Table 8.23: Subjects with One or More Adverse Events

	Controlled Trials		OL + PK
Exposure	**Placebo (n=595)**	**S-Caine (n=1490)**	**S-Caine (n=258)**
Total Number (%) of Subjects with Any Adverse Events	8 (1.3%)	56 (3.7%)	3
Total Number (%) of Subjects with Mild Severity Adverse Events	6 (1.0%)	46 (3.1%)	?
Total Number (%) of Subjects with Moderate Severity Adverse Events	2 (<1%)	10 (0.7%)	?
Total Number (%) of Subjects with Severe Adverse Events	0	0	0
Total Number (%) of Subjects with Any Adverse Events Possibly or Probably Related to Study Drug/Device	7 (1.2%)	40 (2.7%)	3
Total Number (%) of Subjects Who Discontinued Due to Adverse Events	0	0	0

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

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

Table 8.24 and Table 8.25 report the incidence of treatment-related adverse events as of 8/2003 and 12/2004, respectively. Again, addition of the newer data does not appear to have altered adverse event incidence or breakdown.

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Table 8.24: Incidence of Treatment Emergent Adverse Events in Controlled Trials, Adult + Pediatric (as of (8/1/2003)

Body System	COSTART	Dev A	Dev B	Final	Final (no heat)	Placebo	EMLA	Lido	Tetra
	(Number of Subjects)	138	30	821	53	815	82	128	128
SKIN	Applic Site Reaction	4 (3%)	0	6 (1%)	0	1 (<1%)	0	0	0
	Pruritis	0	0	8 (1%)	0	3 (<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%)	1 (<1%)	0	0	0
	Urticaria	0	0	1 (<1%)	0	1 (<1%)	0	0	0
	Edema (+ Face)	0	0	1 (<1%)	0	0	0	1 (<1%)	0
	Vesiculobullous Rash	0	0	2 (<1%)	0	0	0	0	0
BODY	Injury Accident	0	0	3 (<1%)	0	3 (<1%)	0	0	0
	Injury Intentional	0	0	1 (<1%)	0	1 (<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	2 (<1%)	0	1 (<1%)	0	0	0
	Pain Abdomen	0	0	0	0	0	0	0	0
	Pain Back	0	0	2 (<1%)	0	0	0	0	1 (1%)
NER	Dizziness	0	0	2 (<1%)	0	0	2 (2%)	0	0
	Paresthesia	0	0	1 (<1%)	0	1 (<1%)	0	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
	Otitis Media	0	0	1 (<1%)	0	1 (<1%)	0	0	0

Final Formulation: 20-01, 21-01, 22-01, 23-01, 24-01, 28-01, 29-01, 31-01, 40-02, 41-03, 42-03, 27-01 (± Heating element)
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, (Repeat patch PK studies) and SC-01-95 (Pilot)

Table 8.25: Incidence of Treatment Emergent Adverse Events in Controlled Trials, Adult + Pediatric ('New' vs. 'Old' Trials)

Body System	WHEN CONDUCTED POPULATION→ COSTART (Number of Subjects)	NEW+OLD ALL AGES Final 1110	NEW+OLD ALL AGES Final (no heat) 352	NEW ALL AGES Final 289	NEW ALL AGES Final (no heat) 299	OLD ALL AGES Final 821	OLD ALL AGES Final (no heat) 53	OLD PEDS Final (heat) 118	OLD PEDS Develop. 90
SKIN	Applic Site Reaction	6 (1%)	0	0	0	6 (1%)	0	0	2 (2%)
	Pruritis	8 (1%)	0	0	0	8 (1%)	0	0	0
	Rash	11 (1%)	6 (2%)	8 (3%)	6 (2%)	3 (<1%)	0	1 (1%)	1 (1%)
	Skin Discolor	1 (<1%)	0	0	0	1 (<1%)	0	0	0
	Derm Contact	1 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (2%)	0	0
	Urticaria	1 (<1%)	0	0	0	1 (<1%)	0	0	0
	Edema (+ Face)	2 (<1%)	0	1 (<1%)	0	1 (<1%)	0	1 (1%)	0
	Vesiculobullous Rash	2 (<1%)	0	0	0	2 (<1%)	0	0	0
	Maculopapular Rash	0	1 (<1%)	0	1 (<1%)	0	0	0	0
BODY	Injury Accident	3 (<1%)	0	0	0	3 (<1%)	0	0	0
	Injury Intentional	1 (<1%)	0	0	0	1 (<1%)	0	0	0
	Headache	1 (<1%)	0	0	0	1 (<1%)	0	0	0
	Fever	0	0	0	0	0	0	0	0
	Pain	2 <1%)	0	0	0	2 (<1%)	0	0	0
	Pain Abdomen	0	0	0	0	0	0	0	0
	Pain Back	2 <1%)	0	0	0	2 (<1%)	0	0	0
NER	Dizziness	2 <1%)	0	0	0	2 (<1%)	0	0	0
	Paresthesia	0	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0	0
	Hypesthesia	0	1 (<1%)	0	1 (<1%)				
DIG	Nausea	2 <1%)	0	0	0	2 (<1%)	0	0	0
	Vomit	0	0	0	0	0	0	0	0
RES	Pharyngitis	0	0	0	0	0	0	0	0
HAL	Ecchymosis	1 (<1%)	0	1 (<1%)	0				
SS	Taste Perversion	0	1 (<1%)	0	1 (<1%)	0	0	0	0
	Otitis Media	1 (<1%)	0	0	0	1 (<1%)	0	0	0

Excluding SC-25-01, SC-26-01, SC-30-01, (Repeat patch PK studies) and SC-01-95 (Pilot)
Source: Tables 5.4, B5.4, 5.5, B5.5 in Complete Response Volume 22

8.11.4 Assessment of Dermal Reactions

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

Table 8.26: Draize Dermal Reaction 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

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

Based upon studies reviewed during the first cycle, mild to moderate erythema appeared to occur more commonly with the heated patch than with the non-heated version. Once the newer data are added, however, this now longer appears to be the case (Table 8.27).

Table 8.27: Erythema and Edema: Incidence in Controlled Trials, Adults Only

	Dev A [a]	Final [b] Heat	Final No heat	Placebo	EMLA	Lido	Tetra
Number	78	772	352	404	82	128	128
Erythema							
None	6 (8%)	262 (34%)	125 (36%)	202 (50%)	37 (46%)	52 (41%)	56 (44%)
Very Slight	41 (53%)	337 (44%)	177 (50%)	181 (45%)	38 (47%)	68 (53%)	64 (50%)
Well Defined	31 (40%)	164 (21%)	44 (12%)	21 (5%)	6 (7%)	8 (6%)	8 (6%)
Moderate	0	8 (1%)	6 (2%)	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%)	509 (66%)	227 (64%)	205 (50%)	44 (56%)	76 (59%)	72 (56%)
Edema							
None	61 (78%)	694 (90%)	304 (86%)	379 (94%)	80 (99%)	108 (84%)	113 (88%)
Very Slight	12 (15%)	66 (9%)	43 (12%)	24 (6%)	1 (1%)	19 (15%)	15 (12%)
Slight	5 (6%)	10 (1%)	5 (1%)	1 (<1%)	0	1 (1%)	0
Moderate	0	1 (<1%)	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%)	77 (11%)	48 (14%)	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, 53-04, 54-04, 55-04

Source: Modified from Complete Response Table B5.11, Volume 22

Table 8.28: Erythema and Edema in Controlled Trials (as of 12/2004)

	Dev A	Dev B	Final With Heat	Final No Heat	Placebo	Other Controls
Number	138	30	890	352	595	210
Erythema [d]						
None	16 (12%)	3 (10%)	311 (35%)	125 (36%)	312 (52%)	93 (44%)
Very Slight	65 (47%)	20 (67%)	367 (41%)	177 (50%)	247 (42%)	106 (50%)
Well Defined	57 (41%)	7 (23%)	202 (23%)	44 (12%)	36 (6%)	14 (7%)
Moderate	0	0	9 (1%)	6 (2%)	0	0
Severe	0	0	0	0	0	0
No data	0	0	1	0	0	1
Edema [d]						
None	107 (78%)	26 (87%)	802 (90%)	304 (86%)	565 (95%)	193 (92%)
Very Slight	23 (17%)	4 (13%)	73 (8%)	43 (12%)	29 (5%)	20 (10%)
Slight	7 (5%)	0	12 (1%)	5 (1%)	1 (<1%)	1 (<1%)
Moderate	1 (1%)	0	2 (<1%)	0	0	
Severe	0	0	0	0	0	
No data	0	0	1	0	0	1

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 Table B5.9, Complete Response Volume 22

The sponsor also 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. These results are summarized in Table 8.29 below.

Table 8.29: Delayed (24-48 Hours) Skin Reactions in 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, 53-04, 54-04 and 55-04
Source: Table A5.15, 120-Day Safety Update, Volume 1 and Complete Response Volume 22

In SC-27-01, one subject reported two 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.

8.11.4.2 Studies Not Included in the ISS Database

All studies described in NDA 21-623 have been included in the ISS, except for 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.

8.11.5 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 abnormalities in any subjects participating in S-Caine Patch trials (PK results aside).

8.11.5.1 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.

8.11.5.2 Discontinuations for Laboratory Abnormalities

There were no reported discontinuations due to laboratory abnormalities.

8.11.6 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.

9 REVIEW OF INDIVIDUAL STUDY REPORTS

9.1 Review of New Studies Contributing to Conclusions of Efficacy

9.1.1 Study SC-55-04: A Randomized, Double-Blind Study Comparing an S-Caine Patch with Heat to an S-Caine Patch without Heat, Prior to Vascular Access

9.1.1.1 Findings vs. Labeling Claims

In Study SC-55-04 adult subjects pre-treated with an S-Caine Patch containing a functioning heating element had (statistically significantly) lower average VAS scores during venipuncture than subjects treated with an S-Caine Patch without an integrated heating element, supporting an efficacy claim for the to-be-marketed S-Caine Patch. SC-55-04 supports an efficacy claim for use prior to "venipuncture" or "superficial venous access" but not necessarily for [redacted]
Precise label wording will be discussed at the upcoming S-Caine Patch labeling meetings.

The Sponsor includes a brief summary of the results of this study under the "Clinical Studies" section of the proposed product label.

9.1.1.2 Study Plan

The initial version of Protocol SC-55-04 was dated September 13, 2004 and submitted on October 28, 2004 (#25). Two amendments were implemented prior to subject enrollment, dated September 21, 2004 and September 22, 2004 (Amendments 1 and 2, respectively). Both Amendments were submitted along with the protocol on October 28, 2004 (#25)

9.1.1.3 Population, Design, and Objectives

The protocol-specified objectives of the study were:

1. "To compare the effectiveness of an S-Caine Patch with heat to an S-Caine Patch without heat in providing local dermal anesthesia for vascular access in healthy adult subjects
2. "To monitor the nature and frequency of adverse events associated with the safety of an S-Caine Patch."

The protocol was designed as a four center, randomized, double-blind study in healthy adult volunteers. Approximately 250 subjects who met entry criteria would be invited to participate. Subjects were to be randomized (1:1) to receive one of two treatments; S-Caine Patch with integrated heating element, or S-Caine Patch manufactured with no heating element present.

The non-heated patches were to be nearly identical in composition to the heated S-Caine Patch (excipients, adhesives, heating element), but with no heating element present. Investigators were to prospectively designate one staff member to be responsible for handling study drug, applying and removing patches from subjects, and returning both used and unused material to the sponsor. The designated staff member was NOT to be the investigator, who would be responsible for performing the venipuncture and the safety assessments.

Patch application site was always to be the right antecubital surface. After a 20 minute application the patch was to be removed, and then the investigator would evaluate the skin (at the application site) for erythema, edema and other skin reactions. The investigator would then perform the "vascular access procedure."

Efficacy evaluations would consist of subject VAS ratings of venipuncture-induced pain, and Yes/No responses to two "overall subject impression" questions. Subjects were to be dismissed after completion of efficacy evaluations. Subjects were to inspect the treatment site 24-48 hours following drug removal, and telephone the study site if they believed a skin reaction had developed.

Table 9.1: Study SC-55-04 Schedule of Events

Measurement/Evaluation	Day of Procedure	24-48 Hours After Drug
Informed Consent	X	
Subject Eligibility	X	
Medical History	X	
Physical Exam	X	
Vital Signs Pre and Post Treatment	XX	
Medication History	X	
Skin Type Assessment	X	
Study Drug Application (20 minutes)	X	
Evaluation of Skin Reactions	X	X
Vascular Access Procedures	X	
Efficacy Evaluations		
Subject Evaluation Using VAS	X	
Investigator Evaluation of Subject's Pain	X	
Observer Evaluation of Subject's Pain	X	
Investigator Overall Impression	X	
Adverse Events	X	
Subject Assessment of Application Site		X
Study Termination Report		X

Source: NDA 21-623 Complete Response Volume 20

The inclusion criteria were to be:
1. Male or female patients 18 years or older.
2. No known allergies to lidocaine, tetracaine or other local anesthetics.
3. Subject had signed and dated the written informed consent.

The exclusion criteria were to be:
1. Known sensitivity to any component of the test materials (e.g., [redacted] adhesives).
2. Prescription strength analgesic pain medication use during the preceding 24-hour period.
3. Damaged, denuded or broken skin at either designated patch site.
4. Pregnant or breastfeeding.

9.1.1.4 Treatment Summary

Study Medication

Both S-Caine Patches (heated and non-heated) were to be supplied by, and manufactured under the direction of ZARS, Inc., Salt Lake City, Utah. Active Drug components used in the S-Caine Patch were to be supplied by:

Tetracaine Supplier
Lidocaine Supplier [redacted]

Upon meeting eligibility criteria, subjects would be assigned the next available sequential subject number. Treatments would be double-blind, and assigned based on a predetermined computer-generated randomization code, so that one-half of the subjects would receive the heated S-Caine Patch, and one-half would receive the non-heated S-Caine Patch. Subjects were to receive a single 20-minute patch application to their right antecubital surface, prior to undergoing venipuncture.

The CRF for recording study medication would record the patient identification number, skin type (I – VI), patch application and removal times for each arm, and the post-treatment skin assessment. Study drug labels (both) would be affixed to each subject's CRF as well.

Concomitant Medications
Use of any prescription strength analgesic medication during the 24-hour period preceding the study would result in subject exclusion. No other medication use would preclude study participation, however. All concomitant treatments were to be recorded on the CRFs.

9.1.1.5 Efficacy Assessment

9.1.1.5.1 Primary Efficacy Variable

The primary efficacy variable was to be the subject's evaluation of pain caused by insertion of a 16 gauge, one-inch catheter, as rated on a 100 mm VAS where 0 mm = "no pain" and 100 mm = "the worst pain you can imagine."

9.1.1.5.2 Secondary Efficacy Variables

Subject's overall impression of the local anesthetic
Each subject would be asked to evaluate drug efficacy by answering "yes" or "no" to the following questions:

- Did the local anesthetic provide adequate pain relief for the vascular access procedure?
- Would you have local anesthesia administered using this form of anesthesia again if given the option?

9.1.1.5.3 Other Measures

No other efficacy measures were specified *a priori* in the initial protocol.

9.1.1.6 Sponsor's Analysis Plan

Demographic, background and pre-procedure variables were to be summarized using descriptive statistics, and presented in tabular form.

The primary efficacy variable, subject VAS rating of procedure-induced pain, was to be compared using a two-sample t-test. VAS scores were to be log-transformed prior to analysis. The protocol also specified, on page 12, that "An exploratory analysis will be a two-way analysis of variance with fixed terms for treatment and center."

The protocol specified secondary efficacy variables, would be the Yes/No responses to:

- Did this local anesthetic provide adequate pain relief for the vascular access procedure?
- Would you have local anesthesia administered using this form of anesthesia again if given the option?

Subjects' ratings of "adequate pain relief" and whether they would "use again" were to be compared between treatments using Fisher's Exact test. An exploratory analysis was to be a Cochran-Mantel-Haenszel test, stratified by center.

Adverse events were to be tabulated by type, frequency, onset, duration, outcome and relationship to treatment. Incidence of individual effects was to be compared between treatments using sign tests, and the numbers of occurrences overall were to be compared using Wilcoxin signed rank tests.

