8.3.7 Other Controlled Studies, Adult Venipuncture (SC-40-02, 41-03)

In addition to studies SC-24-01, SC-11-01 and SC-31-01, two other studies evaluated the S-Caine Patch for local anesthesia prior to venipuncture in adults. These were SC-40-02 (EMLA comparison) and SC-41-03 (to address FDA "combination rule").

8.3.7.1 Study SC-40-02 (Active Control, Dose Ranging)

Study SC-40-02 was a single site study utilizing a randomized, double-blind, (paired) design to evaluate the effectiveness of the S-Caine Patch, compared with EMLA Cream. Both were administered simultaneously (left and right antecubital, randomized 1:1), for varying treatment durations (10, 20, 30, and 60 minutes) to 82 healthy adult subjects (80 planned). Subjects were randomized into one of four treatment groups: 10 minute, 20 minute, 30 minute or 60 minute anesthetic applications. The primary efficacy variable was the subject's evaluation of pain caused by venipuncture (18 G) as rated on a 100 mm VAS. Secondary efficacy measures were also the same as those used in the other adult venipuncture trials. Efficacy results are summarized in Table 8.X below. S-Caine was (statistically significantly) more effective than EMLA Cream at application durations of 10 minutes, 20 minutes and 30 minutes, but not at 60 minutes. This is the only S-Caine Patch trial to evaluate a 10-minute application period.

Table 8.31. SC-40-02 Efficacy Results

	10 min n=20 (19[a])	20 min n=20	30 min n=22	60 min n=20
Primary Efficacy				
S-Caine VAS < EMLA VAS	68%	65%	82%	45%
EMLA VAS < S-Caine VAS	32%	30%	14%	40%
P-value [b]	0.010 [b]	0.042 [b]	0.001 [b]	0.887 [b]
Median VAS S-Caine	15.5	15.0	2.0	2.0
Median VAS EMLA	33.0	22.0	13.0	2.0
Median Difference	9.0	11.5	9.5	--
P-value [?]	p=sig	p=sig	p=sig	p=ns
Secondary Efficacy				
Anesthetic Eliminated Pain				
S-Caine Patch	65%	90%	95%	95%
EMLA	42%	60%	64%	95%
% with better score for S-Caine	32%	30%	36%	5%
% with better score for EMLA	5%	0%	5%	5%
P-value [c]	0.059	0.014	0.020	1.000
Would Use Anesthetic Again				
S-Caine Patch	80%	95%	100%	90%
EMLA	47%	70%	64%	95%
% with better score for S-Caine	37%	25%	36%	0%
% with better score for EMLA	0%	0%	0%	5%
P-value [c]	0.008	0.025	0.005	0.317

[a] One subject refused EMLA after S-Caine treatment [b] Wilcoxin signed rank test [c] McNemar chi-square
Source: Modified from sponsor Table 11.3, and text (Volume 40)

8.3.7.2 Study SC-41-03 (Combination Rule)

21 CFR 300.50 *Fixed-combination prescription drugs for humans* or "Combination rule"

Study SC-41-03 was a randomized, double-blind, factorial study designed to compare 30-minute applications of the S-Caine Patch to lidocaine patch, to tetracaine patch and to placebo patch for anesthesia prior to venipuncture in healthy adult volunteers. Eighty subjects (of eighty planned), each attended four study sessions over four consecutive days. During each session, subjects received a single 30-minute patch application, prior to venipuncture with an 18-gauge angiocath. Test patches all contained identical excipients, varying only with respect to active drug content. The four treatment conditions were;

1. S-Caine Patch (70 mg lidocaine + 70 mg tetracaine, with heating element)
2. Lidocaine patch 70 mg, with heating element
3. Tetracaine patch 70 mg, with heating element
4. Placebo patch (olive oil substituted for active drug), with heating element

The ordering of patch application sites was the same for all patients (Session 1 right AC, session 2 left AC, session 3 right AC, session 4 left AC).

Disposition of subjects: All 80 enrolled subjects completed all 4 treatment sessions.

Protocol deviations: There was one protocol deviation. For one subject, the follow-up skin evaluation of the treatment session 1 patch (to be conducted at treatment session 2) was not performed.

The primary efficacy variable was the subject's evaluation of pain caused by venipuncture with an 18-gauge angiocath, as rated on a 100 mm VAS where 0 mm = "no pain" and 100 mm = "the worst pain you can imagine." VAS scores were initially compared using repeated measures ANOVA, to test for the presence of a treatment by center interaction. Pairwise Wilcoxin signed-rank tests were than performed. The three primary comparisons were between S-Caine and the three other treatments (p-value < 0.0167 for statistical significance).

Table 8.32.
SC-41-03 VAS Scores Following Venipuncture (18-G) by Treatment (N = 80)

	S-Caine n = 80	Lidocaine n = 80	Tetracaine n = 80	Placebo n = 80
Mean ± SD	7.8 ± 11.6	19.4 ± 16.6	23.0 ± 17.8	25.1 ± 19.4
Median	3.0	16.0	18.0	22.0
Range	0 - 54	0 - 83	0 - 71	1 - 71
p-value (< 0.0167 = sig) [a]	Lidocaine	Tetracaine	Placebo	
S-Caine vs.	< 0.001	< 0.001	< 0.001	
Lidocaine vs.		0.025	0.003	
Tetracaine vs.	0.025		0.439	

[a] Wilcoxin signed-rank test, p-values < 0.0167 are statistically significant
Source: Sponsor Table 11.3, Volume 41

Table 8.33. Study SC-41-03 Efficacy Results

	S-Caine n = 80	Lidocaine n = 80	Tetracaine n = 80	Placebo n = 80
Primary Efficacy				
VAS Mean +/- SD	7.8 ± 11.6	19.4 ± 16.6	23.0 ± 17.8	25.1 ± 19.4
VAS Median	3.0	16.0	18.0	22.0
VAS Range	0 - 54	0 - 83	0 - 71	1 - 71
p-value S-Caine vs.		$p < 0.001$	$p < 0.001$	$p < 0.001$
p-value Lidocaine vs.			$p = 0.025$	$p = 0.003$
p-value Tetracaine vs.				$p = 0.439$
Secondary Efficacy				
No. (%) Reporting Adequate Anesthesia	73 (91%)	49 (61%)	40 (50%)	37 (46%)
S-Caine vs.		$p < 0.001$	$p < 0.001$	$p < 0.001$
No. (%) Reporting Would Use Again	71 (89%)	47 (59%)	40 (50%)	40 (50%)
S-Caine vs.		$p < 0.001$	$p < 0.001$	$p < 0.001$
p-value < 0.0167 = significant for all comparisons				

Source: Tables 11.3 and 11.4, Appendices 16.2.17 through 16.2.20 (Volume 41)

8.3.8 Infant Efficacy/Safety Study, Final Patch (SC-29-01)

SC-29-01 was the only S-Caine Patch efficacy trial in children younger than 3. It was also the only pediatric efficacy trial to utilize the final formulation of the S-Caine Patch, aside from pivotal pediatric trials SC-20-01 and SC-21-01. The study title was "A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the S-Caine Patch for Induction of Local Anesthesia for Immunization in Pediatric Patients." Sixty-seven healthy infants meeting study inclusion criteria were randomized to receive (for 30 minutes) either 2 S-Caine Patches or 2 placebo patches, one on each thigh, immediately prior to receiving their 4 or 6-month immunizations (The protocol called for 80 subjects to be enrolled, but during the study there was a nationwide shortage of one of the protocol immunizations, Prevnar®).

Following 30-minute patch applications (both thighs) the investigator or study nurse administered 2 intramuscular vaccines into each thigh. Another study nurse used a handheld camera to videotape each infant during the each immunization sessions, until at least 30 seconds after the baby stopped crying. The original protocol called for vital sign monitoring, in order to use physiological assessments to gauge subject pain but investigators at (both) sites informed the sponsor that they would be unable to obtain the specified vital signs.

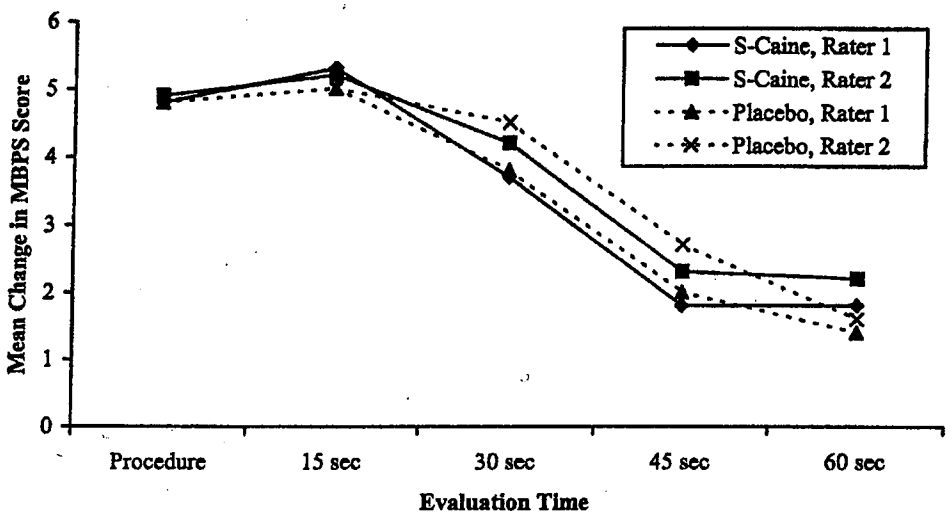
Sixty-seven patients were randomized (34 S-Caine, 33 placebo), to this single session study (received the vaccination injections). There were three minor protocol deviations, none of which appear capable of effecting study (safety or efficacy) results.

Primary Efficacy Results:
The primary efficacy variable was the investigator's evaluation of infant pain as measured by the Modified Behavioral Pain Scale (MBPS), a pain assessment tool that has been validated in infants 4 to 6 months of age. Using the MBPS, two investigators watched each videotape and (independently) rated the child's facial expression, crying, and body movements, immediately prior to, and during the immunization procedures. Investigators scored the patients in 15-second increments from 60 seconds prior until one minute following the last vaccine administration (videotaping began 3 minutes prior to injections). The primary efficacy results demonstrated no statistically significant treatment effect

The secondary efficacy measures also failed to demonstrate treatment effect.

- Investigator Evaluation of Infant's Pain Using VAS. Fifteen seconds after completion of the last injection the investigator assessed the amount of pain that they believed the infant experienced (from the immunizations), on a 100-mm VAS.
- Parent Evaluation of Infant's Pain. Parents (one per infant) were given a survey to complete prior to leaving the study site.
  Parent completed three separate 100-mm VASs rating their infant's:
  Pain, crying and fear
  The survey also asked parents three "yes or no" questions:
  Did the anesthetic provide adequate pain relief?
  Was the anesthetic worth the 30-minute wait?
  Would you use this anesthetic again?
- Latency to First Cry. The latency to the first cry (in seconds) was measured, for infants who were not crying prior to the immunizations.
- Duration of Cry

Diagram 8.2. SC-29-01 Primary Efficacy Results



Source: Sponsor Figure 11.1, Volume 38

Table 8.34. SC-29-01 Efficacy Results

	S-Caine n = 34	Placebo n = 33	p-value
Primary Efficacy			
MBPS (Δ from baseline, at 15, 30, 45 and 60 seconds)			p = 0.821 [a]
Secondary Efficacy			
Investigator Rating (VAS)			
VAS Mean	41.0	51.8	p = 0.025 [b]
VAS Median	37.5	54.0	
Parent ratings			
Pain VAS – Mean (SD)	54.9 (27.8)	58.0 (28.1)	p = 0.639 [b]
Crying VAS – Mean (SD)	50.6 (30.1)	57.1 (30.3)	p = 0.381 [b]
Fear VAS – Mean (SD)	31.7 (31.3)	33.2 (28.2)	p = 0.855 [b]
No. (%) with Adequate Pain Relief	21 (62%)	12 (36%)	p = 0.091 [c]
No. (%) Indicating Worth Wait	25 (74%)	17 (52%)	p = 0.155 [c]
No. (%) Who Would Use Again	25 (74%)	27 (82%)	p = 0.700 [c]
Patient Crying			
No. (%) Crying Before Immunization	6 (18%)	12 (36%)	p = 0.166 [e]
Mean (SD) Seconds to First Cry [d]	7.1 (3.7)	5.5 (3.9)	p = 0.120 [f]
Crying After Immunization			
No. (%) Continuous	9 (27%)	11 (33%)	p = 0.278 [c]
No. (%) Intermittent	17 (52%)	10 (30%)	
No Crying	7 (21%)	12 (36%)	

[a] Repeated measures ANOVA [b] ANOVA, factors treatment, shot series [c] Mantel-Haenszel chi-square [d] S-Caine, n=25 Placebo, n=21 [e] Fisher's Exact Test [f] Two-way ANOVA
Source: Volume 38, pp 33-37, tables, diagrams and text

8.3.9 Adult Efficacy Trials (Developmental A) (SC-03-99, 07-99, 05-99)

8.3.9.1 SC-03-99 and SC-07-99 (Shave Biopsy)

SC-03-99 and SC-07-99 evaluated the efficacy of Developmental Form-A S-Caine Patch in alleviating pain associated with shave biopsies.

