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*APPLICATION NUMBER:*

**21-717**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type N 21-717  
Submission Number 000

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Reviewer Name Mwango Kashoki, MD, MPH  
Review Completion Date June 22, 2006

Established Name: Lidocaine and tetracaine 7%/7% cream  
(Proposed) Trade Name: S-Caine  
Therapeutic Class: Local anesthetic  
Applicant: ZARS, Inc.

Priority Designation: **S**

Formulation: Topical local anesthetic cream  
Indication: Local dermal analgesia  
Intended Population: Individuals undergoing superficial  
dermal procedures

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ON ORIGINAL**

## 1 Executive Summary

### 1.1 Recommendation on regulatory action

I recommend approval of this application.

### 1.2 Summary of clinical findings

#### 1.2.1 Overview of clinical program

*Product name:* S-Caine

*Drug class:* Anesthetic

*Route of administration:* Topical

*Indication sought:* Topical local anesthetic for use on normal intact skin for local dermal anesthesia.

*Population studied:* Adult and pediatric patients undergoing a superficial dermal procedure.

*Number of trials:*

	Adult trials	Pediatric trials
<b>Efficacy</b>		
Original NDA	8	3
NDA resubmission	4	1
<b>Safety</b>		
Original NDA	8 <sup>a</sup>	3 <sup>a</sup>
NDA resubmission	2 <sup>b, c</sup>	1 <sup>b</sup>

<sup>a</sup> Safety data were obtained from the efficacy trials; <sup>b</sup> Open label safety studies

<sup>c</sup> 1 study was a controlled trial aimed at determining the duration of effect of S-Caine

Altogether, 2159 persons have been exposed to S-Caine in clinical trials, including pharmacokinetic trials. A total of 1423 individuals were treated with the final/to-be-marketed formulation. All treated patients had only single exposures to S-Caine. Exposure varied according to the duration of S-Caine application and the size of the area of skin that was treated.

#### 1.2.2 Efficacy

In this NDA resubmission, the Applicant submitted five Phase 3 trials in support of efficacy of S-Caine – 4 trials in adults, and 1 in pediatric patients aged 5-17 years. The trials were of two designs: parallel-group and paired (within-subject) studies. In the paired trials, subjects were treated with concurrent S-Caine or placebo peels, in a randomized and blinded manner. In the parallel group trials, subjects were randomized to either S-Caine or placebo. Drug was applied for 20-30 minutes for minor superficial dermatological procedures, and for 60 minutes for major procedures. Efficacy was

assessed by measuring the pain intensity at the time of the procedure. In the adult trials, the efficacy measure was the 100 mm visual analog scale (VAS). The pediatric trial used the Colored Analog Scale (CAS) which is a continuous pain rating scale from 0-10. The CAS was developed as an alternative for pediatric use because it is relatively easier to administer than the VAS.

Although the Applicant considered the primary efficacy measure and endpoint suitable for assessing an anesthetic effect of S-Caine, the Division deemed the measure and endpoint as assessments of an *analgesic* effect. This is because the Division defines anesthesia as the absence of any sensation, and analgesia as a decrease in painful sensation. In the studies, the VAS evaluated whether there was a change in perceived pain intensity (i.e. analgesia), and not whether there was any sensation at all (i.e. anesthesia) in response to the dermatological procedure.

#### *Adult efficacy*

All four of the studies in adults showed that patients treated with S-Caine reported less pain than placebo-treated patients. That is, S-Caine was more efficacious than in producing local analgesia for the tested superficial dermatological procedures.

#### **Summary of Efficacy of S-Caine in Adults**

Study	VAS Score (mean ± SD)		p-value
	S-Caine	Placebo	
SCP-40-05	24.2 ± 18.13	37.4 ± 23.52	< 0.0001
SCP-41-05	21.4 ± 18.89	38.0 ± 24.46	< 0.0001
SCP-42-05	16.4 ± 19.55	30.9 ± 17.06	0.0008
SCP-43-05	39.1 ± 25.48	58.6 ± 21.59	<0.0001

#### *Pediatric efficacy*

The sole pediatric efficacy study failed to show any difference in efficacy between S-Caine and placebo. In this study, patients underwent a minor vascular access procedure (93% venipuncture; 7% initiation of an IV line) following 30-minute treatment with study drug. The mean pain score associated with the procedure was similar between the S-Caine and placebo groups:

#### **Summary of Efficacy of S-Caine in pediatric patients**

Study	VAS Score (mean ± SD)		p-value
	S-Caine	Placebo	
SCP-46-05	1.77 ± 2.46	2.03 ± 2.34	0.64

This pediatric study therefore confirms the findings of the original NDA, namely S-Caine is not efficacious in children. In the original NDA, 2 of the 3 submitted trials failed to show a difference of S-Caine from placebo. The trial that did show a difference was conducted unethically, however. Therefore none of the pediatric trials has demonstrated efficacy of S-Caine in the pediatric population.

### *Geriatric efficacy*

Controlled trials of S-Caine specifically in patients 65 years and older were not performed. However, the adult clinical trials in the NDA resubmission enrolled 13 elderly patients. Analysis of the mean VAS scores showed that S-Caine treated patients in this age category reported less pain than did placebo-treated patients.

#### Summary of Efficacy of S-Caine in patients aged 65+

	Age category (yrs)	No. of Patients		Mean VAS	
		S-Caine,	Placebo	S-Caine	Placebo
<b>Minor dermal procedures</b>	65-74	9	8	6	26.5
	75+	3	3	9	36
<b>Major dermal procedures</b>	65-74	1	1	75	61
	75+	0	0	N/A	N/A

### 1.2.3 Safety

Usual analyses of safety based on integrated information from all clinical trials (i.e. original and new NDA trials) was not possible due to the manner in which the integrated adverse event (AE) dataset was formatted. Because of this, as well as the Division's previous concern regarding the integrity of the original datasets, only integrated data from the new trials was used to characterize the safety profile of S-Caine.

Safety information was collected in two ways: specific skin evaluation for erythema, edema, and blanching immediately following removal of study drug (all clinical trials); and spontaneous reporting of all experienced reactions (all Phase 3 trials)

Due to the topical route of administration, skin reactions were the anticipated (and observed) adverse effects of S-Caine. Systemic reactions were considered unlikely, given the minimal systemic availability of the product.

There were no deaths or serious adverse events among participants in the clinical trials. Three patients discontinued due to adverse events: 2 from the adult open-label safety trial, and 1 from the duration of effect trial in adults. No patients discontinued from any of the efficacy studies.

Across all controlled studies, the frequency of all spontaneously reported non-serious dermal adverse events (AEs) was similar between the S-Caine and placebo groups (~18%, each). The most commonly spontaneously reported dermal AE was erythema (~26% for both treatment groups). Additional common AEs were edema (18%), echymosis (11%), and rash.

Overall, the pattern of spontaneously reported non-serious dermal AEs was between S-Caine- treated adults and pediatric patients. The AE reported in greater frequency by S-Caine treated pediatric patients than adults was 'application site reaction.' Adults treated with S-Caine reported erythema and edema more commonly than pediatric patients.

Data from the skin evaluations showed that erythema and blanching were the most frequently reactions observed immediately following drug removal, followed by edema. The majority of occurrences were mild in severity. Based on these data, adults were more likely than pediatric subjects to have blanching and edema. Erythema was more common in children.

Overall, the data show that single applications of S-Caine for the prescribed period of time are not associated with serious adverse events. Common reactions to treatment are dermal in nature and can include changes in skin color (erythema, blanching, echymosis, purpura), edema, and rash. Most events are mild in severity. Systemic reactions are rare. Safety in pediatric patients is comparable to safety in adults.

#### **1.2.4 Dosing regimen and administration**

Dosing of S-Caine in adults is based on the duration of peel application, the size of the area to be treated, and the thickness of the peel. The duration of application depends on the procedure performed. For “minor” superficial dermatological procedures (e.g. collagen injection), S-Caine is applied for 20 or 30 minutes. For “major” superficial dermatological procedures (e.g. laser-assisted tattoo removal), S-Caine is applied for 60 minutes. Similarly, the larger the area where the dermatological procedure is to be performed (up to 400 cm<sup>2</sup>), the greater the amount of S-Caine will be applied. Finally, because drug flux ceases once the peel is dry, if too thin an application of S-Caine may result in an incomplete analgesic effect even if the peel is applied for the proper amount of time.

Dosage adjustment does not appear to be indicated for older adults aged 65 years and over.

#### **1.2.5 Drug-drug interactions**

Due to the relative lack of systemic absorption of S-Caine, drug-drug interactions are unlikely. Nevertheless, S-Caine should be cautiously used in patients taking Class I antiarrhythmic drugs and other products containing local anesthetics, since there could be additive, and potentially synergistic, systemic toxic effects with lidocaine and tetracaine.

#### **1.2.6 Special populations**

See Sections 1.2.2 and 1.2.3

## **2 Background**

### **2.1 S-Caine**

S-Caine (Lidocaine and tetracaine 7%/7% cream) is a newly formulated topical cream intended for local anesthesia. Both lidocaine and tetracaine induce anesthesia by preventing both the generation and conduction of the nerve impulse: the drugs increase

cell permeability to sodium thereby increasing the threshold for electrical excitability and blocking conduction.

The S-Caine formulation is an emulsion in which the oil phase is a 1:1 eutectic<sup>1</sup> mixture of lidocaine 7% and tetracaine 7%. Each gram of S-Caine contains lidocaine 70 mg and tetracaine 70 mg. The eutectic mixture has a melting point below room temperature, thus both lidocaine and tetracaine exist as liquid oil. Each gram of S-Caine cream contains lidocaine 70 mg and tetracaine 70 mg. The cream is applied to the skin and forms a pliable peel when exposed to air.

A key factor in delivery of S-Caine is the thickness ( $\text{g}/\text{cm}^2$ ) of the peel. This is because drug flux into the skin stops once the peel has dried. The thickness does not alter the *rate* of drug flux, however. Thicker layers take longer to dry than thinner layers, therefore if a peel is applied too thinly drug flux may stop before the application period is complete.

Dosing of S-Caine is based on the surface area of the treatment site as well as the applied thickness of the applied cream. The proposed duration of administration is 20-30 minutes for “minor” dermatological procedures, and 60 minutes for “major” procedures.

## **2.2 Desired indication**

ZARS is seeking approval of S-Caine as a “topical local anesthetic for use on normal intact skin for local dermal anesthesia.”

## **2.3 Other approved topical formulations of lidocaine and tetracaine**

The Agency has previously approved a combination patch formulation of lidocaine and tetracaine (Synera™, N 21-623). Synera is indicated for local dermal *analgesia* (for superficial dermatological procedures such as excision, electrodesiccation, and shave biopsy of skin lesions) in adults and children aged 3 years and older. Synera is another ZARS, Inc. product, and is also comprised of a eutectic mixture of lidocaine 70 mg and tetracaine 70 mg per gram of Synera. The patch consists of a layer of the anesthetic mixture and a heating component that is intended to enhance the delivery of the anesthetics.

## **3 NDA History**

The original NDA was issued a “not approvable” action based on findings of multiple irregularities regarding data integrity as well as of unethical conduct of one efficacy trial. The content of the initial application and the conclusions drawn following the NDA review are summarized in the sections that follow. The issues with data integrity are discussed in Section 3.4.

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<sup>1</sup> A eutectic or eutectic mixture is a mixture of two or more elements which has a lower melting point than any of its constituents.

*Much of the text regarding the history of the application was obtained from the initial Medical Team Leader memo by Dr. Nancy Chang.*

The initial NDA for S-Caine was submitted on November 14, 2004. The indication sought was topical anesthesia for cutaneous procedures in both adult and pediatric populations.

### **3.1 Review of clinical efficacy**

#### **3.1.1 Efficacy in adults**

The initial NDA submission contained 11 studies in support of efficacy of S-Caine – 7 studies in adults, 1 in geriatric patients, and 3 in pediatric patients. (See the Appendix for a tabular listing of the original NDA trials.) Studies were categorized as involving either “minor” dermal procedures (laser therapy, laser resurfacing, laser hair removal, vascular access, collagen injections, and lidocaine injections) or “major” dermal procedures (laser-assisted tattoo removal and laser ablation of leg veins). One study was aimed at determining the duration of anesthetic effect.

Of the 7 adult trials, 6 had a similar “within-subject” design and also had very similar results. All 6 studies<sup>2</sup> were randomized, double-blind, placebo-controlled trials. Subjects were adults 18 years of age and older, except in the geriatric study<sup>3</sup>, which recruited subjects 65 and older. Subjects were excluded for active atopic dermatitis, prescription analgesic use within 24 hours, or damaged skin at the treatment site. Each subject received concurrent treatment with both the active and placebo peels. Active or placebo peels were randomly applied either to different areas of the same procedure site (e.g. for laser-assisted hair removal), or to similar but separate treatment sites (e.g. left or right antecubital fossa for vascular access procedures). Duration of peel application was pre-specified to be 60 minutes or 30 minutes, for procedures designated by the sponsor as “major” or “minor”, respectively. After application, the peel was removed from both treatment and placebo areas, and the investigator would sequentially treat one area, perform efficacy evaluations for that area, and then treat the second area and repeat efficacy evaluations for that area.

The remaining adult trial, Study 20-02, utilized a parallel group, placebo-controlled design. Subjects scheduled to undergo pulsed dye laser treatment of vascular lesions on the face (i.e. port wine stains, hemangiomas, spider angiomas, and telangiectasias) were randomized 1:1 to receive a single 20-minute application of S-Caine or placebo peel. The primary and secondary efficacy measures were the same as for the within-subject studies.

The primary efficacy variable for each of the 6 studies was the subject's evaluation of pain caused by the procedure, as rated using a 100 mm visual analog scale (VAS). The VAS is a continuous linear scale that ranges from 0 (no pain) to 100 (worst pain). This measure is commonly used to assess pain intensity, and was acceptable for the adult trials. Secondary efficacy endpoints included evaluation of the adequacy of pain relief

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<sup>2</sup> Studies 22-02, 25-02, 26-02, 32-02, 33-02, 21-02, and 23-02

<sup>3</sup> Study 33-02

(yes/no) by the subject and investigator. In addition, the subject was asked if they would choose the drug again, and the investigator and independent observer assessed the amount of pain experienced by the subject using a 4-point categorical scale.