Sample Size Calculation

The sample size calculation was described in the protocol (page 13) as follows:

> The estimated standard deviation and the estimated magnitude of the effect from data in Study SC-53-04 were used to aid in the design of studies 55-04 and 54-04. Sample size was determined based on the pilot study (SC-53-04) with parallel treatments. According to the applicant, the preliminary analysis of log transformed VAS scores had a root mean squared error of 1.2 and observed differences for 16 gauge needle (deactivated minus with heat) of 0.6 (30 minute application) and 1.0 (20 minute application). With 123 subjects per treatment group, there would be 95% power when the standard deviation equals 1.2 and the difference between heat and no heat is 0.55 on the log transformed scale.

9.1.1.7 Protocol Amendments and Changes in the Planned Analyses

There were two amendments to Protocol SC-55-04. Both were implemented prior to subject enrollment.

Amendment 1 (September 21, 2004) substituted the word 'similar' for the word 'identical' in four places within the protocol and changed one sentence entirely in the description of Investigator Supplies (strikethroughs illustrate where 'identical' was changed to 'similar'):

- Study Materials (Section 5.1.1)
  S-Caine Patch without Heat - This patch is ~~identical~~ similar to the patch in 5.1.1 except the heating element has been removed.
- Randomization and Blinding Procedures (Section 6.0)
  The packaging material for the heat and no heat patches will be identical similar.
- Investigational Supplies (Section 12.0)
  "All patches will be identical in appearance and packaged in identical pouches" changed to "The packaging material for the heat and no heat patches will be similar"
- Description of Study Patches (Section 12.1.2)
  S-Caine Patch Without Heat - This patch is ~~identical~~ similar to the patch in 12.1.1 except that the heating element has been removed.
- Packaging (Section 12.2)
  All patches will be in ~~identical~~ similar pouches.

Amendment 2 (September 22, 2004) changed the wording of Section 15.0, Ethical and Regulatory Requirements, to clarify that the study would be conducted in accordance with:

- Declaration of Helsinki
- 21CFR 50, 21CFR 56 and 21CFR 812
- "Applicable laws and the IRB requirements"

9.1.1.8 Study Conduct

Study SC-55-04 was conducted between September 27, 2004 and October 6, 2004. Clinical investigators and sites were identified and registered in a submission dated September 27, 2004 (#24), but the protocol itself, dated September 13, 2004, was not submitted until October 28, 2004 (#25). Amendments 1 and 2 dated September 21 and September 22, respectively, were also submitted on October 28, along with the protocol (#25). In the Study Report (Section 9.6), the Sponsor notes that the study was conducted in accordance with the Good Clinical Practice (GCP) Guidelines of the Declaration of Helsinki, and utilized the following measures to assure data quality assurance:

- On-site study monitoring at "suitable intervals"
- On-site comparison of CRFs with source documents (proportion not specified)
- Single data entry with 100% verification
- Answering of all data clarification or queries, with changes made to CRF recorded in a log
- Prior to unblinding the study, it was determined which subjects randomized would be included in the primary efficacy analysis

Two-hundred-and-fifty (N=250) subjects enrolled, were randomized and completed Study SC-55-04. The study report does not indicate how many patients were screened in total. As noted above, the protocol called for 250 patients to be enrolled

A 16-gauge needle was used for each of the 250 venipunctures performed during this study.

9.1.1.8.1 Investigators

The four SC-55-04 clinical sites were used for SC-53-04 and SC-54-04 as well. Three of these are operated by [redacted] a contract research organization with facilities across the United States. Three SC-55-04 investigators, [redacted]

Table 9.2: SC-55-04 Investigators and Clinical Sites

Investigator (All MD)	Center	Site #	N
[redacted]		1	60
		2	60
		3	70
		4	60

Source: Sponsor Table 8.6.1 and Appendix 16.1.2, Complete Response Volume 20

9.1.1.8.2 Subject Disposition

All enrolled subjects were randomized and completed the study. There were no study dropouts or terminations. One-hundred-and-twenty-four (n=124) subjects received a heated patch and 126 received a non-heated patch.

Table 9.3: SC-55-04 Subject Disposition Summary

Subject Status	No.
Enrolled in Study	250
Received 20-minute Heated S-Caine Patch	124
Received 20-minute Non-Heated S-Caine Patch	126
Completed Study	250
Study Dropouts/Discontinuations	0

Source: Sponsor Table 8.6.2, Complete Response Volume 20

9.1.1.8.3 Protocol Deviations and Violations

ZARS reports a total of 11 protocol deviations or violations in 9 of the 250 enrolled subjects. Protocol violations were defined as those deviations that had the potential to affect the outcome of the study. The most common protocol deviations involved failure to record subject weight, height or temperature (n=8 total). Two subjects received 21 minute patch applications, and one subject received a 19 minute patch application. These protocol deviations are unlikely to have impacted study results in any meaningful or detectable way.

The sponsor also describes a protocol deviation at two of the four study sites, whereby two staff members participated in applying and removing study drug, and in subject monitoring, instead of the single staff member, specified in the protocol. "In each case, the intended deviation was discussed with the sponsor prior to implementation. The sponsor accepted the deviation as a planned protocol deviation contingent upon the additional staff member having no involvement in any post-patch removal study procedures."

It is possible to imagine a scenario in which ZARS found that they were dealing with investigators who insisted on using two staff members to facilitate study procedures. (The fact that three of the four sites were [redacted] franchises seems to make that particular situation less plausible, however.) Faced with the prospect of losing two sites, compliance with this seemingly innocuous investigator demand could have been quite reasonable. ZARS handling of the situation, whatever the explanation was not necessarily appropriate, however. Labeling investigator non-adherence to protocol as "planned protocol deviation," proceeding without notifying the Agency, and then not identifying the culprit sites in the NDA, contravenes IND regulations. Formal protocol amendment, at that time, was called for, regardless of the explanation. Likewise, more detailed information should have been included with the final study report.

It appears that ZARS had no intent to falsify study results, or to deceive the Agency, and that the ramifications of this mistake were likely insignificant.

Table 9.4: SC-55-04 Protocol Deviations and Violations

Description of Protocol Deviation	No.
Study patches applied for 21 minutes instead of 20 minutes	2
Study patches applied for 19 minutes instead of 20 minutes	1
Subject temperature not recorded	1
Weight not recorded	5
Height not recorded	2

Source: Sponsor data listings, Appendix 16.2.3, Complete Response Vol. 20

9.1.1.9 Data Sets Analyzed

All 250 patients who were randomized and received study drug were included in all efficacy and safety analyses.

9.1.1.10 Demographics/Group Comparability/Skin Type

9.1.1.10.1 Demographics

Subject baseline demographic characteristics and skin type are summarized in Table 9.5 and Table 9.6, respectively. Review of these tables indicates that the two subject groups were comparable across treatment conditions with regard to all measured characteristics. Although not necessarily representative of the general US population there was reasonable representation by race, skin type and gender.

Table 9.5: SC-55-04 Subject Demographics

Characteristic	Heated n=124 (%)	Non-Heated n=126 (%)	Total N=250
Gender			
Male (%)	57 (46)	57 (45)	114 (46%)
Female (%)	67 (54)	69 (55)	136 (54%)
Age (years)			
Mean ± SD	35.1 ± 13.4	33.5 ± 13.4	34.3 ± 13.4
Range	18 - 74	18 - 72	18 - 74
Race			
Black (%)	6 (5)	2 (2)	8 (3%)
Caucasian (%)	61 (49)	66 (52)	127 (51%)
Hispanic (%)	19 (15)	8 (6)	27 (11%)
Asian (%)	23 (19)	33 (26%)	56 (22%)
Other (%)	15 (12)	17 (13)	32 (13%)
Height (cm)			
Mean ± SEM	66.6 ± 4.1	66.5 ± 3.9	66.6±4.0
Range	51 - 76	59 - 76	51 - 76
Weight (kg)			
Mean ± SD	171.8 ± 49.9	167.5 ± 42.9	169.7 ± 46.5
Range	96-360	96-304	96 - 360

Source: Sponsor Table 20.11.1 (Complete Response)

Table 9.6: SC-55-04 Subject Skin Type

Skin Type	Heat n=124	No Heat n=126	Total N=250
(I) Always Burns/Rarely Tans	5 (4%)	4 (3%)	9 (4%)
(II) Always Burns/Tans Minimally	26 (21%)	21 (17%)	47 (19%)
(III) Burns Moderately/Tans Gradually	46 (37%)	53 (42%)	99 (40%)
(IV) Burns Minimally/Always Tans	30 (24%)	36 (29%)	66 (26%)
(V) Rarely Burns/Tans Profoundly	16 (13%)	11 (9%)	27 (11%)
(VI) Never Burns/Deeply Pigmented	1 (1%)	1 (1%)	2 (1%)

Source: Sponsor Table 20.11.1 (Complete Response, Volume 20)

9.1.1.10.1 Group Comparability: Medical Conditions

Subject medical conditions, as reported by the sponsor (in Appendix 16.2.6 of the SC-55-04 study report) appear unlikely to have influenced this study's efficacy (or safety) findings. The medical conditions most frequently reported by subjects were allergies (31% of all subjects), reproductive conditions (21%) and musculoskeletal conditions (18%). Medical conditions grouped together as "Other" (history of tonsillectomy, previous surgeries) were reported by 11% of subjects. Gastrointestinal, dermatologic, psychiatric, renal/genitourinary, hematologic, hepatic, and immunologic conditions were all reported (in decreasing order of frequency) by less than 10% of subjects. The conditions most likely to impact upon study results, (allergies and dermatologic conditions), as well as the others most commonly reported (reproductive and musculoskeletal conditions, history of surgery) were approximately equally distributed between the two treatment conditions.

Mean values of vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate and temperature) at screening were within normal range in all subjects (where recorded), and comparable in subjects between the treatment conditions. (Screening vital signs are listed in Appendix 16.2.7 of the study report). Clinical laboratory values at screening were also all within, or very close to, normal range and means and medians of all values were similar between the two treatment conditions Appendices 16.2.8 and 16.2.9 of the SC-55-04 study report).

9.1.1.11 Treatment Compliance

Study drug was administered by the investigator and subjects were monitored during each treatment. Pre-dose and post-dose safety assessments were performed by the investigator. Efficacy assessments were all patient-reported, after the venipuncture had been performed. Additional safety assessment entailed subject self-assessment of the patch application site at 24-48 hours, with instructions to phone the clinical site for any findings suggestive of dermal reaction at the patch application site. The SC-55-04 study report, however, does not indicate how many subjects actually made this optional follow-up telephone call.

9.1.1.12 Unplanned Analyses

ZARS reports that some exploratory analyses that were not specified in the protocol were performed. Exploratory analyses were done "to compare centers, to evaluate consistency among centers and to compare treatments within each center (SC-55-04 study report, page 26)." Descriptive statistics were reported by center and treatment. For continuous variables a two-way analysis of variance was performed with fixed terms for center, treatment and center by treatment

interaction, including unadjusted p-values from pairwise least square means. For categorical variables the following tests were performed (p-values not adjusted for multiplicity):

- Fisher Exact test to compare treatments
- Cochran Mantel Haenszel test stratified on center to compare treatments
- Fisher Exact test on combined treatments to compare centers
- Logistic regression with terms for treatment, center and treatment by center

For ordered categorical variables the following tests were performed (p-values not adjusted):

- Wilcoxin test for each center to compare treatments
- Cochran Mantel Haenszel test stratified on center to compare treatments
- Kruskal-Wallis (Cochran Mantel Haenszel) test on combined treatments to compare centers
- Logistic regression with terms for treatment, center and treatment by center

9.1.1.13 SC-55-04 Efficacy Results

The primary efficacy measure in this study was the subject's evaluation of pain (by 100-mm VAS) following their vascular access procedure (which was done after patch application and removal). Mean VAS scores for the heated S-Caine treatment and the non-heated treatment were 22.1 (± 20.7) and 28.7 (± 22.8), respectively (p=0.018 using two-sample, or p=0.007 using the sponsor's two sample t-test on the log-transformed data). Median VAS scores were 16.5 and 22.0, for the heated and the non-heated patch, respectively (Table 9.7).

Table 9.7: SC-55-04 Efficacy Results by Treatment Group - All Subjects

	Treatment			
	Heated	**Unheated**	**All**	**P-value**
Efficacy Measure	n=122	n=128	N=250	
VAS (mm)				
Mean	22.1	28.7	25.4	0.0183[1]
SD	20.7	22.8	22.0	
Median	16.5	22.0	20.0	
Range	0 – 97	0 – 95	0 – 97	
Geometric Mean	14.2	20.5	17.1	0.0065[2]
% Adequate	88 (71%)	67 (53%)	62%	0.004[3]
% Use Again	88 (71%)	69 (55%)	63%	0.009[3]

[1] Two-sample t-test (Dr. Buenconsejo) [2] Two-sample t-test (Sponsor) [3] Fisher's Exact test (Sponsor)
Sources: Tables 8.11.2 and 8.11.3 (Complete Response Volume 20), Dr. Buenconsejo's statistical review

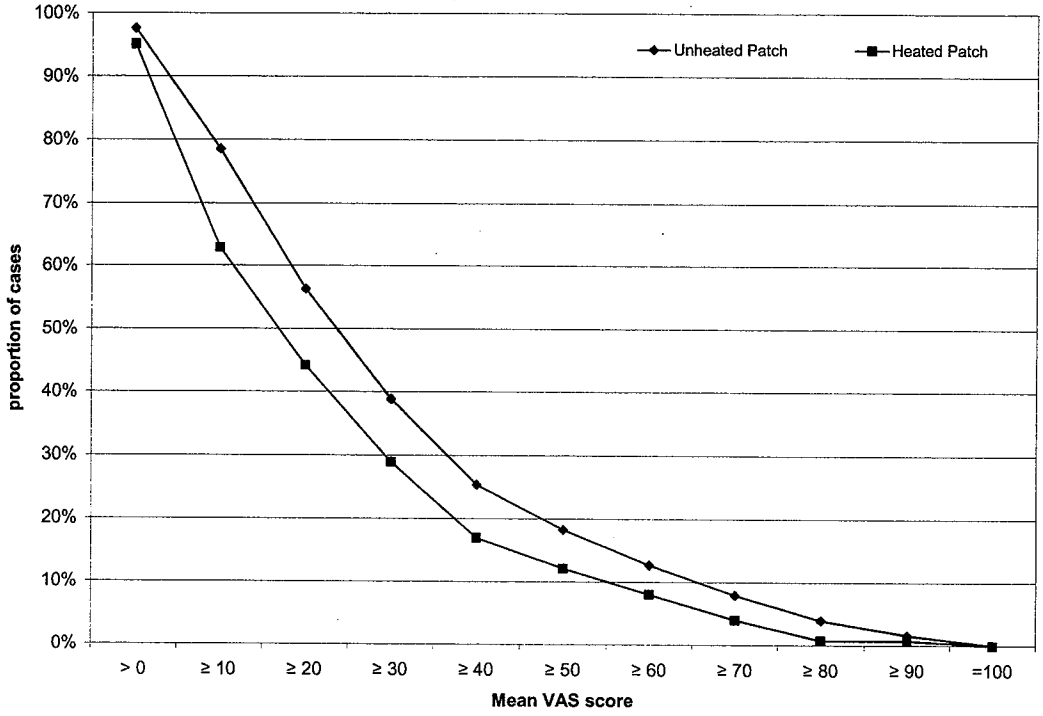
Subject's impression of study treatment

When asked whether the patches "provided adequate pain relief" during the procedure 71% of subjects treated with the heated patch indicated adequate pain relief versus 53% treated with the non-heated patch (p=0.004, Fisher's Exact test). Likewise, 71% of subjects treated with the heated patch said they would opt to use the same treatment again for a similar procedure as opposed to 55% of those treated with the non-heated patch (p=0.009, Fisher's Exact test). These secondary efficacy findings also support the sponsor's claim.

Additional analysis performed by Dr. Buenconsejo, compared VAS scores between subjects treated with the heated patch and those treated with the unheated patch, using cumulative distributions. Higher VAS scores indicate greater (subject self-reported) pain. In Figure 9.1 below, prepared by Br. Buenconsejo, it appears that there is in fact an efficacy difference between treatment groups.

The proportion of subject VAS scores at or above each 10-mm cutoff (of VAS score), is consistently higher for patients treated with the non-heated patch than for those treated with the heated version.

