_{max} [h]	C_{max} [ng/mL]	AUC_t [ng·h/mL]	AUC_{inf} [ng h/mL]	$t_{1/2}$ [h]
N	27	27	27	27	27
mean	2.37	342	5650	5740	8.85
SD	4.82	139	2320	2300	2.78
CV (%)	203.0	40.7	41.1	40.2	31.4
median	1.00	306	5430	5480	8.02
min	0.92	96	2530	2570	4.38
max	23.92	625	13320	13360	17.39

The individual curves from SABER-bupivacaine administration indicated that bupivacaine concentrations may last until 72 hours post administration.

Bupivacaine mean Cmax value from SABER-bupivacaine (660 mg bupivacaine) was 625 ng/mL compared to 342 ng/mL with Marcain (100 mg). Bupivacaine mean AUC value SABER-bupivacaine (660 mg bupivacaine) was 36830 ng.h/mL compared to 5740 ng.h/mL with Marcain (100 mg). It is noted that the SABER-bupivacaine (660 mg bupivacaine) dose is much higher compared to Marcain (100 mg) dose, which resulted in higher Cmax and AUC for SABER-bupivacaine.

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Study C803-025 procedures (laparotomy, laparascopic cholecystectomy, and Laparoscopically-assisted colectomy) using 5 mL (Note: Phase 3 study)

Study C803-025 was a Phase 3, multi-center, randomized, double-blind, active- and placebo-controlled trial evaluating the safety, efficacy, effectiveness and pharmacokinetics of SABER-Bupivacaine 5.0 mL, in patients undergoing laparotomy related surgical procedures with various wound sizes. Treatment groups for this trial were: a) SABER-Bupivacaine 5.0 mL, b) Sensorcaine 30 mL 0.5% solution (5 mg/mL; 150 mg; infiltration with a hypodermic needle into

the peri-incisional tissues), or c) SABER- Placebo 5.0 mL administered into the surgical wound(s). The surgical procedures (or cohorts) are as follows: 1) Cohort 1 – Laparotomy; there were no restrictions on laparotomy incision length (typically with a single incision of 20 cm or more); the drug was evenly distributed within the laparotomy incision; 2) Cohort 2 - Laparoscopic cholecystectomy; there were no restrictions on the number of laparoscopic portals (typically with 4 laparoscopic ports inserted); the larger port incisions received a larger volume of test drug; 3) Cohort 3 - Laparoscopically-assisted colectomy; there was generally a 5-10 cm linear incision for exteriorizing the colon for resection and anastomosis (the hand port); approximately 80-90% of the SABER-Bupivacaine was instilled into the hand port using the irrigation catheter method; the remaining 10-20% of test drug was directly instilled into the laparoscopic port incisions.

Mean bupivacaine plasma concentration profiles from laparatomy, laparoscopic cholecystectomy and laparoscopically-assisted colectomy surgeries are presented in figures below (Figures 35, 36 and 37 respectively).

Figure 35 Mean (SEM) Bupivacaine Plasma Concentration Following Administration of 5.0 mL (660 mg bupivacaine) SABER-Bupivacaine or 150 mg Sensorcaine (Bup. HCl) (Cohort 1)

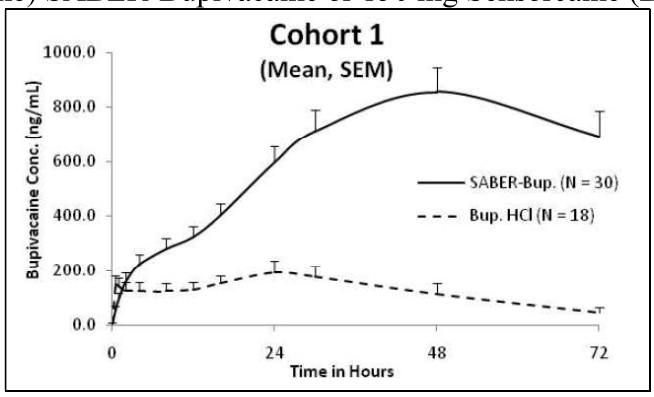


Figure 36 Mean (SEM) Bupivacaine Plasma Concentration Following Administration of 5.0 mL (660 mg bupivacaine) SABER-Bupivacaine or 150 mg Sensorcaine (Bup. HCl) (Cohort 2)

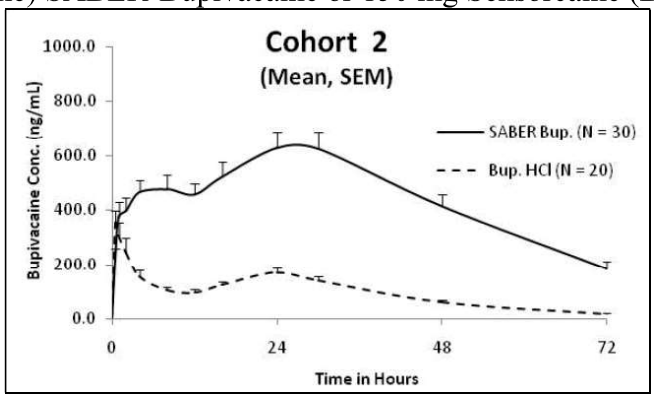
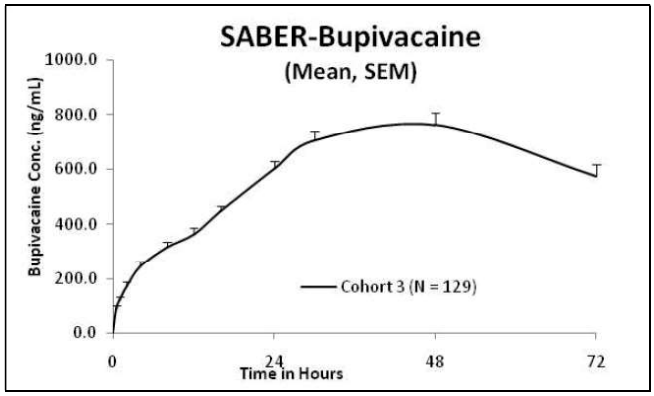


Figure 37 Mean (SEM) Bupivacaine Plasma Concentration Following Administration of 5.0 mL (660 mg bupivacaine) SABER-Bupivacaine only (Cohort 3)



A summary of mean bupivacaine plasma pharmacokinetic parameters from laparatomy, laparoscopic cholecystectomy and laparoscopically-assisted colectomy surgeries are presented in Table 25.

Table 25 Bupivacaine pharmacokinetic parameters following Administration of 5 mL (660 mg bupivacaine) SABER-Bupivacaine or Sensorcaine (150 mg bupivacaine) (Mean (SD)) (Cohorts 1, 2, and 3) in patients undergoing laparatomy, laparoscopic cholecystectomy and laparoscopically-assisted colectomy surgeries

	SABER-Bupivacaine			Sensorcaine (bupivacaine HCl)	
	Cohort 1	Cohort 2	Cohort 3	Cohort 1	Cohort 2
PK Parameter	(N = 30)	(N = 30)	(N = 129)	(N = 18)	(N = 20)
Cmax (ng/mL)	955.6 (485) [133 – 1870]	752.1 (307) [357 – 1850]	849.6 (478) [92 – 2850]	250.6 (190) [19 – 551]	370.5 (246) [101- 1170]
Tmax (hr)a	48.1 [2 – 73]	24.3 [1 – 49]	46.6 [1 – 74]	16.3 [1 – 48]	0.9 [1 – 24]
AUC(0-72) (ng*hr/mL)b	40755 (20876) [5113 – 79464]	29466 (14945) [11095 – 68124]	39437 (22346) [3613 – 110222]	8465 (8316) [495 – 26306]	6772.1 (2561) [1777 – 11985]
AUC(0-last) (ng*hr/mL)	41942 (24344) [635 – 96625]	30997 (12680) [11100 – 68108]	39602 (24049) [1626 – 136309]	7784 (7889) [465 – 26364]	6623 (2555) [1771 – 11868]

a median

For all Cohorts bupivacaine Cmax and AUC values were somewhat comparable, with Cohort 2 producing the smallest values compared to Cohorts 1 and 3. The Applicant speculated that this may be due to smaller laparoscopic incision (2.5 to 6 cm) in Cohort 2. The Applicant stated that there were insufficient data points to adequately characterize the terminal phase; thus half-life and AUCinf values were not obtained.

2.3 Intrinsic Factors

No specific studies were conducted to evaluate the bupivacaine pharmacokinetics in special populations such as hepatic and renal impairments. However, the Applicant presented the bupivacaine exposure information based on age, gender, race and Body Mass Index (BMI) from Phase 3 trial, Trial C803-025. The following table (Table 26) contains bupivacaine Cmax and AUC information with respect to age and gender from C803-025.

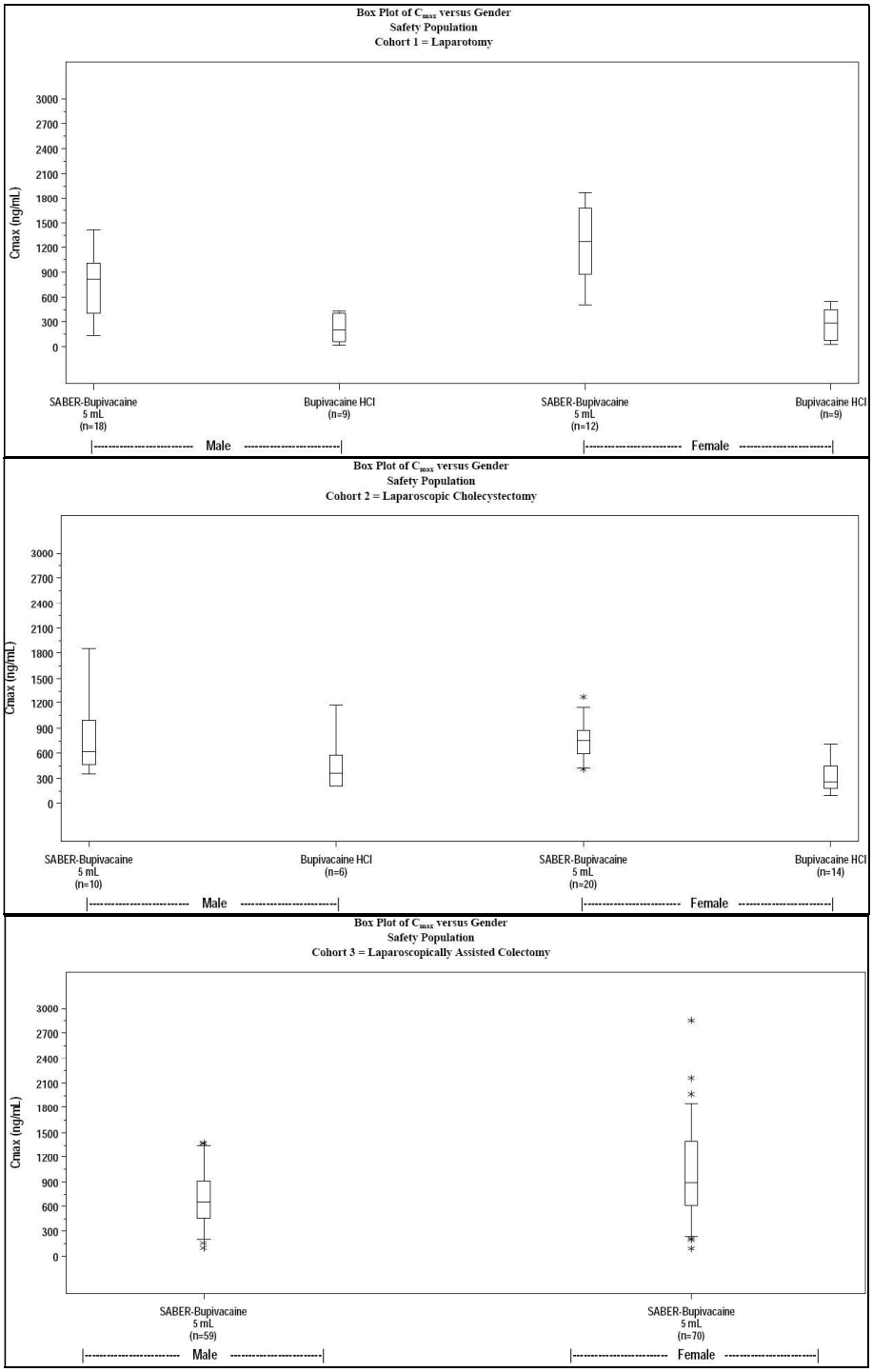
Table 26 Mean (SEM) bupivacaine pharmacokinetic parameters across covariates (gender, race) following administration of SABER-Bupivacaine in Study C803-025 (All 3 Cohorts)

		Mean (SEM)		
Baseline variable	**N**	**C_{max} (ng/mL)**	**T_{max} (hr) Median**	**$AUC_{(0\text{-last})}$ (ng*hr/mL)**
Age				
< 45 years	32	654.3 (50.4)	30.2	28331.2 (2437.2)
45 to 65 years	104	830.1 (46.1)	32.8	37532.3 (2224.6)
> 65 years	53	1010.6 (64.4)	47.7	46921.2 (3408.2)
Gender				
Male	87	717.9 (39.8)	30.7	32465.9 (1929.4)
Female	102	964.4 (48.9)	46.5	43845.6 (2495.4)
Race				
White	170	830.4 (34.3)	46.2	37613.4 (1724.1)
Non-white	19	1034.4 (120.1)	46.1	47499.7 (5674.3)
BMI (kg/m_2)				
< 18.5	4	510.8 (140.4)	26.4	25661.1 (7690.7)
18.5 to 25	34	862.0 (81.9)	28.3	37307.7 (4003.6)
> 25	150	851.4 (36.8)	46.8	38906.5 (1844.5)

The mean bupivacaine Cmax and AUC values from the overall data indicated that younger patients (< 45 yr) have lower exposure (Cmax and AUC) and shorter Tmax than older patients in the study. Similarly male patients in the study had lower Cmax and AUC values than compared to the female patients. After considering the variability (values overlap between younger and older patients as well as male and female patients) observed between younger and older patients and male and female patients as can be seen in box plots, it was considered that the differences observed in age and gender do not warrant dose adjustments.

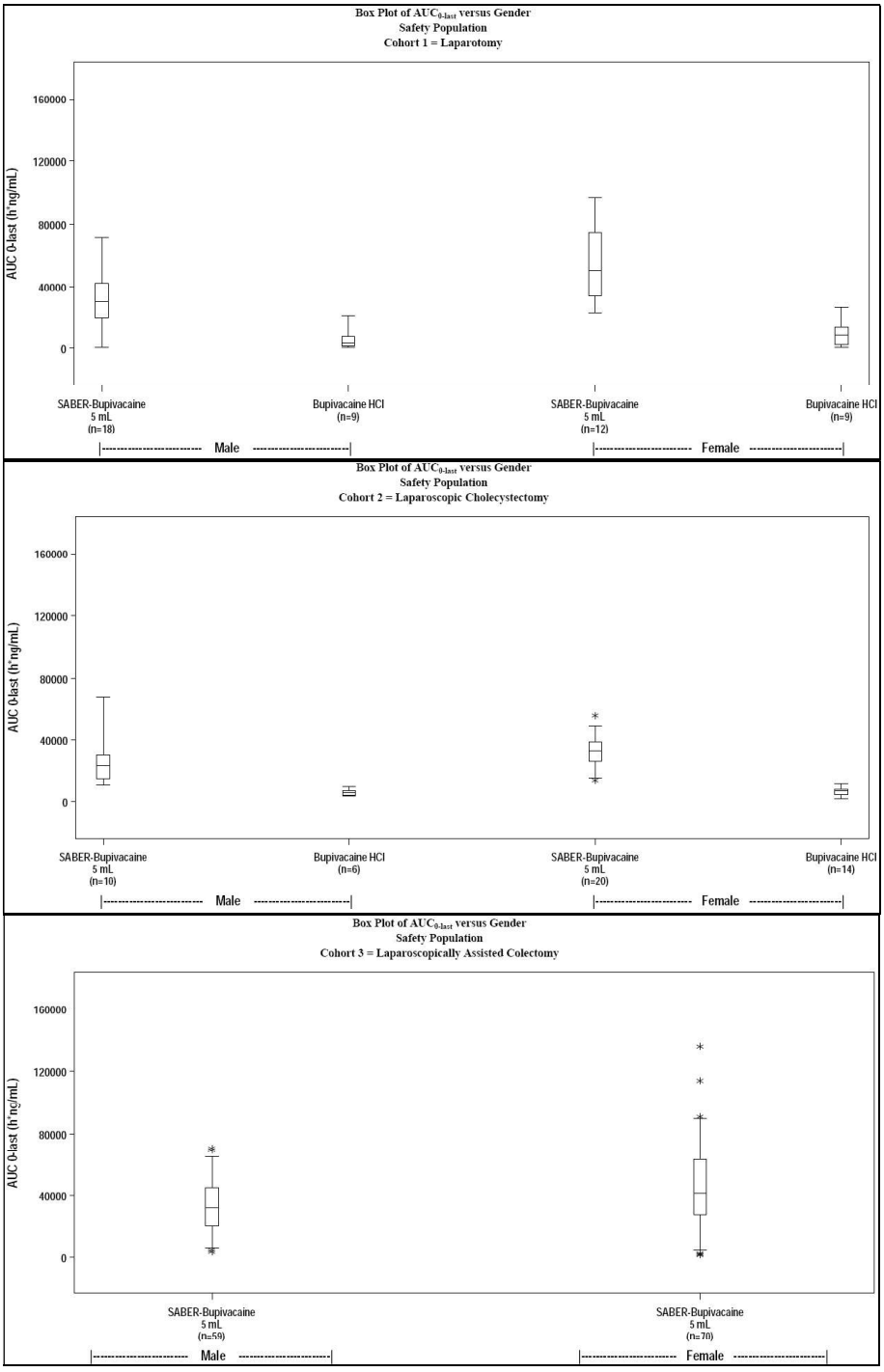
The following box plots (Figure 38) represent Cmax versus gender from laparatomy, laparoscopic cholecystectomy and laparoscopically-assisted colectomy surgeries, respectively.

Figure 38 Box plot of Cmax versus gender from laparatomy (top), laparoscopic cholecystectomy (middle) and laparoscopically-assisted colectomy (bottom) surgeries



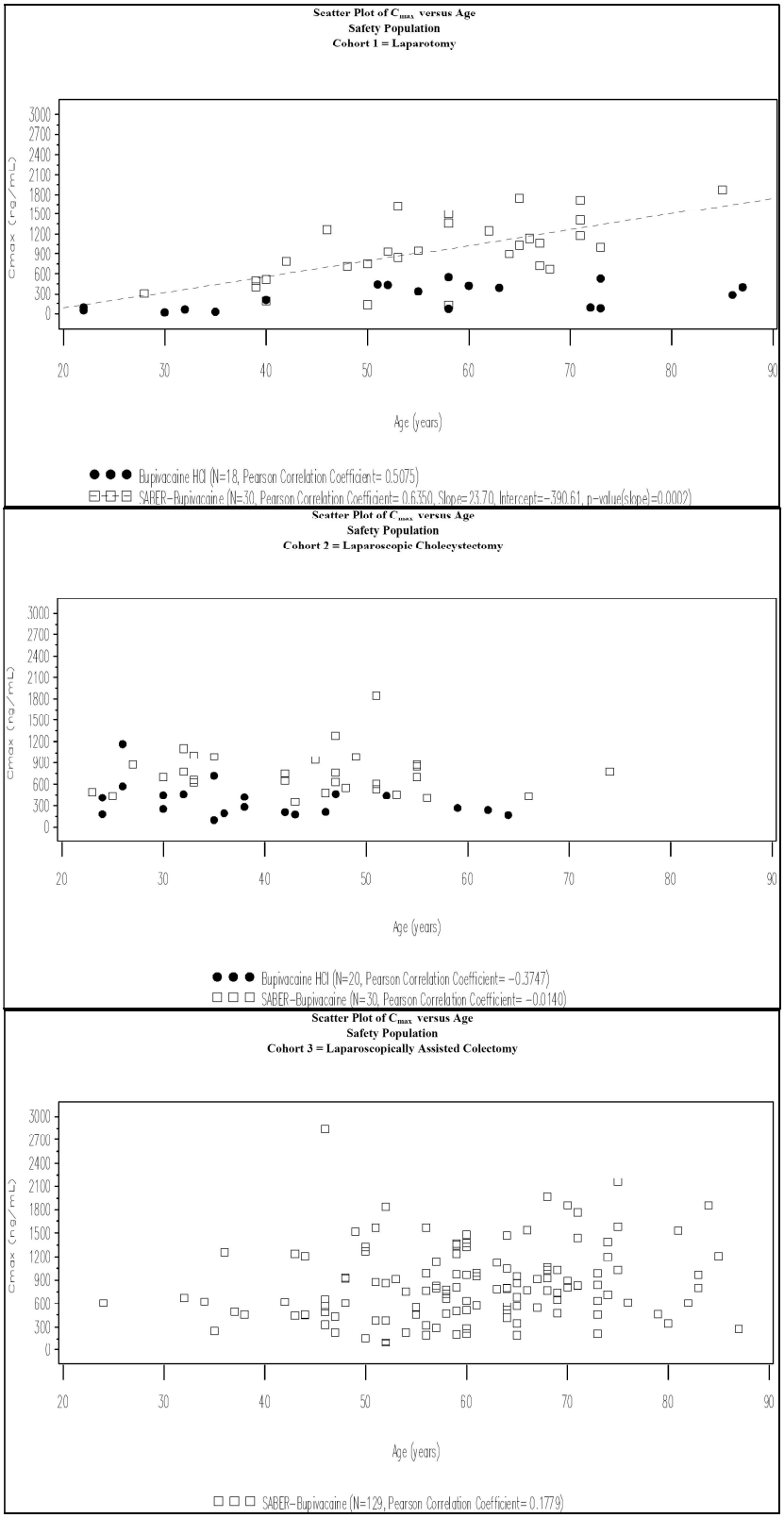
The following box plots (Figure 39) represent AUC(0-last) versus gender from laparatomy, laparoscopic cholecystectomy and laparoscopically-assisted colectomy surgeries, respectively.

Figure 39 Box plot of AUC(0-last) versus gender from laparatomy (top), laparoscopic cholecystectomy (middle) and laparoscopically-assisted colectomy (bottom) surgeries



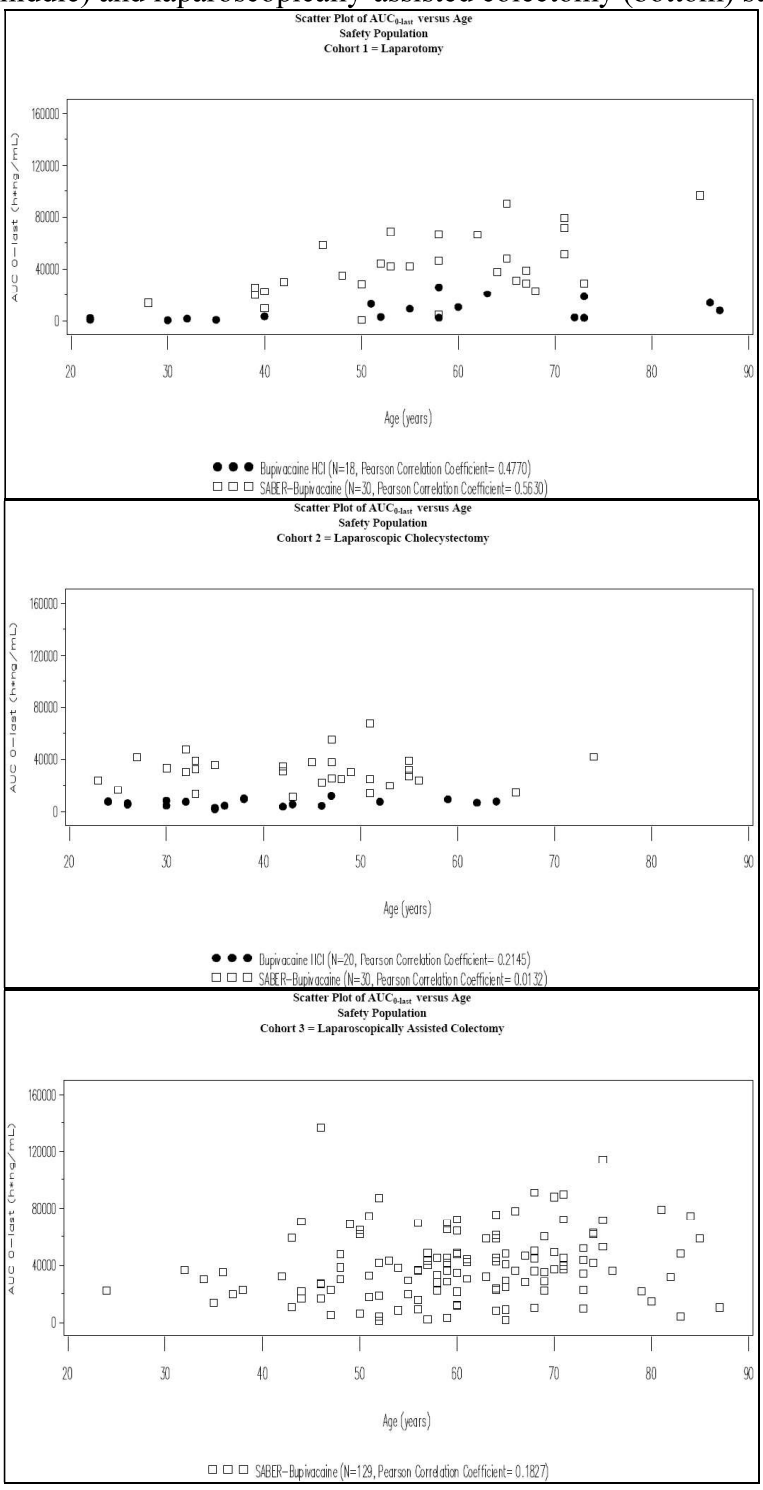
The following box plots (Figure 40) represent Cmax versus age from laparatomy, laparoscopic cholecystectomy and laparoscopically-assisted colectomy surgeries, respectively.

Figure 40 Box plot of Cmax versus gender from laparatomy (top), laparoscopic cholecystectomy (middle) and laparoscopically-assisted colectomy (bottom) surgeries



The following box plots (Figure 41) represent AUC(0-last) versus age from laparatomy, laparoscopic cholecystectomy and laparoscopically-assisted colectomy surgeries, respectively.

Figure 41 Box plot of AUC(0-last) versus age from laparatomy (top), laparoscopic cholecystectomy (middle) and laparoscopically-assisted colectomy (bottom) surgeries



Similar trends were observed for bupivacaine Cmax and AUC(0-last) and BMI and serum creatinine levels.

2.3.1 What is the bupivacaine exposure in pediatric subjects?

Posimir has not been studied in pediatric population. The Applicant seeks waiver for children less than 3 years of age, due to reduced clearance of bupivacaine and benzyl alcohol in the formulation. For children and adolescent (3 to less than 18 years of age), the Applicant seeks deferral. (b) (4)

(b) (4)

2.4 Extrinsic Factors – Not applicable

2.5 General Biopharmaceutics

2.5.1 Relative Bioavailability

Study BU-001-IM: relative bioavailability comparison of 5 mL (660 mg bupivacaine) SABER-Bupivacaine and Marcain (100 mg bupivacaine)

As described above (Section 2.2.5.2.3), Study BU-001-IM provided relative bioavailability information comparing 5.0 mL SABER-Bupivacaine via instillation and 40 mL standard bupivacaine hydrochloride (HCl) (100 mg bupivacaine; Marcain®) via infiltration. Bupivacaine mean Cmax value from SABER-bupivacaine (660 mg bupivacaine) was 625 ng/mL compared to 342 ng/mL with Marcain (100 mg). Bupivacaine mean AUC value SABER-bupivacaine (660 mg bupivacaine) was 36830 ng.h/mL compared to 5740 ng.h/mL with Marcain (100 mg).