Both SC-03-99 and SC-07-99 were randomized, double-blind, placebo-controlled, multi-center studies, designed to evaluate the S-Caine Patch for induction of local anesthesia (of the skin) prior to shave biopsy in adults, very similar in most ways to pivotal trial SC-24-01. SC-03-99 enrolled 59 subjects (of 60 planned) and studied 60 minute patch applications. SC-07-99 enrolled 60 subjects (of 60 planned) and studied 30 minute patch applications. SC-07-99 incorporated a "Verification of Dermal Anesthesia" component.

Efficacy Measures (Identical for SC-03-99 and SC-07-99):
Patient's Evaluation of Pain
Patients completed a 100-mm VAS
Did the patch system "eliminate pain" during the procedure? (Yes/No)
Would you have local anesthesia using this patch system again? (Yes/No)

Investigator's Evaluation of Patient's Pain (Not done if lidocaine injection administered)
Four-point categorical scale (No pain, slight pain, moderate pain, severe pain)

Investigator's Overall Impression of Local Anesthetic (All patients)
Did the local anesthetic provide adequate anesthesia? (Yes/No)
Was the local anesthetic system accepted by the patient? (Yes/No)

Investigator Verification of Dermal Anesthesia
Pinprick (Yes/No)
Rescue lidocaine injection given? (Yes/No)
Additional lidocaine given during procedure? (Yes/No)

8.3.9.2 SC-05-99 (Venipuncture)

SC-05-99 was a randomized, double-blind, placebo-controlled, two-period, crossover study evaluating the efficacy (and pharmacokinetics) of a 30-minute application of the S-Caine Patch (Developmental Form A) for induction of local anesthesia prior to intravenous cannulation (All 20-gauge, except for 22-gauge in 3 subjects). Twenty-two (of twenty planned) healthy adult subjects enrolled, with one withdrawing prior to drug administration.

The primary efficacy variable in this study was the subject's evaluation of pain using a 100-mm VAS, following the vascular access procedure. Also, all but two subjects had lower scores following S-Caine Patch administration than following placebo patch.

Table 8.35 summarizes efficacy results from SC-03-99, SC-05-99 and SC-07-99.

Table 8.35. Efficacy Findings in Adult Developmental Patch Trials

Study	03-99 (60-min) 29 Active, 30 Placebo	07-99 (30-min) 29 Active, 31 Placebo	05-99 (30-min) X-over S-Caine 20, Placebo 21
Primary Efficacy			
Patient Evaluations			
Median VAS S-Caine	2 (0 – 45)	5 (0 – 72)	2.0 (0 – 23)
Median VAS Placebo	33 (1 – 60) p<0.001 Mann-Whitney	19 (0 – 45) p=0.003 Mann-Whitney	30.0 (0 – 95) p<0.001 ANOVA for X-over and Wilcoxin
Mean VAS S-Caine		13 ± 17.4	
Mean VAS Placebo		20 ± 10.3 p=0.074 ANOVA-2	
Patient Evaluations			
S-Caine, Pain Eliminated	86%	55%	90%
Placebo, Pain Eliminated	17% p<0.001 Chi-square	13% p=0.002 Chi-square	24% p=0.001 Sign Test
S-Caine, Use Again	90%	69%	95%
Placebo, Use Again	43% p<0.001 Chi-square	26% p=0.002 Chi-square	14% p<0.001 Sign Test
Anesthesia Verification			
S-Caine, Yes	93%	72%	
Placebo, Yes	10% p<0.001 Chi-square	16% p<0.001 Chi-square	
Rescue Lidocaine	?		
S-Caine	????		
Placebo	????		
Investigator Impression			
S-Caine adequate	90%	66%	85%
Placebo adequate	7% p<0.001 Chi-square	13% p<0.001 Chi-square	14% p<0.001 Sign Test
No Pain with S-Caine	69%		55%
No Pain with Placebo	33% p<0.001 Chi-square		10% p=0.006 Sign Test

[a] McNemar Chi-Square test
[b] Wilcoxin Signed Rank test
Source: Tables and text, volumes 27, 28 and 29

8.3.10 Pediatric Trials (Developmental Patches) (SC-09-99, SC-10-00, SC-04-99)

8.3.10.1 Pediatric Trials, Developmental Patches, Venipuncture

Studies SC-09-99 and SC-10-00 were randomized, double-blind, placebo-controlled studies evaluating the efficacy of the S-Caine patch for induction of local anesthesia prior to a vascular access procedure in pediatric subjects. SC-09-99 evaluated 30-minute applications of S-Caine Developmental Form A, and SC-10-00 evaluated 20-minute applications of Developmental Form B. Each study enrolled sixty subjects, as planned (SC-09-99 enrolled subjects ages 7 to 18, SC-10-00 enrolled subjects ages 7 to 17). Aside from enrolling subjects 7 years of age and up, and using the Numeric Oucher Scale only, study entry criteria, procedures and efficacy measures were the same as those employed in pivotal trial SC-20-01. Efficacy results are summarized in Table 8.45.

8.3.10.2 Pediatric Trial, Developmental Patches, Shave Biopsy

Study SC-04-99 was a randomized, double-blind, placebo-controlled study in 60 pediatric (ages 4–16) patients, evaluating the efficacy of a 60-minute application of Developmental Patch A, in reducing the pain associated with minor dermatological procedures. (Eligible patients included those, undergoing shave or punch biopsy, superficial excision, or removal of a seborrorrheic or keratotic lesion, or of a nevus or skin tag. Over 90% of all enrolled patients, however, had shave biopsies.) Study design and inclusion/exclusion criteria were otherwise similar to those in pivotal trial SC-21-01.

The protocol called for a "pin prick" assessment of anesthesia following patch treatment but prior to the dermatological procedure, and specified how this was to be done. If the patient indicated "no feeling" then the investigator was to proceed with the dermatological procedure, after which patients were to rate their pain. Subjects ages 4 through 6 were to use the photographic version of the Oucher Scale, while subjects ages 8 through 16 would use the numerical version. If the patient reported that they still had sensation (upon pin prick) at the procedure site, then a lidocaine injection would be given, the procedure would be performed, and efficacy evaluations would not be performed. Other efficacy assessments to be obtained, were as in SC-21-01.

The sponsor reports that, in violation of the protocol, investigators at both study sites had all patients complete Oucher Scales after the procedure. Some, but not all subjects rated the pain caused by the lidocaine injection, while other subjects rated the pain caused by the procedure (which was sometimes done after lidocaine injection). Also the planned age stratification (for Oucher Scale choice) was not conducted consistently. There were 46 subjects ages 8 through 16, and 14 subjects ages 4 through 7. Four of the fourteen patients in the younger group used the numerical version of the Oucher, and 3 of the 46 patients in the older group used the photographic Oucher. Most of the efficacy data obtained were thought to be meaningless by the sponsor.

"Adequate anesthesia" was assessed by pinprick following patch treatment. In the S-Caine group 87% had "adequate anesthesia" compared with 20% of patients in the placebo group ($p<0.001$, Mantel Haenszel summary chi-square). Given the problems

with protocol violations, this result, as well as results other efficacy analyses presented in the study report, are of little informative value.

Table 8.36. Efficacy in Pediatric Developmental Patch Trials

	Vascular Access		Derm. Procs.
Study	SC-09-99	SC-10-00	SC-04-99
Ages (years)	7 to 18	7 to 17	7 to 18
Formulation	Dev A	Dev B	Dev A
Subjects (S-Caine/Placebo)	30 / 30	29 / 29	30 / 30
Application Duration	30 minutes	20 minutes	30 minutes
Oucher Scale	Numeric	Numeric	Numeric
Primary Efficacy			
Median Oucher			
S-Caine	0	0	ND
Placebo	35	20	ND
P-value [a]	<0.001	<0.001	ND
Secondary Efficacy			
Investigator Evaluation			
Pain Rating	<0.001	<0.001	<0.001
"Adequate Anesthesia"	<0.001	<0.001	<0.001
Observer Evaluation			
Pain Rating	0.019	<0.001	ND
"Adequate Anesthesia"	0.008	<0.001	ND
Parent Evaluation	0.050	ND	<0.001

[a] Mann-Whitney test [d] Mantel-Haenszel summary chi-square
Source: Tables and text, volumes 27, 29, and 30

Table 8.37. SC-09-99 and SC-10-00 Efficacy Measures

Study	SC-09-99		SC-10-00	
Painful stimulus	Venipuncture 23 Gauge		Venipuncture 23 Gauge	
Ages	7 - 17		7 - 17	
Formulation	Developmental A		Developmental B	
Treatment	S-Caine (n=30)	Placebo (n = 30)	S-Caine (n = 29)	Placebo (n = 29)
Primary Efficacy				
Oucher Mean	12.0	42.7	4.5	23.4
Oucher Median (Range)	0.0 (0 – 100)	35.0 (0 – 100)	0.0(0 – 20)	20.0 (0 – 80)
Oucher SD	23.7	35.5	6.3	20.9
	$p < 0.001$ [a]		$p < 0.001$ [a]	
Secondary Efficacy				
Investigator Rating				
Adequate Anesthesia (Yes) [a]	90%	30%	90%	27%
P-value [b]	p<0.001		p<0.001	
"No Pain"	73.3%	30.0%	83.3%	20.0%
P-value [b]	p<0.001		p<0.001	
Slight Pain	20.0%	36.7%	16.7%	66.7%
Moderate Pain	6.7%	33.3%	0%	13.3%
Severe Pain	0%	0%	0%	0%
Observer Rating				
Adequate Anesthesia (Yes)	80%	43.3%	93%	37%
P-value [b]	p = 0.008		p < 0.001	

[a] Mann-Whitney U [b] Mantel-Haenszel summary chi-square

Source: Sponsor text (Volume 29, pp 245-248) (Volume 30, pp 28-30)

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8.3.11 Efficacy Trials Fulfilling Requirements for Evaluation of Combination Products (21 CFR 300.50 *Fixed-combination prescription drugs for humans*)

8.3.11.1 Study SC-41-03

Study SC-41-03 used a factorial design to compare 30-minute applications of the S-Caine Patch, a lidocaine patch, a tetracaine patch and a placebo patch, (all with the CHADD heating element) for anesthesia prior to venipuncture in healthy adult. This study appears to have adequately demonstrated that a 30-minute application of the S-Caine Patch is more effective than 30-minute patch applications of either lidocaine, tetracaine or placebo. Study SC-41-03 is discussed in detail in Section 8.3.9 above.

8.3.11.2 Heating Element Contribution (SC-27-01)

SC-27-01 was a randomized, double-blind, crossover study in 53 adult volunteers (skin types II and III only) designed to compare the effectiveness of S-Caine Patches containing active heating elements (CHADD) to (otherwise identical) patches with deactivated heating elements. Heating elements were deactivated by exposure to room air prior to use (for "sufficient time for reaction in the heat-generating medium to expire."). Subjects received simultaneous 20-minute applications of the two patches, to the right and left volar forearms (randomized 1:1). Following patch removal and safety evaluation, standardized laser stimuli (via Versapulse® laser) were administered to both patch sites (right arm then left). The settings used for the laser stimuli are summarized in Table 8.38 (Sponsor Table 9.1, NDA Volume 36).

Table 8.38. Settings Used for Laser Stimuli

Laser Type	Spot Size (mm)	Energy (J/cm^2)	Wavelength (nm)	Pulse Width (milliseconds)	# of Pulses
Versapulse®	2	15	532	2	5

Source: Table 9.1, Volume 36

Upon completion of laser stimulation (both sites), efficacy evaluations were performed, first for the right arm and then for the left. Efficacy measures were the same as those done in most other S-Caine adult clinical trials and included subject ratings of pain (100-mm VAS, "adequate anesthesia" and "would use again"), investigator and independent observer ratings of subject pain, and investigator ratings of the "adequacy of the anesthetic."

Sample size was based on an expected difference between the two patches on the primary efficacy measure (VAS score) of 8.5-mm (most of the placebo comparison trials planned for a 15-mm difference in VAS). A sample size of 45 would have been sufficient to detect this difference, assuming a paired standard deviation of 20 points with 80% power and a two-sided significance level of 5%. Fifty subjects were planned "for practical and logistical reasons."

Efficacy analyses failed to demonstrate any difference between the two patches. Table 8.39 summarizes findings for the subject-rated measures, including the primary efficacy

variable. The findings were similar for all of the remaining secondary outcome measures.