Figure 9.1: SC-55-04 Subject Pain Rating, by Treatment Group



Source: Dr. Buenconsejo, statistical review

9.1.1.14 Discussion of Efficacy Findings in Study SC-55-04

The SC-55-04 data appear to provide support for the sponsor's claim that 20-minute application of S-Caine Patch with functional heating element is superior to 20-minute application of S-Caine Patch absent the heating element, in reducing the discomfort experienced by subjects undergoing venipuncture with 16G angiocatheters. From a clinical perspective, the magnitude of the treatment effect (< 7-mm on a 100-mm VAS scale) is not particularly impressive. It is statistically significant, however, and comparable to the VAS differences found in earlier S-Caine Patch venipuncture trials (in which heated S-Caine Patch was compared to placebo). Two issues should be kept in mind, though; ZARS management of protocol deviations and subsequent reporting, and questionable blinding procedures.

It is possible to imagine a scenario in which ZARS found that they had enlisted investigators who insisted on using two staff members to facilitate study procedures. (The fact that three of the four sites used were [redacted] franchises seems to make that particular situation less plausible, however. Also, the same four sites were used in SC-54-04, and no such problem was reported.) Concession to apparently inconsequential investigator demand may have seemed perfectly reasonable to ZARS at that time, especially if faced with the prospect of losing clinical sites. ZARS' handling of the situation was not necessarily appropriate, however, whatever the explanation.

Labeling investigator non-adherence to protocol as "planned protocol deviation," proceeding without notifying the Agency, and then not identifying the culprit sites in the NDA, contravenes IND regulations. Formal protocol amendment, at that time, was called for, regardless of the explanation. Likewise, more detailed information should have been included with the final study report. ZARS may have had no nefarious intent, and the ramifications of this 'mistake' were likely insignificant. Still, this indiscretion (at best) does not help bolster confidence in the integrity of the SC-55-04 data.

Investigator blinding to treatment condition may have been compromised, by virtue of the study's use of S-Caine Patches that had been constructed without heating elements, specifically for the purpose of conducting the study.

9.1.2 Study SC-54-04: A Randomized, Double-Blind Study Comparing an S-Caine Patch with Heat to an S-Caine Patch without Heat, Prior to Vascular Access

9.1.2.1 Findings vs. Labeling Claims

This study found no efficacy difference between the S-Caine Patch with active heating element, and S-Caine Patch with deactivated (by exposure to air) heating element. Adult subjects treated with an S-Caine Patch containing an active heating element did not have (statistically significantly) lower average VAS scores during venipuncture than subjects treated with an S-Caine Patch containing a deactivated heating element.

9.1.2.2 Study Plan

The initial version of Protocol SC-54-04 was dated June 11, 2004 and submitted on August 3, 2004 (Sequence #023). Two amendments were implemented, both prior to subject enrollment, dated September 21, 2004 (Amendment 1), and September 22, 2004 (Amendment 2).

9.1.2.3 Population, Design, and Objectives

The protocol-specified objectives of the study were:

1. "To compare the effectiveness of an S-Caine Patch with heat to an S-Caine Patch without heat in providing local dermal anesthesia for vascular access in healthy adult subjects
2. "To monitor the nature and frequency of adverse events associated with the safety of an S-Caine Patch."

The protocol was designed as a four center, randomized, double-blind study in healthy adult volunteers. Approximately 200 subjects who met entry criteria would be invited to participate. (Amendment One increased the planned number of subjects to 250) Subjects were to be randomized (1:1) to receive one of two treatments; S-Caine Patch with integrated heating element, or an S-Caine Patch without any heating element. The non-heated patches were to be identical in composition to the heated S-Caine Patch (excipients, adhesives, heating element), but with a heating element that had been inactivated by exposure to air.

Investigators were to prospectively designate one staff member to be responsible for handling study drug, applying and removing patches from subjects, and returning both used and unused material to the sponsor. The designated staff member was NOT to be the investigator, who would be responsible for performing the venipuncture and the safety assessments.

Patch application site was always to be the right antecubital surface. After a 20 minute application the patch was to be removed, and then the investigator would evaluate the skin (at the application site) for erythema, edema and other skin reactions. The investigator would then perform the "vascular access procedure."

Efficacy evaluations would consist of subject VAS ratings of venipuncture-induced pain, and Yes/No responses to two "overall subject impression" questions. Subjects were to be dismissed after completion of efficacy evaluations. Subjects were to be instructed to inspect the treatment site 24-48 hours following drug removal, and to telephone the study site if they believed a skin reaction had developed.

Table 9.8: Study SC-54-04 Schedule of Events

Measurement/Evaluation	Day of Procedure	24-48 Hours After Drug
Informed Consent	X	
Subject Eligibility	X	
Medical History	X	
Physical Exam	X	
Vital Signs Pre and Post Treatment	XX	
Medication History	X	
Skin Type Assessment	X	
Study Drug Application (20 minutes)	X	
Evaluation of Skin Reactions	X	X
Vascular Access Procedures	X	
Efficacy Evaluations		
Subject Evaluation Using VAS	X	
Investigator Evaluation of Subject's Pain	X	
Observer Evaluation of Subject's Pain	X	
Investigator Overall Impression	X	
Adverse Events	X	
Subject Assessment of Application Site		X
Study Termination Report		X

Source: SC-54-04 protocol, Complete Response, Appendix 16.1.1, Volume 17

The inclusion criteria were to be:
1. Male or female patients 18 years or older.
2. No known allergies to lidocaine, tetracaine or other local anesthetics.
3. Subject had signed and dated the written informed consent.

The exclusion criteria were to be:
1. Known sensitivity to any component of the test materials (e.g., adhesives).
2. Prescription strength analgesic pain medication use during the preceding 24-hour period.
3. Damaged, denuded or broken skin at either designated patch site.
4. Pregnant or breastfeeding.

9.1.2.4 Treatment Summary

Study Medication

Both S-Caine Patches (heated and non-heated) were to be supplied by, and manufactured under the direction of ZARS, Inc., Salt Lake City, Utah.

Active Drug components used in the S-Caine Patch were to be supplied by:

Tetracaine Supplier

Lidocaine Supplier [redacted]

Upon meeting eligibility criteria, patients would be assigned the next available sequential subject number. Treatments would be double-blind, and assigned based on a predetermined computer-generated randomization code, so that one-half of the subjects would receive the heated S-Caine Patches, and one-half would receive the non-heated S-Caine Patches. Subjects were to receive a

single 20-minute patch application to their right antecubital surface, prior to undergoing venipuncture.

The CRF for recording study medication would record the patient identification number, skin type (I – VI), patch application and removal times, and the post-treatment skin assessment. Study drug labels (both) would be affixed to each subject's CRF as well.

Concomitant Medications
Use of any prescription strength analgesic medication during the 24-hour period preceding the study would result in subject exclusion. No other medication use would preclude study participation, however. All concomitant treatments were to be recorded on the CRFs.

9.1.2.5 Efficacy Assessment

9.1.2.5.1 Primary Efficacy Variable

The primary efficacy variable was to be the subject's evaluation of pain caused by insertion of a 16 gauge, one-inch catheter, as rated on a 100 mm VAS where 0 mm = "no pain" and 100 mm = "the worst pain you can imagine."

9.1.2.5.2 Secondary Efficacy Variables

Subject's overall impression of the local anesthetic
Each subject would be asked to evaluate drug efficacy by answering "yes" or "no" to the following questions:

- Did the local anesthetic provide adequate pain relief for the vascular access procedure?
- Would you have local anesthesia administered using this form of anesthesia again if given the option?

9.1.2.6 Sponsor's Analysis Plan

Demographic, background and pre-procedure variables were to be summarized using descriptive statistics.

The primary efficacy variable, subject VAS rating of procedure-induced pain, was to be compared using paired t-tests or Wilcoxin signed rank tests. "If the results were not severely skewed, analysis of variance for a repeated measures design was potentially to be used so that the effects of center and randomization group could be tested."

Secondary efficacy variables intended to assess subjects' overall impression of the local anesthetic (Yes or No responses):

- "Did this local anesthetic provide adequate pain relief for the vascular access procedure?
- Would you have local anesthesia administered using this form of anesthesia again if given the option?

Subjects' ratings of "adequate anesthesia" and whether they would "use again" were to be compared using McNemar chi-square tests. Other secondary efficacy results (and evaluation of skin reaction results) were to be analyzed using Wilcoxin signed rank tests and sign tests. Summary findings were to be presented using descriptive statistics and graphical displays.

Adverse events were to be tabulated by type, frequency, onset, duration, outcome and relationship to treatment. Incidence of individual effects was to be compared between treatments using sign tests, and the numbers of occurrences overall were to be compared using Wilcoxin signed rank tests.

Sample Size Calculation

The protocol-specified sample size calculation stated (page 12):

> The estimated standard deviation and the estimated magnitude of the effect from data in Study SC-53-04 were used to aid in the design of this study. Sample size was determined based on the pilot study (SC-53-04) with parallel treatments. According to the applicant, the preliminary analysis of log transformed VAS scores had a root mean squared error of 1.2 and observed differences for 16 gauge needle (deactivated minus with heat) of 0.6 (30 minute application) and 1.0 (20 minute application). With 123 subjects per treatment group, there would be 95% power when the standard deviation equals 1.2 and the difference between heat and no heat is 0.55 on the log transformed scale.

9.1.2.7 Protocol Amendments and Changes in the Planned Analyses

One protocol amendment was made to SC-54-04, dated July 16, 2004. This amendment, made prior to enrollment of subjects, increased sample size from 200 to 250 subjects, and reduced application duration from 30 to 20 minutes.

9.1.2.8 Study Conduct

The study was conducted between August 4, 2004 and August 11, 2004. ZARS states (Section 9.6) that the study was conducted in accordance with Good Clinical Practice (GCP) Guidelines from the Declaration of Helsinki. The following measures were utilized in order to ensure data quality:

- On-site study monitoring at "suitable intervals"
- On-site comparison of CRFs with source documents (proportion not specified)
- Single data entry with 100% verification
- Answering of all data clarification or queries, with changes made to CRF recorded in a log
- Prior to unblinding the study, it was determined which subjects randomized would be included in the primary efficacy analysis

The Study Report does not indicate how many patients were screened in total. A 16-gauge angiocath was used for each of the 250 venipunctures performed during this study.

9.1.2.8.1 Investigators

The four SC-54-04 clinical sites were used for SC-53-04 and SC-55-04 as well. Three of these are operated by [redacted], a contract research organization with facilities across the United States. Three SC-54-04 investigators, [redacted]

Table 9.9: SC-54-04 Investigators and Clinical Sites

Investigator (All MD) Center	Site #	N
[redacted]	1	60
	2	70
	3	60
	4	60

Source: Sponsor Table 8.6.1, Complete Response Volume 17

9.1.2.8.2 Subject Disposition

All 250 subjects enrolled completed this single session study. There were no study dropouts or terminations.

Table 9.10: SC-54-04 Subject Disposition Summary

Subject Status	No.
Enrolled in Study	250
Received 20-minute Heated S-Caine Patch	122
Received 20-minute Non-Heated S-Caine Patch	128
Completed Study	250
Study Dropouts/Discontinuations	0

Source: Sponsor data listings, Appendix 14.1.2

9.1.2.8.3 Protocol Deviations and Violations

A total of 14 protocol deviations were reported in 10 of the 250 enrolled subjects. These are listed in Table 9.11 below. The most common of these involved failure to record weight, height or body temperature (n=7 total). Study patches were applied for twenty-one minutes in five subjects, three in the non-heated patch group, and two in the heated patch group. Also, two subjects were not randomized in the proper sequence. Only the last two incidents might possibly be considered to be noteworthy. For now, given the trial's failure (to support the application), and DSI's upcoming inspection of the SC-55-04 clinical sites, no further investigation is warranted.

Table 9.11: SC-54-04 Protocol Deviations and Violations

Type of Deviation	Total	Heat	No Heat
Study patches applied for 21 minutes instead of 20 minutes	5	3	3
Two subjects not randomized in sequential order at Site 1	2	1	1
Subject temperature not recorded	2	1	1
Weight not recorded	4	3	1
Height not recorded	1	1	0

Source: Sponsor data listings, Complete Response Appendix 16.2.3

9.1.2.9 Data Sets Analyzed

All 250 patients who were randomized and received study drug were included in all efficacy and safety analyses.

9.1.2.10 Demographics/Group Comparability/Skin Type

9.1.2.10.1 Demographics

SC-54-04 subject baseline demographic characteristics and skin type are summarized in Table 9.12 and Table 9.13, respectively. Like Study SC-55-04, Study SC-54-04 was conducted at clinical sites in Hawaii (n=120) and California (n=130). As in SC-55-04 subjects in the two treatment conditions were comparable with regard to all measured demographic characteristics. Also, as in SC-55-04, although not necessarily representative of the general US population there was reasonable representation by race, skin type and gender.

Table 9.12: SC-54-04 Subject Demographics

Characteristic	Heated n=122 (%)	Non-Heated n=128 (%)	Total N=250
Gender			
Male (%)	59 (48%0	63 (49%)	122 (49%)
Female (%)	63 (52%)	65 (51%)	128 (51%)
Age (years)			
Mean ± SD	39 ± 16	37 ± 14	38 ± 15
Range	18 - 79	18 - 72	18 - 79
Race			
Black (%)	10 (8%)	11 (9%)	21 (8%)
Caucasian (%)	52 (43%)	54 (43%)	106 (42%)
Hispanic (%)	13 (11%)	16 (12%)	29 (12%)
Asian (%)	25 (20%)	27 (21%)	52 (21%)
Other (%)	22 (18%)	20 (16%)	42 (17%)
Height (cm)			
Mean ± SEM	66.8 ± 4.0	66.0 ± 4.5	66.4±4.3
Range	54 - 76	50 - 75	50 - 76
Weight (kg)			
Mean ± SD	178.3 ± 53.5	179.6 ± 51.0	179.0 ± 52.1
Range	100-427	96-346	96 - 427

Source: Sponsor Table 8.11.1 (Complete Response Volume 20)

Table 9.13: SC-54-04 Subject Skin Type

	Heat n=122	No Heat n=128	Total N=250
Skin Type			
(I) Always Burns/Rarely Tans	4 (3%)	4 (3%)	8 (3%)
(II) Always Burns/Tans Minimally	19 (16%)	1 (9%)	30 (12%)
(III) Burns Moderately/Tans Gradually	44 (36%)	46 (36%)	90 (36%)
(IV) Burns Minimally/Always Tans	28 (23%)	33 (26%)	61 (24%)
(V) Rarely Burns/Tans Profoundly	20 (16%)	25 (20%)	45 (18%)
(VI) Never Burns/Deeply Pigmented	7 (6%)	9 (7%)	16 (6%)

Source: Sponsor Table 8.11.1, Appendix 14.1.2

9.1.2.10.2 Group Comparability: Medical Conditions and Baseline Exam

Subject medical conditions, as reported by the sponsor (in Appendix 16.2.6 of the SC-54-04 study report), are unlikely to have influenced this study's efficacy results. The medical conditions most frequently reported by subjects were allergies (28% of all subjects) and musculoskeletal conditions (24%). Medical conditions grouped together as "Other" (history of tonsillectomy, appendectomy or eye conditions), and respiratory conditions were each reported by 14% of subjects. Gastrointestinal conditions were reported by 12%. Cardiovascular, neurological, psychiatric, endocrine/metabolic, dermatologic, renal/genitourinary, immunologic, hematologic, and hepatic conditions were all reported (in decreasing order of frequency) by less than 10% of subjects. The conditions most likely to impact upon study results, (allergies and dermatologic conditions), as well as the others

most commonly reported (musculoskeletal, respiratory, gastrointestinal), were approximately equally distributed between the two treatment conditions.

Mean values of vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate and temperature) at screening were within normal range in all subjects (where recorded), and comparable in subjects between the treatment conditions. (Screening vital signs are listed in Appendix 16.2.7 of the final study report). Clinical laboratory values at screening were also all within, or very close to, normal range and means and medians of all values were similar between the two treatment conditions Appendices 16.2.8 and 16.2.9 of the study report).

9.1.2.11 Treatment Compliance

Study drug was administered by the investigator and subjects were monitored during each treatment. Pre-dose and post-dose efficacy assessments were performed by the investigator and the subject, but no information is provided (in the study report or datasets) about how many subjects failed to phone for the 24-48 hour post-procedure assessment.

9.1.2.12 Unplanned Analyses

The sponsor reports (SC-54-04 study report, page 25) that "some exploratory analyses that were not specified in the protocol were performed." For continuous demographic variables, a two-way analysis of variance was performed with fixed terms for center, treatment and center by treatment interaction, including unadjusted pairwise least square (LS) means to compare centers and to compare treatments within each center. As these analyses only addressed subject demographic data, and, as pointed out by the sponsor, were not pre-specified, they will not be described or discussed any further in this review.