The differences in median VAS scores between S-Caine and placebo groups (the primary endpoint for these trials) were generally modest but significant. Overall, the results of the 7 adult trials demonstrated that patients can perceive a difference between placebo and active treatments, and that S-Caine exerts an analgesic effect in the context of the superficial cutaneous procedures that were studied. The secondary endpoints also supported an analgesic effect of S-Caine in the context of the tested procedures.

### **3.1.2 Efficacy in the pediatric population**

#### **3.1.2.1 Placebo-controlled trials**

Two of the 3 pediatric trials<sup>4</sup> were randomized, parallel, double-blind, placebo-controlled studies utilizing 30-minute applications of active or placebo peel in pediatric subjects 3-17 years of age. S subjects were randomized 1:1 to receive active or placebo peel prior to antecubital blood draw or IV insertion (study 28-02) or prior to a medically indicated lidocaine injection (study 29-02).

The primary efficacy measure was an Oucher Self-Assessment Pain Scale. A numeric Oucher Scale using numerical values of 1-100 in increments of 10 was generally used in patients 7-17 years of age. A photographic Oucher Scale (6-point categorical scale utilizing children's faces in various degrees of distress) was generally used in patients 3-6 years of age. The investigator determined which scale would be used based on the patient's ability to perform certain cognitive tasks. A few subjects did use a scale that did not correlate with their chronological age; however, the results of cognitive testing were not documented in these studies.

Other outcome measures included investigator assessment of patient anxiety following peel removal and prior to the procedure, investigator and independent observer assessments of pain, and investigator evaluation of adequacy of anesthesia.

The Division concluded that the pediatric efficacy results were mixed. Study 28-02 (venous access procedures) showed a significant improvement in pain scores with S-Caine treatment compared to placebo, but only in the older age group (cognitive age 7-17). Scores in the younger age group trended in the direction of an analgesic effect for S-Caine, however the difference between placebo and treatment arms was not statistically significant. Secondary endpoints also consistently trended in the direction of an analgesic effect for S-Caine. In contrast, in study 29-02, there was not even a trend in the direction of an analgesic effect for S-Caine. Also, secondary endpoints trended to a greater analgesic effect of placebo over S-Caine.

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<sup>4</sup> Studies 28-02 and 29-02

The Division concluded that the data were sufficient to demonstrate that S-Caine produces a decrease in sensation (anesthesia) to the site of application and that this anesthetic effect likely mediates the analgesic effect demonstrated in the clinical trials. However, the data were insufficient to characterize the time course of anesthesia produced by S-Caine.

### **3.2 Review of clinical safety**

No major safety concerns were identified during the initial NDA review. There were no deaths or serious adverse events. Since most of the studies required only a single application of study drug, there were no withdrawals due to adverse events.

The majority of adverse events reported were application site reactions such as erythema and edema. Less common dermal events were purpura, echymosis, application vesiculobullous rash, and maculopapular rash. Most dermal reactions were mild-moderate, brief, and self-limited. Pediatric subjects appeared to have a higher incidence of certain reactions compared to adults: purpura (8% vs. <1%), application site reaction (5% vs. 1%), and vesiculobullous rash (3% vs. <1%).

Nine subjects (3 adult and 6 pediatric subjects) reported systemic adverse events. The most common events were headache and vomiting. There was no appreciable difference in the frequency of the events between the placebo and S-Caine groups.

Review of the safety data identified several limitations regarding the utility of the safety database including:

- The placebo used in all trials was the peel product without any anesthetic (i.e. lidocaine and tetracaine). Therefore, comparison of adverse events between S-Caine and placebo groups can only distinguish events that may have been caused by the local anesthetics. Adverse events, particularly local adverse events that may have been caused by the inactive ingredients, could not be distinguished from "background".
- Routine examination of skin occurred only immediately after peel removal and immediately after the dermal procedure. Thus, capture of delayed local reactions and effects of S-Caine on healing or effectiveness of the procedures could not occur.
- Data regarding exposure and safety in younger pediatric patients was minimal. A total of 9 pediatric subjects less than 3 years of age were studied in PK trials: 3 premature and 6 who were 0-2 years of age. Controlled trials enrolled 15 pediatric subjects 1 month – 1 year of age, and 7 subjects at 1 year of age. All pediatric exposures were for 30 minutes only and the surface areas of exposure were much less than for adults.
- Repeat and multiple exposure data are not available for the final S-Caine formulation. A single trial of 10 subjects entailed simultaneous exposures to a developmental formulation of the drug; no pharmacokinetic data were obtained in this study.

- Extent of exposure and uniformity of application (and methods for assuring uniformity) of S-Caine were not well documented in the clinical trials, and data were not available to assess the effects of varying thickness of application or of application of an occlusive dressing to the peel. Special applicators were provided in some studies to aid in achieving a thin 1-mm uniform layer of cream; however, these applicators will not be marketed with the product.
- Duration of effect is not well characterized, as the trial designed to examine this question (Study 34-03) did not follow subjects to resolution of anesthetic effect.
- Safety of the use of Fleexicaine in certain anatomic sites such as near mucous membranes and around the eye has not been adequately evaluated.

### **3.3 Data integrity issues**

Following preliminary review of the NDA, the Division of Scientific Investigations (DSI) was asked to inspect the pediatric placebo-controlled trial Study 28-02 after it was noted that over half of the enrollment (43 of 83 patients) consisted of pediatric subjects, and that all 43 patients were classified as having unspecified 'protocol violations.' In addition, DSI was consulted to inspect the sponsor, ZARS, upon discovery of a potential data integrity issue: two columns of efficacy data appeared to have been transposed from the S-Caine column to the placebo column in Study 33-02 (geriatric venous access study).

With respect to Study 28-02, DSI found that the protocol violations stemmed from the fact that all 43 patients at one site underwent unnecessary venipuncture: whereas the protocol specified that all subjects were to have "required a vascular access procedure," patients who did not require an IV access procedure were enrolled and they (or their parents) were paid to participate in the study. This was done without submission of a formal protocol amendment to the FDA or to the IRB. Also, although the Applicant's medical monitor visited this site three times during the conduct of the study, the violation was not detected or reported until the study was completed.

With regard to the inspection of ZARS itself, DSI conducted a detailed review of data from both sites for Study 33-02, and a more superficial review of data from other sites and studies. A major finding was that ZARS, after reviewing pre- and post-recorded weights of the tubes of active and placebo creams, decided that the original randomization assignments for subjects in site#1 were reversed (i.e., subjects marked "B" in one arm, which represented the use of placebo, should have been marked "A," which represented the use of the treatment, and vice versa). In an attempt to correct the mistake, the firm switched the active/placebo assignments in the data sets (and the corresponding pain scores), but mistakenly switched the assignments for *both* sites #1 and #2. With resubmission of the datasets to the Agency, the assignments for site were switched on more than one occasion. ZARS could not provide adequate explanation for the various reversals, nor was the Applicant able to conclusively state how the errors were (if ever) straightened out. Of note, the original determination of inaccurate randomization was

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based on differing weights of product in the tubes of drug and placebo. Therefore it is possible that these differing weights could have been detected, and the blind broken.

Overall, DSI's inspection of ZARS found systemic problems in conducting and monitoring its trials as well as inadequate data management procedures.

### **3.4 Regulatory Action on the Initial NDA**

Due to the unethical enrollment and treatment practices, as well as poor medical monitoring practices at the largest site for pediatric Study 28-02, the FDA's Ethicist recommended that the data from study 28-02 should be disregarded. With results from 28-02 discarded, there was no basis for any determination of pediatric efficacy. Additionally, based on the numerous issues regarding the integrity of the data of the adult studies, those data could not be relied upon as support for efficacy or safety of S-Caine. As such, a *"not approvable"* action was taken on the NDA.

The following were required to address the NDA deficiencies:

- Provision of new data from properly performed, monitored and analyzed studies in adults that provide substantial evidence of effectiveness.

Alternatively, ZARS could provide to the FDA clear documentation of data integrity for the studies initially contained in NDA 21-717 that sufficiently address the deficiencies.

- For the pediatric population below the age of 12 years, provision of new data from properly performed, monitored and analyzed studies conducted according to acceptable standards of human subject protection.

## **4 Applicant's response to the "Not Approvable" Action Letter**

Rather than conduct a complete audit of all the data from the original Phase 3 trials, ZARS decided to repeat the trials. No further pharmacokinetic trials or Phase 2 dose ranging trials would be conducted, which was acceptable to the Division.

ZARS has now submitted eight (8) additional safety and efficacy trials in support of efficacy and safety of S-Caine as a "topical local anesthetic for use on normal intact skin for local dermatological anesthesia." Six of the trials were in adults: 4 trials were designed to show efficacy; 1 trial was an open label safety trial, and 1 trial evaluated the duration of the anesthetic effect. The remaining two trials were in pediatric patients: 1 study was an efficacy trial and the other was an open-label safety study.

**Table 1: New Studies Reviewed for Efficacy and Safety**

Study SCP <sup>1</sup> -	Procedure Type	Population	Design	Application Site	Application Duration
<b>“Minor” dermal procedures</b>					
40-05	Dermal filler injection	Adult	W-S <sup>1</sup>	Face	30 min
41-05	Non-ablative facial laser resurfacing	Adult	W-S <sup>1</sup>	Face	30 min
42-05	Pulsed dye laser therapy	Adult	Parallel	Face	20 min
46-05	Vascular access	Pediatric	Parallel	Antecubital fossa	30 min
<b>“Major” dermal procedures</b>					
43-05	Laser-assisted tattoo removal	Adult	W-S <sup>1</sup>	Variable	60 min
<b>Open label safety trial</b>					
45-05	Major or minor dermal procedure	Adult	Open label	Variable	20-30 min <i>or</i> 60 min
47-05	Major or minor dermal procedure	Pediatric	Open label	Variable	20-30 min <i>or</i> 60 min
<b>Duration of analgesia</b>					
44-05	Duration of anesthetic effect	Adult	W-S <sup>1</sup>	Thigh	30 min <i>or</i> 60 min

<sup>1</sup>W-S: within-subject (or paired) design

In addition, ZARS has submitted a revised product label and patient package insert for review, and is seeking additional Agency action on the NDA.

## 5 NDA Resubmission - Efficacy Review

### 5.1 Summary of Efficacy findings

In adults, S-Caine, applied for either 30- or 60-minutes, is efficacious in providing local dermal analgesia for superficial dermal procedures. The data do not show efficacy of S-Caine in pediatric patients.

The mean duration of the analgesic effect is approximately 9.5 hours. However, in at least 50% of patients, analgesia may persist for more than 13 hours.

## **5.2 General discussion of measures and endpoints**

### **5.2.1 Primary efficacy measures and endpoints**

Currently, when evaluating the effects of drugs on pain, the Division defines anesthesia as the absence of sensation, and analgesia as a decrease in painful sensation. Therefore, studies that assess whether a drug causes loss of painful sensation can be considered supportive of anesthesia. In turn, studies that assess whether a drug decreases painful sensation or affects the quality of a painful sensation can be considered supportive of analgesia.

In both the adult and pediatric trials, ZARS' selected primary efficacy endpoint was the patients' perceived pain intensity of the dermal procedure following treatment with study drug. As such, the Applicant was assessing the relative *analgesic* effect (i.e. the degree to which treatment reduced the pain of the procedure) and not an anesthetic effect, as stated in the desired indication.

The primary efficacy measure in the adult trials was the Visual Analog Scale (VAS), a validated linear 100 mm scale that rates patients' self-report of pain. The scale ranges from 0 (no pain) to 100 (worst pain).

In children, the self-report method is also considered to be the gold standard for assessment of pain. Pain measures must be age-related, depending on the cognitive and language development of the child. Children of school age (i.e. 5 years and older) are considered able to understand verbal concepts and numbering, and able to give detailed rating of pain, as well as description of the locality and quality of pain.

The primary measure used in the sole pediatric efficacy trial was the Colored Analog Scale (CAS). The CAS is a 14.5 cm triangular shape varying in width and hue from 1cm wide and light pink at the bottom, to 3 cm wide and deep red hue at the top. A plastic marker slides along the length of the scale to provide a pain rating continuum from no pain (bottom of the scale) to the most pain (top of the scale). On the other side of the scale is a corresponding 0-10 scale. The CAS was developed as an alternative to the VAS, for easier administration and scoring. It has been validated for use among children  $\geq 5$  years of age. Like the VAS, the CAS is a measure of pain intensity (i.e. analgesia), and not a measure of the presence/absence of pain (i.e. anesthesia).

### **5.2.2 Secondary efficacy measures and endpoints**

In the adult trials, secondary efficacy evaluations included the patient and investigator overall impression of the adequacy of pain relief (yes/no). The patients were also asked whether they would choose to use the drug again. The investigator rated whether the drug provided adequate anesthesia for the dermal procedure (yes/no) and subjectively assessed the amount of pain experienced by the study subjects using a 4-point categorical scale.

Secondary efficacy evaluations in the sole pediatric efficacy trial were the same as for the adult trials, except the patients were not asked whether they would choose the drug again, and neither the patients nor the investigators rated the adequacy of pain relief.

### 5.2.3 Duration of effect

Characterization of the period of time over which a drug exerts its effect is important for complete understanding of the drug's efficacy. In both this and the initial NDA submission, the Applicant conducted trials intended to show the "duration of anesthetic effect" of S-Caine. Both trials used pinprick testing to determine how long subjects reported feeling pain upon pricking. The efficacy variable was the number of painful pinpricks at each time point.