Table 8.39. SC-27-01 (± Heating Element) Subject Pain Evaluations

Variable	S-Caine With Heat (n=53)	S-Caine Without Heat (n=53)	P-Value
VAS Score			
Mean ± SD	9.2 ± 14.1	10.4 ± 14.7	0.334[a]
Median	3	4	
Range	0 - 80	0 - 67	
No. (%) with "Adequate Relief"	50 (94%)	50 (94%)	1.000[b]
No. (%) would "Use Again"	50 (94%)	51 (96%)	0.317[b]

[a] Repeated measures ANOVA [b] McNemar chi-square
Source: Sponsor Tables 11.4 and 11.5 , Volume 36

If the S-Caine Patch heating element does increase or accelerate drug release, as suggested by the in vitro release data, then these results are somewhat counterintuitive. The sponsor attributes them to study design issues. Specifically, the laser stimulus "did not produce pain levels sufficient to discriminate between the two patches." Both treatments resulted in very low VAS scores, and other pain ratings that were mostly "No Pain." The sponsor explains the rationale for choice of laser settings:

> "..to reduce the safety risk of burns, scarring, hypopigmentation and excessive pain, a smaller spot size of 2-mm and a less intense pulse of 15 J/cm^2 was chosen.."

While this explanation is plausible it does not change the fact that the S-Caine Patch heating element has not (yet) been demonstrated to have any effect on the product's efficacy. (Unfortunately, all other S-Caine Patch clinical trials evaluated patches with functioning heating elements.) (There is one other possible confounding factor; it seems that the S-Caine Patch heating element does not actually warm, perceptibly, until twenty or more minutes after exposure to air/oxygen.)

8.3.11.3 Study SC-28-01

Study SC-28-01 was a randomized, double-blind study in 48 adult volunteers that was designed to compare the effectiveness of (a single administration of) an S-Caine Patch to a lidocaine patch, a tetracaine patch, and a placebo patch (all 30-minute applications and all with the CHADD heating element). Forty-eight healthy adult volunteers were enrolled at two study sites. Study inclusion and exclusion criteria were similar to those used in most of the other healthy volunteer studies of the S-Caine Patch (i.e. no recent analgesic use, no drug allergies).

The only efficacy measure employed was the subjects' tolerance to a painful electrical stimulus (administered at 2,000-Hz, 250-Hz and 5-Hz frequencies by "Pain Tolerance Threshold Testing"). The maximum tolerated threshold (mA) by frequency, was compared between treatments. The three primary comparisons of S-Caine to the other three patches were pre-specified in the statistical plan. There were no differences between treatment groups.

8.4 Discussion of Efficacy: Adult "Vascular Access Procedures"

Four studies of similar design (randomized, double-blind, placebo-controlled) evaluated the S-Caine Patch for use prior to "vascular access procedures" in adults. The first, SC-05-99 evaluated 30-minute applications of Developmental Patch A. Subsequent studies evaluated 20-minute applications of the final S-Caine Patch formulation. SC-11-01 and SC-24-01 studied adults of all ages, while SC-31-01 studied subjects ages 65 and up. The vascular access procedures performed were, in actuality, venipuncture with standard gauge 20 and 21 needles, except in SC-05-99 in which subjects underwent intravenous cannulation with 22 gauge angiocatheters. Table 8.40, modified from Table 4.1 in NDA Volume 26, summarizes efficacy results for the subject self-rated outcome measures.

Table 8.40. Efficacy, Adult "Vascular Access Procedures"

Study	SC-24-01	SC-31-01	SC-11-01	SC-05-99
Population	Adult (N=40)	Geriatric (N=40)	Adult (N=21)	Adult (N=21)
Formulation	Final	Final	Final	Dev A
Subjects (S-Caine/Placebo)	40 / 39	40 / 40	21 / 21	20 / 21
"Procedure"	Venipun 20G	Venipun 20G	Venipun 21G	IV 22G
Application Duration	20 minutes	20 minutes	20 minutes	30 minutes
Median Patient VAS				
S-Caine	5	8	1	2
Placebo	28	13.5	9	30
P-value [a]	<0.001	0.039	0.004	<0.001
% With "Pain Eliminated"				
S-Caine	73%	85%	81%	90%
Placebo	31%	75%	24%	24%
P-value [b]	<0.002	0.206 [c]	0.003	<0.001 [b]
% Would "Use Again"				
S-Caine	70%	85%	76%	95%
Placebo	33%	75%	14%	14%
P-value [c]	0.006	0.206 [c]	0.001	<0.001 [b]

[a] Wilcoxin signed rank test
[b] Sign test
[c] McNemar chi-square test

8.5 Discussion of Efficacy: Adult Minor Dermatological Procedures

Four studies of similar design (randomized, double-blind, placebo-controlled) evaluated the S-Caine Patch for use prior to "minor dermatological procedures" in adults. The first, SC-03-99 evaluated 60-minute applications of Developmental Patch A. Subsequent studies evaluated 30-minute patch applications. SC-07-99 also evaluated Developmental Patch A. SC-22-01 and SC-23-01 evaluated the final formulation of the S-Caine Patch in geriatric subjects, and in "all adults" respectively. Table 8.41, modified from Table 4.2 (NDA Volume 26) summarizes efficacy results for the subject self-rated outcome measures.

Table 8.41. Efficacy Adult, "Minor Dermatological Procedures"

Study	SC-23-01	SC-22-01	SC-07-99	SC-03-99
Population	Adult (N=94)	Geriatric (N=74)	Adult (N=60)	Adult (N=59)
Formulation	Final	Final	Dev A	Dev A
Subjects (S-Caine/Placebo)	45 / 49	50 / 24	29 / 31	29 / 30
Application Duration	30 minutes	30 minutes	30 minutes	60 minutes
Median Patient VAS				
S-Caine	5	9.5	5	2
Placebo	31	22.5	19	33
P-value [a]	<0.001	0.041 [b]	0.003	<0.001
% Reporting Pain Relief [c]				
S-Caine	73%	56%	55%	86%
Placebo	37%	63%	13%	17%
P-value [d]	<0.001	0.767 [b]	0.002	<0.001
% Would "Use Again"				
S-Caine	76%	56%	69%	90%
Placebo	53%	63%	26%	43%
P-value [d]	0.023	0.726 [b]	0.002	<0.001

[a] Mann-Whitney test

[b] Per-protocol efficacy population #1 (Section 8.3.7)

[c] 03-99 and 07-99 asked "Did the anesthetic eliminate pain?"
23-01 and 22-01 asked "Did the anesthetic provide adequate pain relief?"

[d] Mantel-Haenszel summary chi-square

8.5.1 Efficacy for Adult Dermatological Procedures

Table 8.42. Adult Dermatological Procedures, Primary Efficacy (100-mm VAS)

Study	SC-23-01 Adult (N=94)					SC-22-01 Geriatric (N=74*)				
	S-Caine		Placebo			S-Caine		Placebo		
	n	Median	n	Median	P-value[a]	n	Median	n	Median	P-value[a]
Procedure Type										
All	45	5.0	49	31.0	**<0.001**	50	9.5	24	22.5	**0.041**
Shave Biopsy	4	3.5	7	58.0	0.089	18	13.0	9	21.0	0.877
Excision	18	6.0	22	33.0	0.017	32	7.0	15	25.0	0.020
Curettage	5	1.0	5	12.0	0.341					
Electrodessication	11	3.0	8	32.5	0.028					
Other	7	5.0	7	39.0	0.040					
Anatomic Location										
Head/Neck	9	6.0	15	34.0	0.022	11	2.0	6	20.0	0.043
Back	10	9.0	6	55.5	0.587	9	10.0	2	25.0	0.346
Chest/Abdomen	10	1.0	6	26.0	0.003	6	2.0	6	16.5	0.106
Arm/Shoulder	11	3.0	20	26.5	0.004	16	14.0	2	41.5	0.092
Hip/Leg	5	5.0	2	25.5	---	7	13.0	8	31.5	0.862
Other						1	8.0	0	---	---

[a]Mann-Whitney U test Source: Reviewer post-hoc analysis.

Table 8.43. Patient VAS Score by Procedure Type (N=168)
Pooled Studies SC 22-01 (Only Shave Biopsy and Excision) and SC-23-01

	S-Caine		Placebo		
	N	Mean	N	Mean	P-value*
Shave Biopsy	22	17.1	16	22.8	0.12
Excision	50	35.6	37	55.3	<0.001
Curettage	5		5		
Electrodessication	11		8		
Other	7		7		
Skin tag	3		4		
Keloid injection	2		2		
Cryotherapy	2		1		

*Wilcoxin/Kruskal-Wallis (Rank Sums) Source: Reviewer post-hoc analysis

Table 8.44. Patient VAS Score by (Approximate) Procedure Depth (N=170[a])
Pooled Studies SC 22-01 (All Subjects) and SC-23-01 (All Subjects)

	S-Caine		Placebo		
	N	Mean	N	Mean	P-value[b]
0.5 mm	11	6.72	7	13.86	0.006
1.0 mm	36	28.22	30	39.83	0.015
2.0 mm	46	32.87	30	47.13	0.006
3.0 mm	4	4.86	6	5.92	0.669

[a] Procedure depth not estimable for all patients [b]Wilcoxin rank-sums Source: post-hoc analysis

8.6 Efficacy for Pediatric "Vascular Access Procedures"

Three studies of similar design (randomized, double-blind, placebo-controlled) evaluated the S-Caine Patch for use prior to "vascular access procedures" in children. The primary efficacy variable in each study was the Oucher Scale score. SC-09-99 (30-minute patch application) and SC-10-00 enrolled subjects seven years of age and up, and used only the Numeric Oucher Scale.

Table 8.45 summarizes the primary, and investigator-rated secondary efficacy results for these three studies.

Table 8.45. Efficacy in Pediatric "Vascular Access Procedure" Trials

Study	SC-20-01	SC-20-01	SC-20-01	SC-10-00	SC-09-99
Ages (years)	3 to 6	7 to 17	3 to 17	7 to 17	7 to 18
Formulation	Final	Final	Final	Dev B	Dev A
Subjects (S-Caine/Placebo)	25 / 11	16 / 9	41 / 20	29 / 29	30 / 30
Application Duration	20 min	20 min	20 min	20 min	30 min
Oucher Scale	Photo	Numeric	All	Numeric	Numeric
Primary Efficacy					
Median Oucher					
S-Caine	0	7.5	NA	0	0
Placebo	80	50	NA	20	35
P-value [a]	<0.001	0.159 [b]		<0.001	<0.001
Secondary Efficacy					
Investigator Evaluations					
"No Pain"					
S-Caine			76%	83%	73%
Placebo			20%	20%	30%
P-value			<0.001	<0.001	<0.001
"Adequate Anesthesia"					
S-Caine			80%	90%	90%
Placebo			70%	27%	30%
P-value [b]			0.556	<0.001	<0.001

[a] Mann-Whitney test
[b] Mantel-Haenszel summary chi-square

Table 8.46. Efficacy in Pediatric Developmental Patch Trials

	Vascular Access		Derm. Procs.
Study	SC-09-99	SC-10-00	SC-04-99
Ages (years)	7 to 18	7 to 17	7 to 18
Formulation	Dev A	Dev B	Dev A
Subjects (S-Caine/Placebo)	30 / 30	29 / 29	30 / 30
Application Duration	30 minutes	20 minutes	30 minutes
Oucher Scale	Numeric	Numeric	Numeric
Primary Efficacy			
Median Oucher			
S-Caine	0	0	ND
Placebo	35	20	ND
P-value [a]	<0.001	<0.001	ND
Secondary Efficacy			
Investigator Evaluation			
Pain Rating	<0.001	<0.001	<0.001
"Adequate Anesthesia"	<0.001	<0.001	<0.001
Observer Evaluation			
Pain Rating	0.019	<0.001	ND
"Adequate Anesthesia"	0.008	<0.001	ND
Parent Evaluation	0.050	ND	<0.001

[a] Mann-Whitney test
[d] Mantel-Haenszel summary chi-square

Table 8.47. Pivotal Pediatric Trial SC-20-01 Vascular Access (N=61)

Ages (years)	3 to 6	7 to 17	3 to 17
Formulation	Final	Final	Final
Subjects (S-Caine/Placebo)	25 / 11	16 / 9	41 / 20
Application Duration	20 minutes	20 minutes	20 minutes
Oucher Scale	Photo	Numeric	All
Median Oucher (Primary)			
S-Caine	0	7.5	NA
Placebo	80	50	NA
P-value [a]	<0.001	0.159 [b]	
Secondary Efficacy (P-values)			
Investigator Evaluation			
Pain Rating			<0.001
"Adequate Anesthesia"			0.556
Observer			
Pain Rating			<0.001
"Adequate Anesthesia"			???