9.1.2.13 Efficacy Results

The primary efficacy measure in this study was the subject's evaluation of pain (by 100-mm VAS) following their vascular access procedure. Mean VAS scores for the heated S-Caine treatment and the non-heated treatment were 22.1 ± 20.7 and 28.7 ± 22.8, respectively ($p > 0.40$). Median scores were 16.5 and 22.0, respectively. ZARS tested for statistical significance using a two-sample t-test to compare log-transformed mean VAS scores, as pre-specified in the statistical analysis plan ($p = 0.379$). SC-54-04 efficacy findings are summarized in Table 9.14 below.

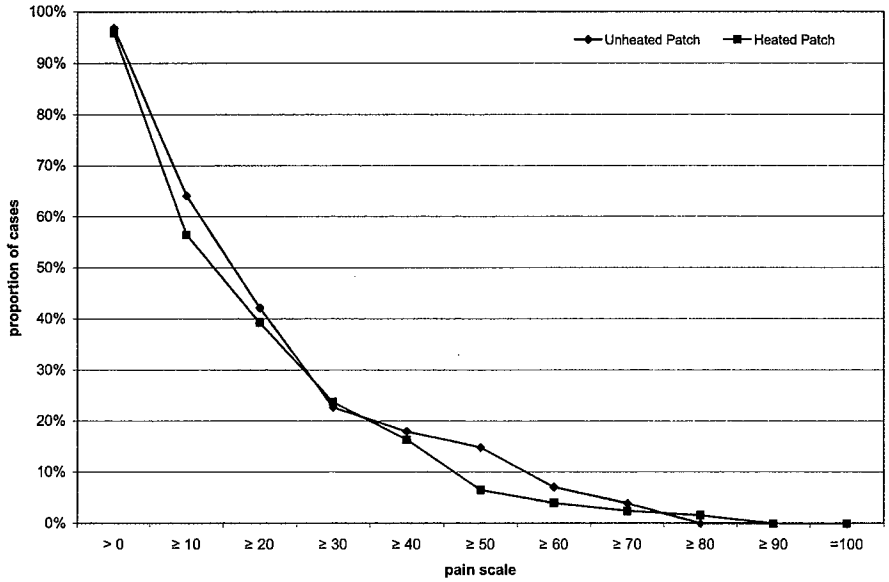
Table 9.14: SC-54-04 Efficacy Results by Treatment Group

	Treatment			
	Heated n=122	**Unheated** n=128	**All** N=250	**P-value**
VAS (mm)				
Mean	19.4	21.2	20.3	0.470[1]
SD	18.8	19.8	19.3	
Median	13.0	14.0	14.0	
Range	0 – 85	0 – 77	0 – 85	
Geometric Mean	12.5	14.1	13.3	0.379[2]
% Adequate	92 (75%)	87 (68%)	179 (72%)	0.209[3]
% Use Again	93 (76%)	91 (71%)	184 (74%)	0.391[3]

[1] Two-sample t-test (Dr. Buenconsejo) [2] Two-sample t-test (Sponsor) [3] Fisher's Exact test (Sponsor)
Sources: Tables 8.11.2 and 8.11.3 (Complete Response Volume 17), Dr. Buenconsejo's statistical review

Additional analysis performed by Dr. Buenconsejo, compared VAS scores between subjects treated with the heated patch and those treated with the unheated patch, using cumulative distributions. Higher VAS scores indicate greater (subject self-reported) pain. It appears that there is no difference between treatment groups, in the percentage of subjects reporting pain at or below each of the decile cutoffs. (See Figure 9.2 below)

Figure 9.2: SC-54-04 Subject Pain Profile, by Treatment Condition



Source: Dr. Buenconsejo, statistical review

9.1.2.14 Discussion of Efficacy Findings in Study SC-54-04

Taken as a whole, the SC-54-04 efficacy findings do not support ZARS' claim that a 20-minute application of S-Caine Patch containing an active heating element is superior to a 20-minute application of S-Caine Patch with an inactivated heating element, in reducing the pain caused by venipuncture with a 16-gauge angiocatheter. ZARS contends that SC-54-04 failed to demonstrate a difference between the heat-inactivated and the heated product because the inactivated patches were still generating heat when they were utilized in the trial. ZARS supports this explanation with data from two *in vitro* studies, IVC018-04 and IVC021-04. In both studies (conducted after SC-54-04) inactivated patches were found to be 'generating heat' days after initial exposure to air, according to ZARS. In IVC021-04 the temperature of inactivated patches "... began to rise after 3 days of storage and increased continuously after 7 and 14 days of storage." (SC-54-04 report, page 33)

This explanation for the failed study seems to be a farfetched, however. Temperature profile data have consistently shown (i.e., SC-52-04) patch temperature to peak within about 30 minutes of exposure to air, and then gradually decline towards baseline over the next several hours. Heat generation is expected to decline asymptotically, in the presence of a fixed atmospheric oxygen concentration. The magnitude of the exothermic reaction may have been diminished in SC-54-04, and its duration extended, once patches were resealed for shipment to investigators, however. The product may remain a few tenths of one degree above ambient temperature one week after first exposure to air, but this would not explain ZARS' findings. It is more likely that the efficacy improvement conferred by addition of heat is quite small, and its detection difficult.

9.1.3 Study SC-53-04: A Randomized, Double-Blind Pilot Study to Obtain Preliminary Information on the Variability and Magnitude of Effect of Heat, Application Time, and Stimulus Intensity on the Efficacy of the S-Caine Patch

9.1.3.1 Findings vs. Labeling Claims

This study found

9.1.3.2 Study Plan

The initial version of Protocol SC-53-04 was dated June 4, 2004 and submitted on June 7, 2004 (Sequence #21). No protocol amendments were made to SC-53-04.

9.1.3.3 Population, Design, and Objectives

The protocol-specified objectives of the study were:

1. "To obtain preliminary information on the variability and magnitude of effect of heat, application time and stimulus intensity on the efficacy of the S-Caine Patch."
2. "To monitor the nature and frequency of adverse events associated with the safety of an S-Caine Patch."

The protocol was designed as a multicenter study in approximately 80 adult subjects. Potential subjects who met entry criteria would be invited to participate. Three factors were to be varied; heated patch vs. unheated patch, 16-gauge vs. 18-gauge catheter, and 20-minute vs. 30-minute application duration. Subjects were to be randomized equally across eight treatment conditions.

The non-heated patches were to be identical in composition to the heated S-Caine Patch (excipients, adhesives, heating element), but heating elements were to have been inactivated. The protocol did not, however, describe the procedure for patch inactivation, or the duration for its exposure to air. Patch application sites were to be randomized (1:1) to the right or left antecubital area.

All subjects were to undergo antecubital venipuncture, after patch application and removal.

Efficacy evaluations would consist of subject VAS ratings of venipuncture-induced pain, and Yes/No responses to two "overall impression" questions. Subjects were to be dismissed after completion of efficacy evaluations. Subjects were to be instructed to inspect the treatment site 24-48 hours following drug removal, and to telephone the study site if they believed a skin reaction had developed.

Table 9.15: Study SC-53-04 Schedule of Events

Measurement/Evaluation	Day of Procedure	24-48 Hours After Drug
Informed Consent	X	
Subject Eligibility	X	
Medical History	X	
Physical Exam	X	
Vital Signs Pre and Post Treatment	XX	
Medication History	X	
Skin Type Assessment	X	
Study Drug Application (20 minutes)	X	
Evaluation of Skin Reactions	X	X
Vascular Access Procedures	X	
Efficacy Evaluations		
Subject Evaluation Using VAS	X	
Investigator Evaluation of Subject's Pain	X	
Observer Evaluation of Subject's Pain	X	
Investigator Overall Impression	X	
Adverse Events	X	
Subject Assessment of Application Site		X
Study Termination Report		X

Source: Protocol SC-53-04 in Appendix 16.1.1, Complete Response Volume 15

The inclusion criteria were to be:
1. Male or female patients 18 years or older.
2. No known allergies to lidocaine, tetracaine or other local anesthetics.
3. Subject had signed and dated the written informed consent.

The exclusion criteria were to be:
1. Known sensitivity to any component of the test materials (e.g., [redacted] adhesives).
2. Prescription strength analgesic pain medication use during the preceding 24-hour period.
3. Damaged, denuded or broken skin at either designated patch site.
4. Pregnant or breastfeeding.

9.1.3.4 Treatment Summary

Study Medication

Both S-Caine Patches (heated and non-heated) were to be supplied by, and manufactured under the direction of ZARS, Inc., Salt Lake City, Utah.

Active Drug components used in the S-Caine Patch were to be supplied by:

Tetracaine Supplier
Lidocaine Supplier [redacted]

Upon meeting eligibility criteria, patients would be assigned the next available sequential subject number. Treatments would be double-blind, and assigned based on a predetermined computer-generated randomization code, so that one-half of the subjects would receive the heated S-Caine Patches, and one-half would receive the non-heated S-Caine Patches. Subjects were to receive a

single 20-minute patch application to their right antecubital surface, prior to undergoing venipuncture.

The CRF for recording study medication would record the patient identification number, skin type (I – VI), patch application and removal times for each arm, and the post-treatment skin assessment. Study drug labels (both) would be affixed to each subject's CRF as well.

Concomitant Medications
Use of any prescription strength analgesic medication during the 24-hour period preceding the study would result in subject exclusion. No other medication use would preclude study participation, however. All concomitant treatments were to be recorded on the CRFs.

9.1.3.5 Efficacy Assessment

9.1.3.5.1 Primary Efficacy Variable

The primary efficacy variable was to be the subject's evaluation of pain caused by insertion of a 16 gauge, one-inch catheter, as rated on a 100 mm VAS where 0 mm = "no pain" and 100 mm = "the worst pain you can imagine."

9.1.3.5.2 Secondary Efficacy Variables

Subject's overall impression of the local anesthetic
Each subject would be asked to evaluate drug efficacy by answering "yes" or "no" to the following questions:

- Did the local anesthetic provide adequate pain relief for the vascular access procedure?
- Would you have local anesthesia administered using this form of anesthesia again if given the option?

9.1.3.6 Sponsor's Analysis Plan

Demographic, background and pre-procedure variables were to be summarized using descriptive statistics. An exploratory analysis of the primary efficacy variable, subject VAS rating of procedure-induced pain, was to be performed, "in order to estimate variability and effect size."

Sample Size Calculation
The protocol included no formal calculation for estimation of sample size. Protocol Section 9.7.2 (Determination of Sample Size) stated "The sample size of 10 per heat/no heat by duration of application (20 or 30 minutes) by pain stimulus group (16- or 18-gauge) group is typical for a pilot study."

9.1.3.7 Protocol Amendments and Changes in the Planned Analyses

No formal protocol amendments were made to SC-53-04.

9.1.3.8 Study Conduct

The study was conducted between July 6, 2004 and July 10, 2004. Investigator registration information was not submitted until August 3, 2004, however, for all four investigators. ZARS states (in Study Report Section 9.6) that SC-53-04 was conducted in accordance with Good Clinical Practice (GCP) Guidelines and utilized the following measures to assure data quality assurance:

- On-site study monitoring at "suitable intervals"

- On-site comparison of CRFs with source documents (proportion not specified)
- Single data entry with 100% verification
- Answering of all data clarification or queries, with changes made to CRF recorded in a log
- Prior to unblinding the study, it was determined which subjects randomized would be included in the primary efficacy analysis

The Study Report does not indicate how many patients were screened in total. As noted above, 250 patients were to be enrolled.

A 16-gauge angiocatheter was used for each of the 250 venipunctures performed during this study.

9.1.3.8.1 Investigators

The four clinical sites employed for SC-53-04 were the same ones used for SC-54-04 and SC-55-04. Three of these are operated by [redacted] a contract research organization with facilities across the United States. Three SC-53-04 investigators, [redacted]

Table 9.16: SC-53-04 Investigators and Clinical Sites

Investigator	Center	Site #	N
[redacted]		1	20
		2	26
		3	30
		4	12

Source: Sponsor Table 8.6.1 and Appendix 16.2, Complete Response Volume 15

9.1.3.8.2 Subject Disposition

All 250 enrolled subjects completed. There were no study dropouts or terminations.

Table 9.17: SC-53-04 Subject Disposition Summary

Subject Status	No.
Enrolled in Study	88
Heat-20 minute-16G	10
Heat-20 minute-18G	9
Heat-30 minute-16G	13
Heat-30 minute-18G	11
No Heat-20 minute-16G	10
No Heat-20 minute-18G	12
No Heat-30 minute-16G	11
No Heat-30 minute-18G	12
Completed Study	88
Study Dropouts/Discontinuations	0

Source: Sponsor data listings, Appendix 16.1.2 Vol. 15

9.1.3.8.3 Protocol Deviations and Violations

ZARS excluded eight subjects, all assigned to the unheated patch condition, from the efficacy analysis; 2101, 2201, 2203, 2204, 3102, 3103, 3107 and 3202. According to ZARS, during the first enrollment day 'sponsor representatives' and the study pharmacist noted that the 'no heat' patches

were, in fact, still giving off some heat. Enrollment was discontinued after the first sixteen subjects had been enrolled; eight had received presumably inactivated patch, and eight had received heated patch (ten subjects had been enrolled at site number three and six at site number two).

ZARS described SC-53-04 as a pilot study, however, and chose to include only a brief, vague, statistical analysis plan. Still, exclusion of all (first day) subjects from only one of the two treatment conditions was not appropriate. The efficacy data have been compromised.

The other seven protocol deviations were reported in six of the remaining subjects. Protocol deviations are listed in Table 9.18 below.

Table 9.18: SC-53-04 Protocol Deviations and Violations

Type of Protocol Deviation	Heat (n=43)	No Heat (n=45)
Excluded from efficacy analysis	0	8
Study patches applied for longer than protocol specified	4	0
Subject not given study handout	0	2
Subject temperature not recorded	0	1

Source: Sponsor data listings, Complete Response Appendix 16.2.3

The most common deviation (aside form the exclusions described above) involved patch application for longer than specified by protocol. Of note, all four such instances occurred in heated-patch subjects, potentially biasing efficacy results in favor of the heated patch.

9.1.3.9 Data Sets Analyzed

All 88 patients who were randomized and received study drug were included in the safety analysis, but eight subjects, all from the 'no heat' condition, were excluded from ZARS' efficacy analysis.

9.1.3.10 Demographics/Group Comparability/Skin Type

9.1.3.10.1 Demographics

Subject demographic characteristics, and baseline height and weight are summarized in Table 9.19, and subject skin type in Table 9.20 below. Review of these tables suggests that the subjects were comparable across treatment conditions, with regard to all measured characteristics, and that there was a reasonable representation of genders and races in the study.

Table 9.19: SC-53-04 Subject Demographics

Characteristic	Heated n=43	No-Heat n=45	Randomized N=88	Evaluable N=80
Gender				
Male (%)	24 (56%)	23 (51%)	47 (53%)	43 (54%)
Female (%)	19 (34%)	22 (49%)	41 (47%)	37 (46%)
Age (years)				
Mean ± SD	42.7 ± (14.1)	39.2 ± (13.8)	40.9 ± 14.1	41 ± 14
Range	18 - 78	18 - 67	18 - 78	
Race				
Black (%)	1 (2%)	2 (4%)	3 (3%)	3 (4%)
Caucasian (%)	29 (67%)	25 (56%)	54 (61%)	46(58%)
Hispanic (%)	1 (2%)	4 (9%)	5 (6%)	5 (6%)
Asian (%)	10 (23%)	13 (29%)	23 (26%)	23 (29%)
Other (%)	2 (5%)	1 (2%)	3 (3%)	3 (4%)
Height (inches)				
Mean ± SEM	67.4 ± (3.4)	66.4 ± 4.0	66.4±4.3	66.4±4.3
Range	61 - 75	53 - 74	---	---
Weight (lbs)				
Mean ± SD	178 ± 54	180 ± 51	179 ± 52	179 ± 52
Range				

Source: Sponsor Table 15.11.1 (Complete Response Volume 15), Dataset DEMO.XPT (53-04)

Table 9.20: SC-53-04 Subject Skin Type

Skin Type	Heat n=43	No Heat n=45	Random. N=88	Evaluable N=80
(I) Always Burns/Rarely Tans			5 (6%)	3 (4%)
(II) Always Burns/Tans Minimally			15 (17%)	14 (18%)
(III) Burns Moderately/Tans Gradually			30 (34%)	25 (31%)
(IV) Burns Minimally/Always Tans			25 (28%)	25 (31%)
(V) Rarely Burns/Tans Profoundly			13 (15%)	13 (16%)
(VI) Never Burns/Deeply Pigmented			0	0

Source: Sponsor Table 11.1, Appendix 14.1.2

9.1.3.10.2 Group Comparability: Medical Conditions

The medical conditions reported by SC-53-04 subjects were unlikely to have influenced study findings. The medical conditions most frequently reported by subjects were allergies (40% of all subjects), "Other conditions" (history of tonsillectomy, appendectomy or eye condition) in 28%, and musculoskeletal conditions (28%). Other commonly reported conditions were metabolic/endocrine (17%), respiratory (17%), gastrointestinal and reproductive (16% each), cardiovascular and dermatologic (15% each), and neurological/CNS (14%).

