2.4.1 Repeat/Multiple Dosing

Five trials evaluated the (PK and/or local dermal) effects of multiple S-Caine Patch applications.

- Three of these were PK studies: 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. SC-30-01 evaluated the application of (up to) two patches simultaneously in infants and children, ages 4 months to 12 years. (Section 5.1 for details)
- SC-29-01 was an efficacy study in infants, calling for administration of two patches simultaneously. (Section 8.3.8) 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 9.9 for details)

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.

The possible effects of pretreatment with another other topical medications, or with systemically acting "dermal sensitizers" were not evaluated. These types of assessments are not routinely required for development of transdermal patch medications at this time (Dr. Luke, 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 proportionately represented in the S-Caine Patch development program, as do all "skin types" (I=VI).

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 subject may not have experienced "enough" pain to differentiate, or appreciate, a treatment effect.

Pediatric:
Despite an adequate number of subjects overall, pediatric efficacy has not necessarily been well demonstrated. This may be the result of underpowered, or otherwise flawed efficacy studies.

Renal and/or Hepatic Insufficiency:
No studies were 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.

PRIMARY CLINICAL REVIEW

3 INTRODUCTION AND BACKGROUND

3.1 Proposed Indications

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

[redacted]

> The S-Caine Patch is not recommended for use on mucous membranes or on areas with a compromised skin barrier. Safe dosing recommendations for use on mucous membranes and areas with a compromised skin barrier cannot be made because it has not been adequately studied."

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, but there were issues with blinding). EMLA is also a eutectic mixture; structurally similar local anesthetics are 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. EMLA Cream and Disc are labeled for

"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)

The sponsor of NDA 21-623, ZARS, Incorporated, is a (1996) startup company based in Salt Lake City, Utah. The S-Caine Patch is their first product, and this, their first NDA.

A pre-IND meeting was held on January 20, 1999. At this meeting DACCADP:

- Recommended blood sampling for lidocaine and tetracaine for at least 10 to 12 hours following patch application in PK trials
- [redacted]
- Discussed potential primary endpoints for efficacy trials. [redacted] had been proposed by the sponsor, but the Agency suggested VAS pain scores.
- Asked for comparison of the heated patch [redacted]
- Stated that exposure in 300 to 500 subjects would be acceptable
- Requested information on the effects of skin pigmentation, on efficacy and safety
- Requested pediatric and geriatric studies at the time of NDA submission

ZARS, Inc. opened IND 58,823 for the S-Caine Patch in July, 1999 in order to develop a local anesthetic patch that could be used prior to painful medical procedures. The proposed drug product would incorporate their 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. [redacted]

The sponsor had indicated intent to file a 505(b)(2) new drug application. Although there were numerous lidocaine NDAs, the last tetracaine NDA had been withdrawn years earlier, for reasons unknown to ZARS. DACCADP Project Management was able to determine that the withdrawal was a marketing decision by the sponsor, not because of any clinical issues or concerns on the Agency's part.

On May 9, 2000 a meeting considered by ZARS to be end-of-phase 2 was held in order to discuss ongoing and proposed clinical studies. The meeting minutes indicate that Dr. McCormick (DACCADP Division Director) stated that the materials presented for the meeting were inadequate for a proper end-of-phase 2 meeting. The sponsor 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). The May 9 meeting was held, however. The main points made by the Division (pertaining to the S-Caine Patch clinical program) were:

- 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, and that "one study should suffice." 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 sponsor inquired how many pediatric subjects (ages 2 through 7) would be satisfactory. They were advised to submit study proposals for review and comment.
- 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 size of the anticipated safety database:

  Approximately 400 subjects would be recruited into Phase 3 trials. Using a 2:1 randomization scheme, the total subject exposure would be between 300 and 320. This would include about 200 "patients" for the main Phase 3 studies (80 adults, 120 pediatric), along with 120 more in special population studies (half geriatric and half neonate). Combined with Phase 1 and 2 exposures, the total number of S-Caine exposures would be approximately 540.
- 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 S-Caine Patch should be better characterized.

In September 2000 the sponsor requested a "formal meeting to discuss elements essential to the continuing drug development of the S-Caine Local Anesthetic Patch." The letter indicated that ZARS had not yet received the Agency's decision regarding the applicability of the combination drug policy, which had been expected "before the end of May 2000." The letter continued:

> "As I am sure you can well understand, a decision regarding the applicability of this policy is crucial to the drug development process of the S-Caine Patch. If the FDA had brought it up in the pre-IND meeting...ZARS could have avoided entering into the expense of clinical trials on this, its first product, until a clarification was forthcoming from the FDA. Now at this late date, as ZARS prepares for Phase 3, the lack of direction from the FDA makes it impossible to design and execute the pivotal clinical trials for the product..."

A teleconference (in lieu of a Type A meeting) was then held on October 9, 2000, "to resolve the issue of the applicability of fixed-dose prescription drug regulation to the S-Caine Patch." Dr. McCormick explained that, contrary to the sponsor's contention at the May 2000 meeting, the prototype drug in this class, EMLA, had been held to the regulatory standards set for combination drug products, as would the S-Caine Patch. 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).

In November 2000 the Division sent the sponsor a letter requesting submission of the required annual progress report, which was then received in January of 2001. The first annual report contained brief summaries of seven efficacy studies, six completed and one in progress (SC-10-00). These studies had all utilized what would later be called "Developmental Patch Formulation A" except for the ongoing study, SC-10-00, which was using "Developmental Patch Formulation B."

Protocol SC-10-00, dated June 2000, a study of the S-Caine Patch prior to vascular access procedures in 7 to 17 year olds, was submitted to the Division in February of 2001. The annual report submitted by the sponsor during January 2001 stated that more than half of the planned 60 subjects had already been enrolled, however.

In April 2001 ZARS submitted this informational amendment. The amendment began with point-by-point responses to the issues raised at the May 2000 meeting. Protocols for eight clinical trials were included, as well as additional questions and a "target label." The letter stated:

> "If FDA would have granted a face-to-face meeting, answers could have been received very quickly (i.e. within thirty days of receiving the informational meeting package). Because the commencement of the Phase 3 program depends on the answers received from FDA, ZARS requests that FDA provide responses to the indicated questions as expeditiously as possible."

A teleconference was then held on June 28, 2001, "to identify pivotal studies in the packet of written questions submitted." Key points included:

- The sponsor 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 included. Sponsor stated the intent to use, as primary endpoints, the subject VAS score in all adult efficacy trials, and the Oucher Scale score in pediatric trials.
- 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.
- Issues related to skin thickness, and the potential for methemoglobinemia in premature infants, were of concern. The sponsor was asked to document that the product does not cause methemoglobinemia, or other problems, in neonates (less than two months old) and premature infants.
- Definitions of "geriatric" per regulations.
- The sponsor's anticipated timetable: 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 amendment. Updated versions would be submitted instead.
- The proposals for skin typing and 24-48 hour follow-up were acceptable.
- The Division would review the six studies identified by the sponsor as "priority studies" and provide comments, by mid-August

Protocol SC-11-01, an additional adult efficacy study, was submitted in July 2001.

DACCADP review (clinical, statistical and biopharm) of the six "priority" Phase 3 trials (22-01, 23-01, 24-01, 25-01, 26-01, 31-01), as well as SC-11-01 was completed by early August. The clinical review concluded that the proposed Phase 3 trials "appear to be adequate to show efficacy" and were safe to proceed.

Updated versions of pediatric protocols SC-20-01 and SC-21-01 were then submitted, along with two new pediatric protocols, SC-29-01, an efficacy study in infants, and SC-30-01, a repeat exposure PK study in children (October 2001). Clinical review of these studies was completed in early November 2001. The resulting advice letter (January 2002) included the following comment:

> "Regarding *Protocol SC-20-01 and Protocol SC-21-01,* the two Oucher scales are very different—one is a 6-category ordinal, and the other is a continuous outcome. Will the outcomes be collapsed into two categories, namely pain/no pain, as was done for the sample size calculations? The differing scales also raises the issue of whether the age groups are directly comparable, and whether there is possibly or likely to be an interaction between treatment and age. If so, even if the outcome measures are made comparable, for example by collapsing into pain/no pain, a greater number of subjects must be enrolled. The proposed sample size (n= 69 in SC-20-01, n=80 in SC-21-01) is not large enough to detect interactions with sufficient power."

The sponsor submitted amendments and revisions to studies SC-22-01 (geriatric efficacy), SC-23-01 (adult efficacy), SC-25-01 (repeat dose PK) and SC-27-01 (combination rule, assessment of role of heating element) in April 2002.

In June 2002 the sponsor responded to the January 2002 advice letter. This response included formal amendments to protocols SC-20-01, SC-21-01 and SC-29-01. 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.

In response to Division concerns and comments pertaining to use of two different Oucher scales the sponsor provided two paragraphs, presumably applicable to SC-20-01 and SC-21-01, respectively:

> "Results for the two age groups will be evaluated separately for the Oucher Scale results so the required sample size will be doubled. In addition, to test whether results from the scales can be combined, Cochrane's test for homogeneity will be used on the proportions of patients with no pain, and if no interaction between treatment and Oucher Scale is evident, treatments will be compared using Mantel-Hansel summary chi-square tests, stratified by the Oucher Scale used."

"Results for the two age groups will be evaluated separately. For the older age group the increased sample size warranted by QST testing is sufficient to detect a difference between treatments in the proportions of patients with no pain of 50%. For the younger age group, the sample size is sufficient to detect a difference of 60%. In addition, to test whether results from the scales can be combined, Cochrane's test for homogeneity will be used on the proportions of patients with no pain, and if no interaction between treatment and Oucher Scale is evident, treatments will be compared using Mantel-Hansel summary chi-square tests, stratified by the Oucher Scale used."

A 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) consult memo dated December 4, 2002 indicated concurrence with the study design as proposed.

- At the pre-NDA meeting held on December 5, 2002 the following items were discussed:
- In response to questions about adequacy of their clinical program to support the "Indications and Usage" and "Dosage and Administration" on the draft package insert, the sponsor was told: "The trials described in the meeting package incorporate, *on superficial review*, replicated studies in the populations that would typically be required to support the indications and dosages listed in the draft label. Final determination of the adequacy of the clinical trials, controlled and uncontrolled, to support the proposed indications and dosages will occur during the NDA review."
- 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.
- The sponsor was informed that the term " [redacted] dermatologic procedure" might need additional clarification in the label.
- 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].
- The sponsor proposed including "some Phase 2 studies in the Controlled Studies section of the NDA." They were advised to provide appropriate bridging information to support the claim that changes do not significantly affect the final product. They were also told "This approach should not affect the presentation of data in the integrated summaries of safety and efficacy."

- 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.
- The sponsor reiterated intent to file a 505(b)(2) new drug application. They were reminded that they would need to choose a reference listed drug (RLD). For application portions referencing outside information (i.e. previous Agency findings of safety and efficacy for lidocaine and tetracaine), they would need to provide a link to demonstrate how their product and the RLD were related. Dr. Rappaport indicated that such a link might be waived for this product if they can demonstrate no meaningful systemic exposure occurs.
- 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, then provide the balance during the review cycle, at approximately the 6-8 month point. Dr. Rappaport stated that with a 10-month review clock, a submission at the 6-8 month point would eliminate much of the time needed to review the material, and that such a submission would necessitate an additional safety update. He strongly encouraged the sponsor to collect all of the data and submit it to the Agency by the 120-day safety update.
- Dr.Al-Fayoumi (Biopharm) stated that overall, the proposed plan for PK studies appeared to be acceptable (including SC-33-02). The sponsor's proposal to provide (in the NDA) only a brief literature summary pertaining to lidocaine and tetracaine, would be acceptable. (The nonclinical ADME and clinical pharmacology sections would include more extensive discussions of drug metabolism and PK.)

DDDDP (Dermatology) response to consult was received on December 4, 2002. The three questions asked appear below, along with summaries of the individual responses.

1. Are skin irritation and sensitization studies needed? If so, how should these be conducted for this patch product?

   Skin irritation and sensitization studies were warranted, in anticipation of repeated uses (hospital stays), and off-label use. Photo-irritation and photo-allergenicity studies were not needed.
2. When is the OGD Guidance applied?

   The OGD guidance applies to the comparative dermal safety of generic comparators and was not intended to be applied for new drug products. However, the format of the studies can be used to support evaluation of dermal safety.
3. Is the proposed use of this product as a [redacted] an indication that can be generalized to based on the studies provided?

The product should be indicated for use only where the studies have supported its use. These should be carefully described in the indications and usage section. Concern exists regarding generalizations to use that has not been studied (e.g. efficacy of pain relief when used on palmar or plantar surfaces where the skin may be thicker and penetration of the drug substances may be diminished or where the pain is substantially greater than that studied such as injection of bleomycin, extensive carbon dioxide laser procedures). The Indications and Usage should reflect specifically what was studied, submitted to NDA, and found acceptable.

In a letter dated December 17, 2002 ZARS requested 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 (March 10, 2003).
NDA 21-623 was submitted on April 8, 2003.

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 CHEMISTRY AND ANIMAL PHARMACOLOGY AND TOXICOLOGY

4.1 Chemistry

The Chemistry and Manufacturing related problems with the S-Caine Patch application (alone) are of sufficient severity to preclude product approval at this time. Concerns related to the integrated heating element include:

- 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 could make *proper* use of the S-Caine Patch impractical in many clinical settings.
- match up with clinical use, as studied, as proposed for the label, and also as is likely to be clinically practical.
- 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 include:

- The drug release specifications of the S-Caine Patch are so wide that they are approach the point of being "meaningless" (CMC team leader, DACCADP)

These issues (and others) are described in detail in the DACCADP CMC review.

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, or nearly [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, the sponsor summarizes evolution of the patch formulation as follows:

Table 4.1. Composition of S-Caine Patch Formulations

	Developmental A Formulation	Developmental B Formulation	Final Formulation
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			
Sorbitan monopalmitate, NF			
Water (			
Methylparaben, USP			
Propylparaben, USP			

Source: Modified from Sponsor Table 1.1 in Volume 26

4.2 Pharmacology and Toxicology

Lidocaine and tetracaine, both approved as injectable local anesthetics prior to 1982 have been used extensively in humans at doses higher than proposed. They have not, however, been approved for use in combination.

Lidocaine was first marketed in the USA in 1948 and is the most widely used local anesthetic (LA), with at least twenty NDAs (held by numerous sponsors). Although considered a class IB antiarrhythmic, it is most often used for its local anesthetic effects. It is considered the prototypical member of the aminoethylamide (amide) class of local anesthetics (Goodman & Gilman, 10th edition).

Lidocaine is absorbed rapidly following parenteral administration, as well as from the gastrointestinal (35% bioavailable) and respiratory tracts. It is frequently administered in combination with a vasoconstrictor (epinephrine) in order to decrease the rate of

absorption, and systemic toxicity (and to increase duration of action). Lidocaine is primarily dealkylated and de-ethylated by mixed-function (hepatic) oxidases. At least two lidocaine metabolites are known to retain local anesthetic activity. One of these, monoethylglycinexylidide (MEGX), is nearly equipotent with lidocaine and believed to contribute to CNS toxicity. Plasma half-life, 1.5 to 2 hours in healthy adults is increased in cirrhotic patients.

Lidocaine toxicity following systemic absorption most often occurs in the CNS and cardiovascular system. CNS toxicity is dose-dependent. Lower (toxic) systemic levels tend to produce CNS depression (2-10 μg/mL), while higher levels result in CNS excitation and seizures (5-15 μg/mL). The rate of intravenous administration of lidocaine also affects CNS toxicity.

