CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-623

MEDICAL REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE:	June 23, 2005
DRUG:	Synera™ (lidocaine 70 mg and tetracaine 70 mg) topical patch
NDA:	21-623
NDA Code:	Type 4S NDA
SPONSOR:	ZARS, Inc.
INDICATION:	For use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision, electrodessication and shave biopsy of skin lesions

ZARS, Inc. originally submitted NDA 21-623 in support of marketing approval for their topical patch formulation consisting of lidocaine 70 mg and tetracaine 70 mg on April 8, 2003. An approvable action was taken on the application on February 4, 2004. The basis for this action was that there were numerous deficiencies in product quality and controls (see my memo dated February 4, 2004). The sponsor submitted a complete response to the approvable letter on December 17, 2004. The CMC portions of this response were reviewed by Jila Boal, Ph.D. Dr. Boal has concluded that all of these deficiencies have been adequately corrected and that, from a CMC perspective, the application is now approvable.

Although, prior to submission of the original application, the Division had agreed that the Segments I and III reproductive toxicity studies for tetracaine could be completed during Phase 4, the studies were completed during the review period for the original submission, and, thus, the Division requested that the final reports be submitted for review with the complete response. These studies were, indeed, submitted with the response and have

been reviewed by Suzanne Thornton-Jones, Ph.D. Dr. Thornton-Jones found that no effects of tetracaine on male or female fertility or pre- and postnatal development were observed in these studies. In addition, the sponsor was asked to address 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. In her review, Dr. Thornton-Jones notes:

> A discussion of the equivocal *in vitro* chromosomal aberration assay results for tetracaine was provided and reviewed. A post-NDA action meeting was held with the Sponsor on 03 May 2004 where the equivocal assay results were further discussed. It was conveyed to the Sponsor the findings would be handled in the package insert and, although not required, the assay could be repeated to clarify the equivocal finding. The Sponsor did not repeat the assay and the after review of their discussion it was decided that the assay results would remain equivocal and the patient insert was revised accordingly.

Upon review of the original application, there was also concern that the literature submitted to characterize the potential effects of lidocaine on fertility in males was deficient. The sponsor chose to perform a male fertility study, the results of which were submitted with the complete response. In her review, Dr. Thornton-Jones notes:

> The labeling recommendations in the current review reflect the results of the study. As such, the sponsor has adequately addressed this deficiency.

Finally, the most significant aspect of this new drug product is the heating element that has been incorporated in order to provide increased efficacy compared to a non-heated patch. The studies submitted with the original application did not demonstrate any advantage of the to-be-marketed product over a control patch that had its heating element deactivated. While no significant additional safety concerns were raised by the presence of this heating element, the Division did have concerns that its presence would imply an effect that did not exist. Thus, the sponsor was informed in the approvable letter that they would need to submit new studies at the time of resubmission that documented the benefit of the heating element, or the product labeling would clearly state that it did not provide any additional efficacy.

The sponsor has submitted three new studies designed to specifically assess any added efficacy provided by the heating element. These studies have been thoroughly reviewed by Howard Josefberg, M.D., and the sponsor's statistical analyses of the studies were reviewed by Joan Buenconsejo, Ph.D. I will briefly summarize these studies.

SC-55-04: This was a randomized, double-blind, multi-center trial that compared the to-be-marketed Synera patch to a patch that was manufactured without the heating element. Two-hundred-fifty normal volunteers were randomized 1:1 and completed the study. The Synera patches or non-heating control patches were applied to the antecubital fossa for 20 minutes prior to venipuncture. The primary outcome measure was "Subject's

Evaluation of Pain" on a 100-mm VAS. The mean scores were 22 and 29 for the Synera and control groups, respectively. This difference was statistically significant with a p-value of 0.02 based on Dr. Buenconsejo's analysis. The result of an analysis of the sponsor's secondary outcome measure, "Subject's Impression of Study Treatment," was supportive of the primary outcome analysis.

SC-54-04: This was a randomized, double-blind, multi-center trial that compared the to-be-marketed Synera patch to a patch that had had its heating element disabled by exposure to air. This study was similar in design to Study SC-55-04, but did not demonstrate that additional efficacy was conveyed by the inclusion of the heating element. The sponsor surmised that the reason this study did not document a treatment effect for the heating element was that the deactivated patches were actually providing a significant level of heat. In additional studies they were able to demonstrate that patches that had been similarly deactivated continued to generate some heat up to 14 days.

SC-53-04: This was a pilot study designed to assess preliminary data on the variability and magnitude of effect of heat, application time and stimulus intensity on the efficacy of the heating element. It was not submitted as a pivotal study to demonstrate efficacy of the heating element.

While Dr. Josefberg did find numerous data quality problems throughout the efficacy studies, he was, in the end, able to perform an adequate review of the studies. Concerns that were raised regarding study blinding and other data integrity matters were allayed after his thorough investigation of the data and the study reports.

While the complete response did provide new data to address the original concern that the proposed in vitro release specifications would require modification (as they were quite wide), Dr. Srikanth Nallani reviewed that data and determined that further testing should be performed with lower concentrations of the [redacted] medium. However, this did not rise to the level of a quality and safety concern that would require non-approval. The sponsor has agreed to perform this additional testing post-marketing.

Additional pharmacokinetic data was also submitted. This data was collected from adult and pediatric normal volunteers who had received multiple simultaneous or sequential patches. While the plasma levels were generally well below the toxic range, the total number of subjects studied was small and may not have adequately assessed normal variability. However, this concern has been adequately addressed by warnings in the package insert against the use of multiple simultaneous or sequential patches.

The sponsor has committed to a Phase 4 study that will evaluate the systemic exposure of lidocaine and tetracaine in neonates and infants. They have also agreed to submit a prior-approval supplement that includes supportive data before changing their labeling to expand use into the home setting.

Conclusion:

This complete response to the Division's approvable letter addresses all of the deficiencies and concerns raised upon completion of the first review cycle. The product appears to be safe and effective when use according to the product labeling, and the sponsor has adequately demonstrated that additional efficacy is provided by the heating element that they have incorporated into Synera.

Action recommended by the Division: Approval

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

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/s/

Bob Rappaport
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	505(b)(2)
Submission Number	N000
Submission Code	AZ
Letter Date	17DEC04
Receipt Date	17DEC04
PDUFA Goal Date	21JUN05
Reviewer Name	Howard Josefberg, M.D.
Review Completion Date	25MAY05
Established Name	Synera (lidocaine 70 mg and tetracaine 70 mg) topical patch
(Proposed) Trade Name	Synera (Formerly S-Caine Patch)
Therapeutic Class	Local anesthetic/topical
Applicant	ZARS, Inc.
Priority Designation	Standard
Formulation	Topical patch
Dosing Regimen	Single-dose pre-procedure
Indication	'For local dermal analgesia'
Intended Population	Adult and pediatric

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DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Medical Officer Review

NDA #	**21-623**
Related IND #	**58,823**
Drug Name	**S-Caine™ Patch → Synera™**
Sponsor	**ZARS, Inc.**
Proposed Indication	**"For local dermal analgesia on intact skin"**
Type of Submission	**Complete Response to Approvable Action**
Date of Receipt	**17DEC04**
PDUFA Goal Date	**21JUN05**
Review Date	**2JUN05**
Reviewer:	**Howard Josefberg, MD**
Supervisory Reviewer	**Bob Rappaport, MD**
Project Manager	**Allison Meyer**

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based upon the clinical information submitted an *Approval* action is recommended, if there are no outstanding CMC issues. Given the sponsor's history of problems with data integrity and ethical study conduct, however, this recommendation should be considered only in the context of the final report from recent DSI inspections of NDA 21-623 clinical sites. Preliminary DSI reports seem to suggest no findings of particular concern. A brief, but relevant summary of DSI findings from investigation of both S-Caine Patch (NDA 21-717) and S-Caine Peel (NDA 21-623) clinical sites appears below in Section 1.1.1.

One additional concern, however, is the relationship between the timing of protocol and amendment submissions and actual study enrollment. This is described in Section 1.1.3. Information detailing all protocol, amendment and submission dates was requested on May 27, 2005, but that response has not yet arrived.

ZARS submitted 505(b)(2) NDA 21-623 in April 2003. Overall, the clinical data submitted for the initial review cycle were considered to provide acceptable evidence for product efficacy and safety, and NDA 21-623 was deemed *Approvable* (2/2004). Chemistry and manufacturing deficiencies were predominantly responsible for withholding approval. No clinical deficiencies were identified, but two issues were outstanding at that time. The S-Caine Patch integrated heating element had not been demonstrated to contribute to product efficacy and the final study report for the cumulative irritation and sensitization study (SC-42-03) had not been received.

Although the heating element appeared unlikely to pose any incremental safety risk, the S-Caine Patch would be the first approved transdermal product with an integrated heating component. Prescribers and patients were expected to assume this heating component contributes to product efficacy, by virtue of its mere presence. The heating element was also expected to feature prominently in product promotion, and in product identification in the minds of potential prescribers. Approval of an S-Caine Patch without a heating element would not have been possible either, however, because all clinical trials had been conducted with the intact (heated) version of the product. The 2/2004 action letter stated that ZARS would need to provide appropriate evidence of heating element efficacy, or alternatively, "... the product will be labeled to state that the heating element is ineffective." ZARS has now submitted acceptable evidence that the integrated heating element affords increased efficacy compared with a non-heated (but otherwise identical) version of their product.

The study report for SC-42-03 (evaluation of the product's cumulative irritation and sensitization potential, a standard requirement for all topically applied products) was incomplete by the end of the first review cycle. Study SC-42-03 was the only trial to evaluate the dermal effects of repeated (more than twice), prolonged (120 minutes) patch application. Although preliminary findings appeared to suggest an acceptable repeat-dose safety profile, ten percent of the 220 enrolled subjects dropped-out, usually by the fourth or fifth of ten planned tri-weekly treatment visits, with no follow-up information provided. Although most of these study drop-outs might have been attributable to typical attrition, the study report and data as submitted did not allow for adequate review.

The study report for SC-42-03 (cumulative irritation and sensitization) is now complete. Although it is not possible to know with certainty that none of the discontinuations were adverse event related (10% study drop-out rate), most seem to have resulted because of subjects' logistical and transportation issues. The patch appeared to be "mildly irritating," but not sensitizing, in some subjects, prior to their drop-out. Similar (irritation) effects were not uncommon in subjects that completed the six-week study, though. Clinical use of S-Caine Patch as labeled is not expected to result in clinically significant dermal irritation or sensitization.

1.1.1 DSI findings from inspection of NDA 21-717

Data integrity and accuracy in NDA 21-623 had been less than ideal. The electronic data contained occasional errors (i.e. transposed data columns, missing values) and peculiar coding, but nothing appeared to have been evidence of outright fraud. These data problems and inconsistencies were *relatively* minor, however, and would not necessarily have constituted an approvable issue, or triggered a request for DSI inspection. The additional uncertainty, however, was not helpful (for ZARS) in the context of efficacy results that were themselves inconsistent, marginal, and in some cases even counterintuitive.

ZARS submitted NDA 21-717, their second application, for the S-Caine Peel in November of 2003, shortly after the *Approvable* action for NDA 21-623. S-Caine Peel, also a eutectic combination of lidocaine and tetracaine, is formulated into a quick drying cream that is supposed to be peeled off between 30 and 60 minutes after application.

Data integrity and study conduct issues have become increasingly relevant, however, because of the information obtained during review of the NDA (21-717) for ZARS' second product, S-Caine Peel, submitted in November 2003. (S-Caine Peel, also a eutectic combination of lidocaine and tetracaine, is formulated into a quick drying cream that is supposed to be peeled off between 30 and 60 minutes after application.) Review of data submitted to NDA 21-717 had led to the preliminary conclusion that the S-Caine Peel had been demonstrated to be reasonably safe and effective in adults, and likely also in children. DSI had been consulted, however, because of dataset errors, as well as questionable (ethical) study conduct during the single successful pediatric trial [redacted]

[redacted]

1.1.2 DSI findings from recent inspection of NDA 21-623 sites

Four clinical sites were inspected. DSI noted several deviations from FDA regulations at two sites (of three in total) that conducted successful pediatric trial SC-21-01. These deviations were characterized as relatively minor. They did not appear to have significantly increased subject safety risks, nor did they appear capable of affecting the efficacy outcome of the study. The DSI report concludes "From the records reviewed, it appears the data from all four studies could be used to support an approval decision for the NDA."

1.1.3 Submission Timing

Several clinical protocols and amendments were submitted to the IND after study completion. Protocol amendments, including designation of investigators, were sometimes not submitted until months after the study had ended. This appears to have been due, in part, to batching of material for submission, particularly investigator documentation. Whatever the reason, submission of protocols and amendments in this manner violates 21CFR 312.30.

One example of this was with protocol SC-55-04, the only study in which the integrated heating element demonstrated efficacy. Protocol SC-55-04 was dated September 13, 2004 but submitted with a cover letter dated October 26, 2004 (received on October 28, 2004, submission #25). SC-55-04 was conducted, however, 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).

1.2 Recommendation on Postmarketing Actions

1.2.1 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.

1.2.2 Required Phase 4 Commitments Phase 4 Studies

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 only three neonates had been enrolled, however. ZARS has revised their timeline for SC-33-02 because of ongoing recruitment difficulties. Study completion is now anticipated in 12/2006.

1.2.3 Marketing Restrictions

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

1.3 Application Deficiencies from First PDUFA Cycle

Chemistry and manufacturing deficiencies

Many of the CMC deficiencies detailed in the 2/2004 action letter related to the product's integrated heating element. Basically, the heating element specifications were determined to be inadequate. The time course of the exothermic reaction, the temperature range and the maximum temperature achieved, were not well characterized, did not support claims or dosing instructions on the proposed product label, and did not match how the product is likely to be used in clinical practice. Specifically, the label indicates that the patch [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 and product quality control issues included:

- The drug release specifications of the S-Caine Patch were so wide that they approached the point of being 'meaningless' (Dr. Harapanhalli, CMC team leader)
- The patch manufacturing process had not been changed, subsequent to completion of (most of) the Phase 3 clinical trials. The [redacted] procedure whereby one of the patch layers is added had been revised subsequent to NDA, without subsequent bridging studies.

Cumulative irritation/sensitivity evaluation (adults)

Study SC-42-03 was a (CDER required) study of the cumulative irritation potential of the S-Caine Patch. The study report and data, as originally submitted with the NDA, did not allow for meaningful review. The paper report contained 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 consisted of a single fifteen-line file (listing fifteen adverse events). The final study report (as well as the rest of the NDA) did not contain a study protocol, or a definition of what would constitute an adverse event. It was 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. were also missing.

Heating element contribution to efficacy was outlined in Section 1.1 and is discussed in more detail in Section 9 (Review of Individual Study Reports). The S-Caine Patch integrated heating element had not been shown to contribute to product efficacy. Had the product otherwise been ready for approval, this would have posed a regulatory dilemma. FDA approval of the S-Caine Patch (with CHADD) would signify that the product and its components had been determined to be both safe and effective. The heating component had not been found to be effective, however, or to add to product efficacy. (The heating component *may* also be associated with a slight 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.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

Most of the clinical information submitted in the Complete Response attempts to addresses Division concerns about the S-Caine Patch integrated heating element. The heating element had not been demonstrated to contribute to product efficacy. The proposed label for the S-Caine Patch, however, describes the product as follows:

[redacted]

The clinical studies conducted subsequent to ZARS' receipt of the 2/2004 action letter are listed in Table 2.1 below.

Table 2.1: Newly Conducted Clinical Studies Reviewed

Study	Purpose	Design	Population (Heat/No Heat)	Duration Minutes
51-04	PK – Multiple simultaneous patches (1 vs. 2. vs. 4 for 60-minutes)	Parallel groups	48 Adult – Heat n=36, 18-64 y/o n=12, ≥65 y/o	60
52-04	Patch effect on skin temperature (CMC)	Parallel groups	32 Adult - Heat n=16, 18-40 y/o n=16, ≥65 y/o	120
53-04	Pilot efficacy trial in venipuncture Heating element present vs. inactive Application duration 20 mins vs. 30 mins Venipuncture – 16G vs. 18G	Parallel groups	80 Adult (37 /43)	20, 30
54-04	Efficacy trial - Venipuncture – 16G Heating element present vs. inactive	Parallel groups	250 Adult (122 / 128)	20
55-04	Efficacy trial - Venipuncture – 16G Heating element present vs. absent	Parallel groups	250 Adult (124 / 126)	20

Source: Prepared by clinical reviewer

Overall, the clinical development program for the S-Caine Patch, conducted under IND 58,823, consisted of studies utilizing three different product 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. Although ZARS included data obtained from studies utilizing the developmental product formulations in the initial NDA submission, only data from trials utilizing the final formulation were considered for the purposes of the first cycle clinical efficacy review. Table 2.2 on the following page lists clinical studies reviewed for efficacy findings during the first PDUFA cycle.