2.6 Analytical Section

2.6.1 How is bupivacaine measured in plasma?

The liquid chromatography mass spectrometry (LC-MS/MS) method was used to measure bupivacaine in plasma samples. The LC-MS/MS method has a typical validated linear range from 1 to 3000 ng/mL for bupivacaine. The precision and accuracy of the method were evaluated and validated by using quality control (QC) samples; the typical values for QC samples were 1, 3, 25, 280, 5, 20, 600 and 1400 ng/mL. The typical intra-assay and inter-assay precision (%CV) ranges from 0.5 to 11.5% and 1.8 to 10.2%, respectively. The typical accuracy (% bias) ranges from -6.5 to 7.8%. The LC-MS/MS method used to assay bupivacaine in pharmacokinetic studies appears to be adequate. As an example, the following tables (Tables 27 to 30) contain assay information from the two 'pivotal' clinical safety/efficacy trials, CLIN803-006-0006 standard and BU-002-IM.

Table 27 Back-calculated values of calibration curve from Study CLIN803-006-0006 (pivotal hernia repair study)

Run number	Concentration (ng/mL)							
	1.00	5.00	10.0	20.0	40.0	80.0	160	320
1	1.15	-[a]	-[a]	18.3	42.5	78.3	158	349
	0.886	4.43	8.76	19.2	39.6	83.4	167	362
2	0.943	4.76	9.82	17.6	42.8	86.6	162	331
	1.10	4.55	9.21	20.8	39.5	83.6	163	330
3	1.04	4.88	8.99	17.5	41.6	81.6	168	363
	1.01	4.58	9.03	17.8	40.9	83.0	166	368
4	1.08	4.88	8.93	18.9	41.4	85.1	172	347
	0.975	4.37	8.91	18.8	41.6	80.4	164	353
6	0.990	-[a]	9.34	17.6	41.4	88.1	169	365
	1.04	-[a]	8.79	17.2	38.3	83.4	164	337
7	1.01	4.75	9.47	18.7	38.9	81.4	163	361
	1.04	4.44	9.50	18.9	38.8	82.5	176	350
8	1.14	4.71	9.94	18.5	41.1	85.8	162	342
	0.898	4.57	9.68	18.6	39.5	81.0	162	349
9	1.07	4.33	9.03	17.6	38.3	80.5	157	344
	0.975	4.84	9.76	20.5	38.4	91.3	180	347
10	1.04	4.74	9.25	18.2	35.9	88.9	-[a]	357
	-[b]	-[b]	8.58	19.2	40.4	84.2	177	342
11	1.03	4.66	10.2	18.7	41.2	82.6	168	336
	0.992	4.90	9.56	18.1	38.1	85.6	165	330
12	0.956	4.53	9.34	18.8	39.4	81.5	169	322
	1.08	4.79	10.4	19.0	39.4	83.9	171	344
Mean	1.02	4.65	9.36	18.6	40.0	83.8	167	347
SD	0.07	0.18	0.49	0.9	1.7	3.1	6	13
CV (%)	6.9	3.9	5.2	4.8	4.2	3.7	3.6	3.6
RE (%)	2.0	-7.0	-6.4	-7.0	0.0	4.8	4.4	8.4
n	21	18	21	22	22	22	21	22

[a] - Outside acceptance criteria - excluded from regression
[b] - Preparation error - excluded from regression

Table 28 Quality Control data from Study CLIN803-066-0006 (pivotal hernia repair study

Quality control data

Run number	Low QC (3.00 ng/mL)	Middle QC (25.0 ng/mL)	High QC (280 ng/mL)
1	3.28	22.2	283
	3.08	23.1	274
2	3.42	22.8	283
	3.14	23.5	296
3	3.11	25.0	293
	3.16	26.0	296
4	3.17	23.7	301
	3.13	23.4	319
6	3.15	25.8	285
	3.34	25.3	306
7	2.84	23.8	303
	3.10	25.1	282
8	3.00	23.7	293
	2.78	24.5	288
9	3.37	26.2	283
	3.13	25.1	293
10	2.83	25.2	299
	3.02	23.0	284
11	2.72	24.1	289
	3.14	23.1	297
12	3.05	21.7	287
	3.27	23.3	290
Mean	3.10	24.1	292
SD	0.19	1.3	10
CV (%)	6.0	5.2	3.4
RE (%)	3.3	-3.6	4.3
n	22	22	22

Table 29 Inter batch accuracy of calibration curve from Study BU-002-IM (pivotal subacromial decompression/shoulder study)

Inter Batch	Nom.Conc.	1.000	10.000	30.000	75.000	300.000	750.000	1500.000	2000.000
	Values Used	26 of 30	29 of 30	30 of 30	27 of 30	30 of 30	30 of 30	30 of 30	29 of 30
	Mean	0.997	10.036	31.378	77.503	296.808	732.221	1472.614	1948.979
	%CV	9.31	5.92	3.92	5.99	4.87	5.73	5.26	5.11
	Accuracy	99.7	100.4	104.6	103.3	98.9	97.6	98.2	97.4

Table 30 Intra-and inter-batch accuracy and precision of Quality Control samples from Study BU-002-IM (pivotal subacromial decompression/shoulder study)

Sample Name	Batch	Concentration (ng/mL)	Values	Average conc.(ng/mL)	CV	Acc
QC2	02	5	0	N/A	N/A	N/A
	03	3	2	3.00	11.31%	100.0%
	05	3	2	2.18	15.28%	72.5%
	07	3	2	2.82	1.00%	94.0%
	09	3	2	2.67	1.86%	88.8%
	11	3	2	3.46	17.17%	115.3%
	13	3	2	2.39	12.16%	79.5%
	15	3	2	2.43	10.48%	81.0%
	17	3	2	2.90	11.22%	96.7%
	19	3	2	3.20	10.61%	106.7%
	20	3	2	3.26	8.68%	108.7%
	21	3	2	2.93	7.24%	97.7%
	22	3	2	3.35	0.00%	111.7%
	25	3	2	3.31	11.34%	110.2%
	26	3	2	3.14	6.76%	104.7%
QC2 Inter Batch		3	28	2.93	15.15%	97.7%
QC3	02	600	2	569.00	7.46%	94.8%
	03	600	2	583.50	3.03%	97.3%
	05	600	2	563.50	5.90%	93.9%
	07	600	2	550.50	1.16%	91.8%
	09	600	2	615.00	2.99%	102.5%
Sample Name	Batch	Concentration (ng/mL)	Values	Average conc.(ng/mL)	CV	Acc
	11	600	2	698.50	6.78%	116.4%
	13	600	2	601.00	5.18%	100.2%
	15	600	2	561.50	0.88%	93.6%
	17	600	2	595.50	2.97%	99.3%
	19	600	2	631.50	0.56%	105.3%
	20	600	2	662.50	15.05%	110.4%
	21	600	2	634.50	4.79%	105.8%
	22	600	2	670.50	6.43%	111.8%
	25	600	2	575.00	2.95%	95.8%
	26	600	2	597.00	2.61%	99.5%
QC3 Inter Batch		600	30	607.27	8.38%	101.2%
QC4	02	1400	2	1370.00	10.32%	97.9%
	03	1400	2	1360.00	0.00%	97.1%
	05	1400	2	1390.00	7.12%	99.3%
	07	1400	2	1345.00	15.25%	96.1%
	09	1400	2	1285.00	6.05%	91.8%
	11	1400	2	1550.00	10.95%	110.7%
	13	1400	2	1315.00	3.76%	93.9%
	15	1400	2	1230.00	5.75%	87.9%
	17	1400	2	1400.00	7.07%	100.0%
	19	1400	2	1410.00	2.01%	100.7%
	20	1400	2	1460.00	2.91%	104.3%
	21	1400	2	1430.00	0.99%	102.1%
Sample Name	Batch	Concentration (ng/mL)	Values	Average conc.(ng/mL)	CV	Acc
	22	1400	2	1515.00	4.20%	108.2%
	25	1400	2	1395.00	0.51%	99.6%
	26	1400	2	1365.00	3.63%	97.5%
QC4 Inter Batch		1400	30	1388.00	7.59%	99.1%

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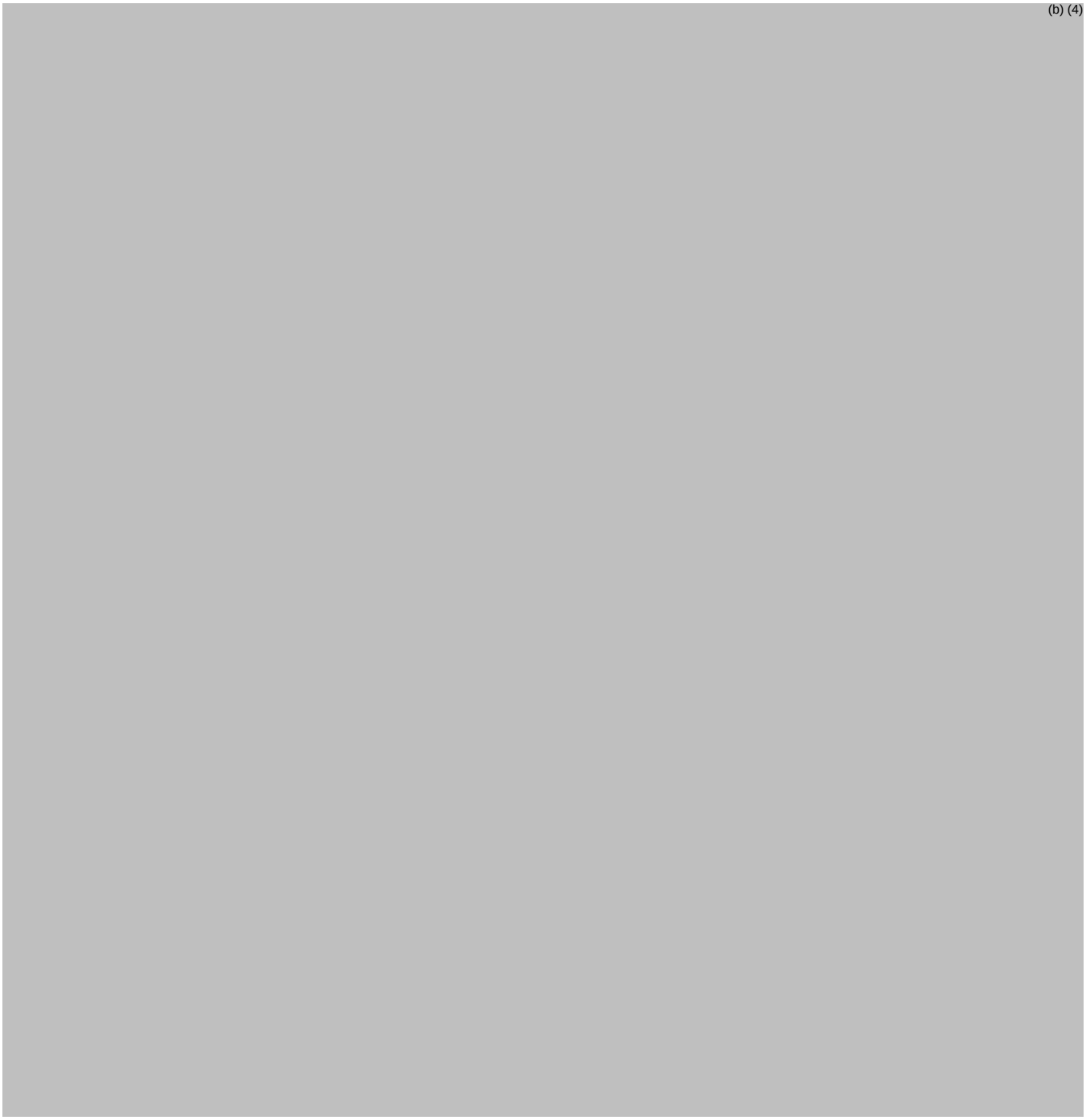


4 Appendices

4.1 Proposed Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRADENAME safely and effectively. See full prescribing information for TRADENAME.

(b) (4)

4.2 Individual Study Reviews

The following table contains studies submitted in the Clinical Pharmacology section.

Protocol	P	Surgery	Study Drug (Dose)	Type of Administration	Note
SABER01-01	I	Healthy Subjects	(b) (4)		**Not reviewed:** not a to-be-marketed formulation
CLIN005-0008	I	Healthy Subjects	SABER-Bup 5.0 mL Bupivacaine HCl IV Infusion (20 mL) Final formulation – NOT an absolute BA study	Two 2.5 mL Trailing subcutaneous Injections	Trailing inj. - advancing a needle into the SC space and inject continuously as the needle was withdrawn.
CLIN004-0001	IIa	Hernia Repair Under general anesthetic	SABER-Bup (2.5, 5.0, 7.5 mL) Bup HCl (15 – 17.5 mL) SABER-Placebo 2 trailing SC injections Salvage 2.5 and 5 mL SC information	Trailing Injections	
CLIN004-0009	IIa	Hernia Repair With local bupi anesthetic (Marcain);	SABER-Bup (5.0, 7.5 mL) Bup HCl (5.0, 7.5 mL)	Infiltration + trailing injections	Interpret data with caution: small number of patients/group; confounding use of local anesthetic.
CLIN005-0002	II	Appendectomy	SABER-Bup (5.0 mL) SABER-Placebo	Trailing Injections Only Infiltration + trailing injections	
CLIN005-0006 (2006-2007)	II	Subacromial Decompression	SABER-Bup (5.0 mL) SABER-Placebo	Subacromial Injection + SC trailing inj. Subacromial Injection	
BU-002-IM (2009-2010)	II	Subacromial Decompression "leakage"	SABER-Bup (5.0, 7.5 mL) SABER-Placebo Bup HCl 50 mg (20 mL)	Subacromial Injection	
CLIN005-0007	II	PILOT study Hernia Repair	SABER-Bup (5.0 mL)	Instillation	**Cursory review:** A pilot study; 'Certain amount of SABER-bupi fluid was seeping out from the wound.' Interpret data with caution.

CLIN803-006-0006	II	Hernia Repair	SABER-Bup (2.5, 5.0 mL) SABER-Placebo Linearity information	Instillation	
BU-001-IM	II	Hysterectomy	SABER-Bup (5.0 mL) SABER-Placebo Bupivacaine HCl 100 mg (40 mL)	Instillation/Infiltration	
C803-025	III	Laparotomy, Laparoscopic Cholecystectomy, Laparoscopically Assisted Colectomy	SABER-Bup (5.0 mL) SABER-Placebo Bupivacaine HCl 30 mL	Instillation/Infiltration	

4.2.1 Study SABER01-01 (subcutaneous) in lower abdomen in healthy subjects 5 mL

This was a Phase 1, first time in human safety, tolerability, sensory effects, and PK study in healthy subjects administered with 2.5 (137.5 mg bupivacaine) and 5 mL (275 mg bupivacaine) SABER-Bupivacaine as subcutaneous trailing injection in the lower abdomen. This study was a 'proof of concept' study which used lower bupivacaine concentration (275 mg vs 660 mg in 5 mL). Additionally the formulation used in this study was not the final to-be-marketed formulation. Therefore, this study was not reviewed.

4.2.2 Study CLIN005-0008 (subcutaneous) in lower abdomen in healthy subjects 5 mL

Title: Study CLIN005-0008 (A Pharmacokinetic Study to Assess Safety and Performance of the Bupivacaine Transdermal Therapeutic System and SABER™ – Bupivacaine in Normal Subjects)

This was an open-label, crossover, Phase 1 study to assess the safety and performance of Bupivacaine Transdermal Therapeutic System (TTS) and SABER™ – Bupivacaine in healthy male and female volunteers. The performances of following treatments were compared: 1) an intravenous (IV) bupivacaine infusion (Part 1a, 4-hour infusion); 2) Bupivacaine TTS (Part 1b: Q24h for 3 days; 3) Bupivacaine TTS (Part 2, one TTS for 72-h application) and 4) SABER-Bupivacaine (Part 3). On Day 0 of study Part 3, subjects received 2 trailing injections of SABER™ – Bupivacaine (12.0 wt%), of 2.5 mL each, into their abdominal subcutaneous space. The trailing injections were accomplished by advancing a needle into the subcutaneous space and injecting SABER™ – Bupivacaine continuously as the needle was withdrawn.

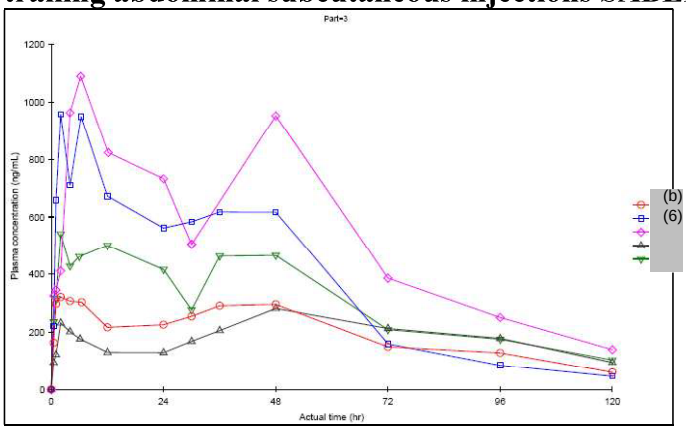
Treatments:

• Bupivacaine injection: a total of 20 mL of 0.4 mg/mL bupivacaine (total 8 mg bupivacaine) delivered by IV infusion at 2 mg/hr for 4 hours;
• Bupivacaine TTS: rectangular-shaped transdermal 140-cm^2 delivery system containing 3% bupivacaine. (140-cm^2 Bupivacaine TTS contains 40.8 mg of bupivacaine base)
• SABER™ – Bupivacaine: 2 trailing abdominal subcutaneous injections of SABER™ – Bupivacaine (12.0 wt%) of 2.5 mL each.

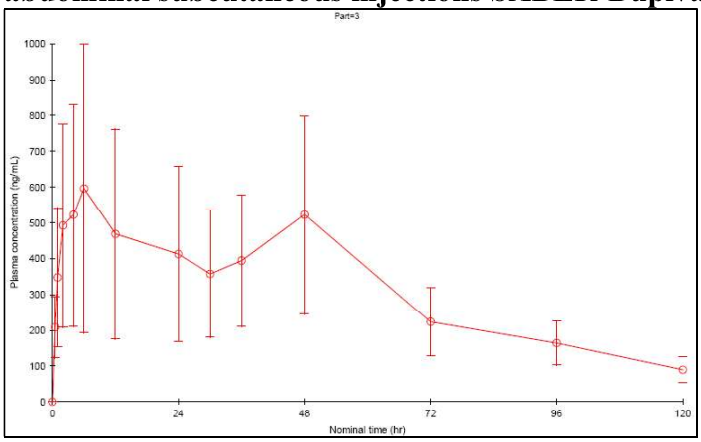
Blood samples were obtained for PK evaluation (4-h infusion: pre-, 1, 2, 3, 4, 4.5, 5, 6, 6.5, 7, 8, 10, 12, and 16 hours post infusion; Bupivacaine TTS Application Q24h for 3 days: pre-, 4, 8, 12, 16, 24, 28, 32, 36, 40, 48, 52, 56, 60, 64, 72, 73, 75, 78, 84, 88, 96, 104, and 112 h; Bupivacaine

TTS single dose: pre-, 4, 8, 12, 16, 24, 30, 36, 40, 48, 54, 60, 64, 72, 78, 84, and 96 h; SABER-Bu: pre-, 0.5, 1, 2, 4, 6, 12, 24, 30, 36, 48, 72, 96, and 120 h).

Plot of Individual Subject Bupivacaine Plasma Concentration-Time Profiles Following two trailing abdominal subcutaneous injections SABER-Bupivacaine Part 3



Mean (SD) Bupivacaine Plasma Concentration-Time Profiles Following two trailing abdominal subcutaneous injections SABER-Bupivacaine (Part 3)



Bupivacaine Plasma Pharmacokinetics Parameters from 2 trailing subcutaneous injections

Subject	AUC0-∞	AUC0-t	Cmax	λz	t1/2	tmax
(b) (6)	26161.15	23198.44	321	0.02	33.89	2
	45329.4	43523.17	957	0.03	26.92	2
	69230.29	62604.35	1090	0.02	32.81	6.28
	28011.97	22297.45	282	0.02	41.48	48
	41559	36207.68	540	0.02	35.67	2
N	5	5	5	5	5	5
Mean	**42058.36**	**37566.22**	**638**	**0.021**	**34.152**	**12.056**
SD	**17315.35**	**16611.8**	**368.407**	**0.003**	**5.246**	**20.179**
Min	26161.15	22297.45	282	0.02	26.92	2
Median	41559	36207.68	540	0.02	33.89	2
Max	69230.29	62604.35	1090	0.03	41.48	48
Range	43069.14	40306.9	808	0.01	14.55	46
CV%	41.2	44.2	57.7	15.9	15.4	167.4

Geometric Mean	39451.94	34799.09	551.439	0.02	33.825	4.747
CV% Geometric Mean	41.098	45.712	67.754	15.7	15.7	241.014

Bupivacaine Cmax and AUC values after two trailing abdominal subcutaneous injections were 638 ng/mL and 42058 ng.h/mL, respectively, in healthy subjects.

4.2.3 Study Clin004-0001 inguinal hernia repair single dose 2.5, 5 and 7.5 mL SABER-bupi with bupivacaine (Sensorcaine)

Title: A Pharmacokinetic/Pharmacodynamic Dose Escalation Study with Subcutaneous and Subfascial Administered SABER-Bupivacaine and/or Bupivacaine HCl Following Open Inguinal Hernia Repair.

This was a single-blind, active-controlled, Phase IIa study to assess the pharmacokinetics/pharmacodynamics, safety and tolerability of SABER as a delivery system in open inguinal hernia repair patients (under general anesthesia). The study also compared the efficacy of a trailing subcutaneous injection of 12.0wt% SABER-Bupivacaine and commercially available 0.5% bupivacaine in the relief of post-operative pain. The study was conducted as three distinct sub-studies, Cohorts 1, 2 and 3.

Treatments: All treatments were administered as two trailing subcutaneous injections administered along each side of the incision (an incision total length of 5 cm). (Note: Infiltration of the wound? How is this done?)

Cohort 1	Cohort 2			Cohort 3	
Total of 2.5 mL SABER-bupi (330 mg bupivacaine) 0.25mL/cm administered along each side of the incision (1.25 mL per side) + 10 mL saline infiltration of the wound (N=6)	Total of 5.0 mL SABER-bupi (660 mg bupivacaine) 0.50mL/cm administered along each side of the incision (2.5 mL per side) + 10 mL saline infiltration of the wound (N=5)	Total of 5.0 mL SABER-bupi (660 mg bupivacaine) 0.50 mL/cm administered along each side of the incision (2.5 mL per side) + 10 mL bupivacaine (0.5%) infiltration of the wound (50 mg bupivacaine) (N=5)	Total of 5.0 mL bupivacaine (Sensorcaine) (25 mg bupivacaine) 0.50 mL/cm administered along each side of the incision (2.5 mL per side) + 10 mL bupivacaine (0.5%) infiltration of the wound (50 mg bupivacaine)	Total of 7.5 mL SABER-bupi (990 mg bupivacaine) Up to 0.75 mL/cm administered along each side of the incision (3.75 mL per side) + 10 mL bupivacaine (0.5%) infiltration of the wound (50 mg bupivacaine) (N=45)	Total of 7.5 mL bupivacaine (Sensorcaine) (37.5 mg bupivacaine) Up to 0.75 mL/cm 0.5% administered along each side of the incision (3.75 mL per side) + 10 mL bupivacaine (0.5%) infiltration of the wound (50 mg

			(N=5)		bupivacaine) (N=15)

Note:
1. The treating Investigator received two syringes containing equal volumes of study drug and two syringes containing equal volumes of infiltrate. The investigator administered the total volume of study drug in the first syringe as a trailing injection adjacent to the incision. The second syringe was used to repeat the trailing injection on the opposite side of the incision. Both study drugs were administered using 19 – 20 gauge spinal needles, with care being taken to avoid intradermal or intravenous injection. Before closure the wound and subfascial area were infiltrated with either saline or 0.5% bupivacaine.
2. 12.0wt% SABER-Bupivacaine Batch Number: 015-04A
3. Bupivacaine: Sensorcaine® Commercially available
4. Cohort 1: 319.25 mg bupi; Cohort 2: 638.5 mg bupi; Cohort 3: 957.8 mg bupi; the Study report stated that 12.0wt% SABER-Bupivacaine is 127.7 mg/mL bupivacaine, rather than 132 mg/mL bupivacaine.

Pharmacokinetic assessments comprised pharmacokinetic evaluation of plasma bupivacaine concentrations. Efficacy assessments were based on pain intensity (visual analogue scale/verbal rating scale), pain relief (verbal rating scale), time to first supplemental analgesia and time to mobilization. Differences between treatment groups were to be assessed using a t-test or Wilcoxon rank sum, as appropriate. The AUC for pain intensity was assessed as the sum of pain intensity. The AUC for pain intensity difference (SPID) was also assessed as the sum of pain intensity adjusted for the baseline value (this was taken as 4 hours). The AUC for pain relief was determined as the total pain relief TOTPAR). The protocol allowed for interim analyses on Cohort 1 and 2 data to ensure safety and efficacy trends, prior to beginning Cohorts 2 and 3, respectively. An interim analysis was also performed on the data from the first 15 patients in Cohort 3.

Blood samples were taken at the following timepoints: Cohort 1 - Day 1 at -5, 15, 30 and 60 minutes, and 2, 2.5, 3, 4, 6, 8 and 12 h, Days 2, 3, 4, 5, 7 and 14 blood samples were collected at approximately the same time of day as study drug injection on Day 1; Cohort 2 and 3 patients - Day 1 at -5, 30 and 60 min, and 2, 4, 8 and 12 hours, Days 2, 3, 4, 5, 7 and 14 blood samples were collected at approximately the same time of day as study drug injection on Day 1.

In this study, the most valuable information is to compare 2.5 and 5 mL SABER-bupi administered along each side of the incision as either 0.25 mL/cm or 0.5 mL/cm, respectively, with 10 mL saline infiltration of the wound. Other treatments were confounded by co-administration with bupivacaine (Sensorcaine).