Lidocaine also exerts cardiovascular effects, principally on the myocardium, where decreases in electrical excitability, conduction rate and contractility occur. Lidocaine (and most other local anesthetics) also cause arteriolar dilatation. Lidocaine is administered systemically for suppression of certain types of ventricular arrhythmias, for which plasma levels of 1.5 to 4.0 or 5.0 μg/mL are considered therapeutic (corresponding to 1-4 mg/min IV infusion, after a 100 mg IV bolus, in most adults). Cardiovascular toxicity is usually seen at concentrations higher than those required to produce CNS toxicity. Cardiovascular toxicity (hypotension, bradycardia, ventricular arrhythmia) is usually seen only at "high" (> 15 μg/mL) systemic concentrations, higher than those required to produce CNS effects.

Methemoglobinemia has occurred following intravenous and topical administration of lidocaine in neonates. In most cases, methemoglobinemia has been mild, not clinically significant, and resolved spontaneously. Rarely patients have required treatment with oxygen and/or methylene blue

Tetracaine, an ester local anesthetic, is approximately two to three times as potent as lidocaine and possesses similar local and systemic effects. Hypersensitivity reactions (allergies) are more common with ester than with amide anesthetics. Tetracaine's toxic effects are also similar to lidocaine's, though "toxic levels" are not as well characterized in the literature. Many clinicians convert systemic tetracaine levels (and doses), to lidocaine equivalents" in order to guide therapy. Systemic tetracaine toxicity, though similar to lidocaine's, is not as well described in the literature, and "toxic levels" not as clearly defined.

Despite anecdotal reports that systemic administration of local anesthetics is relatively common (in clinical practice), available (published) toxicity data is limited data. Lidocaine and tetracaine have similar pharmacologic mechanisms of action and toxicity is thought to be additive.

Intravenous lidocaine boluses of 100 mg (and more) are used therapeutically. Tetracaine dosing is generally one third of lidocaine's for local use (Systemically administered tetracaine is used off-label, in doses that are roughly one-third of those used for lidocaine, as well.) The S-Caine Patch, contains (70 mg of each, for topical use) what could might

be a toxic dose, if the entire dose of both drugs were administered systemically. Under conditions of repeat use, or off-label use on non-intact skin, local anesthetic toxicity could, conceivably be of concern, and appropriate label warnings should be included.

4.2.1 Overview of Nonclinical Findings

(Portions of this section were excerpted from Dr. Mellon's Executive Summary)

In support of this NDA, the sponsor 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 this time, the non-clinical findings do not appear to raise any concerns regarding future use in humans, but reproductive toxicology testing has not been completed. The sponsor conducted segment II studies (embryofetal development) in the rat and rabbit models. Although signs of maternal toxicity were evident, there were no indications that lidocaine or tetracaine were teratogenic under the conditions of the assays. The sponsor has 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 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, which is thought to be the best pre-clinical model for human skin.

The potential for the S-Caine Patch to produce dermal sensitization or toxic plasma levels, following repeated exposure was evaluated in 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 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 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

5.1 Pharmacokinetic and Pharmacodynamic Studies

Dr. Srikanth Nahlani (DACCADP Biopharmaceutics) states in his 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."

5.1.1 Pharmacokinetic Studies

Five studies were conducted in human subjects to determine the extent of systemic absorption of lidocaine and tetracaine from S-Caine Patch administration; three in adults, one in the geriatric population and one in infants and children.

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

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

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

Table 5.1. Studies Reviewed for Pharmacokinetic Findings

Study	Design	Population	Duration	Form
SC-05-99	Single patch, placebo-controlled, XO	21 Adult	30 mins (n=20)	Dev A
SC-25-01	Multiple simultaneous patches	25 Adults		Final
	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 Adults		Final
	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	Final
	Parallel groups (one patch, 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		Final
	Geriatric efficacy, PK sampling in 10 Ss		20 mins (n=10)	

Source: Prepared by clinical reviewer

In SC-25-01 two subjects had systemic lidocaine levels (one tetracaine) that would be considered in the "therapeutic" range for treatment of certain ventricular arrhythmias (no associated AEs or symptoms). This implies that significant (and unpredictable) systemic absorption is possible with clinically plausible ("a few patches") use of the S-Caine Patch. The sponsor claims that in these cases PK samples had been collected in the arms that the patches had been placed on, above the patch sites. (Presumably this was the case for other subjects in the same trial who did not have such extreme systemic lidocaine (+/- tetracaine) levels.) In study SC-30-01 (four study sites) the sponsor's analysis and discussion excludes 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. Nahlani 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. Nahlani's analysis.

6 DESCRIPTION OF CLINICAL DATA AND SOURCES

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 NDA itself (Volumes 20 though 38), the 120-day Safety Update (Volumes 1 through 9) and IND 58,823 (Volumes 1 through 12). All correspondence, meeting minutes and reviews stored in the CDER Document Filing System (DFS) were also reviewed.

A number of teleconferences were held between DACCADP review staff and the sponsor's representatives, subsequent to NDA filing, during which 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, is labeled as such within this review.

6.2 Overview of Clinical Trials

Clinical trials in support of NDA 21-623 were conducted under IND [redacted] between March 1999 and July 2003. (The study report for SC-01-95, not done under IND, states that it was conducted in February 1996). Table 6.1 on the following page (reproduced from Section 8 of this review) lists the clinical studies for which the sponsor has submitted results (to NDA 21-623). In study SC-31-01, an efficacy trial in 40 geriatric subjects, PK samples were obtained on 10. PK sampling was also done in study SC-05-99, an efficacy trial in adults utilizing a developmental patch formulation.

There were also the four dedicated PK trials listed in the preceding Section (5); (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

The S-Caine Patch is not marketed anywhere in the world.

Table 6.1. Studies Reviewed for Efficacy Findings

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

Source: Prepared by clinical reviewer

7 CLINICAL REVIEW METHODS AND DATA INTEGRITY

7.1 Conduct of Review

This New Drug Application was received on April 8, 2003, and upon preliminary review, considered suitable for filing. All necessary items were included with the exception of several that the Division had agreed to allow the sponsor to submit along with the 120-day Safety Update. These were:

- 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, a pharmacokinetic evaluation of exposure to multiple S-Caine Patches, in pediatric population

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

Review of the study reports and data tables submitted revealed that the presentation of data was consistent, overall, with CDER guidance for industry.

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 the sponsor's earlier S-Caine Patch formulations (Developmental A and Developmental B) were included in some efficacy analyses. 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 (the repeat dose skin sensitization study) that experienced any adverse event were, however, submitted, and these were reviewed as well.

7.2 Materials Consulted in Review

Table 7.1 lists the items provided by the sponsor and generated by the FDA that were used during the course of this review.

Table 7.1. Items Consulted for Review of NDA

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

7.3 Evaluation of Data Quality and Integrity

The original NDA submission was evaluated for data integrity and quality by detailed review and retabulation of the data, in order to verify results reported in the Integrated Summary of Efficacy, the Integrated Summary of Safety, and the 120-Day Safety Update. "Hard copies" of study reports, and electronic datasets were compared, and evaluated for completeness, coherence, consistency and accuracy, revealing a number of errors, inconsistencies and missing values. These data problems and inconsistencies do not appear to be attributable to attempts at fraud, however. The following problems with the application and data were observed:

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 two problems, combine to make following the progression from the proposed study to the one ultimately conducted difficult and confusing.

These mistakes were brought to the sponsor's attention for their pivotal trials, and corrections were requested (SC-20-01, SC-21-01, SC23-01, SC24-01). The corrected information arrived on January 7, 2004.

The final data sets do not appear to have been QC tested, or compared against the individual study data files. Questions regarding certain aspects of the data, that arose during the review process were forwarded to the sponsor. Copies of these requests are included in Appendix A of this review.

- The integrated data files (all subjects in all clinical trials) (all AEs) contain many missing values (dates, treatment conditions, efficacy scores)
  - For example, ages, dates of birth, and in some cases treatment condition.
- Portions of data columns (i.e.aeseverity, aeseriousness) appear to have been transcribed in some of the data files.
  - For instance, in the integrated data table "ae_all.xpt" which contains 98 line listings, the variables "AESEVER" and "AESERIO" appeared to be transposed for lines 83 on.
- Treatment conditions are missing or incorrect for some subjects/lines (i.e. for subjects in SC-28-01 in the integrated summary of adverse events).
- In some cases data was otherwise not internally consistent

Within each of the two main study populations, adult and pediatric, treatment conditions, most efficacy measures, and safety measures were the same. The sponsor's data tables for individual studies sometimes use similar, but not identical variable names, for identical measures, however making concatenation of data across studies difficult (and error prone).

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 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" performed 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 include:

- Coded columns of data were not accompanied by corresponding columns of full term descriptors, e.g., AESEVER had undefined codes 1-3 and should have had a corresponding column with "mild," "moderate" and "severe."
- The same entry was sometimes used within a single data column to describe two different things.
- Spaces in data tables were left blank making it ambiguous as to whether there was no data to report or data entry was overlooked.

These issues, along with others, were brought to the sponsor's attention, but despite two 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.

An accounting was made of all subjects who were randomized in 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 who (were) discontinued from studies.

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 "the fifteen adverse events."

7.4 Conduct in Accordance with Accepted Ethical Standards

The initial S-Caine Patch 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 has been advised to submit the final study reports, data tables and the appropriate CRFs.

Within the NDA, each individual study report, except for SC-42-03, stated "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 does not contain these affirmations.

7.5 Evaluation of Financial Disclosure

To comply with 21CFR §54, Certification and Disclosure Requirements, the Sponsor submitted certification on the financial interests and arrangements of the clinical investigators who enrolled subjects into S-Caine Patch clinical studies. On Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) checkbox number one was chosen, stating that:

- All investigators required to disclose (potential conflicts of interest) indicated that they had no such interests
- There had been 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 was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)

8 INTEGRATED REVIEW OF EFFICACY

8.1 Brief Statement of Conclusions

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

Efficacy

- Efficacy in the adult population for venipuncture, and for superficial excision and shave biopsy ([redacted]), 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, their was a great amount of 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 this NDA (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 about [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.

Dosing

- 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 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 efficacy of this dose (application duration) justified by the data. The proposed (three sentence long) label Dosing and Administration section includes "For [redacted] procedures such as excision, shave biopsy [redacted] apply an S-Caine Patch to intact skin [redacted] 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.

Combination Product Rule

- The lidocaine/tetracaine combination patch (S-Caine) appears to be more efficacious than either drug alone (in patch form), as studied in SC-41-03.
- The S-Caine Patch heating component (CHADD) has not been demonstrated to contribute to product efficacy. 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).

Label Claims and Information

- The sponsor proposes the label claim "The S-Caine Patch (lidocaine 70 mg and tetracaine 70 mg) is indicated as a [redacted] EMLA is labeled similarly, but for dermal analgesia.
- 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.
- The breadth of the proposed claim may not be warranted given the limited range of painful dermal stimuli studied.
- Whether or not the product is labeled broadly (i.e. for dermal analgesia) or for specific types of dermal procedures, claims of efficacy for [redacted]

[redacted]

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

- The proposed label section, Clinical Studies, contains a series of misleading claims.
- [redacted]

- The Clinical Studies section also follows references to studies "prior to injection [redacted]

- As noted above, proposed label dosing instructions [redacted] are not supported by the study results submitted to date.

8.2 Approach to Review of Efficacy

Table 8.1 lists the studies reviewed to reach efficacy conclusions. The first four studies listed were designated in the NDA as "pivotal trials." Detailed reviews of these trials appear first. 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 (31-01and 22-01 limited enrollment to geriatric subjects).

Table 8.1. Studies Reviewed for Efficacy Findings

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

Source: Prepared by clinical reviewer

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 as well, but 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 was altered because of issues with tetracaine stability. Excipient and active drug concentrations were altered, 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 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).

Efficacy Measures

Primary

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

Pediatric efficacy trials (except for SC-29-01 in infants) used 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 S-Caine Patch efficacy (no standardization of supplemental lidocaine use within/between trials).

8.3 Review of Individual Studies Contributing to Conclusions of Efficacy

8.3.1 Pivotal Study SC-24-01: A Randomized, Double-blind, Placebo-controlled, Crossover Clinical Study Evaluating the S-Caine™ Patch for Induction of Local Anesthesia Prior to Vascular Access Procedures in Adult Subjects

8.3.1.1 Findings vs. Labeling Claims

Throughout the S-Caine development program ZARS communicated intent to label S-Caine as "indicated [redacted] This study found that adult subjects treated with S-Caine Patch had (statistically significantly) lower average VAS scores during venipuncture than subjects treated with placebo, thus supporting an efficacy claim. The SC-24-01 results support an analgesia claim, [redacted] Precise label wording will be discussed at the upcoming S-Caine Patch labeling meetings. If the product is labeled for specific types of dermal procedures, instead of the broad claim the sponsor seeks, then this study supports efficacy for use in "venipuncture" or for "superficial venous access" [redacted]

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

8.3.1.2 Study Plan

The initial version of Protocol SC-24-01 was dated March 27, 2001 and submitted April 11, 2001. Two amendments were implemented prior to subject enrollment, dated June 19, 2001 (Amendment 1), and June 3, 2002 (Amendment 2). Twenty additional subjects were enrolled, over and above the forty subjects originally planned, because of a drug administration error at one of the two study sites, but this was done without a formal protocol amendment.

8.3.1.3 Population, Design, and Objectives

The protocol-specified objectives of the study were:

1. "To compare the effectiveness of an S-Caine Patch to a placebo patch in providing clinically useful local anesthesia for vascular access procedures in adult subjects; and"
2. "To monitor the nature and frequency of adverse events associated with the safety of an S-Caine Patch."

The protocol was designed as a two center (joint site-stratified), randomized, double-blind, placebo-controlled, crossover study in healthy adult volunteers. Subjects who met entry criteria would be invited to participate. Subjects were to receive simultaneous 20-minute applications of both an S-Caine Patch, and a placebo patch. Placebo patches were to be identical in composition to the S-Caine Patch (excipients, adhesives, heating element), but with no active drug present, that is no lidocaine or tetracaine. The application sites of the active-drug patch were to be randomized (1:1) between the right and left antecubital surfaces. After the 20 minute application the patches were to be removed, and then the investigator would evaluate the skin (under the patches) for

erythema, edema and other skin reactions. Subjects would then undergo two "vascular access procedures". (Amendment 1 specified that the procedure would always be venipuncture with a 20-gauge angiocatheter. The right antecubital would always be accessed first, then efficacy evaluations conducted for that arm/patch, then the left arm would be accessed, and efficacy evaluations repeated.)

Efficacy evaluations would consist of subject VAS ratings of venipuncture-induced pain, investigator ratings of the subjects' pain, and investigator ratings of the adequacy of the anesthetic. Subjects were to be dismissed after completion of efficacy evaluations. Subjects were to return to the study center within 24-48 hours for follow-up skin assessment and adverse event evaluation.

Table 8.2. Study SC-24-01 Schedule of Events

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

Source: NDA Volume 35

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

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

8.3.1.4 Treatment Summary

Study Medication

Both S-Caine and placebo patches were to be supplied by, and manufactured under the direction of ZARS, Inc., Salt Lake City, Utah.

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

Tetracaine Supplier
Lidocaine Supplier [redacted]

Upon meeting eligibility criteria, patients would be assigned the next available sequential subject number. Treatments would be double-blind, and assigned based on a predetermined computer-generated randomization code, so that one-half of the subjects would receive the S-Caine Patch on their right arm and placebo patch on their left, and vice versa. Subjects would receive concurrent 20-minute applications of both the S-Caine Patch and the placebo patch, one on the left arm, and the other on the right arm, prior to undergoing venipuncture in both arms.

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

Concomitant Medications

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

8.3.1.5 Assessments

8.3.1.5.1 Primary Efficacy Variable

The primary efficacy variable was to be the subject's evaluation of pain caused by insertion of a 20 gauge angiocath as rated on a 100 mm VAS where 0 mm = "no pain" and 100 mm = "the worst pain you can imagine." If patients received a rescue lidocaine injection they would be instructed to rate the pain of the procedure prior to the lidocaine injection.