Table 2.2: Studies Reviewed for Efficacy Findings During the First PDUFA Cycle

Study	Efficacy Model	Design	Population Active/PBO	Duration (minutes)
24-01	Venipuncture	W-S [1]	40 Adult	20
23-01	Minor dermatological procedures	W-S [1]	94 Adult	30
20-01	Venipuncture (some IV cannulation)	P-G [2]	64 Child	20
21-01	Lidocaine injection, pretreatment	P-G [2]	88 Child	30
11-01	Venipuncture	W-S [1]	21 Adult	20
31-01	Venipuncture (PK in 10 out of 40 subjects)	W-S [1]	40 Geriatric	20
22-01	Minor dermatological procedures	P-G	79 Geriatric 54 / 25	30
40-02	Dose ranging: 10, 20, 30, 60 minute application Venipuncture (vs. EMLA)	P-G, durat.[3] W-S, RX [3]	82 Adult	10, 20 30, 60
41-03	Combination rule + venipuncture SC vs. Lidocaine vs. Tetracaine vs. Placebo	P-G	80 Adult	30
28-01	Combination rule SC vs. Lidocaine vs. Tetracaine vs. Placebo Pain Tolerance Threshold Testing	P-G	48 Adult	30
27-01	Combination rule: Heating element active vs. inactive Laser stimulation	P-G	53 Adult	20
29-01	Analgesia for immunization Safety in infants	P-G	67 Infant	30
	Trials Utilizing Developmental Formulations			
05-99	IV insertion	W-S	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

[1] Within-subjects, placebo-controlled [2] Parallel treatment groups, placebo-controlled
[3] All subjects treated with both S-Caine & EMLA, Application duration varied between parallel groups

2.1.1 Post Action Meeting

Discussion at the post-action meeting (05/03/04) predominantly focused on CMC and product quality issues. The design for clinical study SC-54-04 was discussed as well. The Division indicated basic agreement with the study design, as outlined in the meeting package. The Division also suggested that ZARS update their proposed Phase 4 commitment to evaluate S-Caine Patch safety and pharmacokinetics in neonates. One clinical comment from the 2/2004 action letter was also reiterated at the post-action meeting; the clinical trials conducted in the pediatric and geriatric populations had not provided particularly compelling evidence for product efficacy in those groups. Approval would not be withheld because of this last concern, however.

2.2 Efficacy Findings

2.2.1 Summary of New Efficacy Findings

According to the proposed product label "The S-Caine Patch (lidocaine and tetracaine topical patch) 70 mg/70 mg is indicated for local dermal analgesia on intact skin." All Phase 3 clinical studies conducted in support of this efficacy claim were randomized, double-blind and placebo-controlled, except for studies SC-53-04, SC-54-04 and SC-55-04, which compared efficacy between heat-generating and non-heat-generating patches, and SC-40-02, which employed an active control; EMLA Cream. Only SC-53-04, SC-54-04 and SC-55-04 were conducted subsequent to the February 2004 *Approvable* action. Data from all other trials were included in the initial NDA submission, and are discussed in detail in the first cycle clinical review.

The sponsor's only apparent goal in conducting new trials SC-53-04, SC-54-04 and SC-55-04 was to demonstrate an efficacy contribution for the heating element. SC-53-04 was a pilot study, and SC-54-04 failed to demonstrate any efficacy difference between the heated and the unheated product. SC-55-04 succeeded in demonstrating a difference between the heated and the unheated product. For SC-55-04 the unheated patches were manufactured with no heating components present, whereas in SC-54-04 patches were rendered heatless by a deactivation process (exposure to air for > 24 hours with manual manipulation). The two studies were otherwise identical. Table 2.3 below lists the newly conducted studies reviewed for efficacy findings.

Table 2.3: Newly Conducted Studies Reviewed for Efficacy Findings
(All Compare Patch with Heating Element to Patch without Functioning Heating Element)

Study	Efficacy Model	Design	Population Heat/No Heat	Duration Minutes
53-04	Pilot study in venipuncture Heating element present vs. inactivated Application duration 20 minutes vs. 30 minutes Venipuncture – 16G vs. 18G	Parallel groups	88 Adult enrolled 80 evaluable 37 / 43	20, 30
54-04	Heating element present vs. **inactivated** Venipuncture – 16G	Parallel groups	250 Adult 122 / 128	20
55-04	Heating element present vs. **absent** entirely Venipuncture – 16G	Parallel groups	250 Adult 124 / 126	20

Source: Clinical reviewer

All three trials evaluated S-Caine Patch use prior to venipuncture, utilizing a parallel group design. In SC-54-04 and SC-55-04 subjects received heated patch or non-heated patch, prior to a single venipuncture, and were then asked to rate procedure-induced pain using a 100-mm VAS scale. Secondary efficacy measures consisted of two Yes/No questions:

- 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?

The primary efficacy measure in all adult S-Caine Patch trials was subject pain rating using a 100-mm Visual Analogue Scale (VAS). Efficacy results from SC-54-04 and SC-55-04 appear in Table 2.4 below. In Study SC-55-04 the mean VAS score in the heated-patch group was 22.1 (±20.7) while in the un-heated patch group it was 28.7 (±22.8) ($p<0.05$, 2-sample t-test). Although not particularly impressive, this finding is statistically significant, and consistent with efficacy findings (VAS score difference between treatment groups) from earlier S-Caine Patch venipuncture trials.

Table 2.4: Summary of Efficacy Findings (SC-55-04 and SC-54-04)

	SC-55-04				SC-54-04			
	Heated n=124	**Unheated** n=126	**All** N=250	**P-value**	**Heated** n=122	**Unheated** n=128	**All** N=250	**P-value**
VAS (mm)								
Mean	22.1	28.7	25.4	0.0183[1]	19.4	21.2	20.3	0.470[1]
SD	20.7	22.8	22.0		18.8	19.8	19.3	
Median	16.5	22.0	20.0		13.0	14.0	14.0	
Range	0 – 97	0 – 95	0 – 97		0 – 85	0 – 77	0 – 85	
Geom. Mean	14.2	20.5	17.1	0.0065[2]	12.5	14.1	13.3	0.379[2]
% Adequate	71%	53%	62%	0.004[3]	75%	68%	72%	0.209[3]
% Use Again	71%	55%	63%	0.009[3]	76%	71%	74%	0.391[3]

[1] Two-sample t-test (Dr. Buenconsejo) [1] Two-sample t-test (Sponsor) [3] Fisher's exact test (Sponsor)
Source: Sponsor Tables 18.11.2, 18.11.3, 17.11.2, 17.11.3 and Dr. Buenconsejo's statistical review

ZARS' analysis of log-transformed primary efficacy data, although pre-specified, was not entirely appropriate. For her statistical review Dr. Buenconsejo analyzed these data (VAS scores) by performing a two-sample t-test on the actual means. Although the p-values increase for VAS scores from both studies, statistical significance (at <0.05) is maintained for the SC-55-04 data.

In pilot Study SC-53-04 three factors were varied; needle gauge (16G vs. 18G), treatment duration (20 minutes vs. 30 minutes), and heating element (active vs. inactive). Approximately ten subjects were studied under each of the eight possible treatment conditions (N=88 total, 9 to 13 subjects per arm). Efficacy measures were the same as those employed in 54-04 and 55-04. These data are discussed in Section 7.3.3.

Dr. Milton Fan, the first cycle statistical reviewer, had also noted numerous instances where the sponsor's analyses of (both primary and secondary) efficacy variables could have utilized more appropriate statistical tests. In his review, Dr. Fan included 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 (for 'new' as well as 'old' trials).

2.2.2 Summary of Earlier Efficacy Findings

ZARS has already provided acceptable evidence that S-Caine Patch is effective across the populations studied. The initial NDA submission designated four trials 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 to the left antecubital area, one to 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 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 in 10 of the 40 participants.

Phase 2/3 trials also assessed S-Caine efficacy in relieving or diminishing the pain caused by what ZARS 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 patient ratings on 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 pediatric 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 most Phase 3 efficacy studies in adults, although fewer were employed in the new efficacy trials (53-04, 54-04, 55-04). In the earlier trials these were:

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

- 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)

Dr. Fan (statistical review, first PDUFA cycle) considered two of the Phase 3 trials in adults to have been fundamentally flawed (SC-24-01 and SC-11-01, both in venipuncture) because of the study design 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 Summary of Safety Findings

The Integrated Summary of Safety (ISS) includes safety data from all subjects who received at least one patch application (active drug or placebo). Table 2.5 below summarizes these trials.

Table 2.5: Summary of Trials Included in Integrated Summary of Safety

Trial	Purpose	Patch	Populat.	N	S-Caine	Control[1]
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 Procedures	Final	Geriatric	79	54	25
23-01	Dermatologic Procedures	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	40	40
40-02	Venipuncture	Final	Adult	82	82	EMLA
41-03	Combo Rule/Venipuncture	Final	Adult	80	80	80
53-04[2]	Heat/No heat – Venipunct.	Final	Adult	88	41	47
54-04[2]	Heat/No heat – Venipunct.	Final	Adult	250	122	128
55-04[2]	Heat/No heat – Venipunct.	Final	Adult	250	124	126
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
51-04[2]	PK, Multiple simultaneous		Adult	48	36 adult	+ 12 geriat.
52-04[2]	Patch effect on skin temp.	Final	Adult	32	32	
Totals				**2075**	**1748**	**868+**

[1] Studies 53-04, 54-04 and 55-04 utilized a 'No Heat" control group in lieu of placebo
[2] Conducted subsequent to initial NDA review/action Source: Clinical reviewer

A total of 2075 subjects enrolled in S-Caine Patch clinical trials; 668 in the newly conducted trials. The number of subjects exposed to one or more applications of the final, to-be-marketed S-Caine Patch formulation was 1580 (299 of these subjects received non-heated patches). The total increases to 1748 subjects with inclusion of those exposed to the Developmental A and Developmental B product formulations.

Demographic characteristics of subjects included in the initial ISS database are shown in Table 2.6 below. Patients and normal volunteers of differing age (from three years of age on up), gender and race were adequately represented.

Table 2.6: Summary Demographics, Subjects Enrolled in Controlled Trials

Demographic	S-Caine Any Form	Final Formulation	Final No Heat	Develop-mental	Placebo	Other Controls*
Number	1630	1110	352	168	815	210
Age						
0m-2m	??	??	0	0	0	0
3m – 2y	34 (2%)	34 (3%)	0	0	33 (4%)	0
3 – 6 y	48 (3%)	42 (4%)	0	6 (4%)	36 (4%)	0
7 - 17	125 (8%)	42 (4%)	0	83 (49%)	120 (15%)	0
7-12 Y	58	18	0	40	--	0
13-17 Y	67	24	0	43	--	0
18-64 years	1279 (78%)	864 (78%)	341 (97%)	74 (44%)	523 (64%)	208 (99%)
65-74	103 (6%)	87 (8%)	11 (3%)	5 (3%)	79 (10%)	2 (1%)
≥75 years	41 (3%)	41 (4%)	0	0	24 (3%)	0
Gender						
Male	706 (62%)	466 (42%)	157 (45%)	83 (49%)	319 (39%)	102 (49%)
Female	924 (57%)	644 (58%)	195 (55%)	85 (51%)	496 (61%)	108 (51%)
Race						
Caucasian	961 (59%)	680 (61%)	188 (53%)	93 (55%)	475 (59%)	171 (81%)
Black	234 (14%)	209 (19%)	15 (4%)	10 (6%)	203 (25%)	15 (7%)
Hispanic	183 (11%)	88 (8%)	38 (11%)	57 (34%)	105 (13%)	3 (1%)
Asian	154 (9%)	74 (7%)	73 (21%)	7 (4%)	13 (2%)	12 (6%)
Other	105 (6%)	59 (5%)	38 (11%)	8 (5%)	28 (3%)	9 (4%)

* EMLA, lidocaine, tetracaine Source: Tables B4.1 and 4.1.1, Complete Response Volume 22

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 only 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 Regimens and Administration

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, as well as skin temperature, could also be

expected to effect transdermal drug delivery. Reliability (consistency) of the integrated heating element had been considered to be problematic, based upon data submitted for the first cycle review. Patch heating characteristics (ramp-up profile, peak temperature) varied widely between units. Consequently, drug delivery and absorption was thought to vary more than with traditional, non-heated transdermal delivery systems.

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. A eutectic mixture (1:1 ratio) of active drug components minimizes the melting point of the mixture. The effect of varying the concentration of active drug was never systematically evaluated, however. 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.

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 was the only S-Caine Patch trial to evaluate a 10-minute application period.

Table 2.7: 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 (NDA Volume 40)

The sponsor states "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 2.8: Dosing Across Vascular Adult Access Studies

Duration→	**20 Minutes**				**30 Minutes**		
Study	11-01	24-01	31-01	53-04	05-99	41-03	53-04
Formulation	Final	Final	Final	Final	Dev A	Final	Final
Median VAS							
S-Caine	1	5	8	13	2	3	9.5
Placebo	9	28	13	NA	30	22	NA
p-value[a]	0.004	<0.001	0.039		<0.001	<0.001	

Source: Tables 6.3A (NDA Volume 26) and 8.11.2 (Response Volume 16) [a] Wilcoxin signed rank test

Table 2.9: Dosing Across Pediatric Vascular Access Studies

Duration→	**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, NDA Volume 26 [c] Wilcoxin signed rank test

Table 2.10: Dosing Across Adult Minor Derm. Procedure Studies

Duration→	**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, NDA Volume 26 [a] Wilcoxin signed rank test

2.4.1 Repeat/Multiple Dosing

Six trials evaluated the (PK and/or local dermal) effects of multiple S-Caine Patch applications. Five of these had already been conducted, and data reviewed, for the first PDUFA cycle.

- SC-25-01 evaluated application of multiple (up to four) patches simultaneously, and SC-26-01 evaluated sequential (up to four) patch applications to the same site, both in adults. These studies are described in Section 5.
- SC-30-01 evaluated the application of (up to) two patches simultaneously in infants and children, ages 4 months to 12 years. (Section 9 for details)
- SC-29-01 was an efficacy study in infants, calling for administration of two patches simultaneously. (Section 7 for details)
- SC-42-03 was conducted in order to assess the cumulative irritation and contact sensitization potential of the S-Caine Patch. SC-42-03 was a six-week study calling for ten separate 120-minute patch applications; nine over the first three weeks, and the tenth at the beginning of the sixth study week. (Section 8 for details)

Study SC-51-04 evaluated single patch, and simultaneous application of two or four patches, all for 60-minutes, in 45 healthy adults (33 ages 18 to 65 and 12 ages 65 and up). Cmax and AUC increased as expected in the two and four patch conditions. Peak plasma lidocaine levels in the subjects (ages 18 to 64) receiving four patches remained below 9 ng/mL. Also, in subjects ages 65 exposed to two simultaneous patches peak plasma lidocaine levels remained under 6 ng/mL. Of note, Dr. Nallani reports that the SC-510-04 data are, on the whole, much cleaner than data from ZARS preceding clinical pharmacology studies, with less variability and no outliers.

2.5 Drug-Drug Interactions

Systemic absorption should be negligible, or "undetectable" with (single-dose) use as labeled, on normal intact skin. To the extent that unintended absorption does occur, however, drug-drug interactions observed with parenterally administered lidocaine and with other amide local anesthetics may be expected.

Possible S-Caine Patch effects in patients pretreated with other topical medications, or with systemically acting dermal sensitizers, were not evaluated. Product assessment in pretreated subjects (skin) is not routinely required for development of transdermal patch medications accornig to Dr. Luke (Medical Team Leader, DDDDP). They are not recommended or required by OGD or DDDDP.

2.6 Special Populations

Gender:
Individual efficacy studies were not adequately powered to allow for meaningful by-gender analyses. There do not appear to be significant differences in S-Caine Patch efficacy or safety between genders.

Race:
All races appear to have been represented in the S-Caine Patch development program, as do all "skin types" (I=VI), though not necessarily parallel to the US population as a whole. Of note, the 'new' studies were conducted in Hawaii and California. This likely explains the increased proportion of 'Asians' and 'Others' (presumably including Pacific Islanders) in these newer studies,

relative to these groups' representation during earlier development. A number of the earlier trials were run in East Coast urban centers, like Washington, DC. In those studies 'Black' subjects accounted for 70% or more of enrollment. This shift in racial representation is most likely of little direct clinical relevance.