Mean values of vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate and temperature) at screening were predominantly within normal range, and similar across

treatment groups. Mean and median values of clinical laboratory values at screening were all normal and were similar across treatment groups as well.

9.1.3.11 Treatment Compliance

Study drug was administered by the investigator and subjects were monitored during treatment. All subjects completed the post-treatment efficacy assessments; VAS rating of venipuncture induced pain, and Yes/No responses to the two questions described above.

9.1.3.12 Unplanned Analyses

Although ZARS did not perform any unplanned analyses, eight subjects (all from the same treatment condition) were excluded from the efficacy analysis, as described above.

9.1.3.13 SC-53-04 Efficacy Findings

SC-53-04 efficacy findings, as reported by the sponsor and by Dr. Buenconsejo are summarized in Table 9.21 and Table 9.22, respectively.

Table 9.21: SC-53-04 Efficacy Findings

	Total	Heat 20 min 16-g	Heat 20 min 18-g	Heat 30 min 16-g	Heat 30 min 18-g	No Heat 20 min 16-g	No Heat 20 min 18-g	No Heat 30 min 16-g	No Heat 30 min 18-g
All Patients (N)	**88**	**10**	**9**	**13**	**11**	**10**	**12**	**11**	**12**
VAS									
Mean	17.9	17.0	10.2	16.7	13.8	30.4	23.8	22.5	8.7
STD	20.2	18.5	14.6	16.0	16.8	17.4	29.9	24.9	14.2
Median	10.5	9.0	4.0	14.0	9.0	24.0	14.0	12.0	3.0
Range	(0 – 97)	(0 – 63)	(1 – 40)	(0 – 52)	(0 – 53)	(11 – 65)	(0 – 97)	(2 – 81)	(0 – 51)
Geo. Mean	10.1	11.2	6.1	11.0	7.8	27.4	10.3	14.1	5.0
% Adequate	74%	80%	100%	62%	91%	30%	67%	73%	92%
% Again	70%	80%	89%	54%	100%	20%	67%	64%	92%
Evaluable Patients	**80**	**10**	**9**	**13**	**11**	**8**	**11**	**8**	**10**
VAS									
Mean	18.7	17.0	10.2	16.7	13.8	34.0	24.0	28.9	10.1
STD	20.9	18.5	14.6	16.0	16.8	17.5	31.3	26.7	15.3
Median	10.5	9.0	4.0	14.0	9.0	32.5	11.0	23.0	5.0
Range	0 – 97	0 – 63	1 – 40	0 – 52	0 – 53	15 – 65	0 – 97	5 – 81	0 – 51
Geo. Mean	10.5	11.2	6.1	11.0	7.8	31.2	9.6	20.3	5.8
% Adequate	73%	80%	100%	62%	91%	13%	73%	63%	90%
% Again	70%	80%	89%	54%	100%	13%	73%	50%	90%

Dr. Buenconsejo retabulated the efficacy data, including results from the eight excluded subjects. She points out that mean VAS score among those excluded from the study are slightly lower than the mean VAS score among those in the evaluable population, as a whole. The percentage of subjects who had 'adequate anesthesia' and percentage of subjects who would 'use the patch again' appeared to increase slightly as well.

Table 9.22: SC-53-04 Efficacy Findings

		Patch		Duration		Needle Gauge		Gender	
	Total	With Heat	No Heat	20 min	30 min	16G	18G	Female	Male
All Patients (N)	**88**	**41**	**47**	**41**	**47**	**44**	**44**	**41**	**47**
VAS									
Mean	17.9	14.7	20.9	20.8	15.3	21.3	14.4	16.6	19.0
STD	20.2	16.1	23.3	22.1	18.3	19.5	20.6	22.6	18.1
Median	10.5	8.0	12.0	15.0	8.0	15.0	5.0	8.0	14.0
Range	0 – 97	0 – 63	0 – 97	0 – 97	0 – 81	0 – 81	0 – 97	0 – 97	0 – 67
Geo. Mean	10.1	8.9	11.4	11.9	8.8	14.4	7.1	8.1	12.3
% Adequate	74%	81%	67%	68	79	61	86	76	72
% Again	70%	79%	62%	63	77	55	86	71	70
Evaluable Patients	**80**	**37**	**43**	**38**	**42**	**39**	**41**	**37**	**43**
VAS									
Mean	18.7	14.7	23.5	21.0	16.7	22.8	14.9	17.4	19.9
STD	20.9	16.1	24.7	22.9	18.9	20.1	21.1	23.5	18.5
Median	10.5	8.0	15.0	13.0	9.5	16.0	6.0	8.0	15.0
Range	0 – 97	0 – 63	0 – 97	0 – 97	0 – 81	0 – 81	0 – 97	0 – 97	0 – 67
Geo. Mean	10.5	8.9	12.7	11.5	9.7	15.5	7.3	8.3	12.9
% Adequate	73%	81%	62%	68	76	56	88	76	70
% Again	70%	79%	59%	66	74	51	88	70	70

Dr. Buenconsejo also performed analyses to assess differences in the mean VAS score between subjects receiving the heated patch and subjects receiving the unheated patch. The higher the mean VAS scores, the greater the pain the subjects had scored. It appears that a higher proportion of subjects receiving unheated patch had more pain compared to subjects receiving heated patch (Figure 9.3 and Figure 9.4).

Figure 9.3: Patient Pain Profile (Study SC-53-04) – All Subjects Randomized

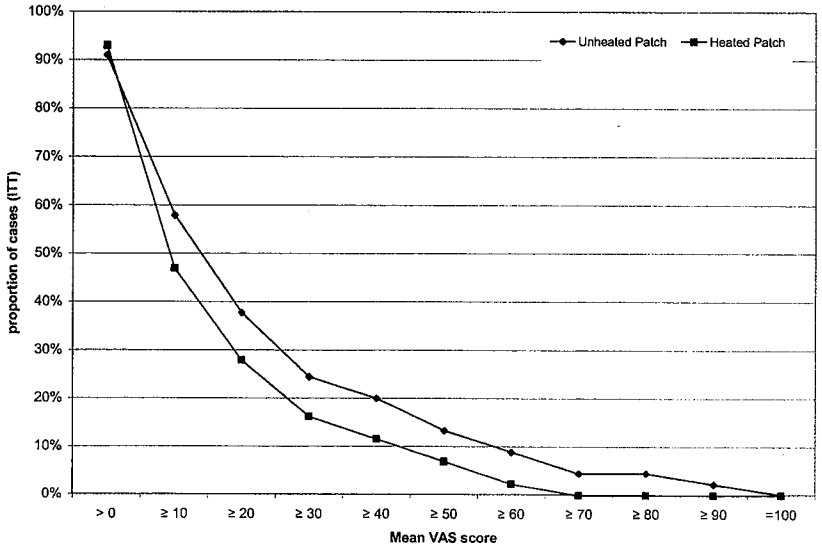
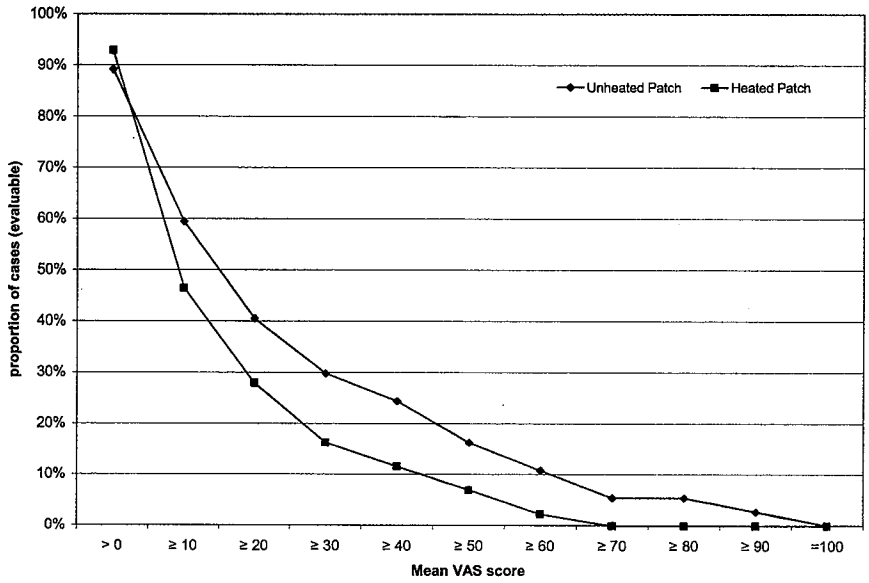


Figure 9.4: Patient's Pain Profile (Study SC-53-04) – All Evaluable Subjects



9.1.3.14 Discussion of Efficacy Findings in Study SC-53-04

ZARS conducted SC-53-04 in order to help determine what needle gauge and application duration to employ in their 'definitive' heating component efficacy study (SC-54-04). That is, the intent seems to have been to maximize the chances of demonstrating an efficacy difference between the heated and the non-heated product, by optimizing two other readily controllable factors. Interestingly, however, Study SC-54-04 (and subsequently SC-55-04) appears not to have been designed taking into account the SC-53-04 findings. The SC-53-04 data suggest that a 30-minute application period would have been preferable to a 20-minute one, yet the subsequent studies utilized the shorter treatment duration. Practical concerns may have dictated use of the shorter application period, in this particular example. In any case, overall the SC-53-04 data appear to suggest that VAS scores were lower in subjects treated with the heated patch than in those treated with the non-heated version (14.7 vs. 20.9 from Table 9.22 above).

The SC-53-04 statistical analysis plan called for only "... an exploratory analysis of VAS scores" to aid in the design of additional studies. Inferential statistics were not to be reported, and exclusion of all (first day) subjects from only one of the two treatment conditions compromises the efficacy data.

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9.2 Trials Discussed in Detail in First Cycle Clinical Review

9.2.1 Trials Fulfilling 21 CFR 300.50 *Fixed-combination prescription drugs*

9.2.1.1 Heating Element Contribution to Efficacy (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 9.23 (Sponsor Table 9.1, NDA Volume 36).

Table 9.23: SC-27-01 Laser Settings

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, NDA Volume 36

Upon completion of laser stimulation (both drug application 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."

The results failed to demonstrate any efficacy difference between the two treatments. Table 9.24 below summarizes findings for subject-rated efficacy measures, including the primary efficacy variable. Secondary outcome measure findings were also non-supportive.

Table 9.24: SC-27-01 (± Heating Element) Subject Pain Evaluations

	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	0.634[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, NDA Volume 36

The sponsor attributed this failure to study design issues. Specifically, the laser stimulus "was thought not to have produced "pain levels sufficient to discriminate between the two patches." Both treatments resulted in very low VAS scores, and most subjects, in both treatment conditions, reported "No Pain" for the secondary outcome measures.

The sponsor explained the rationale for laser setting choice, after-the-fact, as follows:

> "..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 did not change the fact that the S-Caine Patch heating element had not been demonstrated to have any effect on product efficacy. (All other S-Caine Patch clinical trials had evaluated patches with functioning heating elements.)

9.2.1.2 Study SC-41-03 (Drug/Drug Combination)

Study SC-41-03 was a randomized, double-blind study that utilized 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 adults. 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 (all with heating component);

- S-Caine Patch (70 mg lidocaine + 70 mg tetracaine)
- Lidocaine patch 70 mg
- Tetracaine patch 70 mg
- Placebo patch (olive oil substituted for active drug)

Patch application site was rotated in the same order for all patients (Session 1 right AC, session 2 left AC, session 3 right AC, session 4 left AC). Eighty subjects enrolled (of 80 planned), and all completed all four study sessions.

The primary efficacy variable was subject VAS (100-mm) evaluation of venipuncture-induced pain (18-gauge angiocatheter). VAS scores were initially compared using the protocol-specified 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).

The mean VAS scores for subjects treated with S-Caine, lidocaine, tetracaine and placebo were 7.8 (± 11.6), 19.4 ± 16.6, 23.0 ± 17.8 and 25.1 ± 19.4, respectively. All pairwise comparisons were statistically significant ($p<0.001$). SC-41-03 efficacy results are summarized in Table 9.25 below. SC-41-03 appears to have adequately demonstrated that a 30-minute application of the S-Caine Patch is more effective than 30-minute heated patch applications of lidocaine, tetracaine or placebo.

Table 9.25: SC-41-03 VAS Scores Following Venipuncture

	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, NDA Volume 41

9.2.1.3 Study SC-28-01 (Drug/Drug Combination)

Study SC-28-01 was similar to SC-41-03, except for the painful stimulus and outcome measure. S-Caine Patch was compared to its two component drugs, and to placebo (30-minute applications of heated patch formulations) in 48 healthy adult volunteers. The only efficacy measure employed was subject 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. No differences were found between the treatment groups.

9.3 Previous Efficacy Findings: 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. Studies 11-01, 24-01 and 31-01 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 only subjects ages 65 and up. The vascular access procedures performed were, in actuality, venipuncture with standard gauge 20-gauge and 21-gauge catheters, except in SC-05-99 in which subjects underwent intravenous cannulation with 22-gauge catheters. Table 9.26, modified from Table 4.1 in NDA Volume 26, summarizes subject-rated outcome measures for these four studies.

Table 9.26: Efficacy in Previous Adult 'Vascular Access Procedure' Trials

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 Source: Clinical reviewer

9.4 Previous Efficacy Findings: 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-only subjects, and in adults of all ages, respectively. Table 9.27, modified from Table 4.2 (NDA Volume 26) summarizes subject-reported outcomes for these studies.

Table 9.27: Previous Efficacy Findings, 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
[c] 03-99 & 07-99 asked "Did the anesthetic eliminate pain?"
23-01 & 22-01 asked "Did the anesthetic provide adequate pain relief?"
[d] Mantel-Haenszel summary chi-square Source: Clinical reviewer

9.5 Previous Pediatric Efficacy Findings

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 9.28 summarizes patient-reported primary, and investigator-rated secondary efficacy results from these three studies.

Table 9.28: 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
Source: NDA 21-623 Volume 31, Tables 12.3, 12.4, 12.5

Table 9.29 below summarizes efficacy findings from pediatric trials in which developmental patch formulations were employed.

Table 9.29: 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: NDA Table 12.4, Volume 31

Table 9.30: 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: NDA Table 12.3, Volume 32

Table 9.31: Efficacy Findings, 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: Clinical reviewer

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. There do not appear to be significant differences between genders in S-Caine Patch safety or efficacy. Table 10.1 and Table 10.2 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, NDA 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 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.

A total of 139 (9.5%) of subjects who received the final S-Caine Patch formulation (heated + non-heated) in controlled trials were 65 years or older. Fort-one (3.7%) subjects who received the final heated patch formulation in controlled trials were 75 years or older. Over 12% of subjects enrolled in SC-42-03 (repeat exposure sensitization/irritation) were older than 65. Clinical pharmacology study SC-51-04 enrolled 12 (of 48 total) subjects ages 65 and older. The only other 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. Clinical pharmacology 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.

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, according to ZARS. 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 three of thirty planned subjects as of the 12/31/2004.

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 original 120-day safety update included no new information or data. The 120-day safety update contained 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 three of thirty planned subjects, by the time of NDA submission. The Division had agreed to allow completion of SC-33-02 as a Phase 4 commitment.

11 Overall Assessment

11.1 Conclusions

S-Caine Patch efficacy in the adult population for venipuncture, and for superficial excision and shave biopsy [redacted], had been demonstrated previously. Geriatric and pediatric findings also suggested efficacy for similar indications, though less persuasively. The geriatric findings may have been attributable to lower pain scores, across all treatment conditions, for geriatric subjects. The pediatric efficacy findings were 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 S-Caine Patch heating element appears to contribute marginally to product efficacy. Although safety data is somewhat limited (mostly single-dose 20 to 30 minute exposures), the heating element is highly unlikely to contribute any incremental risk to the overall safety profile of the product. 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, however.