8.3.1.5.2 Secondary Efficacy Variables

Subject's overall impression of the local anesthetic

Each subject would be asked to evaluate drug efficacy by answering "yes" or "no" to the following questions:

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

Investigator and independent observer's evaluations of subject's pain

The investigator and the independent observer separately would assess the amount of pain they felt the subject had experienced during the procedure using a 4-point categorical scale (no pain, slight pain, moderate pain, or severe pain).

Investigator's overall impression of the local anesthetic
The investigator was to answer "yes" or "no" to the following question:

- Did the local anesthetic patch provide adequate anesthesia for the vascular access procedure?

8.3.1.5.3 Other Measures

"Difficulty of insertion" was also to be rated by the investigator on a three-point categorical scale; "Insertion at first attempt," "Minor adjustment needed," or "Second Insertion Required" for use as a possible exploratory variable. This rating was not specified as an outcome measure, but as a possible "exploratory variable."

8.3.1.6 Sponsor's Analysis Plan

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

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

The following secondary efficacy variables specified in the protocol were:

- Subject's overall impression of the local anesthetic ("adequate pain relief" and "would use again")
- Investigator and Independent Observer's Evaluations of Subject's Pain
- Investigator's overall impression of the local anesthetic ("provided adequate anesthesia")

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

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

Sample Size Calculation
The protocol-specified sample size calculation was determined to be sufficient to detect a paired difference between treatments of 15 points on the VAS (SD=25 points), or a sign test preference of 80% versus 20% in favor of active treatment, both with 80% power and a two-sided significance level of 5%.

8.3.1.7 Protocol Amendments and Changes in the Planned Analyses

There were two amendments to Protocol SC-24-01. Both were implemented prior to subject enrollment. Of note, although 20 additional patients were enrolled and studied at one of the clinical sites, the Agency was not notified of this in the form of a formal protocol amendment.

Amendment 1 (Amendment Date June 19, 2001; FDA Submission No. 15 on 10/11/2002) provided the following changes:

- Clarified the procedures for administering the study patches, including the randomization process
- Clarified that vascular access would always be attempted with 20 gauge angiocaths.
- Clarified that after removal of both patches, vascular access would always be attempted first in the right arm, then efficacy assessments would be obtained for that arm. Vascular access would be then be attempted in the left arm, followed by efficacy assessments for that arm.
- Added the independent observer efficacy evaluation
- Added the requirement for study subjects to return to the site between 24 and 48 hours after the study drug application

Amendment 2 (Amendment Date June 3, 2002; FDA Submission No.15 on 10/11/2002 2002) provided the following changes:

- Added the names and addresses of the investigators
- Clarified the procedure for the 24 to 48 hour post-treatment visit
- Clarified the procedure for opening the study drug packaging

The study planned for a total of 40 patients to be enrolled, from two clinical sites. One study site erroneously applied the study patches for 30 minutes, instead of the planned 20 minutes, so an additional 20 patients were then enrolled. This was done without submission of a formal protocol amendment. Only the 40 patients who received 20-minute patch applications were included in the sponsor's initial efficacy analysis. All 60 subjects enrolled were included in the safety analysis.

8.3.1.8 Study Conduct

The study was conducted between June 12, 2002 and July 31, 2002. In the Study Report (Section 9.6), the Sponsor notes that the study was conducted in accordance with Good Clinical Practice (GCP) Guidelines and utilized the following measures to assure data quality assurance:

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

The Study Report does not indicate how many patients were screened in total. As noted above, forty patients were to be enrolled. One of the two clinical sites , in error, applied study patches for 30-minutes, instead of the protocol-specified 20-minutes, to all of the initial twenty patients that they enrolled. They then enrolled twenty more subjects, and applied the patches as per protocol.

A 20-gauge angiocath was used for each of the 119 venipunctures performed during this study (Subject #24228 underwent only one venipuncture (S-Caine arm), because of a "defective placebo patch.") "Insertion at first attempt" was achieved for all but one of the venipunctures; the remaining venipuncture required "Minor adjustment." A 20-gauge angiocath was used for each and every venipuncture performed during this study.

8.3.1.8.1 Subject Disposition

There were no study dropouts or terminations. All subjects returned for their follow-up evaluations.

Table 8.3.
Subject Disposition Summary

Subject Status	No.
Enrolled in Study	60
Received 20-minute S-Caine Treatment	40
Received 20-minute Placebo Treatment	39
Completed Study	39
Received 30-minute S-Caine Treatment	20
Received 30-minute Placebo Treatment	20
Study Dropouts/Discontinuations	0

Source: Sponsor Table 10.1, Volume 35

8.3.1.8.2 Protocol Deviations and Violations

A total of 45 protocol deviations or violations were reported in 37 of the 60 enrolled patients. Protocol violations were defined as those deviations that had the potential to affect the outcome of the study. The most significant, and common, deviation has been noted above; twenty subjects received 30-minute patch applications.

Subjects Excluded from Efficacy Analysis (because of 30-minute patch application)
24201, 24202, 24203, 24204, 24205, 24206, 24207, 24208, 24209, 24210,
24211, 24212, 24213, 24214, 24215, 24201, 24217, 24218, 24219, 24220

There were twenty-five additional protocol violations reported as well. Subjects 24201 through 24220 (n=20) all had study patches applied for 30 minutes, instead of the protocol specified 20 minutes, and were excluded from the efficacy analysis. No specific actions were taken in response to any of the other reported violations, which are summarized in the table below.
Tables 8.4 and 8.5 summarize these protocol deviations and violations.

Table 8.4. Protocol Deviations and Violations

Type of Deviation	No.
Study patches applied for 30 minutes instead of 20 minutes	20
S-Caine patch applied for >=21 minutes but < 25 minutes	3
Placebo patch applied for >=21 minutes but < 25 minutes	3
S-Caine patch applied for 19 minutes	1
Placebo patch not applied because patch was defective	1
Some vital signs not recorded	5
Return visit occurred < 24 hours after study drug application	1
Return visit occurred > 48 hours after study drug application	11

Source: Sponsor Table 10.2 and Appendix 16.2.2 (Volume 35)

Table 8.5.
Study SC-24-01: Summary of Additional Sponsor-Defined Protocol Deviations

Site	Subject No.	Protocol Violation
1	24113	S-Caine Patch applied for 21 minutes
1	24115	24-48 hour return visit transpired > 48 hours after patch removal
1	24116	24-48 hour return visit transpired > 48 hours after patch removal
1	24116	Placebo patch applied for 21 minutes
1	24117	24-48 hour return visit transpired > 48 hours after patch removal
1	24117	Placebo patch applied for 21 minutes
1	24119	S-Caine Patch applied for 24 minutes
1	24119	Placebo patch applied for 22 minutes
2	24201	24-48 hour return visit transpired > 48 hours after patch removal
2	24202	24-48 hour return visit transpired > 48 hours after patch removal
2	24203	24-48 hour return visit transpired > 48 hours after patch removal
2	24204	24-48 hour return visit transpired > 48 hours after patch removal
2	24213	24-48 hour return visit transpired > 48 hours after patch removal
2	24222	Subject's temperature not recorded
2	24223	Subject's temperature not recorded
2	24224	Subject's temperature not recorded
2	24225	24-48 hour return visit transpired > 48 hours after patch removal
2	24226	Subject's blood pressure not recorded
2	24228	S-Caine Patch applied for 19 minutes (omitted from sponsor table)
2	24228	No venipuncture attempt (Placebo patch defective and not applied)
2	24232	S-Caine Patch applied for 21 minutes
2	24234	24-48 hour return visit transpired > 48 hours after patch removal
2	24236	Subject's temperature not recorded
2	24239	24-48 hour return visit transpired > 48 hours after patch removal
2	24240	24-48 hour return visit transpired > 48 hours after patch removal

Source: Table 16.2.2, Volume 35 (SC-24-01 Study Report, Appendix)

8.3.1.9 Data Sets Analyzed

All 60 patients who were randomized and received study drug were included in the safety population, and all safety analyses were conducted on the safety population. Efficacy was based only on subjects who received the 20-minute patch applications. Otherwise, data from subjects with application times slightly greater than or less than 20 minutes were included in the efficacy analyses. Subject #24228 (no placebo patch, 20-minute S-Caine Patch) completed all evaluations for the S-Caine Patch. Data from subject #24228 was included in those efficacy analyses not requiring within-subject comparison.

8.3.1.10 Demographics/Group Comparability/Skin Type

8.3.1.10.1 Demographics

Baseline characteristics and other demographic characteristics are summarized in Tables 8.6 and 8.7 (from Sponsor Table 11.1) below. Review of these tables indicates that the two subject groups were comparable across centers with regard to all measured characteristics, and there was a reasonable representation of genders and races in the study.

Table 8.6. SC-24-01 Demographics
Subjects who Received 20-Minute Patch Application

	Center 1 (n=20)	Center 2 (n=20)	p-value
Gender			
Male (%)	7 (35)	8 (40)	1.00[a]
Female (%)	13 (65)	12 (60)	
Age (years)			
Mean ± SD	31.1 ± 8.9	39.8 ± 0.7	0.009[b]
Min, Max	22-52	21-61	
Race			0.756[a]
Black (%)	3 (15)	11 (55)	
Caucasian (%)	10 (50)	8 (40)	
Hispanic (%)	5 (25)	0 (0)	
Asian (%)	0 (0)	1 (5)	
Mixed (%)	2 (10)	0 (0)	
Height (cm)			
Mean ± SEM	66.3 ± 5.8	67.8 ± 4.3	0.361[b]
Min, Max	55-76	60-76	
Weight (kg)			
Mean ± SD	160.7 ± 39.4	176 ± 49.5	0.297[b]
Min, Max	108-260	113-298	

[a] Mantel-Haenzel summary chi-square stratified by center
[b] 2-way ANOVA, factors: treatment, group, center, treatment by center
Source: Sponsor Table 11.1 Volume 35 (SC-24-01 Study Report)

Table 8.7. SC-24-01 Subject Skin Type
Subjects who Received 20-Minute Patch Application

	Center 1 n=20	Center 2 n=20	p-value
Skin Type			0.495[a]
(I) Always Burns/Rarely Tans	0 (0%)	0 (0%)	
(II) Always Burns/Tans Minimally	2 (10%)	3 (15%)	
(III) Burns Moderately/Tans Gradually	8 (40%)	4 (20%)	
(IV) Burns Minimally/Always Tans	2 (10%)	3 (15%)	
(V) Rarely Burns/Tans Profoundly	5 (25%)	5 (25%)	
(VI) Never Burns/Deeply Pigmented	3 (15%)	5 (25%)	

[a] Mantel-Haenzel summary chi-square

Source: Sponsor Table 11.1, Appendix 14.1.2, Vol. 35

8.3.1.10.1 Group Comparability: Medical Conditions

The medical conditions reported are unlikely to have influenced this study's efficacy results. The medical conditions most frequently reported by subjects were allergies (32% of all subjects) and reproductive conditions (18%). Cardiovascular conditions (15%), gastrointestinal conditions (12%) and neurologic conditions (10%) were also commonly reported. Other medical conditions were all reported in less than 10% of subjects, except for hepatic and immunologic conditions which none of the subjects reported. The enrolled subjects' medical histories are summarized in Sponsor Table 14.1.3, and are reproduced in the table below.

Table 8.8. Study SC-24-01 Summary of Subjects' Medical History

	20 Minutes Center 1	20 Minutes Center 2	30 Minutes Center 2	Total
Number of Subjects	20	20	20	60
Body System				
EENT	1	1	1	3
Cardiovascular	2	2	5	9
Respiratory	0	1	3	4
Renal	1	2	1	4
Hepatic	0	0	0	0
Gastrointestinal	3	2	2	7
Reproductive	3	4	4	11
Metabolic/Endocrine	0	1	3	4
Immunologic	0	0	0	0
Musculoskeletal	1	0	0	1
Dermatologic	2	0	0	2
Neurological/CNS	4	0	2	6
Hematologic	1	1	1	3
Allergies	5	5	9	19
TOTALS	23	19	31	73

Source: Sponsor Table 14.1.3, Volume 35

Seven of the sixty subjects had abnormal findings noted on screening physical examination. Four subjects were noted to be obese, one subject had facial hyperpigmentation and post-juvenile acne, one subject had a III/IV systolic ejection murmur and one subject had bilateral upper lobe "congestion." The frequency of abnormal findings on the screening physical examinations of enrolled subjects is in Sponsor Table 14.1.4, reproduced below.

Table 8.9. Study SC-24-01 Subjects' Physical Exam Abnormalities

	20 Minutes Center 1	30 Minutes Center 2	30 Minutes Center 2	Total
Number of Subjects	20	20	20	60
Body System				
Head and Neck	0	0	0	0
Skin and Mucosa	1	0	0	1
ENT	0	0	0	0
Neurological	0	0	0	0
Musculoskeletal	0	0	0	0
Lymph Node	0	0	0	0
Cardiovascular	1	0	0	1
Chest and Lungs	0	0	1	1
Abdomen	0	0	0	0
Other	0	2	2	4
TOTAL	2	2	3	7

Source: Sponsor Table 14.1.4, Volume 35

Mean values of vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate and temperature) at screening were normal and were similar between the two sites.

Mean and median values of clinical laboratory values at screening were all normal and were similar between the two treatment sites.

8.3.1.11 Treatment Compliance

Study drug was administered by the investigator and subjects were monitored during each treatment. Pre-dose and post-dose assessments were performed by the investigator, an independent observer, and the subject. All subjects returned for their scheduled follow-up visit, although as noted above, some of the follow-ups were done outside the protocol-specified 24-48 hour window.

8.3.1.12 Unplanned Analyses

The sponsor's efficacy analyses exclude the twenty initial patients enrolled at [redacted] (Center #2); those treated with study drug for 30 minutes instead of 20. Three requests for intention-to-treat analysis (details in Appendix A) have been sent to the sponsor, but as of January 2, 2003 this has not been received.

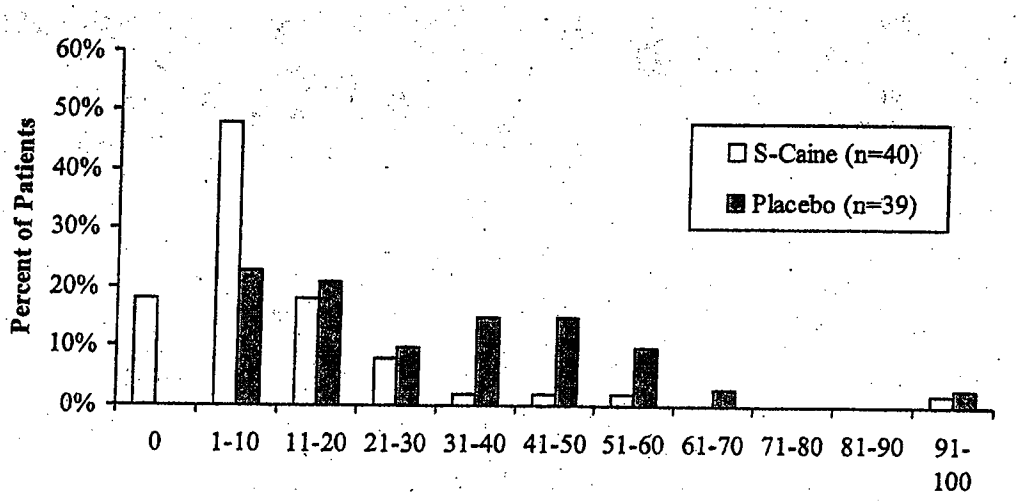
No other unplanned analyses were substituted or performed.

8.3.1.13 Sponsor's Report of Efficacy Results

8.3.1.13.1 Primary Efficacy Variable

The primary efficacy measure in this study was the subject's evaluation of pain (by 100 mm VAS) following each vascular access procedure, and the sponsor achieved the prespecified VAS difference of 15-mm. Mean VAS scores for the S-Caine treatment and the placebo treatment were 12.0 ± 18.3 and 29.3 ± 21.7, respectively. Median scores were 5.0 and 28.0, respectively. VAS scores were lower with S-Caine than placebo for 49% of subjects, and VAS scores were lower with placebo than with S-Caine for 17% of subjects ($p<0.001$, Wilcoxin Signed Rank test).