Although described by the Applicant as measuring duration of anesthesia, the trials actually assessed duration of *analgesia*. Subjects were not asked to report whether they could feel *any* pinpricks at all (i.e. whether they had absence of sensation or anesthesia) following treatment. Instead, subjects were to count only the number of *painful* pinpricks felt. In this way, subjects reported an analgesic effect of drug and the data collected characterized only the duration of analgesia.

## 5.3 Study design

Overall, the design of the efficacy trials did not vary considerably from that of the studies submitted in the initial NDA submission. Refer to the Appendix for detailed descriptions of each of the submitted trials.

Three of the 4 adult efficacy studies<sup>6</sup> were identical in design, with exception of the type of dermal procedure used. All of the trials were randomized, double-blind, placebo controlled, within-subject trials in subjects with intact skin. Each subject served as his/her own control, with concurrent administration of both placebo and S-Caine peel. The duration of drug application was 30 minutes for 'minor' dermatological procedures<sup>7</sup>, and 60 minutes for 'major' procedures<sup>8</sup>. After drug removal, the subjects would rate their pain intensity, and both the investigator and the subjects would rate the adequacy of the drug effect.

The limitations of a within-subject design have already been described (refer to the Team Leader memo by Dr. Nancy Chang). Briefly, in a within-subject study with simultaneous application of S-Caine and placebo, the absolute differences in effect are likely to have been magnified because the subjects were aware that one site was active drug and the other was placebo. The differences between placebo and active groups with respect to the secondary outcome measures are likely to have been similarly affected. Consequently, the best way to view within-subject trials is as trials aimed at determining whether or not

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<sup>6</sup> Studies SCP-40-05, -41-05, and -43-05

<sup>7</sup> Studies SCP-40-05 and 41-05

<sup>8</sup> Study SCP-43-05

subjects can perceive a difference between test drug and placebo. Nevertheless, a within-subject design was acceptable to the Division.

There was one parallel-group adult trial (Study SCP-42-05), where patients were randomized to *either* S-Caine or placebo. In this trial, drug was applied for 30 minutes prior to the ‘minor’ dermatological procedure. Again, efficacy and safety assessments were made immediately after study drug was removed.

The pediatric efficacy study (SCP-46-05) also utilized a parallel group design. The study evaluated the effects of S-Caine applied for 30 minutes to children aged 5-17 years and who were undergoing a minor dermatological procedure (mainly venipuncture). Approximately 40% of the patients were between 5 and 12 years.

REVIEWER COMMENT: The selected population did not specifically address the Agency’s requirement that ZARS study the efficacy of S-Caine in pediatric patients aged 12 years and younger. However, a subgroup analysis can provide the desired efficacy information.

## 5.4 Dosing

The dosing of S-Caine used in the new studies is unchanged from the initial NDA. Dosing was based on the known pharmacologic properties of lidocaine and tetracaine, the size of the area to be treated, as well as the type of dermal procedure previously studied:

Study drug was applied for 30 minutes for “minor” dermatological procedures, and 60 minutes for “major” procedures. The amount (length) of drug squeezed from the tubes would depend on the size of the area to be treated. If the amount of drug exceeded the length of the treatment area, with multiple strips would be applied. A flat surfaced instrument (e.g. tongue depressor) was used to spread the drug evenly to a 1mm thick layer.

**Table 2: Dosing time by study procedure:**

Procedure	Population	Dosing time (minutes)
Pulsed dye laser therapy for vascular malformations	Adult	20
	Pediatric	30
Laser assisted hair removal	Adult	30
CO <sub>2</sub> ablative laser facial resurfacing	Adult *	30
Non-ablative laser facial resurfacing	Adult	30
Dermal filler injections	Adult	30
Vascular access procedures	Adult	30
	Pediatric	30
Lidocaine injections	Pediatric	30
Laser leg vein ablation	Adult	60
Laser assisted tattoo removal	Adult	60

\* Not studied in a phase 3, placebo-controlled trial

**Table 3: Dosage based on surface area to be treated:**

Surface area (cm <sup>2</sup> ) of treatment site	Length (cm) of study drug for 1mm peel thickness	Weight (g) of study drug dispensed
10	3	1
20	6	3
40	12	5
80	24	11
100	30	13
150	46	20
200	61	26

## 5.5 Review of efficacy

### 5.5.1 Adult trials

The Division's review of the adult efficacy data confirmed the Applicant's results: all of the adult trials supported a greater analgesic effect of S-Caine over placebo. The numeric differences in VAS scores (i.e. pain intensity) were modest, but reached statistical significance.

The differences in VAS scores between the S-Caine and placebo groups ranged between 13 and 20 mm. The greatest numerical difference in VAS scores observed between the treatment groups occurred in Study SCP-43-05, the only trial that evaluated effects of treatment following a major dermatological procedure (laser tattoo removal). The smallest difference in pain scores was observed in the dermal filler (collagen) study, SCP-40-05.

**Table 4: Summary of efficacy results – Adult trials\***

Study	VAS Score (mean ± SD)		p-value
	S-Caine	Placebo	
SCP-40-05	24.2 ± 18.13	37.4 ± 23.52	< 0.0001
SCP-41-05	21.4 ± 18.89	38.0 ± 24.46	< 0.0001
SCP-42-05	16.4 ± 19.55	30.9 ± 17.06	0.0008
SCP-43-05	39.1 ± 25.48	58.6 ± 21.59	<0.0001

\*Summary based on data from the Applicant's efficacy analyses, and consistent with Agency calculations.

### 5.5.2 Pediatric trials

Per its own analysis, ZARS did not find a difference in analgesic efficacy between S-Caine and placebo for the sole pediatric efficacy study, SCP-46-05. Regarding the primary efficacy endpoint, the mean CAS score was 1.77 for the S-Caine-treated patients, and 2.03 for the placebo group (p = 0.6). There were no numerical or statistically significant differences between the groups with respect to the secondary efficacy outcomes.

ZARS has argued that it is difficult to obtain a positive result in pain trials conducted in pediatric patients because:

- ZARS considers children unable to report moderate changes in pain intensity, but are instead only able to report extremes of pain
- It is unethical to expose children to a procedure that is painful enough to allow them to distinguish an effect of treatment, in a placebo-controlled trial which lacks benefit of any analgesic
- The clinical, emotional, and psychological contexts in which the participants of Study SCP-46-05 received treatment adversely impacted the accuracy of patients' pain intensity reporting

While these arguments may have some merit in trials of younger children (e.g. < 5 years old), they are less relevant for older children, particularly children aged 12-17 years. This population of pediatric patients has cognitive maturity and is well able to distinguish injuries that are likely to cause minimal to severe pain, and can reliably describe even moderate changes in pain intensity.

Consequently, Dr. Katherine Meaker, the statistical reviewer, conducted a subgroup analysis to evaluate whether efficacy was suggested for older pediatric patients (i.e. 12-17 years). The results of her analysis are shown in Table 5 below. Because Dr. Meaker's analysis was post-hoc and involved comparisons of results among groups of very small size, p-values were not calculated.

**Table 5: Reviewer's analysis of efficacy by age group – Study SCP-46-05**

	Age 5-11		Age 12-17	
	S-Caine	Placebo	S-Caine	Placebo
CAS for Pain Intensity:				
N	17	16	24	23
Mean (SD)	1.76 (2.62)	1.44 (1.84)	1.78 (2.40)	2.43 (2.59)
Median	0.25	0.25	0.88	1.75
Min, Max	0, 9.5	0, 5	0, 8	0, 8.5
Investigator Assessment of Pain:				
n (%)				
No pain	11 (65%)	13 (81%)	12 (50%)	11 (48%)
Slight pain	3 (18)	2 (13)	8 (33)	9 (39)
Moderate pain	2 (12)	1 (6)	4 (17)	1 (4)
Severe pain	1 (6)	0	0	2 (9)
Investigator Adequate Anesthesia:				
n (%)				
Yes	12 (71%)	14 (88%)	16 (67%)	14 (61%)
No	5 (29)	2 (13)	8 (33)	9 (39)

The table shows that placebo patients aged 5-11 years reported a lower pain/CAS score than S-Caine patients in that age group (1.44 vs. 1.76, respectively). Better efficacy of placebo compared to S-Caine was also seen in terms of the investigators' perception of

no pain associated with the procedure, and induction of an adequate anesthetic effect. These results strongly suggest that the S-Caine was not efficacious in the 5-11 year old population.

Among patients aged 12-17 years, the S-Caine group had a slightly numerically lower pain intensity/CAS score than the placebo group (1.78 vs. 2.43). However, there were no considerable differences between groups in terms of the majority of secondary endpoints, including the investigators assessment of no pain associated with the dermal procedure. Together, the findings of a non-clinically relevant difference in patient pain intensity scores and the absence of a consistent difference in secondary endpoints between the treatment groups suggest that S-Caine is not efficacious in this subgroup of older pediatric patients.

REVIEWER COMMENT: Of the 4 pediatric efficacy trials submitted in the initial and subsequent NDA submissions, ZARS has had only 1 trial (Study 28-02) that showed efficacy of S-Caine in children. However, as described in Sections 3.1.2 and 3.3, there were significant protocol and ethical violations associated with Study 28-02, and the data were ultimately considered unreliable and unresponsive of efficacy.

Overall, therefore, none of the pediatric trials has shown definitive efficacy of S-Caine as an analgesic for superficial dermal procedures.

### 5.5.3 Duration of analgesic effect

Study SCP-44-05 was a randomized, double-blind, placebo-controlled, within-subject study whose objective was to determine the “duration of anesthetic effect” of both the 30- and 60-minute S-Caine applications.

The study was conducted in 40 adult volunteers. Subjects were treated with both a placebo and S-Caine peel, applied to a 200 cm<sup>2</sup> area of the anterior thigh for either 30 minutes or 60 minutes. After the peel was removed, the study investigator or technician administered 5 pinpricks to the treated area using a 21-gauge needle. Subjects indicated the number of pinpricks that elicited pain. Pinprick testing was done at 30-minute intervals, until 13 hours (780 minutes) post drug application.

The primary efficacy variable was the “duration of anesthesia,” which was the difference between the time of onset and end of anesthesia. Onset of anesthesia was defined as the first time the subject reported  $\leq 2$  painful pinpricks for two consecutive time points. End of anesthesia was defined as the first time the subject reported  $\geq 2$  painful pinpricks for two consecutive time points. As discussed in Section 5.2.3, because subjects were not asked to report whether they could feel *any* pinpricks at all (i.e. whether they had absence of sensation or anesthesia) and instead only counted only the number of *painful* pinpricks they felt, the selected efficacy variable actually assessed duration of *analgesia*. Consequently, the data collected characterized only the duration of analgesic effect for S-Caine.

Efficacy results:

*Primary efficacy variable*

The mean duration of analgesia for the 30-minute S-Caine peel was 551 (95% CI 459, 643) minutes, compared to 158 (95% CI 51, 265) minutes for the 30-minute placebo peel. The mean duration of analgesia for the 60-minute peel was 582 (95% CI 498, 665) minutes, versus 27 (95% CI 3, 51) minutes for the 60-minute placebo peel. There was no statistically significant difference in mean analgesia duration between the 30- and 60-minute S-Caine applications ( $p = 0.62$ ).

REVIEWER COMMENT: The Applicant noted that, because 55% ( $n = 22$ ) of S-Caine subjects and 6% ( $n = 6$ ) of placebo subjects still had analgesia at the end of the 780 minute evaluation period, these drug applications were censored for duration of analgesia. Therefore, the CIs may underestimate the actual duration of analgesia, and the width of the CI is probably smaller than it would be if there were no censored data.

*Secondary efficacy analyses*

a) Mean onset of analgesia

The mean onset of analgesia time for the combined 30- and 60-minute S-Caine applications was 93 minutes, and 240 minutes for the combined placebo peels ( $p = 0.008$ ). There was no difference in mean onset of analgesia between the 30- and 60-minute S-Caine applications (87 and 100 minutes, respectively;  $P = 0.37$ ).

b) End of analgesia

For the combined S-Caine applications, the mean end of analgesia time was 658 minutes, compared to 473 minutes for the placebo group ( $p = 0.03$ ). End of analgesia times were statistically similar for the 30- and 60-minute S-Caine applications (638 and 682 minutes, respectively ( $p = 0.45$ )).

As described above, a considerable number of patients still reported analgesia at the end of the 13 hour evaluation period: 55% ( $n = 22$ ) of the combined S-Caine applications, and 6% ( $n = 6$ ) of the combined placebo applications ( $p < 0.001$ ).

c) Complete analgesia (zero painful pinpricks for two consecutive time points)

To determine whether the 30- and 60-minute S-Caine applications varied with respect to the degree of analgesia, I calculated the number of patients who reported absolutely no painful sensation (zero painful pinpricks) at key study time points. I considered zero painful pinpricks to be indicative of a “complete” analgesic effect.

**Table 6: Reviewer’s analysis of frequency of zero painful pinpricks (i.e. “complete” analgesia) at selected study time points – Study SCP-44-05**

Time point (post-drug application)	N (%)			
	S-Caine application		Placebo application	
	30 min N = 22	60 min N = 18	30 min N = 22	60 min N = 18
30 min	3 (14%)	0 (0%)	0 (0%)	0 (0%)
120 min (2 h)	12 (54%)	9 (50%)	2 (9%)	1 (6%)
390 min (6.5 h)	15 (68%)	14 (78%)	2 (9%)	0 (0%)
480 min (8 h)	13 (59%)	10 (56%)	1 (4%)	0 (0%)
780 min (13 h) – Study end	4 (18%)	3 (17%)	3 (14%)	0 (0%)

The analysis shows that considerably more S-Caine than placebo patients groups reported zero painful pinpricks (“complete” analgesia), at each of the selected time points. This was true for both the 30- and 60-minute applications. Additionally, the proportions of patients who had no painful pinpricks were similar for both the 30- and 60-minute S-Caine groups, indicating no difference in “complete” analgesic effect between the two applications. The data show that by 2 hours post-dose, at least half of S-Caine-treated patients did not have pain upon pinprick testing.