Elderly:
There was sufficient representation of geriatric subjects in the S-Caine Patch development program. Efficacy results in the geriatric-only efficacy studies (SC-22-01, SC-31-01) do not appear to be as robust as for the general adult population; the S-Caine Patch treatment effect may be diminished. Pain ratings (100-mm VAS scores) were lower, across treatment conditions, in these two studies, than in otherwise identical trials including 18 to 65 year olds. The median VAS scores in SC-22-01 (dermatological procedures in geriatric subjects) for the S-Caine and placebo treated subjects were 8.0 and 13.5 mm, respectively. The median VAS scores, for S-Caine and placebo, in SC-23-01 (similar study in subject 18 years and older) were 5.0 and 31.0, respectively. The geriatric subjects may not have experienced sufficient pain to differentiate, or appreciate, a treatment effect.

Pediatric:
An adequate number of subjects have been studies in the overall pediatric population. Adequate safety data are not available, however for the neonatal population.

Renal and/or Hepatic Insufficiency:
No studies have been conducted specifically to evaluate S-Caine Patch application in these populations. Most studies excluded subjects with histories of significant systemic disease. The specific effects, if any, of these conditions on S-Caine Patch safety and efficacy were not characterized, then. Although systemic absorption should be negligible with use as labeled, it does occur in the setting of repeat and multiple patch applications (and presumably with prolonged application of a single patch) and lidocaine is hepatically metabolized. These considerations will be important for product labeling.

3 INTRODUCTION AND BACKGROUND

3.1 Proposed Indication

The sponsor proposes the following text for the S-Caine Patch "Indications and Usage" label section:

[redacted]

The wording for the S-Caine Patch label appears to have been based on that for the approved product EMLA® (lidocaine 2.5% and prilocaine 2.5%). EMLA was used as an active control in S-Caine dose-ranging study SC-40-02 (and was to be used in study SC-20-01 for QST comparison, before blinding issues forced a change in design). EMLA is also a eutectic mixture; comprised of structurally similar local anesthetics combined in a 1:1 ratio in order to depress the melting point of the resulting emulsion. EMLA Cream was initially approved in 12/1992 (NDA 19-941) "as a topical anesthetic for use on **normal intact skin** for local analgesia." The EMLA Anesthetic Disc (NDA 20-962, 02/1998) is marketed as a single-dose unit, consisting of one gram of EMLA emulsion within an occlusive dressing, with its own laminate backing and adhesive tape ring.

EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) and Anesthetic Disc share the same label (last revision 1999), in which the "Indications and Usage" section states:

"EMLA is indicated as a topical anesthetic for use on:

- Normal intact skin for local analgesia
- Genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia"

The EMLA "Dosage and Administration" section contains dosing information for adults, and for pediatric and for neonatal patients, for several different indications. For the indication most similar to the one proposed by ZARS, EMLA Cream and Disc are labeled for use in

"Minor dermal procedures such as intravenous cannulation and venipuncture"

EMLA Anesthetic Disc is also labeled for:

-
- [redacted]

3.2 Milestones in Product Development (Regulatory History)

3.2.1 Post Action Meeting

Discussion at the post-action meeting (05/03/04) predominantly focused on CMC and product quality issues. The design for clinical study SC-54-04 was discussed as well. The Division indicated basic agreement with the study design, as outlined in the meeting package. The Division

also suggested that ZARS update their proposed Phase 4 commitment to evaluate S-Caine Patch safety and pharmacokinetics in neonates. One clinical comment from the 2/2004 action letter was also reiterated at the post-action meeting; the clinical trials conducted in the pediatric and geriatric populations had not provided particularly compelling evidence for product efficacy in those groups. Approval would not be withheld because of this last concern, however.

3.2.2 Regulatory History through the First PDUFA Review Cycle

ZARS, Inc. opened IND 58,823 for the S-Caine Patch in July, 1999 intending to develop a local anesthetic patch that could be used prior to painful dermal procedures. The proposed drug product would incorporate ZARS' patented CHADD® (Controlled Heat-Aided Drug Delivery) system, a heat-generating layer designed to enhance transdermal drug absorption. The sponsor had already conducted a proof-of-concept study in 12 healthy volunteers, in which sensory and pain thresholds were tested using a calibrated depth gauge.

ZARS indicated intent to file a 505(b)(2) new drug application. Although there are numerous lidocaine NDAs, the last tetracaine NDA had been withdrawn years earlier, for reasons unknown to ZARS. DACCADP Project Management determined tetracaine withdrawal was the result of a marketing decision by the last NDA holder. The Agency had not voiced any clinical or CMC issues or concerns prior to the withdrawal.

Another meeting was held on May 9, 2000. At the time ZARS considered this to be an 'end-of-phase 2' meeting. The meeting minutes indicate that Dr. McCormick (DACCADP Division Director) stated that the background information submitted suggested that ZARS was not actually at that stage in their development process for a fruitful end-of-phase 2 meeting. ZARS was advised to prepare for another meeting, in addition to a pre-NDA meeting. The next meeting would be to discuss in detail the pivotal studies, the pediatric studies, and the final number of subjects necessary for an adequate safety assessment (as well as to address potentially serious CMC issues). Points made by the Division (pertaining to the S-Caine Patch clinical program) included:

- One primary efficacy endpoint should be specified for each Phase 3 trial.
- Repeat dose application testing (same site repeatedly, and multiple sites concurrently) should be evaluated. The main goals should be to obtain safety and PK information. A one to two hour interval between patch applications would be desirable.
- Different populations and skin types should be studied, including patients over 75 years, and children under 7.
    - The sponsor indicated that they were planning two special population studies; a single site study in geriatric patients (ages 60 to 85) and another single site study in neonates, to be conducted after appropriate nonclinical testing.
- The need for plasma sampling in infants and newborns would be informed by evidence of drug absorption in the piglet studies.
- [redacted]
- Subjects should return to study sites for visual skin inspection 24 to 48 hours after patch application.
- The anticipated total number of S-Caine exposures (approximately 540) would likely suffice.
- The S-Caine Patch (development program) could be required to satisfy the requirements of the combination drug policy. The Division was seeking guidance from the CDER Medical Policy Coordinating Committee.

- The amount and the uniformity of the heat delivered by the product should be better characterized.

During a teleconference (in lieu of a Type A meeting) held on October 9, 2000 Dr. McCormick reiterated the Division's position that S-Caine Patch would be held to the regulatory standards set for combination drug products. She pointed out that contrary to ZARS' contention, the prototype drug in this class, EMLA, had been held to the regulatory standards set for combination drug products. Study design and details were discussed for the remainder of the teleconference and an informational amendment was requested (addressing issues discussed at the May 2000 meeting).

Key points discussed during a June 28, 2001 teleconference "... to identify pivotal studies in the packet of written questions submitted" included:

- ZARS had defined two or three primary endpoints for each trial. The Division's earlier recommendation of a single efficacy endpoint for each trial was reiterated. Secondary measures could be designated also, however. ZARS stated their intent to use, as primary endpoint in all adult efficacy trials, subject VAS score. Pediatric trials would utilize the Oucher Scale.
- The Modified Behavioral Pain Scale score seemed an appropriate primary endpoint in subjects ages 2 and younger. If the product demonstrates efficacy in adults and older children, the Division would not be likely to question efficacy in younger children; only PK, dosing and safety data would be required in infants.
- Issues related to skin thickness, and the potential for methemoglobinemia in premature infants, were still of concern to the Division. ZARS was asked to document that the product does not cause methemoglobinemia, or other problems, in neonates and premature infants.
- ZARS outlined their anticipated timetable for product development: Adult and geriatric efficacy studies would be conducted first (beginning August 2001), followed by the multiple patch/dose PK studies, and then the pediatric efficacy trials.
- The sponsor requested that the Division not review the pediatric protocols (SC-20-01, SC-21-01) included with the April 2001 amendment. Updated versions would be submitted instead.

In June 2002 the sponsor responded to a January 2002 advice letter, including formal amendments to protocols SC-20-01, SC-21-01 and SC-29-01. In response to Division concerns and comments pertaining to use of two different Oucher scales the sponsor indicated that they intended to analyze efficacy results separately for the two groups. With respect to the evaluation of S-Caine use in newborns and neonates the sponsor proposed:

- Another redesign of SC-21-01; instead of comparing S-Caine Patch to EMLA, a traditional placebo-control would be used.
- Changes to SC-30-01 (multiple patch applications in children) in accordance with Division requests.
- A Phase 4 commitment of an additional safety study in newborns, similar in design to SC-30-01.

Another teleconference was held in September 2002 during which details of the skin sensitization and irritation testing study were discussed, and agreed upon, including deviations from the FDA Skin Irritation and Sensitization Guidance Document. The Dermatology (DDDDP) consultation memo (12/4/2002) indicated concurrence with the study design as proposed (SC-42-03).

At the pre-NDA meeting held on December 5, 2002 the following items were discussed:

- The sponsor stated that they had designed the S-Caine Patch clinical program to support the indication as a [redacted]
  They sought Agency concurrence regarding adequacy of their Phase 3 program "to support an NDA." They were reminded that the final decision on indication(s) will be made after full review of the clinical program.
- Agency concerns were reiterated, about repeat exposure at the same site, dermal sensitization with repeated uses over time, and prolonged product exposure (forgetting to remove the patch).
- The sponsor asked whether their projected totals for the adult, pediatric and geriatric populations were satisfactory (approximately 500, 200, 100, respectively). They were told that while the overall numbers appear adequate, the breakdown within the pediatric and the geriatric populations needs to be better specified. Specifically;
  - Pediatric subjects should include adequate representation of neonates, infants, children and adolescents.
  - Geriatric trials should include a significant number of subjects 75 years of age [and older].
- Dr. Chang referred the sponsor to the OGD guidance on dermatologic products, in which a 21-day protocol is the standard study we would request even for acute-use products, but noted that we would not request such a study if it would put patients at risk. The sponsor was advised to propose a study. Animal toxicity might be required in the labeling (if human sensitivity testing fell short of OGD recommendations. Dr. Rappaport noted that a DDDDP consult was pending.
- Dr. Chang inquired about two subjects that had drug levels the Division would regard as clinically meaningful. The sponsor stated that the doses were intentionally increased in those studies and they felt it unlikely such observations would be seen at normal exposure levels. Dr. Chang stated that the Division would look for evidence to support this in the NDA that is pharmacologically relevant systemic levels under clinical conditions that might be reasonable anticipated. Dr. Rappaport stated that such observations might be addressed in the labeling.
- The sponsor inquired if it would be acceptable to provide interim data on study SC-33-02 (neonatal PK) at filing of the application and then provide the balance during the review cycle, at approximately the 6-8 month point. ZARS was strongly encouraged to collect all of the data and submit it to the Agency by the 120-day safety update.

ZARS requested (12/17/2002) a waiver of the human drug application fee for NDA 21-623 under section 736(d)(1)(D), the small business waiver program. This waiver was granted (3/10/03).

NDA 21-623 was submitted on 4/8/03, and an *Approvable* action letter sent in February 2004.

3.3 Foreign Marketing

The S-Caine Patch has not been approved or withdrawn from market anywhere in the world. The sponsor reports no pending applications for this product outside of the USA.

4 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

4.1 Chemistry and Manufacturing

Chemistry and Manufacturing related problems with the S-Caine Patch application (alone) were of sufficient severity to preclude product approval during the first review cycle. Most of the major CMC concerns related to the integrated heating element. These included:

- The heating element does not begin to warm (significantly) until approximately 20 minutes after exposure to air. This does not correspond with how the product was studied in clinical trials; the foil packets containing the patches were opened just prior to application. This delay in warming could also make proper use of the S-Caine Patch impractical in many clinical settings.
- The heating element specifications are lower [redacted] than indicated on the proposed product label [redacted]. The [redacted] range is cited and discussed in parts of the NDA as well, such as during the sponsor's explanation of the rationale for incorporating it.
- The [redacted] range itself is too wide.
- Topical/dermal drug delivery would not be expected to increase as a result of achieving patch temperatures within most of the ' [redacted] range (The sponsor has not submitted evidence to the contrary).

Other CMC problems included:

- 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)

These issues (and others) were described in detail in Dr. Harapanhalli's first cycle CMC review.

Dr. Jila Boal (CMC) has determined that ZARS has provided adequate information in response to the February 2, 2004 action letter, for the most part. The updated DMFs for lidocaine and tetracaine are now adequate to support the application. Four issues awaiting resolution were discussed in a June 6, 2005 teleconference between Drs. Boal and Duffy, and ZARS.

- [redacted]
- ZARS and the Agency agreed that the proposed [redacted] drug release specifications would be accepted on an interim basis. Release specifications will be reassessed once commercial manufacturing begins.
- The specification for viscosity of the SBM will be determined at the time of release of the Bulk material, as well as during SBM stability testing.
- The specification for [redacted] levels has been modified to [redacted] in order to match the DMF [redacted] specification.

4.1.1 Summary of Drug Formulation Development

As discussed in Section 2.4 (Dosing) clinical studies utilizing three different S-Caine Patch formulations were submitted in support of this NDA (Study SC-01-95, conducted prior to the opening of IND 58,823 [redacted] Patches of each formulation contained the same absolute amounts of active drug, 70 mg each of lidocaine and tetracaine, but overall excipient volume decreased with each patch reformulation. The relative concentration of active drug increased with each reformulation, then. The final S-Caine Patch formulation contains

approximately [redacted] active drug, by weight, [redacted] the concentration of Developmental Patch A. The compositions of the three patch formulations are shown in Table 4.1 below.

In the clinical section of the NDA (Volume 26, page 12) the sponsor states "As discussed with FDA during the End of Phase 2 meeting on May 9, 2000, modifications to the formulation were required to improve the chemical stability of tetracaine." The meeting minutes indicate that tetracaine stability, and degradation product delivery were discussed, and that Dr. Uppoor (Biopharmaceutics Team Leader) stated that a pivotal bioequivalence study would not be necessary to link the commercial and the clinical batches if the commercial product (meaning the final patch formulation) is used in the Phase 3 clinical studies.

In NDA Volume 26 of the original NDA submission, the sponsor summarized evolution of the patch formulation as follows:

[redacted]

Table 4.1: Composition of S-Caine Patch Formulations

	Developmental A Formulation	Developmental B Formulation	Final Formulation
	[redacted]		
Components			
Lidocaine base, USP	70.00 mg	70.00 mg	70.00 mg
Tetracaine base, USP	70.00 mg	70.00 mg	70.00 mg
Polyvinylalcohol, USP			
[redacted]			
Sorbitan monopalmitate, NF		[redacted]	
Water [redacted]			
Methylparaben, USP			
Propylparaben, USP			

Source: Modified from Sponsor Table 1.1 in Volume 26, NDA 21-623

4.2 Animal Pharmacology/Toxicology

In support of NDA 21-623, the sponsor had conducted acute local tissue irritation studies, a 28-day repeat dose toxicology study, the standard battery of genetic toxicology studies for both lidocaine and tetracaine and segment II reproductive toxicology studies for lidocaine, tetracaine and the combination of the two in both rat and rabbit. As of the end of the first PDUFA cycle, the non-clinical findings had not raised concerns regarding future use in humans, but reproductive toxicology testing had not been completed.

Reproductive toxicology testing has now been completed (as of 4/1/05). ZARS testing program, considered to be adequate, is described in Dr. Suzanne Thornton-Jones' review.

4.2.1 Nonclinical Findings Previously Reviewed

The sponsor had conducted segment II studies (embryofetal development) in the rat and rabbit models. Although signs of maternal toxicity were evident, there were no indications that either lidocaine or tetracaine would be teratogenic under the conditions of the assays. The sponsor had agreed to complete segment I and segment III studies post-approval should the NDA be approved in the first cycle.

Collectively, the non-clinical studies suggest the potential for a mild local tissue reaction following acute exposure to non-abraded skin. Two studies were completed to characterize the potential for the S-Caine Patch to produce a local tissue reaction acutely, one in the rabbit, and the other in the neonatal pig. One hour exposures in the rabbit produced only very slight erythema, and no evidence of edema (while the placebo patch produced no erythema or edema), suggesting that the S-Caine Patch was a mild irritant. There was no clear evidence for local tissue irritation, from studies conducted in the neonatal pig model, thought to be the best pre-clinical model for human skin.

The potential for the S-Caine Patch to produce dermal sensitization and/or toxic plasma levels, following repeated exposure was evaluated in both guinea pig and rabbit models. The results indicated that the S-Caine Patch induced sensitization in guinea pigs, although with less intensity than the positive control, dinitrochlorobenzene (DNCB). The repeat-dose rabbit study used three patches per animal, applied for two hours once daily for 28-days, exceeding maximum daily exposures studied in humans. Repeated exposure in rabbits did result in increased local tissue irritation compared to placebo. (Microscopic skin changes evident with the S-Caine Patch were not evident in the skin treated with the placebo patch.) Plasma concentrations of lidocaine and tetracaine did not differ between animals with intact vs. abraded skin (beneath the patch) or between males and females.