Diagram 8.1. SC-24-01 Primary Efficacy Analysis (30 minute applications excluded)



Source: Sponsor Figure 11.1, Volume 35

8.3.1.13.2 Secondary Efficacy Variables

Findings for each of the secondary efficacy variables describing subjects' and investigator's overall impressions, as well as investigator and observer evaluations of subject pain also reach statistical significance.

Subject's Overall Impression of the Local Anesthetic		
"Adequate"		(p=0.002[a])
S-Caine adequate and placebo not adequate	59%	
Placebo adequate and S-Caine not adequate	15%	
"Would use again"		(p=0.002[a])
Would use S-Caine again, but not placebo	51%	
Would use placebo again, but not S-Caine	15%	
Investigator and Independent Observer's Evaluation of Subject's Pain		
Investigator ratings of subject pain		(p=0.021[b])
S-Caine < placebo	46%	
Placebo < S-Caine	15%	
Observer ratings of subject pain		(p=0.015[b])
S-Caine < placebo	46%	
Placebo < S-Caine	15%	
Investigator's Overall Impression		
Subject experienced adequate anesthesia		(p=0.004[a])
S-Caine "yes", and placebo "no"	54%	
Placebo "yes", and S-Caine "no"	15%	
S-Caine Patch, "yes"	73%	
Placebo Patch, "yes"	31%	

[a] McNemar Chi-Square Test [b] Wilcoxin Signed Rank test
Source: Prepared from text, Volume 35 pages 30-31

8.3.1.14 Discussion of Efficacy Findings in Study SC-24-01

Taken as a whole, the SC-24-01 efficacy findings support the effectiveness of a twenty-minute application of the S-Caine Patch, in reducing the pain caused by venipuncture with a 20-gauge angiocatheter.

The Sponsor's primary efficacy variable was the subject's evaluation of pain (by VAS) experienced during intravenous cannulation of the antecubital vein. Mean VAS scores for the S-Caine treatment and the placebo treatment were 12.0 ± 18.3 and 29.3 ± 21.7, respectively ($p<0.001$). While the clinical significance of this absolute difference between groups in mean VAS scores may be questionable, the within-subjects comparison also demonstrates a statistically significant S-Caine effect. Forty-nine percent of subjects reported lower VAS scores with S-Caine than with placebo, and 17%

reported lower scores with placebo than with S-Caine ($p<0.001$, Wilcoxin Signed Rank test).

Subject's overall impression of the local anesthetic

When asked whether the patches "provided adequate pain relief" during the procedure 73% of subjects indicated adequate anesthesia with S-Caine patch versus 31% with placebo patch. Fifty-nine percent of subjects indicated adequate anesthesia with S-Caine but not placebo, and 15% indicated adequate pain relief with placebo and not S-Caine ($p=0.002$, McNemar Chi-Square test).

Seventy percent of subjects indicated that they would use the S-Caine patch again, and 33% of subjects indicated that they would use the placebo patch again. Fifty-one percent of subjects indicated that they would use S-Caine again but not placebo, and 15% indicated that they would use placebo again but not S-Caine ($p=0.006$, McNemar Chi-Square test).

Investigator and Independent Observer's Evaluation of Subject's Pain

Investigators considered 46% of subjects to have less pain with S-Caine than with placebo, and 15% to have less pain with placebo than with S-Caine ($p=0.021$, Wilcoxin Signed Rank test). The independent observers considered 46% of subjects to have less pain with S-Caine than placebo, and 15% to have less pain with placebo than with S-Caine ($p=0.015$, Wilcoxin Signed Rank test).

Investigator's Overall Impression

Based on the investigator ratings 54% percent of subjects experienced adequate anesthesia with S-Caine but not placebo, and 15% experienced adequate pain relief with placebo and not S-Caine ($p=0.004$, McNemar Chi-Square test).

Review of the subjects' preexisting medical conditions, and of the reported protocol deviations, finds them unlikely to have significantly affected the efficacy results of this study. PP and ITT analysis with and without the 20 patients who inadvertently received the 30-minute application were consistent with one another.

8.3.2 Pivotal Study SC-23-01: A Randomized, Double-blind, Placebo-Controlled, Clinical Study Evaluating the S-Caine™ Patch for Induction of Local Anesthesia Prior to Minor Dermatological Procedures in Adults

8.3.2.1 Findings vs. Labeling Claims

This study was designated (in the NDA) as a pivotal trial. Subjects treated with S-Caine Patch had (statistically significantly) lower average VAS scores during protocol defined "minor dermatological procedures" than subjects treated with placebo. This finding is consistent with a label claim for use prior to the types of minor dermatological surgical procedures that were evaluated in SC-23-01. The sponsor proposes to label the product as [redacted]

The proposed claim may be inappropriately broad, and use of the word "analgesia" instead of [redacted] may be more appropriate. Final label wording will be discussed during several upcoming meetings dedicated to that purpose.

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

8.3.2.2 Study Plan

The initial version of Protocol SC-23-01 was dated March 27, 2001. Two amendments were implemented prior to subject enrollment, dated November 27, 2001 (Amendment 1), and March 28, 2002 (Amendment 2).

8.3.2.3 Population, Design, and Objectives

The protocol-specified objectives of the study were:

1. To compare the effectiveness of an S-Caine Patch to a placebo patch in providing clinically useful local anesthesia for minor dermatological procedures in adults.
2. To monitor the nature and frequency of adverse events associated with the safety of an S-Caine Patch.

This protocol was designed as a randomized, double-blind, placebo-controlled study in adults scheduled to undergo "minor dermatological procedures." Approximately 60 subjects, at least 18 years of age, were to be randomized 1:1 into one of the two treatment groups (Active S-Caine Patch vs. placebo patch). Treatment groups were to be further stratified by procedure, 2:1, shave biopsy: excision. Patients who presented to the study site for minor dermatological procedures, and who met entry criteria would be invited to participate. Each patient was to receive a 30-minute patch administration (S-Caine Patch or placebo patch) prior to undergoing their procedure. At the end of the 30-minute patch application the patch was to be removed, and then the investigator was to evaluate the skin (under the patch) for erythema, edema and other skin reactions. Subjects would then undergo their scheduled procedure. At any time during the procedure a rescue lidocaine injection would be available for patients experiencing inadequate analgesia. Following the dermatological procedure, efficacy evaluations would be performed. The primary efficacy measure would be the patient's rating of procedure-induced pain using a 100-millimeter Visual Analog Scale. Other efficacy evaluations would include patient overall assessment of local anesthetic, investigator ratings of patient pain, investigator ratings of

the adequacy of the anesthetic, and an independent observer's score of his/her perception of the patient's pain. If the patient received a rescue lidocaine injection, they were to assess the amount of pain experienced during the procedure, prior to receiving the rescue injection. After completion of the procedure, and the efficacy and safety evaluations, patients would be dismissed. Patients that received rescue lidocaine injections were to be dismissed after the dermatological procedure, without completion of the remainder of the pain assessment forms.

Table 8.10. SC-23-01: Schedule of Events

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

Source: Modified from Sponsor Table 9.2, Volume 34

The initial protocol planned for a total of approximately 60 patients to be enrolled at two study sites.

The inclusion criteria were to be:
1. Male or female patients 18 years or older of any race.
2. Would require anesthesia for a shave biopsy or excision.
3. No known allergies or sensitivities to lidocaine, tetracaine or other local anesthetics of the amide or ester type.
4. Subject had signed and dated the written informed consent.

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

5. Pregnant or breastfeeding.

8.3.2.4 Treatment Summary

Study Medication

Both S-Caine and placebo patches were to be supplied by, and manufactured under the direction of ZARS, Inc., Salt Lake City, Utah.

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

Tetracaine Supplier
Lidocaine Supplier [redacted]

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

Subjects were to receive a single 30-minute application of either an S-Caine Patch or a placebo patch, over the site of their planned dermatological procedure, immediately prior to the procedure.

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

Concomitant Medications

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

8.3.2.5 Assessments

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

8.3.2.5.1 Primary Efficacy Variable

The primary efficacy variable was to be the subjects' evaluation of pain, as rated on a 100 mm VAS, where 0 mm = "no pain" and 100 mm = "the worst pain you can imagine." If patients received a rescue lidocaine injection they would be instructed to rate the pain of the dermatological procedure prior to the lidocaine injection.

8.3.2.5.2 Secondary Efficacy Variables

Subject's overall impression of the local anesthetic

Each subject was to be asked to evaluate the efficacy of study drug by answering "yes" or "no" to the following questions:

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

Investigator and independent observer's evaluations of subject's pain
The investigator and the independent observer separately would assess the amount of pain they felt the subject had experienced during the procedure using a 4-point categorical scale (no pain, slight pain, moderate pain, or severe pain).

Investigator's overall impression of the local anesthetic
The investigator would answer "yes" or "no" to the following question:
- Did the local anesthetic patch provide adequate anesthesia for the minor dermatological procedure?

8.3.2.5.3 Safety Assessments

Adverse Events
Adverse events were to be recorded on the CRF including the event's time of occurrence, type, severity, and duration. "Because mild and transient incidences of localized erythema and edema are reported as expected reactions from topical lidocaine and tetracaine use, the investigators recorded only moderate to severe cases of erythema and edema as adverse events."
Evaluation of Skin Reactions
Immediately after patch removal the investigator would examine patch sites for erythema, eschar formation and edema. Safety assessments are described in detail in this review's Integrated Summary of Safety.

8.3.2.6 Sponsor's Analysis Plan

Demographic, background and pre-procedure variables were to be summarized using descriptive statistics and compared between treatment groups, stratified by procedure and center using analysis of variance for continuous variables and Mantel-Haenszel summary chi-square tests for dichotomous or ordered categorical data.

The primary efficacy variable, subject VAS rating of procedure-induced pain, was to be compared over all procedures using ANOVA with the factors: center, treatment, procedure and associated interactions. If the results exhibited skewness and the treatment by center interaction was not significant, a Mann-Whitney test was to be used to assess final significance.

Assessment scales for secondary efficacy variables ("adequate anesthesia" and "would use again") and for evaluation of skin reactions were to be compared between groups stratified by study center and procedure type using Mantel-Haenszel summary chi-square tests for ordered or dichotomous data.

Exploratory analysis of treatment differences in pain as a function of procedure type were to be performed using two-way ANOVA with procedures with ten or more patients grouped separately, and those procedures with less than ten cases grouped together.

Individual treatment comparisons by procedure were to be performed using rank sum tests.

Adverse effects were to be tabulated by center, type, frequency, onset, duration, outcome and relationship to treatment. Overall incidence of any effect and the incidence of individual effects was to be compared between treatment groups using Mantel-Haenszel summary chi-square tests. Incidence of individual effects was to be compared between treatments using sign tests, and the numbers of occurrences overall were to be compared using Wilcoxin signed rank tests.

Sample Size Calculation

Earlier S-Caine studies, demonstrated a treatment difference of approximately 15 mm in VAS rating with a standard deviation of 15. Sixteen patients per group would be necessary, using a two-sided significance level of 5% and a power of 80%. This study was designed for three centers (n=30 each) for a total of 90 patients, in order to allow for exploration of efficacy differences among different types of procedures.

8.3.2.7 Protocol Amendments and Changes in the Planned Analyses

Two amendments were made to Protocol SC-23-01.

Amendment 1 (Amendment date November 27, 2001; FDA Submission No. 15 on 10/11/2002) was implemented prior to patient enrollment and provided the following changes:

- Expanded list of protocol defined "minor dermatological procedures" to include skin tag removal, electrodessication, keloid injection in addition to superficial excision and shave biopsy.
- Increased the number of patients planned for each of the two sites 30 to 45, for a total of 90 patients
- Eliminated the plan to stratify the patients by procedure
- Added investigational sites to the protocol
- Defined minor dermatological procedures as skin tag removal, superficial excisions, electrodessication, keloid injection and shave biopsy.
- Clarified the amount of drug contained in the active formulation
- "Added procedures of providing patients with verbal instructions and a handout regarding potential delayed skin reactions and of instructing patient to call site if any skin reactions developed after the treatment
- Clarified the procedure for opening study drug packaging
- Deleted the name of one of the study monitors

Amendment 2 (Amendment date March 28, 2002; FDA Submission No. 15 on 10/11/2002) was implemented following initiation of the study and provided the following changes:

- Replaced one study site with another
- Added an additional study site, for a total of three study sites
- Clarified that the handout that patients received regarding potential delayed skin reactions did not contain pictures

8.3.2.8 Study Conduct

The study was conducted between March 4 and June 3, 2002. In the Study Report (Section 9.6), the Sponsor notes that the study was conducted in accordance with Good Clinical Practice (GCP) Guidelines and utilized the following measures to assure data quality assurance:

- On-site study monitoring at "suitable intervals"
- On-site comparison of CRFs with source documents (proportion not specified)
- Single data entry with 100% verification
- Answering of all data clarification or queries, with changes made to CRF recorded in a log

8.3.2.8.1 Subject Disposition

The Study Report does not indicate how many patients were screened in total. Ninety subjects were to be enrolled. All enrolled subjects completed the study.

Table 8.11. SC-23-01 Subject Disposition Summary

Disposition	S-Caine (n=45)	Placebo (n=49)
Randomized	45	49
Completed	45	49
Study Dropouts/Discontinuations	0	0

Source: Sponsor Table 10.2 and Appendix 16.2.2

8.3.2.8.2 Protocol Deviations and Violations

A total of 40 protocol deviations or violations were reported in 37 of the 94 enrolled patients. Protocol violations were defined as those deviations that had the potential to affect the outcome of the study. No patients were discontinued, or excluded from analysis because of protocol violation. The majority of violations (30/40) occurred because study site number two instructed all patients to phone the study site to report whether or not they experienced a delayed skin reaction. The protocol actually specified that subjects were to phone only if they experienced a delayed reaction. While this may bias safety results, it is not likely to have had any effect on the efficacy evaluations.

The table below, based on Sponsor Table 10.2, summarizes protocol deviations and violations.

Table 8.12. SC-23-01 Protocol Deviations and Violations

Type of Deviation	S-Caine (n=45)	Placebo (n=49)
Study patch applied for 31 to 35 minutes	3	2
Unapproved dermatologic procedure performed (Cryotherapy)	2	1
Patient number not assigned in sequential order	0	2
Site #2 only, instructed all patients to call study site, to report whether or not a delayed skin reaction occurred.	15	15

Source: Sponsor Table 10.2 and Appendix 16.2.2, Volume 34

Table 8.13. SC-23-01 Sponsor-Defined Protocol Violations

S-Caine		
	Subject No.	Protocol Violation
	23126	Cryotherapy procedure performed
	23132	Cryotherapy procedure performed
	23203	Patient instructed to call study site to report re: delayed skin reaction
	23204	S-Caine Patch applied for 35 minutes instead of 30 minutes
	23204	Patient instructed to call study site to report re: delayed skin reaction
	23205	S-Caine Patch applied for 32 minutes instead of 30 minutes
	23205	Patient instructed to call study site to report re: delayed skin reaction
	23206	Patient instructed to call study site to report re: delayed skin reaction
	23211	S-Caine Patch applied for 33 minutes instead of 30 minutes
	23211	Patient instructed to call study site to report re: delayed skin reaction
	23212	Patient instructed to call study site to report re: delayed skin reaction
	23213	Patient instructed to call study site to report re: delayed skin reaction
	23214	Patient instructed to call study site to report re: delayed skin reaction
	23218	Patient instructed to call study site to report re: delayed skin reaction
	23219	Patient instructed to call study site to report re: delayed skin reaction
	23221	Patient instructed to call study site to report re: delayed skin reaction
	23222	Patient instructed to call study site to report re: delayed skin reaction
	23225	Patient instructed to call study site to report re: delayed skin reaction
	23226	Patient instructed to call study site to report re: delayed skin reaction
Placebo		
	23103	Subject ID number not assigned in sequential order
	23127	Cryotherapy procedure performed
	23201	Patient instructed to call study site to report re: delayed skin reaction
	23202	Patient instructed to call study site to report re: delayed skin reaction
	23207	Patient instructed to call study site to report re: delayed skin reaction
	23208	Patient instructed to call study site to report re: delayed skin reaction
	23209	Placebo patch applied for 34 minutes instead of 30 minutes
	23209	Patient instructed to call study site to report re: delayed skin reaction
	23210	Placebo patch applied for 31 minutes instead of 30 minutes
	23210	Patient instructed to call study site to report re: delayed skin reaction
	23215	Patient instructed to call study site to report re: delayed skin reaction
	23216	Patient instructed to call study site to report re: delayed skin reaction
	23217	Patient instructed to call study site to report re: delayed skin reaction
	23220	Patient instructed to call study site to report re: delayed skin reaction
	23223	Patient instructed to call study site to report re: delayed skin reaction
	23224	Patient instructed to call study site to report re: delayed skin reaction
	23227	Patient instructed to call study site to report re: delayed skin reaction
	23228	Subject ID number not assigned in sequential order
	23228	Patient instructed to call study site to report re: delayed skin reaction
	23229	Patient instructed to call study site to report re: delayed skin reaction
	23230	Patient instructed to call study site to report re: delayed skin reaction

Source: Modified from Table 16.2.2, Volume 34 (Appendix)

8.3.2.8.3 Data Sets Analyzed

All 94 patients who were randomized were included in all efficacy and safety analyses.