[a] Mann-Whitney test
Source: Table 12.4, Volume 31

Table 8.48. Pivotal Pediatric Trial SC-21-01 Lidocaine Injection (N=88)

Ages (years)	3 to 6	7 to 17	3 to 17
Formulation	Final	Final	Final
Subjects (S-Caine/Placebo)	21 / 22	20 / 25	41 / 47
Application Duration	30 minutes	30 minutes	30 minutes
Oucher Scale	Photo	Numeric	All
Median Oucher (Primary)			
S-Caine	0	10	NA
Placebo	70	10	NA
P-value [a]	<0.005	0.322 [b]	
Secondary Efficacy (P-values)			
Investigator Evaluation			
Pain Rating			0.401
"Adequate Anesthesia"			0.028
Observer			
Pain Rating			0.269
"Adequate Anesthesia"			

[a] Mann-Whitney test
Source: Table 12.3, Volume 32

9 INTEGRATED REVIEW OF SAFETY

9.1 Brief Statement of Findings

- A total of 1080 adult and pediatric subjects were exposed to the S-Caine Patch (including developmental formulations), 912 of these received the final S-Caine Patch formulation. Most of these subjects received single 20 or 30-minute patch exposures, in controlled trials. Two-hundred and twenty subjects were evaluated in the six-week, ten-dose dermal irritation and sensitization study. Ninety-one subjects were treated in (dedicated) pharmacokinetic studies.
- One-hundred and sixty-eight subjects received developmental S-Caine Patch formulations, 79 adult and 89 pediatric.
- There were no subject deaths during the S-Caine Patch clinical development program.
- There was one SAE (a subject suffered a gunshot wound during her participation in the six-week cumulative irritation study).
- There were a total of 98 AEs, fifteen of which occurred during study SC-42-03 (10-exposure cumulative irritation study).
- Aside from the single SAE, all AEs were self-limited and brief (lasting minutes), and resolved without treatment.
- "Slight" or mild erythema at the patch application site was common, occurring with approximately 60% of applications. Erythema resolved without treatment in all cases (usually within 20 to 30 minutes after patch removal).
- There might be a (non statistically significant) trend towards a higher incidence of "very slight" erythema from the (heated) S-Caine Patch compared to the S-Caine Patch with an inactivated heating element.
- Repeat patch applications at the same site, and multiple simultaneous patch applications are anticipated in clinical practice, though not addressed in the Dosage and Administration section of the proposed label. In order to characterize the possible results of such "excessive" patch use (i.e., systemic absorption resulting in toxic serum concentrations and/or increased incidence of local toxicity), these scenarios were addressed in studies SC-25-01, SC-26-01, SC-30-01 and SC-42-03.
- Use of the S-Caine Patch in accordance with the proposed product labeling (single applications of 20 to 30 minutes over intact skin) is not expected to result in detectable systemic lidocaine or tetracaine levels. Findings pertaining to systemic exposure to lidocaine and tetracaine in the settings of multiple and repeat patch applications are discussed in greater detail in Section 5 (Human Pharmacokinetics and Pharmacodynamics) above.
- The study report for SC-42-03, the cumulative irritation and sensitization evaluation, is incomplete. It is not possible to ascertain the reasons behind the 10% (of 220 subjects) drop-out rate. The patch appeared to be "mildly irritating" but not sensitizing, in some subjects, prior to their drop-out. Similar, and sometimes greater (irritation) effects were not uncommon in subjects that completed the six-week study, though.

9.2 Adequacy of Exposure and Safety Assessment

Twenty-three clinical studies were conducted under IND 58,823. All pediatric trials enrolled patients who were scheduled to undergo "medically-indicated" procedures (i.e. venipuncture, immunization). Some of the studies conducted in adults also enrolled patients scheduled to undergo procedures, but others recruited healthy volunteers who underwent venipuncture, or who were exposed to painful stimuli solely for the purpose of evaluating the S-Caine Patch.

The majority of subjects received a single S-Caine Patch exposure of 10, 20, 30 or 60 minutes duration. Twelve of these studies (11-01, 20-01, 21-01, 22-01, 23-01, 24-01, 27-01, 28-01, 29-01, 31-01, 40-02, 41-03) administered single doses of the final S-Caine Patch formulation. Six studies (03-99, 04-99, 05-99, 07-99, 09-99, 10-00) administered single doses of developmental S-Caine Patch formulations. In total, 818 subjects were exposed to a single administration of one S-Caine Patch; Developmental A, Developmental B or Final S-Caine Patch formulation.

Some studies utilized a paired design, by which subjects received simultaneous treatment with an S-Caine Patch and with a comparator (placebo, EMLA, lidocaine or tetracaine). Subjects that received more than one type of treatment are tabulated under each treatment group in the Extent of Exposure tables below.

Three studies (25-01, 26-01, 30-01) called for administration of multiple patches during a single study session, in order to assess PK and safety parameters. One study, SC-42-03 (dermal irritation and sensitization assessment) exposed each subject to 10 separate 120-minute patch applications over a six-week period. Study SC-01-95 was a preliminary proof of concept study (conducted prior to opening of the IND) and exposed 12 subjects to single 30-minute patch applications. The precise patch formulation employed is not given in the NDA.

Tables 9.1, 9.2 and 9.3 summarize all trials, all single-dose trials, and all multiple-dose trials, respectively, included in the integrated safety summary. Table 9.4 lists separately the studies evaluated for safety findings, that utilized developmental patch formulations.

Table 9.1. Trials Included in Integrated Summary of Safety

Trial	Purpose	Enrolled	Popul.	S-Caine	Placebo
				Completed / Planned	
Efficacy Trials					
03-99*	Shave biopsy	59	Adult	29/29	30/30
04-99*	Shave biopsy	60	Peds	30/30	30/30
05-99*	IV insert + PK	22	Adult	20/22	21/22
07-99*	Shave biopsy	60	Adult	29/29	31/31
09-99*	Venipuncture	60	Peds	30/30	30/30
10-00*	Venipuncture	60	Peds	30/30	30/30
11-01	Venipuncture	21	Adult	21/21	21/21
20-01	Venipuncture (+ IV)	65	Peds	41/43	21/22
21-01	Lidocaine inject	88	Peds	41/41	47/47
22-01	Dermatologic Procs.	79	Geriatric	54/54	25/25
23-01	Dermatologic Procs.	94	Adult	45/45	49/49
24-01	Venipuncture	60	Adult	60/60	59/60
27-01	Combo ± heat	53	Adult	With heat 53/53	No heat 53/53
28-01	Combo rule	48	Adult	48/48	48/48
29-01	Immunization	67	Infant	34/34	33/33
31-01	Venipuncture + PK	40	Geriatric	40/40 10 PK	40/40
40-02	Venipuncture	82	Adult	81/82	EMLA 81/82
41-03	Combo Rule/Venip.	80	Adult	80/80	80/80
Safety and PK Trials					
25-01	Repeat applications	26	Adult	24/26	0
26-01	Simultaneous	24	Adult	23/24	0
30-01	Simultaneous	42	Peds	42/42	0
33-02	Single	0	Neonate	0/12	Ongoing
42-03	10 exposures over 6 weeks	220	Adult	198/220	198/220
Totals w/o 42-03	Enrollment	**1150**		**881/887**	**649/653**
Totals	Enrollment	**1370**		**1085/1107**	**847/873**

* Studies SC-03-99 through SC-10-00 used developmental patch formulations;
Totals = 321 enrolled, 170 (planned) S-Caine, 173 (planned) placebo
Source: Prepared by clinical reviewer

Table 9.2 Single Patch Studies Reviewed for Safety Findings, Final Patch Formulation

Study	Efficacy Measure	Population	Treatment	Duration	Numb	AEs
24-01 P	Venipuncture	60 Adult	S-Caine	30 m	20	
			S-Caine	20 m	40	
			Placebo	30 m	20	
			Placebo	20 m	39	
23-01 P	Derm Procedures	94 Adult	S-Caine	30 m	45	1
			Placebo	30 m	49	0
20-01 P	Venipuncture	61 Child	S-Caine	20 m	43*	0
			Placebo	20 m	22*	0
21-01 P	Lidocaine Injection	88 Child	S-Caine	30 m	41	2
			Placebo	30 m	47	0
31-01	Venipuncture AND	40 Geriatric	S-Caine	20 m	40	0
	PK Measures		Placebo	20 m	40	0
11-01	Venipuncture	21 Adult	S-Caine	20 m	21	0
			Placebo	20 m	21	0
22-01	Derm Procedures	74 Geriatric	S-Caine	30 m	54	0
		79 Enrolled	Placebo	30 m	25	0
40-02	Venipuncture (vs. EMLA) . 10, 20, 30, 60 min	82 Adult	S-Caine	10, 20 30, 60 m	20 each	
			EMLA	10, 20 30, 60 m	20 each	
41-03	Venipuncture Combination Rule	80 Adult	S-Caine	30 m	80	5
			Lidocaine	30 m	80	3
			Tetracaine	30 m	80	1
			Placebo	30 m	80	1
28-01	Pain Threshold Test	48 Adult	S-Caine	30 m	48	8
	Combination Rule		Lidocaine	30 m	48	2
			Tetracaine	30 m	48	4
			Placebo	30 m	48	3
27-01	Combination Rule: Heating Element	53 Adult	SC heat	20 m	53	1
			SC no heat	20 m	53	1
29-01	Immunization	67 Infant	2 S-Caine	30 m	34	0
			2 Placebo	30 m	33	1

* SC-20-01 43 subjects randomized to S-Caine (and treated), but 2 withdrew prior to venipuncture

* SC-20-01 22 Ss randomized to placebo, 2 withdrew, 1 prior to patch and 1 after patch before venipuncture

Source: Prepared by clinical reviewer

Table 9.3 Multiple-Dose Studies Reviewed for Safety Findings (Final Patch)

Study	Assessments/Design	Population	Treatment	Duration	n	Subjects
25-01	PK and local effects					**With AEs**
	2 simultaneous vs. 4 simult.	25 Adult				
	(Crossover)					
	Group 1, n=12, 30 min	(n=13, 30 m)	SC X 2	30 m	12	0
			SC X 4	30 m	13	0
	Group 2, n=12, 60 min	(n=12, 60 m)	SC X 2	60 m	12	0
			SC X 4	60 m	12	1 (6%)**
26-01	PK and local effects					
	1 patch vs. 2 sequential	24 Adult				
	(Crossover)					
	Group 1, n=12, 30 min	(n=12, 30 m)	SC X 1	30 m	12	4 (33%)
			SC X 2	30 m	11	5 (45%)
	Group 2, n=12, 60 min	(n=12, 60 m)	SC X 1	60 m	12	2 (17%)
			SC X 2	60 m	12	5 (42%)
30-01	PK and local effects					
	1 patch vs. 2 simultaneous	42 Pediatric			42	
		(4 m – 12 yr)				
			SC X 1	30 m	21	3 (4 AEs)
			SC X 2	30 m	21	2 (3 AEs)
42-03	Irritation/sensitivity/No PK					
	10 exposures over 6 wks	220 Adult		120 m	220	15
	120 minutes each	198 Complete				
29-01	Efficacy/ Immunization	67 Infants		30 m		
	No PK	4 M – 6 M	SC X 2	30 m	34	0
	Placebo-controlled		Placeb X 2	30 m	33	0

** One subject (#25105, 44 year-old female), experienced moderate erythema at each of the four patch sites. Her erythema (all sites) resolved within 30 minutes, without intervention

Table 9.4. Studies Reviewed for Safety Findings, Developmental Patches (Single Dose)

Study	Efficacy Measure	Population	Treatment	Duration	N	Subjects With AEs
DEV A						
05-99	IV Insertion AND	21 Adult	S-Caine	30 m	20	0
	PK Measures		Placebo	30 m	21	0
			Preceding			1
03-99	Shave Biopsy	59 Adult	S-Caine	60 m	29	0
			Placebo	60 m	30	1
07-99	Shave Biopsy	60 Adult	S-Caine	30 m	29	2
			Placebo	30 m	31	0
09-99	Venipuncture	60 Child	S-Caine	30 m	30	1
			Placebo	30 m	30	0
04-99	Shave Biopsy	60 Child	S-Caine	60 m	30	2
			Placebo	60 m	30	0
DEV B						
10-00	Venipuncture	60 Child	S-Caine	20 m	30	0

Source: Prepared by clinical reviewer

Table 9.5 Extent of Exposure: Number of Subjects with a Single Patch Exposure

	Dev A	Dev B	Final	Final No heat	Placebo	EMLA	Lido	Tetra
Controlled								
10 Minute	0	0	20	0	0	20	0	0
20 Minute	0	30	217	53	151	20	0	0
30 Minute	79	0	310	0	351	22	128	128
60 Minute	59	0	20	0	60	20	0	0
Total Controlled	138	30	567	53	562	82	128	128
PK Studies								
30 Minute	0	0	18	0	0	0	0	0
60 Minute	0	0	12	0	0	0	0	0
Total PK	0	0	30	0	0	0	0	0
Total Single Dose	138	30	597	53	562	82	128	129

Source: 120-Day Safety Update, Volume 1

Table 9.6. Extent of Exposure: Number of Subjects with Multiple Patch Exposures (Including SC-42-03, Cumulative Skin Sensitization/Irritation Study)

	2 Simul [a]	4 Simul [b]	3 Repeat [c]	4 Repeat [c]	2 Placebo	10 Repeat [d]	10 Placebo [d]
20 Minute	0	0	0	0	0	0	0
30 Minute	67	13	0	11	33	0	0
60 Minute	12	12	12	0	0	0	0
120 Minute	0	0	0	0	0	220 enrolled 198 complete	220 enrolled 198 complete
Total	79	25	12	11	33	198	198

[a] 2 simultaneous SC-25-01, SC-29-01, SC-30-01
[b] 4 simultaneous SC-25-01
[c] 3 repeat OR 4 repeat SC-26-01
[d] SC-42-03 10 applications over 6 weeks

Overall, the extent of exposure in the S-Caine Patch clinical studies appears adequate for safety review, for both the pediatric and adult (including geriatric) populations. Ongoing trial SC-33-02 is expected to provide data for safety review of S-Caine Patch use in newborns (including premature infants).