The sponsor also completed a standard genetic toxicology battery for both lidocaine and tetracaine. Lidocaine base tested negative in the *in vitro* bacterial reverse mutation assay (Ames assay), the *in vitro* chromosome aberrations assay in Chinese Hamster Ovary (CHO) cells and an *in vivo* mouse micronucleus assay. Tetracaine tested negative in the *in vitro* bacterial reverse mutation assay and the *in vivo* mouse micronucleus assay. Although tetracaine tested negative in the absence of metabolic activation in the *in vitro* chromosome aberrations assay, in the presence of metabolic activation, tetracaine was equivocal.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetic and Pharmacodynamic Studies

Dr. Srikanth Nallani (DACCADP Biopharmaceutics) stated in his first cycle review:

> "Adequate data was provided to evaluate the systemic levels of lidocaine and tetracaine following single and multiple-repetitive or multiple-simultaneous S-Caine Patch application in healthy adults, pediatric and geriatric subjects. Overall, systemic exposure to the local anesthetics in subjects receiving topical S-Caine Patch is minimal and systemic pharmacological effects may not occur following the indicated usage. From a Clinical Pharmacology and Biopharmaceutics perspective, the submitted data is acceptable provided that a mutually acceptable agreement can be reached between the Agency and ZARS, Inc. regarding the text in the package insert and *in vitro* release method specifications."

Some of these data were of suboptimal quality, however, as described below. In response to the 2/2004 action letter, ZARS has conducted one additional clinical pharmacology study, SC-51-04 which is summarized below.

Six studies were conducted in human subjects to determine the extent of systemic absorption of lidocaine and tetracaine from S-Caine Patch administration; four in adults, one in the geriatric population and one in the pediatric population. Only one of these studies, SC-51-04, was conducted subsequent to the 2/2004 action.

Table 5.1: Studies Reviewed for Pharmacokinetic Findings

Study	Design	Population	Duration
SC-05-99	Single patch, placebo-controlled, XO	21 Adult	30 mins (n=20)
SC-25-01	Multiple simultaneous patches (30, 60 mins)	25 Adult	
	Period 1: 2 patches		30 mins (n=13)
	Period 2: 4 patches		60 mins (n=12)
SC-26-01	Multiple consecutive patches (same site)	24 Adult	
	Period 1: 1 (one) patch		30 mins (n=12)
	Period 2: 4 consecutive patches		60 mins (n=12)
SC-30-01	One vs. two simultaneous patches	42 Pediatric	30 mins
	Parallel group (one patch or two patches)	4 mo-2 yr	n=9 (3, 6)
		3 yr-6 yr	n=16 (8, 8)
		7 yr-12 yr	n=17 (10, 7)
SC-31-01	Single patch	40 Geriatric	
	Geriatric efficacy, PK sampling in 10 Ss		20 mins (n=10)
SC-51-04*	Multiple simultaneous patches (60 mins)		
	Parallel group (one, two, or four patches)	36 Adult (n=12/group)	60 mins (n=36)
	Parallel group (one, two, or four patches)	12 Geriatric	60 mins (n=12)

* SC-51-04 was the only newly conducted clinical pharmacology trial Source: Prepared by clinical reviewer

Two subjects in SC-25-01 had systemic lidocaine levels that would be considered in the therapeutic range for treatment of certain ventricular arrhythmias. Neither was reported as having been symptomatic, or experiencing an AE. One of these subjects also had detectable plasma tetracaine. These findings suggested that unpredictable systemic absorption was possible with clinically

plausible product use. ZARS attributed these elevated drug levels to sample above patch sites in the treated arm. (Presumably this would also have been the case for other subjects in the same trial who did not have elevated systemic drug levels, however.)

SC-51-04 (N=48 adults in total, 12 older than 65 years)
1 single 60-minute patch application (12 adult)
2 simultaneous 60-minute patch applications (12 adult + 12 geriatric)
4 simultaneous 60-minute patch applications (12 adult)

SC-31-01 (10 geriatric subjects, ages 66 to 78)
1 single 30-minute patch (n=10)

SC-30-01 (42 children ages 4 months to 12 years)
1 single 30-minute patch (n=21)
OR
2 simultaneous 30-minute patches (n=21)

SC-26-01 (24 adults)

Session 1	-----→	Session 2
1 single 30-minute patch (n=12)		4 repeat 30-minute patches (n=11)
	OR	
Session 1	-----→	Session 2
1 single 60-minute patch (n=12)		3 repeat 60-minute patches (n=12)

SC-25-01 (25 adults)

Session 1	-----→	Session 2
4 simultaneous 30-minute patches (n=13)		2 simultaneous 30-minute patches (n=12)
	OR	
Session 1	-----→	Session 2
4 simultaneous 60-minute patches (n=12)		2 simultaneous 60-minute patches (n=12)

SC-05-99 (Developmental Patch Formulation) (21 adults ages 20 to 34)
1 single 30-minute patch (n=20)

In study SC-30-01 (four study sites) the sponsor's analysis and discussion excluded data from five subjects because "the blood collection site was the same as the patch application site." Four of these subjects were from study site #302 (11 subjects enrolled), where patches were applied variously to the hands, the antecubital fossae and the thigh; the protocol dictated patch application to the thigh. DACCADP Biopharmaceutical review of the complete study reports has concluded that the sponsor's explanations and exclusions are plausible and acceptable.

For all outliers and excluded subjects, Dr. Nallani examined plasma drug levels obtained at the sampling times immediately before and after the unexpected value. In each case, comparison of the suspect value with those obtained before and after, indicated that the drug level in question was, in fact, almost certainly not attainable, or real. The sponsor's contention that these were incorrectly obtained, or contaminated blood samples, was supported by Dr. Nallani's analysis.

6 DATA SOURCES, REVIEW STRATEGY, DATA INTEGRITY

6.1 Sources of Clinical Data

The primary source of data used for this review was the sponsor's clinical trial program, as reported in the original NDA (Volumes 20 though 38), the 120-day Safety Update to that NDA (Volumes 1 through 9), the Complete Response to the February 2004 *Approvable* letter (Volumes 1, 12 to 23), and in IND 58,823 (Volumes 1 through 12). All correspondence, meeting minutes and reviews stored in the CDER Document Filing System (DFS) were also reviewed.

During the first review cycle two teleconferences were held subsequent to NDA filing between DACCADP review staff and the sponsor's representatives. During these teleconferences clarifications and corrections were requested of the sponsor. Information considered in the evaluation of S-Caine Patch safety and efficacy, not included at the time of initial NDA filing, was labeled as such within the first cycle NDA review. No such teleconferences were necessary during the second cycle (clinical) review.

6.2 Overview of Clinical Trials

Clinical trials in support of the initial NDA 21-623 submission were conducted under IND [redacted] between March 1999 and July 2003. (Results from Study SC-01-95, conducted in February 1996, were also submitted to the NDA. (SC-01-95 was conducted prior to ZARS' opening [redacted]

6.2.1 New Clinical Trials

Five clinical trials were conducted since the 2/2004 *Approvable* action. Three of these (SC-53-04, SC-54-04 and SC-55-04) were efficacy trials, utilizing similar study design, pain model, outcome measures and patient population. Results from pilot study SC-53-04 were supposed to guide the final design of SC-54-04. SC-54-04 was intended to be the definitive heat vs. no-heat trial, but failed to demonstrate any difference between the two (subjects in the no-heat arm were treated with S-Caine Patches with heating elements that had been inactivated by exposure to air). SC-55-04 was a repeat of SC-54-04, using (for the control group) patches especially manufactured for the trial, with no heating components present at all.

SC-51-04 was conducted in order to provide additional, 'cleaner' pharmacokinetic data. Study SC-51-04 was a clinical pharmacology trial in which subjects were treated for 60-minutes with one single patch, or with two or four simultaneous patches.

SC-52-04, although conducted in humans, was actually intended to address deficiencies in, and concerns about, the product's integrated heating component. Specifically, SC-52-04 aimed to provide data adequate to characterize heating component reliability.

These five trials are summarized in Table 6.1 below.

Table 6.1: Clinical Trials Conducted Subsequent to 2/2004 *Approvable* Action

Study	Purpose	Design	Population (Heat/No Heat)	Duration Minutes
51-04	PK – Multiple simultaneous patches One vs. two vs. four simultaneous	Parallel groups	48 Adult – Heat n=36, 18-64 y/o n=12, ≥65 y/o	60
52-04	Patch effect on skin temperature	Parallel groups	32 Adult - Heat n=16, 18-40 y/o n=16, ≥65 y/o	120
53-04	Pilot efficacy trial in venipuncture Heating element present vs. inactive Application duration 20 mins vs. 30 mins Venipuncture – 16G vs. 18G	Parallel groups	80 Adult (37 /43)	20, 30
54-04	Efficacy trial - Venipuncture – 16G Heating element present vs. inactive	Parallel groups	250 Adult (122 / 128)	20
55-04	Efficacy trial - Venipuncture – 16G Heating element present vs. absent	Parallel groups	250 Adult (124 / 126)	20

Source: Prepared by clinical reviewer

6.2.2 Previous Clinical Trials

Table 6.2 on the following page (reproduced from Section 9 of this review) lists the clinical studies for which the sponsor submitted results with the original NDA (21-623). In study SC-31-01, an efficacy trial in 40 geriatric subjects, PK samples were obtained in 10 subjects. PK sampling was also done in study SC-05-99, an efficacy trial in adults utilizing a developmental patch formulation.

Four dedicated PK trials, listed in Section 5 above; (SC-25-01 and SC-26-01 in adults and SC-30-01 in pediatric subjects, ages 4 months through 12 years. SC-42-03 was a repeat-dose cumulative irritation and sensitization study that enrolled 220 subjects.

6.3 Postmarketing Experience

As of May 1, 2005 the S-Caine Patch had not been approved for marketing anywhere in the world, nor had ZARS' other, very similar product, the S-Caine Peel (NDA 21-717).

Table 6.2: Controlled Trials Conducted in Support of NDA 21-623 (as of 8/2003)

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

Source: Prepared by clinical reviewer

6.4 Review Strategy

ZARS' *Complete Response* to the February 2004 *Approvable* letter, including electronic datasets, was received on 12/17/2004, and deemed acceptable for filing at the 2/15/2005 meeting. Each deficiency described in the letter appeared to have been addressed, as had some, though not all, of the Division's other comments and concerns. Preliminary review of the study reports and data tables revealed that the presentation of data was consistent, overall, with CDER guidance for industry. The study reports and data table format were very similar to those already submitted to the NDA (except, of course for the actual content) and considered to be acceptable.

Review focused on data from newly conducted clinical studies (SC-51-04, SC-52-04, SC-53-04, SC-54-04 and SC-55-04). Efficacy data from the latter three were reviewed in detail, with the most attention on successful trial SC-55-04. 'New' efficacy data were than compared with the older data, checking for consistency (i.e. magnitude of treatment effect, VAS score comparability).

For the safety review, data from the individual study reports were verified, and then cross-checked with the applicable line listings in the electronic datasets, as well as with corresponding tables in ZARS' updated Integrated Review of Safety. All CRFs were also reviewed. As with the earlier trials, because CRFs were only to have been submitted in case of SAE, very few (<15) were actually available.

6.4.1 Conduct of First Cycle Review

New Drug Application 21-623 had first been received on April 8, 2003, and upon preliminary review, also considered suitable for filing. All necessary items had been included with the exception of those the Division agreed cold be submitted with the 120-day Safety Update.

- Results of a rabbit dermal irritation study
- Requested information regarding outstanding reproductive toxicology issues
- Results from study SC-41-03, a repeat exposure skin irritation/sensitization evaluation
- Results from study SC-30-01, pharmacokinetic evaluation of multiple patch exposure, in the pediatric population

Although the sponsor had indicated intent to provide electronic data the NDA was initially submitted entirely on paper. Electronic data from the initial six clinical trials (developmental patches) were submitted in early August 2003, with the remainder to arrive within two weeks. Electronic data for the rest of the clinical trials eventually arrived in mid September.

Data from the four pivotal trials, as well as all other controlled clinical trials conducted in support of the proposed efficacy claims, were reviewed in detail. Trials utilizing early product formulations (Developmental A and Developmental B) were reviewed, but in less detail. For the safety review the sponsor's Integrated Summary of Safety was verified, and cross-checked with each individual study report. Additional analyses of the safety data, including review of all applicable line listings and case report tabulations was also done. By prior agreement, CRFs were only to be submitted in case of SAE. The CRFs for all fifteen subjects in SC-42-03 (repeat dose skin sensitization study) that experienced any adverse event were, however, submitted, and these were reviewed as well.

6.5 Materials Consulted for Review

Table 7.1 lists the items utilized during the course of this review. Items submitted to the NDA and to the IND were provided by the sponsor, while those from the Document Filing System were generated by the Agency.

Table 6.3: Items Consulted for Review of Complete Response

Item	Date	Description
Complete Response (Volumes 1; 15 - 22)	12/17/2004	Deemed fileable 2/15/2005
Electronic datasets	12/17/2004	Studies 51-04, 52-04, 53-04, 54-04, 55-04 only, and Updated ISS datasets
SC-42-03 Study Report	8/2004	Including CRFs
NDA 21-623 (Volumes 1; 20 - 38)	4/8/2003	Initial NDA submission Deemed filable 5/19/2003
NDA 21-623 120-Day Safety Update (Volumes 1 - 9)	8/4/2003	120-Day Safety Update
NDA 21-717	9/2004	DSI consultation/report
NDA 21-717	9/2004	Medical Ethics consultation/report
NDA 21-623 Document Filing System	08/2003 – 05/2005	Correspondence with sponsor (DACCADP PM)
NDA 21-623	06/06/05	Information requested re: timing of submissions

Source: Prepared by clinical reviewer

Table 6.4: Items Consulted for Initial Review of NDA 21-623

Item	Date	Description
NDA 21-623 (Volumes 1; 20 - 38)	4/8/2003	Initial NDA submission – deemed filable 5/19/2003
NDA 21-623 120-Day Safety Update (Volumes 1 - 9)	8/4/2003	120-Day Safety Update
NDA 21-623 120-Day Safety Update	8/4/2003	Study reports, SC-30-01 (PK) and SC-42-03 (irritation/sensitivity evaluation)
NDA 21-623	8/4/2003	Electronic data from PK studies
NDA 21-623	9/10/2003	Revisions (corrections) to electronic data
NDA 21-623	9/16/2003	Electronic data from remaining clinical studies
NDA 21-623	01/07/2004	ITT analysis for pivotal study SC-24-01 (requested)
	01/07/2004	Requested clarifications re: protocol amendments to SC-20-01, SC-21-01, SC-23-01, SC-24-01
	01/07/2004	Revisions (corrections) to electronic data (requested)
NDA 21,623 Document Filing System	04/2003 – 01/2004	Correspondence with sponsor (DACCADP PM) Teleconference minutes prepared by Lisa Malandro, PM
IND 58,823 (Volumes 1 - 12)	07/1999 – 02/2003	All clinical protocols, written reviews
Document Filing System IND 58,823	07/1999 - 03/2003	Division reviews, minutes of teleconferences, and meetings with sponsor, and correspondence (PM)

Source: Prepared by clinical reviewer

6.6 Evaluation of Data Quality and Integrity

6.6.1 Data Submitted with the Complete Response

The Complete Response was evaluated for data integrity and quality, with particular scrutiny to problematic areas identified during the first cycle review. First, the electronic datasets were reviewed for readily apparent errors or inconsistencies; none were found. Then individual study reports were reviewed, with careful cross-checking between report tables, and the data as presented in the electronic datasets. No errors or inconsistencies were identified. Finally, summary safety tables from my own first cycle review were revised manually, by addition of data from the new trials. These reviewer generated ISS tables were then compared with those presented by the sponsor in the Complete Response ISS.

No inconsistencies or errors have been identified in the Complete Response study reports and datasets. This could be attributable to increased vigilance and diligence on ZARS' part. As similar as the three new efficacy trials were to each other, ZARS was able to utilize identical file structures for study datasets, facilitating pooling of the data for the revised ISS. And, of course, the volume of electronic (clinical) data actually submitted, was only a fraction of what came before.