While the sponsor's choice of 20 and 30 minute doses (patch application) periods seems appropriate,

[redacted]

11.2 Recommendation on Regulatory Action

Product approval is recommended. There are no outstanding approvability issues at the end of the second review cycle. Neonatal safety concerns are to be addressed in a Phase 4 commitment.

11.3 Recommendation on Postmarketing Actions

11.3.1 Risk Management Activity

Risk management planning is not necessary at this time. 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.

11.3.2 Phase 4 Commitments

Neonatal Safety

The sponsor had previously agreed to complete a study evaluating S-Caine Patch/Peel safety in the neonatal population, including premature infants down to 34 weeks estimated gestational age (Study SC-33-02). Enrollment began prior to the first cycle NDA review. ZARS had anticipated difficulties and delays in recruiting adequate numbers (approximately 30) of hospitalized premature infants and newborns, however. At the end-of-phase 2 meeting ZARS requested, and received,

Division agreement with their proposal to complete this trial as a Phase 4 commitment. As of 3/1/05 no neonates had been enrolled, however, because of ongoing recruitment difficulties. (Three newborns were evaluated during development for the S-Caine Peel, however.) ZARS has decreased the number of anticipated subjects to nine. Study completion is now anticipated in 12/2006.

11.3.3 Marketing Restrictions

At this time there are no grounds for marketing restrictions on the S-Caine Patch. No marketing restrictions are anticipated.

11.4 Labeling and Trade Name

11.4.1 Package Insert

Discussion at the upcoming labeling meetings should address the points outlined below.

Description
The S-Caine™ Patch (lidocaine and tetracaine topical patch) 70 mg/70 mg consists of a thin, uniform layer of a local anesthetic formulation with an integrated, oxygen-activated heating component [redacted] The drug formulation is an emulsion in which the oil phase is a eutectic mixture of lidocaine 70mg and tetracaine 70mg.

- [redacted]

  It would be more appropriate to state that the product "... consists of a thin, uniform layer of a local anesthetic formulation with an integrated, oxygen-activated heating component intended to enhance the delivery of local anesthetic."

Indication and Usage
ZARS proposes the following "Indications and Usage" label section:

[redacted]

- The second paragraph need not be included in the Indications and Usage section.
- Whether or not the product is labeled broadly (i.e. for dermal analgesia) or for specific types of dermal procedures, claims of efficacy for [redacted] as previously proposed, were unwarranted. These statements were misleading. The term [redacted] evaluated by the sponsor, or for which the S-Caine Patch is likely to offer any benefit ([redacted]). References to "venipuncture" or perhaps to "superficial venous access" are more appropriate.

Dosing and Administration

- [redacted]

Clinical Studies

- The "Clinical Studies" label section includes a considerable amount of non-informative detail. Each positive trial is described, along with primary and secondary efficacy findings.

11.4.2 Proposed Trade Name

ZARS anticipated use of the trade name 'S-Caine Patch' for this product. Office of Drug Safety (ODS) reviewers considered 'S-Caine' to be an appropriate trade name, from a promotional perspective. Concerns were raised, however, that 'S-Caine' might be considered to be an abbreviation of the existing trade name 'Sensorcaine.' After these safety concerns were communicated to ZARS several alternative names were proposed.

[redacted]

Office of Drug Safety objected to these names on similar grounds. The only name proposed by ZARS that has been considered to be acceptable is 'Synera.' ZARS now plans to use the trade name Synera.

11.5 Comments to Applicant

The action letter should specify that ZARS has agreed to complete, as a Phase 4 commitment, a clinical pharmacology study in neonates and infants (in order to assess systemic exposure to lidocaine and tetracaine).

12 Appendix

12.1 Communication with sponsor during first review cycle

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.

12.2 Communication with sponsor during second review cycle

A teleconference was held on June 9, 2005 during which ZARS was asked to describe in greater detail (than the protocol) the protocol deviations mentioned in the SC-55-04 final study report. ZARS was also asked to describe the measures employed to ensure investigator blinding in SC-55-04 investigator blinding.

Three items were discussed during a June 14, 2005 teleconference with ZARS.

- Does ZARS anticipate using the product name 'Synera' or 'Synera Patch' (now that the trade name Synera has been accepted by our Office of Drug Safety)?
  Response: ZARS will use the trade name 'Synera' without the word 'patch'

- The last paragraph of the DESCRIPTION section of the proposed label contains the sentence

  [redacted]

  Response: These numbers were based upon the data from Study SC-52-04

- How does ZARS anticipate marketing this product? More specifically, does ZARS anticipate promoting the product for use by patients themselves? That is, will the product be available in retail pharmacies, so that office-based practitioners will be able to prescribe the product to their outpatients?
  Response: ZARS has (or will) license the product to Ferndale Laboratories, Inc. (formerly J.F. Hartz Company). Because Ferndale employs a sales force of approximately 75-80, initial marketing will concentrate on pediatric hospital based physicians and clinics (i.e.., pediatric oncology). Dr. Ashburn stated that marketing to office-based practitioners and retail pharmacies might be contemplated "perhaps in the long run," but was not part of Ferndale's short-term plan, to his knowledge. Ferndale's web site states that the company specializes in products, both OTC and Rx, that help treat dermatological conditions (i.e., eczema, psoriasis, inflamed/irritated/dry skin, pain and itching), as well as products for nasal congestion, allergies and constipation.

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
6/21/05 02:55:15 PM
MEDICAL OFFICER

Bob Rappaport
6/21/05 03:45:30 PM
MEDICAL OFFICER
I concur with Dr. Josefberg's conclusions and recommendation for approval

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	February 4, 2004
DRUG:	S-Caine Patch (lidocaine 70 mg and tetracaine 70 mg, topical patch)
NDA:	21-623
NDA Code:	Type 4S NDA
SPONSOR:	ZARS, Inc.
INDICATION:	[redacted]

ZARS, Inc. has submitted NDA 21-623 in support of marketing approval for their topical patch formulation consisting of lidocaine 70 mg and tetracaine 70 mg.

Review of the CMC portion of this application was completed by Ravi S. Harapanhalli, Ph.D. Review of the pharmacology and toxicology data presented in this application was completed by R. Daniel Mellon, Ph.D. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by Srikanth C. Nallani, Ph.D. A statistical review and evaluation was completed by Milton C. Fan, Ph.D. Thomas Permutt, Ph.D., Team Leader for the Biostatistics review team, provided a secondary review of the statistical issues. Consultation on this application was obtained from the Microbiology team, the Division of Drug Marketing, Advertisement and Communications, and the Office of Drug Safety. The sponsor has submitted four studies in support of efficacy. A detailed review of these studies and of the safety of the product was performed by Howard Josefberg, M.D., with oversight by Nancy Chang, M.D., Medical Team Leader for the anesthetic drug products.

Efficacy:

The sponsor denoted four studies (SC-24-01, SC 23-01, SC-20-01 and SC-21-01) as pivotal in support of a finding of efficacy. SC-11-01, SC-31-01, SC-22-01, SC-40-02, SC-41-03, SC-28-01, and SC-27-01 were also designed to assess features related to the efficacy of the to-be-marketed formulation of the S-Caine patch. Six studies were performed with developmental formulations and were submitted as supportive evidence of efficacy of the final formulation.

Study SC-24-01 (24)

This was a two-center, randomized, placebo-controlled, double-blind, "crossover" study comparing S-Caine Patch to placebo in healthy, adult, volunteer subjects. Twenty-gauge angiocatheters were inserted at the S-Caine Patch site and the placebo site after concurrent administration of the active and placebo patches in a randomization pattern designating one-half of the active patches to right arm and one half to left arm, and the opposite pattern for the placebo patches.

The primary efficacy variable was defined as the patient's assessment of pain from the catheter insertion measured on a 100 mm VAS.

Secondary efficacy measures included:

- Subject's overall impression of the local anesthetic using "yes" or "no" answers to queries regarding adequacy of pain relief, and
- Whether they would consider having anesthesia of this "form" again;
- Investigator and observer evaluations of subjects' pain on a 4-point categorical scale;
- Investigators' overall impression of the anesthetic using "yes" or "no" answers to a query regarding the adequacy of the anesthesia for the procedure; and

Sixty subjects were enrolled in the study, 40 receiving the prespecified (20 min.) application of the S-Caine Patch and 39 of those 40 receiving 20-minute applications of the placebo patch. The other 20 subjects had the drug and placebo patches applied for 30 minutes each, were considered protocol violators by the sponsor, and were not included in their analyses of efficacy.

The mean VAS scores for the S-Caine group and the placebo group were 12 mm and 29 mm, respectively. The median scores for the S-Caine group and the placebo group were 5 mm and 28 mm, respectively. The VAS scores were lower with the S-Caine Patch than the placebo patch for 49% of subjects, and VAS scores were lower with placebo patch than the S-Caine Patch for 17% of subjects. Based on a Wilcoxin Signed Rank test, this represented a statistically significant treatment effect for the study drug with a p-value of

less than 0.001. Each of the secondary outcome measures also demonstrated a statistically significant treatment effect for the S-Caine Patch.

Study SC-23-01 (23)

This was a three-center, randomized, placebo-controlled, double-blind, parallel-group study comparing S-Caine Patch to placebo in adult patients undergoing minor dermatologic procedures. Patients scheduled for a shave biopsy or excision of a dermal lesion were randomized and underwent a 30-minute patch administration prior to the procedure.

The primary efficacy variable was defined as the patient's assessment of pain from the catheter insertion measured on a 100-mm VAS.

Secondary efficacy measures included:

- Subject's overall impression of the local anesthetic using "yes" or "no" answers to queries regarding adequacy of pain relief, and
- Whether they would consider having anesthesia of this "form" again;
- Investigator and observer evaluations of subjects' pain on a 4-point categorical scale;
- Investigators' overall impression of the anesthetic using "yes" or "no" answers to a query regarding the adequacy of the anesthesia for the procedure; and

Forty-five patients were randomized to the S-Caine group and 49 to the placebo group. All patients completed the study.

The median VAS scores for the S-Caine group and the placebo group were 5 mm and 31 mm, respectively. This represented a statistically significant difference with a p-value of less than 0.001. The secondary outcome measures also demonstrated a statistically significant treatment effect for the S-Caine Patch.

Study SC-20-01 (20)

This was a two-center, randomized, placebo-controlled, double-blind, parallel-group study in pediatric patients comparing the S-Caine Patch to a placebo patch. Patients scheduled for vascular access procedures (venipuncture or IV cannulation) were randomized and underwent a 20-minute patch administration prior to the procedure.

The primary efficacy variable was stratified based on the patient's age. Patients 3 to 6 years of age were evaluated with the faces component of the Oucher Scale. Patients 7 to 17 years of age were evaluated with the numerical component of the Oucher Scale. Of note, the Division notified the sponsor (in a January 2002 advice letter) that the planned

sample size was likely to be inadequate to demonstrate a treatment effect of the expected magnitude. However, the sponsor chose not to increase the sample size.

Secondary efficacy measures included:

- Investigator and observer evaluations of subjects' pain on a 4-point categorical scale;
- Investigators' overall impression of the anesthetic using "yes" or "no" answers to a query regarding the adequacy of the anesthesia for the procedure; and

Forty-three patients were randomized to the S-Caine group and 22 to the placebo group. One placebo patient withdrew consent. Two S-Caine patients and one placebo patient were excluded from the efficacy analyses as they did not undergo their vascular access procedures after receiving treatment. Thus, 41-S-Caine and 20-placebo patients completed the study and were included in the efficacy analyses.

The median scores for the S-Caine group and the placebo group in the faces (3-6 year olds) stratum were 0 and 80, respectively. This represented a statistically significant treatment effect with a p-value of 0.001. The median scores for the S-Caine group and the placebo group in the numerical (7-17 year olds) stratum were 7.5 and 50, respectively. The p-value for this difference in treatment effect was not statistically significant at 0.2. However, this stratum appeared to be underpowered with only 16 subjects in the S-Caine group and 9 subjects in the placebo group.

In a *post-hoc* analysis performed by Dr. Josefberg, the p-value for the treatment effect when both strata are combined was statistically significant at less than 0.001. It is important to note that the sponsor's decision to stratify the groups in this study was based on a recommendation from the Division due to concerns regarding combining results from the two different components of the Oucher Scale.

The secondary efficacy outcome measures of Observer Rating and the Pain Rating component of the Investigator Rating for the combined strata (the prespecified analyses for these measures) also revealed statistically significant results with p-values of less than 0.001. For the Adequate Anesthesia component of the Investigator Rating, the treatment effect was determined to be of borderline statistical significance with a p-value of 0.6.

Study SC-21-01 (21)

This was originally designed as a randomized, active-comparator, double-blind, parallel-group study in pediatric patients comparing the S-Caine Patch to EMLA in patients age 7 to 17 years old undergoing curettage or shave biopsies and patients age 3 to 6 years undergoing subcutaneous injection of lidocaine. Based on study design changes submitted as protocol amendments, the final study compared the effect of the S-Caine patch versus a placebo patch in reducing pain due to lidocaine injection in patients age 3 to 17 years of age receiving the injections prior to undergoing minor dermatologic procedures.

The primary outcome variable was stratified by age. Three to 6 year olds were evaluated with the faces component of the Oucher Scale and patients 7 and older were evaluated with the numerical component of the Oucher Scale. The median scores for the S-Caine group and the placebo group were 0 and 70, respectively, for the younger stratum. This represented a statistically significant effect with a p-value of 0.005. The median scores were 10 for both treatment groups in the older stratum, with a p-value of 0.3. Only one of the six secondary outcome evaluations (Investigator Rating in the younger stratum) was found to have a statistically significant treatment effect (p-value of 0.05).

Imporant flaws in the design and conduct of this study should be noted. The conditions for lidocaine injection (volume delivered, concentration utilized, whether or not a vasoconstrictor or bicarbonate was utilized, needle gauge, and whether the drug was delivered subcutaneously or intradermally) were not controlled, and were quite variable. As these inconsistencies may have affected the results, this study cannot be considered adequate and well-controlled.

Study SC-11-01 (11) and **Study SC-31-01** (31)

These two studies utilized the same basic design as Study 24, with the most significant difference being that Study 31 enrolled only subjects aged 65 and older. Study 11 again documented statistically significant treatment effects for the S-Caine Patch compared to the placebo patch in both the primary and secondary outcome measures. In Study 31 the primary outcome measure was statistically significantly different from placebo ($p = 0.05$). The results for the secondary outcome analyses did not reveal statistically significant differences between the treatment groups, although most did show trends in favor of the study drug.

Study SC-22-01 (22)

This was a multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy of the S-Caine Patch in patients 65 years of age and older. Patients received 30-minute patch applications prior to scheduled dermatologic procedures, i.e., predominantly shave biopsies or superficial excisions. Fifty-four subjects were randomized to the S-Caine group and 25 to the placebo group. Although there were quite a number of protocol violations, including one Center that did not use the protocol-specified randomization scheme, the primary outcome measure did result in a statistically significant treatment effect for the S-Caine Patch with a p-value of 0.041.

Study SC-40-02 (40)

This was a "dose-controlled," parallel-design trial comparing S-Caine patches applied for 10, 20, 30 and 60 minutes with EMLA Cream in healthy adult subjects undergoing venipuncture. Dr. Josefberg's Table 8.28 documents the results of this study. The 10-, 20- and 30-minute dose groups showed a statistically significant treatment effect for the S-Caine Patch compared to EMLA Cream on all primary and secondary measures

(except for "Anesthetic Eliminated Pain" in the 10-minute group), while the 60-minute dose group did not reveal any statistically significant differences compared to the EMLA group.

Study SC-41-03 (41)

This was a factorial study designed to satisfy the combination product rule. The four treatment conditions were:

- S-Caine Patch (70-mg lidocaine and 70-mg tetracaine, with heating component);
- Lidocaine Patch (70 mg, with heating component);
- Tetracaine Patch (70 mg, with heating component); and
- Placebo Patch (olive oil, with heating component)

The results of this study are documented in Dr. Josefberg's Table 8.32. The S-Caine Patch had a statistically significantly better treatment effect compared to the component and placebo patches.