9.3 Cumulative Dermal Irritation and Sensitization Evaluation (SC-42-03)

Study SC-42-03 was conducted in accordance with OGD guidelines, in order "to determine the cumulative irritation and contact sensitization potential of an S-Cane Patch in healthy adult subjects." The sponsor was permitted to submit study results at the 120-Day Safety Update because of a prior agreement with DACCADP.

SC-42-03 enrolled 220 essentially healthy subjects, ages 18 to 70 for a six-week assessment of S-Caine Patch cumulative irritation and sensitivity potential. A study schematic appears below (Table 9.7).

Table 9.7. SC-42-03 Treatment and Assessment Schedule

Study Week	Patch Administration	Skin Assessment
Week 1	Monday, Wednesday, Friday	Monday, Wednesday, Friday
Week 2	Monday, Wednesday, Friday	Monday, Wednesday, Friday
Week 3	Monday, Wednesday, Friday	Monday, Wednesday, Friday
Week 4	Monday ("make-up" session only)	Monday
Week 5	Rest Week (No treatment)	(No assessment)
Week 6	Monday	Monday, Wednesday, Thursday

Source: Text, 120-Day Safety Update (Volume 9, page 5)

During the first three study weeks each subject presented to the study site every Monday, Wednesday and Friday, for simultaneous 120-minute applications of S-Caine Patch and placebo patch. At each treatment visit, subjects were evaluated twice for each patch site using an eight-point "Skin Irritation Grading Scale," immediately before patch application, and then 5-minutes after the 120-minute application period. After each treatment period, patch adherence (0 to 4 scale) was also graded prior to removal. (Subjects were not required to stay on premises during these treatment periods, only to return after wearing the patches for 120-minutes.) Dermal irritation was graded using the following scale:

Skin Irritation Grading Scale

0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; minimal edema or minimal papular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema and papules
6 = vesicular eruption
7 = strong reaction spreading beyond test site

On Monday of Study Week 4 subjects returned for skin irritation grading (and one "make-up" treatment session, if necessary). Subjects were not seen during Week 5. During Week 6 subjects wore (their tenth) S-Caine Patch for 120-minutes on Monday, and underwent skin irritation on Monday, Wednesday and Thursday.

The SC-42-03 final study report consists of tables containing the individual irritation and adherence scores for each subject (line listings), and photocopies of fifteen adverse event reports, but no summary tables or tabulations, and no descriptive statistics. The report (and the NDA) does not include the study protocol, or enough detail to ascertain what would actually qualify as an adverse event in this study. It is not possible to ascertain the reasons for study drop-out (of 22 of the 220 enrolled subjects). Some drop-outs (i.e. 10, 13, 64, 79) appear to have had a number of treatment sessions in which they did react to the patches (preapplication dermal irritation = 0, post-treatment dermal irritation = 2), prior to dropping. Of the 22 drop-outs, the mean number of completed treatment visits prior to dropout was 3.4 (median 3). Seven enrolled subjects dropped after one treatment visit (and one dropped after zero treatment visits. Most noncompleters experienced a number of post-treatment (2-hour) skin irritation scores of two, from zero baselines. On cursory review, it appears that many (even most) of the study completers also scored 2s for some of their post-treatment skin irritation grades. Also, post-treatment skin irritation grades do not appear to increase, as the number of patch applications increases. The subjects who had pre-treatment skin irritation scores of 0, and post-treatment scores of 2, at visits 2 and 3, continued to experience post-treatment scores no greater than 2.

(Sections and statements addressing regulatory requirements for financial disclosure, ethical study conduct, etc. are also missing from the study report).

9.4 Review of Safety Data (ISS)

9.4.1 Methods for Review of Safety Data

The safety review consisted of review and analyses of the sponsor's ISS database, review of the data from the individual study reports, and comparison of the non-integrated with the integrated safety data. By prior agreement with the Division, individual CRTs were not submitted with the NDA, except in the event of SAE. During the course of this review, several questions arose regarding the sponsor's Integrated Summary of Safety, mostly pertaining to the electronic files submitted on September 15, 2003, but also concerning the "paper" NDA. Requests for clarifications, for corrections, and in some cases for additional analyses, were communicated via electronic mail and telephone. These issues are described in full in section YY, as well as in the appropriate review subsections.

9.5 Subject Demographics

The demographic characteristics for subjects who participated in S-Caine Patch clinical studies are summarized in Tables 9.8 and 9.9. Overall, the subjects were predominantly Caucasian, and (roughly) equally divided between males and females.

Table 9.8. Summary Demographics, All Subjects Included in the ISS Database (Total Subjects Enrolled in All Trials = 1407)

Demographic	S-Caine All Forms	Final	Final No Heat	Develop-mental	Placebo
Number	1084	863	53	168	815
Age					
3m – 2y	76	76 (4%)	0	0	33 (4%)
3 – 6 y	48	42 (5%)	0	6 (4%)	36 (4%)
7 - 17	125	42 (5%)	0	83 (49%)	120 (15%)
7-12 Y	58	18	0	40	
13-17 Y	67	24	0	43	
18-64 years	704	577 (70%)	53	74 (44%)	523 (64%)
65-74	93	88 (11%)	0	5 (3%)	79 (10%)
≥75 years	38	38 (5%)	0	0	24 (3%)
Gender					
Male	423	326 (40%)	14 (26%)	83 (49%)	319 (39%)
Female	619	495 (60%)	39 (74%)	85 (51%)	496 (61%)
Race					
Caucasian	672	536 (65%)	43 (81%)	93(55%)	475 (59%)
Black	208	198 (24%)	0	10 (6%)	203 (25%)
Hispanic	121	54 (7%)	10 (19%)	57 (34%)	105 (13%)
Other	41	33 (4%)	0	8 (5%)	28 (3%)

Source: Modified from sponsor Tables A4.1 and A4.2, 120-Day Safety Update, Volume 1

Table 9.9. Demographics of Subjects Enrolled in Controlled Trials (PK Trials Excluded)

	Dev A	Dev B	Final	Final No Heat	Placebo	EMLA	Lido	Tetra
Number	138	30	601	53	595	82	128	128
Age								
0–2 M	0	0	0	0	0	0	0	0
3 M–2Y	0	0	34 (6%)	0	33 (6%)	0	0	0
3-6	6 (4%)	0	42 (7%)	0	36 (6%)	0	0	0
7-17	53 (38%)	30 (100%)	42 (7%)	0	120 (20%)	0	0	0
18-64	74 (54%)	0	387 (64%)	53 (100%)	333 (56%)	80 (98%)	128 (100%)	128 (100%)
65-74	5 (4%)	0	58 (10%)	0	49 (8%)	2 (2%)	0	0
75+	0	0	38 (6%)	0	24 (4%)	0	0	2
Race								
Caucasian	73 (53%)	20 (67%)	446 (74%)	43 (81%)	389 (65%)	81 (99%)	90 (70%)	90 (70%)
Black	9 (7%)	1 (3%)	69 (11%)	0	74 (12%)	0	15 (12%)	15 (12%)
Hispanic	53 (38%)	4 (13%)	54 (9%)	10 (19%)	105 (18%)	0	3 (2%)	3 (2%)
Other	3 (2%)	5 (17%)	32 (5%)	0	27 (5%)	1 (1%)	20 (16%)	20 (16%)
Skin Type								
I	3 (3%)	3 (10%)	57 (9%)	1 (2%)	36 (6%)	13 (16%)	9 (7%)	9 (7%)
II	14 (13%)	6 (20%)	144 (24%)	19 (36%)	121 (21%)	12 (15%)	29 (23%)	29 (23%)
III	58 (54%)	11 (37%)	187 (31%)	33 (62%)	189 (33%)	24 (29%)	44 (34%)	44 (34%)
IV	26 (24%)	4 (13%)	126 (21%)	0	134 (24%)	23 (28%)	32 (25%)	32 (25%)
V	6 (6%)	3 (10%)	48 (8%)	0	51 (9%)	9 (11%)	5 (4%)	5 (4%)
VI	1 (1%)	3 (10%)	39 (6%)	0	34 (6%)	1 (1%)	9 (7%)	9 (7%)
No data	30	0	0	0	30	0	0	0
Gender								
Male	68 (49%)	15 (50%)	272 (45%)	14 (26%)	265 (45%)	37 (45%)	65 (51%)	65 (51%)
Female	70 (51%)	15 (50%)	329 (55%)	39 (74%)	330 (55%)	45 (55%)	63 (49%)	63 (49%)

Source: Table A4.1 (120-day safety update, volume 1, page 76)
Final Formulation: SC-20-01, SC-21-01, SC-22-01, SC-23-01, SC-24-01, SC-28-01, SC-29-01, SC-31-01, SC-40-02, SC-41-03
Final Formulation +/- Heating Element: SC-27-01
Developmental A: SC-03-99, SC-04-99, SC-05-99, SC-07-99, SC-09-99 Developmental B: SC-10-0

Table 9.10. Demographics of Subjects Enrolled In PK Trials
(Includes Subjects from SC-05-99 and SC-31-01)

Formulation	Final	Final	Dev A
Trials	25-01, 26-01, 30-01	31-01	05-99
Number	91 (91 total)	10 PK (40 total)	20 PK (22 total)
Age			
0–2 M	0	0	
3 M–2Y	9 (10%)	0	
3-6	16 (18%)	0	
7-17	17 (19%)	0	
18-64	49 (54%)	0	22 (100%)
65-74	0	8 (80%)	
75+	0	2 (20%)	
Race			
Caucasian	71 (78%)	10 (100%)	22 (100%)
Black	12 (13%)	0	0
Hispanic	7 (8%)	0	0
Other	1 (1%)	0	0
Skin Type			
I	9 (10%)	4 (40%)	0
II	14 (15%)	6 (60%)	2 (9%)
III	35 (38%)	0	12 (55%)
IV	23 (25%)	0	4 (18%)
V	1 (1%)	0	3 (14%)
VI	9 (10%)	0	1 (4%)
Gender			
Male	35 (38%)	5 (50%)	14 (64%)
Female	56 (62%)	5 (50%)	8 (36%)

Source: Sponsor Table A4.2 (120-Day Safety Update Volume 1), Table 11.1 (NDA Volume 28), Table 11.1 (NDA Volume 39)

Table 9.11. Ages of Subjects Enrolled In PK Trial SC-30-01*

Number	30-01 1 Patch Analyzed	30-01 2 Patches Analyzed	30-01 Total Treated
Age			
4 M–2Y	2	6	9
3 Y –6 Y	7	7	16
7 Y - 12 Y	9	6	17

* 5 subjects excluded from PK analysis (contaminated samples)
Source: Sponsor Table A4.2 (120-Day Safety Update Volume 1)

9.6 Subject Disposition

Most trials required only one study visit, during which subjects received single (or simultaneous) patch applications.

Table 9.12. Subject Disposition in S-Caine Patch Studies (Controlled and PK)

Disposition	All Studies Totals n	All Studies Before treatment n	All Studies S-Caine group n	All Studies Placebo group n	SC-42-03 n
Total Number of Subjects Enrolled	1407		887	653	220
Total Number of Subjects Who Received Study Treatment (Safety)	1370				220
Total Number of Subjects Who Completed Study Treatment	1339				198
Total Number of Subjects Who Prematurely Discontinued	9 (+ 22)[3]		←	←	22
Reason for Not Completing the Study:					
Withdrew Consent Prior to any Treatment	2	2			
Consent Withdrawn	3		3		0
"Procedure No Longer Required" (Venipuncture)	2		2[2]		
Technical Failure (patch did not stick well)					0
Unable to Obtain Blood for PK; DCd	1		1		
Vasovagal (apparent) Prior to Treatment	1	1			
Adverse Event Leading to Discontinuation	0 (?)		0	0	?
Lost to Follow-Up	0		0	0	22?