Almost 20% of both S-Caine 30- and 60-minute patients reported a complete analgesic effect at 13 hours post-dose. In comparison, 14% of the 30-minute placebo patients and 0% of the 60-minute placebo patients reported complete analgesia at study end.

REVIEWER CONCLUSIONS: Overall, the data from this study lend further support for the efficacy of S-Caine as a topical analgesic. There are no significant differences between the 30- and 60-minute S-Caine peels with respect to onset, end, and duration of analgesia. However, the study does not completely characterize the duration of analgesic effect, since a considerable number of patients reported either partial analgesia ( $\leq 2$  painful pinpricks) or complete analgesia (zero painful pinpricks) at the end of the 13 hour evaluation period.

## 6 NDA Resubmission - Safety Review

### Reporting of adverse events

The procedure for collecting adverse event (AE) information varied between the Phase 2 and 3 trials. During the Phase 2 trials, events that were ‘expected’ outcomes of the dermal procedure being studied (e.g. erythema) were not recorded as AEs. However, in the Phase 3 trials, all AEs – regardless of whether they were ‘expected’ outcomes of the procedure – were recorded. One consequence of this differential AE reporting method is that, because the Final formulation of S-Caine was used in the Phase 3 trials, in ZARS’ calculations of the the incidence of AEs by S-Caine formulation, some ‘expected’ AEs appear to have higher for the Final formulation compared to previous formulations.

The COSTART dictionary was used to report spontaneously reported AEs. Since all AEs related to edema were skin reactions, the Applicant coded edema under the “SKIN” body system and not “Metabolic and Endocrine; MAN” as stipulated by the COSTART default. Perifollicular edema was also coded to “SKIN,” but was listed separately from edema. Additional AEs that were localized to the area of peel application or dermal procedure and therefore coded to “SKIN”, but which would usually fall under other body systems were ‘echymosis and purpura’ (normally under body system “HAL”), and pain (normally under body system “BODY”).

In addition to spontaneously reported dermal events, information regarding specific skin reactions immediately after removal of the peel was elicited. Based on the known effects of lidocaine and tetracaine, all clinical studies incorporated a post-treatment skin evaluation for the presence and severity of erythema, edema, and blanching. Only occurrences of erythema, edema, and blanching that were considered ‘moderate’ or ‘severe’ were recorded as AEs.

#### **Methods of review of safety data**

The safety review consisted of an evaluation of the Integrated Summary of Safety (ISS) and related its related datasets. In the ISS, ZARS presented the new safety data from the most recent (i.e. 2005) clinical trials and integrated it with data previously submitted in the initial NDA and the 120-day safety update.

In the NDA resubmission, ZARS provided integrated datasets for only the 2005 clinical trials. However, because of the sizeable number of S-Caine exposed patients across all trials, and in order to determine the full safety experience with S-Caine and verify the Applicant’s data in the ISS and proposed package insert, ZARS was asked to resubmit integrated datasets for all enrolled patients (i.e. both original and new NDA trials).

ZARS reported that integration of all the original and new safety datasets was difficult because the datasets were in different formats (e.g. used different variables) and simply merging them was not possible. Also, errors were found in the original AE dataset that had to be corrected prior to integrating the information with the new integrated AE dataset. ZARS claims the errors were only in the counts of continuing and delayed AEs, and that the errors had occurred because the counts had been generated manually.

#### **REVIEWER COMMENT:**

Due to the way in which the safety data were collected (i.e. spontaneous AE reporting and recording of specific AEs after skin evaluation), there were, in essence, two integrated datasets describing specifically observed skin reactions following study treatment. The former ‘spontaneously reported AEs’ dataset that combined information from both the original and new studies dataset would clearly provide greater and more useful information. However, this dataset proved to be of limited utility because:

- There were four variables corresponding to treatment assignment<sup>9</sup> that were either incomplete for some patients, or otherwise coded in a manner that did not allow for attribution of a specific AE to a given treatment. For example, for a patient given concurrent treatment of the S-Caine and placebo, only the 'FORMULAT' treatment assignment variable was complete, and coded as "S-Caine, Placebo." With such coding, it was not possible to determine whether the listed AE was due to S-Caine or Placebo, unless this was recorded in the verbatim text field.
- In the integrated AE dataset, there was only 1 line per patient. Thus even if a patient who had concurrent drug application had AEs at both treatment sites, there was only 1 line listing for that patient (instead of 2 lines to separate out each instance of an AE).
- The AE field/variable, "CSTCODE," showed a single AE per patient. There was no flag to indicate, for patients who had concurrent drug applications, at which drug site the AE occurred. Only in some cases was this information recorded in the verbatim text field.
- For some patients, even though one variable ("AENONE") indicates that they had an AE, there is no AE listed.

Ultimately, the problems with the "spontaneously reported AEs" dataset made it impossible to generate the standard tables for the combined safety population that list AEs by type and treatment assignment, and that are used for comparison to the Applicant-generated tables found in the ISS and the proposed PI.

With respect to the use of the "specific skin evaluation" integrated dataset, the types of problems described above do not exist. Information on the frequency of erythema, edema, and blanching by treatment assignment was easily obtained for the combined safety populations. However, because this dataset contains information regarding only certain clinical signs associated with treatment, and lacks information about patient symptoms or other signs of an adverse reaction, the conclusions about the dermal effects of S-Caine are limited to just erythema, edema, and blanching.

Therefore, in light of the above described issues, due to the fact that there were concerns regarding the integrity of the original NDA data, and because the integrated safety datasets in the NDA resubmission are acceptable, only information from the new clinical trials was used to evaluate the safety profile of S-Caine. The summary tables that were generated were compared to the ones based on original NDA data to determine whether the types and frequencies of AEs were similar. The summary tables were also used incorporated into the product label.

However, by necessity, information regarding exposure and systemic AEs was obtained from the combined original and new studies.

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<sup>9</sup> "TRT" = applicable treatment; "TRTCODE" = treatment group for parallel/S-Caine only; "FORMULAT" = formulation; "FORMULA" = applicable formula

## **6.1 Summary of safety findings**

The data show that the risks of mortality and a serious adverse event (SAE) were 0% for both placebo and S-Caine treated patients.

The risk of systemic adverse effects from S-Caine treatment is low (0.3% for both S-Caine and placebo). This finding is supported by the pharmacokinetic data which show minimal systemic absorption of S-Caine when the drug applied as directed.

Due to the topical route of administration, dermal adverse effects are the most likely type of AE associated with S-Caine. Data from controlled trials indicate that erythema, blanching, echymosis, rash, and edema were the most frequently reported AEs, and generally occurred with greater frequency among S-Caine-treated subjects than placebo subjects. These events tended to be mild and short-lived.

Overall, therefore, treatment with S-Caine appears to be associated with predictable and mild dermal adverse effects.

## **6.2 Exposure**

The formulation for S-Caine was modified four times during the clinical studies in order to optimize homogeneity of the product and to improve the chemical stability of tetracaine. ZARS refers to the formulations as Developmental A, B, C, and D/Final. Developmental C is the proposed marketed formulation, and is identical to Developmental D/Final except that the manufacturing processes to D/Final were changed from laboratory scale to full production scale. ZARS determined patient exposure for each of the four clinical formulations as well as the overall exposure to S-Caine.

As previously described, several studies were a within-subject (or paired) design whereby subjects were treated simultaneously with S-Caine and a comparator (e.g. placebo). Consequently, if subjects were given more than one type of treatment, ZARS counted the subject under each treatment. In addition, 10 subjects were administered simultaneous S-Caine applications for different lengths of time (15, 30, 45, and 60 minutes). The data from these subjects were included under each application time. All subjects were given only single applications of study drug. Therefore, where indicated, the data represent reflect the number of *single exposures* to S-Caine as opposed to the number of patients treated.

### Total extent of exposure

Altogether, when considering both the initial NDA submission (2003) trials and the resubmission (2005) trials, there were 2159 patients exposed to S-Caine (Developmental A, B, C, or D formulations). There were 1358 subjects in the initial NDA trials, and 801 subjects in the new trials (Table 7). Of the 801 new subjects, 164 (20%) were pediatric patients.

With regard to the D/Final S-Caine formulation, there have been 1423 single exposures. In the new (2005) trials, subjects were treated with the final formulation, 310 (39%) of whom were treated in controlled trials and 491 (61%) in uncontrolled trials.

The minimum and maximum S-Caine application periods studied were 15 minutes (n = 30 exposures) and 120 minutes (n = 12 exposure), respectively.

**Table 7: Total exposure, by S-Caine formulation – All trials**

	A <sup>a</sup>	B <sup>b</sup>	C <sup>c</sup>	Final <sup>d</sup>	Placebo	EMLA
<b>Controlled Studies<sup>e</sup>:</b>						
15 Minute	---	30	---	---	---	30
20 Minute	17	13	---	72	83	---
30 Minute	40	168	123	586	796	58
45 Minute	---	20	---	---	20	---
60 Minute	89	105	35	191	371	68
90 Minute	30	20	---	---	20	---
120 Minute	---	---	---	---	---	60
Total controlled	176	356	158	849	1290	216
<b>Pharmacokinetic<sup>f</sup>:</b>						
30 Minute	---	12	---	47	---	---
60 Minute	---	11	---	24	---	---
90 Minute	---	13	---	---	---	---
120 Minute	---	---	---	12	---	---
Total Pharmacokinetic	---	36	---	83	---	---
<b>Uncontrolled<sup>g</sup></b>						
15 Minute	10	---	---	---	---	---
20-30 Minute <sup>h</sup>	---	---	---	471	---	---
30 Minute	10	---	---	---	---	---
45 Minute	10	---	---	---	---	---
60 Minute	10	---	---	20	---	---
Total Uncontrolled	40	---	---	491	---	---
<b>Total of All Single Exposures</b>	<b>216<sup>i</sup></b>	<b>392</b>	<b>158</b>	<b>1423</b>	<b>1290</b>	<b>216</b>

<sup>a</sup>Developmental A S-Caine Peel Formulation; <sup>b</sup>Developmental B S-Caine Peel Formulation; <sup>c</sup>Developmental C S-Caine Peel Formulation; <sup>d</sup>Final S-Caine Peel Formulation; <sup>e</sup>See tables A2.2 and B2.2 for a list of Controlled Trials; <sup>f</sup>See table 2.1 for a list of Pharmacokinetic Trials; <sup>g</sup>Studies: SCP-05-00, SCP-45-05, and SCP-47-05; <sup>h</sup>10 subjects received 4 concurrent applications for different lengths of time. Each application was tabulated, and this number represents the number of exposures. <sup>i</sup>In studies SCP-45-05 and SCP-47-05, application periods of 20-30 minutes and 60 minutes were allowed depending on the procedure. Since no other studies allowed for a range (ie, 20-30 minutes) this data will not be combined with past data. <sup>j</sup>The total number of subjects is 186.

(Source: Applicant's Table C.31, ISS, Vol. 1, p. 3-226)

### Demographics of exposed subjects

#### *Distribution by age*

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

Altogether, 2159 persons (both adult and pediatric) were treated with S-Caine during the development program. The majority of enrollees were adults 18 – 65 years (71%), followed by pediatric patients (16%) and persons aged 65 years and older (12%).

**Table 8: Total S-Caine exposure, by subject age – all trials**

*Demographics of Subjects Who Received S-Caine Peel (all formulations) in All Trials, Adults and Children Combined*

Age Category	PK Trials n=119	Controlled Trials n=1539	Uncontrolled Trials n=501	Total* N=2159
28 – 37 Weeks EGA	4	0	0	4 (0.2%)
0 – <1 Month	2	0	7	9 (0.4%)
1 Month – <1 Year	2	15	12	29 (1.3%)
1 Year – <2 Year	1	7	8	16 (0.7%)
2 Years – <12 Years	22	113	49	184 (8.5%)
12 Years – <18 Years	3	95	7	105 (4.9%)
18 Years – <65 Years	73	1148	328	1549 (71.7%)
65 Years – <75 Years	10	111	52	173 (8%)
75+ Year	2	50	38	90 (4.2%)

\* Percentages listed are percent of total (N=2159)

(Source: Applicant's table, submitted 5/26/06 in response to Agency's request for information)

*Distribution by skin type*

Almost 60% of subjects treated with the final S-Caine formulation had a skin type of II or III.

**Table 9: Exposure to the final S-Caine formulation, by skin type – all adult and pediatric subjects**

Skin type	D/Final formulation, N = 1340
(I) Always Burns/Rarely Tans	100 (7%)
(II) Always Burns/Tans Minimally	341 (25%)
(III) Burns Moderately/Tans Gradually	461 (34%)
(IV) Burns Minimally/Always Tans	256 (19%)
(V) Rarely Burns/Tans Profoundly	114 (9%)
(VI) Never Burns/Deeply Pigmented	68 (5%)

<sup>a</sup> Controlled trials only; <sup>b</sup> All trials

(Based on Applicant's Tables A11.1, B11.1, and B11.7; ISS, Vol. 1)

**6.3 Deaths**

There were no deaths among any of the study participants in either the original or the new trials.

**6.4 Other serious adverse events**

There were no serious adverse events reported for any of the original or the new trials.

## 6.5 Discontinuations due to adverse events

Because the clinical trials were single-dose studies requiring only 1-2 clinic visits, the overall frequency of treatment discontinuations was minimal, as was the frequency of withdrawals due to adverse events.