Study SC-29-01 (29)

This was a double-blind, placebo-controlled trial comparing the S-Caine Patch to a placebo patch in pediatric patients receiving their 4 or 6-month immunizations. The children were randomized to receive either two S-Caine Patches or two placebo patches, one on each thigh. Following 30-minute patch applications, the investigator administered one intramuscular vaccine into each thigh. A study nurse videotaped the infants during the procedure until at least 30 seconds after the child stopped crying. Thirty-four patients were randomized to the S-Caine group and 33 to the placebo group.

The primary efficacy variable was the investigator's evaluation of the infant's pain measured by the Modified Behavioral Pain Scale (MBPS). Two investigators watched each videotape and independently completed the MBPS, scoring the infants at 15-second intervals.

The primary efficacy results and the majority of the secondary results did not demonstrate statistically significant differences between the treatment groups.

Study SC-27-01 (27)

This was a randomized, double-blind, crossover study in adult volunteers designed to compare the effectiveness of S-Caine Patches containing active heating elements to patches with deactivated heating elements. The heating elements were deactivated by exposure to room air prior to use. Subjects received simultaneous 20-minute applications of the two patches to the right and left volar surfaces. A standardized laser stimulus was then administered to each site. The efficacy evaluations were essentially the same as for those used in the majority of the other adult trials. These analyses failed to demonstrate any difference between the two patches.

Study SC-28-01 (28)

This was a randomized, double-blind study in adult volunteers that compared the efficacy of a 30-minute application of an S-Caine Patch, a lidocaine patch, a tetracaine patch, and a placebo patch, each with a functioning heating element. The only efficacy measure employed was the subjects' tolerance to a painful electrical stimulus. There were no statistically significant differences between the groups.

Clinical Safety:

Nine hundred and twelve adult and pediatric subjects were exposed to the to-be-marketed formulation of the S-Caine Patch, most with single 20 or 30-minute exposures. Two hundred and twenty subjects were included in the six-week, ten-dose dermal irritation and sensitization study (SC-42-03). There were no deaths or treatment-related serious adverse events in the clinical trial population. The two adverse events leading to discontinuation in the single-dose studies were due to apparent vasovagal responses to venipuncture.

Based on prior agreement with the Division, the data from Study-42-03 were submitted with the 120-day safety update. On review of that study, Dr. Josefberg found that the database was incomplete and that it is not possible to ascertain any explanation for why 22 of the 220 subjects that were enrolled did not complete the study. However, he did find that some of the subjects reported dermal irritation prior to dropping out of the study.

Mild erythema was the only commonly noted adverse event. More well-defined erythema and mild edema were noted in the multiple-simultaneous and the repeat patch-application studies.

Nonclinical Safety:

Dr. Mellon found no new safety concerns during his review of the application. However, as the application will not be approved at this time, and as the Segment I and III reproductive toxicity studies of tetracaine that were previously relegated to an agreed upon Phase 4 commitment have already been completed and submitted to the sponsor's other NDA, he is now recommending that submission of those studies to this NDA be required with the complete response to the approvable action. In addition, Dr. Mellon has determined that the literature submitted to characterize the effects of lidocaine on fertility and early embryonic development are inadequate and that further information will be required with the complete response.

He is also recommending clarification of the results of the *in vitro* chromosomal aberrations assay for tetracaine, which was negative in the absence of metabolic activation but equivocal in the presence of metabolic activation.

Biopharmaceutics:

Dr. Nallani's review documents that overall systemic exposure to the active components is low and not likely to result in systemic pharmacological effects. He also notes that the proposed *in vitro* release specifications will require modification as they are quite wide.

Chemistry, Manufacturing and Controls:

Two facilities have received "withhold" evaluations after site inspection. In addition there are a number of other drug quality concerns that must be addressed prior to approval. These are carefully delineated and discussed in Dr. Harapanhalli's review, and include:

- The specifications for the acceptance of lidocaine and tetracaine from the DMF holders are inadequate.

- Quality control of the components (e.g., physical test attributes for the [redacted] has not been adequately established and, therefore, reasonable quality has not been built into the system.

- The specifications for the bulk material and the characterization of the bulk materials have not been adequately addressed.

- The manufacturing process has not been adequately described.

    - The master batch production records of the in process controls in the heat sealing operations of the [redacted] to the tray and of the form-fill pouch are inadequate.

    - The in process testing is too infrequent.

- The drug product specifications need to be revised.

- The [redacted] levels need to be reduced to the lowest possible level.

- The acceptance criteria for the temperature testing of the patch need to be revised.

- The *in vitro* drug release rate declined significantly over time possibly affecting the efficacy of the older patches; this finding must be addressed.

- The discussion of pharmaceutical development is incomplete.

- There is no data to support the safety of the heating element, which contains activated iron powder.

- DMF [redacted] for tetracaine is deficient.

Nomenclature:

The Division of Medication Errors and Technical Support in the Office of Drug Safety has found the proprietary name, "S-Caine Patch," to be acceptable. A second review will be necessary, however, prior to an approval action.

Discussion:

This application cannot be approved at this time due to significant deficiencies in product quality control, including "withhold" recommendations from the Office of Compliance for two of the manufacturing facilities. In addition, the sponsor has not provided adequate preclinical data to characterize the reproductive toxicity of the active components of the product.

The clinical review team and the primary statistical reviewer are also recommending that the application not be approved at this time due to less than compelling evidence of efficacy. Drs. Josefberg and Chang have expressed concern that the results from the multiple studies are patchy, without consistent evidence of efficacy on all endpoints, and that, when efficacy is documented, the size of the treatment effect is small. Dr. Fan has expressed concern that the "crossover" design in Studies 11 and 24 would allow the introduction of bias. Dr. Permutt has written that he disagrees with this interpretation and that, indeed, he finds the evidence of efficacy in these studies to be rather compelling precisely because of this study design. Dr. Fan also agrees with the clinical team's evaluation that the overall "weight of evidence" does not appear to support a finding of efficacy for this product. In addition, the clinical reviewers have expressed particular concern related to the lack of statistical significance in the results from the older stratum of pediatric patients in Study 20. On page 3 of his review, Dr. Permutt writes:

> The data from these six studies (or eight strata) are not consistent with the hypothesis of no effect in any study or stratum. Nor is there the slightest reason to suspect beneficial effects in some studies or strata and harmful effects in others: at worst, some of the strata show little effect at all, and some suggest an effect in the right direction without being statistically significant individually. The only tenable hypothesis, given the data, is that the drug at least sometimes has a beneficial effect and that it has a beneficial effect on average.

I agree with Dr. Permutt that there is undeniable evidence that this product is effective in all populations studied. In light of this and the product's unremarkable safety profile, I see no reason why, from a clinical perspective, it could not be approved. I do not agree with the clinical team's recommendation for requiring further evidence of efficacy in pediatric and/or geriatric patients.

However, I do agree with Drs. Josefberg and Chang that the sponsor has provided no evidence to support their contention that the heating component provides any additional efficacy to the product. The results of Study 27 in combination with the finding that the

patch only reaches skin temperature maximally, and then only after 20 minutes when most patients will have completed their treatments with the product, lead me to the inevitable conclusion that the heating component provides no additional benefit either in rapidity of onset of efficacy or in degree of efficacy. It also does not appear to cause any increased risk. There is, of course, always a slight risk that it could cause some unforeseen adverse event and, therefore, requiring removal of the component from the product would be the failsafe position. However, I think that that risk is truly minimal. Removal of this component would necessitate additional clinical trials with the "new" to-be-marketed product. Therefore, while I would approve this product with the heating component, adequate language in the label to disclaim any benefit related to the component will be required. If the sponsor wants to promote the heating component as having any beneficial effect they will have to document that effect in an adequate and well-controlled trial.

Action recommended by the Division: Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

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

/s/

Bob Rappaport
2/4/04 08:07:11 PM
MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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Medical Officer Review

NDA #	**21-623**
Related IND #	**58,823**
Drug Name	**S-Caine Patch**
Sponsor	**ZARS, Inc.**
Proposed Indication	[redacted]
Type of Submission	**New Drug Application**
Date of Submission	**04APR2003**
Date of Receipt (CDR)	**08APR2003**
Review Date	**04FEB2004**
Reviewer:	**Howard Josefberg, MD**
Supervisory Reviewer	**Nancy Chang, MD**
Project Manager	**Lisa Malandro**

EXECUTIVE SUMMARY

PRIMARY CLINICAL REVIEW

Executive Summary

1 RECOMMENDATIONS

1.1 Recommendation on Approvability

Significant chemistry and manufacturing deficiencies preclude approval of the S-Caine Patch at this time. If the outstanding CMC deficiencies and issues are believed to be remediable, an approvable action is most appropriate at this time.

Had there been no CMC deficiencies, based on the clinical information submitted and reviewed to date, I would still recommend an approvable action. NDA 21-623, as submitted, leaves several clinical issues unresolved. None of these necessarily constitute approvable issues, but taken as a whole they leave too many questions with, and "holes" in, the clinical evidence in support of S-Caine Patch efficacy and safety. Specifically, the areas in which the (clinical) evidence is either lacking, or short of compelling, are:

- Heating element efficacy: The S-Caine Patch integrated heating element (CHADD) has not been shown to contribute to product efficacy. This poses a regulatory dilemma. FDA approval of the S-Caine Patch (with CHADD) would signify that the product, and its components, have been determined to be both safe and effective. The heating component has not been found to be effective, however, or to add to product efficacy. (The heating component *may* also be associated with a small increase in the incidence of "very slight" erythema at the patch application site, compared with the non-heated patch.) Because the S-Caine Patch would be the first marketed transdermal product to incorporate a heating element, prescribers and patients are likely to assume that the heating element contributes something; if it didn't it wouldn't be there. The heating element is also expected to feature prominently in product promotion (implied or otherwise), and in product identification in the minds of potential prescribers. Approval of an S-Caine Patch without a heating element would not be possible at this point, either, however, because all clinical trials were conducted with the intact, or heated version of the S-Caine Patch.
- Pediatric efficacy findings were inconclusive, and inconsistent (in the trials that utilized the "final formulation," the to-be-marketed product).
- Geriatric efficacy findings barely achieved statistical significance in the two "geriatric only" trials, on the primary outcome measure. Treatment effect size was smaller in the "geriatric only" trials (than in otherwise identical trials enrolling adults of all ages) and of questionable clinical significance. For example, in geriatric trial SC-22-01 the median VAS scores (primary efficacy measure) were 8.0 and 13.5 for S-Caine treated and placebo treated subjects, respectively ($p=0.053$). In study SC-23-01 (enrolling adults of all ages but otherwise identical to SC-22-01), median VAS scores were 5.0 and 31.0 (S-Caine and placebo, $p < 0.001$). There were five secondary outcome measures in each geriatric study, chosen to assess clinical relevance of the primary efficacy findings, and identical to those used in most other adult efficacy trials. Not one of the secondary efficacy results approached statistical significance in the geriatric trials.

- Assessment of cumulative irritation and sensitization potential is a standard requirement for all topically applied products. Study SC-42-03 was the only trial to evaluate the dermal effects of repeat (> 2) patch application. Ten percent of the 220 enrolled subjects dropped-out (often by the fourth or fifth of ten planned tri-weekly treatment visits). Although most of these study drop-outs might reasonably be attributed to normal attrition, the study report and data as submitted do not allow for adequate review.
- Data integrity and accuracy in this application are less than ideal. The electronic data contains occasional errors (i.e. transposed data columns, missing values), and peculiar coding, but nothing that appears to be evidence of outright fraud. These data problems and inconsistencies are *relatively* minor, and would not necessarily constitute an approvable issue. The additional uncertainty is not helpful, however, in the context of efficacy results that are themselves inconsistent, marginal, and in some cases even counterintuitive.

1.2 Marketing Restrictions

At this time there are no grounds for marketing restrictions on the S-Caine Patch. No marketing restrictions are anticipated.

1.3 Recommended Phase 4 Studies

Neonatal Safety

The sponsor has agreed to complete a study evaluating S-Caine Patch safety in the neonatal population, including premature infants down to 34 weeks estimated gestational age (study SC-33-02). Enrollment began prior to NDA submission. The sponsor anticipated difficulties and delays in recruiting adequate numbers (approximately 30) of hospitalized premature infants and newborns, however. A request to complete this trial as a Phase 4 commitment was made at the end-of-phase-2 meeting, and agreed to by the Division.

Pediatric Efficacy

Once approved, this product will be used in children (including infants and toddlers), whether or not the product label carries specific instructions (or disclaimers) for pediatric use. The sponsor was advised that in addition to their planned pediatric trials (ages three through seventeen) an efficacy study in infants (down to about four months of age) would be required, but expressed concerns about the feasibility of pain (and treatment effect) assessment in this population. The Division acknowledged possible difficulties, but reiterated that study of the S-Caine Patch in infants was important for evaluation of both safety and efficacy. If the product were to demonstrate efficacy in adults and older children (ages three and up) efficacy in younger children might be "extrapolated." Unfortunately, the basis for such an extrapolation, efficacy in older children, has not necessarily been adequately demonstrated.

An additional (and adequately sized) pediatric efficacy study should be required. Specifically, better evidence in support of efficacy in seven to seventeen year-olds is desirable. This could be provided in a number of ways. Two possibilities include:

- A "supplemental" efficacy trial in 7 to 17 year-olds might be sufficient to fill in the "gap" in existing pediatric efficacy findings. Alternatively;

•

Geriatric efficacy results might also require supplementation.

Efficacy of the CHADD heating component
Were the S-Caine Patch to be approved at this time, a prominently featured label disclaimer should be required. "The S-Caine Patch includes an integrated heat generating element (CHADD). This heating element has not been demonstrated to contribute to S-Caine Product efficacy." Removal could be contingent upon submission of adequate evidence to the contrary. If the product is not approved during this review cycle, the sponsor should be encouraged to (attempt to) demonstrate that the heating element does, in fact, contribute to product efficacy, prior to resubmission.

Safety: Cumulative Irritation and Sensitization Potential
The results from study SC-42-03 (repeat dose cumulative irritation and sensitization evaluation) suggest that the S-Caine Patch will not be particularly irritating or sensitizing. As submitted, however, the data do not allow for complete review. A complete study report (with full CRFs for all study drop-outs, and for subjects that experienced AEs) should be required, whether from SC-42-03 or another similar study.

Considering the population most likely to receive multiple S-Caine Patch administrations, a pediatric sensitization and irritation study would have been desirable. The sponsor anticipated significant difficulties in recruiting for this trial, however, and the Division agreed to forego such a requirement. Analysis of the safety database demonstrates that mild to moderate erythema at the patch application site occurs commonly (with use according to the proposed label instructions) in all populations. "Well defined" erythema (as opposed to "very slight") appears to be more common in some of the pediatric studies than in the adult studies (Table 9.22), however. These transient skin reactions, which were not classified as adverse events, are likely of no clinical significance, and may be attributable more to differences in dermal ratings between investigators. The overall adverse event rate, however, was so low that an assessment by age is not meaningful. If early post-marketing reports suggest a higher incidence of clinically relevant adverse events or dermal reactions in the pediatric population, a pediatric irritation/sensitization study should be required.

Safety: Assessment of Anesthetic Endpoints
The anesthetic properties of the S-Caine Patch (i.e. onset, duration) should be characterized, if not for labeling purposes, to allow for safe product use.

Other requirements for Phase 4 studies should be guided by deficiencies in the evidence in support of product indication(s) and label claims, at the time of initial product approval. At this time the precise indication(s) to be granted have not been decided, thus a determination of whether the evidence submitted to date is adequate is not possible.

The sponsor might choose to conduct additional efficacy trials if they consider the approved indication to be too narrow, for instance [redacted] Adding to, or broadening the approved indication would require submission of (study results as) efficacy supplements, however, not as Phase 4 submissions.

1.4 Application Deficiencies

Chemistry and manufacturing deficiencies

Several of the CMC concerns relate to the S-Caine Patch integrated heating element. Basically, the heating element specifications are inadequate. The time course of the exothermic reaction, the temperature range and the maximum temperature achieved, are not well characterized, do not support claims or dosing instructions on the proposed product label, and do not match how the product is likely to be used in clinical practice. Specifically, the label indicates that the [redacted] but the sponsor's own acceptance criteria indicate that the patch warms to [redacted] quite a wide range. Furthermore, warming occurs only 15 to 20 minutes after exposure to air. Dosing instructions call for 20 or 30 minute applications, without any preliminary "patch warm-up" period (which would be impractical in most cases anyway).