[1] All clinical trials except SC-42-03

[2] SC-20-01: 2 subjects (both S-Caine group) "no longer required treatment" and 1 subject (placebo group assignment) refused after further participation prior to patch treatment

[3] Study SC-42-03 cumulative patch sensitization/irritation study, reasons for discontinuation not available

In pediatric trial SC-20-01, there were 2 withdrawals attributed to the subject "no longer requiring" the planned procedure (i.e., venipuncture or intravenous cannulation). In both cases the child was withdrawn after administration of study medication (both S-Caine). Post patch application efficacy measures would not have been possible in the absence of the "painful procedure." Scheduled safety assessments would have been possible in these cases, but were not done (and/or not included in the NDA). One may hypothesize that the patch itself may have been sufficiently noxious, and upsetting to the child, to have actually contributed to the investigator's decision to forego the procedure. Clinicians

(and investigators and study nurses) may have lower thresholds for deciding to forego painful procedures, including venipuncture, in children, though. It seems plausible, and acceptable that a small percentage (< 3%) of the pediatric subjects recruited because they were scheduled for blood draws simply "no longer needed the procedure."

9.7 Deaths

There were no deaths reported during any of the clinical trials (including protocol designated post-treatment monitoring periods) for the S-Caine Patch.

9.8 Non-Fatal Serious Adverse Events

There was one serious adverse event during the clinical development program for the S-Caine Patch. In study SC-42-03 (six-week repeat dose cumulative irritation study) subject 42187 suffered a gunshot wound to the stomach [redacted] during Study Week Four. The study report states that the investigators attempted to obtain hospital records, in order to provide more information for the study report, but the subject did not consent to their release. The information available in the 120-Day Safety Update is scanty, but it seems very unlikely that this incident is attributable to study drug exposure.

9.9 Adverse Events Leading to Study Discontinuation

Most of the S-Caine Patch clinical trials were single dose studies requiring only one clinic visit. Some studies (placebo controlled crossover) involved two visits. Study SC-42-03 was a ten-exposure, six week study involving fourteen study site visits.

SC-42-03 aside, it appears that during the S-Caine Patch clinical development program, there was only one withdrawal readily attributable to a treatment emergent adverse event. In study SC-40-01 a 24 year old male (subject 40144) who had received concurrent 10 minute applications of S-Caine Patch and EMLA, felt nauseated and faint following the first venipuncture, 4 minutes after removal of the S-Caine Patch. His BP and HR were 145/71 and 68 bpm (150/75 and 80 bpm at baseline) while he was symptomatic. He withdrew (or was withdrawn) from the study, and the second venipuncture was not performed. His symptoms resolved without treatment within 15 minutes.

In study SC-05-99 one subject (Number 106) withdrew prior to treatment. This 32 year old male reportedly experienced a possible vasovagal event at the time of the baseline blood draw, prior to study patch application.

As discussed above (Section 9.5) there were two pediatric withdrawals, attributed to "procedure no longer required." Both of these occurred after study drug administration. The information provided in the NDA does not permit further scrutiny of these withdrawals, and it is not possible to definitively conclude that study drug (and/or placebo patch) played no role in these cases. If there were an unexpectedly high number of such withdrawals, a request for more information from the sponsor would be in order. Based on the number reported (< 3%) it is reasonable to accept the sponsor's explanation.

9.9.1 Study SC-42-03 Drop-Outs

The only clinical trial that called for more than two study visits was Study SC-42-03, which required twelve visits over six weeks. Of 220 subjects enrolled, 198 were classified as completers. The SC-42-03 study report and electronic data do not contain information indicating reasons for study drop-out, and missing data values. There is no information about investigator efforts to follow-up on any of these subject or ascertain possible study-drug causality. The report contains a one-page "Adverse Event Form" for each of the fifteen reported adverse events, but most of these are not for the study drop-outs. The SC-42-03 investigator's clinical impression was presented in one sentence; "As tested this product was irritating and not a sensitizer."

It is not possible to ascertain the reasons for study drop-out in SC-42-03. Some subjects (i.e. 10, 13, 64, 79) appear to have had a number of treatment sessions in which they did react to the patches (preapplication dermal irritation = 0, post-treatment dermal irritation = 2), prior to dropping. Of the 22 drop-outs, the mean number of completed treatment visits prior to dropout was 3.4 (median 3). Seven enrolled subjects dropped after one treatment visit (and one dropped after zero treatment visits. Most of these noncompleters experienced a number of post-treatment (2-hour) skin irritation scores of two, from zero baselines. Systematic comparison with the irritation scores for the study completers would be difficult, because only paper copies of the data line listings have been submitted with the NDA, but on cursory review, it appears that many (even most) of the study completers also scored 2s for some of their post-treatment skin irritation grades.

Also, on cursory review, post-treatment skin irritation grades do not appear to increase, as the number of patch applications increases. That is, the subjects who had pre-treatment skin irritation scores of 0, and post-treatment scores of 2, at visits 2 and 3, continued to experience post-treatment scores no greater than 2.

9.10 Distribution of Subjects by Skin Type

Table 9.13. Subjects in Controlled Trials

	Dev A, B 168	Final n=821	Placebo n=815
Skin Type			
(I) Always Burns/Rarely Tans	6 (4%)	57 (7%)	36 (6%)
(II) Always Burns/Tans Minimally	20 (12%)	144 (18%)	121 (21%)
(III) Burns Moderately/Tans Gradually	69 (41%)	187 (23%)	189 (33%)
(IV) Burns Minimally/Always Tans	30 (18%)	126 (15%)	134 (24%)
(V) Rarely Burns/Tans Profoundly	9 (5%)	48 (6%)	51 (9%)
(VI) Never Burns/Deeply Pigmented	4 (2%)	39 (5%)	34 (6%)
Missing Data	30 (18%)	220 (27%)	250 (31%)

Source: Modified from Sponsor Tables A4.2 and A4.3 in 120-day safety update, volume 1

9.11 Overall Evaluation of Adverse Events

9.11.1 Approach to Eliciting Adverse Events in the Development Program

Adverse events (AEs) were defined as any unintended, unfavorable clinical sign, symptom, medical complaint or clinically relevant change in laboratory value, regardless of perceived cause. In all studies, the investigators detected, and reported most adverse events. Subject initiated adverse event reporting was predominantly spontaneous, occurring while the subject was at the study site, although some protocols (i.e., SC-21-01, SC-27-01, SC-29-01) did call subjects to phone the study site, or vice versa, 24-48 hours after patch application, to report on their condition. Some trials included a return visit for follow-up skin evaluation at 24-48 hours (i.e. SC-24-01, SC-25-01, SC-26-01, SC-30-01, SC-31-01).

Adverse events were recorded on the CRFs including the event's time of occurrence, type, severity, and duration. "Because mild and transient incidences of localized erythema and edema are reported as expected reactions from topical lidocaine and tetracaine use, the investigators recorded only moderate to severe cases of erythema and edema as adverse events."

Adverse events were coded using COSTART terminology, and were characterized by type, incidence, intensity (mild, moderate, severe) (and perceived causality). For each trial, adverse event information was collected from study onset until the protocol-defined post-treatment endpoint.

In all trials, immediately after patch removal(s) the investigator examined patch sites for erythema, eschar formation and edema. The Draize scoring system was used to grade post-treatment dermal erythema and edema (although not referred to as the "Draize" system within this NDA) (Table 9.14). By prior agreement with the Division mild skin reactions were not classified as adverse events. "Because mild and transient incidences of localized erythema and edema are reported as expected reactions from topical lidocaine and tetracaine use, the investigators recorded only moderate to severe cases of erythema and edema as

adverse events." Draize scores of 3 or 4 on either measure were classified as adverse events, however.

Table 9.14. Draize Scoring

Symptom	Description	Value
Erythema (redness)	No Erythema	0
	Very Slight Erythema—barely perceptible	1
	Well Defined Erythema	2
	Moderate to Severe Erythema	3
	Severe Erythema—beet redness to slight eschar formation (injuries in depth)	4
Edema (swelling)	No Edema	0
	Very Slight Edema—barely perceptible	1
	Well Defined Edema—edges of area well defined/raising	2
	Moderate to Severe Edema—raised approximately 1mm	3
	Severe Edema—raised more than 1mm beyond exposed area	4

9.11.2 Appropriateness of Adverse Event Categorization and Preferred Terms

Reported adverse events were categorized by organ system and preferred term using the COSTART dictionary. Review of the pooled (Phases 2 and 3) AE database was notable for the paucity of reported adverse events.

9.11.3 Selection of Adverse Events for Characterizing the Overall Profile

9.11.4 Analyses and Explorations

Table 9.15.
Subjects in Controlled Trials: Experienced One or More Treatment Emergent AEs

	Dev A	Dev B	Final	Final No heat	Placebo	EMLA	Lido	Tetra
# of Subjects	138	30	601	53	595	82	128	128
# with AEs	5 (4%)	0	18 (3%)	1 (2%)	8 (1%)	2 (2%)	5 (4%)	4 (3%)
# Moderate AEs	1 (1%)	0	9 (1%)	0	2 (<1%)	2 (2%)	2 (2%)	3 (2%)
# Severe AEs	0	0	0	0	0	0	0	0

Source: 120-Day Safety Update, Volume 2

9.11.5 Incidence of Adverse Events in All (Single Dose) Integrated Studies

Table 9.16. Subjects with One or More Adverse Events

Exposures	Controlled		Open Label	
	Placebo (n=595)	S-Caine (n=822)	Placebo (n=12)	S-Caine (n=12)
Total Number (%) of Subjects with Any Adverse Events	8 (1.3%)	24 (2.9%)	0	3
Total Number (%) of Subjects with Mild Severity Adverse Events	6 (1.0%)	14 (1.7%)	?	?
Total Number (%) of Subjects with Moderate Severity Adverse Events	2 (<1%)	10 (1.2%)	?	?
Total Number (%) of Subjects with Severe Adverse Events	0	0	0	0
Total Number (%) of Subjects with Any Adverse Events Possibly or Probably Related to Study Drug/Device	7 (1.2%)	20 (2.4%)	0	3
Total Number (%) of Subjects Who Discontinued Due to Adverse Events	0	0	0	0

[1]Placebo-controlled studies excluding SC-25-01, 26-01, 30-01, 42-03
[2]Open-label study SC-01-95

9.11.5.1 Incidence of Treatment-Related Adverse Events in All (Single Dose) Integrated Studies

Table 9.17. Incidence of Treatment Emergent Adverse Events in Controlled Single Dose Trials

Body System	COSTART	Dev A	Dev B	Final	Final (no heat)	Placebo	EMLA	Lido	Tetra
	(Number of Patients)	138	30	601	53	595	82	128	128
SKIN	Applic Site Reaction	4 (3%)	0	3 (<1%)	0	1 (<1%)	0	0	0
	Pruritis	0	0	6 (1%)	0	2 (<1%)	0	2 (2%)	3 (2%)
	Rash	1 (1%)	0	3 (<1%)	0	0	0	0	1 (1%)
	Skin Discolor	0	0	1 (<1%)	0	0	0	0	0
	Derm Contact	0	0	1 (<1%)	1 (2%)	0	0	0	0
	Urticaria	0	0	1 (<1%)	0	1 (<1%)	0	0	0
	Edema	0	0	1 (<1%)	0	0	0	0	0
BODY	Injury Accident	0	0	0	0	2 (<1%)	0	0	0
	Headache	0	0	1 (<1%)	0	0	0	1 (1%)	0
	Fever	0	0	0	0	1 (<1%)	0	0	0
	Pain	0	0	1 (<1%)	0	0	0	0	0
	Pain Abdomen	0	0	0	0	0	0	0	1 (1%)
	Pain Back	0	0	2 (<1%)	0	0	0	0	0
	Edema Face	0	0	0	0	0	0	1 (1%)	0
NER	Dizziness	0	0	2 (<1%)	0	0	2 (2%)	0	0
DIG	Nausea	0	0	2 (<1%)	0	0	2 (2%)	0	0
	Vomit	0	0	0	0	1 (<1%)	0	0	0
RES	Pharyngitis	0	0	0	0	0	0	1 (1%)	0
SS	Taste Perversion	0	0	0	0	1 (<1%)	0	0	0

Final Formulation: SC-20-01, SC-21-01, SC-22-01, SC-23-01, SC-24-01, SC-28-01, SC-29-01, SC-31-01, SC-40-02, SC-41-03
Final Formulation +/- Heating Element: SC-27-01
Developmental A: SC-03-99, SC-04-99, SC-05-99, SC-07-99, SC-09-99 Developmental B: SC-10-00
Excluding SC-25-01, SC-26-01, SC-30-01, SC-42-03 (Repeat patch application studies) and SC-01-95 (Pilot)

9.11.6 Assessment of Dermal Reactions

As discussed earlier, the Draize dermal scoring system was used, throughout the S-Caine Patch clinical development program.