Median AUCs of Pain Intensity and Pain Intensity Difference (ITT Population)

	Cohort 1	**Cohort 2**	**Cohort 3**

	0.25mL/cm SABER + saline infiltrate (N=6)	0.50mL/cm SABER + saline infiltrate (N=5)	0.50mL/cm SABER + bupivacaine infiltrate (N=5)	0.50mL/cm bupivacaine + bupivacaine infiltrate (N=5)	0.75mL/cm SABER + bupivacaine infiltrate (N=45)	0.75mL/cm bupivacaine + bupivacaine infiltrate (N=15)
At Rest						
1 – 84 hours	1471.59	155.10	380.05	**1563.86**	1249.63	**820.16**
1 – 4 hours	82.14	31.08	64.38	**108.00**	52.75	**45.47**
4 – 84 hours	1389.45	105.99	315.68	**1455.86**	1199.81	**741.32**
SPID 4 – 84 hours	611.00	-14.37	262.91	**514.36**	-26.02	**281.13**
On Coughing						
1 – 84 hours	2678.48	562.67	876.60	**3528.23**	2124.97	**1421.52**
1 – 4 hours	137.01	69.33	79.70	**147.38**	98.50	**66.15**
4 – 84 hours	2517.84	511.36	800.38	**3381.42**	2017.44	**1261.63**
SPID 4 – 84 hours	256.46	208.34	174.16	**1809.26**	0.00	**284.33**

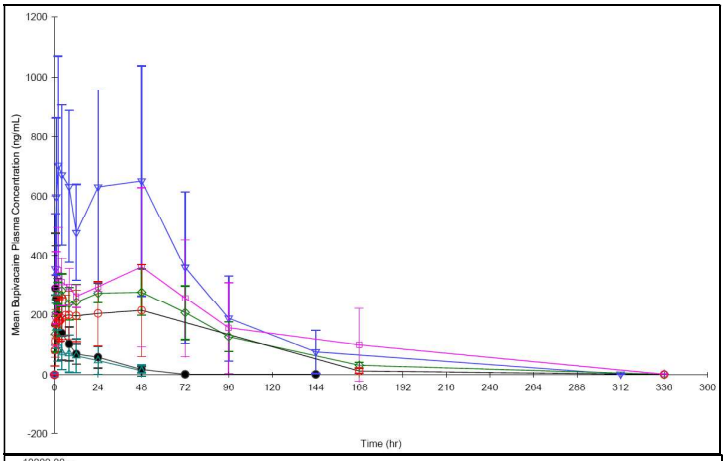
Comparison of the AUCs for patients in Cohort 1 (0.25mL/cm SABER-Bupivacaine + saline infiltrate) and Cohort 2 Treatment Group 1 (0.50mL/cm SABER-Bupivacaine + saline infiltrate) showed that increasing the dose of SABER-Bupivacaine from 0.25 mL/cm to 0.50 mL/cm resulted in a notable reduction in pain intensity at all time periods, both at rest and on coughing.

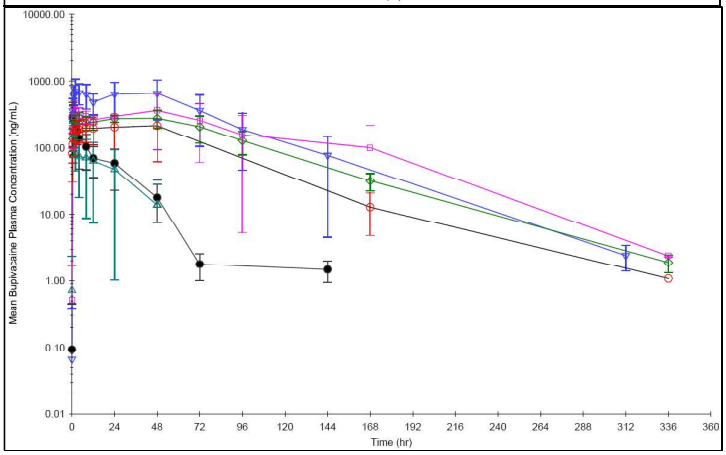
Median AUC of Pain Relief (TOTPAR) (ITT Population)

	Cohort 1	Cohort 2			Cohort 3	
	0.25mL/cm SABER + saline infiltrate (N=6)	0.50mL/cm SABER + saline infiltrate (N=5)	0.50mL/cm SABER + bupivacaine infiltrate (N=5)	0.50mL/cm bupivacaine + bupivacaine infiltrate (N=5)	0.75mL/cm SABER + bupivacaine infiltrate (N=45)	0.75mL/cm bupivacaine + bupivacaine infiltrate (N=15)
At Rest						
1 – 84 hours	313.48	402.38	352.69	**293.96**	308.36	311.51
1 – 4 hours	8.50	12.00	11.75	**8.17**	9.25	9.00
4 – 84 hours	307.59	392.45	342.00	**285.02**	300.92	304.54
On Coughing						
1 – 84 hours	255.27	319.66	314.74	**219.42**	242.72	267.65
1 – 4 hours	6.39	9.75	10.74	**6.02**	7.98	6.50
4 – 84 hours	249.98	313.41	304.00	**212.03**	237.40	261.91

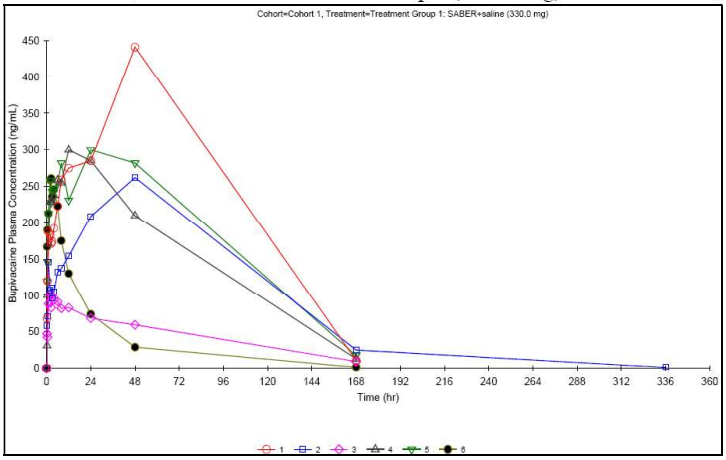
Comparison of the AUCs for patients in Cohort 1 (0.25mL/cm SABER-Bupivacaine + saline infiltrate) and Cohort 2 Treatment Group 1 (0.50mL/cm SABER-Bupivacaine + saline infiltrate) showed that increasing the dose of SABER-Bupivacaine from 0.25 mL/cm to 0.50 mL/cm resulted in a notable increase in pain relief for all time periods, both at rest and on coughing.

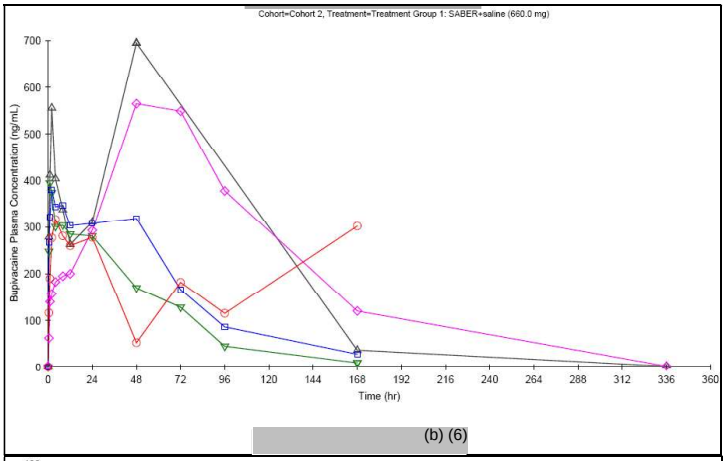
Mean (+/- SD) Bupivacaine plasma concentration-time profiles



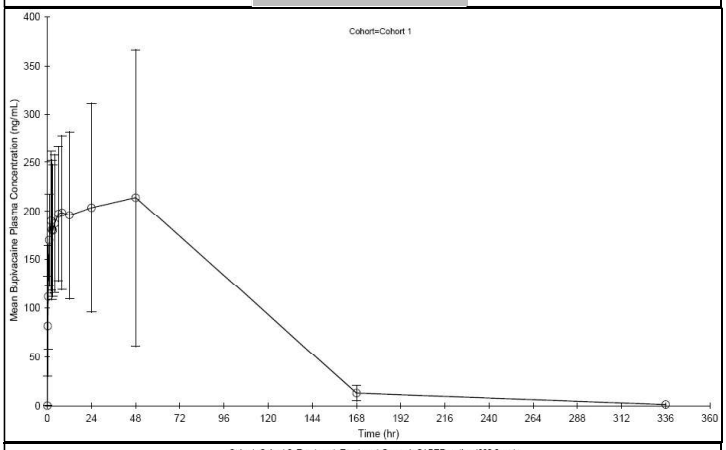


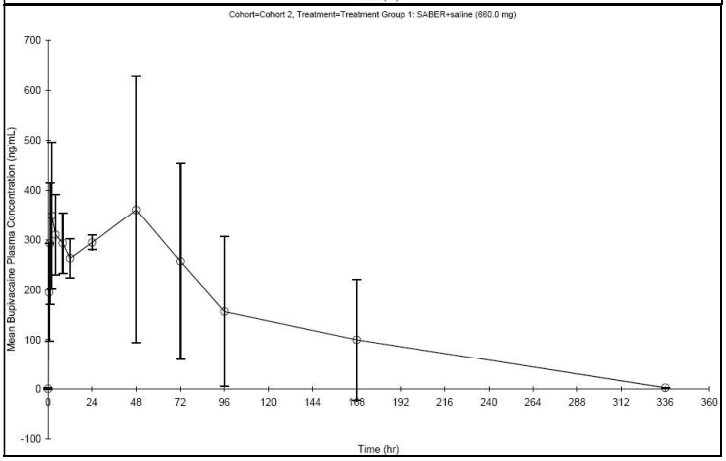
○ Cohort 1, Treatment 1. SABER+Saline (330.0 mg)
◇ Cohort 2, Treatment 2. SABER+0.5% bupiv (710.0 mg)
▽ Cohort 3, Treatment 2. SABER+0.5% bupiv (1040.0 mg)
□ Cohort 2, Treatment 1. SABER+Saline (660.0 mg)
△ Cohort 2, Treatment 3. 0.5% bipiv+0.5% bupiv (75 mg)
● Cohort 3, Treatment 3. 0.5% bipiv+0.5% bupiv (87.5 mg)





(b) (6)





Summary Statistics Of Estimated Pharmacokinetic Parameters By Cohort And Treatment Group

Cohort	Treatment	Subject	λ_z (1/hr)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	AUC_{144hr} (hr*ng/mL)
Cohort 1	Treatment Group 1: SABER+saline Total Bupivacaine: 330.0 mg							
		N	3	3	6	6	6	6
		Mean	0.0211	35.1	22.8	278	18173	17554
		SD	0.0062	11.5	21.1	109	9610	9337

		SE	0.0036	6.6	8.6	45	3923	3812
		Min	0.0145	25.8	2.0	101	5792	5746
		Median	0.0221	31.4	18.0	281	21723	20496
		Max	0.0268	47.9	48.0	441	28605	28221
		CV%	29.6	32.8	92.9	39.3	52.9	53.2
Cohort 2	Treatment Group 1: SABER+saline Total Bupivacaine: 660.0 mg							
		N	3	3	5	5	5	5
		Mean	0.0217	32.7	20.6	470	37263	33430
		SD	0.0039	5.9	25.0	156	17078	14629
		SE	0.0023	3.4	11.2	70	7638	6542
		Min	0.0179	27.0	1.0	317	19474	19172
		Median	0.0215	32.3	4.0	395	29631	26613
		Max	0.0257	38.8	48.0	695	60964	52400
		CV%	18.0	18.0	121.5	33.1	45.8	43.8
Cohort 2	Treatment Group 2: SABER+0.5% Bupivacaine Total Bupivacaine: 710.0 mg							
		N	5	5	5	5	5	5
		Mean	0.0180	39.2	25.2	311	27893	25477
		SD	0.0025	5.5	22.5	61	7370	6672
		SE	0.0011	2.4	10.1	27	3296	2984
		Min	0.0150	33.0	2.0	232	21977	19532
		Median	0.0172	40.4	24.0	342	23979	23272
		Max	0.0210	46.1	48.0	371	37782	34386
		CV%	14.1	14.0	89.4	19.6	26.4	26.2
Cohort 2	Treatment Group 3: 0.5% Bupivacaine+0.5% Bupivacaine Total Bupivacaine: 75 mg							
		N	5	5	5	5	5	5
		Mean	0.0753	14.7	0.6	181	2168	2583
		SD	0.0482	11.4	0.2	89	1616	2132
		SE	0.0215	5.1	0.1	40	723	953
		Min	0.0228	5.3	0.5	64	809	830
		Median	0.0801	8.7	0.5	168	1344	1646
		Max	0.1298	30.5	1.0	311	4046	5722
		CV%	64.0	77.2	37.3	49.0	74.6	82.6
Cohort 3	Treatment Group 2: SABER+0.5% Bupivacaine Total Bupivacaine: 1040.0 mg							
		N	24	24	44	44	44	43
		Mean	0.0220	33.1	21.0	954	55347	55358
		SD	0.0052	7.8	20.3	402	27102	26652
		SE	0.0011	1.6	3.1	61	4086	4064
		Min	0.0143	19.6	1.0	213	15480	15480
		Median	0.0213	32.5	16.0	873	49595	49242

		Max	0.0353	48.6	48.0	1960	152058	152058
		CV%	23.5	23.5	96.6	42.2	49.0	48
Cohort 3	Treatment Group 3: 0.5% Bupivacaine+0.5% Bupivacaine Total Bupivacaine: 87.5 mg							
		N	13	13	15	15	15	13
		Mean	0.0500	16.3	1.2	299	3319	3465
		SD	0.0205	6.9	2.0	184	1230	1248
		SE	0.0057	1.9	0.5	47	318	346
		Min	0.0235	8.1	0.5	142	1772	1853
		Median	0.0503	13.8	0.5	194	2868	3046
		Max	0.0860	29.6	8.0	734	5399	5970
		CV%	41.0	42.2	162.8	61.5	37.1	36.0

Looking at the incidence of adverse events table, Cohort 3, Group 2 did not appear to have additional adverse events than other groups. However, the Applicant stated that there were a couple of cases of severe adverse events in Cohort 3, Group 2.

Summary of Adverse Events (Safety Population)

	Cohort 1 n (%)	**Cohort 2 n (%)**			**Cohort 3 n (%)**	
	0.25mL/cm SABER + saline infiltrate (N=6)	**0.50mL/cm SABER + saline infiltrate (N=5)**	**0.50mL/cm SABER + bupivacaine infiltrate (N=5)**	**0.50mL/cm bupivacaine + bupivacaine infiltrate (N=5)**	**0.75mL/cm SABER + bupivacaine infiltrate (N=45)**	**0.75mL/cm bupivacaine + bupivacaine infiltrate (N=15)**
Patients with at Least One AE	5 (83.3)	4 (80.0)	5 (100.0)	4 (80.0)	37 (82.2)	15 (100.0)
Maximum Severity Mild Moderate Severe	 3 (50.0) 2 (33.3) 0 (0.0)	 2 (40.0) 2 (40.0) 0 (0.0)	 5 (100.0) 0 (0.0) 0 (0.0)	 4 (80.0) 0 (0.0) 0 (0.0)	 31 (68.9) 5 (11.1) 1 (2.2)	 12 (80.0) 2 (13.3) 1 (6.7)
Treatment Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)
Patients with at Least One SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)	1 (6.7)

Between 80% and 100% of patients in the different cohort/treatment groups reported at least one AE. Three SAEs were reported: patient 1022 in Cohort 3 Treatment Group 2 (0.75mL/cm SABER-Bupivacaine + bupivacaine infiltrate) experienced post-procedural haematoma, patient 2047 in Cohort 3 Treatment Group 2 (0.75mL/cm SABER Bupivacaine + bupivacaine infiltrate) experienced lack of response to pain stimuli and patient 2026 in Cohort 3 Treatment Group 3 (0.75mL/cm bupivacaine + bupivacaine infiltrate) experienced suicidal ideation. No patients withdrew from the study due to an AE.

4.2.4 Study Clin004-0009 inguinal hernia repair single dose 5 mL

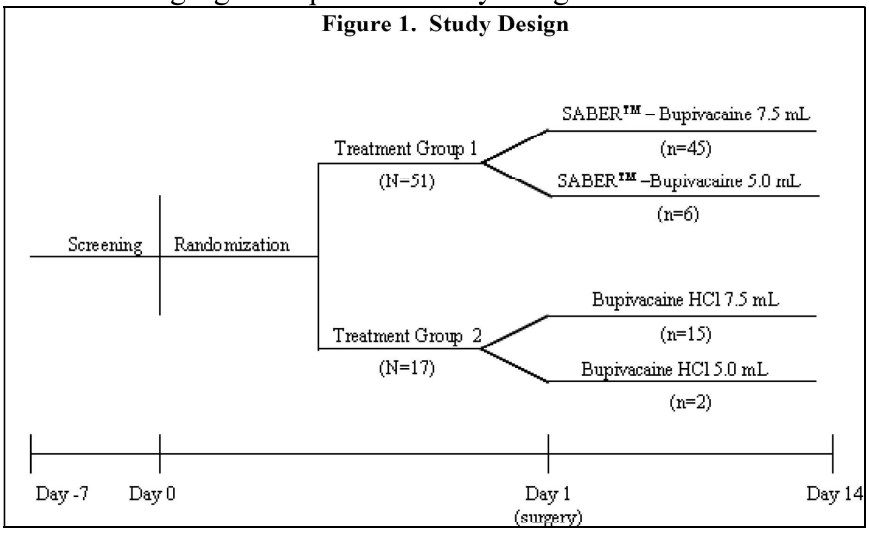
Title: A pharmacodynamic/pharmacokinetic study of SABER-bupivacaine and/or bupivacaine HCl administered Intra-operatively during open inguinal hernia repair Under local anesthesia

This was a Phase IIa study to compare the efficacy of 12.0wt% SABER-Bupivacaine administered subcutaneously (Group 1) and as a wound infiltrate to Bupivacaine HCl (Marcain® 0.25%) administered subcutaneously (Group 2) and as a wound infiltrate in open inguinal hernia repair patients (suggested incision total length was 5 cm). Additionally, this study assessed the pharmacokinetics, safety, and tolerability of SABER as a delivery system. Operative procedures in all patients were performed under local anesthesia (30 mL of Bupivacaine HCl (Marcain® 0.25%) as the local anesthetic, 75 mg of Bupivacaine HCl). The following blood samples were obtained: pre-, 30 min, 60 min, 2, 4, 8 , and 12 h post administration.

For efficacy assessment, the following measures were collected from the patients: incision Pain Intensity, incision Pain Relief (none, a little, some, a lot, or complete, while "At Rest", "When Coughing", and "On Movement" (standardized as sitting upright from the supine position), Pain Control (poor, fair, good, very good, excellent, while "At Rest" and "On Movement" (standardized as sitting upright from the supine position), Overall Incision Pain Intensity (none, mild, moderate, severe, very severe), Overall Pain Relief (none, a little, some, a lot, complete, Overall Pain Control (poor, fair, good, very good, excellent), Time to first supplemental analgesic, the name of the medication, and total analgesic consumption for each dose and day were recorded throughout the study period. The primary efficacy endpoint analysis was based on the difference between treatment groups for the efficacy endpoints sum of pain intensity difference (SPID; comparison of 1-108 h, 1-4 h, 4-108 h) and total pain relief (TOTPAR; comparison of 1-108 h, 1-4 h, 4-108 h) was tested using a general linear model with study center and treatment group as factors.

The following figure depicts the study design:

Figure 1. Study Design



Treatment groups are as follows:

Treatment Group	Local anesthetic for	SABER-Bupivacaine	Bupivacaine HCl (Marcain® 0.25%)	Note

	inguinal hernia procedure			
1	75 mg bupivacaine	2.5 mL SABER-Bupi administered into the deeper wound tissues after hernia repair and prior to wound closure. Then, 5.0 mL SABER-Bupi administered up to 0.5 mL/cm as 2 trailing SC injections, 2.5 mL in each side of the incision. The total delivered volume of SABER-Bupi was 7.5 mL.		**NOTE:** For the first 6 patients only administered SC 2.5 mL in each side of the incision; total delivered volume SABER-Bupi 5.0 mL
2	75 mg bupivacaine		2.5 mL Bupivacaine HCl (Marcain® 0.25%) administered into the deeper wound tissues after hernia repair and prior to wound closure. Then, 5.0 mL Bupi HCl 0.25% Administered up to 0.5 mL/cm as 2 trailing SC injections, 2.5 mL Bupivacaine HCl 0.25% in each side of the incision; Total delivered 7.5 mL (18.75 mg of Bupi HCl)	**NOTE:** For the first 2 patients only administered SC 2.5 mL in each side of the incision; total delivered volume Bupivacaine HCl 0.25% 5.0 mL.

Note:
1. 'Administered into' – not clear how this was conducted; the protocol stated that 'administered 2.5 mL as an infiltrate deep into the wound tissues.' Specifically, "The injector/investigator who will perform the injections will receive two syringes each containing 5.0 mL of study drug. The contents of the first study drug syringe will be used to infiltrate the wound prior to closure, taking care to avoid intradermal or intravenous injection, identified nerves, large blood vessels and the spermatic cord. After wound closure, using the second syringe identified as study drug, the injector/investigator will subcutaneously inject 2.5 mL into the 5.0 cm vertical line 0.5 to 1.0 cm below the incision line. The remaining 2.5 mL of study drug will then be injected into the vertical line 0.5 to 1.0 cm above the incision line. A trailing subcutaneous injection is used to ensure even distribution over the length of the treatment line. For trailing injections a 19-22 gauge spinal needle will be used. Care should be taken to avoid intradermal or intravenous injection.
2. SABER-Bupi: 12.0wt%, 132 mg/mL bupivacaine

The Applicant made the following efficacy conclusions from the study results.
• SABER-Bupivacaine 7.5 mL (990 mg) administered subcutaneously and as a wound infiltrate effectively managed pain in patients who underwent open inguinal hernia repair.
• SABER-Bupivacaine and Bupivacaine HCl were similar with respect to the SPID from 1 to 4 hours and 1 to 108 hours. Statistically significant improvements were observed with SABER-Bupivacaine for AUC of pain intensity difference on coughing from 4 to 108 hours compared with Bupivacaine HCl in some populations.
• SABER-Bupivacaine and Bupivacaine HCl were similar with respect to TOTPAR from 1 to 108 hours and 4 to 108 hours. Statistically significant improvements were observed with SABER-Bupivacaine in the AUC of pain relief at rest, on coughing, and on movement in from 1 to 4 hours compared with Bupivacaine HCl in some populations.

• SABER-Bupivacaine and Bupivacaine HCl were similar with respect to total pain control; total pain control from 1 to 4 hours was significantly improved with SABER-Bupivacaine compared with Bupivacaine HCl in the EVAL population.
• Time to first supplemental analgesia was sooner in patients treated with SABER-Bupivacaine compared with Bupivacaine HCl in most populations.
• There were no significant differences between the SABER-Bupivacaine and Bupivacaine HCl groups in total daily use of supplemental analgesic or the average daily morphine equivalent dose for Days 1 to 14.
• Overall incision pain intensity, overall incision pain relief, and overall pain control improved with time from Day 1 through 13 in both treatment groups.
• Improvements in individual incision pain intensity scores and individual pain control scores over time were greater with SABER-Bupivacaine than with Bupivacaine HCl.
• Individual incision pain relief over time improved over time with Bupivacaine HCl, but not with SABER-Bupivacaine.

Following parameters were presented by the Applicant.

Mean (SEM) [Range] Pharmacokinetic Parameters of Bupivacaine

Pharmacokinetic Parameter	SABER Bupivacaine		Commercial Bupivacaine	
	5.0 mL (N=6)	7.5 mL (N=9)	5.0 mL (N=2)	7.5 mL (N=1)
Tmax (hr)	18.0 (7.26)	3.06 (0.81)	1.25 (0.75)	0.5
	[2.0 – 48.0]	[0.5 – 8.0]	[0.5 – 2.0]	
Cmax (ng/mL)	674.7 (58.01)	1479 (126.5)	477 (307.9)	452
	[550 – 891]	[826 – 2150]	[170 – 784]	
AUC (ng*hr/mL)	49192 (2551)	68135 (5652)	5154 (1373)	6344
	[40301 – 57632]	[45866 – 101596]	[3784 – 6523]	

The time to (T_{max}), and the maximum plasma bupivacaine (C_{max}) concentration after each study treatment is confounded by the use of local anesthetic, thus highly variable data was observed after the SABER-Bupivacaine administration.

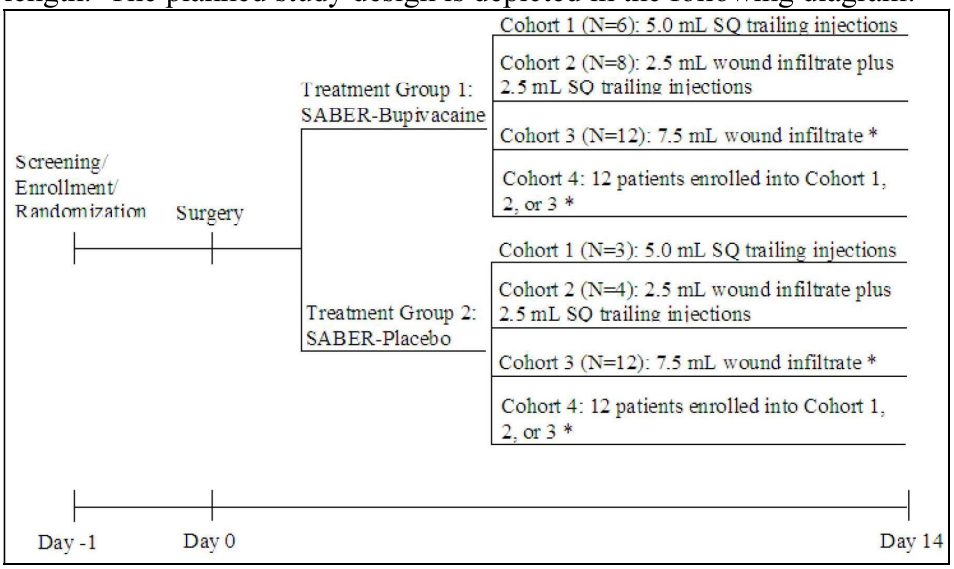
The range of maximum plasma bupivacaine concentration after 5.0 mL and 7.5 mL dose of SABER-Bupivacaine was 550 – 891 ng/ mL and 826 – 2150 ng/mL, respectively. The difference in C_{max} for the 2 doses of SABER-Bupivacaine treatment could also be due to variability in absorption between the deep tissue administration and subcutaneous trailing injections. The overall exposure (AUC) appeared to be somewhat proportional to the administered dose of SABER-Bupivacaine.

Overall, the pharmacokinetic results are not interpretable because of the small number of patients in each treatment group and the confounding use of local anesthetic.

4.2.5 Study CLIN005-002 open appendectomy 5 mL ('wound infiltrate')

Title: A double-blind, placebo-controlled, pharmacodynamic and Pharmacokinetic pilot study with SABER-bupivacaine Administered as a wound infiltrate following semi-elective Open appendectomy

This was a Phase II, single-center, randomized, double-blind, placebo-controlled, parallel-group study. Patients had suspected acute uncomplicated appendicitis, and were planned to undergo a semi-elective open appendectomy surgery that required an incision of approximately 5 cm in length. The planned study design is depicted in the following diagram:



*Cohorts 3 and 4: The study was terminated early because of sponsor changes in the clinical development plan. No patients were enrolled into Cohorts 3 and 4.

Patients were randomized prior to surgery to receive SABER-Bupivacaine 12.0wt% (660 mg bupivacaine) (Treatment Group 1), or SABER-Placebo (Treatment Group 2) administered as a wound infiltrate. For Cohort 1, the total 5.0 mL volume (either SABER-Bupivacaine 12.0wt% or SABER-Placebo) was administered subcutaneously, and equally divided between trailing injections 0.5 cm on each side of the length of the incision. For Cohort 2, the total 5.0 mL volume (either SABER-Bupivacaine 12.0wt% or SABER-Placebo) was administered in two 2.5 mL aliquots: 2.5 mL administered as a wound infiltrate into deeper tissues prior to wound closure and 2.5 mL administered subcutaneously, and equally divided between trailing injections 0.5 cm on each side of the length of the incision. Blood samples were collected at pre-, 1, 2, 4, 8, 12, 24, 48, 72, 96, 168, and 336 h post administration.