6.6.2 Data Originally Submitted to the NDA

The original NDA submission had also been evaluated for data integrity and quality by detailed review and retabulation of the data. Results reported in the Integrated Summary of Efficacy, the Integrated Summary of Safety, and the 120-Day Safety Update were crosschecked with the electronic data. The paper copies of study reports were compared with the electronic data, and evaluated for completeness, coherence, consistency and accuracy, revealing a number of errors, inconsistencies and missing values. These data problems and inconsistencies appeared to have been more readily attributable to poor data management and record keeping and to inadequate quality assurance procedures than to outright attempts at fraud, however. The most prominent of these mistakes were brought to the sponsor's attention during two teleconferences (12/2/2003 and 12/10/2003). Specific corrections and clarifications were requested for study reports and data from the four 'pivotal' efficacy trials (SC-20-01, SC-21-01, SC-23-01, SC-24-01). Revised electronic datasets arrived on January 7, 2004.

An accounting was then made of all subjects randomized, in all trials, and of all subjects who received the drug product during any trial. Comparisons were made between case report tabulations and individual line listings for all subjects with adverse events or who (were) discontinued.

All trials, except for SC-42-03, were conducted at academic medical centers subject to the rules and regulations of their own institutions. Study SC-42-03 (Cumulative irritation and contact sensitization evaluation) was conducted by a contract research organization, [redacted] The final study report for SC-42-03 was prepared by the CRO as well, and submitted to NDA 21-623 as part of the 120-Day Safety Update. This report includes tables containing the individual irritation and adherence scores for each subject (line listings basically), and photocopies of fifteen adverse event reports, but no summary tables or tabulations, or descriptive statistics. The electronic data for SC-42-03 consists only of a fifteen line file listing fifteen adverse events.

Problems with the study reports in the original NDA submission included:

- Protocol amendments, revisions and appendices were sometimes numbered and dated incorrectly. In at least one case a protocol amendment (dropping an entire component of the efficacy evaluation (QST) in a pivotal study SC-20-01) seems to be missing entirely. Indexing of the individual study reports (volumes) is inadequate. These problems made it difficult to trace the logical progression from initial submission of a proposed study, to results from the study ultimately conducted.

There were also scattered problems with the electronic datasets. These datasets did not appear to have been tested and reviewed for errors by the sponsor, or compared against the individual study data files. Questions regarding certain aspects of the data arose during the review process. These were sent to the sponsor. Copies of these requests are included in Appendix A of the first cycle clinical review.

- The integrated data files (all subjects in all clinical trials) (all AEs) contained numerous missing values (dates, treatment conditions, efficacy scores), including in some cases information about treatment condition
- Portions of data columns (AESEVERITY ↔ AESERIOUSNESS, lines 83 to 98) appear to have been transcribed in one of the ISS datasets (AE_ALL.XPT)
- Treatment condition information was also missing, or seemingly incorrect for some subjects/lines in the SC-28-01 datasets
- In some cases data was otherwise not internally consistent

The datasets for individual studies sometimes used similar, but not identical variable names, for identical measure. This made pooling of data difficult and error prone. Within each of the two main study populations, adult and pediatric, treatment conditions, most efficacy measures, and safety measures were the same, but variable or field names were not always consistent across studies.

Many variables that should have been coded as numeric, or categorical (ordinal or integer) were coded alphanumerically, making tabulation and analysis difficult. Furthermore, many of the data file entries appear to have been transcribed verbatim from the CRFs and contained spelling errors. For instance, the five erythema ratings using Draize Scoring, typically 0, 1, 2, 3, 4, or sometimes "None" "Very Slight" "Well Defined" "Moderate" and "Severe" appeared in the data tables as dozens of unique entries; "Very Slight" "v slight" "V slight" "Very slight-mild" "VS' "Slight" "slight" and others were all used for the "Very Slight" category.

Coding of the "minor dermatological procedure" data was done similarly. In SC-22-03, there should only have been two possible entries for the variable PROCTYPE ("Shave Biopsy" or "Superficial Excision"). There were over 50 unique entries including "superficial shave excision" "superficial biopsy" "biopsy" "biapsy" "superficial shave" etc. In this case failure to define and adhere to coding conventions was particularly problematic because the sponsor analyzed efficacy results by procedure type, but provided no key or map for determining how individual entries (and subjects) got classified. There were other summary tables and analyses presented in the NDA, not replicable for the same reasons. The dermatological procedures in SC-23-01 were grouped into five "anatomical location" categories; back/trunk, head/neck, arms/legs, etc. In the SC-23-01 data files there were 75 different (unique) entries for 94 subjects.

Other problems that complicated interpretation and analysis of the data included:

- Datasets contained numerically coded columns with no accompanying full-term descriptor columns (e.g., AESEVER was coded as '1', '2' or '3' but had no corresponding column containing "mild," "moderate" and "severe.")
- The same entry was sometimes used within a single data column to describe two different things
- Data cells were sometimes left blank making it ambiguous as to whether there was no data to report, or the data point was missing or overlooked.

These issues, along with others, were brought to the sponsor's attention during the first review cycle. Despite two additional submissions containing (minor) database revisions, many were never resolved. In the revised submission, integrity was evaluated by using the data tables to regenerate summary reports and key results from the trials used for determination of efficacy. Attempts to recreate summary tables using the sponsor's integrated table often proved fruitless, because of the many data problems, and (reviewer generated) summary reports often had to be tabulated and created manually.

6.7 Conduct in Accordance with Accepted Ethical Standards

[redacted]

Within the initial NDA 21-623 submission, as well as the Complete Response, each individual study report states "The study was conducted in compliance with Good Clinical Practices (GCP), the Declaration of Helsinki (as subsequently amended), and 21CFR§50 and 21CFR§56." The SC-42-03 report now also includes these affirmations (earlier it had not).

The initial clinical study, SC-01-95 was conducted outside of IND, in mid-1996, under the [redacted] A brief summary of study results is included in NDA 21-623, and the twelve subjects have been included in the sponsor's ISS database. The sponsor had been asked to submit a final study report, with data tables, but this has not been received.

6.7.1 Timing of Protocol and Amendment Submissions

ZARS appears to have conducted at least one trial, in its entirety, prior to submission of the protocol to the IND (SC-55-04). Investigational sites were rarely specified in the clinical protocols. Instead, they were designated in protocol amendments, many of which were not received until months after study completion. These practices both violate 21CFR Section 312.30. Table 6.5 on the following page summarizes submission dates for clinical study protocols and amendments.

Table 6.5: Timing of Protocol and Amendment Submissions to IND 58,823

Study		Pop	Dated	Submit	Conducted
24-01	Venipuncture	40 A	3/27/01	4/16/01	6/12 to 7/31/02
	Amend #1 date 6/19/01	#15		10/11/02	
	Amend #2 date 6/3/02	#15		???	
	Added twenty subjects without protocol amendment			NOT	
23-01	Minor dermatological procedures	94 A	3/27/01	4/16/01	3/04 to 6/3/02
	Amend #1 date 11/27/01	#15		10/11/02	
	Amend #2 date 3/28/02	#15		10/11/02	
20-01	Venipuncture (some IV cannulation)	64 P		4/16/01	5/16-12/12/02
	Amend #1 date 10/01/01, submit 10/1/01				
	Amend #2 date 3/29/02, submit		#12	5/10/02	
	Amendment #3 reportedly 12/11/02 ??? BIG		NOT	RECEIVED	Deleted QST
	But synopsis in 11/02 meeting package says				
	45/69 enrolled, still describes QST				
21-01	Lidocaine injection, pretreatment	88 P		10/12/01	6/06-11/20/02
	Amendment #1 5/09/02 (SN 12) in IND				
	Amendment #1 2/20/02 per sponsor NDA			6/4/02	CHANGE DESIGN
	Amendments #2-#6 dates		SN#15	10/11/02	Add/remove sites
11-01	Venipuncture	21 A		?	
31-01	Venipuncture (PK in 10 out of 40 Ss)	40 G			
22-01	Minor dermatological procedures	79 G		4/16/01	
	Amendment #1			10/02	
40-02	Dose ranging: 10, 20, 30, 60 minutes Venipuncture (vs. EMLA)	82 A			
41-03	Combination rule + venipuncture SC/Lidocaine/Tetracaine/Placebo	80 A			
28-01	Combination rule SC/Lidocaine/Tetracaine/Placebo Pain Tolerance Threshold Testing	48 A			
27-01	Combination rule: Heating element present/absent Laser stimulation	53 A			
29-01	Analgesia for immunization Safety in infants	67 I		10/16/01	
	Amend #1 dated 9/19/01			10/11/02	

Source: Clinical reviewer

6.8 Evaluation of Financial Disclosure

ZARS has included an FDA From 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) for each participating investigator. Review of the individual investigator documentation reveals that all (new trials as well as old) have denied direct financial interests in, or other arrangements with ZARS. ZARS reported that no investigators had potential conflicts of interest.

This statement is consistent with the affirmations made by the investigators themselves. ZARS also stated that:

- There were no financial arrangements between any of the listed investigators, and the sponsor, whereby the value of the compensation to the investigator could be affected by study outcome
- No listed investigator received 'significant payments of other sorts' as defined in 21 CFR 54.2(f)

6.9 Selection of sites for DSI inspection

Studies thought to represent crucial components of the overall S-Caine Patch development program were chosen for DSI inspection. These were:

- Both clinical sites used for SC-21-01, one of only two pediatric studies with the final product
- Two of the four sites used for SC-55-04 (and also SC-54-04), the study in which evaluation of the heating component demonstrated an efficacy contribution

7 INTEGRATED REVIEW OF EFFICACY

7.1 Studies Conducted Subsequent to Approvable Action

ZARS conducted three new efficacy trials in their endeavor to provide evidence for heating element efficacy. SC-53-04 was designed as a pilot study. Results from SC-53-04 were to guide ZARS' choice of application duration and needle gauge for their definitive heat vs. no-heat efficacy trial, SC-54-04.

Study SC-54-04, a randomized, double-blind trial, parallel group trial, was intended to be the definitive demonstration of the heating element's contribution to product efficacy. In SC-54-04 subjects were treated either with a to-be-marketed S-Caine Patch, containing an active heating element, or with a patch that had had its heating element inactivated by overnight exposure to air. The study failed to demonstrate any difference in efficacy. ZARS contends that the heat-inactivation process was inadequate; some of the patches were still capable of generating heat.

SC-55-04 was conducted after SC-54-04 failed to provide the hoped for findings. The two studies were essentially identical, except for the method by which the 'no heat' patch was prepared. ZARS manufactured patches that contained no heating element, specifically for use in SC-55-04, in order to ensure that the 'no heat' patches were incapable of generating heat. ZARS contends that these heatless patches were otherwise the same as the to-be-marketed product.

7.2 Earlier Efficacy Conclusions

Based upon the data initially submitted to NDA 21-636 (first review cycle), the following conclusions were drawn regarding the S-Caine Patch efficacy trials and proposed label claims:

- Efficacy in the adult population for venipuncture, and for superficial excision and shave biopsy (to approximately 3-mm depth), has been demonstrated.
  - Post-hoc analysis suggests that efficacy might be greater for procedures, (estimated by the investigator) [redacted]
- Geriatric findings suggest efficacy for the same indications, though less persuasively.
- Efficacy in 3 to 6 year-olds for use prior to venipuncture and lidocaine injection/infiltration has been adequately demonstrated.
- Efficacy in 7 to 17 year-olds has not been demonstrated. This may be the result of inadequate numbers of subjects in this age group in trials SC-20-01 and SC-21-01, or other issues related to study design and conduct. In study SC-21-01, for example, there was substantial variability between subjects in how the painful stimulus (lidocaine injection) was administered.
- Efficacy in infants (4 to 6 months of age) has not been demonstrated (SC-29-01).

Results from six efficacy trials utilizing developmental patches were submitted with NDA 21-623 (five with patch A, and one with patch B). Each of these trials was very similar in design to one or more of the Phase 3 trials (population, sample size, painful stimulus, efficacy measures). Active drug concentration in the developmental patches was only [redacted] that in the final patch ([redacted] Still, each study achieved (statistically significant) results on the primary, and some secondary efficacy measures, in some case where the matching Phase 3 trial did not. In particular, the developmental patch trials in 7-17 year olds appear to offer support for S-Caine efficacy, where the pivotal Phase 3 trials failed to. The sponsor conducted no bridging-type studies, however, that

might allow for direct comparisons between the developmental and the final patch formulations, or extrapolation of results.

7.2.1 Previous Dosing Conclusions

- The effects on patch efficacy of varying absolute amounts and concentration of active drug were not evaluated. The drug concentration in the initial developmental patch appears to have been selected arbitrarily. The evolution from Developmental Patch A (through Patch B) to the final S-Caine Patch formulation was dictated solely by chemistry and manufacturing concerns.
- The sponsor's choice of twenty and thirty minute patch application periods for all Phase 3 efficacy studies appears warranted based on the preliminary patch studies, and justified, by demonstration of efficacy at these doses (application duration). The proposed label Dosing and Administration section includes instructions not necessarily based upon any of the actual studies conducted, for instance: [redacted] procedures such as excision, shave biopsy [redacted], apply an S-Caine Patch to intact skin for at least 30 minutes." Applications of greater than 30 minutes duration (of the final formulation) were studied in only one efficacy trial, SC-40-02 in which S-Caine Patch was compared to EMLA application of identical duration (10, 20, 30 or 60 minutes). No efficacy difference was demonstrated between 60 minute S-Caine Patch and EMLA application.
- In SC-40-02, S-Caine Patch did "beat" EMLA at 10, 20 and 30 minute application durations, but not at 60 minutes (for venipuncture). This was the only S-Caine Patch trial to evaluate a 10-minute application.

7.2.2 'Combination Product' Conclusions

- The lidocaine/tetracaine combination patch (S-Caine) appears to be more efficacious than either drug alone (in patch formulations), as studied in SC-41-03.
- The S-Caine Patch heating component (CHADD) appears to contribute to product efficacy, as demonstrated in Study SC-55-04. This had not been the case previously, as Study SC-27-01 failed to demonstrate any efficacy difference between the S-Caine Patch with, and without, an active heating element (Section 8.3.12).

7.2.3 Label Claims and Information

- ZARS now proposes the label claim "The S-Caine Patch (lidocaine and tetracaine topical patch) 70 mg / 70 mg) is indicated for

[redacted]

- The use of the word "analgesia" instead of [redacted] would be more appropriate. Few trials attempted to assess [redacted] endpoints, and those that did failed.
- Whether or not the product is labeled broadly (i.e. for dermal analgesia) or for specific types of dermal procedures,

[redacted]

[redacted]. References to "venipuncture" or perhaps to "superficial venous access" would be more appropriate.

- The proposed label section, Clinical Studies, still contains a series of misleading claims, though fewer than in the original submission
- As noted above, proposed label dosing instructions [redacted] are not supported by the study results submitted to date.

7.3 Approach to Review of Efficacy

Table 7.1 lists all studies reviewed in order to reach efficacy conclusions. Only the first three (53-04, 54-04 and 55-04) were conducted subsequent to the 2/2004 *Approvable* action. They represent the main focus of this efficacy review. (All others were reviewed during the first PDUFA cycle. Discussion of efficacy findings from the 'old' studies has, for the most part, been excerpted from the first cycle clinical review.) The next four studies listed were sponsor designated as "pivotal trials." Each of the next three trials (11-01, 31-01, 22-01) was nearly identical to one of the "pivotal" trials, in terms of study design, painful stimulus employed, and efficacy and safety measures (31-01 and 22-01 limited enrollment to geriatric subjects).

Table 7.1: Studies Reviewed for Efficacy Findings

Study	Efficacy Contribution	Population	Duration (minutes)
	Newly Conducted Trials		
53-04*	Combination rule (±Heat) (Venipuncture) - Pilot	88 Adult	20, 30
54-04*	Combination rule (±Heat) (Venipuncture)	250 Adult	20
55-04*	Combination rule (±Heat) (Venipuncture)	250 Adult	20
	Pivotal Trials		
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
	Additional Phase 3 Trials		
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
	Phase 2 Trials		
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: (Pain Tolerance Threshold Testing) SC vs. Lidocaine vs. Tetracaine vs. Placebo	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
	Trials with Developmental Patch Formulations		
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

Source: Prepared by clinical reviewer

7.3.1 Efficacy trials conducted subsequent to the 2/2004 *Approvable* action

The sponsor's only apparent goal in conducting trials SC-53-04, SC-54-04 and SC-55-04 was to demonstrate an efficacy contribution for the heating element. SC-53-04 was a pilot study, intended to guide the choice of application duration, and needle gauge to be used, for (what was to be) the definitive efficacy trial, SC-54-04. SC-54-04 failed to demonstrate an efficacy difference between the heated and the unheated product, however. Study SC-55-04 was then conducted. SC-55-04 was identical to SC-54-04, except for the method by which non-heated patches were supplied. In SC-54-04 patches were inactivated by exposure to air (for greater than 24 hours) along with manual (mechanical) manipulation intended to ensure such exposure. For Study SC-55-04, though, the unheated patches were purpose-manufactured, with no heating element components present. Table 7.2 below summarizes these three studies

Table 7.2: Efficacy Trials Conducted Subsequent to 2/04 *Approvable* Action

Study	Purpose	Design	Population (Heat/No Heat)	Duration Minutes
53-04	Pilot efficacy trial in venipuncture Heating element present vs. inactive Application duration 20 mins vs. 30 mins Venipuncture – 16G vs. 18G	Parallel groups	88 Adult enrolled 80 evaluable (37 /43)	20, 30
54-04	Efficacy trial - Venipuncture – 16G Heating element present vs. inactive	Parallel groups	250 Adult (122 / 128)	20
55-04	Efficacy trial - Venipuncture – 16G Heating element present vs. absent	Parallel groups	250 Adult (124 / 126)	20

All three trials evaluated S-Caine Patch use prior to venipuncture, utilizing a parallel group design. In SC-54-04 and SC-55-04 subjects received either heated patch or non-heated patch, prior to a single venipuncture, and were then asked to rate procedure-induced pain using a 100-mm VAS scale. Secondary efficacy measures consisted of two Yes/No questions:

- 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?