Across all (original and new) studies, 3 subjects discontinued due to adverse events, all of whom were adult participants in the new (2005) trials (n = 801). Two subjects were enrolled in Study SCP-45-05, an open-label safety trial of S-Caine. The other subject was in the duration of analgesia trial (Study SCP-44-05). The AEs are described in the table below:

**Table 9: Discontinuations due to AEs – All trials**

Subject	Treatment	AE leading to discontinuation
SCP44-01-44 29 yo F	SCP 60-min application	Pt reported moderate <b>burning pain</b> at the application site, 7 hours after drug removal. AE resolved after 7 h.
SCP45-03-013 70 yo M	SCP 20-min applicaiton	Pt experienced <b>hypotension, dizziness, pallor, sweating, and stupor</b> after 15 min of drug application.
SCP45-04-011 27 yo F	SCP 20-min applicaiton	Pt reported <b>edema</b> at the facial application site, 4 min after drug removal. Peel was applied for 20 min. AE resolved after 5h, and with treatment

REVIEWER COMMENT: The two application site reactions of edema and burning pain were likely due to study treatment. Subject SCP45-03-013 who had symptomatic hypotension reportedly had a history of diabetes and recent diarrhea, and had fasted the day before the study. He was treated with IV fluids and improved within 1 hour. Therefore, his symptoms could have been due to dehydration and/or hypoglycemia and not necessarily to study drug.

## 6.6 Other adverse events

Due to concerns regarding the adequacy of the integrated AE dataset for both the original and new trials (see Section 6, “Methods of review of safety”), only data from the new trials was used to determine the type and frequency of the non-serious/common adverse events. However, where indicated or necessary, information from the combined trials is discussed.

### 6.6.1 Systemic adverse events

When considering all (original and new) trials, there were 19 subjects (0.5%, 19/3695) who experienced a systemic AE: 3 in pharmacokinetic trials, 7 in uncontrolled trials, and 9 in controlled trials. Four subjects were treated with placebo, and 15 with S-Caine. Seven patients were adults, and 12 were pediatric patients.

In the controlled trials, the frequency of systemic AEs was similar between the two treatment groups: 0.3% (4/1290) for placebo and 0.3% (5/1539) for S-Caine

Across all trials, the most common systemic AEs were headache, vomiting, dizziness, and fever, all of which occurred with a frequency of <1%. The specific types of systemic AEs reported are listed in Table 10.

Table 10: Systemic AEs, all trials

Table C5.1 Specific Systemic Adverse Events by Subjects, Combined Data

Body System	COSTART	Final <sup>a</sup>	Placebo
Number of Subjects		1423	1290
Controlled Trials <sup>b</sup>			
BODY	Headache	1 (<1%)	0 (0%)
CV	Syncope	0 (0%)	1 (<1%)
DIG	Nausea	0 (0%)	1 (<1%)
DIG	Vomiting	1 (<1%)	3 (<1%)
NER	Confusion	1 (<1%)	0 (0%)
NER	Dizziness	0 (0%)	1 (<1%)
RES	Hyperventilation	1 (<1%)	0 (0%)
RES	Pharyngitis	1 (<1%)	0 (0%)
Pharmacokinetic <sup>c</sup>			
BODY	Headache	2 (<1%)	0 (0%)
DIG	Vomiting	1 (<1%)	0 (0%)
NER	Dizziness	2 (<1%)	0 (0%)
CV	Syncope	1 (<1%)	0 (0%)
Uncontrolled Trials <sup>d</sup>			
CV	Hypotension	1 (<1%)	0 (0%)
CV	Pallor	1 (<1%)	0 (0%)
CV	Syncope	1 (<1%)	0 (0%)
DIG	Nausea	1 (<1%)	0 (0%)
DIG	Vomiting	1 (<1%)	0 (0%)
NER	Dizziness	1 (<1%)	0 (0%)
NER	Nervousness	1 (<1%)	0 (0%)
NER	Stupor	1 (<1%)	0 (0%)
BODY	Fever	3 (<1%)	0 (0%)
BODY	Headache	1 (<1%)	0 (0%)
MAN	Dehydration	1 (<1%)	0 (0%)
SKIN	Sweating	1 (<1%)	0 (0%)

<sup>a</sup> Final S-Caine formulation

(Source: Applicant's Table C5.1, ISS, Vol. 1, p. 3-238)

REVIEWER COMMENT: The clinical biopharmaceutical review of the human pharmacokinetic data in the original NDA found that overall, there is minimal systemic exposure to lidocaine and tetracaine following application of S-Caine, and that systemic pharmacological effects are not likely to occur. This conclusion is supported by the low frequency of systemic AEs in S-Caine treated subjects, and the similar rate of these events compared to the placebo peel.

## 6.6.2 Other adverse events

Because of the lack of significant systemic drug exposure, and because the drug is topically applied, the expected and observed AEs associated with S-Caine are predominantly dermal in nature.

### 6.6.2.1 All treatment-emergent (i.e. ‘spontaneously reported’) adverse events

#### *Controlled trials – New NDA trials*

Of the 388 subjects who participated in the new (2005) controlled trials, 310 were treated with S-Caine, and 305 were treated with placebo. The 388 subjects spontaneously reported a total of 502 adverse events. The frequency of at least 1 spontaneously reported AE was similar between the two groups: 38.7% (120/310) for the S-Caine group, and 38.0% (116/305) for the placebo group.

Table 10 shows the incidence of all spontaneously reported AEs across the new controlled trials. The majority (99%) of the spontaneously reported AEs were dermal in nature. Note that, because the COSTRT dictionary was used to report AEs, some events that occurred at the skin were by default coded under the designated body system. For example, dermal events of echymosis were coded under the default COSTART body system, “HEMIC AND LYMPHATIC” (see Section 6).

**Table 10: Spontaneously reported AEs – New NDA (2005) controlled clinical trials**

COSTRT Code		S-Caine, N= 310		Placebo, N = 305	
Body System	Preferred Term	N	%	N	%
BODY	PAIN	11	3.55	11	3.65
CARDIOVASCULAR	SYNCOPE	0	0.00	1	0.33
DIGESTIVE	NAUSEA	0	0.00	1	0.33
	VOMITING	0	0.00	1	0.33
HEMIC AND LYMPHATIC	ECCHYMOSIS	34	10.97	34	11.30
	PURPURA	2	0.65	1	0.33
NERVOUS	CONFUSION	1	0.32	0	0.00
	DIZZINESS	0	0.00	1	0.33
SKIN	ERYTHEMA	81	26.13	76	25.25
	EDEMA	58	18.71	55	18.27
	RASH PETECHIAL	24	7.74	24	7.97
	RASH VESICULAR BULLOUS	13	4.19	13	4.32
	SKIN DISCOLOR	6	1.94	7	2.33
	PRURITUS	3	0.97	2	0.66
	RASH	1	0.32	1	0.33
	RASH MACULAR PAPULAR	1	0.32	1	0.33

For both treatment groups, the most common spontaneously reported events were erythema, edema, echymosis, petechial rash, and vesicular bullous rash. Overall, the frequencies of these AEs were similar between the S-Caine subjects and placebo subjects: 26% of subjects had erythema, 18% had edema, 11% had echymosis, 8% had a petechial rash, and 4% had a petechial bullous rash.

REVIEWER COMMENT: In the new NDA trials, AEs were reported regardless of whether they were 'expected' outcomes of the dermal procedure (e.g. bruising). Given the nature of the dermal procedures, it is likely that the echymosis and pain noted were due to the procedure and not to study treatment. However, the reports of rash are more likely to have been due to study drug. The similar incidence of rash between the placebo and active groups suggests that perhaps a non-active ingredient in the peel formulation is responsible for this dermal reaction.

ZARS used the combined data from both the original and new trials to analyze the frequency of adverse events (Table 11). ZARS also found that erythema, echymosis, edema, and rash were the most frequently reported events.

Note that Table 11, ZARS' calculation of spontaneously reported AEs, suggests that the Final S-Caine formulation was associated with a higher frequency of dermal events (27%) compared to the other formulations (6-10%) and to placebo (18%). However, as was previously discussed, all Phase 3 trials used the Final formulation. Also, the methods for capturing dermal AEs varied over the course of clinical development, with more complete capture of AEs in the Phase 3 trials. Therefore, the higher incidence of AEs for the Final formulation that was noted in the combined controlled data likely reflects a difference in AE reporting, and not a greater risk of treatment with that formulation. This conclusion is verified by ZARS calculation of the frequency of AEs by study phase which showed that in the Phase 3 trials only, the rates of dermal AEs for the S-Caine and placebo groups were essentially the same (38% and 37%, respectively).

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Table 11: Applicant's Analysis – Spontaneously reported AEs in all (original and new) controlled clinical trials

Body System	COSTART	A <sup>b</sup>	B <sup>c</sup>	C <sup>d</sup>	Final <sup>e</sup>	Placebo	EMLA	Non – Treated <sup>f</sup>
	Number of Subjects	176	356	158	849	1290	216	NA
BODY	Pain	0 (0%)	0 (0%)	0 (0%)	11 <sup>g</sup> (1%)	12 <sup>g</sup> (1%)	0 (0%)	0
HAL	Ecchymosis	0 (0%)	0 (0%)	0 (0%)	47 <sup>g</sup> (6%)	45 <sup>g</sup> (3%)	0 (0%)	9
	Purpura	9 (5%)	12 (3%)	0 (0%)	14 (2%)	11 (1%)	11 (5%)	4
SKIN	Application Site Reaction	0 (0%)	15 (4%)	1 (1%)	10 <sup>g</sup> (1%)	5 (<1%)	16 (7%)	18 <sup>g</sup>
	Contact Dermatitis	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)	0
	Edema <sup>h</sup>	2 (1%)	1 (<1%)	2 (1%)	108 <sup>g</sup> (13%)	104 <sup>g</sup> (8%)	1 (<1%)	31
	Erythema <sup>h</sup>	1 (1%)	25 <sup>g</sup> (7%)	16 (10%)	140 <sup>g</sup> (16%)	150 <sup>g</sup> (12%)	22 <sup>g</sup> (10%)	68 <sup>g</sup>
	Maculopapular Rash	0 (0%)	0 (0%)	0 (0%)	2 (<1%)	1 (<1%)	0 (0%)	2
	Perifollicular Edema	0 (0%)	0 (0%)	0 (0%)	13 (2%)	12 (1%)	0 (0%)	11
	Perifollicular Erythema	0 (0%)	0 (0%)	0 (0%)	14 (2%)	13 (1%)	0 (0%)	11
	Petechial Rash	0 (0%)	1 (<1%)	1 (1%)	25 (3%)	25 (2%)	0 (0%)	0
	Pruritus	0 (0%)	0 (0%)	1 (1%)	5 (1%)	5 (<1%)	0 (0%)	0
	Rash	0 (0%)	0 (0%)	0 (0%)	2 (<1%)	1 (<1%)	0 (0%)	3
	Skin Discoloration	0 (0%)	12 (3%)	0 (0%)	9 (1%)	10 (1%)	11 (5%)	12
	Vesiculobullous Rash	0 (0%)	0 (0%)	0 (0%)	17 (2%)	14 (1%)	1 (<1%)	3

<sup>b, c, d</sup> Developmental S-Caine formulations A, B, and C; <sup>e</sup> Final S-Caine formulation; <sup>f</sup> Non-treated areas that were not administered drug, yet received a dermal procedure; <sup>g</sup> At least one subject in this group experienced multiple occurrences of the same adverse event; <sup>h</sup> Only moderate, severe or post procedure cases were collected.

(Source: Applicant's Table C5.4, ISS, Vol. 1, p. 3-245)

*Spontaneously reported AEs – Adult vs. pediatric trials*

Of the 81 pediatric patients enrolled in the new NDA controlled trials, 7% (3/41) S-Caine patients had a spontaneously reported AE, compared to 5% (2/40) placebo patients. The reported dermal AEs were erythema and skin discoloration (n=1 patient each). Three patients (1 S-Caine, 2 placebo) had systemic AEs: 1 S-Caine patient reported confusion; 1 placebo patient fainted ('syncope') following a blood draw; and 1 placebo patient had nausea, vomiting and dizziness.

ZARS found that considerably more adults than pediatric patients in controlled trials reported a dermal AE. For both groups of patients, echymosis, erythema, and edema were the most common dermal AEs and were more frequent for the S-Caine treatment compared to placebo. Because most pediatric patients were treated with the Final S-Caine formulation, only those data are presented for comparison to placebo:

**Table 12: Applicant's Analysis: Dermal AEs in all (original and new) controlled trials, by age group**

Body system	COSTART term	Adults		Pediatric patients N =	
		SCP <sup>a</sup> N = 683	Placebo N = 1129	SCP <sup>a</sup> N = 166	Placebo N = 161
BODY	Pain	11 (2%)	12 (1%)	-	-
HAL	Echymosis	46 (7%)	45 (4%)	10 (6%)	0
	Purpura	4 (1%)	11 (1%)	1 (1%)	0
SKIN	Application site reaction	4 (1%)	3 (<1%)	6 (4%)	2 (1%)
	Contact dermatitis	1 (<1%)	1 (<1%)		
	Edema <sup>b</sup>	100 (15%)	101 (9%)	8 (5%)	3 (2%)
	Erythema <sup>b</sup>	131 (19%)	146 (13%)	9 (5%)	4 (2%)
	Maculopapular rash	1 (<1%)	1 (<1%)	1 (1%)	0
	Perifollicular edema	13 (2%)	12 (1%)	-	-
	Perifollicular erythema	14 (2%)	13 (1%)	-	-
	Petechial rash	24 (4%)	25 (2%)	-	-
	Pruritus	5 (1%)	4 (<1%)	0	1 (1%)
	Rash	1 (<1%)	1 (<1%)	1 (1%)	0
	Skin discoloration	7 (1%)	9 (1%)	2 (1%)	1 (1%)
Vesiculobullous rash	15 (2%)	14 (1%)	2 (1%)	0	

<sup>a</sup> Final S-Caine formulation; <sup>b</sup> Only moderate, severe, or post-procedure cases were recorded  
 (Adapted from Applicant's Table sC5.6 and C5.7, ISS, Vol. 1, p. 3-250 and 3-252)

*Dermal AEs in uncontrolled trials*

All dermal AEs in uncontrolled trials occurred during the new (2005) trials which used the Final formulation of S-Caine. There were 491 enrollees in these trials (408 adults, 83 pediatric patients).

The most common AE was 'post-operative wound' (13% adults and 7% pediatric patients), followed by pain (5% adults, 1% pediatric patients). Erythema and echymosis were reported with similar frequency between the pediatric and adult groups (2% each).