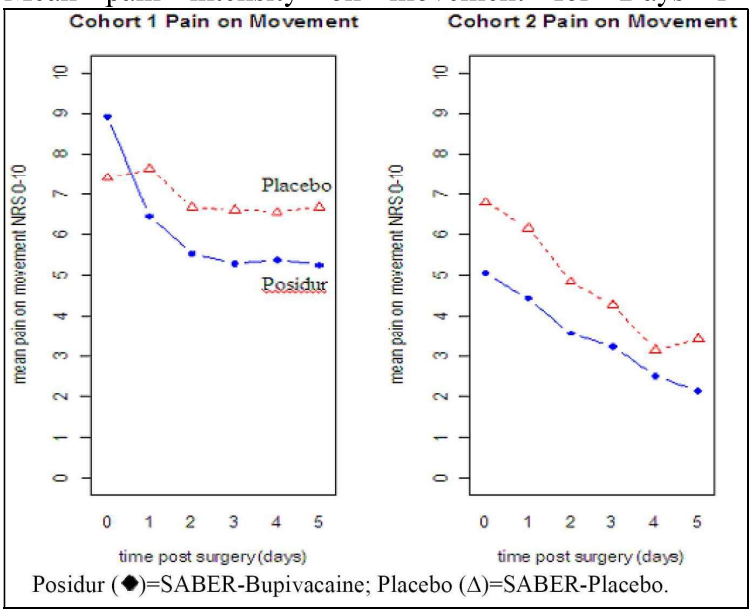
For primary efficacy, pain intensity “at rest” and “on movement” (standardized as sitting upright from the supine position) was measured. On Surgical Day 0 pain intensity scores were recorded at 4 hours post last Study Drug injection, continue every 2 hours through the 12-hour, Day 1, 2, 3, 4, and 5 (e.g., each day at approximately 8, 16 and 20 h). In addition, a pain intensity evaluation was completed immediately prior to dosing with rescue analgesia by all patients.

The Applicant stated that the AUC of pain intensity on movement and at rest for Days 0 through 5 was lower in SABER-Bupivacaine–treated patients compared with SABER-Placebo–treated patients.

Subject Evaluations - AUC of Pain Intensity (1-120 hours) (ITT Population)

	Median	Mean	SD	N	Min	Max	95% CI of Median
AUC on movement 1-120 hr							
Cohort 1: SABER-Bupivacaine	659.21	685.68	132.535	6	516.0	881.6	515.98, 881.58
Cohort 1: SABER-Placebo	810.37	823.22	195.234	3	634.7	1024.6	634.73, 1024.57
Cohort 2: SABER-Bupivacaine	409.51	419.62	130.455	8	267.1	645.1	275.38, 645.13
Cohort 2: SABER-Placebo	499.50	564.11	211.711	4	397.1	860.3	397.13, 860.33
AUC at rest 1-120 hr							
Cohort 1: SABER-Bupivacaine	364.01	395.04	137.982	6	219.1	602.4	219.10, 602.42
Cohort 1: SABER-Placebo	589.14	464.52	334.619	3	85.5	719.0	85.48, 718.95
Cohort 2: SABER-Bupivacaine	231.64	220.67	116.832	8	6.0	379.8	126.21, 379.77
Cohort 2: SABER-Placebo	199.17	270.99	255.099	4	70.3	615.3	70.29, 615.32

Mean pain intensity on movement for Days 1 through 5 in Cohorts 1 and 2



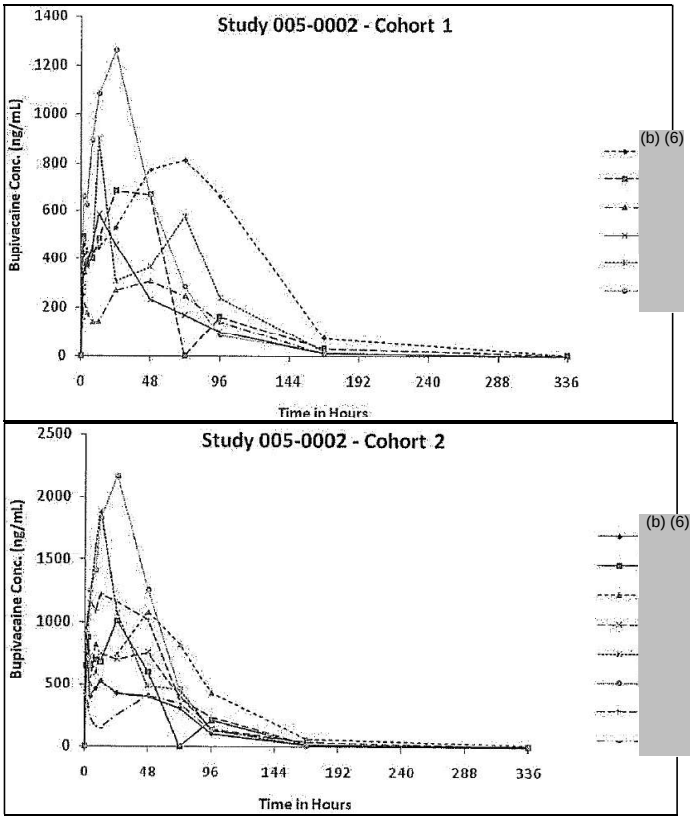
Posidur (◆)=SABER-Bupivacaine; Placebo (Δ)=SABER-Placebo.

The mean AUC of pain control for Days 0 through 5 was higher in SABERBupivacaine–treated patients (308.00) compared with SABER-Placebo–treated patients (216.00) in Cohort 1 and was similar between the 2 treatment groups in Cohort 2 (330.00 for both).

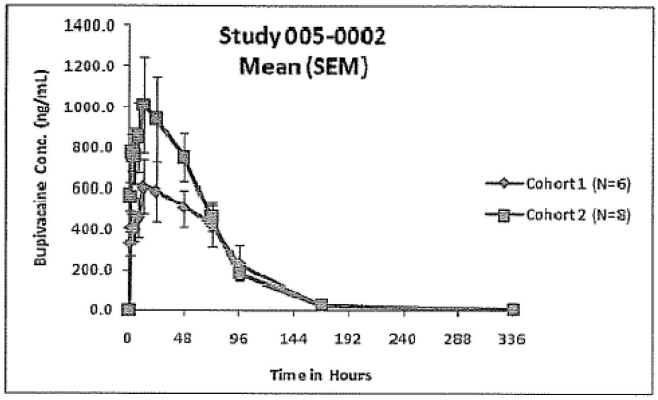
Subject Evaluations - AUC of Pain Control (1-120 hours) (ITT Population)

	Median	Mean	SD	N	Min	Max	95% CI of Median
Cohort 1: SABER-Bupivacaine	288.00	308.00	57.633	6	240.0	408.0	240.0, 408.0
Cohort 1: SABER-Placebo	216.00	216.00	24.000	3	192.0	240.0	192.00, 240.00
Cohort 2: SABER-Bupivacaine	324.00	330.00	72.285	8	216.0	456.0	288.00, 456.00
Cohort 2: SABER-Placebo	324.00	330.00	22.978	4	312.0	360.0	312.00, 360.00

Individual patient and mean plasma bupivacaine concentration time profiles of Cohorts 1 and 2



Pharmacokinetic Profile – Plot of Mean (SEM) Plasma Bupivacaine Concentrations for Cohorts 1 and 2



Individual patient bupivacaine PK parameters for Cohorts 1 and 2

Cohort 1: 5 mL of SABER™- Bupivacaine Administered SC as **Trailing Injection** on each side of incision

Pt. ID	Cohort	Tmax (hr)	Cmax (ng/mL)	Tlast (hr)	Clast (ng/mL)	Kel (1/hr)	Half-life (hr)	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)
(b) (6)									
	1	72	811	336	4.04	0.0205	33.75	86017.62	86214.31
	1	24	682	336	4.17	0.0146	47.50	52885.97	53171.74
	1	48	309	168	7.68	0.0372	18.61	25907.47	26113.66
	1	12	588	168	12	0.028	24.79	30083.16	30512.29
	1	12	898	168	21	0.0344	20.17	47200.31	47811.53
	1	24	1260	168	14.8	0.0294	23.57	63150.10	63653.36
Mean		-	**758.00**	-	**10.62**	**0.03**	**28.06**	**50874.11**	**51246.15**
SD		-	**319.59**	-	**6.64**	**0.01**	**10.89**	**22176.15**	**22152.88**
SEM		-	**130.47**	-	**2.71**	**0.00**	**4.44**	**9053.37**	**9043.88**
Minimum		**12.00**	**309.00**	**168.00**	**4.04**	**0.01**	**18.61**	**25907.47**	**26113.66**
Maximum		**72.00**	**1260.00**	**336.00**	**21.00**	**0.04**	**47.50**	**86017.62**	**86214.31**
Median		**24.00**	**746.50**	**168.00**	**9.84**	**0.03**	**24.18**	**50043.14**	**50491.63**

Cohort 2: 2.5 mL of SABER™- Bupivacaine Administered as **Wound Infiltrate** and 2.5 mL as **Trailing Injection** on each side of incision

Pt. ID	Cohort	Tmax (hr)	Cmax (ng/mL)	Tlast (hr)	Clast (ng/mL)	Kel (1/hr)	Half-life (hr)	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)
(b) (6)									
	2	2	762	336	4.04	0.0127	54.59	39233.27	39551.47
	2	24	1010	336	1.4	0.0196	35.34	61181.23	61252.60
	2	48	1080	336	11.8	0.014	49.50	93911.67	94754.27
	2	48	756	336	3.42	0.0151	45.85	60966.31	61192.55
	2	12	1890	168	11.8	0.037	18.74	72062.69	72381.72
	2	24	2170	168	10	0.0389	17.82	107394.09	107651.19
	2	12	1220	168	22.2	0.0303	22.85	82501.68	83233.53
	2	48	403	168	35.9	0.022	31.50	31733.87	33365.27
Mean		-	**1161.38**	-	**12.57**	**0.02**	**34.52**	**68623.10**	**69172.83**
SD		-	**595.24**	-	**11.50**	**0.01**	**14.29**	**25872.58**	**25715.52**
SEM		-	**210.45**	-	**4.07**	**0.00**	**5.05**	**9147.34**	**9091.81**
Minimum		**2.00**	**403.00**	**168.00**	**1.40**	**0.01**	**17.82**	**31733.87**	**33365.27**
Maximum		**48.00**	**2170.00**	**336.00**	**35.90**	**0.04**	**54.59**	**107394.09**	**107651.19**
Median		**24.00**	**1045.00**	**252.00**	**10.90**	**0.02**	**33.42**	**66621.96**	**66817.16**

Mean (SEM) Pharmacokinetic Parameters

PK Parameter	**Cohort 1 (N=6)**	**Cohort 2 (N=8)**
T_{max} (hr) [a]	24.0 [12.0-72.0]	24.0 [2.0-48.0]
C_{max} (ng/mL)	758.0 (130.5)	1161.4 (210.5)
$T_{1/2}$ (hr) [a]	24.18 [18.61-47.50]	33.42 [17.82-54.59]
AUC_{last} (ng*hr/mL)	50874.1 (9053.4)	68623.1 (9147.3)
AUC_{inf} (ng*hr/mL)	51246.2 (9043.9)	69172.8 (9091.8)
a Median [range].		

Measurable plasma concentrations were observed following administration of SABER-Bupivacaine with sustained levels for 24 to 96 hours. Infiltration along with SC injections in Cohort 2 resulted in higher maximal concentration and exposure as compared to just SC injections in Cohort 1.

4.2.6 Study CLIN005-0006 arthroscopic shoulder surgery (subacromial injection and SC injection) 5 mL – no leakage

Study CLIN005-0006 was a randomized, double-blind, placebo-controlled, Phase 2 study to examine the efficacy and safety of SABER-Bupivacaine **administered subcutaneously** or into the **subacromial space in subjects undergoing elective arthroscopic shoulder surgery**. Surgical procedures were performed under local or general anesthesia according to standard local practice. The study was conducted in 2 separate and sequential cohorts (Cohort 1 and Cohort 2). For all treatment groups if the procedure was performed arthroscopically, the subcutaneous doses of study drug were administered evenly around all arthroscopic portals. Upon completion of Cohort 1, enrollment of subjects into Cohort 2 was started. Protocol Amendment (#04, 11/15/06) changed the amount of drug to be administered in Cohort 2 from 7.5 mL to 5.0 mL (FDA recommendation that additional safety data be collected on the 7.5-mL dose before its use in clinical trials); however, 3 subjects were administered with 7.5 mL SABER-Bupivacaine before this amendment was put into effect.

		Prior to wound closure	After wound closure	During wound closure	Total mg bup	Comments
Cohort 1	TRT 1	5 mL SABER-PL subacromial space injection	5 mL SABER-Bup as 2 trailing SC injections along each side of the incision line (suggested incision total length to be 3 to 6 cm)	-	660 mg	For all treatment groups if the procedure was performed arthroscopically, the subcutaneous doses of study drug were administered evenly around all arthroscopic portals.
	TRT 2	5 mL SABER-Bup subacromial space injection	5 mL SABER-PL as 2 trailing SC injections along each side of the incision line	-	660 mg	
	TRT 3	5 mL SABER-PL subacromial space injection	5 mL SABER-PL as 2 trailing SC injections along each side of the incision line	-	-	
Cohort 2	TRT 4			5.0 mL of SABER-PL subacromial space injection	-	
	TRT 4a			7.5 mL of SABER-PL subacromial space injection	-	
	TRT 5			5.0 mL of SABER-Bup subacromial space injection	660 mg	
	TRT 5a			7.5 mL of SABER-Bup subacromial space injection	990 mg	

In this study, the following comparisons are made:
• Treatment 1 (SABERTM-Bupivacaine subcutaneous inj. 5 mL after wound closure)
• Treatment 2 (SABERTM-Bupivacaine subacromial inj. 5 mL prior to wound closure)
• Treatment 5 (SABERTM-Bupivacaine subacromial inj. 5 mL during wound closure)
• Treatment 5a (SABERTM-Bupivacaine subacromial inj. 7.5 mL during would closure)

In Cohort 2, inclusion was restricted to arthroscopic surgery only (vs. Clinical features of pain indicative of rotator cuff disease and subacromial impingement, necessitating arthroscopic shoulder surgery; and, procedures involving but not limited to subacromial decompression); additionally, open or Mini-open shoulder surgery procedures were excluded.

On Day 0, the blood samples were collected at baseline (pre-dose), 1, 2, 4, 8, and 12 hours post dose. During follow-up visits (Days 1, 2, 3, 4, 5, and 7), daily blood samples was collected at approximately the same time of day that SABER-Bupivacaine was administered on the Day of Surgery. Approximately 5.0 mL of blood was collected at each time point. The total amount of blood collected from each patient over the 7 days was approximately 60 mL.

On Day 0, the pain intensity (PI) was evaluated approximately 4, 6, 8, 10, and 12 hours following surgery and administration of the study drug. On Day 1 through Day 6, the PI was evaluated at approximately 08:00, 12:00, 16:00, and 20:00. On Day 7, the PI was evaluated at 08:00 and 12:00. The actual time of assessment was reported for each evaluation. In addition to the determination of total bupivacaine concentration (as described in the PK Substudy protocols), the PK samples from subjects receiving a 5.0-mL dose of SABER-Bupivacaine were also analyzed for the determination of 'free (unbound)' bupivacaine concentration using an HPLC method. These results will be discussed in a separate report.

The primary efficacy variables were PI_{move} and PI_{rest}, assessed using the time-weighted average scores (AUCs) for the PP Population (0=no pain, 10=worst pain possible).
Mean PI_{move} values in the SABER™-Bupivacaine treatment groups were 5.47, 3.27, and 5.12 (Treatments 1, 2, and 5, respectively), compared to 5.22 in the Pooled Placebo group. Treatment 2 had the lowest mean value (least pain). The comparison to the Pooled Placebo group demonstrates that Treatment 2 was significantly better than Pooled Placebo (treatment difference = -1.95, 95% CI = -3.59 to -0.31, P=0.02). The SABER™-BUP group was numerically better than Pooled Placebo (treatment difference = -1.03, 95% CI = -2.14 to 0.09); this difference did not reach statistical significance (P=0.072). For average PI during rest, Treatment 2, Treatment 5, and SABER™-BUP were numerically better than Pooled Placebo; these differences did not reach statistical significance.

The tables below are based on ANOVA model and details are provided in the statistical analysis plan. The term "pooled placebo" implies that all summaries, simple and least square (LS) means, will give equal weight to each subject. A single ANOVA is described with treatment classifications that include Treatment 2, Treatment 5, and SABER™- BUP. The model-based LS-Mean for SABER™-BUP gives equal weight to the means of
Treatments 1 and 2, but the pooled placebo is defined as a single classification and so gives equal weight to each subject.

Table 10.2	Summary of Baseline Demographic Characteristics (ITT Population)							
		Treatment 1 (n=14)	Treatment 2 (n=10)	Treatment 5 (n=21)	Treatment 5a (n=3)	SABER™-BUP (n=31)	Pooled Placebo (n=44)	All Subjects (N=92)
Age (years)	Mean (SD)	57.1 (10.72)	51.9 (12.76)	53.6 (9.97)	39.0 (17.69)	53.0 (10.76)	55.0 (12.23)	54.1 (11.91)
	Range (min – max)	42 – 77	20 – 65	36 – 72	20 – 55	20 – 72	25 – 82	20 - 82
Gender, n (%)	Female	6 (42.9%)	3 (30.0%)	12 (57.1%)	1 (33.3%)	15 (48.4%)	16 (36.4%)	38 (41.3%)
	Male	8 (57.1%)	7 (70.0%)	9 (42.9%)	2 (66.7%)	16 (51.6%)	28 (63.6%)	54 (58.7%)
Race, n (%)	White	9 (64.3%)	9 (90.0%)	20 (95.2%)	3 (100.0%)	29 (93.5%)	39 (88.6%)	80 (87.0)
	Asian	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (3.2%)	1 (2.3%)	2 (2.2%)
	Black or African American	5 (35.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.5%)	7 (7.6%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	2 (4.5%)	3 (3.3%)
Ethnicity, n (%)	Hispanic or Latino	0 (0.0%)	1 (10.0%)	3 (14.3%)	1 (33.3%)	4 (12.9%)	3 (6.8%)	8 (8.7%)
	Not Hispanic or Latino	14 (100.0%)	9 (90.0%)	18 (85.7%)	2 (66.7%)	27 (87.1 %)	41 (93.2%)	84 (91.3%)
Height (cm)	Mean (SD)	172.31 (13.506)	176.89 (10.315)	169.33 (11.771)	172.00 (3.606)	171.77 (11.714)	171.40 (10.626)	171.68 (11.182)
	Range (min – max)	154.9 – 196.0	154.9 – 190.0	152.0 – 191.0	168.0 – 175.0	152.0 – 191.0	150.0 – 195.6	150.0 – 196.0
Weight (kg)	Mean (SD)	90.67 (13.915)	90.28 (13.111)	83.27 (13.376)	82.73 (17.437)	85.53 (13.490)	86.81 (17.991)	86.83 (15.833)
	Range (min – max)	63.6 - 107.3	66.8 - 107.9	60.9 - 107.0	70.3 - 102.7	60.9 - 107.9	62.7 - 135.2	60.9 -135.2

Treatments (5.0 mL):
1 = SABER™-Bupivacaine Subcutaneous
2 = SABER™-Bupivacaine Subacromial
3 = SABER™-Placebo
4 = SABER™-Placebo
5 = SABER™-Bupivacaine
Treatments 4a and 5a are the same as Treatments 4 and 5, but using 7.5 mL
SABER™-BUP = Treatments 2 and 5
Pooled Placebo = Treatments 3, 4a, and 4

Table 11.1 Summary of Pain Intensity During Movement Time-weighted Average Scores (AUC/120), PP Population

			Comparison to Pooled Placebo	
Treatment	n	Mean (SD)	Mean Difference (95% CI)	*P*-value
Treatment 1	14	5.47 (2.352)	0.25 (-1.13 – 1.62)	0.720
Treatment 2	9	3.27 (1.648)	-1.95 (-3.59 – -0.31)	0.020
Treatment 5	21	5.12 (2.230)	-0.10 (-1.29 – 1.09)	0.866
SABER™-BUP	30	4.56 (2.219)	-1.03 (-2.14 – 0.09)	0.072
Pooled Placebo	44	5.22 (2.281)		

Source: Table 14.2.1, Table 14.2.2, and Listing 16.2.7.1
Treatments (5.0 mL):
1 = SABER™-Bupivacaine Subcutaneous
2 = SABER™-Bupivacaine Subacromial
3 = SABER™-Placebo
4 = SABER™-Placebo
5 = SABER™-Bupivacaine
Treatments 4a and 5a are the same as Treatments 4 and 5, but using 7.5 mL
SABER™-BUP = Treatments 2 and 5
Pooled Placebo = Treatments 3, 4a, and 4

Table 11.2 Summary of Pain Intensity During Rest Time-weighted Average Scores (AUC/120), PP Population

			Comparison to Pooled Placebo	
Treatment	n	Mean (SD)	Mean Difference (95% CI)	*P*-value
Treatment 1	14	3.53 (2.331)	0.43 (-0.76 – 1.63)	0.473
Treatment 2	9	2.16 (1.496)	-0.95 (-2.37 – 0.48)	0.190
Treatment 5	21	2.58 (1.674)	-0.52 (-1.56 – 0.51)	0.315
SABER™-BUP	30	2.45 (1.609)	-0.73 (-1.71 – 0.24)	0.136
Pooled Placebo	44	3.10 (1.995)		

Source: Table 14.2.1, Table 14.2.2, and Listing 16.2.7.1
Treatments (5.0 mL):
1 = SABER™-Bupivacaine Subcutaneous
2 = SABER™-Bupivacaine Subacromial
3 = SABER™-Placebo
4 = SABER™-Placebo
5 = SABER™-Bupivacaine
Treatments 4a and 5a are the same as Treatments 4 and 5, but using 7.5 mL
SABER™-BUP = Treatments 2 and 5
Pooled Placebo = Treatments 3, 4a, and 4

Table 11.3 Pain Control on Study Days 1 through 7 by Treatment, PP Population							
	Mean Pain Control by Day						
Treatment Group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Treatment 1	3.0	2.7	3.1	3.0	3.2	3.1	3.1
Treatment 2	3.3	3.4	3.2	3.4	3.4	3.7	3.8
Treatment 5	3.3	3.4	3.4	3.7	3.6	3.6	3.7
SABER™-BUP	3.3	3.4	3.3	3.6	3.5	3.6	3.7
Pooled Placebo	2.5	3.0	3.4	3.4	3.4	3.4	3.6
P-value (SABER™-BUP vs. Pooled Placebo)	0.008	0.111	0.767	0.532	0.608	0.380	0.689

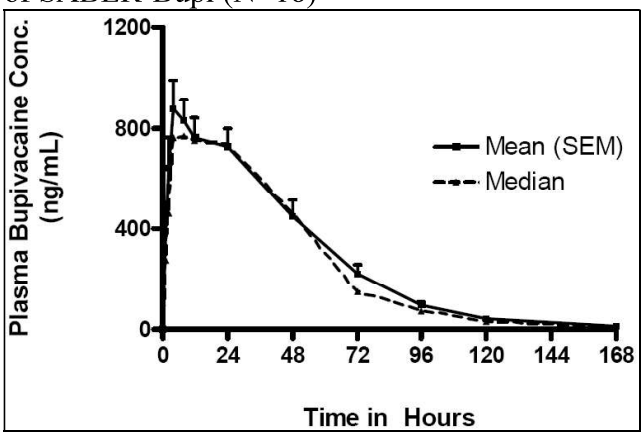
Source: Table 14.2.5 and Listing 16.2.7.2
Treatments (5.0 mL):
1 = SABER™-Bupivacaine Subcutaneous
2 = SABER™-Bupivacaine Subacromial
3 = SABER™-Placebo
4 = SABER™-Placebo
5 = SABER™-Bupivacaine
SABER™-BUP = Treatments 2 and 5
Pooled Placebo = Treatments 3, 4a, and 4

The results of the per-protocol (PP) analysis showed that, for the primary endpoint of PI during movement, the PI on movement for Treatment 2 (SABERTM-Bupivacaine Subacromial) was significantly better than the Pooled Placebo group (*P*=0.02); Treatment 1 (SABERTM-Bupivacaine Subcutaneous), Treatment 5 (SABERTM-Bupivacaine), and SABER™-BUP (Treatments 2 and 5) were not significantly better than the Pooled Placebo group (Treatments 3, 4a, and 4). For the primary endpoint of PI at rest, there were no statistically significant differences between the SABERTM-Bupivacaine treatment groups and the Pooled Placebo groups. For the primary endpoint of pain control, the only statistically significant difference was observed at Day 1 between the SABERTM-BUP treatment group (Treatment 2 and 5, SABERTM-Bupivacaine Subacromial and SABERTM-Bupivacaine, respectively) and the Pooled Placebo group (*P*=0.008). For the secondary endpoints, there were no statistically significant differences between the SABERTM-Bupivacaine treatment groups and the Pooled Placebo group.

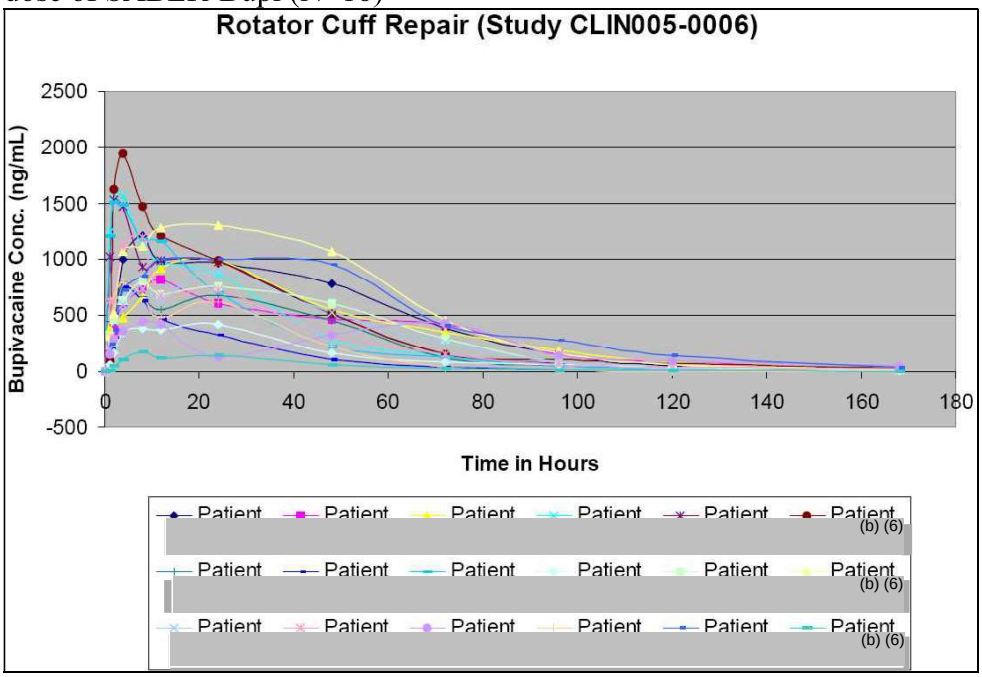
A post hoc analysis of PI over time was conducted for the 2 cohorts separately. In Cohort 1, the SABERTM-Bupivacaine subacromial treatment group (Treatment 2) had a lower PI on movement compared with the placebo group (Treatment 3) and no difference was observed between the SABERTM-Bupivacaine subcutaneous treatment group (Treatment 1) and the placebo group (Treatment 3). In Cohort 2, no reduction in PI on movement was observed in the SABERTM-Bupivacaine subacromial treatment group (Treatment 5) versus placebo (Treatment 4). No differences in opioid rescue analgesia use were observed between the treatment groups in Cohort 1 and Cohort 2. A subgroup analysis was performed on subjects from both cohorts who had minimal or no glenohumeral pathology. In this subanalysis, those treatment groups using subacromial administration of SABERTM-Bupivacaine (Treatments 2 and 5) had a lower PI on movement compared to placebo (Treatments 3 and 4). Treatment 1, which used subcutaneous

administration of SABER™-Bupivacaine, did not show a reduction in PI on movement compared to placebo. No differences between treatment groups were observed in consumption of opioid supplementation in the subgroup analysis.