In pilot Study SC-53-04 three factors were varied; needle gauge (16G vs. 18G), treatment duration (20 minutes vs. 30 minutes), and heating element (active vs. inactive). Approximately ten subjects were studied under each of the eight possible treatment conditions (N=88 total, 9 to 13 subjects per arm). Efficacy measures were the same as those employed in 54-04 and 55-04.

7.3.2 Efficacy trials previously reviewed

Controlled trials of the final patch in adults

Five randomized, controlled, double-blind, placebo-controlled studies utilizing the final formulation of the S-Caine Patch were conducted in adult (including geriatric) subjects.

- SC-24-01 (deemed pivotal by the sponsor), SC-11-01 and SC-31-01 evaluated the S-Caine patch for use prior to venipuncture. These studies employed healthy volunteers.
- SC-23-01 (pivotal per sponsor) and SC-22-01 evaluated the S-Caine Patch prior to protocol-defined "minor dermatological procedures" which were predominantly superficial excisions and shave biopsies. These subjects were also "healthy," except for their dermatologic lesion necessitating treatment.

Four other adult trials also utilized the final S-Caine Patch formulation.

- Venipuncture was the painful stimulus in two of these (SC-40-02, SC-41-03)
  - SC-40-02 was termed a "dose-ranging" study by the sponsor, and utilized an active control. Subjects underwent simultaneous administrations of S-Caine and EMLA, for 10, 20, 30 or 60 minutes.
  - SC-41-03 addressed "the combination rule." S-Caine Patch was compared to lidocaine patch, tetracaine patch and placebo patch (all with CHADD).
- SC-28-01 also addressed the combination rule, comparing S-Caine Patch to lidocaine patch, tetracaine patch and placebo patch (all with CHADD). "Pain Tolerance Threshold testing" was employed as the painful stimulus.

- SC-27-01 addressed the combination rule with respect to the S-Caine Patch heating element. Efficacy was compared between patches with active and with inactivated heating elements. Dermal laser stimulation (using a Versapulse®) was employed as the painful stimulus.

Venipuncture
In all, five (healthy adult volunteer) studies evaluated the S-Caine Patch for local anesthesia prior to "vascular access procedures" which were, in fact, exclusively venipuncture; SC-24-01 (pivotal), SC-31-01 (geriatric), SC-11-01, SC-40-02 (dose-ranging and active-control) and SC-41-03 (combination rule)
"Minor dermatological procedures"
Two trials evaluated S-Caine prior to minor dermatological surgical procedures; SC-23-01 (pivotal) and SC-22-01 (geriatric only)

Controlled trials of the final patch in pediatric populations
Three Phase 3 studies were conducted in pediatric subjects using the final patch formulation.
- SC-20-01 (pivotal per sponsor) evaluated S-Caine Patch prior to venipuncture (and IV cannulation in approximately one quarter of subjects) in 3 to 17 year-olds.
- SC-21-01 (pivotal per sponsor) evaluated S-Caine prior to a lidocaine injection (which was being administered for "minor dermatological procedures") in 3 to 17 year olds.
- SC-29-01) evaluated S-Caine prior to immunization in infants (3 to 6 months old).

Controlled trials utilizing developmental patch formulations
The six earliest S-Caine efficacy studies utilized "developmental" patch formulations (SC-01-95 conducted out of IND also employed an earlier patch formulation).
- Adult efficacy studies utilizing Developmental Patch A
  SC-03-99 and SC-07-99 evaluated S-Caine prior to shave biopsy. S-Caine prior to IV cannulation was studied in SC-05-99.
- Pediatric efficacy studies utilizing Developmental Patches A and B
  SC-09-99 (Patch A) and SC-10-00 (Patch B) evaluated S-Caine prior to venipuncture. SC-04-99 evaluated S-Caine (Patch A) prior to shave biopsy.

As noted in Section 4.1, the patch formulation had been altered because tetracaine stability concerns. Excipient and active drug concentrations were changed, but the absolute amounts of lidocaine and tetracaine in the patches remained unchanged, as did patch adhesive and heating elements. The "final formulation" of the S-Caine Patch contains greater lidocaine and tetracaine concentrations (by weight and volume) than earlier patches (details in Section 4.1 and Table 4.1 above). Still, the sponsor contends that "that the developmental patches are not expected to exhibit significant differences from the final patch with respect to clinical safety and/or efficacy." There were no bridging studies comparing the different patch formulations.

Combination Rule
Three efficacy studies were conducted in order to satisfy the "combination rule."
- SC-41-03 (listed above under adult Phase 3 trials) measured S-Caine effect on venipuncture induced pain, compared with lidocaine alone, tetracaine alone or placebo (all patches).
- SC-28-01 measured S-Caine effect on "Pain Threshold Testing" compared with lidocaine alone, tetracaine alone or placebo (all patches with heating element).

- SC-27-01 compared the effect of the S-Caine Patch with intact heating element to S-Caine Patch with deactivated heating element (on pain induced by laser stimulation).

Dose-Ranging Study
SC-40-02 was conducted as a standalone "dose-ranging" study.

- In SC-40-02 patch application time was systematically varied (10, 20, 30 and 60 minute applications) and compared with EMLA. Section 2.4 (Dosing) above also discusses sponsor reasoning behind the proposed dosing recommendations. "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."

Studies Incorporating Assessment of Anesthetic Endpoints
Four of the earlier trials proposed varying methods for utilizing identically repeatable painful stimuli. Three of these included assessment of anesthetic endpoints. (Study 01-95 conducted out of IND also purportedly assessed depth of anesthesia)

- Pediatric efficacy trial SC-20-01 originally planned to incorporate "Quantitative Sensory Testing" or QST at one of two sites. QST was described as an objective, repeatable (and validated) measure of local dermal anesthesia. The sponsor claims that because of logistical and time constraints, the investigator was unwilling to conduct the QST portion of the protocol. The QST component was dropped prior to study initiation.
- Study SC-28-01 (combination drug rule) utilized "Pain Tolerance Threshold Testing" a proprietary device (and scheme) for electrical stimulation of the skin. This factorial study failed to show any efficacy differences between treatments. The sponsor attributed this to inadequacies inherent to PTT testing (The stimulus induced insufficient pain due to investigator reservations about utilizing high enough current levels)
- Study SC-04-99 incorporated pin-prick testing of investigator-rated "adequate anesthesia." This was a crude (rough) attempt at assessment of dermal sensation, in that consistency (between subjects, and between investigators) of both the stimulus, and the outcome measure, are difficult to ensure.
- Study SC-27-01 (assessment of heating element contribution) employed laser stimulation with a Versapulse® laser, which is used clinically for dermal procedures such as tattoo removal. This allowed for repeatable, identical (between subjects) dermal stimulation. Efficacy endpoints, however, were the same as those used in most of the other adult S-Caine trials (VAS and patient and investigator ratings of pain).

ZARS failure to demonstrate S-Caine Patch local dermal anesthetic characteristics was most likely the result of inadequate study design and flawed study conduct. More details are available in the first cycle clinical review.

7.3.3 Efficacy Measures

Primary
All Phase 3 efficacy trials in adults, both new and old, 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 one of two "Oucher Scales" as the primary efficacy measure. 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 six pictures (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 the secondary efficacy measures were:

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

In the pediatric trials (except SC-29-01 in infants) the secondary efficacy measures were:

- 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)

Two of the developmental patch trials also included parent evaluations of subject's pain, using the same four-point categorical scale.

Some of the "dermatological procedures" trials also recorded "Use of rescue lidocaine (Yes/No)" as an intended outcome measure. This measure, recorded inconsistently, is not likely to be useful in any discussion of efficacy (no standardization of supplemental lidocaine use within/between trials).

7.4 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 7.3, modified from Table 4.1 in NDA Volume 26, summarizes subject-rated outcome measures for these four studies.

Table 7.3: 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

7.5 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 7.4, modified from Table 4.2 (NDA Volume 26) summarizes subject-reported outcomes for these studies.

Table 7.4: 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

7.6 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 7.5,

Table 7.6 and Table 7.7 summarize patient-reported primary, and investigator-rated secondary efficacy results from these three studies.

Table 7.5: 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: Tables 12.1, 12.2, NDA 21-623 Volume 31

Table 7.6: Pivotal Pediatric Trial SC-20-01 Vascular Access (N=61)

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

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

Table 7.7: 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	40	NA
P-value [a]	<0.005	0.322 [b]	
Secondary Efficacy (P-values)			
Investigator Evaluation			
Pain Rating			0.401
"Adequate Anesthesia"			0.028
Observer			
Pain Rating			0.269
"Adequate Anesthesia"			

[a] Mann-Whitney test

Source: Table 12.3, Volume 32

Table 7.8 below summarizes efficacy findings from pediatric trials in which developmental patch formulations were employed.

Table 7.8: 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: Table 12.5, NDA Volume 36

8 INTEGRATED REVIEW OF SAFETY

8.1 Brief Statement of Findings

- A total of 1748 adult and pediatric subjects have been exposed to the S-Caine Patch (including developmental formulations) to date. One thousand five hundred and eighty (N=1580) received the final product formulation. Two hundred and ninety nine (N=299) of these 1580 received non-heated versions of the final product. Most subjects received single 20 or 30-minute patch exposures, in controlled trials. Two-hundred and twenty subjects were evaluated in the six-week, ten-dose dermal irritation and sensitization study. One hundred and thirty nine (N=139) subjects were treated in (dedicated) clinical pharmacology studies.
- One-hundred and sixty-eight subjects received developmental S-Caine Patch formulations, 79 adult and 89 pediatric.
- There have been no subject deaths during S-Caine Patch clinical development.
- There was one SAE (a subject suffered a gunshot wound during participation in the six-week cumulative irritation study). There was one TEAE leading to discontinuation in SC-40-02.
- In the controlled trials there were a total of 64 AEs in 56 S-Caine treated subjects. Forty-four (n=44) of these occurred in the previously conducted trials. Fifteen of these occurred in patients enrolled in SC-42-03 (10-exposure cumulative irritation study).
- All AEs (except the GSW) were self-limited and brief. Most lasted only minutes, and resolved without treatment. The frequency and pattern of adverse events do not appear to differ between the newer clinical studies (SC-52-04, SC-53-04, SC-54-04 and SC-55-04) and the earlier ones.
- "Slight" or mild erythema at the patch application site was common, occurring with approximately 50% of product applications. Erythema was reported to have resolved without treatment in all cases (usually within 20 to 30 minutes after patch removal).
- Based upon the earlier data (SC-28-01 alone), there appeared as if there might have been a (non statistically significant) trend towards a higher incidence of "very slight" and "slight" erythema with the (heated) S-Caine Patch, compared with the non-heated version. The newer safety data (from SC-53-04, SC-54-04 and SC-55-04) do not suggest this to be the case, however.
- Repeat patch applications at the same site, multiple simultaneous patch applications, and prolonged single patch application are anticipated in clinical practice. In order to characterize the possible results of such "excessive" patch use (i.e., systemic absorption resulting in toxic serum concentrations and/or increased incidence of local toxicity), these scenarios were addressed in studies SC-25-01, SC-26-01, SC-30-01, SC-42-03, SC-51-04 and SC-52-04. Adverse events were rare in these trials also (even in SC-42-03), but prolonged application duration, especially for 120-minutes or greater, does appear to increase the incidence of local adverse events such as rash. Adverse events possibly attributable to systemic lidocaine or tetracaine exposure do not appear to have been more common in these trials, however.
- Use of the S-Caine Patch in accordance with the proposed product labeling (single 20 to 30 minute application over intact skin) is not expected to result in detectable systemic tetracaine levels, or in clinically relevant lidocaine levels. Section 5 (Human Pharmacokinetics and Pharmacodynamics) summarizes findings pertaining to systemic drug exposure.
- The study report for SC-42-03 (cumulative irritation and sensitization) is now complete. Although it is not possible to know with certainty that none of the discontinuations were adverse event related (10% study drop-out rate), most seem to have resulted because of subjects' logistical and transportation issues. The patch appeared to be "mildly irritating," but not

sensitizing, in some subjects, prior to their drop-out. Similar (irritation) effects were not uncommon in subjects that completed the six-week study, though.

8.2 Adequacy of Exposure and Safety Assessment

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

The majority of exposures occurred in subjects that received a single S-Caine Patch application of 10, 20, 30 or 60 minutes duration. Seventeen studies (the five 'new' trials and 11-01, 20-01, 21-01, 22-01, 23-01, 24-01, 27-01, 28-01, 29-01, 31-01, 40-02, 41-03) administered single doses of the final S-Caine Patch formulation. Six studies (03-99, 04-99, 05-99, 07-99, 09-99, 10-00) administered single doses of developmental S-Caine Patch formulations. In total, 1506 subjects were exposed to a single administration of one S-Caine Patch; Developmental A, Developmental B or the final S-Caine Patch formulation (heated and non-heated combined).

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

Four trials (25-01, 26-01, 30-01 and new Study SC-51-04) called for administration of multiple patches during a single study session, in order to obtain blood samples for pharmacokinetic analysis, and to assess safety parameters. One study, SC-42-03 (dermal irritation and sensitization assessment) exposed each subject to 10 separate 120-minute patch applications over a six-week period. Study SC-01-95 was a preliminary proof of concept study in which 12 subjects received single 30-minute patch applications. SC-01-95 was conducted prior to opening of the IND, and the precise patch formulation employed is not fully described (in either the original NDA submission, or in the Complete Response). ZARS reports that there were no adverse events during SC-01-95, but these 12 subjects/exposures have not been included in the safety database.