Table 9.18. Draize Scoring

Symptom	Description	Value
Erythema (redness)	No Erythema	0
	Very Slight Erythema—barely perceptible	1
	Well Defined Erythema	2
	Moderate to Severe Erythema	3
	Severe Erythema—beet redness to slight eschar formation (injuries in depth)	4
Edema (swelling)	No Edema	0
	Very Slight Edema—barely perceptible	1
	Well Defined Edema—edges of area well defined/raising	2
	Moderate to Severe Edema—raised approximately 1mm	3
	Severe Edema—raised more than 1mm beyond exposed area	4

9.11.6.1 Dermal Effects: Edema and Erythema (All Integrated Studies)

Table 9.19.
Incidence of Erythema, Edema and Blanching All Integrated Studies
(Developmental A, Developmental B and Final S-Caine Patch)

Skin Reaction	Occurrences
Erythema (n=863 [a])	
Very Slight	303 (35%)
Well Defined	250 (29%)
Moderate to Severe	2 (<1%)
Severe	0
Total Erythema	555 (64%)
Edema (n=863 [a])	
Very Slight	78 (9%)
Slight	16 (2%)
Moderate	2 (<1%)
Total Edema	96 (11%)
Blanching (n=337 [a, b])	
Slight	39 (12%)
More Intense	1 (1%)
Total Blanching	40 (12%)

[a] Subject 40144 in SC-40-02 not evaluated
[b] Blanching prospectively evaluated only in 21-01, 28-01, 29-01, 30-01, 40-02, 41-03

Table 9.20. Erythema and Edema: Incidence in Controlled Trials, Adults Only

	Dev A [a]	Final [b] Heat	Final No heat	Placebo	EMLA	Lido	Tetra
Number	78	483	53	404	82	128	128
Erythema							
None	6 (8%)	200 (41%)	31 (58%)	361 (89%)	37 (46%)	52 (41%)	56 (44%)
Very Slight	41 (53%)	179 (37%)	18 (34%)	42 (10%)	38 (47%)	68 (53%)	64 (50%)
Well Defined	31 (40%)	103 (21%)	4 (8%)	1 (<1%)	6 (7%)	8 (6%)	8 (6%)
Moderate	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
No data	0	1	0	0	1	0	0
Total Erythema	72 (92%)	282 (58%)	22 (42%)	43 (11%)	44 (56%)	76 (59%)	72 (56%)
Edema							
None	61 (78%)	443 (92%)	53 (100%)	379 (94%)	80 (99%)	108 (84%)	113 (88%)
Very Slight	12 (15%)	32 (7%)	0	24 (6%)	1 (1%)	19 (15%)	15 (12%)
Slight	5 (6%)	7 (1%)	0	1 (<1%)	0	1 (1%)	0
Moderate	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
No data	0	1	0	0	1	0	0
Total Edema	18 (23%)	39 (8%)	0	25 (6%)	1 (1%)	20 (16%)	15 (12%)

[a] Developmental A used in 03-99, 05-99, 07-99

[b] 11-01, 22-01, 23-01, 24-01, 27-01, 28-01, 31-01, 40-02, 41-03

Source: Modified from Table 5.2, 120-Day Safety Update, Volume 1

Table 9.21. Erythema and Edema: All Controlled Trials

	Pediatric[a]				Adult
	Dev A[b]	Dev B[c]	Final	Placebo	Final w/ Heat
Number	60	30	118	191	483[e]
Erythema[d]					
None	10 (17%)	3 (10%)	49 (42%)	110 (58%)	200 (41%)
Very Slight	24 (40%)	20 (67%)	30 (25%)	66 (35%)	179 (37%)
Well Defined	26 (43%)	7 (23%)	38 (32%)	15 (8%)	103 (21%)
Moderate	0	0	1 (1%)	0	0
Severe	0	0	0	0	0
Total Erythema	50 (83%)	27 (90%)	68 (58%)	81 (42%)	282 (58%)
Edema[d]					
None	46 (77%)	26 (87%)	108 (92%)	186 (97%)	443 (92%)
Very Slight	11 (18%)	4 (13%)	7 (6%)	5 (3%)	32 (7%)
Slight	2 (3%)	0	2 (2%)	0	7 (1%)
Moderate	1 (2%)	0	1 (1%)	0	0
Severe	0	0	0	0	0
Total Edema	14 (23%)	4 (13%)	10 (8%)	5 (3%)	39 (8%)

[a] 04-99, 09-99, 10-00, 20-01, 21-01, 29-01
[b] Developmental A used in 04-99 and 09-99
[c] Developmental B used in 10-00
[d] SC-29-01 administered either 2 S-Caine (final) or 2 placebo patches
[e] All controlled adult trials, "No Heat" in 27-01 excluded; 1 subject missing both ratings
If assessments differed between locations, the greater severity was tabulated
Source: Modified from sponsor Tables A5.16 and A5.17, 120-Day Safety Update, Volume 1

The sponsor has collected data regarding delayed skin reactions (occurring within 24-48 hours after patch administration). In SC-24-01, SC-25-01, SC-26-01, SC-30-01, and SC-31-01 subjects were instructed to return to the study site for skin evaluation. In SC-21-01, SC-27-01 and SC-29-01 subjects were contacted by telephone. In SC-20-01, SC-22-01, SC-23-01, SC-28-01 and SC-40-02 subjects received handouts describing potential skin reactions, and were asked to contact the site if any skin reaction developed. (variably by required follow-up

Table 9.22. Delayed Skin Reactions, 24-48 Hours Post Treatment (Phase 3 Trials)[a]

Treatment	Erythema	Edema	Application Site Reaction
Final S-Caine (n=651)	14 (2%)	0	1 (<1%)
Placebo (n=382)	6 (3%)	0	0

[a] SC-20-01, 21-01, 22-01, 23-01, 24-01, 25-01, 26-01, 27-01, 28-01, 29-01, 30-01, 31-01, 40-02, 41-03
Source: Table A5.15, 120-Day Safety Update, Volume 1

Table 9.23.
Erythema and Edema:
PK Trials SC-25-01, SC-26-01

	Final
Number	49
Erythema [a]	
None	0
Very Slight	5 (10%)
Well Defined	43 (88%)
Moderate	1 (2%)
Severe	0
Missing Data	
Edema [a]	
None	37 (76%)
Very Slight	12 (24%)
Slight	0
Moderate	0
Severe	0
Missing Data	0

[a] If multiple patches, site of greatest severity was tabulated

Source: Sponsor Table 12.2 (Vol. 38)

Table 9.24.
Erythema and Edema:
Final (+/- Heat) SC-27-01

	Heat SC-27-01	No Heat SC-27-01		Final All Others
Number	53	53	P-Value	430
Erythema [a]				
None	27 (51%)	31 (58%)	0.157 [b]	173 (40%)
Very Slight	22 (42%)	18 (34%)		157 (37%)
Well Defined	4 (8%)	4 (8%)		99 (23%)
Moderate	0	0		0
Severe	0	0		0
Missing Data				1
Edema [a]				
None	53 (100%)	53 (100%)		390 (91%)
Very Slight	0	0		32 (7%)
Slight	0	0		7 (2%)
Moderate	0	0		0
Severe	0	0		0
Missing Data	0	0		1

[b] Wilcoxin signed rank test

Source: Sponsor Table 12.3 (Vol. 36)

In SC-27-01, one subject had both of the reported adverse events. These were patch site reactions of equal severity, at her two patch sites (heated patch, and non-heated patch. There might be a (non statistically significant) trend towards a higher incidence of "very slight" erythema in recipients of the intact (heated) S-Caine Patch. Cases of "very slight" and "well defined" erythema were not considered (by the Division) to warrant counting as AEs. Given that the efficacy contribution of the heating element is in question, though, even a small increase in the incidence of "very slight" erythema may not be acceptable. If this finding proves to be more robust, notifying potential prescribers and patients via the product insert would certainly be warranted.

It is also worth noting that the incidence of "well defined" erythema is much greater in the overall development program than in either arm of study SC-27-01. This difference could be accounted for by differences in the patches used for SC-27-01, in the subjects (skin types) in SC-27-01, or most likely, in the reporting rates of "well defined" and "very slight edema." In any case, generalizing based on the safety results in SC-27-01 may not be appropriate.

Table 9.25.
Erythema and Edema: Maximum Score Multiple Simultaneous Patches (SC-25-01)

	30 Minute Applications		60 Minute Applications	
	2 Patches n=12	4 Patches n=13	2 Patches n=12	4 Patches n=12
Erythema				
None	0	0	0	0
Very Slight	5 (42%)	1 (8%)	2 (17%)	0
Well Defined	7 (58%)	12 (92%)	10 (83%)	11 (92%)
Moderate to Severe	0	0	0	1 (8%)
Severe	0	0	0	0
Edema				
None	12 (100%)	13 (100%)	12 (100%)	10 (83%)
Very Slight	0	0	0	2 (17%)
Slight	0	0	0	0
Moderate	0	0	0	0
Severe	0	0	0	0

Source: Sponsor Table 9.1 in Volume 26

Table 9.26.
Erythema and Edema: Maximum Score Repeat Patch Application (SC-26-01)

	30 Minute Applications		60 Minute Applications	
	Single n=12	4 Repeat n=11	Single n=12	3 Repeat n=12
Erythema				
None	3 (25%)	0	1 (8%)	0
Very Slight	7 (58%)	2 (18%)	3 (25%)	2 (17%)
Well Defined	2 (17%)	9 (82%)	8 (67%)	10 (83%)
Moderate to Severe	0	0	0	0
Severe	0	0	0	0
Edema				
None	11 (92%)	5 (45%)	12 (100%)	8 (67%)
Very Slight	1 (8%)	6 (55%)	0	4 (33%)
Slight	0	0	0	0
Moderate	0	0	0	0
Severe	0	0	0	0

Source: Sponsor Table 9.2 in Volume 26

9.11.6.2 Studies Not Included in the ISS Database

All studies reported on in NDA 21-623 have been included in the ISS, except for the 12 subjects studied in SC-01-95 (pilot study, prior to opening of IND 58,823). Subjects from SC-42-03 (cumulative sensitization evaluation) have been included in the ISS, and where possible, in summary tables.

9.11.7 Laboratory Findings, and Extent of Testing in Development Program

Aside form the pharmacokinetics trials (Section 5), only a subset of the S-Caine Patch clinical trials incorporated laboratory testing into the protocol. These were generally in those trials evaluating (the S-Caine Patch in) subjects undergoing dermatological surgery procedures, and follow-up or repeat laboratory evaluations were not dictated, or recorded as being done. There were no reported laboratory abnormailities in any of the subjects participating in S-Caine Patch trials (PK results aside).

9.11.7.1 Selection of Studies and Analyses for Overall Drug-Control Comparisons

Comparisons of laboratory values between S-Caine treated subjects and placebo treated subjects were only done

- In the pharmacokinetic studies, where lidocaine and tetracaine levels were compared between groups.
- In the parallel group design studies (S-Caine for minor dermatological procedures). Baseline laboratory values were compared, in order to demonstrate lack of differences between active drug and control groups.

9.11.7.2 Discontinuations for Laboratory Abnormalities

There were no reported discontinuations due to laboratory abnormalities.

9.11.8 Vital Signs

Screening vital signs were recorded in all trials, but not pre and post treatment, except in cases of adverse event. There were no reported discontinuations for vital sign abnormalities. Vital signs were analyzed in order to assess treatment group comparability (either between study sites, or between treatment conditions), and in no case did there appear to be any statistically significant differences. Given the lack of data, further exploration or analysis is not possible.

10 USE IN SPECIAL POPULATIONS

10.1 Adequacy of By-Gender Investigation and Analyses

Individual efficacy studies were not adequately powered to allow for meaningful by-gender analyses, however, there does not appear to be significant differences in S-Caine Patch safety or efficacy between genders. Tables X and Y below summarize primary efficacy measures, by gender, for a subset of the Phase 3 S-Caine Patch studies (SC-07-99, "Minor Dermatological Procedures" used Developmental Patch A).