Linear plot of observed plasma bupivacaine concentrations following subacromial 5.0 mL dose of SABER-Bupi (N=18)



Individual plot of observed plasma bupivacaine concentrations following subacromial 5.0 mL dose of SABER-Bupi (N=18)



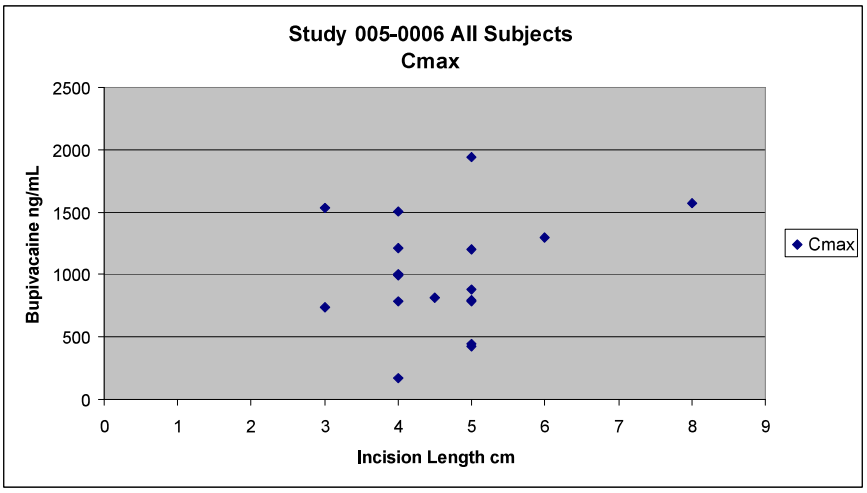
Mean (SEM) Pharmacokinetic Parameters of Bupivacaine Following 5.0 mL dose of SABER™-Bupivacaine administered in the subacromial space Parameter Mean and SD [Range]. All subjects had acromioplasty, subacromial decompression procedure.

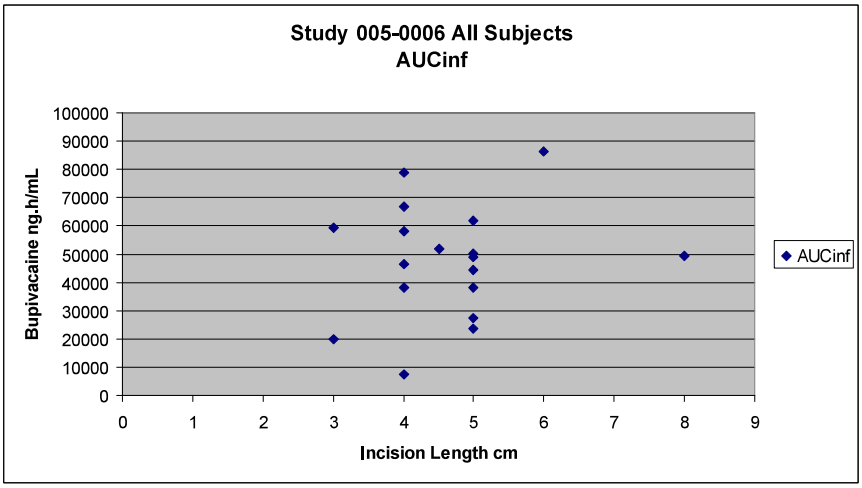
Subj.	Age	Gender	Incision length cm	Cmax ng/mL	Tmax h	AUCinf ng.h/mL	T1/2 h
(b) (6)	58	M	4	1210.00	7.9	66929	18.58
	42	M	4.5	813	11.85	51964	18.92

(b) (6)	72	F	4	990	23.13	58226	22.55
	59	M	8	1570	4.25	49420	22.96
	45	F	3	1530	2.08	59417	28.4
	54	M	5	1940	4.25	61797	30.4
	56	M	4	785	4.10	38233	21.14
	66	F	3	741	4.52	20112	24.36
	28	M	4	1510	2.47	46573	28.02
	43	M	5	423	25.15	23676	32.73
	59	F	5	798	8.10	50003	20.03
	60	F	6	1300	25.43	86448	20.38
	74	F	5	885	26.85	49066	16.64
	50	M	5	1200	7.82	44196	36.41
	51	M	5	445	8.17	38038	50.84
	53	M	5	787	4.13	27515	20.88
	69	F	4	1000	11.77	78715	26.74
	37	M	4	172	8.03	7346	29.83
Mean				1006	10.56	47649	26.1
SD				453.6	8.51	20116	5.22
Min				172	2.08	7346	16.64
Max				1940	26.85	86448	50.84

S3-28, 29, 33, 34: Treatment 5 (5.0 mL subacromial space injection during wound closure);

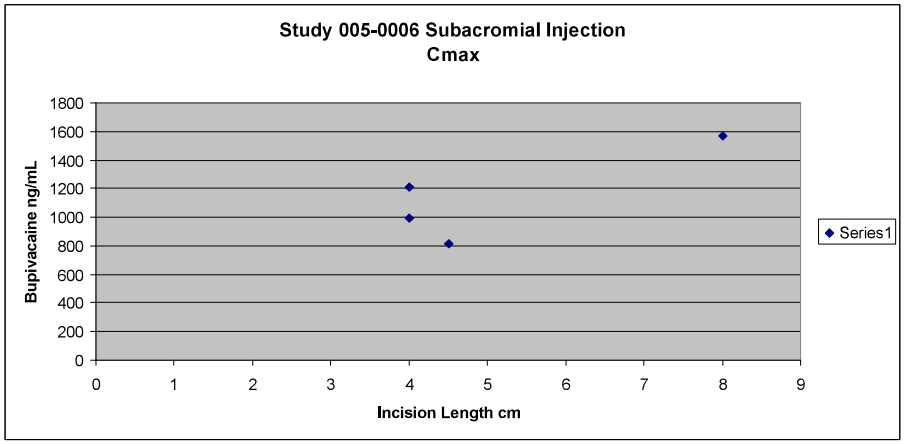
All other subjects: Treatment 1 (5.0 mL 2 trailing subcutaneous inj. along side of the incision line after wound closure)

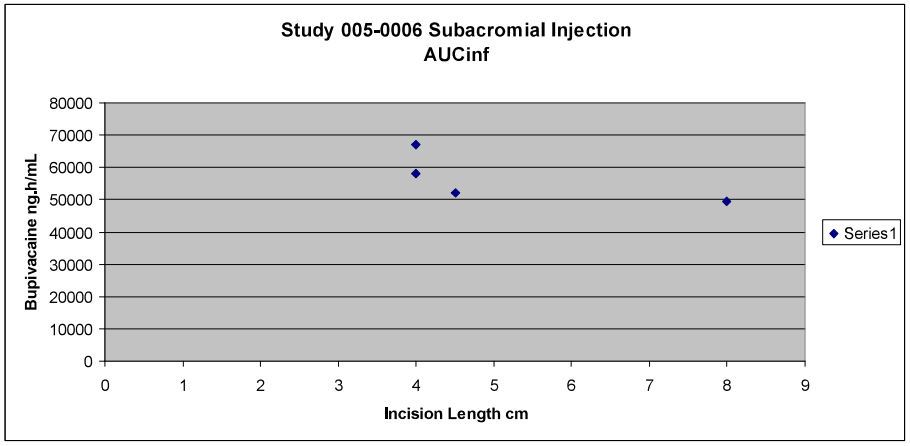




Treatment 5 (5.0 mL subacromial space injection during wound closure);

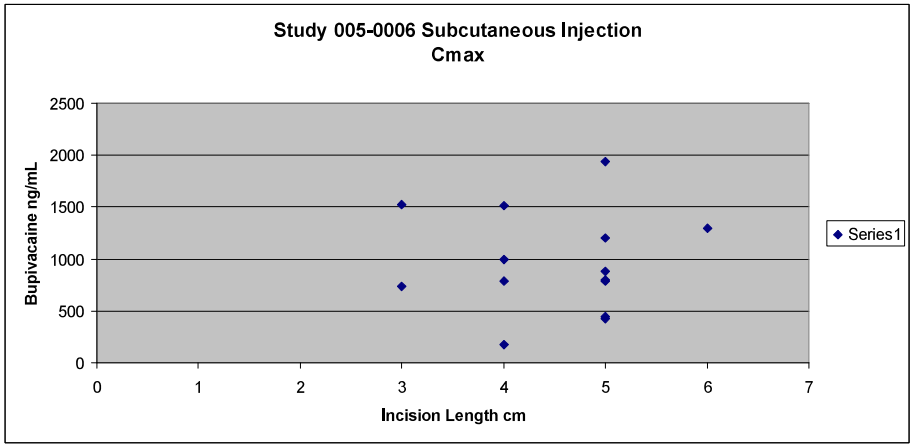
Subj.	Age	Gender	Incision length cm	Cmax ng/mL	Tmax h	AUCinf ng h/mL	T1/2 h
(b) (6)	58	M	4	1210	7.9	66929	18.58
	42	M	4.5	813	11.85	51964	18.92
	72	F	4	990	23.13	58226	22.55
	59	M	8	1570	4.25	49420	22.96
Mean				1146	11.78	56635	20.75
SD				326	8.18	7797	2.32
Min				813	7.9	49420	18.58
Max				1570	23.13	66929	22.96

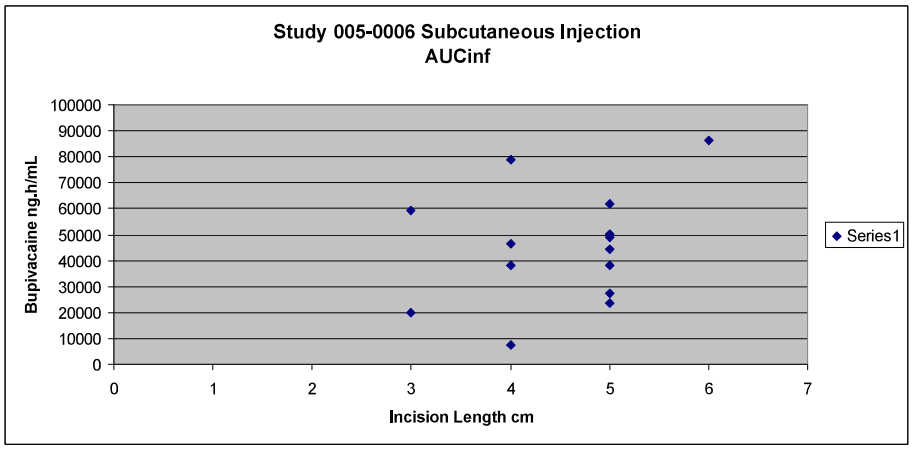




Treatment 1 (5.0 mL 2 trailing subcutaneous injection along side of the incision line after wound closure)

Subj.	Age	Gender	Incision length cm	Cmax ng/mL	Tmax h	AUCinf ng h/mL	T1/2 h
(b) (6)	45	F	3	1530	2.08	59417	28.4
	54	M	5	1940	4.25	61797	30.4
	56	M	4	785	4.10	38233	21.14
	66	F	3	741	4.52	20112	24.36
	28	M	4	1510	2.47	46573	28.02
	43	M	5	423	25.15	23676	32.73
	59	F	5	798	8.10	50003	20.03
	60	F	6	1300	25.43	86448	20.38
	74	F	5	885	26.85	49066	16.64
	50	M	5	1200	7.82	44196	36.41
	51	M	5	445	8.17	38038	50.84
	53	M	5	787	4.13	27515	20.88
	69	F	4	1000	11.77	78715	26.74
	37	M	4	172	8.03	7346	29.83
Mean				965	10.21	45081	27.63
SD				487	8.86	21981	8.71
Min				172	2.08	7346	16.64
Max				1940	26.85	86448	50.84





The mean maximum plasma concentration of bupivacaine observed was 1006 ng/mL, which occurred at the mean time of 10.56 hours post dosing. The mean AUC (0-inf) was 47649 ng*hr/mL.

Patients, (b) (6) received 7.5 mL SABER-Bupivacaine – note that there are no PK information from 7.5 mL SABER-Bupivacaine.

4.2.7 Study BU-002-IM arthroscopic shoulder surgery 5 mL ('administered into the subacromial space') – suspected 'leakage' of drug from the surgical site

Title: An international, randomized, double-blinded, multi-centre, active- and placebo-controlled dose response trial to evaluate the efficacy and safety of SABER-Bupivacaine for post-operative pain control in patients following arthroscopic shoulder surgery

Study BU-002-IM was a parallel group, randomized, double-blinded, active- and placebo-controlled, dose response trial of SABER-Bupivacaine with post-operative assessments of pain intensity (PI), PK, safety, and health economics in patients undergoing elective **arthroscopic shoulder surgery**. The objective of this clinical trial was to identify the optimal dose of SABER-Bupivacaine for post-operative pain control administered into the subacromial space in patients undergoing elective arthroscopic shoulder surgery on the basis of PK, efficacy, and

safety evaluations. There were two Cohorts. Both cohorts had three treatment groups: a) 5 mL or 7.5 mL SABER-Bupivacaine (660 mg or 990 mg bupivacaine, respectively) subacromial administration; b) 5 mL or 7.5 mL SABER-placebo subacromial administration; and c) 20 mL standard bupivacaine hydrochloride (HCl) (50 mg bupivacaine; AstraZeneca. The trade name of the product (Marcain®) administered subacromially. The correct volume to be administered was drawn at room temperature into a syringe via a 16G (large bore) needle. The needle was then removed and the product was administered within 1 hour of being drawn up into the syringe. The product was administered as a single administration into the subacromial space through one of the arthroscopic portals. First cohort was administered initially followed by second cohort, based on the efficacy, safety and PK results. (The Applicant stated that they suspect leakage from the administration site.) No incision lengths information was provided for this study.

It is noted that the protocol was amended not to increase to the 7.5 mL dose (Data Review Committee recommendation) as it was not expected that an increase of 50% would provide a clinically significant improvement in the efficacy over an appropriate time period (at least 24 hours) compared to standard bupivacaine.

The primary efficacy endpoints were: Pain intensity (PI) on movement area under the curve AUC over the time period 1 to 72 hours post-surgery measured by an 11-point Numerical Rating Scale (NRS); and total use of opioid rescue analgesia 0 to 72 hours after surgery. For the primary endpoints to be met, non-inferiority of PI on movement as well as superiority in total use of opioid analgesia needed to be shown.

On Day 0, the blood samples were collected at baseline (pre-dose), 1, 4, 8, 12, 24, 36, 48, 72 and 96 hours post dose. Total and unbound bupivacaine concentration analyses were performed using validated liquid chromatography-mass spectrometry (LC-MS) methods.
On Day 0, the pain intensity (PI) was evaluated approximately 4, 6, 8, 10, and 12 hours following surgery and administration of the study drug. On Day 1 through Day 6, the PI was evaluated at approximately 8 AM, 12:00 noon, 4 PM, and 8 PM. On Day 7, the PI was evaluated at 8 AM and 12:00 Noon.

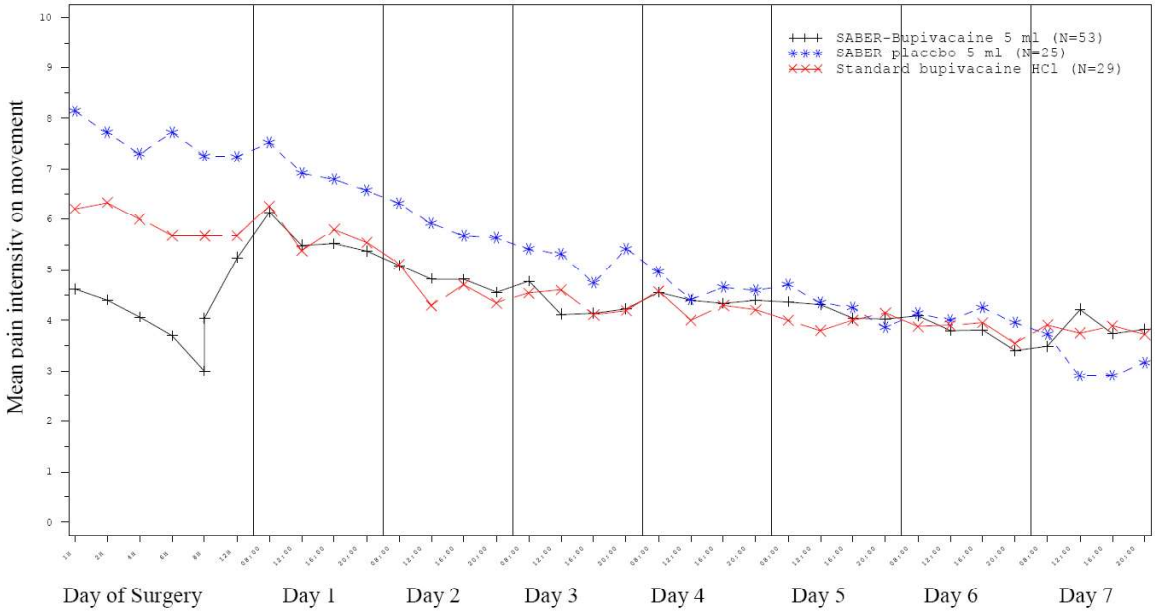
Pain intensity on movement, mean AUC (LOCF) (ITT population)

Treatment	Variable	n	Mean	SD	95% CI	p-value
Difference: SABER-Bupi (5 mL) - SABER-PL (5 mL)	AUC (1-24 hours)	106	-2.14	0.52		
	AUC (24-48 hours)	104	-1.22	0.58		
	AUC (48-72 hours)	107	-0.68	0.56		
	AUC (72-96 hours)	103	-0.70	0.54		
	AUC (1-36 hours)	106	-1.82	0.52		
	AUC (1-48 hours)	107	-1.56	0.50	[-2.56; -0.56]	0.002
	AUC (1-72 hours)	107	-1.27	0.50	[-2.25; -0.28]	0.012
	AUC (1-96 hours)	107	-1.11	0.49		
Difference: SABER-Bupi (5 mL) – Std Bupi HCl	AUC (1-24 hours)	106	-0.66	0.49		
	AUC (24-48 hours)	104	0.03	0.54		
	AUC (48-72 hours)	107	0.48	0.54		
	AUC (72-96 hours)	103	0.03	0.51		
	AUC (1-36 hours)	106	-0.39	0.49		
	AUC (1-48 hours)	107	-0.27	0.48	[-1.22; 0.69]	

	AUC (1-72 hours)	107	-0.02	0.47	[-0.96; 0.92]	
	AUC (1-96 hours)	107	0.06	0.47		

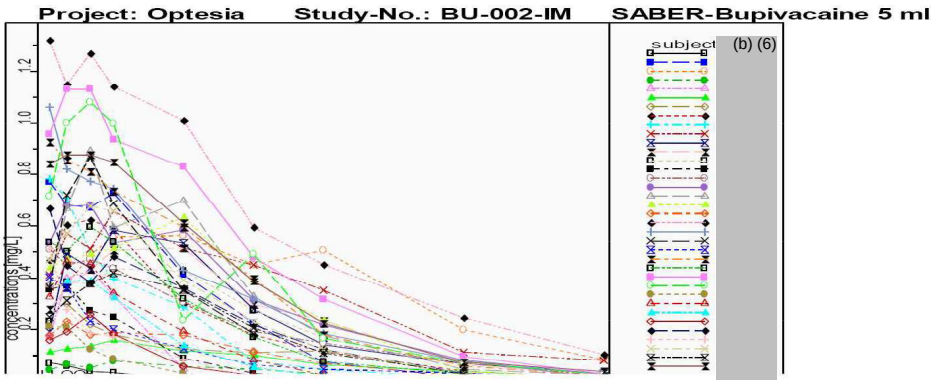
The Applicant stated that non-inferiority of SABER-Bupivacaine to SABER-placebo for the time period 1 to 72 hours was shown; the upper limit of the 95% CI was -0.28. A subsequent test for superiority of SABER-Bupivacaine over SABER-placebo showed that the SABER-Bup was shown to be statistically superior over SABER-placebo for the time period 1 to 72 hours post-surgery (p-value: 0.012). Non-inferiority of SABER-Bupivacaine to standard bupivacaine for the time period 1 to 72 hours HCl was not shown, as the upper limit of the 95% CI was 0.92. Similar results were obtained for the time period 1 to 48 hours. The following figure represents the mean pain intensity on movements over time.

Pain intensity on movement over time (ITT population)

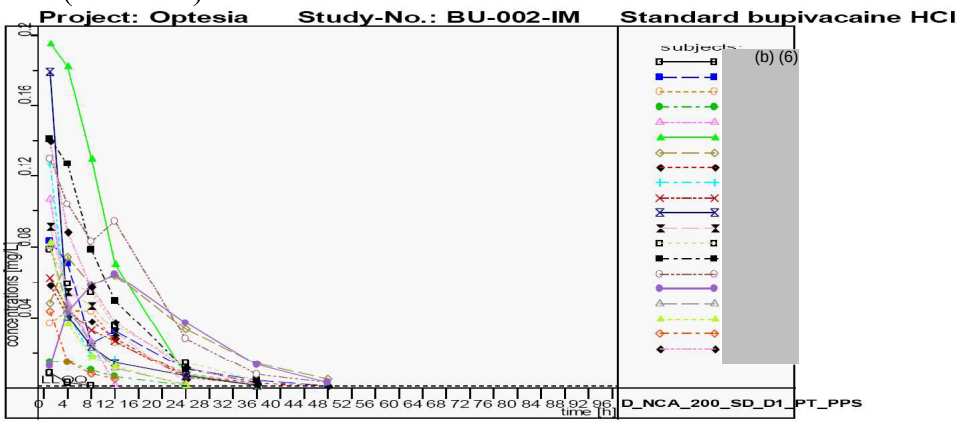


The Applicant reported that the total mean use of rescue analgesia (morphine equivalent dosage [mg], ITT population) from 0 to 72 hours for the SABER-Bupivacaine group, SABER-placebo and standard bupivacaine groups were 14.15 mg (± 29.15 mg), 22.85 mg (± 25.17 mg) and 13.31 mg (± 18.69 mg), respectively. In general, standard deviations were large and pair-wise comparisons (ANOVA) did not show statistical superiority of SABER-Bupivacaine over SABER-placebo or standard bupivacaine HCl for the 0 to 72 hour period (p-values were 0.075 and 0.837, respectively. However, the non-parametric Friedman test showed a statistical significant difference between SABER-Bupivacaine and SABER-placebo over the 0 to 72 hour period (p-value 0.013).

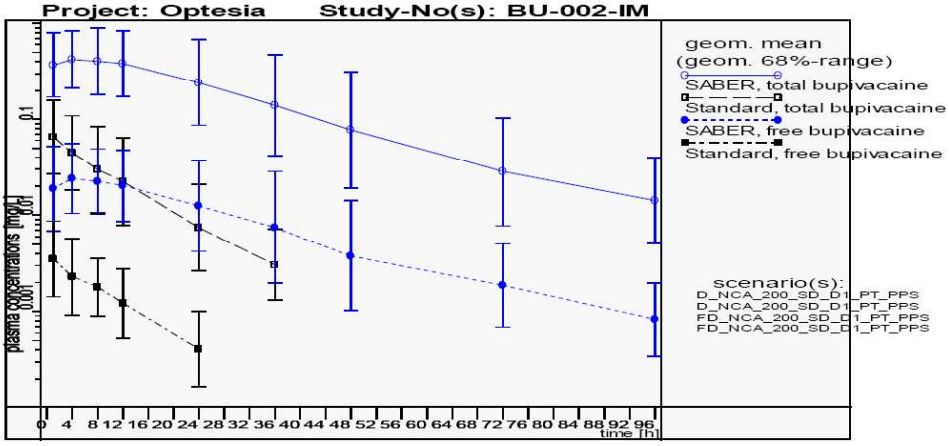
Individual bupivacaine plasma concentrations following administration of SABER-Bupivacaine (cohort 1a*)*



Individual bupivacaine plasma concentrations following administration of standard bupivacaine HCl (cohort 1c)



Geometric mean (68%-range) total and free bupivacaine plasma concentrations following administration of SABER-Bupivacaine (cohort 1a) or standard bupivacaine HCl (cohort 1c)



Total bupivacaine

Table 14.4.18 (continued): Individual and mean total bupivacaine PK-parameters, SABER-Bupivacaine

Treatment = SABER-Bupivacaine 5 ml

Analyte: bupivacaine										
PK-parameter										
	λ_z [h^{-1}]	$t_{1/2}$ [h]	t_{lag} [h]	t_{max} [h]	C_{max} [mg/L]	AUC_t [mg·h·L^{-1}]	extrap. [%]	AUC_{inf} [mg·h·L^{-1}]	CL/F [L/h]	V_z/F [L]
N	36	36	36	36	36	36	36	36	36	36
N_{obs}	36	36	36	36	36	36	36	36	36	36
mean	**0.0460**	**16.44**	**0.03**	**6.98**	**0.593**	**19.39**	**2.7**	**19.96**	**66.29**	**1391.10**
SD	0.0136	5.08	0.17	6.58	0.299	12.06	2.6	12.60	106.57	1660.45
SEM	0.0023	0.85	0.03	1.10	0.050	2.01	0.4	2.10	17.76	276.74
CV (%)	29.6	30.9	600.0	94.3	50.4	62.2	97.5	63.1	160.7	119.4
median	**0.0462**	**15.00**	**0.00**	**5.94**	**0.591**	**18.81**	**1.6**	**19.25**	**34.25**	**724.32**
min	0.0240	8.40	0.00	0.00	0.070	1.03	0.2	1.05	10.70	326.35
max	0.0825	28.87	1.00	24.00	1.320	55.37	10.7	59.20	629.46	7630.58
geom. mean	**0.0441**	**15.73**	**n.v.**	**n.v.**	**0.500**	**14.98**	**n.v.**	**15.40**	**41.27**	**936.86**
lower 68%	0.0327	11.66	n.v.	n.v.	0.255	6.47	n.v.	6.65	17.93	417.97
upper 68%	0.0594	21.23	n.v.	n.v.	0.982	34.69	n.v.	35.64	94.98	2099.95

Table 14.4.18: Individual and mean total bupivacaine PK-parameters, SABER-Bupivacaine

Treatment = SABER-Bupivacaine 5 ml

Analyte: bupivacaine										
PK-parameter										
Subject	λ_z [h^{-1}]	$t_{1/2}$ [h]	t_{lag} [h]	t_{max} [h]	C_{max} [mg/L]	AUC_t [mg·h·L^{-1}]	extrap. [%]	AUC_{inf} [mg·h·L^{-1}]	CL/F [L/h]	V_z/F [L]
(b) (6)	0.0825	8.40	0.00	1.33	0.070	1.03	1.9	1.05	629.46	7630.58
	0.0731	9.48	0.00	1.00	0.771	21.78	0.2	21.82	30.25	413.54
	0.0415	16.70	0.00	24.00	0.563	35.06	5.5	37.10	17.79	428.67
	0.0242	28.62	0.00	11.98	0.077	3.47	10.7	3.89	169.68	7007.03
	0.0361	19.20	0.00	8.03	0.430	17.72	7.1	19.07	34.61	958.61
	0.0310	22.33	0.00	11.83	0.160	7.31	6.4	7.81	67.58	2177.02
	0.0331	20.91	1.00	4.00	0.298	9.18	5.4	9.71	61.19	1846.20
	0.0429	16.16	0.00	7.83	0.622	19.00	1.7	19.32	34.16	796.48
	0.0462	15.01	0.00	1.10	0.783	14.79	0.7	14.89	44.32	959.98
	0.0287	24.18	0.00	12.03	0.656	31.70	7.5	34.25	19.27	672.04
	0.0360	19.26	0.00	12.00	0.584	22.82	3.4	23.62	25.15	698.90
	0.0489	14.19	0.00	23.92	0.515	23.35	1.6	23.74	27.81	569.20
	0.0379	18.29	0.00	12.03	0.436	20.05	3.5	20.77	25.42	670.75
	0.0552	12.56	0.00	4.00	0.371	6.92	0.3	6.94	76.07	1378.20
	0.0365	18.98	0.00	1.00	0.511	18.61	3.5	19.28	27.39	749.73
	0.0418	16.57	0.00	8.02	0.680	27.39	2.4	28.05	23.53	562.41