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

Table 8.1: Trials Included in Integrated Summary of Safety

Trial	Purpose	Enrolled	Popul.	S-Caine	Control
				(Completed / Planned)	
Efficacy Trials					
03-99*	Shave biopsy	59	Adult	29/29	30/30
04-99*	Shave biopsy	60	Peds	30/30	30/30
05-99*	IV insert + PK	22	Adult	20/22	21/22
07-99*	Shave biopsy	60	Adult	29/29	31/31
09-99*	Venipuncture	60	Peds	30/30	30/30
10-00*	Venipuncture	60	Peds	30/30	30/30
11-01	Venipuncture	21	Adult	21/21	21/21
20-01	Venipuncture (+ IV)	65	Peds	41/43	21/22
21-01	Lidocaine inject	88	Peds	41/41	47/47
22-01	Dermatologic Procedures	79	Geriatric	54/54	25/25
23-01	Dermatologic Procedures	94	Adult	45/45	49/49
24-01	Venipuncture	60	Adult	60/60	59/60
27-01	Heating element ± active	53	Adult	Heat 53	No heat 53
28-01	Combo rule (vs. Lido vs. Tetra)	48	Adult	48/48	NA
29-01	Immunization	67	Infant	34/34	33/33
31-01	Venipuncture (PK, n=10)	40	Geriatric	40/40	40/40
40-02	Venipuncture (vs. EMLA)	82	Adult	81/82	81/82
41-03	Combo Rule/Venipuncture	80	Adult	80/80	80/80
53-04	Heating element pilot ± active	88	Adult	43/43	45/45
54-04	Heating element ± active	250	Adult	122/122	128/128
55-04	Heating element present/absent	250	Adult	124/124	126/126
Safety and PK Trials					
25-01	Repeat applications	26	Adult	24/26	0
26-01	Simultaneous applications	24	Adult	23/24	0
30-01	Simultaneous applications	42	Peds	42/42	0
33-02	Single application	0	Neonate	0/12	Ongoing
42-03	10 exposures over 6 weeks	220	Adult	198/220	198/220
51-04	Simultaneous applications	48	Adult	48/48	NA
52-04	Heating element/skin temperature	32	Adult	32/32	NA
Totals w/o 42-03	Enrollment	**1838**		**1270/1276**	**948/952**
Totals	Enrollment	**2075**		**1474/1496**	**1146/1172**

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

Table 8.2: Single-Dose Studies Reviewed for Safety Findings (Final Formulation)

Study	Efficacy Model	Population	Treatment	Duration	N	AEs
55-04	Venipuncture	250 Adult	Heat Present	20 m	124	5
			Heat Absent	20 m	126	2
54-04	Venipuncture	250 Adult	Heat Active	20 m	122	1
			Heat Inactive	20 m	128	3
24-01	Venipuncture	60 Adult	S-Caine	30 m	20	
			S-Caine	20 m	40	
			Placebo	30 m	20	
			Placebo	20 m	39	
23-01	Dermatologic Procedures	94 Adult	S-Caine	30 m	45	1
			Placebo	30 m	49	0
20-01	Venipuncture	61 Pediatric	S-Caine	20 m	43*	0
			Placebo	20 m	22*	0
21-01	Lidocaine Injection	88 Pediatric	S-Caine	30 m	41	2
			Placebo	30 m	47	0
31-01	Venipuncture AND	40 Geriatric	S-Caine	20 m	40	0
	PK Measures		Placebo	20 m	40	0
11-01	Venipuncture	21 Adult	S-Caine	20 m	21	0
			Placebo	20 m	21	0
22-01	Dermatologic Procedures	74 Geriatric	S-Caine	30 m	54	0
		79 Enrolled	Placebo	30 m	25	0
------	↓ ------- Phase 2 ------- ↓					
53-04	Venipuncture ±heat pilot	88 Adult	Heat Active	20 m/30 m	19 / 24	
			Heat Inactive	20 m/30 m	22 / 23	
52-04	Heat – skin temperature	32 Adult	Heat Active	120 m	32	
40-02	Venipuncture (vs. EMLA, 10-60 mins.)	82 Adult	S-Caine	10, 20 30, 60 m	20 each	
			EMLA	10, 20 30, 60 m	20 each	
41-03	Venipuncture Combination Rule	80 Adult	S-Caine	30 m	80	5
			Lidocaine	30 m	80	3
			Tetracaine	30 m	80	1
			Placebo	30 m	80	1
28-01	Pain Threshold Test	48 Adult	S-Caine	30 m	48	8
	Combination Rule		Lidocaine	30 m	48	2
			Tetracaine	30 m	48	4
			Placebo	30 m	48	3
27-01	Combination Rule: Heating Element	53 Adult	SC heat	20 m	53	1
			SC no heat	20 m	53	1
29-01	Immunization	67 Infant	2 S-Caine	30 m	34	0
			2 Placebo	30 m	33	1

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

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

Source: Prepared by clinical reviewer

Table 8.3: Multiple-Dose Studies Reviewed for Safety Findings (Final Formulation)

Study	Assessment/Design	Population	Treatment	Duration	N	Ss with AE
51-04	PK and local effects	48 Adult				
	1 vs. 2. vs. 4 simultaneous		SC X 1	60 m	12	0
			SC X 2	60 m	24	0
			SC X 4	60 m	12	0
25-01	PK and local effects					
	2 simultaneous vs. 4 simult.	25 Adult				
	(Crossover)					
	Group 1, n=12, 30 min	(n=13, 30 m)	SC X 2	30 m	12	0
			SC X 4	30 m	13	0
	Group 2, n=12, 60 min	(n=12, 60 m)	SC X 2	60 m	12	0
			SC X 4	60 m	12	1 (6%)**
26-01	PK and local effects					
	1 patch vs. 2 sequential	24 Adult				
	(Crossover)					
	Group 1, n=12, 30 min	(n=12, 30 m)	SC X 1	30 m	12	4 (33%)
			SC X 2	30 m	11	5 (45%)
	Group 2, n=12, 60 min	(n=12, 60 m)	SC X 1	60 m	12	2 (17%)
			SC X 2	60 m	12	5 (42%)
30-01	PK and local effects					
	1 patch vs. 2 simultaneous	42 Pediatric			42	
		(4 m – 12 yr)				
			SC X 1	30 m	21	3 (4 AEs)
			SC X 2	30 m	21	2 (3 AEs)
42-03	Irritation/sensitivity/No PK					
	10 exposures over 6 wks	220 Adult		120 m	220	15
	120 minutes each	198 Complete				
29-01	Efficacy/ Immunization	67 Infants		30 m		
	No PK	4 M – 6 M	SC X 2	30 m	34	0
	Placebo-controlled		Placebo X 2	30 m	33	0

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

Source: Clinical reviewer

Table 8.4: Single-Dose Developmental Patch Studies Reviewed for Safety Findings

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

Source: Prepared by clinical reviewer

Overall, the extent of exposure in the S-Caine Patch clinical studies appears sufficient to enable adequate safety review, for both the pediatric and adult (including geriatric) populations. Ongoing trial SC-33-02 had been expected to provide safety data in newborns (and premature infants), but no additional patients have been enrolled (total neonatal exposure n=3).

Table 8.5: Extent of Exposure; Number of Subjects with a Single Patch Exposure

	Dev A	Dev B	Final	Final No heat	Placebo	EMLA	Lido	Tetra
Controlled								
10 Minute	0	0	20	0	0	20	0	0
20 Minute	0	30	482	329	151	20	0	0
30 Minute	79	0	334	23	351	22	128	128
60 Minute	59	0	20	0	60	20	0	0
Total Controlled	138	30	856	352	562	82	128	128
PK/Safety Studies								
30 Minute	0	0	33	0	0	0	0	0
60 Minute	0	0	24	0	0	0	0	0
120 Minute	0	0	32	0	0	0	0	0
Total PK/Safety	0	0	89	0	0	0	0	0
Total Single Dose	138	30	609	53	562	82	128	129

Source: Complete Response Table 22.B3.1 and data listings in Appendix 16.1.2 (Comp. Resp. Volume 22)

Table 8.6: Extent of Exposure, Subjects with Multiple Simultaneous Patches (Including SC-42-03, Cumulative Dermal Sensitization/Irritation Study)

	2 Simul [a]	4 Simul [b]	3 Repeat [c]	4 Repeat [c]	2 Placebo	10 Repeat [d]	10 Placebo [d]
20 Minute	0	0	0	0	0	0	0
30 Minute	67	13	0	11	33	0	0
60 Minute	36	24	12	0	0	0	0
120 Minute	0	0	0	0	0	220 enrolled 198 complete	220 enrolled 198 complete
Total	103	37	12	11	33	198	198

[a] 2 simultaneous SC-25-01, SC-29-01, SC-30-01, SC-51-04
[b] 4 simultaneous SC-25-01, SC-51-04
[c] 3 repeat OR 4 repeat SC-26-01
[d] SC-42-03 10 applications over 6-wks

8.3 Clinical Safety Studies

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

Study SC-42-03 was conducted in accordance with OGD guidelines, in order to determine the cumulative irritation and contact sensitization potential of S-Cane Patch in healthy adult subjects.

SC-42-03 was a six-week study calling for ten separate 120-minute patch applications; nine over the first three weeks, and the tenth at the beginning of the sixth study week. By agreement with the Division, The SC-42-03 study report was submitted with the 120-Day Safety Update. Ten-percent of the 220 (ages 18 to 70) enrolled subjects failed to complete all ten visits. The S-Caine Patch was deemed to be "mildly irritating" (2 on a scale of 6) but not sensitizing, for many subjects; drop-outs as well as completers. Mild irritation effects were not uncommon and skin irritation scores did not appear to have any correlation with study drop-out.

A study timetable appears below in Table 9.7.

Table 8.7: SC-42-03 Treatment and Assessment Schedule

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

Source: SC-42-03 study report (Amendment to NDA 21-717, submitted 8/2004, page 5)

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

Skin Irritation Grading Scale

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

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

Table 8.8: SC-42-03 Subject Disposition

Subject Disposition	Number
Enrolled in Study	220
Withdrew During Study	22 (10%)
Missed Visits (True Drop-Outs)	14 (6%)
Subject Request	8 (4%)
Completed Study	198 (90%)

Source: Applicant Table 10.1, prelim. SC-42-03 report (9/7/04)

Table 8.9: Number of Visits Completed

Study Sessions Completed	Subjects N = 220	Percent
10	182	83%
10 *	16	7%
9 **	2	1%
7	2	1%
6	3	1%
5	2	1%
4	1	<1%
3	3	1%
2	2	1%
1	7	3%

*Missed one study session during sequence, but completed a 'make-up' session

**Missed only the final session, which was three weeks after The main part of the study (3 sessions weekly X 3 wks.)

Source: Applicant Table

Skin scoring for severity of irritation

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

Table 8.10: Skin Irritation Scores and AEs, Drop-Outs*

Subject	Sessions Completed	Most Severe Skin Score	AE
42010	9	2A	N
42013	6	2	N
42064	6	2	N
42079	5	2A	N
42083	1	0	N
42088	3	2A	N
42100	5	2	N
42104	2	1A	N
42121	2	2	N
42135	4	2	N
42143	0	NA	N
42189	7	2	N
42219	1	0	N
42220	3	2	N

*Some SC-42-03 subjects gave reasons for not being able to complete the trial, whereas others simply never returned to the clinical site

*See Table below for list of subject reasons for discontinuation

Source: Applicant Table 10.2, prelim. SC-42-03 report (9/7/04)

Table 8.11: Reasons Given by Subjects for 'Foreseen Discontinuation'

Subject	Reasons Given By Subject	Visits Completed	Most Severe Skin Score	AE
42033	New job and unable to commit time	5	2	N
42036	Anticipated drop due to foreseen misses	6	2A	N
42044	Family emergency	9	2	N
42049	No reason given	7	2	N
42141	Family emergency	1	1	N
42165	Change in work schedule	2	1	N
42177	Working overtime	1	2	N
42180	Working overtime	1	0	N

Source: Applicant Table 10.3, prelim. SC-42-03 report (9/7/04)

Review of the data listings shows that in all but two cases, the greatest severity skin score was not at the last study visit attended, but earlier in the subjects' participation.

8.3.2 SC-51-04: An Open-Label Study Evaluating S-Caine Patch Heating Characteristics

ZARS conducted SC-52-04 (on 7/14/04 and 7/15/04) in order to obtain *in vivo* temperature profile data on the S-Caine Patch. Thirty-two healthy adult volunteers each had S-Caine Patch applied to the right volar forearm surface for 120-minutes (after 30-minutes of baseline temperature measures). Using a thermocouple attached to the center of the patch application site, skin temperature was recorded every 60 seconds for 180-minutes; from 30-minutes prior to S-Caine application until 30-minutes after patch removal. Visual safety evaluations and reporting were the same as those used throughout the development program.

ZARS reports that mean baseline skin temperature was 32° C. ZARS also reports that the mean time to reach 36° C was 5.3 minutes, but also that the mean skin temperature five minutes after patch application was 37° C. It is unclear how both of these last two findings could be correct, however. Mean skin temperature at 20, 30 and 119 minutes after patch application are reported as 37° C, 38° C and 34° C, respectively.

The only reported adverse event occurred in a 69 year old female who experienced mild bruising at the patch application site. The bruising resolved completely within four days, without specific treatment.

The lack of reported adverse events in Study SC-52-04 is reassuring, as inadvertent 120-minute exposures may be expected with routine clinical use of this product. The temperature profile reported, however, is probably less informative, however, and study results should not be quoted in the product label or in promotional materials. Although the temperature probe measured, on average 4° C increases at 5-minutes, these probes were in direct contact not only with subjects' skin, but also with the heated patches. SC-52-04 did not evaluate whether or not the stratum corneum, [redacted], increased in temperature as well.

8.4 Review of Safety Data (ISS)

8.4.1 Methods for Review of Safety Data

The safety review consisted of review and analyses of the sponsor's ISS database, review of the data from the individual study reports, and comparison of the non-integrated with the integrated safety data. By prior agreement with the Division, individual CRTs were not submitted with the NDA, except in the event of SAE. During the first review cycle, several questions arose regarding the sponsor's Integrated Summary of Safety, mostly pertaining to the electronic files submitted on September 15, 2003, but also concerning the "paper" NDA. Requests for clarifications, for corrections, and in some cases for additional analyses, were communicated at that time, via electronic mail and telephone. No such issues arose during the second review cycle.

These issues are described in detail in Section **Error! Reference source not found.**, as well as in the appropriate review subsections.

8.5 Subject Demographics

Subject demographic characteristics are summarized in Table 8.12 through

Table 8.16. Overall, the subjects were predominantly Caucasian, and (roughly) equally divided between genders. 'Asian' subjects were more prevalent in the recently conducted trials than in the earlier ones, presumably because of clinical site location. More than half of the 53-04, 54-04 and 55-04 subjects were enrolled in Hawaii, with the remainder from Southern California.

Table 8.12: Demographics of Subjects in Controlled Trials (as of 12/2004)

Demographic	S-Caine Any Form	Final Formulation	Final No Heat	Develop-mental	Placebo	Other Controls*
Number	1630	1110	352	168	815	210
Age						
0m-2m			0	0	0	0
3m – 2y	34 (2%)	34 (3%)	0	0	33 (4%)	0
3 – 6 y	48 (3%)	42 (4%)	0	6 (4%)	36 (4%)	0
7 - 17	125 (8%)	42 (4%)	0	83 (49%)	120 (15%)	0
7-12 Y	58	18	0	40	--	0
13-17 Y	67	24	0	43	--	0
18-64 years	1279 (78%)	864 (78%)	341 (97%)	74 (44%)	523 (64%)	208 (99%)
65-74	103 (6%)	87 (8%)	11 (3%)	5 (3%)	79 (10%)	2 (1%)
≥75 years	41 (3%)	41 (4%)	0	0	24 (3%)	0
Gender						
Male	706 (62%)	466 (42%)	157 (45%)	83 (49%)	319 (39%)	102 (49%)
Female	924 (57%)	644 (58%)	195 (55%)	85 (51%)	496 (61%)	108 (51%)
Race						
Caucasian	961 (59%)	680 (61%)	188 (53%)	93 (55%)	475 (59%)	171 (81%)
Black	234 (14%)	209 (19%)	15 (4%)	10 (6%)	203 (25%)	15 (7%)
Hispanic	183 (11%)	88 (8%)	38 (11%)	57 (34%)	105 (13%)	3 (1%)
Asian	154 (9%)	74 (7%)	73 (21%)	7 (4%)	13 (2%)	12 (6%)
Other	105 (6%)	59 (5%)	38 (11%)	8 (5%)	28 (3%)	9 (4%)

* EMLA, lidocaine, tetracaine

Source: Tables B4.1 and 4.1.1, Complete Response Volume 22

Table 8.13: Demographics of Subjects Enrolled in Controlled Trials as of August 1, 2003

	Dev A	Dev B	Final	Final No Heat	Placebo	EMLA	Lido	Tetra
Number	138	30	821	53	815	82	128	128
Age								
0–2 M	0	0	0	0	0	0	0	0
3 M–2Y	0	0	34 (4%)	0	33 (4%)	0	0	0
3-6	6 (4%)	0	42 (5%)	0	36 (4%)	0	0	0
7-17	53 (38%)	30 (100%)	42 (5%)	0	120 (15%)	0	0	0
18-64	74 (54%)	0	590 (70%)	53 (100%)	536 (66%)	80 (98%)	128 (100%)	128 (100%)
65-74	5 (4%)	0	75 (9%)	0	66 (8%)	2 (2%)	0	0
75+	0	0	38 (5%)	0	24 (3%)	0	0	2
Race								
Caucasian	73 (53%)	20 (67%)	538 (66%)	43 (81%)	481 (59%)	81 (99%)	90 (70%)	90 (70%)
Black	9 (7%)	1 (3%)	192 (23%)	0	196 (24%)	0	15 (12%)	15 (12%)
Hispanic	53 (38%)	4 (13%)	55 (7%)	10 (19%)	107 (13%)	0	3 (2%)	3 (2%)
Asian	2 (1%)	5 (17%)	16 (2%)	0	13 (2%)	0	12 (9%)	12 (9%)
Other	1 (1%)	0	20 (2%)	0	18 (2%)	1 (1%)	8 (6%)	8 (6%)
Skin Type								
I	3 (3%)	3 (10%)	57 (9%)	1 (2%)	36 (6%)	13 (16%)	9 (7%)	9 (7%)
II	14 (13%)	6 (20%)	144 (24%)	19 (36%)	121 (21%)	12 (15%)	29 (23%)	29 (23%)
III	58 (54%)	11 (37%)	187 (31%)	33 (62%)	189 (33%)	24 (29%)	44 (34%)	44 (34%)
IV	26 (24%)	4 (13%)	126 (21%)	0	134 (24%)	23 (28%)	32 (25%)	32 (25%)
V	6 (6%)	3 (10%)	48 (8%)	0	51 (9%)	9 (11%)	5 (4%)	5 (4%)
VI	1 (1%)	3 (10%)	39 (6%)	0	34 (6%)	1 (1%)	9 (7%)	9 (7%)
No data	30	0	0	0	30	0	0	0
Gender								
Male	68 (49%)	15 (50%)	326 (40%)	14 (26%)	319 (39%)	37 (45%)	65 (51%)	65 (51%)
Female	70 (51%)	15 (50%)	495 (60%)	39 (74%)	496 (61%)	45 (55%)	63 (49%)	63 (49%)