8.3.2.9 Demographics/Group Comparability/Skin Type

Baseline characteristics and other demographic characteristics are summarized in Table YY.1 and YY.2 (from Sponsor Table 11.1) below. Review of this table indicates that the two treatment groups were comparable with regard to all measured characteristics.

Table 8.14. SC-23-01 Subject Demographics

Characteristic	S-Caine (n=45)	Placebo (n=49)	p-value
Gender			
Male (%)	14 (31%)	15 (31%)	0.889 [a]
Female (%)	31 (69%)	34 (69%)	
Age (years)			
Mean ± SD	39.6 ± 13.4	41.4 ± 13.8	0.455 [b]
Min, Max	20 - 67	20 - 80	
Race			
Black (%)	4 (9%)	6 (12%)	0.890 [c]
Caucasian (%)	26 (58%)	28 (57%)	
Hispanic (%)	15 (33%)	15 (31%)	
Height (inches)			
Mean ± SEM	65.9 ± 3.5	65.8 ± 4.0	0.974 [b]
Min, Max	57 - 72	60 - 76	
Weight (lbs)			
Mean ± SD	171.2 ± 37.5	171.3 ± 41.6	0.981 [b]
Min, Max	113 - 260	105 - 255	
Skin Type			
I	6 (13%)	3 (6%)	0.206 [a]
II	12 (27%)	9 (18%)	
III	11 (24%)	16 (33%)	
IV	11 (24%)	13 (27%)	
V	3 (7%)	7 (14%)	
VI	2 (4%)	1 (2%)	

[a] Mantel-Haenzel summary chi-square stratified by center
[b] 2-way ANOVA, factors: treatment, group, center, treatment by center
[c] Mantel-Haenzel summary chi-square (Caucasion vs. other) by center
Source: Sponsor Table 11.1, Volume 34

8.3.2.9.1 Group Comparability: Medical Conditions

The medical condition most frequently reported by patients in both the S-Caine and the placebo groups was "a dermatologic condition" (i.e., nevus, skin tag or seborrheic keratosis). Although a study entry requirement, though, only 40% of subjects (40% S-Caine group, 39% placebo group) actually reported this as "a medical condition." And at study Center 2, which enrolled nearly one-third of all subjects, not one reported their dermatologic lesion as a "medical condition." The thoroughness and care with which this

data was elicited is questionable, particularly from Center 2. This is somewhat disconcerting, given that patient self-report figures so prominently in this study, for both efficacy and safety outcome measures.

Other medical conditions most frequently reported by subjects were reproductive conditions (22% of all subjects) and allergies (19% of all subjects). Cardiovascular conditions, gastrointestinal conditions, ENT, endocrine/metabolic and neurologic conditions were also commonly reported. Other medical conditions, reported in less than 10% of subjects, were renal, respiratory, hepatic, hematologic and immunologic. The enrolled subjects' medical histories are summarized in the Table 8.15.

Table 8.15. Study SC-23-01
Summary of Medical History ("Conditions") All Subjects Enrolled in Study

Center	Center 1		Center 2		Center 3		Total	
Treatment	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
Number of Subjects	16	18	14	16	15	15	45	49
Body System								
ENT	0	0	4	4	1	0	5	4
Cardiovascular	2	5	1	3	2	1	5	9
Respiratory	0	0	1	1	1	0	2	1
Renal	0	0	1	0	0	0	1	0
Hepatic	0	0	0	0	0	0	0	0
Gastrointestinal	0	0	2	4	4	1	6	5
Reproductive	0	0	3	8	6	4	9	12
Metabolic/Endocrine	3	2	1	2	0	1	4	5
Immunologic	0	0	0	0	0	0	0	0
Musculoskeletal	1	1	2	5	3	1	6	7
Dermatologic	3	4	0	0	15	15	18	19
Neurological/CNS	0	1	1	3	2	1	3	5
Hematologic	0	0	0	1	0	0	0	1
Allergies	1	1	9	6	0	1	10	8
TOTAL	10	14	25	37	34	25	69	76

Source: Sponsor Table 14.1.3, Volume 34

8.3.2.9.2 Group Comparability: Physical Examination Findings

The investigators report that all enrolled subjects had skin and/or mucosa findings. Two patients also were noted to have scars, but otherwise, there were no other abnormal physical examination findings. Mean values of vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate and temperature) at screening were normal and were similar between the two treatment groups. Mean and median values of clinical laboratory values at screening were also normal and similar between the two treatment groups. It is unlikely that the physical examination or laboratory findings influenced study results.

8.3.2.9.3 Group Comparability: Dermatologic Procedure Performed

Table 8.16. SC-23-01
Group Comparability by Dermatological Procedure

	S-Caine n=45 [a]	Placebo n=49 [a]	P-value
Procedure			
Shave Biopsy	4 (9%)	7 (14%)	0.920 [b]
Excision	18 (40%)	22 (45%)	
Curettage	5 (11%)	5 (10%)	
Electrodessication	11 (24%)	8 (16%)	
Skin tag	3 (7%)	4 (8%)	
Keloid injection	2 (4%)	2 (4%)	
Cryotherapy	2 (4%)	1 (2%)	
Procedure Depth (mm)			
Mean ± SD	1.5 ± 0.7	1.6 ± 0.8	0.381 [c]
Range	0.5 - 3	0.5 - 3	
Procedure Location			
Neck/Head	9 (20%)	15 (31%)	
Back	10 (22%)	6 (12%)	
Chest/Abdomen	10 (22%)	6 (12%)	
Arm/Shoulder	11 (24%)	20 (41%)	
Leg	5 (11%)	2 (4%)	
Procedure Duration			
Mean ± SD	2.3 ± 1.5	2.7 ± 2.4	0.412 [c]
Range	0 - 6	0 - 12	
Rescue Medication	10 (22%)	4 (49%)	0.008 [d]

[a] One missing data point for depth in both groups
[b] Pearson chi-square
[c] Two-way ANOVA, factors: treatment, group, center, treatment by center
[d] Mantel-Haenszel chi-square
Source: Sponsor Table 14.1.7, Volume 34

8.3.2.9.4 Group Comparability: Concomitant Medications

The types of medications used, and the number per patient, were similar between groups, and unlikely to have significantly influenced study results. Forty-two percent of S-Caine treated patients were using a concomitant medication at the time of enrollment, as were 39% of placebo-treated patients. The most commonly used medications were for contraception and endometriosis, musculoskeletal conditions such as osteoarthritis and osteoporosis, and cardiovascular conditions such as hypertension.

8.3.2.10 Treatment Compliance

Each patient received one application of either an S-Caine patch or a placebo patch, dispensed from the clinic pharmacy and labeled with their individual ID number. A second, identical label was affixed to each patient's CRF form. Predose and postdose assessments were performed by the investigator, an independent observer, and the subject.

8.3.2.11 Unplanned Analyses

The sponsor did not conduct any unplanned statistical analyses.

8.3.2.12 Efficacy Results

8.3.2.12.1 Primary Efficacy Variable

The primary efficacy measure in this study was the subject's evaluation of pain (by 100 mm VAS) caused by the dermatologic procedure. Table 8.17 presents patients' VAS ratings of pain during the procedure, broken out by procedure type. Median scores were 5 mm (range 0 – 92) in the S-Caine group and 31 mm (range 0 – 95) in the placebo group ($p<0.001$, Mann-Whitney test). Statistically significant center differences existed for VAS scores ($p=0.003$, ANOVA on log transformed data), but treatment comparisons were comparable for all centers ($p=0.553$, ANOVA on log transformed data). Median VAS scores were significantly lower than placebo for excision (6.0 vs. 33.0, $p=0.017$) and for electrodessication (3.0 vs. 32.5, $p=0.028$). Differences between S-Caine and placebo VAS scores for shave biopsy and curettage were consistent with results for the other procedures (lower pain scores in the S-Caine group), but were not statistically significant, possibly due to the small numbers of patients. Table 8.18 summarizes patient VAS scores by anatomic location of the procedure.

Table 8.17. Patient VAS Score by Procedure Type (N=94)

	S-Caine		Placebo		
	N	Median	N	Median	P-value*
All	45	5.0	49	31.0	<0.001
Shave Biopsy	4	3.5	7	58.0	0.089
Excision	18	6.0	22	33.0	0.017
Curettage	5	1.0	5	12.0	0.341
Electrodessication	11	3.0	8	32.5	0.028
Other	7	5.0	7	39.0	0.040
Skin tag	3		4		
Keloid injection	2		2		
Cryotherapy	2		1		

*Mann-Whitney test

Source: Sponsor Table 11.4, text, and Appendix 16.2.12 (NDA Volume 33)

Table 8.18. Patient VAS Score by Anatomic Location (N=94)

	S-Caine		Placebo		
	N	Median	N	Median	P-value*
Head/Neck	9	6.0	15	34.0	0.022
Back	10	9.0	6	55.5	0.587
Chest/Abdomen	10	1.0	6	26.0	0.003
Arm/Shoulder	11	3.0	20	26.5	0.004
Hip/Leg	5	5.0	2	25.5	---
Other					

*Mantel-Haenszel summary chi-square

Source: Sponsor Table 11.5, Volume 34

8.3.2.12.2 Secondary Efficacy Variable

Findings for each of the secondary efficacy variables also reach statistical significance.

Subject's overall impression of the local anesthetic		
"Adequate"		($p<0.001^a$)
S-Caine adequate	73%	
Placebo adequate	37%	
"Would use again"		($p=0.023^a$)
Would use S-Caine again	76%	
Would use placebo again	53%	
Investigator and Independent Observer's Evaluation of Subject's Pain		
Investigator rating of "No subject pain"		($p<0.001^b$)
S-Caine	51%	
Placebo	10%	
Observer ratings of "No subject pain"		($p<0.001^b$)
S-Caine	53%	
Placebo	10%	
Investigator's Overall Impression		
Subject experienced adequate anesthesia		($p=0.004^a$)
S-Caine yes	71%	
Placebo yes	39%	

[a, b] Mantel-Haenszel summary chi-square

The variable "required rescue lidocaine injection" was not specified prospectively as an efficacy measure in the protocol proposal. The sponsor found, however, that 22% of S-Caine treated patients required rescue lidocaine, compared with 49% of placebo treated patients (p=0.008, Mantel Haenszel chi-square).

8.3.2.13 Discussion of Efficacy Findings in Study SC-23-01

Taken as a whole, the efficacy findings in Study SC-23-01 appear to support the effectiveness of a thirty-minute application of S-Caine Patch, in reducing the pain associated with protocol-specified "minor dermatological procedures."

8.3.3 Pivotal Study SC-20-01: A Randomized, Double-blind, Placebo-Controlled, Clinical Study Evaluating the S-Caine™ Patch for Induction of Local Anesthesia for Vascular Access Procedures in Pediatric Patients

8.3.3.1 Findings vs. Labeling Claims

The results of this clinical trial may offer support some evidence in support of the effectiveness of S-Caine Patch (over placebo) in reducing the pain caused by venipuncture and intravenous cannulation in pediatric subjects.

8.3.3.2 Study Plan

Protocol SC-20-01 was first submitted on April 11, 2001. By agreement with the Division (teleconference June 28, 2001), the original protocol submission was withdrawn, and SC-20-01 was resubmitted as a new protocol on October 1, 2001. There were then, according to the sponsor three amendments to the protocol.

Amendment 1, dated October 1, 2001 (the same as the protocol) specified the second study site.

Amendment 2, dated March 29, 2002 was also implemented prior to subject enrollment and contained further details on the conduct of the Quantitative Sensory Testing (QST) portion of SC-20-01.

Amendment 3, reportedly was dated December 11, 2001 (according to the SC-20-01 final study report submitted with this NDA). According to the NDA Amendment 3 formally deleted the Quantitative Sensory testing arm from the study. There are no study amendments (or other submissions) within IND 58,823 between November 2001 and January 2002. Upon review of COMIS, DFS and the entire IND, no references to a third amendment to SC-20-01 were found.

Note: Although the sponsor had specifically sought comments and advice on their pediatric protocols (December 2001), there was no amendment to change the planned sample size. The January 2002 advice letter contained a warning from our statistical reviewer. Given the plan to analyze primary efficacy results separately for the two age subgroups, the planned sample size was not likely to be adequate to detect a treatment effect of the expected magnitude.

8.3.3.3 Population, Design, and Objectives

The protocol-specified objectives of the study were:

1. To compare the clinical effectiveness of an S-Caine Patch to a placebo patch in providing clinically useful local anesthesia for vascular access procedures in pediatric patients.
2. To assess and compare thermal and vibratory sensations (age 7-17 years) following applications of both the S-Caine Patch and EMLA Anesthetic Disc as measured by Quantitative Sensory Testing (QST).
3. To monitor the nature and frequency of adverse events associated with S-Caine Patch.

The protocol was designed to be a randomized, double-blind, placebo-controlled study in (N=60 planned) pediatric patients. Subjects were to be stratified into two age groups (3-6 years, 7-17 years). Subjects were to be randomized (2:1) to receive either a twenty-minute application of an S-Caine Patch, or a placebo patch, prior to undergoing a vascular access procedure. Following a 20-minute patch application, the investigator was to remove the study patch, and then evaluate the treatment area for adverse skin reactions. The investigator was then to assess the patient's behavior using a 3-point categorical scale (calm, slightly frightened, frightened).

The "vascular access procedure" was then to be performed. Detailed plans regarding what type of vascular access procedure was to be performed were not provided in the original protocol. (The final study report contained in the NDA provides the following breakdown; Center 1 used 22-g for all; Center 2 used 18, 20, 21 and 23-g; Center 1 performed only IV cannulation; Center 2 performed blood draws and IV cannulation.)

After the vascular access procedure subjects were to assess the amount of pain caused by the procedure by completing the Oucher Scale (ages 3 to 6, Photographic; ages 7 to 17 Numeric). The investigator and an independent observer would then (separately) evaluate the degree of anesthesia they believed was provided by the study drug, by completing a 4-point categorical scale (no pain, slight pain, moderate pain, severe pain). The investigator was also to evaluate whether they thought that "adequate" anesthesia was provided by the study drug (yes/no).