Table 14.4.18 (continued): Individual and mean total bupivacaine PK-parameters, SABER-Bupivacaine

Treatment = SABER-Bupivacaine 5 ml

Analyte: bupivacaine										
PK-parameter										
Subject	λ_z [h^{-1}]	$t_{1/2}$ [h]	t_{lag} [h]	t_{max} [h]	C_{max} [mg/L]	AUC_t [mg·h·L^{-1}]	extrap. [%]	AUC_{inf} [mg·h·L^{-1}]	CL/F [L/h]	V_z/F [L]
(b) (6)	0.0452	15.35	0.00	8.00	0.893	28.25	1.5	28.70	23.00	509.20
	0.0623	11.13	0.00	24.00	0.633	26.15	0.6	26.31	25.08	402.90
	0.0486	14.25	0.00	4.05	0.231	8.70	1.5	8.83	59.80	1229.72
	0.0289	23.97	0.00	0.97	1.320	55.37	6.5	59.20	10.70	370.11
	0.0469	14.79	0.00	1.05	1.060	28.37	1.3	28.75	22.95	489.91
	0.0567	12.22	0.00	7.97	0.867	19.12	0.5	19.22	34.34	605.70
	0.0240	28.87	0.00	1.02	0.403	8.62	6.8	9.25	71.35	2972.02
	0.0480	14.45	0.00	1.00	0.927	30.81	1.3	31.23	21.13	440.48
	0.0358	19.37	0.00	8.00	0.597	17.59	2.0	17.95	36.76	1027.38
	0.0475	14.60	0.00	4.00	1.130	41.96	1.5	42.59	15.50	326.35
	0.0462	14.99	0.00	7.95	1.080	30.91	1.7	31.44	21.00	454.09
	0.0608	11.39	0.00	1.08	0.212	2.99	0.8	3.01	218.91	3597.87
	0.0620	11.18	0.00	3.98	0.462	10.71	0.3	10.74	61.48	991.61
	0.0290	23.90	0.00	0.00	0.602	8.69	1.5	8.82	74.81	2579.23
	0.0641	10.82	0.00	7.93	0.259	4.69	0.6	4.72	139.85	2182.55
	0.0509	13.62	0.00	1.00	0.668	18.44	1.0	18.62	35.44	696.25

Table 14.4.18 (continued): Individual and mean total bupivacaine PK-parameters, SABER-Bupivacaine

Treatment = SABER-Bupivacaine 5 ml

Analyte: bupivacaine										
PK-parameter										
Subject	λ_z [h^{-1}]	$t_{1/2}$ [h]	t_{lag} [h]	t_{max} [h]	C_{max} [mg/L]	AUC_t [mg·h·L^{-1}]	extrap. [%]	AUC_{inf} [mg·h·L^{-1}]	CL/F [L/h]	V_z/F [L]
(b) (6)	0.0609	11.38	0.00	1.00	0.511	5.99	0.2	6.00	109.95	1805.07
	0.0483	14.35	0.00	8.00	0.675	21.39	1.1	21.64	30.50	631.45
	0.0546	12.69	0.00	12.03	0.419	15.91	0.9	16.06	41.11	752.65
	0.0389	17.83	0.00	4.03	0.878	33.36	2.6	34.24	19.28	495.82

Table 14.4.17 (continued): Individual and mean total bupivacaine PK-parameters, Standard bupivacaine HCl

Treatment = Standard bupivacaine HCl

Analyte: bupivacaine										
PK-parameter										
	λ_z [h^{-1}]	$t_{1/2}$ [h]	t_{lag} [h]	t_{max} [h]	C_{max} [mg/L]	AUC_t [mg·h·L^{-1}]	extrap. [%]	AUC_{inf} [mg·h·L^{-1}]	CL/F [L/h]	V_z/F [L]
N	20	20	20	20	20	20	20	20	20	20
N_{obs}	20	20	20	20	20	20	20	20	20	20
mean	**0.1289**	**5.93**	**0.00**	**1.87**	**0.090**	**0.94**	**3.5**	**0.96**	**146.03**	**860.83**
SD	0.0463	1.72	0.00	2.56	0.050	0.62	4.3	0.63	329.11	1223.19
SEM	0.0104	0.39	0.00	0.57	0.011	0.14	1.0	0.14	73.59	273.51
CV (%)	36.0	29.1	0.0	137.1	55.1	65.6	123.6	64.9	225.4	142.1
median	**0.1162**	**5.97**	**0.00**	**1.03**	**0.081**	**0.77**	**2.0**	**0.78**	**63.12**	**534.55**
min	0.0719	2.57	0.00	0.92	0.008	0.03	0.3	0.03	20.30	116.94
max	0.2700	9.64	0.00	12.02	0.195	2.21	18.0	2.22	1516.71	5617.53
geom. mean	**0.1224**	**5.67**	**n.v.**	**n.v.**	**0.073**	**0.69**	**n.v.**	**0.71**	**66.53**	**543.73**
lower 68%	0.0889	4.12	n.v.	n.v.	0.034	0.25	n.v.	0.27	24.18	228.79
upper 68%	0.1683	7.79	n.v.	n.v.	0.159	1.89	n.v.	1.90	183.02	1292.21

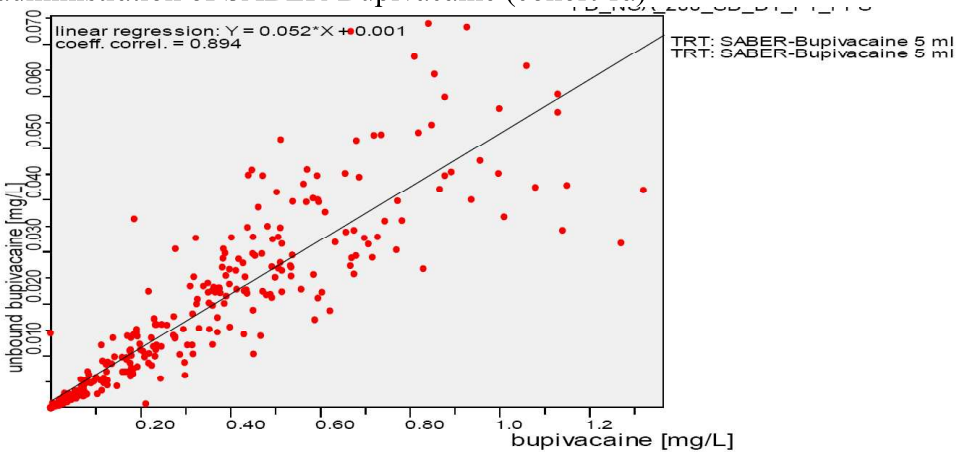
Plasma PK-parameters of total and free bupivacaine following administration of SABER-Bupivacaine or standard bupivacaine HCl (geometric mean / 68%-range):

Table 11-16:	Plasma PK-parameters of total and free bupivacaine following administration of SABER-Bupivacaine or standard bupivacaine HCl (geometric mean):			
PK-parameter	SABER-Bupivacaine (total)	SABER-Bupivacaine (free)	Standard bupivacaine HCl (total)	Standard bupivacaine HCl (free)
$t_{1/2}$ [h]	15.73	14.71	5.67	6.20
t_{max} [h] a)	5.94	4.00	1.03	1.03
C_{max} [mg/L	0.500	0.0291	0.0732	0.0040
AUCt [$mg \cdot h \cdot L^{-1}$]	14.98	0.795	0.686	0.033
AUCinf $mg \cdot h \cdot L^{-1}$]	15.40	0.817	0.712	0.046

There was a large inter-individual variability of Cmax of both total and free bupivacaine. The highest individual Cmax-values of total and free bupivacaine were 1.320 mg/L and 0.074 mg/L, respectively.

The correlation of free and total individual bupivacaine plasma concentration following individual bupivacaine plasma concentration following SABER-Bupivacaine is presented.

Correlation of free (unbound) and total individual bupivacaine plasma concentrations following administration of SABER-Bupivacaine (cohort 1a)



The Applicant stated that the mean bupivacaine Cmax and AUC values obtained from the current study (initiation – 4/29/09 and completion – 9/16/10), in both the SABER-Bupivacaine and standard bupivacaine HCl groups, were considerably lower (approximately 50%) than previously observed (BU-001-IM, CLIN005-0006 (initiation – 6/12/06 and completion – 12/10/07), CLIN803-006-0006).

This is assumed to have occurred by seepage of variable volumes of the administered dose from the wound between the time of drug administration and closure of the wound (arthroscopic portals) thereby leading to a significantly reduced local and systemic exposure to bupivacaine. However, the Study Report did not have any documentation of such observation.

Regarding assessment of efficacy and safety, an average loss of approximately 50% of the target dose for SABER-Bupivacaine may have altered the results…

5 mL SABER-Bupi comparison

	Cmax (SD) ng/mL	AUC (SD) ng.h/mL
BU-002-IM Single administration into the subacromial space through one of the arthroscopic portals	593 (299) [Range 70 – 1320]	19960 (12600) [Range 1050 – 59200]
CLIN005-0006 Subacromial injection	1146 (326) [Range 813 – 1570]	56635 (7797) [Range 49420 – 66929]
CLIN005-0006 Subcutaneous injection	965 (487) [Range 172 – 1940]	45081 (21981) [Range 7346 – 86448]

Looking at the combined Cmax and AUC values, Study BU-002-IM values were, in fact, smaller than the Study CLIN005-0006 (**RED** font: shoulder subacromial injection; **BLUE** font: shoulder subcutaneous injection)

Cmax	AUCinf
70	1050
77	3010
160	3890
172	4720
212	6000
231	6940
259	**7346**
298	7810
371	8820
403	8830
419	9250
423	9710
430	10740
436	14890
445	16060
462	17950
511	18620
511	19070
515	19220
563	19280
584	19320

597	**20112**
602	20770
622	21640
633	21820
656	23620
668	**23676**
675	23740
680	26310
741	**27515**
771	28050
783	28700
785	28750
787	31230
798	31440
813	34240
867	34250
878	37100
885	**38038**
893	**38233**
927	42590
990	**44196**
1000	**46573**
1060	**49066**
1080	**49420**
1130	**50003**
1200	**51964**
1210	**58226**
1300	59200
1320	**59417**
1510	**61797**
1530	**66929**
1570	**78715**
1940	**86448**

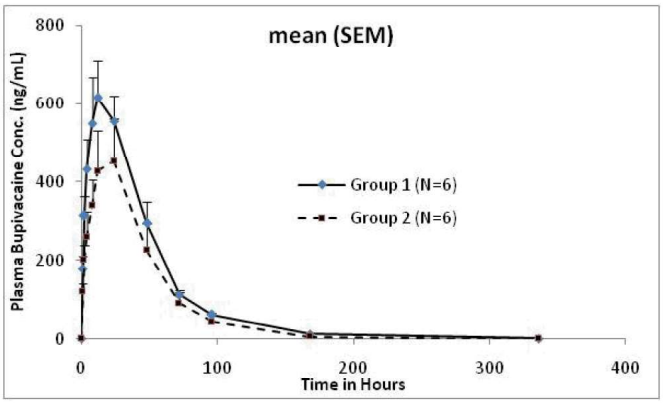
4.2.8 Study Clin005-0007 pilot study (instillation) inguinal hernia repair single dose 5 mL

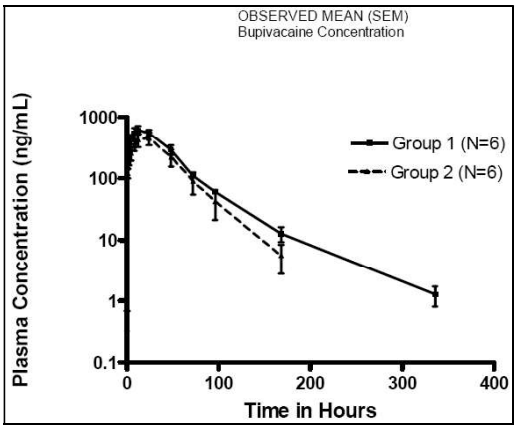
Title: A pilot study of the pharmacokinetics and safety of SABER-Bupivacaine instilled into the wound in patients undergoing Open inguinal hernia repair

This was a pilot, patient-blinded, Phase II study to assess the PKs, safety, tolerability and efficacy of SABER™ as a delivery system in open inguinal hernia repair patients. The study investigated instillation of 12.0 wt% SABER™-Bupivacaine directly into the wound, with patients being enrolled into two treatment groups: Treatment Group 1 – During wound closure 2.5 mL of SABER™-Bupivacaine was placed topically, in approximately equal volumes, into

the superior, medial and inferior subaponeurotic spaces. After closure of the external oblique aponeurosis (and prior to skin closure) another 2.5 mL of SABER™-Bupivacaine was placed topically along the length of the sutured external oblique aponeurosis. The total delivered volume of SABER™-Bupivacaine was 5.0 mL. Treatment Group 2 – After closure of the external oblique aponeurosis (and prior to skin closure) 5.0 mL of SABER™-Bupivacaine was placed topically along the length of the sutured external oblique aponeurosis. The total delivered volume of SABER™-Bupivacaine instilled into the wound was 5.0 mL. Blood samples were collected on Day 0 pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 168 and 226 hours post drug administration.

Mean (SEM) Plasma Bupivacaine Concentrations





Mean (SD) Pharmacokinetic Parameters of Bupivacaine

PK Parameter	**Subaponeurotic Spaces + Oblique Aponeurosis (Group 1) (N=6)**	**Oblique Aponeurosis Alone (Group 2) (N=6)**
Cmax (ng/mL)	717.3 (279.3)	506.8 (248.5)
Tmax (hr)	24.06 (8.07 - 24.18)	18.03 (8.03 - 24.07)
AUClast (ng*hr/mL)	33233.7 (7148.3)	23851.3 (15859.6)
AUCinf (ng*hr/mL)	33393.5 (7079.3)	24085.1 (16070.4)

The mean (SD) Cmax in Groups 1 and 2 were 717.3 (279.3) and 506.83 (248.52) ng/mL, respectively. The median (range) Tmax in Groups 1 and 2 were 24.06 (8.07 - 24.18) and 18.03 (8.03 - 24.07) hours, respectively. The mean (SD) AUC0-t for Groups 1 and 2 were 33233.7 (7148.3) and 23851.3 (15859.6) ng*hr/mL, respectively.

The Applicant stated that a certain amount of SABER-bupivacaine fluid was seeping out from the wound (Group 2). Therefore the information derived from this study should be interpreted with caution.

4.2.9 Study Clin-803-006-0006 (instillation) inguinal hernia repair single dose 2.5 and 5 mL linearity

Study CLIN-803-006-0006 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response, Phase II study to examine the efficacy, pharmacokinetics, and safety of SABER-Bupivacaine instilled directly into the wound in patients undergoing elective open unilateral tension-free inguinal hernia repair. Patients (95% men and 5% women; 95% White) received one of the following 4 treatments: SABER-Bupivacaine (12.0 wt%, 132 mg/mL bupivacaine) 5.0 mL (660 mg), SABER-Bupivacaine 2.5 mL (330 mg), SABER-Placebo 5.0 mL, or SABER-Placebo 2.5 mL.

For each patient, the pharmacist or qualified study staff drew up 2.5 mL or 5.0 mL of treatment using the 10 mL plastic syringe provided. The medication was drawn into a syringe using a large-bore needle (16G). Treatment was administered within 1 hour of being drawn up into the syringe. No needle was used for topical instillation of treatment into the wound.

Pharmacokinetic plasma samples were collected in the first 32 patients only. Plasma samples were collected as follows: -5 min, 1, 2, 3, 4, 8, 12, 24, 48, 72, 96 and 168 hours. Collection time was based upon the time of completion of treatment topical instillation. On Days 1, 2, 3, 4, and 7, blood samples were collected at approximately the same time of day that the treatment was administered on Surgery Day 0. All plasma bupivacaine analyses were conducted using a validated LC-MS/MS method with a lower limit of quantitation of 1 ng/mL. Pharmacokinetic analysis was done using the WinNonlin™ software program (Version 5.0, Pharsight Corporation, CA).

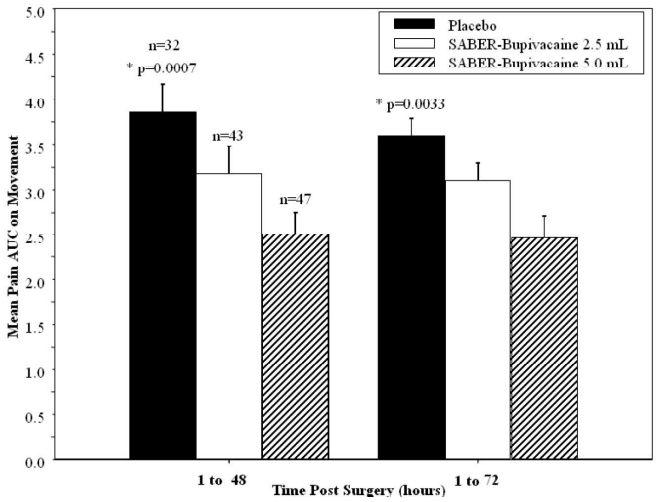
The primary objectives were to assess the dose-response efficacy and pharmacokinetics of SABER-Bupivacaine instilled directly into the wound in patients undergoing elective open inguinal hernia repair. The secondary objectives were to examine the safety and tolerability of SABER-bupivacaine instilled directly into the wound in patients undergoing elective open inguinal hernia repair. The efficacy assessment will not be discussed in this review for this study. However, there were 2 efficacy endpoints measured in the study: the mean pain intensity on movement normalized AUC over the time period 1 to 72 hours post-surgery, and, the proportion of patients receiving opioid rescue medication during the study.

Normalized AUC of Pain Intensity on Movement (1-72 hours)

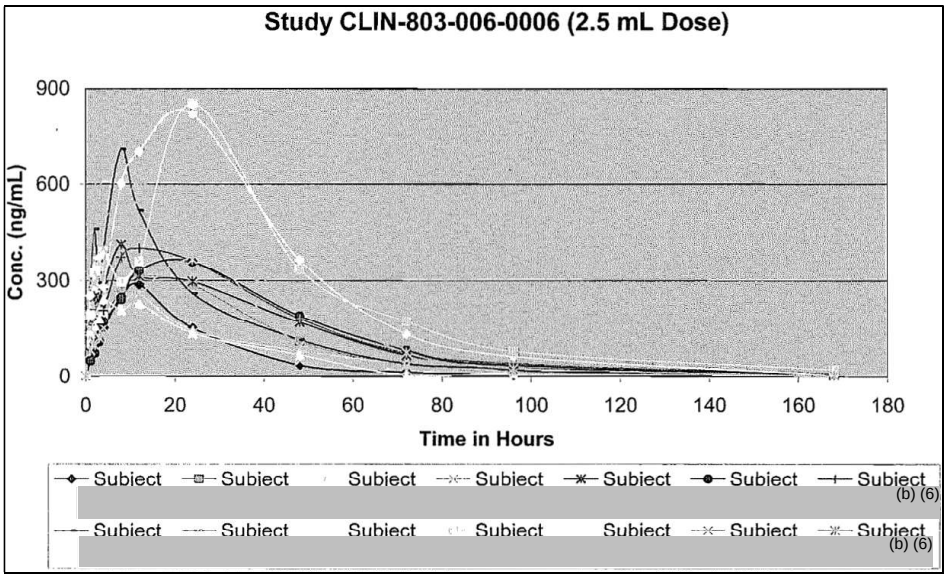
	SABER-Bupivacaine 2.5 mL	SABER-Bupivacaine 5.0 mL	Placebo
ITT Population			
Mean (SEM)	3.11 (0.25) *	2.47 (0.19) †	3.60 (0.30)
Median (95% CI)	2.73 (2.29, 3.28)	2.42 (1.85, 3.05)	3.77 (2.94, 4.13)
Efficacy Evaluable Population			
Mean (SEM)	3.11 (0.26) ‡	2.47 (0.19) §	3.61 (0.31)
Median (95% CI)	2.72 (2.28, 3.28)	2.42 (1.85, 3.05)	3.80 (2.94, 4.14)

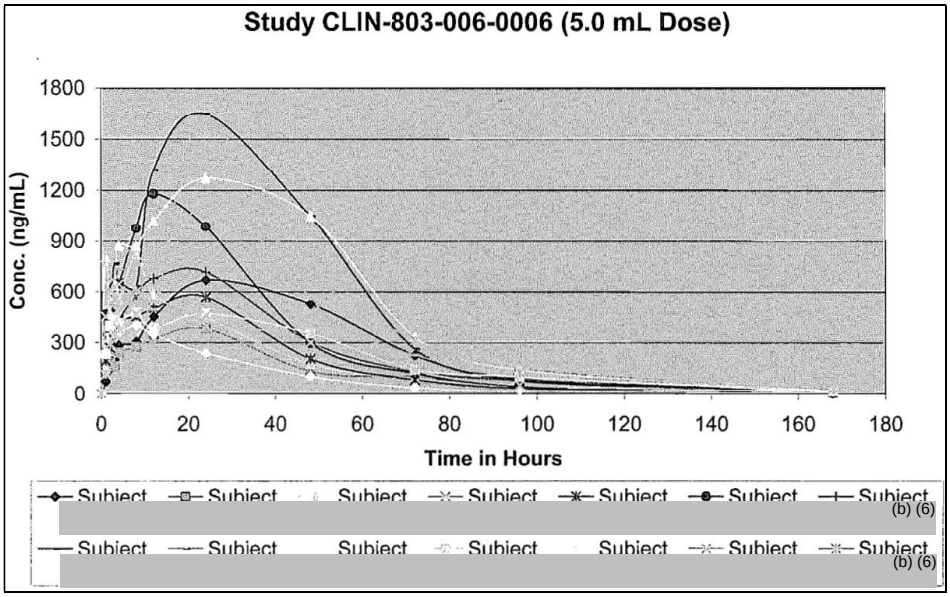
* p=0.1574 versus placebo.
† p=0.0033 versus placebo.
‡ p=0.1733 versus placebo.
§ p=0.0036 versus placebo

Mean Pain Intensity on Movement Normalized AUC (1-48 and 1-72 Hours)

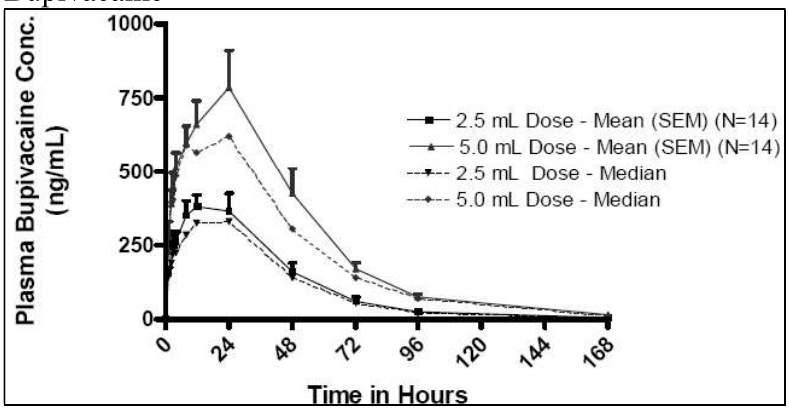


Pharmacokinetic results obtained from a total of 28 patients (receiving 2.5 mL SABER-Bupivacaine [n=14] and 5.0 mL SABER-Bupivacaine [n=14]) are discussed below. Individual and mean plasma concentrations of total bupivacaine following instillation of 2.5 mL and 5.0 mL SABER-Bupivacaine (660 mg bupivacaine) are shown below.