More pediatric patients than adults reported pruritus (2% vs. 0.2%), and more adults than pediatric patients reported petechial rash (2% vs. 0%). Table 13 lists the AEs in the new NDA uncontrolled trials that occurred in at least 1% of patients

**Table 13: Spontaneously reported AEs – New NDA (2005) uncontrolled clinical trials, adults vs. pediatric patients**

COSTART Coding		Adults N = 408		Pediatric patients, N = 83	
Body system	Preferred Term	N	%	N	%
SKIN	POST-OP WOUND	53	12.99	6	7.23
BODY	PAIN	22	5.39	1	1.20
SKIN	ERYTHEMA	10	2.45	2	2.41
SKIN	EDEMA	6	1.47	4	4.82
SKIN	RASH PETECHIAL	8	1.96	0	0.00
HAL	ECCHYMOSIS	5	1.23	1	1.20
BODY	FEVER	0	0.00	3	3.61
SKIN	PRURITUS	1	0.25	2	2.41
HAL	PURPURA	0	0.00	1	1.20
NER	NERVOUSNESS	0	0.00	1	1.20

REVIEWER COMMENT: The cases of post-operative wounds were the procedural outcomes of skin biopsies or excision of dermal lesions. None of the cases appeared related to study treatment. Thus, excluding the reports of post-operative wounds, the pattern of dermal AEs in uncontrolled trials was similar to that in controlled studies.

#### 6.6.2.2 Edema, erythema, and blanching

Immediately after removal of study drug and prior to initiation of the dermal procedure, the investigator evaluated the application site specifically for development of edema, erythema, and blanching. These signs were rated according to severity, and only moderate to severe occurrences were recorded as AEs.

#### New NDA controlled clinical trials – All subjects

##### *Erythema*

Table 14 shows that erythema was the most observed skin reaction in both the S-Caine and placebo groups, and was generally slight-well defined in severity. Erythema was more frequent among S-Caine treated patients (44%) compared to placebo patients (37%).

##### *Edema*

Edema was the next most frequent event, occurring in 8% of S-Caine patients and 5% of placebo patients. Among the patients who had edema, the severity was primarily slight.

**Table 14: Observed skin reactions – New NDA controlled trials**

Observed skin reaction	S-Caine, N = 310 N (%)	Placebo, N = 305 N (%)
<i>Erythema</i>		
No Erythema	173 (56%)	192 (63%)
Very Slight Erythema	97 (31%)	98 (32%)
Well Defined Erythema	49 (16%)	33 (11%)
Moderate to Severe Erythema	4 (1%)	2 (1%)
<i>Edema</i>		
No Edema	274 (92%)	289 (95%)
Very Slight Edema (barely perceptible)	27 (9%)	13 (4%)
Slight Edema	9 (3%)	5 (2%)
Moderate Edema (raised approximately 1 mm)	3 (1%)	0 (0%)
<i>Blanching</i>		
No Blanching	288 (93%)	296 (97%)
Slight, diffuse blanching with indistinct outline	21 (7%)	9 (3%)
More intense blanching with half of the treated site perimeter outlined	1 (0.3%)	0 (0%)

*Blanching*

Blanching was the least common of the observed skin reactions. It was, however, more common in the S-Caine group (7%) than in the placebo group (3%). Again, the cases were mainly slight in severity.

New NDA controlled clinical trials – Pediatric trials (n = 1 trial)

The data show that the pattern of erythema, edema, and blanching among pediatric patients was similar to the entire group of patients in controlled trials. Erythema was the most frequently observed skin reaction, however it occurred with greater frequency in the placebo group (42%) than the S-Caine group (32%). The incidence of edema and blanching was low (2% each).

New NDA - All uncontrolled trials

In the uncontrolled trials, the frequency of observed skin reactions was the same as for the controlled trials, with most patients experiencing erythema (33%), followed by blanching (16%), and edema (5%).

**6.7 Laboratory findings**

Systemic absorption of S-Caine is negligible therefore no clinical laboratory evaluations were performed.

## 6.8 Vital signs

In all trials, vital signs (heart rate, blood pressure, respiratory rate) were measured prior to study treatment. However, post-treatment vital signs were not routinely collected in all trials, due to the minimal systemic absorption of S-Caine. Investigators would collect post-treatment vital signs only when clinically warranted.

Only the pharmacokinetic trials<sup>10</sup> (submitted in the original NDA) incorporated vital sign assessments at specific time periods. These trials specified criteria for identification of clinically significant changes from baseline. Data were collected for 116 trial participants, and were evaluated in the primary review of the original NDA<sup>11</sup>. The review found that these data did not show any significant differences between S-Caine and placebo. However, due to the paucity of vital signs data, additional exploration of the effect of treatment of vital signs was not possible.

Nevertheless, an effect of S-Caine is not likely, because the drug does not have much systemic exposure.

## 6.9 Electrocardiograms

Electrocardiograms were not conducted in the clinical trials, due to the presumed negligible systemic absorption of S-Caine.

## 7 Data Quality and Integrity

The Division of Scientific Investigations (DSI) inspected five sites for inspection, each located in the United States. The sites were selected for inspection if

- At least 1 adult efficacy study was conducted there
- Study SCP-46-05 (the sole pediatric efficacy study) was conducted there
- The site conducted multiple studies (open label and efficacy)
- The site conducted the sole duration of effect trial (Study SCP-44-05)
- A relatively high number of patients was enrolled at that site

As of the writing of this review, DSI had not found any irregularities in study conduct that were not otherwise explained in protocol amendments or amendments to the statistical analysis plan while the database was still locked and blinded.

## 8 Product Label Review

Review of the proposed Package Insert focused solely on the clinically-related sections. *Note that the review contains only draft language for the label which may not reflect the exact language agreed upon for the final label, should the drug be approved.*

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<sup>10</sup> Studies SCP-08-00, SCP-30-02, and SCP-31-02

<sup>11</sup> Refer to the clinical NDA review by Dr. Howard Josefberg

6 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

~~X~~ § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

## 9 Conclusions

The resubmitted clinical trials support the efficacy of S-Caine as a local dermal analgesic in adult patients undergoing superficial dermatological procedures. The data also show that S-Caine is reasonably safe to use in this population.

There is no evidence of efficacy of this product in pediatric patients undergoing “minor” superficial dermatological procedures (e.g. venipuncture). However, the data suggest that the adverse event profile in pediatric patients is similar to that for adults.

## 10 Recommended Regulatory Action

I recommend approval of S-Caine in adults only. My recommended indication is “local dermal anesthetic analgesia for superficial dermatological procedures such as collagen injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.”

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## 11 Appendix

### 11.1 Appendix 1: Efficacy trials -Initial NDA submission

Study	Procedure Type	Population (n) <sup>1</sup>	Design	Site	Duration <sup>2</sup> (minutes)
"Minor"	Dermal Procedures				
20-02	Pulsed Dye Laser Therapy	Adult (30/30)	parallel	face	20
22-02	Laser-Assisted Hair Removal	Adult (50/50)	W-S <sup>3</sup>	face, arm/underarm, bikini area	30
25-02	"Vascular Access"	Adult (55/55)	W-S <sup>3</sup>	antecub	30
26-02	Collagen Injection (Face)	Adult (52/52)	W-S <sup>3</sup>	face	30
27-02	Pulsed Dye Laser Therapy (vs. EMLA 60 min)	Peds 1-3 yrs (40/40)	parallel	face/neck	30
28-02	"Vascular Access"	Peds 3-17 yrs (40/43)	parallel	antecub	30
29-02	Pre-Lidocaine Injection	Peds 3-17 yrs (45/48)	parallel	limbs, trunk, head/neck	30
32-02	Non-Ablative Facial Laser Resurfacing	Adults (41/41)	W-S <sup>3</sup>	face	30
33-02	"Vascular Access"	Geriatric (55/55)	W-S <sup>3</sup>	antecub	30
"Major"	Dermal Procedures				
21-02	Laser-Assisted Tattoo Removal	Adult (30/30)	W-S <sup>2</sup>	?	60
23-02	Laser Ablation of Leg Veins	Adult (60/60)	W-S <sup>2</sup>	leg	60
	Anesthetic Endpoints				
34-03	Duration of Anesthetic Effect	Adult (41/41)	W-S	forearms	30, 60

<sup>1</sup> number of exposures to S-Caine/Placebo. In the within-subject control studies, S-Caine and Placebo treatments were both applied to each subject.

<sup>2</sup>duration of S-Caine peel application

<sup>3</sup>within-subject placebo control

The selected durations of application for S-Caine Peel were based on the results of Phase 2 trials where application duration times varied from 15 minutes to 90 minutes across a limited number of dermal procedures. These studies were generally consistent with an increase in analgesic efficacy with increasing application times up to 90 minutes. The application times selected for study in the pivotal trials generally reflected an attempt to select an effective dosing duration for which further increases in dosing duration were not associated with large incremental analgesic benefits.

(Source: Team Leader memo by Dr. Nancy Chang, September 14, 2004)

### **11.2 Appendix 2: Study SCP-40-05 – Efficacy in adults, NDA resubmission**

“A randomized, double-blind, placebo-controlled, paired study evaluating S-Caine (lidocaine 7% and tetracaine 7% cream), when applied for 30 minutes, for induction of local dermal anesthesia for dermal filler injection on the face of adults.”

#### Objectives

- To evaluate the efficacy of S-Caine (S-Caine) for induction of dermal anesthesia for dermal filler injection
- To assess the nature and frequency of adverse events associated with S-Caine use

#### Study design

This was a Phase 3, single dose, randomized, double-blind, placebo-controlled, within-subject trial conducted at 3 sites in the United States.

Study population and procedures:

The protocol specified enrollment of 70 adult subjects. Patients would be randomized 1:1 to be administered S-Caine on either the top/right or bottom/left treatment area, and placebo on the alternate treatment area. Study drug would be applied for 30 minutes.

Eligibility criteria were:

- Age  $\geq$  18 years
- Undergoing facial dermal filler injection

Subjects were excluded for:

- Damaged, denuded, or broken skin at the designated treatment area
- Atopic dermatitis in the designated treatment area
- Use of prescription-strength analgesics within the 24 hours prior to the procedure
- Use of any analgesics within 8 hours of the procedure (Patients taking a preventive “cardiac” dose of aspirin 80 mg were not excluded)
- Sensitivity, allergy, or contraindications to lidocaine, tetracaine, or other local anesthetics of the amide or ester type
- Pregnancy or breastfeeding

#### Study procedures

Eligible subjects were to have two treatment areas<sup>12</sup> identified on the face, designated “top/right” and “bottom/left.” Subjects would then be randomized to one of two sequences: S-Caine on the top/right and placebo on the bottom/left, *or* placebo on the top/right and S-Caine on the bottom/left.

Study drugs (S-Caine and placebo peel) were concurrently administered in to the appropriate areas: the amount (length) of drug required was determined by the size of

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<sup>12</sup> A treatment area was defined as two similar anatomical locations that required similar amounts of dermal filler

the area to be treated (see table below) and then a thin layer (~ 1 mm) was applied evenly across the treatment area. If the length of drug required exceeded the length of the treatment area, multiple strips of drug were to be applied and then spread. Drug was to be left in place for 30 minutes ( $\pm 2$  min) and then peeled away, first from the top/right area and then from the bottom/left area.

**Dosage and administration information – Study SCP-40-05:**

Surface area of treatment site (cm <sup>2</sup> )	Length of study drug for 1mm thickness (cm)	Weight of study drug dispensed (g)
10	3	1
20	6	3
40	12	5
80	24	11
100	30	13
150	46	20
200	61	26

Immediately after removal, the treatment areas were to be evaluated for erythema, blanching, or edema (using pre-specified evaluation criteria). The dermal filler injections would be given, beginning with the top/right area and patients were to rate their pain intensity and overall impression of adequacy of the drug. The investigator would determine the patients' pain intensity and provide an impression of the adequacy of the drug. Any rescue medication given for pain was to be recorded.

Following drug administration, patients would be discharged with information regarding potential delayed skin reactions and information to contact the study center in case of an adverse event (AE). Telephone contact with the patient was to occur between 20 and 72 hours following the procedure, to assess for AEs.

#### Statistical analysis

##### *Efficacy measures*

- Visual analog scale (VAS) for pain intensity (continuous) – from 0 mm (no pain) to 100 mm (worst pain). To be completed by the patient.
- Patient overall impression of drug adequacy:
  - Did study drug provide adequate pain relief? (yes/no)
  - Would you have topical anesthesia using this study drug again? (yes/no)
- Categorical post-procedure pain intensity scale, to be completed by the investigator
  - 0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = severe pain
- Investigator's overall impression of study drug effectiveness:
  - Did the study drug provide adequate anesthesia for the procedure? (yes/no)

##### *Safety measures*

- Evaluation of skin reactions
  - Erythema Scale (categorical) – from 0 = no erythema, to 4 = severe erythema to slight eschar formation
  - Edema Scale (categorical) – from 0 = no edema, to 4 = severe edema
  - Blanching Scale (categorical) - from 0 = no blanching, to 5 = extreme blanching

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

NOTE: Only erythema, edema, and blanching events that were rated moderate to severe were to be recorded as an adverse event

- Adverse events

*Primary efficacy endpoint*

- Pain intensity (VAS) in the S-Caine group vs. the placebo group

Protocol amendments:

*Amendment – June 6, 2005*

The protocol was amended to allow non-physician sub-investigators to:

- Determine patient eligibility
- Complete the skin evaluations
- Complete the efficacy evaluations

**Applicant’s Study Results**

Enrollment

Three sites in the United States participated in the trial. Enrollment was as follows:

**Enrollment – Study SCP-40-05**

Center/PI/Site #	Total # patients
Tennessee Clinical Research Ctr., Nashville TN; Dr. M. Gold; Site #1	14
AboutSkin Dermatology, Englewood CO; Dr. J. Cohen, Site # 2	21
J&S Studies Inc., Bryan TX; Dr. T. Jones, Site #3	35

Protocol deviations

There were 17 patients noted to have a protocol deviation. Study sites 1 and 2 had at least 1 protocol deviation, while Site #3 had none. Site #2 had the most patients with deviations (n=8).