Patients who were between 7 and 17 years old, at study site number 2 (of 2 planned) only, were then to undergo Qualitative Sensory Testing. According to a randomized code, the vascular access procedure was to be performed on the antecubital surface of one arm, and the QST on the volar surface of the opposite forearm. For the QST evaluations, subjects were to be administered both an active S-Caine Patch, and an EMLA Local Anesthetic Disc for application times of 20 minutes, 30 minutes or 60 minutes (8 subjects each determined by randomization). The QST evaluation was to assess the subject's sensation of cold pain ("until it hurts"), heat pain (also "until it hurts") and vibration. Complete details pertaining to the procedures for the QST were submitted in the original protocol, dated October 1, 2001.

The study planned for a total of 60 patients to be enrolled.

The inclusion criteria were to be:
1. Male or female 3 to 17 years old.
2. Subject or parent had signed and dated the written informed consent.

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

4. Pregnant or breastfeeding.
5. Known, active atopic dermatitis.
6. Known to have multiple allergies.
7. Severe cognitive impairment, or unable to understand and use the pain assessment tool.

8.3.3.4 Treatment Summary

Study Medication

The S-Caine Patches were to be manufactured under the direction of ZARS, but the specific manufacturer was not specified.

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

Tetracaine Supplier
Lidocaine Supplier [redacted]

Upon meeting eligibility criteria, patients were to be assigned the next available sequential subject number. Treatment arm for the active drug (left arm vs. right arm) was to be randomized. Treatments would be double-blind, and assigned based on a predetermined computer-generated randomization code, so that "two-thirds of the subjects would receive the S-Caine Patch and one-third would receive the placebo patch." This contradicts protocol objective number two, "To assess and compare thermal and vibratory sensations (age 7-17 years) following applications of both the S-Caine Patch and EMLA Anesthetic Disc as measured by Quantitative Sensory Testing (QST)."

Concomitant Medications

Use of a prescription strength analgesic medication during the 24-hour period preceding the study would result in subject exclusion. No other medications would preclude participation. All concomitant treatments were to be recorded on the CRF.

8.3.3.5 Assessments

8.3.3.5.1 Primary Efficacy Variable

The primary efficacy variable was to be the subject's evaluation of pain immediately following vascular access, as rated on the Oucher Scale. Based on "cognitive tests" to be administered by the investigator, the subjects were to use either the numeric Oucher Scale (0-100 in 10 mm increments = 11-point categorical) or the photographic Oucher Scale (six-point categorical scale). Subjects 3 to 6 years of age (developmental equivalency) were to use an Oucher Scale that utilized children's faces as the method for measuring pain, and subjects 7 to 17 years of age were to use an Oucher Scale that utilized numerical values (0 to 100 in increments of 10). "The patient's ability to perform certain cognitive tasks as judged by the investigator determined which scale the patient used."

8.3.3.5.2 Secondary Efficacy Variables

Investigator and independent observer's evaluations of subject's pain

The investigator and the independent observer were both to be asked (separately) to assess the amount of pain they felt the subject experienced during the procedure, using a 4-point categorical scale (no pain, slight pain, moderate pain, or severe pain).

Investigator's overall impression of the local anesthetic
The investigator was to be asked to answer "yes" or "no" to the following question:

- Did the local anesthetic patch provide adequate anesthesia for the vascular access procedure?

8.3.3.5.3 Other (Exploratory) Measurements

"Clinical Response"
The investigator was to do a pre-assessment of the child's behavior prior to the dermatological procedure (vascular access) using a three-point categorical scale (Calm, Slightly Frightened, Frightened)

8.3.3.6 Sponsor's Analysis Plan

Demographic, background and pre-procedure variables were to be summarized using descriptive statistics and compared between treatment groups, stratified by center using ANOVA for continuous variables and Mantel-Haenszel summary chi-square tests for dichotomous or ordered categorical data.

Oucher pain scales and secondary efficacy assessments were to be compared between groups stratified by center using Mantel-Haenszel summary chi-square tests. Oucher scale results were to be further stratified by the scale used (picture vs. numerical).

For the QST temperature and frequency measurements, time comparisons within administration time groups were to be made using repeated measures analysis of variance with tests for time trends.

Adverse effects were to be tabulated by group, type, frequency, onset, duration, outcome and relationship to treatment. Overall incidence of any effect and the incidence of individual effects was to be compared between treatment groups stratified by study center using Mantel-Haenszel summary chi-square tests.

Sample Size Calculation
Sample size was calculated based on the primary efficacy measure, subject pain rated by Oucher scale. Earlier studies had demonstrated that the percent of placebo subjects with "no pain" did not exceed 30%. The S-Caine Patch was expected to be effective (= "no pain") in greater than 70% of subjects. With a power of 80% and a two-sided significance level of 5%, 36 active and 18 placebo patients would be necessary. This study was designed for two centers, each to recruit 30 subjects, for a total of 40 active and 20 placebo subjects.

To accommodate QST testing at one center, an additional nine patients (six active and three placebo) in the 7-17 age group would be added.

8.3.3.7 Protocol Amendments and Changes in the Planned Analyses

There were (reportedly) three amendments to Protocol SC-20-01.

The first, "Amendment 1" was submitted October 1, 2001 and added a second clinical site to the study.

According to the sponsor "Amendment 2 and Amendment 3, dated March 29, 2002 and December 11, 2001, respectively, pertained to the Quantitative Sensory Testing arm of the study described in the original protocol." Amendment 2, contained in submission number 12 (May 10, 2002) provided details about how the Quantitative Sensory Testing was to be conducted at study site number 2. "Amendment 3 formally deleted the QST arm of the study from the protocol." The final study report states that the investigator was unwilling to participate in the QST arm of the study.

As discussed above, Amendment 3, reportedly dated December 11, 2001 appears to never have reached the FDA.

In the NDA study report (Appendix. after Amendment 2) there is a two-page document, dated (and signed) January 14, 2003, titled "Detailed Statistical Analysis Plan." This would have been after the final subject was enrolled, but according to the sponsor prior to unblinding the study. It described the statistical analysis plan as follows:

> "The primary efficacy variable, Oucher Scale rating of procedure-induced pain, was to be analyzed separately by type of scale (numerical for older subjects, photographic for younger subjects). A two-way ANOVA was to be used to test for center by treatment interactions. If no interactions were evident, overall significance was to be assessed using Mann-Whitney tests. In addition, if results appeared comparable between the two types of Oucher Scales, Cochrane's test for homogeneity was to be used on the proportions of patients with "no pain", stratifying on the scale used, and on center. If no interaction between treatment and Oucher Scale were found, an overall comparison of patients with "no pain" was to be performed using a Mantel-Haenszel summary chi-square, stratified by center and scale.
>
> The investigator and observer pain evaluations, were to be compared between treatments using Mantel-Haenszel summary chi-square test for ordered categories, stratified by center. Assessment of "adequate anesthesia" as rated by investigator and observer was to be compared using Mantel-Haenszel summary chi-square tests."

The sponsor had specifically sought comments and advice on their pediatric protocols (December 2001). The January 2002 advice letter contained a warning from our statistical reviewer that given the plan to analyze primary efficacy results separately for the two age subgroups, the planned sample size (40 active drug, 20 placebo) was not likely to be adequate to detect a treatment effect of the expected magnitude. None of the study amendments change the planned sample size, though.

8.3.3.8 Study Conduct

The study was conducted between May 16 and December 12, 2002. In the Study Report (Section 9.6), the Sponsor notes that the study was conducted in accordance with Good Clinical Practice (GCP) Guidelines and utilized the following measures to assure data quality assurance:

- On-site study monitoring at "suitable intervals"
- On-site comparison of CRFs with source documents (proportion not specified)
- Single data entry with 100% verification
- Answering of all data clarification or queries, with changes made to CRF recorded in a log

Table 8.19. SC-20-01 Vascular Access Procedures (All Subjects Randomized)

Variable	S-Caine (n=43)	Placebo (n=21)	p-value
Pre-Procedure Behavior			0.596 [a]
Calm	21 (49%)	9 (43%)	
Slightly Frightened	14 (32%)	7 (33%)	
Frightened	8 (19%)	5 (24%)	
Procedure (n %)			0.696 [b]
Blood Draw	16 (35%) [d]	7 (33%) [f]	
IV Access	26 (60%)	14 (67%)	
Not Specified	1 (5%) [e]	0 (0%)	
IV Catheter Gauge			
18 Gauge	1 (2%)	0 (0%)	0.361 [c]
20 Gauge	5 (12%)	3 (15%)	
21 Gauge	14 (33%) [d]	4 (20%)	
22 Gauge	20 (46%)	10 (50%)	
23 Gauge	2 (5%)	3 (15%)	
Body Site			
Right Antecubital Vein	20 (46%) [d]	8 (38%) [f]	
Left Antecubital Vein	13 (32%)	7 (33%)	
Right Hand	1 (2%)	1 (5%)	
Left Hand	9 (21%) [e]	5 (24%)	
Procedure Duration (min)	(N = 41)	(N = 20)	0.638 [a]
< 1	29 (71%)	13 (65%)	
1 – 1.9	9 (22%)	5 (25%)	
≥ 2	3 (7%)	2 (10%)	

Source: Sponsor Table 11.3 and Appendix 16.2.10, 16.2.11 and 16.2.12, Volume 31

[a] Mantel-Haenszel summary chi-square, stratified by center

[b] Fisher's Exact Test, center 2 only

[c] Pearson Chi-Square, center 2 only

[d] Patient 20201 was scheduled to undergo a blood draw (from the right antecubital vein) using a 21-gauge catheter, but "the patient became uncooperative and the procedure was not performed."

[e] Patient 20237 was scheduled to undergo an unspecified procedure on the left hand. Site staff determined the procedure was not necessary.

[f] Patient 20231 was scheduled to undergo a blood draw from the right antecubital vein. "The site staff determined the procedure was not necessary and did not perform the procedure."

8.3.3.8.1 Subject Disposition

The Study Report does not indicate how many patients were screened in total. Sixty subjects were to be enrolled.

Table 8.20. SC-20-01 Subject Disposition

Disposition	S-Caine (n=43)	Placebo (n=22)
Randomized	43	22
Withdrew Consent	0	1
Received Treatment	43	21
Withdrew from Study	2	1
Completed Study	41	20

Source: Sponsor Table 10.1 and Appendix 16.2.1, Volume 31

8.3.3.8.2 Protocol Deviations and Violations

Protocol violations were defined as those deviations that had the potential to affect the outcome of the study. Two patients from the S-Caine group (20201 and 20237, both age 4) and one patient from the placebo group (20231, age 7) did not undergo their vascular access procedures and were excluded from the efficacy analysis, despite having received study drug. In the cases of 20231 and 20237 the staff determined that the patients no longer required intravenous catheters. Subject 20201, 4 years old, refused to allow the investigator to proceed with insertion of the IV.

The table below, based on Sponsor Table 10.2, summarizes protocol deviations and violations.

Table 8.21. SC-20-01 Protocol Deviations and Violations

Protocol Deviation	S-Caine (n=43)	Placebo (n=22)
No procedure performed after patch treatment (staff determined subject didn't require)	1	1
Subject refused procedure after patch treatment	1	0
Handout re: side effects not given	1	0
Non-sequential ID number assignment	2	1
Patient enrolled despite concomitant oxy/APAP	0	1
Patch administration 14 minutes (not 20)	1	0
Patch administration between 22 and 25 minutes	3	0
Subject allowed to score 5 on Oucher scale (scale is 0 to 10 in 10 point increments)	1	0

Source: Sponsor Table 10.1 and Appendix 16.2.1

S-Caine Patch group

Patient 20201 was scheduled to undergo a blood draw (from the right antecubital vein) using a 21-gauge catheter, but "the patient became uncooperative and the procedure was not performed."

Patient 20237 was scheduled to undergo an unspecified procedure on the left hand, however, the site staff determined the procedure was not necessary and did not perform the procedure."

Placebo Patch group
Patient 20231 was scheduled to undergo a blood draw from the right antecubital vein. "The site staff determined the procedure was not necessary and did not perform the procedure."

8.3.3.8.3 Data Sets Analyzed

Data from 41 of the 43 patients in the S-Caine group and from 20 of 21 patients in placebo group were included in the efficacy analysis. Subjects 20201 and 20237 in the S-Caine group and 20231 in placebo group did not have data for efficacy analysis because they did not undergo vascular access procedure (Two by staff decision one by subject refusal).

8.3.3.8.4 Treatment Compliance

At study Center 1 patches were applied to only the left or right antecubital surface. At Center 2 patches were also applied to the (dorsum of?) the hands.

8.3.3.8.5 Unplanned Analyses

No unplanned analyses were conducted according to the sponsor.

8.3.3.9 Sponsor's Efficacy Results

8.3.3.9.1 Primary Efficacy Variable

The primary efficacy measure in this study was the subject's evaluation of pain caused by the vascular access procedure, as rated using one of two "Oucher Scales." The Photographic Oucher is a series of six photographs showing a child in varying degrees of discomfort (corresponding to 0, 20, 40 ,60 , 80 and 100). The Numeric Oucher includes a vertical number scale (0 – 100, with increments of 10) adjacent to the same six photographs.

In general, 3 to 6 year olds were to use the Photographic Oucher, and subjects 7 and older were to use the Numeric Oucher. The decision to use the Numeric Oucher was actually to be made based on "cognitive tests" (counting tasks); ability to count forwards corresponds with ability to use the Numeric Oucher. Whether this testing was done is not recorded, however. All subjects 6 and younger did use the Photographic Oucher. Out of seven 7 year-olds, four used the Photographic Oucher and two the Numeric Oucher; one was discontinued from the study ("procedure no longer necessary"). Two of the three 8 year-olds also used the Photographic Oucher scale.

Photographic Oucher Scale
Median Oucher scores for the S-Caine Patch group and for the placebo patch group were 0 (range 0 to 100) and 80 (range 0 to 100) respectively ($p < 0.001$, Mann-Whitney).

Numeric Oucher Scale
The median Oucher score for the S-Caine Patch group was 7.5 (range 0 to 100) compared with 50 (range 0 to 80) for the placebo group (p=0.159, Mann-Whitney test).

8.3.3.9.2 Secondary Efficacy Variables

Investigator and Independent Observer's Evaluations of Subject's Pain
The investigator and an independent witness separately assessed the amount of pain they felt the subject experienced during the lidocaine injection using a four-point categorical scale. The investigator rated 76% of patients who received the S-Caine Patch as having "No Pain" or compared with 20% of patients who received placebo (p<0.001, Mantel-Haenszel summary chi-square). The independent observer rated 76% of patients who received S-Caine Patch treatment as having "No Pain" compared with 15% of patients who received placebo (p<0.001, Mantel-Haenszel summary chi-square).

Investigator's Overall Impression of the Local Anesthetic
The investigator felt that the local anesthetic provided adequate anesthesia for the procedure in 80% of patients who received the S-Caine Patch treatment compared with 70% of patients who received placebo treatment (p=0.556, Mantel-Haenszel summary chi-square).

Table 8.22, on the following page, summarizes primary and key secondary efficacy findings from study SC-20-01.

Table 8.22. SC-20-01 Efficacy Results

	SC-20-01	SC-20-01	SC-20-01
Ages (years)	3 to 6	7 to 17	3 to 17
Subjects (S-Caine/Placebo)	25 / 11	16 / 9	41 /20
Application Duration	20 minutes	20 minutes	20 minutes
Oucher Scale	Photo	Numeric	All
Primary Efficacy			
Median Oucher			
S-Caine	0	7.5	NA
Placebo	80	50	NA
P-value [a]	<0.001	0.159	<0.001 **
Mean Oucher			
S-Caine	16.8	18.4	NA
Placebo	61.8	42.2	NA
P-value			
Secondary Efficacy			
Investigator Rating			
"Adequate Anesthesia"			
S-Caine			80%
Placebo			70%
P-value [b]			0.556
Pain Rating = "No Pain"			
S-Caine			76%
Placebo			20%
P-value [b]			<0.001
Observer Rating			
Pain Rating = "No Pain"			
S-Caine			76%
Placebo			15%
P-value [b]			<0.001

[a] Mann-Whitney test
[b] Mantel-Haenszel summary chi-square
** Post-hoc analysis (clinical reviewer)

8.3.3.10 Discussion of Efficacy Findings in Study SC-20-01

The primary outcome measure in SC-20-01 was the Photographic Oucher for children ages 3 – 6, and the Numeric Oucher for children ages 7 – 17. Results for the younger group achieved statistical significance. In the older, and smaller, group (subjects that used the Numeric Oucher), the findings were in the expected direction, but failed to reach statistical significance. Secondary efficacy measures were analyzed, as planned, for the entire group of subjects, and (with some exceptions) support an efficacy claim. The sponsor may have achieved "a win" on their primary efficacy measure, for 7 to 17 year olds, had they increased their sample size (as advised). Strictly (or statistically) speaking, this trial has failed to demonstrate S-Caine Patch efficacy for a large portion of the pediatric population.