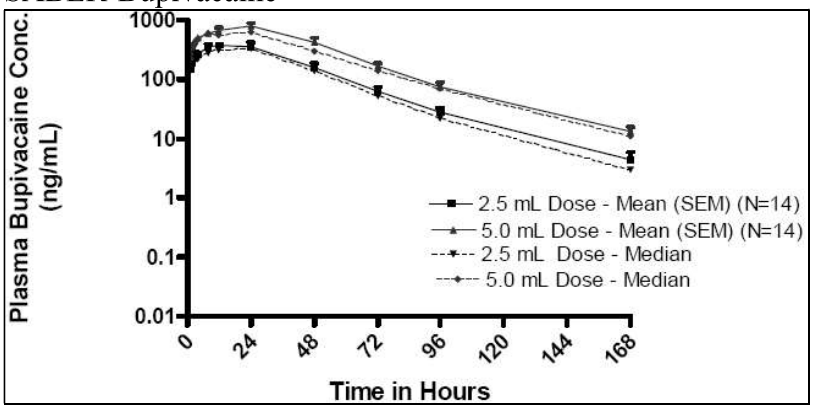




Observed Plasma Bupivacaine Concentrations Following 2.5 mL and 5.0 mL Dose of SABER-Bupivacaine



Observed Plasma Bupivacaine Concentrations Following the 2.5 mL and 5.0 mL Dose of SABER-Bupivacaine



Mean (SEM) bupivacaine PK parameters from the 2.5 and 5.0 mL dose of SABER-Bupivacaine

2.5 mL dose:

Patient #	Tmax (hr)	Cmax (ng/mL)	Half-life (hr)	Tlast (hr)	Clast (ng/mL)	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)
(b) (6)	12.00	288.00	13.47	96.10	3.06	7512.06	7571.53
	12.00	315.00	13.02	96.20	8.50	12853.93	13013.64
	12.00	257.00	22.16	168.30	1.95	9957.24	10019.59
	12.20	190.00	46.50	168.20	4.14	7277.07	7554.82
	8.00	414.00	28.66	168.00	6.30	17696.39	17956.86
	24.00	360.00	19.98	168.30	2.40	17518.35	17587.52
	12.10	403.00	24.01	167.80	4.72	19570.95	19734.41
	8.10	712.00	31.97	168.60	5.09	18048.75	18283.50
	2.90	707.00	30.32	168.20	10.40	27689.16	28144.15
	24.10	820.00	17.57	168.00	3.16	37279.31	37359.41
	24.10	854.00	32.99	168.40	21.00	36399.34	37398.75
	4.00	242.00	27.30	167.90	1.29	7749.35	7800.16
	12.00	605.00	23.00	168.10	1.65	19203.67	19258.41
	24.00	368.00	20.64	167.50	2.78	17833.76	17916.55
Mean	**13.68**	**466.79**	**25.11**	**157.83**	**5.46**	**18327.81**	**18542.81**
SD	**7.44**	**226.31**	**8.82**	**26.13**	**5.19**	**9719.51**	**9865.13**
SEM	**1.99**	**60.48**	**2.36**	**6.98**	**1.39**	**2597.65**	**2636.57**
Minimum	**2.90**	**190.00**	**13.02**	**96.10**	**1.29**	**7277.07**	**7554.82**
Maximum	**24.10**	**854.00**	**46.50**	**168.60**	**21.00**	**37279.31**	**37398.75**
%CV	**54.39**	**48.48**	**35.10**	**16.56**	**95.04**	**53.03**	**53.20**
Median	**12.00**	**ND**	**23.50**	**168.05**	**ND**	**ND**	**ND**

	Tmax (hr)	Cmax (ng/mL)	Half-life (hr)	Tlast (hr)	Clast (ng/mL)	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)
Mean	**13.68**	**466.79**	**25.11**	**157.83**	**5.46**	**18327.81**	**18542.81**
SD	**7.44**	**226.31**	**8.82**	**26.13**	**5.19**	**9719.51**	**9865.13**
SEM	**1.99**	**60.48**	**2.36**	**6.98**	**1.39**	**2597.65**	**2636.57**
Minimum	**2.90**	**190.00**	**13.02**	**96.10**	**1.29**	**7277.07**	**7554.82**
Maximum	**24.10**	**854.00**	**46.50**	**168.60**	**21.00**	**37279.31**	**37398.75**
%CV	**54.39**	**48.48**	**35.10**	**16.56**	**95.04**	**53.03**	**53.20**
Median	**12.00**	**ND**	**23.50**	**168.05**	**ND**	**ND**	**ND**

5.0 mL dose:

Patient #	Tmax (hr)	Cmax (ng/mL)	Half-life (hr)	Tlast (hr)	Clast (ng/mL)	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)
(b) (6)	24.00	671.00	22.28	168.00	10.50	38790.43	39127.89
	24.00	383.00	24.27	168.00	6.09	18380.22	18593.47
	8.00	820.00	22.17	168.60	4.56	27065.32	27211.14
	12.00	623.00	33.77	168.80	17.80	28710.63	29577.89
	23.90	570.00	26.80	167.50	6.87	25758.13	26023.78
	12.00	1180.00	21.32	168.20	5.17	44433.50	44592.54
	24.00	719.00	26.80	168.10	11.60	35747.58	36196.05
	24.00	1650.00	20.87	167.60	10.20	78602.04	78909.23
	24.10	1630.00	26.55	168.30	19.50	62501.74	63248.55
	8.00	402.00	73.33	168.10	26.00	15337.89	18088.47
	8.00	479.00	27.45	167.80	13.90	31617.88	32168.31
	24.10	1270.00	23.80	168.10	19.40	75277.93	75943.97
	4.00	645.00	21.80	169.10	6.27	30403.66	30600.82
	24.00	1090.00	29.54	167.80	30.10	58894.76	60177.41
Mean	**17.44**	**866.57**	**28.62**	**168.14**	**13.43**	**40822.98**	**41461.39**
SD	**8.10**	**426.61**	**13.37**	**0.44**	**8.06**	**20311.58**	**20220.87**
SEM	**2.16**	**114.02**	**3.57**	**0.12**	**2.15**	**5428.50**	**5404.26**
Minimum	**4.00**	**383.00**	**20.87**	**167.50**	**4.56**	**15337.89**	**18088.47**
Maximum	**24.10**	**1650.00**	**73.33**	**169.10**	**30.10**	**78602.04**	**78909.23**
%CV	**46.45**	**49.23**	**46.70**	**0.26**	**60.06**	**49.76**	**48.77**
Median	**23.95**	**ND**	**25.41**	**168.10**	**ND**	**ND**	**ND**

	Tmax (hr)	Cmax (ng/mL)	Half-life (hr)	Tlast (hr)	Clast (ng/mL)	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)
Mean	**17.44**	**866.57**	**28.62**	**168.14**	**13.43**	**40822.98**	**41461.39**
SD	**8.10**	**426.61**	**13.37**	**0.44**	**8.06**	**20311.58**	**20220.87**
SEM	**2.16**	**114.02**	**3.57**	**0.12**	**2.15**	**5428.50**	**5404.26**
Minimum	**4.00**	**383.00**	**20.87**	**167.50**	**4.56**	**15337.89**	**18088.47**
Maximum	**24.10**	**1650.00**	**73.33**	**169.10**	**30.10**	**78602.04**	**78909.23**
%CV	**46.45**	**49.23**	**46.70**	**0.26**	**60.06**	**49.76**	**48.77**
Median	**23.95**	**ND**	**25.41**	**168.10**	**ND**	**ND**	**ND**

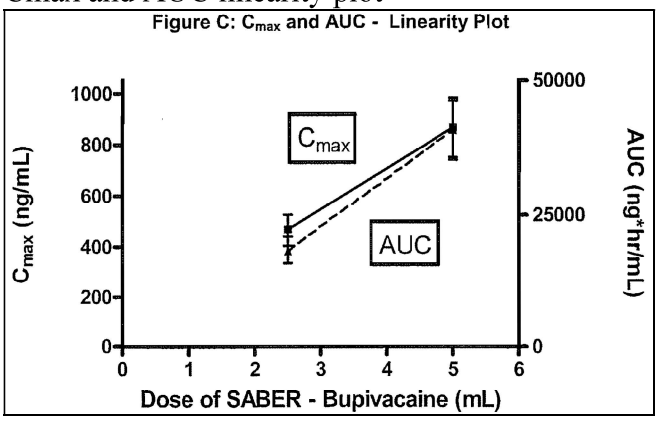
Mean (SEM) Pharmacokinetic Parameters of Bupivacaine Following the 2.5 and 5.0 mL Dose of SABER-Bupivacaine

Pharmacokinetic Parameter	SABER-Bupivacaine 2.5 mL (N=14)	SABER-Bupivacaine 5.0 mL (N=14)
C_{max} (ng/mL)	466.79 (60.48)	866.57 (114.02)
T_{max} (h) *	12.0 (2.9–24.10)	23.95 (4.0–24.10)
$T_{1/2}$ (h)	25.11 (13.02–46.5)	28.62 (20.87–73.33)
C_{last} (ng/mL)	5.46 (1.39)	13.4 (2.15)
T_{last} (hr)	157.8 (6.98)	168.4 (0.12)
$AUC_{(0-t)}$ (ng•hr/mL)	18327.8 (2597.7)	40822.9 (5428.5)
$AUC_{(0-inf)}$ (ng•hr/mL)	18542.8 (2636.6)	41461.4 (5404.3)

* Tmax data presented as median (range); t=168 h

Evaluating the exposure parameters (C_{max} and AUC) of bupivacaine from the 2.5 and 5.0 mL dose of SABER-Bupivacaine administered predominantly in men, dose proportional pharmacokinetics is observed.

Cmax and AUC linearity plot



Available incision length:

patient (b) (6)	2.5 mL	7 cm
(b) (6)	2.5	8
	5	6.5
	2.5	7
	2.5	7.5
	2.5	6
	2.5	7
	2.5	10
	5	7
	2.5	8

Comparison between two inguinal studies

Mean (SD) Pharmacokinetic Parameters of Bupivacaine 5 mL: Pilot study

PK Parameter	Subaponeurotic Spaces + Oblique Aponeurosis (Group 1) (N=6)	Oblique Aponeurosis Alone (Group 2) (N=6)
Cmax (ng/mL)	717.3 (279.3)	506.8 (248.5)
Tmax (hr)	24.06 (8.07 - 24.18)	18.03 (8.03 - 24.07)
AUClast (ng*hr/mL)	33233.7 (7148.3)	23851.3 (15859.6)
AUCinf (ng*hr/mL)	33393.5 (7079.3)	24085.1 (16070.4)

Mean (SEM) Pharmacokinetic Parameters of Bupivacaine Following the 2.5 and 5.0 mL Dose of SABER-Bupivacaine

Pharmacokinetic Parameter	SABER-Bupivacaine 2.5 mL (N=14)	SABER-Bupivacaine 5.0 mL (N=14)
C_{max} (ng/mL)	466.79 (60.48)	866.57 (114.02)
T_{max} (h) *	12.0 (2.9–24.10)	23.95 (4.0–24.10)
$T_{1/2}$ (h)	25.11 (13.02–46.5)	28.62 (20.87–73.33)
C_{last} (ng/mL)	5.46 (1.39)	13.4 (2.15)
T_{last} (hr)	157.8 (6.98)	168.4 (0.12)
$AUC_{(0-t)}$ (ng•hr/mL)	18327.8 (2597.7)	40822.9 (5428.5)
$AUC_{(0-inf)}$ (ng•hr/mL)	18542.8 (2636.6)	41461.4 (5404.3)

* Tmax data presented as median (range); t=168 h

4.2.10 Study BU-001-IM abdominal hysterectomy relative BA 5 mL to Marcain

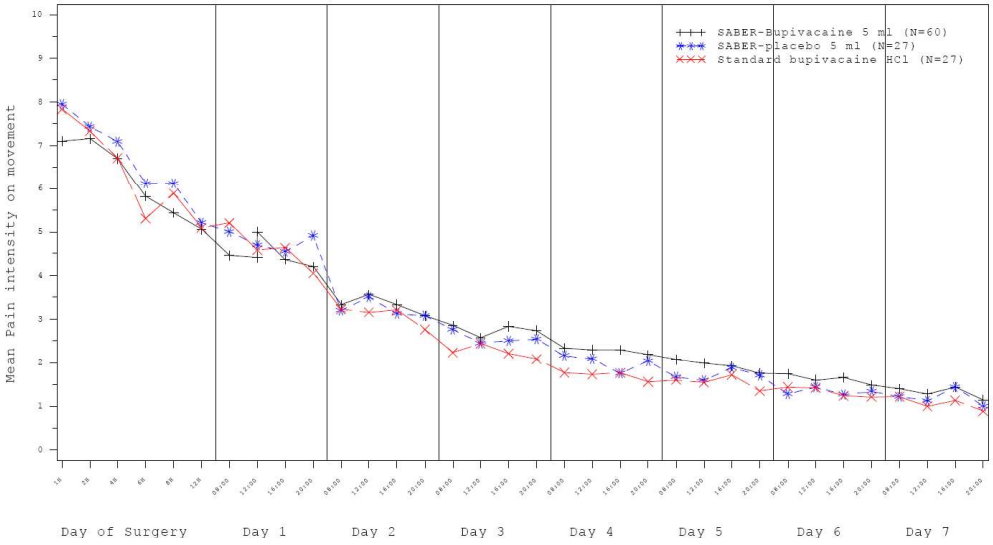
Study BU-001-IM was a Phase 2, randomized, multi-center, double-blind, parallel group, placebo- and active-controlled study in women (a total of 115 patients were randomized) undergoing primary elective open non-malignant abdominal hysterectomy (a major abdominal surgery with a visceral pain component; also the surgery requires a longer surgical incision). Surgery was performed and the study drug administered on Day 0 as a single administration (2:1:1 ratio): a) 5.0 mL SABER-Bupivacaine (132 mg/mL; 660 mg bupivacaine) instillation; b) 5.0 mL SABER-placebo instillation; and c) 40 mL standard bupivacaine hydrochloride (HCl) (100 mg bupivacaine) infiltration (commercially available bupivacaine solution 2.5 mg/ml (Marcain®*; AstraZeneca*)). Following closure of the fascia, a 16G (large bore) needle was used to draw up the correct volume of drug (room temperature and administered within one hour) into a syringe, needle removed, and, drug instilled covering the whole fascia area and ensuring containment of the entire dose. Marcain® was injected into the wound as follows: 1) 10 mL into the proximal muscle layer; 2) 10 mL into the distal layer; and 3) 20 mL into the SC layer. All patients were administered paracetamol as background treatment.

There were two primary efficacy variables measured in the study: Pain Intensity (PI) was measured on movement (rising to a sitting position from a supine position, assistance was allowed) using the 11 point (0 to 10; where 0 was no pain and 10 was the worst pain imaginable). The use of total opioid rescue medication after surgery was assessed. The secondary endpoints

in this study were: the time to first opioid rescue medication usage, the time to rescue medication, opioid-related side effects, PI at rest on the same days and using the same NRS as detailed for the measurement on movement, Pain treatment satisfaction scale, and home readiness using the Post-Anesthetic Discharge Scoring System (PADS). Subgroup analyses were conducted by age and race for the primary efficacy endpoints: age categories (< 45, 45 to 65, and > 65); race categories (White, Black, Asian, Hispanic and Other); weight categories (≤ 60 kg, > 60 kg to 70 kg, 70 kg to 80 kg and > 80 kg).

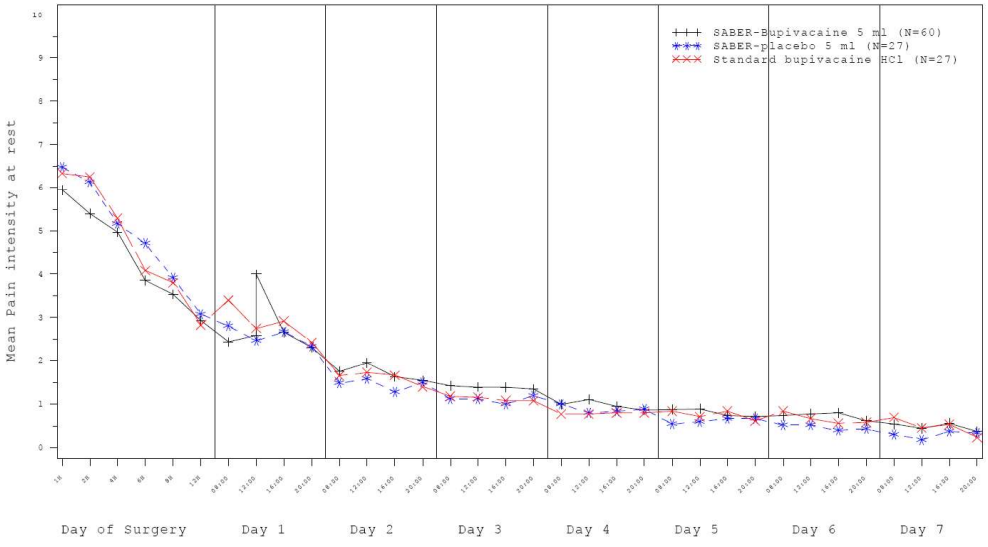
Pain intensity on movement over time - Intention-to-treat population

Figure 3.1: Pain intensity on movement over time - Intention-to-treat population



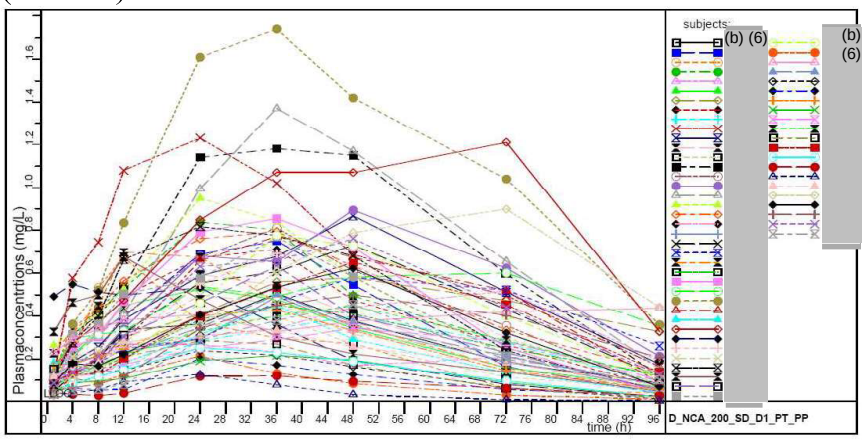
Pain intensity at rest over time - Intention-to-treat population

Figure 3.2: Pain intensity at rest over time - Intention-to-treat population

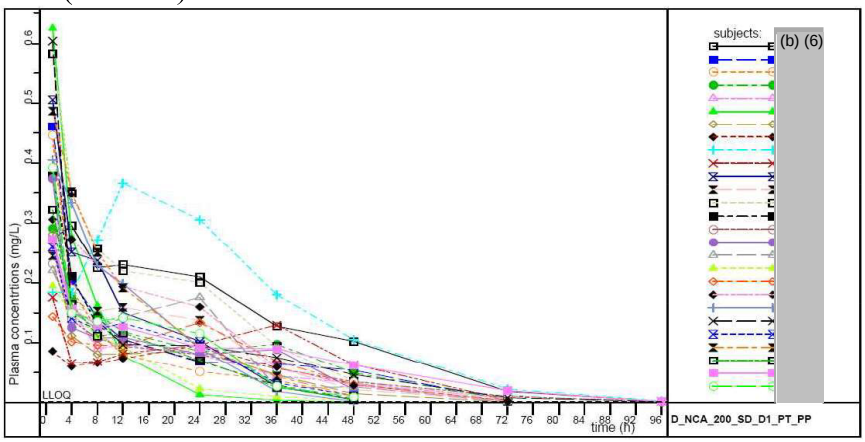


It is noted that benzyl alcohol reached maximum plasma concentrations at the first measuring point (1 hour), and decreased very rapidly, and by 24 hours post-dose individual benzyl alcohol plasma concentrations were either below or close to the lower limit of quantitation (5 ng/mL). Individual plasma concentrations of total bupivacaine following instillation of 5.0 mL SABER-Bupivacaine (660 mg bupivacaine) and Marcain® are shown below.

Individual bupivacaine plasma concentrations following administration of SABER-Bupivacaine (cohort a)

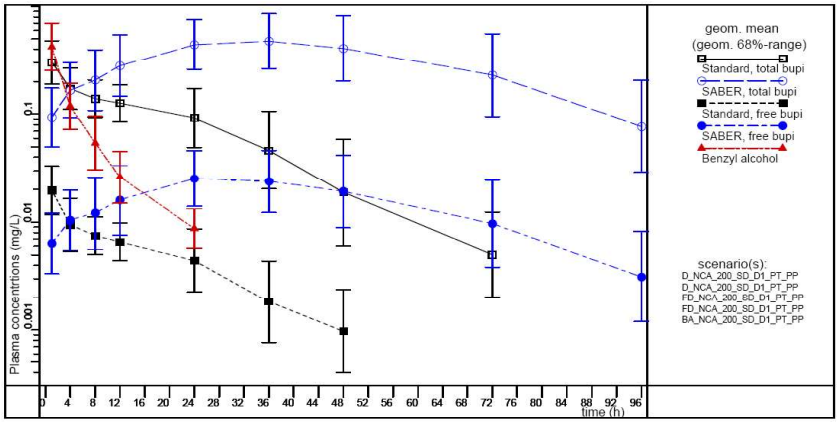


Individual bupivacaine plasma concentrations following administration of Standard bupivacaine HCl (cohort c)



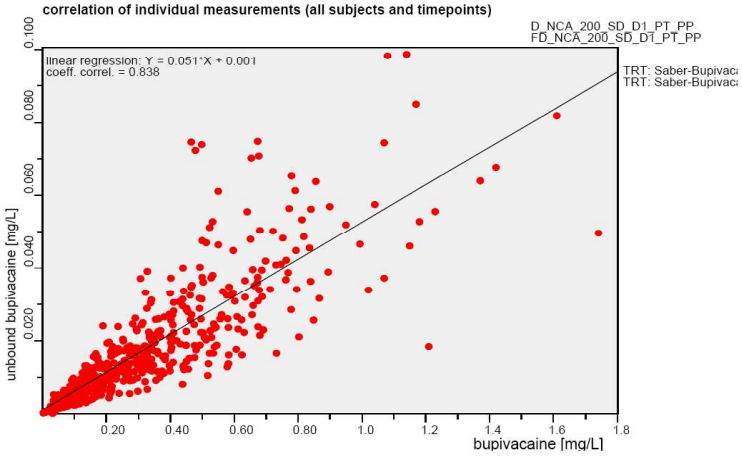
For SABER-bupivacaine, the Cmax values showed high inter-subject variability (C_{max} range: 0.119 - 1.740 µg/mL), as well as Tmax (Tmax range: 4.0 - 95.92 h). The majority of patients had Cmax values below 0.8 µg/mL. The observed T1/2 was approximately 18.9 h.

Geometric mean (68%-range) total and free bupivacaine and benzyl alcohol plasma concentrations following administration of SABER-Bupivacaine (cohort 1a) or standard bupivacaine HCl (cohort 1c)



The following figure shows a correlation of all individual plasma concentrations of total and free bupivacaine for SABER-Bupivacaine. The correlation indicated that free bupivacaine plasma concentrations increase in proportion with total bupivacaine.

Correlation of free (unbound) and total individual bupivacaine plasma concentrations following administration of SABER-Bupivacaine (cohort 1a)



Plasma PK-parameters of total and free bupivacaine and benzyl alcohol following administration of SABER-Bupivacaine or Standard bupivacaine HCl (geometric mean):

PK-parameter	SABER-Bupivacaine (total)	SABER-Bupivacaine (free)	Standard Bupivacaine (total)	Standard Bupivacaine (free)	Benzyl alcohol [b]
$t_{1/2}$ [h]	18.93	17.45	8.48	8.59	4.73
T_{max} [a] [h]	36.00	35.97	1.00	1.00	1.00
C_{max} [mg/L]	0.548	0.033	0.313	0.020	0.388
AUC_t [mg·h·L^{-1}]	30.29	1.56	5.29	0.27	1.70
AUC_{inf} [mg·h·L^{-1}]	31.13	1.66	5.39	0.27	1.78

a: median (min/max) b: applicable to SABER-bupivacaine only

Treatment: Std bupivacaine HCl Analyte: bupivacaine

	λ_z [h^{-1}]	$t_{1/2}$ [h]	t_{lag} [h]	t_{max} [h]	C_{max} [mg/L]	AUC_t [mg·h·L^{-1}]	extrap. [%]	AUC_{inf} [mg·h·L^{-1}]	CL/F [L/h]	V_z/F [L]
N	27	27	27	27	27	27	27	27	27	27
N_{obs}	27	27	27	27	27	27	27	27	27	27
mean	0.0851	8.85	0.00	2.37	0.342	5.65	1.7	5.74	19.61	247.54
SD	0.0244	2.78	0.00	4.82	0.139	2.32	2.8	2.30	6.45	105.19
SEM	0.0047	0.53	0.00	0.93	0.027	0.45	0.5	0.44	1.24	20.24
CV (%)	28.7	31.4	0.0	203.0	40.7	41.1	162.8	40.2	32.9	42.5
median	0.0864	8.02	0.00	1.00	0.306	5.43	0.8	5.48	18.26	236.61
min	0.0399	4.38	0.00	0.92	0.096	2.53	0.3	2.57	7.48	100.86
max	0.1583	17.39	0.00	23.92	0.625	13.32	14.4	13.36	38.87	458.97
geom. mean lower 68%	0.0818 0.0610	8.48 6.33	n.v. n.v.	n.v. n.v.	0.313 0.201	5.29 3.72	n.v. n.v.	5.39 3.80	18.57 13.11	227.11 148.17
upper 68%	0.1095	11.35	n.v.	n.v.	0.488	7.53	n.v.	7.63	26.30	348.09

n.v. = no value
Date/Time = 08.06.10 14:53:19
Study-No: BU-001-IMS
Scenario: D_NCA_200_SD_D1_PT_PP

Treatment: SABER bupivacaine HCl Analyte: bupivacaine

	λ_z [h^{-1}]	$t_{1/2}$ [h]	t_{lag} [h]	t_{max} [h]	C_{max} [mg/L]	AUC_t [mg·h·L^{-1}]	extrap. [%]	AUC_{inf} [mg·h·L^{-1}]	CL/F [L/h]	V_z/F [L]
N	54	54	59	59	59	59	54	54	54	54
N_{obs}	59	59	59	59	59	59	59	59	59	59
mean	0.0377	19.48	0.00	37.32	0.625	35.23	7.2	36.83	26.00	708.67
SD	0.0092	4.67	0.00	16.47	0.310	18.72	4.2	21.06	21.60	555.93
SEM	0.0013	0.67	0.00	2.14	0.040	2.44	0.6	3.01	3.09	79.42
CV (%)	24.5	24.0	0.0	44.1	49.7	53.1	58.0	57.2	83.1	78.4
median	0.0375	18.48	0.00	36.00	0.595	33.02	6.8	33.15	19.91	514.71
min	0.0238	11.27	0.00	4.00	0.119	4.42	1.2	4.47	5.40	189.71
max	0.0615	29.18	0.00	95.92	1.740	105.32	16.7	122.17	125.40	3007.82
geom. mean lower 68%	0.0366 0.0288	18.93 14.87	n.v. n.v.	n.v. n.v.	0.548 0.317	30.29 16.67	n.v. n.v.	31.13 16.59	20.98 11.34	573.08 306.32
upper 68%	0.0466	24.10	n.v.	n.v.	0.947	55.04	n.v.	58.42	38.81	1072.15

Treatment: Std bupivacaine HCl Analyte: FREE bupivacaine

	λ_z [h^{-1}]	$t_{1/2}$ [h]	t_{lag} [h]	t_{max} [h]	C_{max} [mg/L]	AUC_t [mg·h·L^{-1}]	Extrap. [%]	AUC_{inf} [mg·h·L^{-1}]	CL/F [L/h]	V_z/F [L]

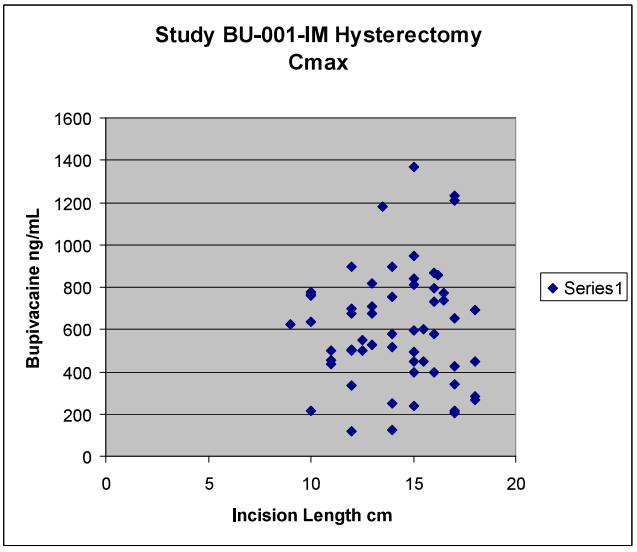
						⁻¹]		⁻¹]		
N	27	27	27	27	27	27	27	27	27	27
N_{obs}	27	27	27	27	27	27	27	27	27	27
mean	0.0842	9.02	0.00	2.47	0.023	0.286	2.2	0.292	386.65	4781.18
SD	0.0244	3.16	0.00	4.60	0.011	0.114	1.9	0.115	149.64	1707.18
SEM	0.0047	0.61	0.00	0.89	0.002	0.022	0.4	0.022	28.80	328.55
CV (%)	29.0	35.1	0.0	186.2	49.2	40.1	83.9	39.4	38.7	35.7
median	0.0772	8.98	0.00	1.00	0.023	0.266	1.9	0.270	371.05	4297.35
min	0.0329	4.86	0.00	0.92	0.006	0.101	0.3	0.103	138.42	2009.71
max	0.1425	21.05	0.00	24.00	0.063	0.720	9.5	0.722	971.90	9475.97
geom. mean lower 68%	0.0807 0.0594	8.59 6.32	n.v. n.v.	n.v. n.v.	0.020 0.012	0.268 0.189	n.v. n.v.	0.275 0.193	364.04 256.23	4511.89 3189.81
upper 68%	0.1096	11.67	n.v.	n.v.	0.033	0.382	n.v.	0.390	517.21	6381.93

Treatment: SABER bupivacaine HCl Analyte: FREE bupivacaine

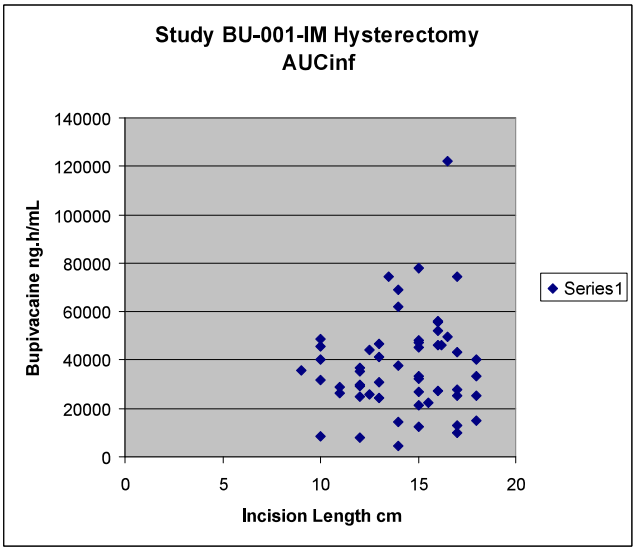
	λ_z [h^{-1}]	$t_{1/2}$ [h]	t_{lag} [h]	t_{max} [h]	C_{max} [mg/L]	AUC_t [$mg \cdot h \cdot L^{-1}$]	extrap. [%]	AUC_{inf} [$mg \cdot h \cdot L^{-1}$]	CL/F [L/h]	V_z/F [L]
N	53	53	59	59	59	59	53	53	53	53
N_{obs}	59	59	59	59	59	59	59	59	59	59
mean	0.0411	18.06	0.02	32.27	0.039	1.824	5.5	1.973	495.43	12805.59
SD	0.0112	4.76	0.13	14.20	0.023	0.958	3.5	1.103	428.95	11789.16
SEM	0.0016	0.67	0.02	1.85	0.003	0.125	0.5	0.154	60.06	1650.81
CV (%)	27.3	26.3	768.1	44.0	58.4	52.5	64.0	55.9	86.6	92.1
median	0.0388	17.86	0.00	35.97	0.033	1.727	5.8	1.875	342.82	8631.50
min	0.0225	9.74	0.00	4.05	0.006	0.216	0.8	0.219	114.25	2613.51
max	0.0712	30.75	1.02	72.00	0.099	5.059	14.1	5.777	2562.12	67893.42
geom. mean lower 68%	0.0397 0.0304	17.45 13.37	n.v. n.v.	n.v. n.v.	0.033 0.018	1.563 0.851	n.v. n.v.	1.657 0.867	394.01 208.81	9920.50 5074.72
upper 68%	0.0519	22.79	n.v.	n.v.	0.062	2.868	n.v.	3.165	743.47	19393.45

The following figures are plotted in order to assess if there are any correlation between bupivacaine exposure and incision length.