**Summary of protocol deviations – Study SCP-40-05**

Deviation	# patients
Patient randomized out of sequence	4
Patient contacted before or after the 20-72 hour follow-up window	6
Patient on a daily regimen of naproxen 250 mg	1
Patient on a daily regimen of aspirin 325 mg	1
Patient received 4 injections on the top/right area, and 5 injections on the bottom/left area	1
The top/right study drug was applied to the bottom/left area, and vice versa. Study procedures were done first at the bottom/left area	1
Study drug was applied for 33 minutes	1
Screening visit occurred 26 days prior to the study procedure	1

(Adapted from Applicant’s Table 10.2, CSR for Study SCP-40-05, Vol. 4, p. 8-34)

Of these deviations, only the cases of three patients (the 2 receiving continuous analgesic treatment and the one whose study drugs were applied to the wrong areas) could potentially have affected the efficacy outcome. Daily use of the analgesics could have reduced the patients’ ability to detect an anesthetic difference between the active and placebo peels). However, the small number of patients involved makes an adverse effect on the overall efficacy outcome unlikely.

For the patient for which the randomized top/right study drug was applied to the bottom/left treatment area (and vice versa), the intent to treat approach was used. That is, data from the top right was analyzed as if it was placebo, even though the actual drug was S-Caine.

Subject disposition

The study enrolled a total of 70 patients, and all patients completed the study.

Demographics and Medical History

Nearly all patients (94%) were Caucasian, and the majority were female (96%). The mean age was 50 ( $\pm$  9) years. All skin types (I-VI)<sup>13</sup> were represented, with Type III being the most common (44%). All patients had normal skin at the applications sites. The reported medical conditions and vital signs obtained were consistent with a generally healthy adult population.

Restylane was used as the dermal filler for all patients. The median number of dermal filler injections given was 4 for both the placebo- and Flexicane-treated sites.

**Demographics, Safety Population<sup>14</sup> (N = 70) – Study SCP-40-05**

Parameter	Category or Statistic	Total
Age (yr)	N	70
	Mean $\pm$ SD	50.5 $\pm$ 8.9
Gender, N (%)	Female	67 (96%)
	Male	3 (4%)
Race, N (%)	Caucasian	66 (94%)
	Black	1 (1%)
	Hispanic	1 (1%)
	Other	2 (3%)
Skin Type, N (%)	I	5 (7%)
	II	12 (17%)
	III	31 (44%)
	IV	14 (20%)
	V	7 (10%)
	VI	1 (1%)
Type dermal filler, N (%)	Restylane	70 %100%
# dermal injections	N	70
	Median	4 (S-Caine) 4 (Placebo)

(Adapted from Applicant’s Table 11.1 and 11.3, CSR for Study SCP-40-05, Vol. 4, p. 8-36., 8-38)

Applicant’s efficacy results

*Primary efficacy variable*

<sup>13</sup> Skin types: I – always burns easily, rarely tans; II – always burns easily, tans minimally; III – burns moderately, tans gradually; IV – burns minimally, always tans well; V – rarely burns, tans profoundly; VI – never burns, deeply pigmented

<sup>14</sup> Safety population = all patients who had study drug applied and had at least one subsequent safety evaluation

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

The mean VAS score for S-Caine was 24.2, compared to 37.4 for the placebo group. The difference in pain intensity scores reached statistical significance.

**Primary efficacy analysis – Study SCP-40-05**

Parameter	Statistic	S-Caine	Placebo	p-value (paired t test)
VAS	N	70	70	< 0.0001
	Mean ± SD	24.2 ± 18.13	37.4 ± 23.52	
	Median	21.5	32.5	
	Min, Max	1, 79	1, 91	

(Adapted from Applicant’s Table 11.4, CSR for Study SCP-40-05, Vol. 4, p. 8-39)

*Secondary efficacy variables*

The secondary endpoints were all consistent with an analgesic effect of S-Caine and significant differences were found between the active and placebo groups.

**Applicant’s secondary efficacy analysis – Study SCP-40-05**

Parameter	Statistic	S-Caine	Placebo	p-value
Drug provides pain relief Yes	N (%)	46 (66%)	30 (43%)	0.0052
Would use drug again Yes	N (%)	47 (67%)	33 (47%)	0.0094
Investigator’s rating of pain intensity No pain	N (%)	25 (36%)	11 (16%)	< 0.0001
Investigator’s rating of drug adequacy Adequate anesthesia	N (%)	55 (79%)	36 (51%)	0.0013

(Adapted from Applicant’s Table 11.5, CSR for Study SCP-40-05, Vol. 4, p. 8-41)

REVIEWER COMMENT: No adjustments were made for multiplicity, with respect to secondary analyses.

The Applicant concluded that a 30 minute application of S-Caine is efficacious in inducing local dermal anesthesia.

REVIEWER CONCLUSION: The primary efficacy measure (the VAS) is a measure of pain intensity (i.e. analgesia) as opposed to whether or not there is a total absence of sensation (i.e. anesthesia). Similarly, the secondary measures assess the degree of pain felt, and do not assess if absolutely no pain can be felt. Therefore, the most appropriate conclusion to be drawn from the Applicant’s analysis is that S-Caine treatment produces a greater amount of *analgesia* for dermal filler injections than does placebo treatment.

### **11.3 Appendix 3: Study SCP-41-05 – Efficacy in adults, NDA resubmission**

“ A randomized, double-blind, placebo-controlled, paired study evaluating the efficacy of S-Caine (lidocaine 7% and tetracaine 7% cream) in providing local dermal anesthesia for non-ablative facial laser resurfacing in adults.”

#### Objectives

- To evaluate the efficacy of S-Caine (S-Caine) in providing local dermal anesthesia for non-ablative facial laser resurfacing
- To assess the nature and frequency of AEs associated with S-Caine

#### Study design

This was a Phase 3, single-dose, randomized, double-blind, placebo-controlled, within-subject trial conducted at 4 sites in the United States

#### Study population and procedures:

Enrollment of 50 patients was planned. Patients undergoing non-ablative facial laser resurfacing were to serve as their own controls, with study drug (S-Caine and placebo) randomly administered to right and left areas of the face. Study drugs would be simultaneously applied for 30 minutes.

Inclusion and exclusion criteria were the same as for Study SCP-40-05.

#### Study procedures

After identification of the appropriate treatment areas, study drugs were to be applied (see Appendix 2) for 30 ( $\pm$  2) minutes. Study drug would be applied to the right area, and then to the left. Drug removal would also occur first at the right, and then at the left. Following removal, the investigator was to conduct an evaluation of the skin. The laser procedure was to start with the right, using 25-50 pulses. Evaluation of efficacy, as described in Appendix 2 would then immediately occur, with subsequent repetition of the process on the left. After completion of the efficacy evaluations, laser treatment could be resumed if needed. Follow-up with the patients was to occur via telephone, between 20 and 72 hours after the procedure.

#### Statistical analysis

Efficacy and safety analyses were the same as for Study SCP-40-05 (see Appendix 2).

#### Protocol amendments

*Amendment – May 12, 2005*

The protocol clarified the procedures to follow in case of discontinuation of the laser resurfacing procedure due to intolerance of pain.

### **Applicant’s Study Results**

The first patient was enrolled on June 1, 2005 and the last patient completed the study on September 27, 2005.

Clinical Review NDA resubmission  
N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

### Enrollment

Four US-based sites participated in the trial, with enrollment of 54 patients:

#### **Enrollment – Study SCP-41-05**

Center/PI/Site #	Total # patients
Washington Institute of Dermatologic Laser Surgery, Washington DC Dr. T. Alster; Site #1	6
Macrene Alexiades-Armenakas, MD; New York, NY; Site #2	16
Midwest Cutaneous Research, Clinton Township MI; Dr. D. Stewart; Site #3	19
Skin Care Doctors, Cambridge MA; Dr. R. Hirsch; Site # 4	13

### Protocol deviations

A total of 69 protocol deviations were noted. Study Site #3 had the highest number of violations, with all the patients at that site (n = 19) having skin and efficacy evaluations conducted by the study nurse rather than by a study investigator.

#### **Summary of protocol deviations – Study SCP-41-05**

Deviation	# patients
Patient randomized out of sequence	14
Number of pulses on right and left areas differed	2 <sup>a</sup>
Patient did not sign HIPAA form before study participation	5
Study staff member did not sign informed consent form	5
Study nurse, and not the investigator, conducted the skin evaluation	19 <sup>b</sup>
Study nurse, and not the investigator, conducted the efficacy evaluation	19 <sup>b</sup>
Patient contacted outside of the 2-072 hour follow-up window	5 <sup>c</sup>

<sup>a</sup> Patient #301 had 49 pulses on the left, and 45 on the right; Patient #3102 had 43 pulses on the right, and 47 on the left

<sup>b</sup> All patients enrolled at Study Site #3

(Adapted from Applicant's Table 10.1, CSR for Study SCP-41-05, Vol. 5, p. 8-465)

REVIEWER COMMENT: The deviation likely to have the greatest impact on the study results is the performance of both the skin and efficacy evaluations by the study nurse on all patients at Site #3. If the nurse were relatively unskilled in these assessments, information about the dermal effects of the product, as well as the observer's assessment of efficacy could be useless. However, because the primary efficacy measure was patient-based (i.e. patient's perception of pain intensity) and not observer-based, and because the skin evaluation process was relatively simple and did not require specialized training, this deviation is not likely to have seriously impacted the data collected.

### Subject disposition

All 54 enrolled patients completed the study.

### Demographics and Medical History

The majority of patients were Caucasian (94%) and most enrollees were female (78%). The sites differed with respect to the mean age of patients: patients at Sites 1 and 3 (mean ages 30 and 34, respectively) were younger than those at Sites 2 and 4 (mean ages of 47 and 54 years, respectively).

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

All skin types were represented. Again, there were differences by center with respect to the predominant skin type: patients at Site #3 had fewer patients with skin types I and II compared to the other sites. The most common medical condition reported was “dermatologic” (59% of patients). This was consistent with the patient population, i.e. patients undergoing facial laser resurfacing. Otherwise the patients were generally healthy.

**Demographics, Safety population (n = 54) – Study SCP-41-05**

Parameter	Category or Statistic	Total
Age (yr)	N	54
	Mean ± SD	42.3 ± 14.1
Gender, N (%)	Female	42 (78%)
	Male	12 (22%)
Race, N (%)	Caucasian	51 (94%)
	Black	1 (2%)
	Hispanic	1 (2%)
	Asian	1 (2%)
Skin Type, N (%)	I	5 (9%)
	II	24 (44%)
	III	14 (26%)
	IV	10 (19%)
	V	0 (0%)
	VI	1 (2%)

(Adapted from Applicant’s Table 11.1, CSR for Study SCP-41-05, Vol. 5, p. 8-467)

Applicant’s efficacy results

*Primary efficacy variable*

The mean VAS score for the S-Caine group was statistically significantly lower than that for the placebo group (21.4 vs. 38.0, p<0.0001).

**Applicant’s primary efficacy analysis – Study SCP-41-05**

Parameter	Statistic	S-Caine	Placebo	p-value (paired t test)
VAS	N	54	54	< 0.0001
	Mean ± SD	21.4 ± 18.89	38.0 ± 24.46	
	Median	15.5	36.0	
	Min, Max	0, 71	1, 89	

(Adapted from Applicant’s Table 11.4, CSR for Study SCP-41-05, Vol. 4, p. 8-471)

*Secondary efficacy variables*

All of the secondary analyses favored S-Caine treatment over placebo treatment. Statistically significant differences between the active and placebo groups were found for all secondary parameters (without adjustment for multiplicity).

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

**Applicant's secondary efficacy analysis – Study SCP-41-05**

Parameter	Statistic	S-Caine	Placebo	p-value
Drug provides pain relief Yes	N (%)	45 (83%)	20 (37%)	<0.0001
Would use drug again Yes	N (%)	45 (83%)	21 (39%)	<0.0001
Investigator's rating of pain intensity	N (%)			0.0005
No pain		25 (46%)	17 (31%)	
Slight pain		22 (41%)	15 (28%)	
Moderate pain		6 (11%)	16 (30%)	
Severe pain		1 (2%)	6 (11%)	
Investigator's rating of drug adequacy	N (%)			0.0013
Adequate anesthesia		47 (87%)	30 (56%)	

(Adapted from Applicant's Table 11.5, CSR for Study SCP-41-05, Vol. 4, p. 8-472)

REVIEWER CONCLUSION: Pre-treatment with S-Caine produces greater analgesia than placebo, in patients undergoing facial non-ablative laser resurfacing.

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#### **11.4 Appendix 4: Study SCP-42-05 – Efficacy in adults, NDA resubmission**

“ A randomized, double-blind, placebo-controlled, parallel study evaluating the efficacy of S-Caine (lidocaine 7% and tetracaine 7% cream) in providing local dermal anesthesia for pulsed dye laser therapy in adults.”

##### Objectives

- To evaluate the efficacy of S-Caine (S-Caine) for induction of local dermal anesthesia before pulsed dye laser therapy (PDL)
- To assess the nature and frequency of AEs associated with S-Caine

##### Study design

This was a Phase 3, single-dose, randomized, double-blind, placebo-controlled, parallel group trial conducted at 5 sites in the United States

Study population and procedures:

Approximately 80 adult patients undergoing PDL were to be enrolled in the trial.

Patients would be randomized to either S-Caine or placebo peel, applied for 20 ( $\pm$  2) minutes.

Eligibility criteria were the same as for Study SCP-40-05 (see Appendix 2).