8.3.4 Pivotal Study SC-21-01: Initial Title: A Randomized, Double-Blind, Clinical Study Comparing the S-Caine Patch to EMLA Anesthetic Disc for Induction of Local Anesthesia in Pediatric Patients

Note: The study conducted was substantially different (design, treatments, painful stimulus) from the one initially proposed (See Amendment 1)

8.3.4.1 Findings vs. Labeling Claims

The results of SC-21-01 do not support an efficacy claim in pediatric subjects for the S-Caine Patch (30-minute application) in reducing the pain caused by dermal injection of lidocaine. SC-21-01 does demonstrate effectiveness in 3 to 6 year old children (subjects that used the "Photographic" rather than the "Numeric" version of the primary efficacy measure).

8.3.4.2 Study Plan

Protocol SC-21-01 was first submitted on October 12, 2001 (Supplement 008). There were six protocol amendments.

Amendment 1, dated February 20, 2002 (SN 12, June 4, 2002) changed the study design entirely. The study that was ultimately performed was substantially different from the one originally planned. Amendments 2 through 6 added, and removed investigators and study sites (SN 15, October 11, 2002).

8.3.4.3 Population, Design, and Objectives

The (initial) protocol-specified objectives of this study were:

1. To compare the clinical effectiveness of an S-Caine Patch to an EMLA Anesthetic Disc in providing clinically useful local anesthesia in pediatric patients undergoing:
   - Curettage or shave biopsy procedures (Ages 7-17)
   - Subcutaneous injection of lidocaine (Ages 3-6)
2. To monitor the nature and frequency of adverse events associated with S-Caine Patch.

This protocol was originally designed to be a randomized, double-blind, study comparing the effectiveness of the S-Caine Patch to the EMLA Anesthetic Disc in providing clinically useful anesthesia for minor dermatological procedures (curettage or shave biopsy), or for the injection of lidocaine, in pediatric patients.

Approximately eighty patients, ages 3 through 17 were to be enrolled. Subjects were to be randomized (1:1) into one of two treatment groups:

1. Active S-Caine Patch applied for 30 minutes, or
2. EMLA Anesthetic Disc applied for 60 minutes.

As indicated by the study title, the sponsor intended for this to be "a double-blind study" in 80 pediatric subjects. Subjects were to be stratified into two age groups (3-6 years, 7-17 years). Subjects were to be randomized (1:1) to receive either a thirty-minute application of an S-Caine Patch, or a sixty minute application of EMLA. "Treatment will

be double-blind, and assigned based on a computer-generated randomization code. Each pouch will be accompanied by a separate label, identical to the one on the investigational patch, which must be affixed to the appropriate space on the drug accountability CRF. If randomized to receive EMLA, the lot number should be recorded on the designated CRF....Someone other than the investigator should apply the study drug so the investigator remains blinded to the study treatment..."

Immediately following study drug treatment, the investigator was to perform the 'Evaluation of Skin Reactions" and also assess the subject's behavior employing the "Pre-Procedure Behavior Scale." The investigator was then to begin the minor dermatological procedure which would be either;

- Scheduled curettage or shave biopsy in 7 to 17 year olds, or
- A lidocaine injection in 3 to 6 year olds

After the dermatological procedure subjects were to assess the amount of pain caused by the procedure by completing the Oucher Scale (ages 3 to 6, Photographic Oucher; ages 7 to 17, Numeric Oucher). The investigator and an independent observer would then (separately) evaluate the degree of anesthesia provided by the study drug, by completing a 4-point categorical scale (no pain, slight pain, moderate pain, severe pain). The investigator was also to evaluate whether they thought that "adequate" anesthesia was provided by the study drug (yes/no).

The original study protocol indicated that a total of 80 patients were to be enrolled.

The inclusion criteria were to be:

1. Male or female 3 to 17 years old.
2. "Subject requires a minor dermatological procedure (curettage or shave biopsy, ages 7-17) or requires a lidocaine injection (ages 3-6)."
3. Subject or parent had signed and dated the written informed consent.

The exclusion criteria were to be:

1. Known allergies to lidocaine, tetracaine, prilocaine, other local anesthetics, to sympathomimetic amines, or known sensitivity to any component of the test materials (e.g., adhesives).
2. Prescription strength analgesic pain medication use during the 24-hour period preceding the procedure.
3. Damaged, denuded or broken skin at either designated patch site.
4. Pregnant or breastfeeding.

8.3.4.4 SC-21-01 Study as performed

Prior to subject enrollment SC-21-01 was redesigned into a randomized, double-blind, placebo-controlled study, comparing the efficacy of 30-minute applications of S-Caine Patch to placebo, for "induction of local anesthesia prior to a lidocaine injection administered for a minor dermatologic procedure." The reasons for study redesign are not entirely clear (from review of the original protocol, amendments and NDA final study report). One factor seems to be anticipated difficulties with blinding between EMLA and

S-Caine Patch, especially in light of different planned treatment periods (60 minutes for EMLA, 30 minutes for S-Caine). Once there was no longer an active control arm, there may have been concerns about conducting a placebo controlled study in children undergoing dermatological surgery, however minor. The sponsor had made many of the arrangements (investigators and study sites, subject recruitment plans and parameters) to begin an S-Caine Patch study in children undergoing minor dermatological surgery. They seem to have gone ahead with the planned study population, but a different comparator (placebo instead of EMLA) and a different painful stimulus (lidocaine injection prior to dermatological surgery, and not the surgery itself). Efficacy measures were unchanged, however.

Review of the protocol amendments and final study report indicates that the conditions for the lidocaine injection (volume, concentration, +/- vasoconstrictor, needle gauge, +/- bicarbonate, subcutaneous vs. intradermal) do not appear to have been carefully controlled for. The final study report states "It was expected that in most cases the lidocaine injection would be buffered with sodium bicarbonate ([redacted]) and would be delivered by a 30-gauge needle."

8.3.4.5 Treatment Summary

Study Medication

S-Caine Patches were to be supplied by, and manufactured under the direction of ZARS, Inc. but the specific manufacturer was not specified.

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

Tetracaine Supplier
Lidocaine Supplier [redacted]

The EMLA Anesthetic Discs (manufactured by Astra USA, Inc.) used for this study would be obtained from a supplier of marketed product.

Concomitant Medications

Use of a prescription strength analgesic medication during the 24-hour period preceding the study would result in subject exclusion. No other medications would preclude participation.

8.3.4.6 Assessments

8.3.4.6.1 Primary Efficacy Variable

The primary efficacy variable was to be the subject's evaluation of pain immediately following the dermatological procedure (or lidocaine injection in 3 to 6 year olds), as rated using the Oucher Scale. Subjects 3 to 6 years of age (developmental equivalency) were to use a Photographic Oucher Scale that utilized children's faces as the method for measuring pain, and subjects 7 to 17 years of age were to use an Oucher Scale that utilized numerical values (0 to 100 in increments of 10). "The patient's ability to perform certain cognitive tasks as judged by the investigator determined which scale the patient used."

8.3.4.6.2 Secondary Efficacy Variables

Investigator and independent observer's evaluations of subject's pain

The investigator and the independent observer were both to be asked (separately) to assess the amount of pain they felt the subject experienced during the procedure, using a 4-point categorical scale (no pain, slight pain, moderate pain, or severe pain).

Investigator's overall impression of the local anesthetic

The investigator was to be asked to answer "yes" or "no" to the following question:

- Did the local anesthetic patch provide adequate anesthesia for the vascular access procedure?

8.3.4.6.3 Other (Exploratory) Measurements

"Clinical Response"

The investigator was to do a pre-assessment of the child's behavior prior to the dermatological procedure/lidocaine injection using a three-point categorical scale (Calm, Slightly Frightened, Frightened)

8.3.4.7 Sponsor's Analysis Plan

Demographic, background and pre-procedure variables were to be summarized using descriptive statistics and compared between treatment groups, stratified by study center using ANOVA for continuous variables and Mantel-Haenszel summary chi-square tests for dichotomous or ordered categorical data.

Oucher pain scales and secondary efficacy assessments were to be compared between groups stratified by center using Mantel-Haenszel summary chi-square tests. Oucher scale results were to be further stratified by the scale used (picture vs. numerical).

Adverse effects were to be tabulated by group, type, frequency, onset, duration, outcome and relationship to treatment. Overall incidence of any effect and the incidence of individual effects was to be compared between treatment groups stratified by study center using Mantel-Haenszel summary chi-square tests.

Sample Size Calculation

Sample size was calculated based on the primary efficacy measure, subject pain rated by Oucher scale. Earlier studies had demonstrated that the percent of placebo subjects with "no pain" was 67%, compared to 10% of placebo patients. In order to detect a difference of 33% between EMLA and S-Caine, using a two-sided significance level of 5% and a power of 80%, forty subjects at each of two study centers (twenty patients receiving each treatment at each site) were planned for.

8.3.4.8 Protocol Amendments and Changes in the Planned Analyses

According to the sponsor there were six amendments to Protocol SC-21-01.

Amendment 1 was dated February 20, 2002 per NDA (dated May 9, 2002 in the IND) (SN 12, June 4, 2002), and changed many aspects of the study. The following changes:

- Modified the study design, from a double-blind study comparing the S-Caine Patch to EMLA, to a double-blind placebo controlled study;
- Changed the painful procedure to be evaluated from a minor dermatological procedure, or a lidocaine injection, to lidocaine injection only;
- Clarified the procedures to be used for contacting subject's parents in case of adverse events;
- Deleted from the protocol the statement "All deaths, whether considered study drug related or not, must be reported immediately to the study sponsor and a copy of the autopsy report (if available) and death certificate must be forwarded to ZARS."
- Sample size doubled in order to evaluate the two age groups separately;
- Modified the statistical procedures to be used, as a result of the change in study design;
- "Clarified the appropriate use of the Oucher Scale;" and
- Required that the research nurse telephone the parent within 48 hours and ask the parent to inspect for delayed skin reactions at patch application site.

In the NDA the sponsor reports that Amendments 2 through 6 "altered only the number of study sites that would participate in the study and/or alters the investigators." (NDA Volume 32, page 26) Amendments 2,3, 4, 5 and 6 were submitted in SN 15, October 11, 2002, doing so.

A detailed statistical analysis plan was submitted on December 11, 2002 (this was not included with any of the official protocol amendments). This does not appear to address all of the concerns expressed by the Division in the January, 2002 advice letter, specifically, with respect to sample size (Section 3.2 (Regulatory History):

> "The primary efficacy variable, Oucher Scale rating of procedure-induced pain, was to be analyzed separately by type of scale (numerical for older subjects, photographic for younger subjects). A two-way ANOVA was to be used to test for center by treatment interactions. If no interactions were evident, overall significance was to be assessed using Mann-Whitney tests. In addition, if results appeared comparable between the two types of Oucher Scales, Cochrane's test for homogeneity was to be used on the proportions of patients with "no pain", stratifying on the scale used, and on center. If no interaction between treatment and Oucher Scale were found, an overall comparison of patients with "no pain" was to be performed using a Mantel-Haenszel summary chi-square, stratified by center and scale.
>
> The investigator and observer pain evaluations, were to be compared between treatments using Mantel-Haenszel summary chi-square test for ordered categories, stratified by center. Assessment of "adequate anesthesia" as rated by investigator and observer was to be compared using Mantel-Haenszel summary chi-square tests."

8.3.4.9 Study Conduct

The study was conducted between June 6 and November 20, 2002. In the Study Report (Section 9.6), the Sponsor notes that the study was conducted in accordance with Good Clinical Practice (GCP) Guidelines and utilized the following measures to assure data quality assurance:

- On-site study monitoring at "suitable intervals"
- On-site comparison of CRFs with source documents (proportion not specified)
- Single data entry with 100% verification
- Answering of all data clarification or queries, with changes made to CRF recorded in a log

8.3.4.9.1 Summary of Lidocaine Injection Performed

The SC-21-01 study report indicates that a 30 gauge needle was used in 93% of S-Caine subjects and 96% of placebo subjects. The "Summary of Lidocaine Injection Procedure" section goes on to give a breakdown of pre-procedure behavior (i.e. calm, slightly frightened, frightened) by treatment.

8.3.4.9.2 Subject Disposition

The Study Report does not indicate how many patients were screened in total. Forty subjects were to be enrolled.

Table 8.23. SC-21-01 Subject Disposition Summary

Disposition	S-Caine (n=41)	Placebo (n=47)
Randomized	41	47
Completed Study	41	47
Discontinued	0	0

Source: Sponsor Table 10.1 and Appendix 16.2.1, Volume 32

8.3.4.9.3 Protocol Deviations and Violations

Protocol violations were defined as those deviations that had the potential to affect the outcome of the study. Two patients from the S-Caine group (20201 and 20237, both age 4) and one patient from the placebo group (20231, age 7) did not undergo their vascular access procedures and were excluded from the efficacy analysis. In the cases of 20231 and 20237 the staff determined that the patients no longer required intravenous catheters. Subject 20201, 4 years old, refused to allow the investigator to proceed with insertion of the IV. Table 8.24 summarizes protocol deviations and violations.

Table 8.24. SC-21-01 Protocol Deviations/Violations

Protocol Deviation	S-Caine (n=41)	Placebo (n=43)
Patient contacted outside the 24-48 hour period for follow-up skin assessment	17	22
Patch applied for only 20 minutes instead of 30	0	1
Pre-behavioral assessment not conducted (All patients at Centers 4 and 5, one pt at Center 3)	14	14
Identifier not assigned sequentially	1	1
Vital signs (some) and/or height not recorded	4	3

Source: Sponsor Table 10.2 and Appendix 16.2.1, Volume 32

8.3.4.9.4 Data Sets Analyzed

Data from all patients were included in the efficacy analysis. Forty-five patients used the Oucher numeric scale and 43 patients used the Oucher photographic scale.

8.3.4.9.5 Treatment Compliance/Study Drug Administration

The most common locations for patch placement were the arms, shoulders, back, hips, legs, head and neck. The patch was administered for 30 minutes in all patients in the S-Caine Patch group and for 98% in the placebo group. The study patch was administered for 20 minutes to one patient in the placebo group.

8.3.4.9.6 Unplanned Analyses

In addition to the planned analyses the sponsor compared Numeric and Photographic Oucher score results (for secondary efficacy variables) separately using Mann Whitney U tests, instead of the protocol specified Mantel-Haenszel summary chi-square.

8.3.4.10 Sponsor's Efficacy Results

The sponsor analyzed primary and secondary efficacy measures by dividing subjects into two subgroups, those that rated their pain using the Photographic Oucher Scale, and those that rated their pain using the Numerical Oucher Scale.

8.3.4.10.1 Primary Efficacy Variable

The primary efficacy measure in this study was the subject's evaluation of pain caused by the lidocaine injection, as rated using one of two "Oucher Scales." The Photographic Oucher is a series of six photographs showing a child in varying degrees of discomfort (corresponding to 0, 20, 40 ,60 , 80 and 100). The Numeric Oucher includes a vertical number scale (0 – 100, with increments of 10) adjacent to the same six photographs.