Other CMC problems include:

- The drug release specifications of the S-Caine Patch are so wide that they are approach the point of being "meaningless" (CMC team leader, DACCADP)
- The patch manufacturing process has been changed, subsequent to completion of (most of) the Phase 3 clinical trials. The [redacted] whereby one of the patch layers is added has been changed subsequent to NDA submission.

Heating element contribution to efficacy was outlined in Section 1.1 and is discussed in more detail in Section 8.3.11.

Pediatric efficacy findings were inconsistent, as discussed in Section 8.

Cumulative irritation/sensitivity evaluation (adults)

Study SC-42-03 was a (CDER required) study of the cumulative irritation potential of the S-Caine Patch. Submission of the study report and data with the 120-Day Safety Update was permitted, by prior agreement. The study report and data, as submitted do not allow for meaningful review. The paper report contains individual line listings of dermal irritation and patch adherence scores, as well as photocopies of fifteen adverse event reports. The "electronic data" for SC-42-03 consists only of a fifteen-line file listing "the fifteen adverse events." The final study report (as well as the rest of the NDA) does not contain a study protocol, or a definition of what would constitute an adverse event. It is not possible to ascertain the reasons for study drop-out (of 22 of the 220 enrolled subjects). Sections and statements addressing regulatory requirements for financial disclosure, ethical study conduct, etc. are also missing.

[redacted]

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

The information submitted in this New Drug Application pertains to the S-Caine Patch. The sponsor describes the S-Caine Patch in their proposed label as follows:

> "The S-Caine™ Patch (lidocaine 70 mg and tetracaine 70 mg) [redacted]
>
> The S-Caine Patch consists of a thin, uniform layer of a local anesthetic formulation with an integrated, oxygen-activated heating [redacted]

The clinical development program for the S-Caine Patch, conducted under IND 58,823, consisted of studies utilizing three different patch formulations, Developmental A, Developmental B, and the S-Caine Patch final formulation. The developmental patch formulations each contained the same amount of active drug (70 mg each of lidocaine and tetracaine) as the final patch formulation, but varying amounts of excipient, principally polyvinyl alcohol and water. All required studies (pivotal trials, "combination rule," skin irritation/sensitization) were conducted using the final patch formulation. The sponsor has included data obtained from studies utilizing the developmental patches in their integrated safety database, as well as in their efficacy assessment and analyses.

2.2 Efficacy

According to the proposed product label "The S-Caine Patch (lidocaine 70 mg and tetracaine 70 mg) is indicated [redacted] All clinical studies conducted in support of this efficacy claim were randomized, double-blind and placebo-controlled (SC-40-02 used EMLA Cream as an active control). Table 2.1 below lists the trials reviewed for efficacy findings.

Table 2.1. Studies Reviewed for Efficacy Findings

Study	Contribution to Efficacy	Population	Duration (minutes)
24-01	Venipuncture	40 Adult	20
23-01	Minor dermatological procedures	94 Adult	30
20-01	Venipuncture (some IV cannulation)	64 Child	20
21-01	Lidocaine injection, pretreatment	88 Child	30
11-01	Venipuncture	21 Adult	20
31-01	Venipuncture (PK in 10 out of 40 subjects)	40 Geriatric	20
22-01	Minor dermatological procedures	79 Geriatric	30
40-02	Dose ranging: 10, 20, 30, 60 minute application Venipuncture (vs. EMLA)	82 Adult	10, 20 30, 60
41-03	Combination rule + venipuncture SC vs. Lidocaine vs. Tetracaine vs. Placebo	80 Adult	30
28-01	Combination rule SC vs. Lidocaine vs. Tetracaine vs. Placebo Pain Tolerance Threshold Testing	48 Adult	30
27-01	Combination rule: Heating element present/absent Laser stimulation	53 Adult	20
29-01	Analgesia for immunization Safety in infants	67 Infant	30
	Developmental Patch Trials		
05-99	IV insertion	21 Adult	30
03-99	Shave biopsy	59 Adult	60
07-99	Shave biopsy	60 Adult	30
09-99	Venipuncture	60 Child	30
04-99	Shave biopsy	60 Child	60
10-00	Venipuncture	60 Child	20

Four studies are designated in the NDA as "pivotal"; two in adults (SC-23-01, SC-24-01) and two in children (SC-20-01, SC-21-01). In study SC-24-01 subjects received simultaneous applications of both S-Caine Patch and placebo (one on the left antecubital area and one on the right), prior to undergoing venipuncture (at both patch sites). Study SC-20-01 evaluated the use of the S-Caine Patch prior to venipuncture in children, utilizing a parallel group design; subjects received either S-Caine Patch or placebo, prior to a single venipuncture. Study SC-23-01 evaluated the S-Caine Patch prior to protocol-defined minor dermatological procedures in adults(predominantly superficial excision and shave biopsy), and SC-21-01 examined S-Caine use prior to lidocaine injection in children. Like study SC-20-01, SC-23-01 and SC-21-01 employed parallel group study designs. Subjects received either S-Caine or placebo, prior to their painful procedure (venipuncture, "minor dermatological procedure," or lidocaine injection) and subsequent efficacy measurement.

Three additional studies conducted were each, in most ways, identical to one of the above four "pivotal" efficacy trials. Study SC-11-01 utilized the same study design, inclusion and exclusion criteria, and efficacy and safety measures as SC-24-01 (venipuncture in adults). Study SC-22-01 was much like SC-23-01, but included only geriatric subjects. SC-31-01 was very similar to SC-24-01, again including only geriatric subjects. SC-31-01 also incorporated PK sampling for 10 of the 40 participants.

Phase 2/3 trials assessed S-Caine efficacy in relieving or diminishing the pain caused by what the sponsor refers to as "dermal procedures." Procedures evaluated included "vascular access procedures" (venipuncture and intravenous cannulation), lidocaine injection, and "minor dermatological surgical procedures." Eligible "minor dermatological procedures" were specified within each protocol. Overall these included superficial excision, shave biopsy, skin tag removal, keloid injection and electrodessication. The majority of evaluable subjects, however (> 80%), underwent superficial excision or shave biopsy. Likewise, nearly all of the vascular access procedures were, in fact, venipuncture.

Primary Efficacy Measure

All of the Phase 3 efficacy trials in adults utilized a standard 100-mm Visual Analog Scale score as the primary efficacy measure (of "dermal procedure" induced pain).

Pediatric efficacy trials (except for SC-29-01 in infants) used an "Oucher Scale" score as the primary efficacy measure. There are two basic Oucher Scales. The Photographic Oucher is a series of six photographs showing a child in varying degrees of discomfort. It is used in children who are unable to count by number, and has been validated for use in those as young as three. The Numeric Oucher includes a vertical number scale (0 – 100, with increments of 10) adjacent to the same faces. The Oucher Scales have been evaluated for construct validity and for reliability across numerous clinical and research settings. They have both also been used in pediatric clinical trials for other local anesthetics, including EMLA and ELA-Max.

In the S-Caine trials, children ages 3 through 6 used the Photographic Oucher scale. For the efficacy analyses the six–point categorical pain rating was expressed as a number

between 0 and 100 (0, 20, 40, 60, 80 or 100). Children ages 7 through 17 used the Numeric Oucher scale (0, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100).

Secondary Efficacy Measures

Secondary endpoints were similar across studies, with minor variations between those used in adults and in children. In the adult trials these included:

- Subject's Overall Impression of the Local Anesthetic
  - "Was the local anesthetic adequate?" (Yes/No)
  - "Would you use the local anesthetic again" (Yes/No)

All trials, adult and pediatric also assessed:

- Investigator and Observer's Evaluation of Subject's Pain
  - Investigator rating (No Pain/Slight Pain/Moderate Pain/Severe Pain)
  - Observer rating (No Pain/Slight Pain/Moderate Pain/Severe Pain)
- Investigator's Overall Impression
  - "Did the subject experience adequate anesthesia?" (Yes/No)

Most of the "dermatological procedures" trials also recorded

- Use of rescue lidocaine (Yes/No)

This was defined prospectively as a secondary outcome measure in most of the "dermatological procedures" trials. The procedures for notifying patients of lidocaine availability were usually not standardized, or even explicitly stated, in the clinical protocols, however. Rates of rescue lidocaine use, regardless of treatment condition, varied considerably across centers within the same study, making it appear that administration might have been very much surgeon (investigator) driven. Furthermore, in some study reports (SC-23-01) rates of rescue lidocaine use are reported in the demographics/group comparability tables, rather than in the section discussing efficacy results. For these reasons, there will be limited consideration or discussion of the "use of rescue lidocaine" outcome measure in this review.

The DACCADP statistical reviewer (by Dr. Milton Fan) noted numerous instances where the sponsor's analyses of (primary and secondary) efficacy variables could have utilized more appropriate statistical tests. In his written review, Dr. Fan includes results of his re-analyses (where indicated). In each instance results of the sponsor's analysis and Dr. Fan's analysis are given side-by-side. Treatment effect sizes were always comparable, and in no case did the statistical significance of a result change. In this review, except where otherwise stated, the sponsor's statistical analyses and results are reported.

Dr. Fan considered two of the Phase 3 trials in adults to be fundamentally flawed (SC-24-01 and SC-11-01, S-Caine Patch prior to venipuncture) because of the study design(s) employed. In both trials subjects received simultaneous applications of S-Caine Patch and placebo patch, one to the right antecubital area, the other to the left, randomized 1:1. After patch removal, venipuncture (and then efficacy measures) was always performed on the right arm first, and then the left. Dr. Fan felt that this design compromised subject blinding, and made it difficult to control for potential biases (an "order effect"). Dr. Permutt (supervisory statistical review) felt that the advantages of this type of crossover design outweigh the disadvantages, however.

2.3 Safety

The Integrated Summary of Safety (ISS) includes safety data from all subjects who received at least one patch application (active drug or placebo) during the course of S-Caine Patch clinical development program. Table 2.2 below summarizes the trials from which data was obtained for the ISS database.

Table 2.2 Summary of Trials Included in Integrated Summary of Safety

Trial	Purpose	Patch	Popul.	N	S-Caine	Placebo
Efficacy Trials						
03-99	Shave biopsy	Dev A	Adult	59	29	30
04-99	Shave biopsy	Dev A	Peds	60	30	30
05-99	IV insert + PK	Dev A	Adult	21	20	21
07-99	Shave biopsy	Dev A	Adult	60	29	31
09-99	Venipuncture	Dev A	Peds	60	30	30
10-00	Venipuncture	Dev B	Peds	60	30	30
11-01	Venipuncture	Final	Adult	21	21	21
20-01	Venipuncture (+ IV)	Final	Peds	64	43	21
21-01	Lidocaine inject	Final	Peds	88	41	47
22-01	Dermatologic Procs.	Final	Geriatric	79	54	25
23-01	Dermatologic Procs.	Final	Adult	94	45	49
24-01	Venipuncture	Final	Adult	60	60	59
27-01	Combo ± heat	Final	Adult	53	53	53
28-01	Combo rule	Final	Adult	48	48	48
29-01	Immunization	Final	Infant	67	34	33
31-01	Venipuncture (PK in 10)	Final	Geriatric	40 (10)	40 (10)	40
40-02	Venipuncture	Final	Adult	82	82	EMLA
41-03	Combo Rule/Venipuncture	Final	Adult	80	80	80
Safety and PK Trials		**All Final**				
25-01	Repeat applications	4 X 60m	Adult	25	25	0
26-01	Simultaneous	3 X 60m 4 X 30m	Adult	12 12	12 12	0
30-01	Simultaneous	2 X 30m	Peds	42	42	0
33-02	Single	1 X 30m	Neonate	0	0	Ongoing
42-03	10 exposures over 6 weeks 198 Completers (N = 220)	10 X 120m	Adult	220	220	220
Totals				**1407**	**1080**	**868**

A total of The number of 1407 subjects enrolled in S-Caine Patch clinical trials. The number of subjects/patients exposed to one or more applications of the final, to-be-marketed S-Caine Patch formulation was 912. The total increases to 1080 subjects with inclusion of those exposed to the Developmental A and Developmental B patch formulations.

The demographics of subjects included in the ISS database are shown in the Table 2.3 below. Different age groups (3 years of age and up), genders and races were adequately represented.

Table 2.3. Summary Demographics, Subjects Included in the ISS Database

Demographic	Received S-Caine Any Form	Final	Final No Heat	Develop-mental	Placebo
Enrolled = 1407					
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%)

There were no deaths reported during the clinical development period. One serious adverse event occurred during the cumulative irritation/sensitization study, a multi-week, ten-exposure evaluation. Most of the efficacy trials required a single clinic visit, thus protocol compliance was high. Loss to follow-up, including post-treatment evaluations, was rare. Monitoring of adverse events was performed by investigators, subjects, and in the case of pediatric subjects, parents or guardians. Safety monitoring consisted primarily of visual assessment of patch application sites immediately upon patch removal, following the procedure, and 24 – 48 hours following patch application.

2.4 Dosing

The absolute amounts of lidocaine and tetracaine present in each S-Caine Patch are fixed, as are patch dimensions. Drug dose delivered, then, is dependent, for the most part, on the duration of patch contact with the skin. Patch and drug temperature could also be expected to effect transdermal drug delivery. If reliability (consistency) of the integrated heating element proves problematic, patch temperature, and consequently drug delivery and absorption might actually vary more between administrations for the S-Caine Patch, compared with traditional transdermal delivery systems.

A eutectic mixture (1:1 ratio) of active drug components was employed in an attempt to minimize melting point of the mixture. All clinical trials evaluated patches containing 70 mg each of lidocaine and tetracaine, but the rationale for the choice of these absolute amounts was never elucidated. According to the sponsor, modifications to the patch formulation (subsequent to initiation of efficacy trials) were necessary to improve tetracaine stability. The concentration of active drug increased from approximately [redacted] (by weight) in Developmental Patch A to about [redacted] in the final patch formulation. The effect of varying the concentration of active drug was never systematically evaluated, however.

Study SC-40-02 varied patch (and EMLA) application duration, in order to assess the time-point at which continued application would be unlikely to yield any incremental benefit/efficacy. Study SC-40-02 discussed in detail in Section 8.3.7) results appear below. 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. This is the only S-Caine Patch trial to evaluate a 10-minute application period.

Table 2.4. SC-40-02 Efficacy Results (Duration of Application)

	10 min	20 min	30 min	60 min
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
Secondary Efficacy				
Anesthetic Eliminated Pain				
% 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				
% 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] McNamara chi-square
Source: Modified from sponsor Table 11.3, and text (Volume 40)

According to the sponsor's efficacy summary, "Initial studies evaluated extended patch application periods where there was a high probability that anesthesia would be achieved...Application times were reduced in subsequent studies in an effort to identify the minimum application time that would produce acceptable anesthesia." The following three tables (2.5, 2.6 and 2.7), adapted from tables prepared by the sponsor, compare primary efficacy results, and duration of patch application, across studies (NDA Volume 26, page 57).

Table 2.5. Across Study Dosing
Vascular Access Procedures, Adults (Placebo Control)

		20 minutes			30 minutes
Study	11-01	24-01	31-01	05-99	41-03
Formulation	Final	Final	Final	Dev A	Final
Median VAS					
S-Caine	1	5	8	2	3
Placebo	9	28	13	30	22
p-value [a]	0.004	<0.001	0.039	<0.001	<0.001

Source: Table 6.3A, Volume 26 [a] Wilcoxin signed rank test

Table 2.6. Across Study Dosing
Vascular Access Procedures, Pediatric (Placebo Control)

		20 minutes		30 minutes
Study	20-01	20-01	10-00	09-99
Formulation	Final	Final	Dev B	Dev A
Oucher Scale	Photo[a]	Numeric[b]	Photo[a]	Numeric[b]
Median Oucher				
S-Caine	0	7.5	0	0
Placebo	80	50	20	35
p-value [c]	<0.001	0.159	<0.001	<0.001

[a] 6-point categorical converted to 0, 20, 40, 60, 80, 100
[b] 11-point categorical converted to 0, 10, 20 ... 90, 100
Source: Table 6.3B, Volume 26 [c] Wilcoxin signed rank test

Table 2.7. Across Study Dosing
Minor Dermatological Procedures, Adults (Placebo Control)

		30 minutes		60 minutes
Study	22-01	23-01	07-99	03-99
Formulation	Final	Final	Dev A	Dev A
Median VAS				
S-Caine	9.5	5	5	2
Placebo	22.5	31	19	33
p-value [a]	0.041	<0.001	0.003	<0.001

Source: Table 6.3C, Volume 26 [a] Wilcoxin signed rank test