Cmax vs Incision Length:



AUCinf vs. Incision Length:



4.2.11 Study C803-025 Phase 3 procedures (laparotomy, laparascopic cholecystectomy, and Laparoscopically-assisted colectomy) using 5 mL

Study C803-025 was a Phase 3, multi-center, randomized, double-blind, active- and placebo-controlled trial evaluating the safety, efficacy, effectiveness and pharmacokinetics of SABER-Bupivacaine 5.0 mL, in patients undergoing general surgical procedures with various wound sizes. Patients were assigned to one of the three trial cohorts: SABER-Bupivacaine 5.0 mL (660 mg), Sensorcaine 30 mL 0.5% solution (5 mg/mL; 150 mg), or SABER- Placebo 5.0 mL administered into the surgical wound(s). Bupivacaine HCl 0.5% solution (5 mg/mL, 150 mg bupivacaine) was administered by infiltration with a hypodermic needle into the peri-incisional tissues. For the SABER-Bupivacaine was drawn up and administered using a NORM-JECT® 5-

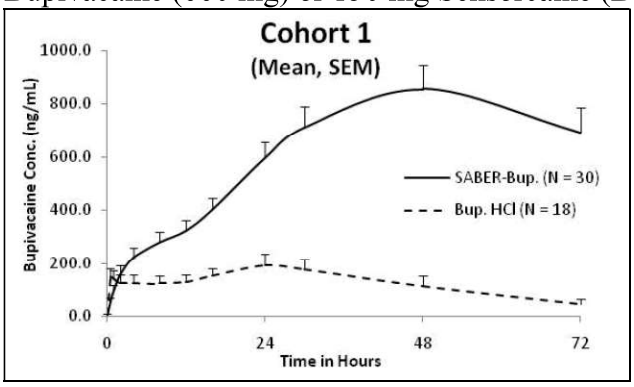
mL Luer Lock syringe connected to a Tunneltip™ irrigation catheter with a Luer Lock fitting or by the syringe tip.

The surgical procedures (or cohorts) are as follows:
1) Cohort 1 – Laparotomy: SABER-Bupivacaine 5.0 mL or Sensorcaine 30 mL 0.5% solution in a 3:2 ratio, respectively. The majority of patients (N= 48) had surgical diagnoses of colon cancer, diverticulitis, and other diagnoses including splenectomy, cholecystectomy, ostomy creation or takedown, reversal of Hartmann's procedure, colectomy not otherwise specified (NOS), pelvic abscess, fistula repair, or exploratory laparotomy. There were no restrictions on laparotomy incision length (typically with a single incision of 20 cm or more), closure of stoma, or anatomical placement of the incision. The entire 5 mL dose of SABER-Bupivacaine was evenly distributed within the laparotomy incision.
2) Cohort 2 - Laparoscopic cholecystectomy: SABER-Bupivacaine 5.0 mL or Sensorcaine 30 mL 0.5% solution in a 3:2 ratio, respectively. The majority of patients (N=50) had surgical diagnosis of symptomatic cholelithiasis or cholecystitis. There were no restrictions on the number of laparoscopic portals (typically with 4 laparoscopic ports inserted) or conditions encountered during the operation to require conversion into open surgery. The larger port incisions received a larger volume of test drug.
3) Cohort 3 - Laparoscopically-assisted colectomy: SABER-Bupivacaine 5.0 mL or SABER-Placebo 5.0 mL in a 3:2 ratio, respectively. The majority of patients (N = 207) had surgical diagnoses of diverticulitis, colon cancer, polyp, tumor, or unspecified mass.
This cohort included patients undergoing laparoscopically-assisted colectomy without planned formation or closure of stoma for colon cancer, diverticulitis, or polyps. Conversion from laparoscopically-assisted to open surgery with an incision length of up to 15 cm was allowed at the surgeon's discretion for the patient's safety and technical difficulties. Patients were not to be dosed with the investigational product if extensive concomitant surgical procedures were performed and/or conversion to open surgery required an incision greater than 15 cm. There was generally a 5-10 cm linear incision for exteriorizing the colon for resection and anastomosis (the hand port). Approximately 80-90% of the SABER-Bupivacaine was instilled into the hand port using the irrigation catheter method. The remaining 10-20% of test drug was directly instilled into the laparoscopic port incisions.

Serial blood samples (5 mL each) were collected at baseline (pre-dose, t = 0), and at 0.5, 1, 2, 4, 8, 12, 16, 24, 30, 48, and 72 hours post-dose. The plasma samples were analyzed for determination of total bupivacaine concentration using a validated LC-MS/MS detection method (lower limit of detection of 1 ng/mL). For the purpose of plotting the data, below the limit of quantification (BLQ) plasma concentrations embedded between 2 measurable concentrations were set to missing; however, BLQ values occurring before the first measurable concentration and after the last measurable concentration were set to zero. For each patient, the PK parameters were determined using a non-compartmental approach. The PK parameters included, Cmax, Tmax, AUC0-t, and AUC0-last.

<u>Cohort 1 – Laparotomy surgery:</u>
Mean bupivacaine plasma concentration profiles from laparatomy surgery are presented in below.

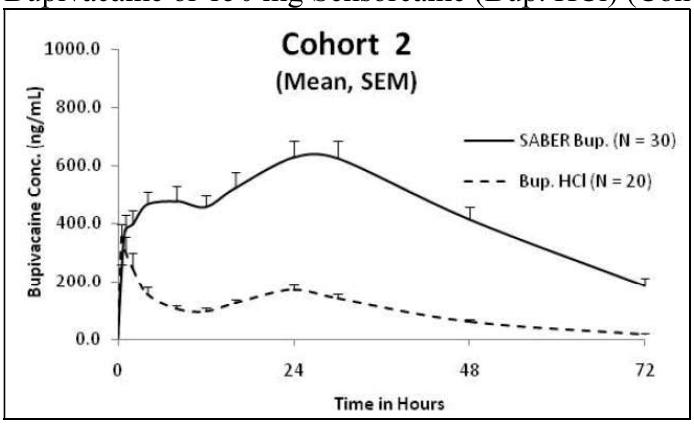
Mean (SEM) Bupivacaine Plasma Concentration Following Administration of 5.0 mL SABER-Bupivacaine (660 mg) or 150 mg Sensorcaine (Bup. HCl) (Cohort 1)



Cohort 2 – Laparoscopic cholecystectomy surgery:

Mean bupivacaine plasma concentration profiles from laparoscopic cholecystectomy surgery are presented in figure below.

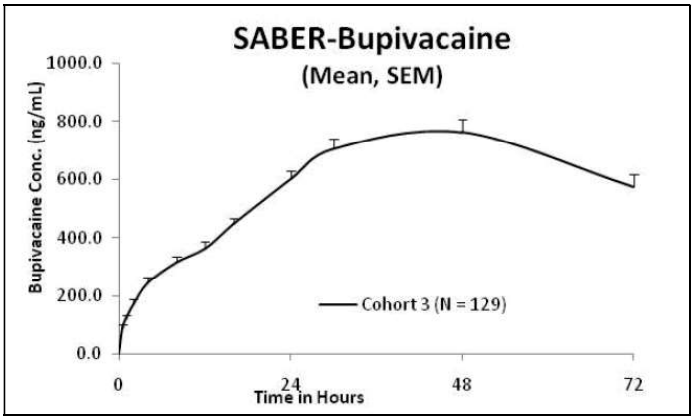
Mean (SEM) Bupivacaine Plasma Concentration Following Administration of 5.0 mL SABER-Bupivacaine or 150 mg Sensorcaine (Bup. HCl) (Cohort 2)



Cohort 3 – Laparoscopically-Assisted Colectomy surgery:

A total of 129 patients received 5.0 mL SABER-Bupivacaine and 78 patients received SABER-Placebo in this cohort. The mean bupivacaine plasma profile from laparoscopically-assisted colectomy surgery following instillation of 5.0 mL SABER-Bupivacaine is presented below.

Mean (SEM) Bupivacaine Plasma Concentration Following Administration of 5.0 mL SABER-Bupivacaine (Cohort 3)



Composite of three surgeries:

Plasma Pharmacokinetic Parameters of Total Bupivacaine Following Administration of SABER-Bupivacaine or Sensorcaine (Mean (SEM)) (Cohorts 1, 2, and 3)

	SABER-Bupivacaine			Sensorcaine (bupivacaine HCl)	
	Cohort 1	Cohort 2	Cohort 3	Cohort 1	Cohort 2
PK Parameter	(N = 30)	(N = 30)	(N = 129)	(N = 18)	(N = 20)
Cmax (ng/mL)	955.6 (485) [133 – 1870]	752.1 (307) [357 – 1850]	849.6 (478) [92 – 2850]	250.6 (190) [19 – 551]	370.5 (246) [101- 1170]
Tmax (hr)a	48.1 [2 – 73]	24.3 [1 – 49]	46.6 [1 – 74]	16.3 [1 – 48]	0.9 [1 – 24]
AUC(0-72) (ng*hr/mL)b	40755 (20876) [5113 – 79464]	29466 (14945) [11095 – 68124]	39437 (22346) [3613 – 110222]	8465 (8316) [495 – 26306]	6772.1 (2561) [1777 – 11985]
AUC(0-last) (ng*hr/mL)	41942 (24344) [635 – 96625]	30997 (12680) [11100 – 68108]	39602 (24049) [1626 – 136309]	7784 (7889) [465 – 26364]	6623 (2555) [1771 – 11868]

a median

Study C803-025; Plasma Pharmacokinetic Parameters of Total Bupivacaine Following Administration of SABER-Bupivacaine or Sensorcaine (Mean only)

Pharmacokinetic Parameter	Mean (SEM) [Range]	
	Cohorts 1, 2, and 3 SABER-Bupivacaine (N = 189)	Cohorts 1 and 2 Bupivacaine HCl (N = 38)
C_{max} (ng/mL)	850.9 [92 – 2850]	313.7 [19 – 1170]
T_{max} (hr)a Median	46.2 [1 – 74]	1.2 [1 – 48]
$AUC_{(0-72)}$ (ng*hr/mL)b	38016.6 [3613 – 110222]	7518.8 [495 – 26306]

$AUC_{(0\text{-last})}$ (ng*hr/mL)	38607.3 [635 – 136309]	7172.8 [465 – 26364]

Instillation of 5.0 mL SABER-Bupivacaine in all 3 surgical models was evaluated. The overall integrated mean Cmax was 850.9 ng/mL, which was similar across the mean values observed in the individual cohorts. The overall mean AUC(0-last) was 38607.3 ng.h/mL.

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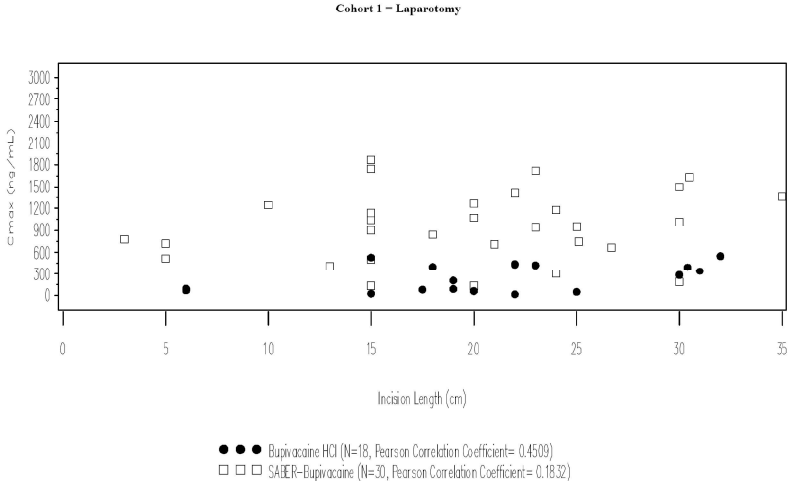
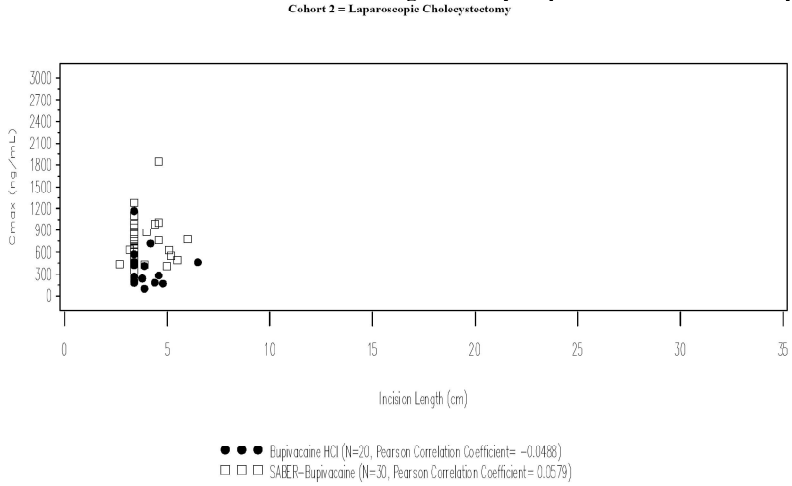
The following scatter plots compare incision lengths and PK parameters.

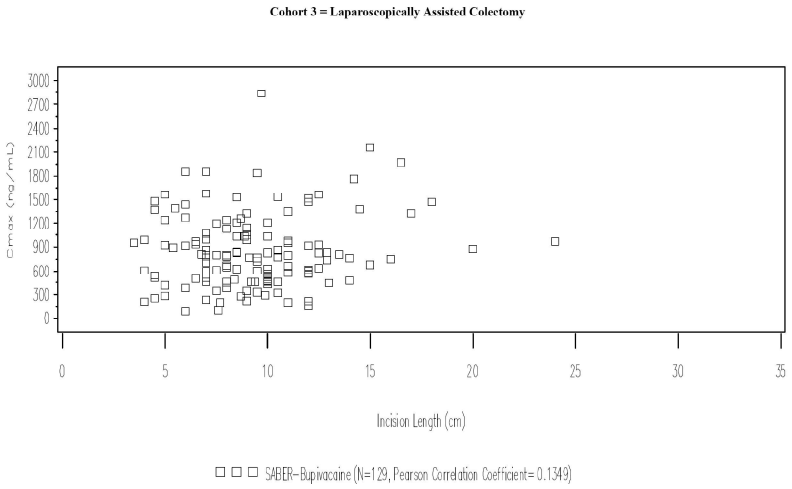
Scatter Plot of C_{max} versus Incision Length Safety Population Cohort 1 = Laparotomy



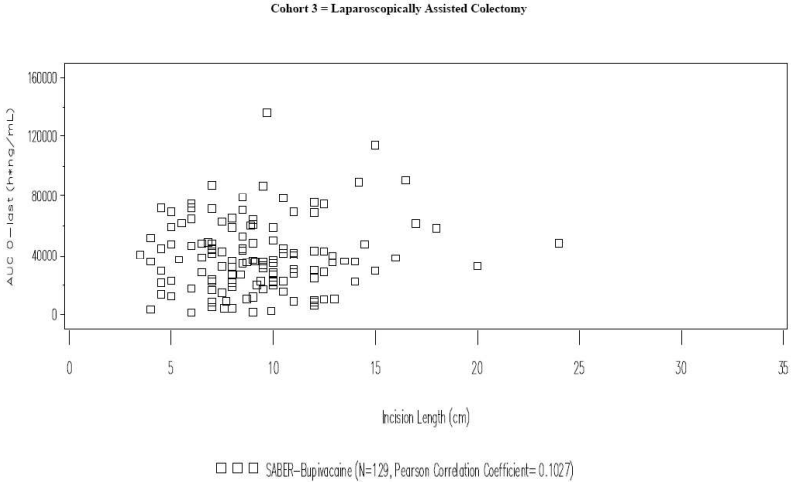
Scatter Plot of C_{max} versus Incision Length Safety Population Cohort 2 = Laparoscopic Cholecystectomy



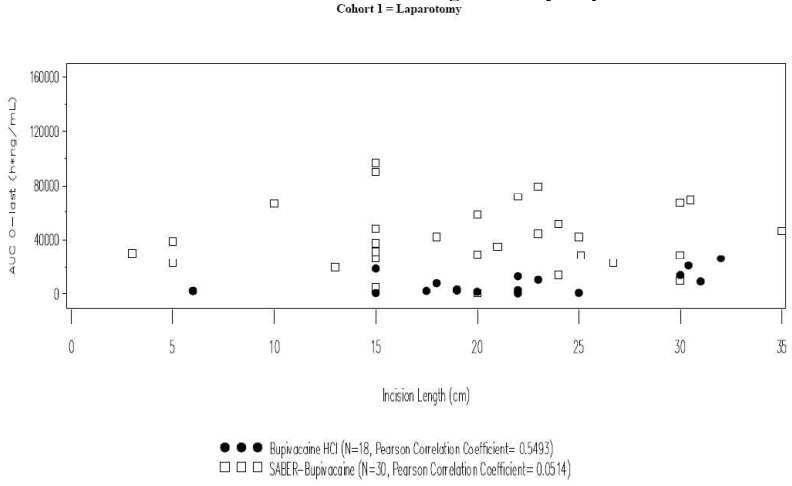
Scatter Plot of C_{max} versus Incision Length Safety Population Cohort 3 = Laparoscopically Assisted Colectomy



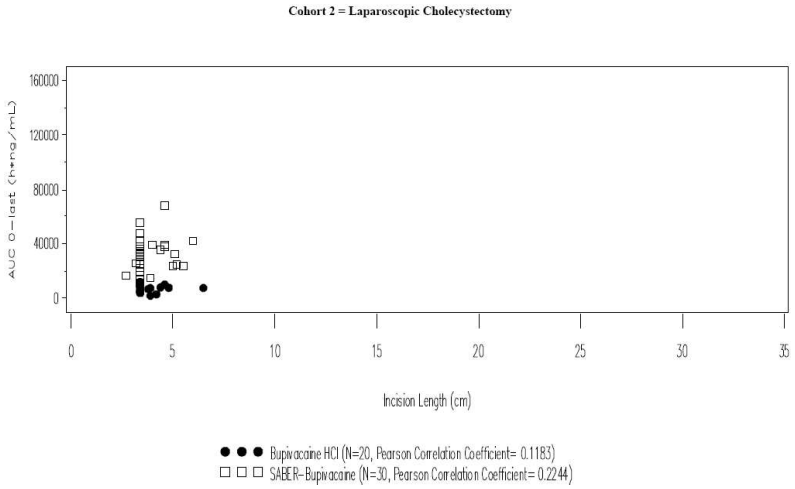
Scatter Plot of $AUC_{0\text{-last}}$ versus Incision Length Safety Population Cohort 3 = Laparoscopically Assisted Colectomy



Scatter Plot of $AUC_{0\text{-last}}$ versus Incision Length Safety Population Cohort 1 = Laparotomy



Scatter Plot of $AUC_{0\text{-last}}$ versus Incision Length Safety Population Cohort 2 = Laparoscopic Cholecystectomy



4.3 Consult Review (including Pharmacometric Reviews) – Not applicable

4.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form					
General Information About the Submission					
	Information			**Information**	
NDA/BLA Number	**204803**	**Brand Name**		**Posimir™**	
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**		**Bupivacaine ER solution**	
Medical Division	**DAAAP**	**Drug Class**		**Anesthetic**	
OCP Reviewer	**David Lee, Ph.D.**	**Indication(s)**		**Post-surgical analgesia**	
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**		**Solution for instillation**	
Pharmacometrics Reviewer	**-**	**Dosing Regimen**		**660 mg bupivacaine single use**	
Date of Submission	**4/12/13**	**Route of Administration**		**Instillation into the surgical incision before closure**	
Estimated Due Date of OCP Review	**1/8/14**	**Sponsor**		**Durect Corporation**	
Medical Division Due Date	**1/8/14**	**Priority Classification**		**1S**	
PDUFA Due Date	**2/12/14**				
Clin. Pharm. and Biopharm. Information					
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**	
STUDY TYPE					
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**				
Tabular Listing of All Human Studies	**X**				
HPK Summary	**x**				
Labeling	**x**				
Reference Bioanalytical and Analytical Methods	**x**				
I. Clinical Pharmacology					
Mass balance:					
Isozyme characterization:					
Blood/plasma ratio:					
Plasma protein binding:					
Pharmacokinetics (e.g., Phase I) -					
Healthy Volunteers-					
single dose:	**x**	**2**			
multiple dose:					
Patients-					

single dose:	x			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X			
gender:	X			
pediatrics:				
geriatrics:	X			
renal impairment:	X			**Per Marcaine Labeling**
hepatic impairment:	X			**Per Marcaine Labeling**
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:		6		
Phase 3 clinical trial:	x	1		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	x	1		**Marcaine as listed drug (infiltration injection)**
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
In vivo alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x			**Deferral for 3–18 y of age; Waiver under 3 y of age**
Literature References				
Total Number of Studies		11		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical	X			

	assay?				
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the	X			

	label?				
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____yes___

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Durect Corporation submitted a New Drug Application (NDA) for Posimir™ (bupivacaine extended release solution, 660 mg bupivacaine/5 mL, 132 mg/mL, 13.2%), also referred to throughout its development as SABER®-Bupivacaine or SABERCAINE, under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. As a 505(b)(2) application, the Applicant is relying in part on the Agency's findings of safety and efficacy for the Marcaine® (bupivacaine HCl) Injection (NDA 16964).

The proposed indication is for post-surgical analgesia and is to be administered by instillation into the surgical incision before closure. The proposed dosing regimen is a single dose of 5 mL administered during surgery. The Sponsor claimed that the extended release component of Posimir is sucrose acetate isobutyrate (SAIB), which is a hydrophobic, fully esterified sucrose derivative, with a nominal ratio of six isobutyrate groups to two acetate groups. As a mixed ester, SAIB is a non-crystalline, non-polymeric clear viscous liquid. When SAIB is formulated with bupivacaine dissolved in benzyl alcohol, the liquid solution is fluid enough to be instilled using a standard syringe with a large bore blunt needle. Once the liquid solution is instilled the benzyl alcohol diffuses into the local tissue, leaving a viscous hydrophobic film. Bupivacaine is released slowly from the film into the local tissues for pain relief.

The clinical program was conducted under IND 66086. The Applicant conducted the following studies:

Table 1: Overview on Clinical Trials with SABER-Bupivacaine with Clinical Pharmacokinetic Component

Protocol Number	Phase	Surgery	Study Drug (Dose)[b]	Type of Administration	# of Safety Subjects
SABER01-01[a]	I	N/A Healthy Subjects	(b) (4)		12
CLIN005-0008	I	N/A Healthy Subjects	SABER-Bupivacaine 5.0 mL Generic Bupivacaine HCl[e] - IV Infusion (20 mL)	Trailing Injection Infusion	8[c]
CLIN004-0001	IIa	Hernia Repair	SABER-Bupivacaine (2.5, 5.0, 7.5 mL) Marcaine[e] 0.5% (15 – 17.5 mL) SABER-Placebo	Trailing Injections	81
CLIN004-0009	IIa	Hernia Repair	SABER-Bupivacaine (5.0, 7.5 mL) Marcaine[e] 0.25%l (5.0, 7.5 mL)	Infiltration + trailing injections	42
CLIN005-0007	II	Hernia Repair	SABER-Bupivacaine (5.0 mL)	Instillation	12
CLIN803-006-0006	II	Hernia Repair	SABER-Bupivacaine (2.5, 5.0 mL) SABER-Placebo	Instillation	123
CLIN005-0006	II	Subacromial Decompression	SABER-Bupivacaine (5.0, 7.5 mL) SABER-Placebo	Subacromial Injection + SC trailing injections Subacromial Injection	106[d]
BU-002-IM	II	Subacromial Decompression	SABER-Bupivacaine (5.0, 7.5 mL) SABER-Placebo Marcaine[e] 2.5 mg/mL injection (Bupivacaine HCl) 50 mg (20 mL)	Subacromial Injection	107
CLIN005-0002	II	Appendectomy	SABER-Bupivacaine (5.0 mL) SABER-Placebo	Trailing Injections Only Infiltration + trailing injections	21
BU-001-IM	II	Hysterectomy	SABER-Bupivacaine (5.0 mL) SABER-Placebo Marcaine[e] 2.5 mg/mL injection (Bupivacaine HCl) 100 mg (40 mL)	Instillation Infiltration	114
C803-025	III	Laparotomy, Laparoscopic Cholecystectomy, Laparoscopically Assisted Colectomy	SABER-Bupivacaine (5.0 mL) SABER-Placebo Sensorcaine[e] 0.5% injection MPF (Bupivacaine HCl) 30 mL	Instillation Infiltration	305

[a] Early Development formulation containing 55 mg/mL of bupivacaine base
[b] SABER-Bupivacaine contains 132 mg/mL of bupivacaine base
[c] In CLIN005-0008 5 subjects were administered SABER-Bupivacaine
[d] CLIN005-0006 includes 92 subjects from double-blind portion and 14 subjects from open label PK sub-study
[e] Marcaine, Sensorcaine and generic bupivacaine HCl are all therapeutically equivalent approved products of bupivacaine HCl.

Posimir in the following studies was administered as the proposed route, i.e., instillation: BU-001-IM (relative BA), CLIN005-0007, CLIN803-006-0006, and C803-025. We plan to review these studies in detail since they have the same administration route as the proposed label. Based on the discussion in the filing meeting, it is unclear at this early stage whether the study results

with other routes will support the proposed route. If it is determined during the review process that such results can be used to support approval of the product, we will also review them in detail.

The to-be-marketed formulation was used in pertinent clinical studies, including relative bioavailability and Phase 3 study. The Applicant requests deferral and waiver of pediatric studies in children and adolescent (3 to less than 18 years of age) and pre-term and Term Newborn infants, children up to 3 years of age, respective.

Conclusion:

From a clinical pharmacology perspective, the application is recommended for filing.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID J LEE
01/08/2014

YUN XU
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