In general, 3 to 6 year olds were to use the Photographic Oucher, and subjects 7 and older were to use the Numeric Oucher. The decision to use the Numeric Oucher was actually to be made based on "cognitive tests" (counting tasks); ability to count forwards corresponds with ability to use the Numeric Oucher. Whether this testing was done is not recorded, however. One six year old used the Numeric Oucher, but otherwise all subjects 6 and younger did use the Photographic Oucher. One of three seven year-olds used the Photographic Oucher. All three eight year-olds used the Numeric Oucher, but one of three nine year-olds used the Photographic Oucher.

Photographic Oucher Scale

Median Oucher scores for the S-Caine Patch group and for the placebo patch group were 0 and 70 respectively (p=0.005, Mann-Whitney).

Numeric Oucher Scale

70% of subjects receiving the S-Caine Patch had an Oucher score of 10 or less, compared with 52% of subjects that received placebo. Median Oucher scores for both test groups were 10, however (p=0.322, Mann-Whitney test).

8.3.4.10.2 Secondary Efficacy Variables

Investigator and Independent Observer's Evaluations of Subject's Pain

The investigator and an independent witness separately assessed the amount of pain they felt the subject experienced during the lidocaine injection using a four-point categorical scale. Results are summarized in Table YY.ZZ below. The investigator rated 44% of patients who received the S-Caine Patch as having "No Pain" compared with 36% of patients who received placebo (p=0.401, Mantel-Haenszel summary chi-square). The independent observer rated 46% of S-Caine subjects as having "No Pain" compared with 34% of placebo subjects (p=0.269, Mantel-Haenszel summary chi-square). The investigator felt that the local anesthetic provided "adequate anesthesia" for the procedure in 78% of patients who received the S-Caine Patch treatment compared with 51% of patients who received placebo treatment (p=0.028, Mantel-Haenszel summary chi-square).

Although not planned for in the protocol, the sponsor analyzed secondary efficacy measures by patient subgroup (Photographic vs. Numeric Oucher Scale) also.

> "Because the results of the patient's Oucher Scale indicated that the S-Caine Patch was significantly more effective than placebo in the younger patients (i.e., those who used the photographic scale), but not in the older patients (i.e., those who used the numeric scale) an analysis of the investigator and independent witness ratings by type of Oucher Scale used was performed."

Primary and secondary efficacy findings, along with results of the sponsor's analyses appear in Table 8.25 on the following page.

Table 8.25. SC-21-01 Efficacy Results

	S-Caine Patch n=41	Placebo Patch n=47	p-value
Primary Efficacy Measure			
Photographic Oucher (n= 43)	n=21	n=22	p=0.005
Oucher Mean (Photographic)	23.8	58.2	
Oucher Median	0.0	70.0	
Oucher Range	0 - 100	0 - 100	
Numeric Oucher (n= 45)	n=20	n=25	p=0.322
Oucher Mean (Numeric)	18.0	20.0	
Oucher Median	10.0	10.0	
Oucher Range	0 - 80	0 - 80	
Secondary Efficacy Measures			
Rating of Patient Pain (Group)			
Investigator Rating (All subjects)			0.401 [a]
No Pain	18 (43.9%)	17 (36.2%)	
Slight Pain	14 (34.1%)	12 (25.5%)	
Moderate Pain	6 (14.6%)	15 (31.9%)	
Severe Pain	3 (7.3%)	3 (6.4%)	
Observer Rating (All subjects)			0.269 [a]
No Pain	19 (46.3%)	16 (34.0%)	
Slight Pain	14 (34.1%)	14 (29.8%)	
Moderate Pain	5 (12.2%)	14 (29.8%)	
Severe Pain	3 (7.3%)	3 (6.4%)	
Investigator Rating (Photograph)	n=21	n=22	0.050 [b]
No Pain	8 (38%)	5 (23%)	
Slight Pain	8 (38%)	3 (14%)	
Moderate Pain	3 (14%)	11 (50%)	
Severe Pain	2 (10%)	3 (14%)	
Observer Rating (Photograph)	n=21	n=22	0.057 [b]
No Pain	9 (43%)	6 (27%)	
Slight Pain	8 (38%)	3 (14%)	
Moderate Pain	2 (10%)	10 (45%)	
Severe Pain	2 (10%)	3 (14%)	
Investigator Rating (Numeric)	n=20	n=25	0.941 [b]
No Pain	10 (50%)	12 (48%)	
Slight Pain	6 (30%)	9 (36%)	
Moderate Pain	3 (15%)	4 (16%)	
Severe Pain	1 (5%)	0 (0%)	
Observer Rating (Numeric)			0.748 [b]
No Pain	10 (50%)	10 (40%)	
Slight Pain	6 (30%)	11 (44%)	
Moderate Pain	3 (15%)	4 (16%)	
Severe Pain	1 (5%)	0 (0%	

[a] Mantel-Haenszel summary chi-square
[b] Mann-Whitney test, sponsor table 11.5 (Volume 32)
Source: Sponsor Tables 11.4 and 11.5 (Volume 32), text, and Dr. Fan's review

8.3.4.10.3 Discussion of Efficacy Findings in Study SC-21-01

Taken as a whole, these efficacy findings do not support the effectiveness, in "pediatric subjects" of a thirty-minute application of an S-Caine Patch, in reducing the pain associated with "lidocaine injection." These results do offer support for an effectiveness claim in 3 to 6 year olds (subjects that rated their pain using the Photographic Oucher scale). Interestingly, the secondary efficacy measures also, "Investigator Rating" and "Observer Rating" of subject pain only reach (or approach) statistical significance in the "Photographic Oucher" subset of subjects. This makes it difficult to blame failure to achieve the hoped for primary efficacy result on "the instrument" (the Numeric Oucher scale), or even on a small sample size (the Numeric scale was used with more subjects than the Photographic version).

As noted above, the conditions for the lidocaine injection (volume, concentration, +/- vasoconstrictor, needle gauge, +/- bicarbonate, subcutaneous vs. intradermal) do not appear to have been carefully controlled for. In most of the S-Caine venipuncture clinical trials (adult and pediatric) the gauge and the type of needle to be used was specified. The SC-21-01 final study report states only "It was expected that in most cases the lidocaine injection would be buffered with sodium bicarbonate [redacted] and would be delivered by a 30-gauge needle." This type of broad definition of "lidocaine injection" mirrors clinical practice, and is not necessarily inappropriate. Variability in stimulus pain should be roughly evenly distributed between treatment groups. In this situation, however, the sponsor had already been warned that they were under-powering their study (because two different primary efficacy variables necessitated two separate primary efficacy analyses).

Review of the data line listings indicates that doses from 0.05 cc up to 1.2 cc (some unspecified) of several different lidocaine concentrations (1%, 2 %, "10%" or unspecified) were administered. In some cases the lidocaine was buffered with (different volumes and concentrations of) bicarbonate. Introducing this "noise" might have hindered sponsor attempts to demonstrate an S-Caine treatment effect. This possible explanation for the "failed" study was not raised by the sponsor, however. While a post-hoc exploratory analysis would be interesting, it is not feasible given the incompleteness (and the format) with which the "lidocaine injection variables" were recorded.

8.3.5 Controlled Trials: Geriatric and Adult Venipuncture (SC-31-01, SC-11-01)

Both SC-11-01 and SC-31-01 utilized the same basic study design as pivotal trial SC-24-01. As in SC-24-01, SC-11-01 and SC-31-01 were both randomized, double-blind, placebo-controlled, crossover studies in healthy volunteers, designed to evaluate the efficacy and safety of a 20-minute S-Caine Patch application, prior to a "vascular access procedure." SC-31-01 included only "geriatric" subjects, defined by protocol as age 65 or older (The protocol initially stipulated 70 or older, but was amended prior to subject enrollment, to include subjects ages 65 and older). SC-11-01 attempted enrollment of subjects 18 years and up, with no upper age limit, but the oldest participant was 58.

Aside from the age restriction in SC-31-01, inclusion and exclusion criteria for SC-11-01 and SC-31-01 were identical to those for SC-24-01. While study SC-24-01 called for venipuncture with a 20-gauge angiocath (as did SC-31-01), SC-11-01 did not specify what gauge catheter or needle was to be used. In SC-11-01 twenty-one gauge catheters were used for 86% of subjects, twenty-two gauge were used in 10%, and twenty-three gauge were used in 5%, or one subject.

As in SC-24-01, the primary efficacy variable in SC-11-01 and SC-31-01 was to be the subject's evaluation of pain caused by insertion of a 20 gauge angiocath as rated on a 100 mm VAS where 0 mm = "no pain" and 100 mm = "the worst pain you can imagine."

Table 8.26. Primary Efficacy Results, SC-11-01, SC-31-01, SC-24-01

Study	SC-11-01	SC-31-01	SC-24-01
Population	Adult	Geriatric	Adult
Number (S-Caine/Placebo)	21/21	40/40	40/39
Median (range) VAS S-Caine	1 (0-22)	8.0 (0-78)	5.0
Median (range) VAS placebo	9 (1-95)	13.5 (0-88)	28.0
	p=0.004 [b]	p=0.053 [a]	p<0.001 [a]
VAS S-Caine < VAS placebo	76%	65%	49%
VAS placebo < VAS S-Caine	10%	28%	17%
	p<0.001 [a]	p=0.039 [a]	p<0.001 [a]
Mean ± SD S-Caine	3.3	13.9±17.9	12.0±18.3
Mean ± SD Placebo	19.9	20.9±22.5	29.3±21.7

[a] Wilcoxin signed rank test

Source: Modified from sponsor tables and text , volumes 31, 35, 39

Secondary efficacy variables were also identical to those used in SC-24-01;

Subject's overall impression of the local anesthetic

- "Adequate pain relief for the vascular access procedure?" (Yes, No)
- "Would you use this form of anesthesia again if given the option?" (Yes, No)

Investigator and independent observer's evaluations of subject's pain

Investigator and the independent observer separately would assess the amount of pain they felt the subject had experienced during the procedure using a 4-point categorical scale (no pain, slight pain, moderate pain, or severe pain).

Investigator's overall impression of the local anesthetic

- "Did the patch provide adequate anesthesia for the procedure?" (Yes, No)

"Difficulty of insertion" was also to be rated by the investigator on a three-point categorical scale; "Insertion at first attempt," "Minor adjustment needed," or "Second Insertion Required." This was recorded, not as an outcome measure, but for use as a possible exploratory variable.

Table 8.27. Secondary Efficacy Findings in Adult Venipuncture Trials

	SC-11-01	SC-31-01	SC-24-01
Subject's Overall Impression of the Local Anesthetic			
"Adequate"			
S-Caine adequate/placebo not adequate		8%	59%
Placebo adequate/S-Caine not adequate		8%	15%
S-Caine eliminated pain	81%	85%	73%
Placebo eliminated pain	24%	75%	31%
p=(McNemar chi-square)	(p=0.003)	(p=0.206)	(p=0.002)
"Would use again"			
Would use S-Caine again/not placebo		18%	51%
Would use placebo again/not S-Caine		8%	15%
Would use S-Caine again	76%	85%	70%
Would use placebo again	14%	75%	33%
p=(McNemar chi-square)	(p<0.001)	(p=0.206)	(p=0.006)
Investigator and Observer's Evaluation of Subject's Pain			
Investigator ratings of subject pain			
S-Caine < placebo		10%	46%
Placebo < S-Caine		5%	15%
"No Pain" with S-Caine	91%	90%	63%
"No Pain" with placebo	24%	83%	33%
p= (Wilcoxin signed rank test)	(p=0.001)	(p=0.739)	(p=0.021)
Observer ratings of subject pain			
S-Caine < placebo		15%	46%
Placebo < S-Caine		10%	15%
"No Pain" with S-Caine	86%	90%	68%
"No Pain" with placebo	29%	85%	38%
p= (Wilcoxin signed rank test)	(p=0.003)	(p=0.782)	(p=0.015)
Investigator's Overall Impression			
Subject experienced adequate anesthesia			
S-Caine yes, and placebo no		3%	54%
Placebo yes, and S-Caine no		5%	15%
S-Caine adequate	90%	93%	60%
Placebo adequate	24%	95%	23%
p=(McNemar chi-square)	(p<0.001)	(p=0.564[a])	(p=0.004)

[a] McNemar Chi-Square Test
[b] Wilcoxin Signed Rank test

8.3.6 Controlled Trial: Geriatric Minor Dermatological Procedures (SC-22-01)

Study SC-22-01 was a randomized, double-blind, placebo-controlled evaluation of S-Caine Patch effectiveness in "providing clinically useful local anesthesia for minor dermatological procedures" in patients ages sixty-five and older. Study design, inclusion (original) and exclusion criteria (except for age), treatments and efficacy measures were similar to those employed in pivotal study SC-23-01. Protocol SC-22-01 originally called for enrollment of 50 subjects at two study sites (with a 2:1 (active drug:placebo) randomization scheme at each site). The intended sample size was increased from 50 to 75 (Amendment 2) and then to 80 (Amendment 3, one month following study initiation) in order to power for detection of efficacy differences among different types of procedures. The number of intended investigational sites was increased from two to four (Amendment 3).

In SC-22-02 patients were randomized (2:1 active drug to placebo) to receive 30-minute patch applications prior to scheduled dermatological procedures (predominantly shave biopsy or superficial excision). A rescue lidocaine injection could be administered at investigator discretion, or at patient request. After completion of the procedure efficacy evaluations were done.

The primary efficacy measure was the subject's rating (by 100-mm VAS) of their pain, from the dermatological procedure (prior to lidocaine injection, if given).

Secondary efficacy measures were those used in most of the other adult S-Caine trials:

Subject's Overall Impression of the Local Anesthetic

"Adequate"	Yes/No
"Would use 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

"Subject experienced adequate anesthesia"	Yes/No

Rescue Lidocaine Use Yes/No

8.3.6.1 SC-22-01 Results

Seventy-nine subjects were randomized at four study sites; 54 to the S-Caine group, 25 to the placebo group. One study site (Center 3) failed to adhere to the assigned randomization scheme, and chose patches "at random." Another site enrolled one patient scheduled for dermal cryotherapy, which was not a protocol-approved procedure (1 in placebo group). Four patients underwent cauterization following their shave biopsies (4 in S-Caine group).

The sponsor defined two different per-protocol efficacy populations. Per-protocol population #1 (considered primary) excluded the four patients that underwent cauterization after another dermatologic procedure, as well as the single cryotherapy patient (S-Caine subjects 22301, 22302, 22303, 22304 and placebo patient 22402). Per-protocol population #2 excluded those already excluded from PP #1, as well as all patients enrolled from Study Center #3 (14 S-Caine and 6 placebo).

Table 8.28. Patient VAS Score by Procedure Type (Per-Protocol #1, n=74)

	S-Caine		Placebo		
	N	Median	N	Median	P-value*
All	50	9.5	24	22.5	0.041
Shave Biopsy	18	13.0	9	21.0	0.877
Excision	32	7.0	15	25.0	0.020

*Mann-Whitney test Source: Table 11.4 and text, Volume 33

Table 8.29. Patient VAS Score by Anatomic Location (Per-Protocol #1, n=74)

	S-Caine		Placebo		
	N	Median	N	Median	P-value*
Head/Neck	11	2.0	6	20.0	0.043
Back	9	10.0	2	25.0	0.346
Chest/Abdomen	6	2.0	6	16.5	0.106
Arm/Shoulder	16	14.0	2	41.5	0.092
Hip/Leg	7	13.0	8	31.5	0.862
Other	1	8.0	0	---	---

*Mantel-Haenszel summary chi-square Source: Table 11.5, NDA Volume 33

Table 8.30. Patient VAS Score (Per-Protocol #2, n=58 and Intent-to-Treat, n=79)

	S-Caine		Placebo		
	N	Median	N	Median	P-value
Per-Protocol 2					
Shave + Excision	40	7.0	18	24.5	0.020[a]
Intent-to-Treat	54	11.0	25	21.0	0.089[a]

[a] Wilcoxin signed rank Source: NDA text, Volume 33

Secondary Efficacy Variables

None of the findings for analysis of the secondary outcome measures (for per-protocol population #1) approached statistical significance.