Source: Table 8.4.1 (Complete Response, Volume 8)
Final Formulation: SC-20-01, SC-21-01, SC-22-01, SC-23-01, SC-24-01, SC-28-01, SC-29-01, SC-31-01, SC-40-02, SC-41-03, SC-42-03
Final Formulation +/- Heating Element: SC-27-01
Developmental A: SC-03-99, SC-04-99, SC-05-99, SC-07-99, SC-09-99 Developmental B: SC-10-00, 11-01

Table 8.14: Demographics of Subjects Enrolled in All Controlled Trials, Integrated as of December 1, 2004

	Dev A	Dev B	Final	Final No Heat	Placebo	EMLA	Lido	Tetra
Number	138	30	1110	352	815	82	128	128
Age								
0–2 M	0	0	0	0	0	0	0	0
3 M–2Y	0	0	34 (3%)	0	33 (4%)	0	0	0
3-6	6 (4%)	0	42 (4%)	0	36 (4%)	0	0	0
7-17	53 (38%)	30 (100%)	42 (5%)	0	120 (15%)	0	0	0
18-64	74 (54%)	0	864 (78%)	341 (97%)	536 (66%)	80 (98%)	128 (100%)	128 (100%)
65-74	5 (4%)	0	87 (8%)	11 (3%)	66 (8%)	2 (2%)	0	0
75+	0	0	41 (4%)	0	24 (3%)	0	0	2
Race								
Caucasian	73 (53%)	20 (67%)	680 (61%)	188 (53%)	481 (59%)	81 (99%)	90 (70%)	90 (70%)
Black	9 (7%)	1 (3%)	209 (19%)	15 (4%)	196 (24%)	0	15 (12%)	15 (12%)
Hispanic	53 (38%)	4 (13%)	88 (8%)	38 (11%)	107 (13%)	0	3 (2%)	3 (2%)
Asian	2 (1%)	5 (17%)	74 (17%)	73 (21%)	13 (2%)	0	12 (9%)	12 (9%)
Other	1 (1%)	0	59 (5%)	38 (11%)	18 (2%)	1 (1%)	8 (6%)	8 (6%)
Skin Type								
I	3 (3%)	3 (10%)	67 (8%)	13 (4%)	36 (6%)	13 (16%)	9 (7%)	9 (7%)
II	14 (13%)	6 (20%)	197 (22%)	58 (16%)	121 (21%)	12 (15%)	29 (23%)	29 (23%)
III	58 (54%)	11 (37%)	291 (31%)	148 (42%)	189 (33%)	24 (29%)	44 (34%)	44 (34%)
IV	26 (24%)	4 (13%)	197 (22%)	81 (23%)	134 (24%)	23 (28%)	32 (25%)	32 (25%)
V	6 (6%)	3 (10%)	91 (10%)	42 (12%)	51 (9%)	9 (11%)	5 (4%)	5 (4%)
VI	1 (1%)	3 (10%)	47 (5%)	10 (3%)	34 (6%)	1 (1%)	9 (7%)	9 (7%)
No data	30	0	220	0	30	0	0	0
Gender								
Male	68 (49%)	15 (50%)	326 (40%)	157 (45%)	319 (39%)	37 (45%)	65 (51%)	65 (51%)
Female	70 (51%)	15 (50%)	495 (60%)	195 (55%)	496 (61%)	45 (55%)	63 (49%)	63 (49%)

Source: Table 8.B4.1 (Complete Response, Volume 8)
Final Formulation: SC-20-01, SC-21-01, SC-22-01, SC-23-01, SC-24-01, SC-28-01, SC-29-01, SC-31-01, SC-40-02, SC-41-03, SC-42-03
Final Formulation +/- Heating Element: SC-27-01, SC-53-04, SC-54-04, SC-55-04
Developmental A: SC-03-99, SC-04-99, SC-05-99, SC-07-99, SC-09-99 Developmental B: SC-10-00, 11-01

Table 8.15: Demographics of Subjects Enrolled in New* Trials vs. Older* Trials vs. PK + OL (Integrated)

	NEW Final Heat	NEW Final No Heat	ALL PK + OL	NEW PK + OL
Number	289	299	171	80
Age				
0–2 M	0	0	0	0
3 M–2Y	0	0	9 (5%)	0
3-6	0	0	16 (9%)	0
7-17	0	0	17 (10%)	0
18-64	274 (95%)	288 (96%)	100 (58%)	51 (64%)
65-74	12 (4%)	11 (4%)	23 (13%)	23 (29%)
75+	3 (1%)	0	6 (4%)	6 (8%)
Race				
Caucasian	142 (49%)	145 (48%)	143 (84%)	72 (90%)
Black	17 (6%)	15 (5%)	15 (9%)	6 (8%)
Hispanic	33 (11%)	28 (9%)	11 (6%)	1 (1%)
Asian	58 (20%)	73 (24%)	1 (1%)	1 (1%)
Other	39 (13%)	38 (13%)	1 (1%)	0
Skin Type				
I	10 (3%)	12 (4%)	21 (12%)	12 (15%)
II	53 (18%)	39 (13%)	44 (26%)	30 (38%)
III	104 (36%)	115 (38%)	46 (27%)	11 (14%)
IV	71 (25%)	81 (27%)	41 (24%)	18 (22%)
V	43 (15%)	42 (14%)	8 (5%)	7 (9%)
VI	8 (3%)	10 (3%)	11 (6%)	2 (2%)
Gender				
Male	140 (48%)	143 (48%)	75 (44%)	40 (50%)
Female	149 (52%)	156 (52%)	96 (56%)	40 (50%)

Source: Tables 8.B4.1, 8.4.2.1 and 8.B4.2 (Complete Response, Volume 8)
Final Formulation: SC-20-01, SC-21-01, SC-22-01, SC-23-01, SC-24-01, SC-28-01, SC-29-01, SC-31-01, SC-40-02, SC-41-03, SC-42-03
Final Formulation +/- Heating Element: SC-27-01, SC-53-04, SC-54-04, SC-55-04
Developmental A: 03-99, 04-99, 05-99, 07-99, 09-99 Developmental B: 10-00, 11-00

Table 8.16: Demographics of Subjects Enrolled In PK and Open-Label Trials

Conducted	ALL	NEW	OLD	OLD	OLD
Formulation	Final	Final	Final	Final	Dev A
Trials	All except* 05-99, 31-01	51-04, 52-04	25-01, 26-01, 30-01	31-01	05-99
Number	171	80	91 (91 total)	10 PK (40 total)	20 PK (22 total)
Age					
0–2 M	0	0	0	0	0
3 M–2Y	9 (5%)	0	9 (10%)	0	0
3-6	16 (9%)	0	16 (18%)	0	0
7-17	17 (10%)	0	17 (19%)	0	0
18-64	100 (58%)	51 (64%)	49 (54%)	0	22 (100%)
65-74	23 (13%)	23 (29%)	0	8 (80%)	0
75+	6 (4%)	6 (8%)	0	2 (20%)	0
Race					
Caucasian	143 (84%)	72 (90%)	71 (78%)	10 (100%)	22 (100%)
Black	15 (9%)	6 (8%)	12 (13%)	0	0
Hispanic	11 (6%)	1 (1%)	7 (8%)	0	0
Asian	1 (1%)	0	0	0	0
Other	1 (1%)	1 (1%)	1 (1%)	0	0
Skin Type		0			
I	21 (12%)	12 (15%)	9 (10%)	4 (40%)	0
II	44 (26%)	30 (38%)	14 (15%)	6 (60%)	2 (9%)
III	46 (27%)	11 (14%)	35 (38%)	0	12 (55%)
IV	41 (24%)	18 (22%)	23 (25%)	0	4 (18%)
V	8 (5%)	7 (9%)	1 (1%)	0	3 (14%)
VI	11 (6%)	2 (2%)	9 (10%)	0	1 (4%)
Gender					
Male	75 (44%)	40 (50%)	35 (38%)	5 (50%)	14 (64%)
Female	96 (56%)	40 (50%)	56 (62%)	5 (50%)	8 (36%)

* SC-25-01, SC-26-01, SC-30-01, SC-51-04 and SC-52-04
Source: Sponsor Tables A4.2 (120-Day Safety Update Volume 1), and 1.B4.2 (Complete Response Volume 1) And Table 11.1 (NDA Volume 28), Table 11.1 (NDA Volume 39)

Table 8.17: Ages of Subjects Enrolled In PK Trial SC-30-01*

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

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

8.6 Subject Disposition

Except for Study SC-42-03, most trials required only one study visit, during which subjects received single (or simultaneous) patch applications.

Table 8.18: Subject Disposition in S-Caine Patch Studies (Controlled and Non-Controlled)

Disposition	All Studies Totals n	All Studies Before treatment n	All Studies S-Caine group n	All Studies Placebo group* n	SC-42-03 n
Total Number of Subjects Enrolled	2075		887	653	220
Total Number of Subjects Who Received Study Drug (Safety)	2038				220
Total Number of Subjects Who Completed Study Treatment	2007				198
Total Number of Subjects Who Prematurely Discontinued	9 (+ 22)[3]		←	←	22
Reason for Not Completing the Study:					
Withdrew Consent Prior to any Treatment	2	2			
Consent Withdrawn	3		3		0
"Procedure No Longer Required" (Venipuncture)	2		2[2]		
Technical Failure (patch did not stick well)					0
Unable to Obtain Blood for PK; DCd	1		1		
Vasovagal Prior to Treatment	1	1			
Adverse Event Leading to Discontinuation	1		1	0	?
Lost to Follow-Up	0		0	0	22

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

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

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

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

that a small percentage (< 3%) of the pediatric subjects recruited because they were scheduled for blood draws simply "no longer needed the procedure."

8.7 Deaths

No deaths have been reported during S-Caine Patch or the S-Caine Peel (NDA 21-717) clinical trials (or during the designated post-treatment monitoring periods).

8.8 Non-Fatal Serious Adverse Events

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

8.9 Adverse Events Leading to Study Discontinuation

Study discontinuations were rare during clinical development. Most of the S-Caine Patch clinical trials were single dose studies requiring only one clinic visit, making subject discontinuation exceedingly unlikely. A few studies called for two visits, and one (SC-28-01, four-period crossover) for four visits. Study SC-42-03 was a ten-exposure, six week study involving fourteen study site visits.

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

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

As discussed above (Section 8.6) there were two pediatric withdrawals during single session studies, both attributed to "procedure no longer required." Both of these occurred after study drug administration. The information provided in the NDA does not permit further scrutiny of these withdrawals, and it is not possible to definitively conclude that study drug (and/or placebo patch) played no role in these cases. If there were an unexpectedly high number of such withdrawals, a request for more information from the sponsor would be in order. Based on the number reported (< 2% of pediatric subjects), however, it is reasonable to accept the sponsor's explanation.

8.9.1 Study SC-42-03 Drop-Outs

The only clinical trial that called for more than two study visits was Study SC-42-03, which required twelve visits over six weeks. Of 220 subjects enrolled, 198 were classified as completers. The SC-42-03 study report and electronic data do not contain information indicating reasons for

study drop-out, and missing data values. There is no information about investigator efforts to follow-up on any of these subject or ascertain possible study-drug causality. The report contains a one-page "Adverse Event Form" for each of the fifteen reported adverse events, but most of these are not for the study drop-outs. The SC-42-03 investigator's clinical impression was presented in one sentence; "As tested this product was irritating and not a sensitizer."

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

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

8.10 Distribution of Subjects by Skin Type

Table 8.19: Subject Skin Type (Controlled Trials)

	New Trials		Old Trials		
	Final-Heat 289	Final-NoHeat 299	Final-Heat n=821	Dev A, B 168	Placebo n=815
Skin Type					
(I) Always Burns/Rarely Tans	10 (3%)	12 (4%)	57 (7%)	6 (4%)	36 (6%)
(II) Always Burns/Tans Minimally	53 (18%)	39 (13%)	144 (18%)	20 (12%)	121 (21%)
(III) Burns Moderately/Tans Gradually	104 (36%)	115 (38%)	187 (23%)	69 (41%)	189 (33%)
(IV) Burns Minimally/Always Tans	71 (25%)	81 (27%)	126 (15%)	30 (18%)	134 (24%)
(V) Rarely Burns/Tans Profoundly	43 (15%)	42 (14%)	48 (6%)	9 (5%)	51 (9%)
(VI) Never Burns/Deeply Pigmented	8 (3%)	10 (3%)	39 (5%)	4 (2%)	34 (6%)
Missing Data			220 (27%)	30 (18%)	250 (31%)

Source: Modified from Sponsor Tables A4.2 and A4.3 in 120-day Safety Update, and Table 1.B4.2 in CR

8.11 Overall Evaluation of Adverse Events

8.11.1 Approach to Eliciting Adverse Events in the Development Program

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

Adverse events were to have been recorded on the CRFs, and include information about time of occurrence, event type, severity, and duration. "Because mild and transient incidences of localized erythema and edema are reported as expected reactions from topical lidocaine and tetracaine use, the investigators recorded only moderate to severe cases of erythema and edema as adverse events." During the first review cycle it became apparent that very few CRFs had been submitted to the NDA, because the Division had agreed that CRFs would only be submitted in cases of death, SAE or discontinuation due to AE. Subsequently, CRFs for all SC-42-03 patients that experienced an AE were requested.

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

In all trials, immediately after patch removal(s) the investigator examined patch sites for erythema, eschar formation and edema. The Draize scoring system was used to grade post-treatment dermal erythema and edema (although not referred to as the 'Draize' system within this NDA) (Table 8.20). By prior agreement with the Division mild skin reactions were not classified as adverse events. "Because mild and transient incidences of localized erythema and edema are reported as expected reactions from topical lidocaine and tetracaine use, the investigators recorded only moderate to severe

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

Table 8.20: Draize Scoring for Dermal Reactions

Finding	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

Source: Sponsor Table B8.7 (Complete Response, Volume 8)

8.11.2 Appropriateness of Adverse Event Categorization and Preferred Terms

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

8.11.3 Analyses and Explorations

Adverse events during development were uncommon. Most were dermal reactions at or around the product application site, lasting minutes to a few hours, and resolving without specific treatment. The overall adverse event rate, and the breakdown by severity do not appear to have been altered with addition of the newer data (Table 8.21 and Table 8.22).

Table 8.21: Subjects in Controlled Trials: Experienced ≥ One Treatment Emergent AE (Data submitted with original application, as of 8/1/03)

	Dev A	Dev B	Final	Final No Heat	Lido	Tetra	EMLA	Placebo
# of Subjects	138	30	821	53	128	128	82	595
# with AEs	5 (4%)	0	31 (4%)	1 (2%)	5 (4%)	4 (3%)	2 (2%)	8 (1%)
# Moderate AEs	1 (1%)	0	10 (1%)	0	2 (2%)	3 (2%)	2 (2%)	2 (<1%)
# Severe AEs	0	0	1 (<1%)	0	0	0	0	0

Source: 120-Day Safety Update, Volume 2

Table 8.22: Subjects in Controlled Trials: Experienced ≥ One Treatment Emergent AE (Integrated data, as of 12/31/04)

	ALL Final	ALL Final No Heat	NEW* Final	NEW* Final No Heat	OLD Final	OLD Final No Heat	OLD Placebo
# of Subjects	1110	352	289	299	821	53	595
# with AEs	41 (4%)	10 (3%)	10 (3%)	9 (3%)	31 (4%)	1 (2%)	8 (1%)
# Moderate AEs	10 (1%)	0	0	0	10 (1%)	0	2 (<1%)
# Severe AEs	1 (<1%)	0	0	0	1 (<1%)	0	0

* 'New' controlled trials are SC-53-04, SC-54-04 and SC-55-04

Source: 120-Day Safety Update, Volume 2 and Complete Response Table 5.1 (Volume 1)