Table 10.1. VAS Scores in Adult Subjects by Gender

	Number		Median VAS		% with VAS ≤10	
Gender	S-Caine	Placebo	S-Caine	Placebo	S-Caine	Placebo
Vasc. Access [a]						
Men	36	36	5.5	19.5	67%	36%
Women	65	64	4.0	18.5	66%	33%
Minor Derm [b]						
Men	54	38	6.0	27.0	65%	16%
Women	70	66	5.5	22.0	60%	23%

[a] 20-minute application for vascular access (11-01, 24-01, 31-01)
[b] 30-minute application for minor dermatological procedures (07-99, 22-01, 23-01)
Source: Sponsor Table, Volume 26

Table 10.2. Oucher Scores in Pediatric Subjects by Gender (Venipuncture Studies)

	Number		Median Oucher		% Oucher = 0	
	S-Caine	Placebo	S-Caine	Placebo	S-Caine	Placebo
Vasc. Access Photo [b]						
Boys	18	7	0.0	40.0	67%	14%
Girls	8	5	0.0	80.0	75%	0%
Numeric [c]						
Boys	24	18	7.5	15.0	88%	50%
Girls	21	20	0.0	20.0	81%	30%

[a] 20-minute application for vascular access (10-00, 20-01)
[b] 6-point categorical converted to 0, 20, 40, 60, 80, 100
[c] 11-point categorical converted to 0, 10, 20 ... 90, 100
Source: Sponsor Table, Volume 26

10.2 Elderly Population

A total of 96 (16%) of subjects who received the final S-Caine Patch formulation were 65 years or older. Thirty-eight (6%) of subjects who received the final patch formulation were 75 years or older. Over 12% of subjects enrolled in SC-42-03 (repeat exposure sensitization/irritation) were older than 65. Pharmacokinetic studies SC-25-01, SC-26-01 and SC-30-01 (multiple patch exposures) enrolled no subjects 65 or older, though, nor did SC-05-99, a combination efficacy/pharmacokinetic study. The only study to assess

pharmacokinetic parameters in the geriatric population was SC-31-01, an efficacy study in subjects ages 65 and older. In SC-31-01, ten subjects (out of forty) also underwent PK sampling. Eight of these were ages 65 to 75, and two were between 76 and 80.

A sufficient range and number of older subjects was included for assessment of safety with respect to local skin effects, and most other adverse events. Differences in systemic drug absorption in the geriatric population may not necessarily have been adequately characterized, however.

S-Caine efficacy in the elderly population has not necessarily been adequately demonstrated. S-Caine pharmacokinetics, or lack of systemic absorption, in the geriatric population was studied in only ten subjects.

10.3 Pediatric Population

A total of 160 subjects who received the final S-Caine Patch formulation were between 3 months and 17 years of age, or 20% of evaluable subjects (that received the final formulation). Seventy-six of these were between 3 months and 2 years of age, 42 were between 3 and 6 years old, and 42 were between 7 and seventeen years old. Six of the subjects (4%) that received Developmental Patch A were between 3 and 6 years old, and 53 (38%) were between 7 and 17. All 30 subjects that received Developmental Patch B were between 7 and 17 years old.

There were sufficient numbers of subjects, with a uniformly distributed population in terms of age to adequately label the S-Caine Patch for safe use in the pediatric population ages 3 years and older. Efficacy in 6 to 17 year holds, has not necessarily been conclusively demonstrated. This may be due to inadequacies in study design and sample size.

Although the pediatric population is probably most likely to receive repeated doses of S-Caine Patch, the cumulative irritation and skin sensitization study (SC-42-03) enrolled only adults. The adverse event rates, and the incidence of minor dermal reactions (erythema) with single-dose administration appear to be similar to those in the adult population, and there are no other reason at this time to expect differential rates of dermal irritation or sensitization in children. At this time, if the irritation and sensitization results from SC-42-03 are considered acceptable, then there would be no cause to evaluate S-Caine Patch dermal sensitivity potential in the pediatric population.

One additional study safety study (SC-33-02) is in progress at this time. This study is intended to provide information about S-Caine Patch safety in the neonatal population, including in premature infants down to 34 weeks estimated gestational age. The sponsor reports having enrolled eight of thirty planned subjects as of the 120-Day Safety Update.

10.4 Abuse Liability

Neither lidocaine nor tetracaine has been scheduled or labeled as a controlled substance. Neither has been associated with psychological or physiological dependence. The excipients employed in drug product formulation are commonly used, and none have

been implicated as potential drugs of abuse. The abuse liability of this product is likely negligible, and scheduling under the CSA is not called for.

10.5 120-Day Safety Update

The 120-day safety update included:

- Data and study report for study SC-30-01 which evaluated the systemic exposure (from S-Caine Patch application) of lidocaine and tetracaine in pediatric subjects
- Data and study report for SC-42-03. This study evaluated the sensitization and cumulative irritation potential of the S-Caine Patch in approximately 200 adults.
- Reports from studies requested by Chemistry and Pharmacology/Toxicology
- Electronic data from all clinical studies
- Updated safety database, including results from studies SC-30-01 and SC-42-03 Results from SC-30-01 and SC-42-03 were tabulated into a number of the composite safety tables (i.e. extent-of-exposure), but there were no additions or changes to safety (or efficacy) data, for any of the previously completed clinical studies. Studies SC-30-01 and SC-42-03 are discussed in detail in the relevant sections of this review.

The 120-day safety update contains no progress report, or mention of, study SC-33-02, an evaluation of S-Caine Patch systemic absorption and pharmacokinetics in the neonatal population. The sponsor reported having enrolled zero of twelve planned subjects, by the time of NDA submission. The Division had agreed to allow completion of SC-33-02 as a Phase 4 commitment.

1 Page(s) Withheld

____ Trade Secret / Confidential

✓ Draft Labeling

____ Deliberative Process

Withheld Track Number: Medical- 2

12 CONCLUSIONS

S-Caine Patch efficacy in the adult population for venipuncture, and for superficial excision and shave biopsy [redacted], has been demonstrated. Geriatric findings suggest efficacy for the same indications, though less persuasively (This may have been due to lower pain scores, across all treatment conditions, for geriatric subjects). The pediatric efficacy findings are more difficult to reconcile, in terms of "known" lidocaine and tetracaine local anesthetic effects (and transdermal absorption), and also given the "positive" results in other (nearly identical) pediatric trials.

The presence of the "heating element" in the S-Caine Patch as tested, poses a greater regulatory dilemma, I believe, than the inconsistent, and somewhat unexpected efficacy findings. Common sense, and clinical experience with other transdermal drug delivery systems, suggest that in theory, the heating element should speed drug delivery. And, although the data is limited, it seems the heating element is highly unlikely to contribute any incremental risk to the overall safety profile of the product. Unfortunately, given what the sponsor has been able to demonstrate both clinically and "chemically" (CMC findings), the CHADD may also be unlikely to contribute any incremental efficacy. Even if CMC deficiencies are adequately addressed, the clinical utility of a local anesthetic patch that must be removed from it's packaging to be exposed to air for twenty minutes, and then applied to the skin for another twenty to thirty minutes, prior to a venipuncture, is questionable.

Although the sponsor's explanation for failed trial SC-27-01 (the laser didn't cause enough dermal pain) may be plausible the sponsor may, in fact, never be capable of adequately demonstrating superiority of the (present formulation) heated patch; it may just not work, as implemented. Furthermore, the sponsor may never be able to adequately satisfy their CMC deficiencies. The problem, then, could be whether to approve a product with a component that does not contribute to efficacy, but will almost certainly be touted, implicitly or otherwise, as doing so.

Inclusion of a label statement similar to "The S-Caine Patch includes an integrated heat generating element (CHADD) which has not been demonstrated to contribute to patch efficacy" might be one solution, although the utility of, and the precedent for doing so are questionable. Advising the sponsor to pursue development of a patch with a more reliable heating element (temperature range, maximum, time to appreciable warming) might also be desirable.

One alternative to a recommendation to "improve" the present heating component, might be to point out its many problems, along with the difficulties we anticipate in achieving acceptable CMC specifications, and in demonstrating its clinical utility. Removal of the heating component might relieve the sponsor of, possibly unachievable, CMC and clinical requirements. For the sponsor, marketing a non-heated patch might not be entirely desirable, but if the alternative were continued testing of a product incapable of approval, then it might be an acceptable alternative.

A sponsor choice to pursue development of an S-Caine Patch without the CHADD would raise another set of problems, though. All of the S-Caine Patch clinical trials (developmental formulations included) were conducted using patches with the integrated heating component. No studies were conducted using patches without heating components. Although SC-27-01 failed to show any difference between the heated and the non-heated S-Caine Patch, and we believe that the majority of S-Caine Patches had been removed by the time they warmed up (throughout the entire clinical development program), it is possible that elimination of the heating component may impact negatively on product efficacy. The sponsor would need then, to conduct a new series of efficacy studies, in both adult and pediatric populations. It might also be possible for the sponsor to (attempt to) demonstrate, through use of a non-inferiority study design, similar efficacy between heated and unheated patch versions. If this type of approach were to be permissible, the conditions for inclusion of bridged "heated patch" efficacy data in a new application for an unheated version, should be communicated in the action letter along with other recommendations and advice.

In any case, better demonstration of efficacy in the pediatric population should be required. The sponsor should be advised that where possible, future trials should incorporate head-to-head testing of heated and non-heated patch formulations, and that these studies need to be sized accordingly.

Finally, while the sponsor's choice of 20 and 30 minute "doses" or patch application periods seems appropriate, the results from SC-40-02 suggest that patch applications of ten minutes duration might be as efficacious as twenty-minute applications. Labeling for a ten-minute "dose" would probably increase the product's appeal, and usefulness, to clinicians and patients alike. Ten-minute patch application (dosing) probably warrants further investigation, though this may be contingent upon what course of action the sponsor chooses with respect to the heating component deficiency.

13 Appendices

13.1 Appendix A – Communication with sponsor during NDA review

Teleconference minutes prepared by Ms. Lisa Malandro (DACCADP Project Management) appear below.

Teleconference to discuss submission of data electronically (July 24, 2003)
A teleconference was held on July 24, 2003, so that reviewers could discuss electronic formatting of data. The Sponsor had asked the reviewers if there were particular files that would assist their review if they were submitted in an electronic format. Dr. Josefberg stated that it would be helpful to have the Integrated Summary of Safety (ISS), the efficacy data from the pivotal trials and the individual line listings of the safety data for the pivotal trials. The files should be submitted in a .PDF format as discussed in the Guidance. The Sponsor stated that this information could be submitted with the 120-day update.

Teleconference regarding clinical efficacy data (December 2, 2003)
In a teleconference held on December 2, 2003, Dr. Chang informed the Sponsor there appeared to be inaccuracies and missing data within the application. Dr. Josefberg stated that, additionally, given the number of protocol amendments and the extensiveness of the changes, it was difficult to follow the progression of events and difficult to interpret the Sponsor's intent with respect to the study design. The Division requested that the Sponsor submit a copy of the original protocol, the amended changes and the dates when the changes occurred. Dr. Josefberg stated that the Sponsor should incorporate this procedure into the S-Caine Peel application. For NDA 21-623, the Sponsor should concentrate on only the pivotal studies. The Sponsor was also asked to clarify the data definition tables for each NDA to include the expected values and the format of the expected values.

Teleconference to discuss progress of response to Division requests (December 10, 2003)
In a teleconference held on December 10, 2003, Dr. Chang asked the Sponsor to provide the Division with an update on their progress with the response to the Division requests (December 2, 2003). Dr. Chang stated that the Division would prioritize their needs for the Sponsor since the application is late in the review cycle. The Sponsor stated that the erythema scale was consistent in each protocol. Dr. Chang requested that the Sponsor correct the inconsistent categorical values in the datasets. The Sponsor asked if, in the interest of time for the S-Caine Patch application, this be completed only for the combined database rather than each individual one. Dr. Chang agreed that this would be satisfactory, however, she stated that the entire S-Caine Peel application should be corrected in its entirety.
The Sponsor stated that they were submitting a new file to the Integrated Summary of Safety (ISS) containing the categorical values. Dr. Chang encouraged the Sponsor to also correct the individual datasets for the S-Caine Peel application. The Sponsor stated that they would submit the information for the S-Caine Patch application in one week.
Dr. Josefberg stated that the contribution of the heating element of the S-Caine Patch has not been demonstrated. He asked the Sponsor if they had any other data to support the

contribution of the heating element. The Sponsor stated that the pain stimulus in the study that was meant to address this issue was ineffective. Dr. Chang stated that the Sponsor has an opportunity to provide more justification as to why the product should be approved with the heating element. [redacted] Dr. Chang stated that there were numerous possibilities for addressing this, but at this time, the Sponsor should make a proposal for justifying the heating element and the Division will review it.

13.2 Appendix B

The following items (issues) remain outstanding at the end of the first review cycle: SC-42-03 amended (completed) study report with complete CRFs for all 15 (subjects that experienced) adverse events, and for all subjects that discontinued or dropped-out.

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

/s/

Howard Josefberg
2/4/04 02:51:04 PM
MEDICAL OFFICER

Nancy Chang
2/4/04 03:29:30 PM
MEDICAL OFFICER
concur