##### Study procedures

Subjects meeting eligibility criteria would have randomized study drug (S-Caine or placebo) administered to the treatment area (up to 200 cm<sup>2</sup>). The size of the treatment area would determine the amount of study drug applied (see Appendix 2 for dosing instructions). Immediately following drug removal, the skin was to be examined, and then the PDL procedure would be done. PDL was to be limited to 25-125 pulses on the treatment area. Efficacy assessments were to be made thereafter. After discharge, telephone contact to evaluate for delayed adverse effects would occur between 20 and 72 hours post PDL.

##### Statistical analysis

Efficacy and safety analysis were the same as for Study SCP-40-05 (see Appendix 2).

##### **Applicant's study results**

Enrollment of the first patient occurred on June 14, 2005, and the last patient completed the trial on October 3, 2005.

##### Enrollment

A total of 5 sites participated in the trial which enrolled 80 patients.

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

**Enrollment – Study SCP-42-05**

Center/PI/Site #	Total # patients
Washington Institute of Dermatologic Laser Surgery, Washington DC Dr. T. Alster; Site #1	9
Laser and Skin Surgery Center of New York, New York, NY; Dr. Geronemus; Site #2	1
Midwest Cutaneous Research, Clinton Township MI; Dr. D. Stewart; Site #3	5
Palm Beach Esthetic, Palm Beach FL; Dr. K. Beer; Site # 4	25
Gateway Aesthetic Institute and Laser Center, Salt Lake City UT; Dr. Taylor; Site #4	40

Subject disposition

Of the 80 enrolled patients, 79 completed the study. One patient (patient #3101, placebo) had study drug applied, but did not undergo the laser procedure. Therefore no efficacy measures were obtained for this patient.

Protocol deviations

Altogether, 18 protocol deviations were noted. Of these deviations, daily use of aspirin and treatment with a different laser could have affected the efficacy results. However, the small number of patients involved (n = 1, each) makes this unlikely.

**Summary of protocol deviations – Study SCP-42-05**

Deviation	# patients
Non PDL laser therapy was used	1 <sup>a</sup>
Patient received more than 125 initial pulses for the initial PDL procedure	2
Patient did not sign HIPAA form before study participation	1
Study staff member signed informed consent form at a later date	2
Patient on a daily regimen of 325 mg aspirin	2
Drug was applied for 15 minutes instead of 20 minutes	2
Patient was not given the patient handout	4
Patient contacted outside of the 2-072 hour follow-up window	4

<sup>a</sup> Patient SCP42-02-101. The investigator elected to use KTP therapy with the Versapulse laser. Laser settings for spot size, energy, wavelength, DCD spray, and DCD delay were slightly different from the recommended PDL settings. Pulse duration was within range.

(Adapted from Applicant's Tables 10.2 and Appendix Table 16.2.2, CSR for Study SCP-42-05, Vol. 6, p. 8-896; Vol 7, p. 8-1315)

Demographics and medical history

The study sites differed in terms of age, with Site # 4 enrolling older patients (mean age 59 years) than those at Site #5 (mean age 42 years), or the combined Sites 1, 2, and 3 (mean age 48 years). However, as shown in the table that follows, the *treatment groups* (placebo vs. S-Caine) were similar with respect to age, gender, race, skin type, and medical history.

The group differences were somewhat comparable in terms of the lesion being treated. Most patients were undergoing PDL for facial telangiectasis (74% of S-Caine patients vs. 89% of placebo patients). Facial port wine stain was the next most common indication (21% of Flexicaine patients, and 8% of placebo patients).

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

**Demographics, Safety Population (n = 80) – Study SCP-42-05**

Parameter	Category or Statistic	S-Caine	Placebo
Age (yr)	N	42	38
	Mean ± SD	46.8 ± 14.5	50.8 ± 14.2
Gender, N (%)	Female	27 (64%)	22 (58%)
	Male	15 (36%)	16 (42%)
Race, N (%)	Caucasian	40 (95%)	38 (100%)
	Hispanic	1 (2%)	0
	Asian	1 (2%)	0
Skin Type, N (%)	I	0	1 (3%)
	II	17 (40%)	16 (42%)
	III	17 (40%)	12 (32%)
	IV	5 (12%)	8 (21%)
	V	3 (7%)	1 (3%)
	VI	0	0
Type of lesion, N (%)	Facial/spider angioma	1 (2%)	0
	Facial hemangioma	1 (2%)	1 (3%)
	Facial port wine stain	9 (21%)	3 (8%)
	Facial telangiectasis	31 (74%)	34 (89%)

(Adapted from Applicant's Tables 11.1 and 11.3, CSR for Study SCP-42-05, Vol. 6, p. 8-899; p. 8-902)

Applicant's efficacy results

*Primary efficacy variable*

The mean VAS score for the S-Caine group was 16.4, and 30.9 for the placebo group. This difference was statistically significant (p = 0.0008).

**Applicant's primary efficacy analysis – Study SCP-42-05**

Parameter	Statistic	S-Caine	Placebo	p-value (paired t test)
VAS	N	42	37	0.0008
	Mean ± SD	16.4 ± 19.55	30.9 ± 17.06	
	Median	11.0	30.0	
	Min, Max	0, 84	4, 81	

(Adapted from Applicant's Table 11.4, CSR for Study SCP-42-05, Vol. 6, p. 8-904)

*Secondary efficacy variables*

All of the secondary analyses supported efficacy of S-Caine over placebo treatment, with statistically significant differences between the active and placebo groups. As in the previously described studies, no adjustments were made for multiplicity.

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

**Applicant's secondary efficacy analysis – Study SCP-42-05**

Parameter	Statistic	S-Caine	Placebo	p-value
Drug provides adequate pain relief				
Yes	N (%)	38 (90%)	22 (59%)	0.0016
Patient would use drug again				
Yes	N (%)	38 (90%)	24 (65%)	0.0069
Investigator's rating of pain intensity				
No pain	N (%)	28 (67%)	8 (22%)	<0.0001
Slight pain		13 (31%)	22 (59%)	
Moderate pain		1 (2%)	7 (19%)	
Severe pain		0	0	
Investigator's rating of drug adequacy				
Adequate anesthesia	N (%)	39 (93%)	24 (65%)	0.0040

(Adapted from Applicant's Table 11.5, CSR for Study SCP-42-05, Vol. 6, p. 8-906)

REVIEWER CONCLUSION: Pre-treatment with S-Caine produces greater analgesia than placebo, in patients undergoing laser therapy for superficial dermal vascular lesions.

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### **11.5 Appendix 5: Study SCP-43-05 – Efficacy in adults, NDA resubmission**

“A randomized, double-blind, placebo-controlled, paired study evaluating the efficacy of S-Caine (lidocaine 7% and tetracaine 7% cream) in providing local dermal anesthesia for laser assisted tattoo removal in adults.”

#### Objectives

- To evaluate the efficacy of S-Caine (S-Caine) for induction of local dermal anesthesia before laser assisted tattoo removal
- To assess the nature and frequency of AEs associated with S-Caine

#### Study design

This was a Phase 3, single-dose, randomized, double-blind, placebo-controlled, parallel group trial conducted at 3 sites in the United States

Study population and procedures:

Approximately 60 adult patients undergoing elective laser assisted tattoo removal were to be enrolled in the trial. Patients would be randomized to concurrent administration of S-Caine at the top/right treatment area and placebo at the bottom/left, *orto* S-Caine at the bottom/left treatment area, and placebo at the top/right. Treatment areas were defined as “two similar anatomical locations that have similar tattoo characteristics.” The S-Caine or placebo peels were to be applied for 60 ( $\pm$  2) minutes.

Eligibility criteria were the same as for Study SCP-40-05 (see Appendix 2).

#### Study procedures

Subjects meeting eligibility criteria would have study drug (S-Caine and placebo) administered to the treatment areas at the same time. The size of the treatment area would determine the amount of study drug applied (see Appendix 2 for dosing instructions). After 60 minutes, drug was to be removed, with the top/right area removed first. The skin would immediately be examined per the pre-specified skin evaluation, and then the laser procedure would be done, beginning with the top/right area. Laser therapy was to be limited to 10-25 pulses. Efficacy assessments were to be made thereafter. After discharge, telephone contact to evaluate for delayed adverse effects would occur between 20 and 72 hours post laser therapy.

#### Statistical analysis

Efficacy and safety analysis were the same as for Study SCP-40-05 (see Appendix 2).

#### Protocol amendment

*Amendment – May 12, 2005*

The protocol was revised to clarify the procedures to follow in the event that laser treatment had to be stopped due to intolerance of pain. The amendment occurred prior to enrollment of any patients.

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

### Applicant's study results

Enrollment of the first patient occurred on June 15, 2005, and the last patient completed the trial on September 26, 2005.

#### Enrollment

Three US sites, enrolling 63 patients, took part in the trial.

#### Enrollment – Study SCP-43-05

Center/PI/Site #	# patients
Sadick Aesthetic Surgery and Dermatology, New York NY; Dr. N. Sadick; Site #1	26
Laser and Skin Surgery Center of New York, New York NY; Dr. Geronemus; Site #2	4
Gateway Aesthetic Institute and Laser Center, Salt Lake City UT; Dr. Taylor; Site #3	33

#### Subject disposition

One of the 63 enrolled patients, one (patient #4105, placebo) withdrew consent after application of study drug (but before the laser procedure). No efficacy measures were obtained for this patient.

#### Protocol deviations

The protocol violations are listed below. None is considered to have the potential to significantly affect the efficacy results.

#### Summary of protocol deviations – Study SCP-43-05

Deviation	# patients
Patient did not have informed consent obtained in accordance with GCP	6
Patient's top/right tattoo removal procedure started 1-3 minutes before the bottom/left skin evaluation	5
Patient contacted outside of the 2-72 hour follow-up window	2
Patient's bottom/left study drug was applied for 57 minutes	1

(Adapted from Applicant's Table 11.2, CSR for Study SCP-43-05, Vol. 7, p. 8-1477)

These violations were either too few in number or not significant enough to have adversely affected the efficacy outcome.

#### Demographics and Medical History

Three quarters of the patients were Caucasian, and 75% were female. The mean age of the enrollees was 33 years. The predominant skin types were III and IV. The most common sites for tattoo removal were the arm, leg, and chest/back.

#### Demographics, Safety Population (n = 63) – Study SCP-43-05

Parameter	Category or Statistic	Total
Age (yr)	N	63
	Mean ± SD	33.0 ± 11.2
Gender, N (%)	Female	47 (75%)
	Male	16 (25%)
Race, N (%)	Caucasian	47 (75%)
	Hispanic	9 (14%)
	Asian	3 (5%)
	Black	1 (2%)

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

**Demographics, Safety Population (n = 63) – Study SCP-43-05 (continued)**

Parameter	Category or Statistic	Total
Skin Type, N (%)	I	2 (3%)
	II	9 (14%)
	III	25 (40%)
	IV	26 (41%)
	V	1 (2%)
	VI	0
Laser site, N (%)	Arm	18 (29%)
	Chest/back	12 (19%)
	Face/scalp	3 (5%)
	Foot	1 (2%)
	Hand	2 (3%)
	Leg	14 (23%)
	Neck	2 (3%)
	Other	10 (16%)

(Adapted from Applicant's Tables 11.1 and 11.3, CSR for Study SCP-43-05, Vol. 7, p. 8-1479 and 8-1482)

Applicant's efficacy results

*Primary efficacy variable*

The mean VAS score was statistically significantly lower for Flexicane compared to placebo ( $p < 0.0001$ ).

There was a significant interaction between study site and treatment area, indicating that the side that responded the best depended on the patient's center.

**Applicant's primary efficacy analysis – Study SCP-43-05**

Parameter	Statistic	S-Caine	Placebo	p-value (paired t test)
VAS	N	62	62	<0.0001
	Mean ± SD	39.1 ± 25.48	58.6 ± 21.59	
	Median	32.0	61.5	
	Min, Max	2, 88	0, 98	

(Adapted from Applicant's Table 11.4, CSR for Study SCP-43-05, Vol. 7, p. 8-1484)

*Secondary efficacy variables*

All of the secondary analyses supported efficacy of S-Caine over placebo treatment, with statistically significant differences between the active and placebo groups. As in the previously described studies, no adjustments were made for multiplicity.

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

**Applicant's secondary efficacy analysis – Study SCP-43-05**

Parameter	Statistic	S-Caine	Placebo	p-value
Drug provides adequate pain relief Yes	N (%)	33 (53%)	11 (18%)	<0.0001
Patient would use drug again Yes	N (%)	34 (55%)	8 (13%)	<0.0001
Investigator's rating of pain intensity No pain Slight pain Moderate pain Severe pain	N (%)	8 (13%) 25 (40%) 21 (34%) 8 (13%)	3 (5%) 8 (13%) 28 (45%) 23 (37%)	<0.0001
Investigator's rating of drug adequacy Adequate anesthesia	N (%)	33 (53%)	10 (16%)	<0.0001

(Adapted from Applicant's Table 11.5, CSR for Study SCP-43-05, Vol. 7, p. 8-906)

REVIEWER CONCLUSION: Pre-treatment with S-Caine produces greater analgesia than placebo, in adult patients undergoing laser assisted tattoo removal.

**APPEARS THIS WAY  
 ON ORIGINAL**

### **11.6 Appendix 6: Study SCP-46-05 – Efficacy in pediatrics, NDA resubmission**

“A randomized, double-blind, placebo-controlled, parallel study evaluating the efficacy of S-Caine (lidocaine 7% and tetracaine 7% cream) for induction of local dermal anesthesia before vascular access procedures in children.”

#### Objectives

- To evaluate the efficacy of S-Caine in providing local dermal anesthesia before a venous vascular access procedure in children
- To assess the nature and frequency of adverse events associated with S-Caine

#### Study design

This was a Phase 3, single dose, randomized, double-blind, placebo-controlled, parallel group study. Three US sites participated in the trial.

Study population and procedures:

The protocol was to enroll approximately 80 pediatric patients who required venous vascular access. Patients would be randomized to either S-Caine or placebo, and drug applied for 30 minutes.

Eligibility criteria were similar to those for Study SCP-40-05 (see Appendix 2), except patients were included if they were:

- between 5 and 17 years, inclusive
- medically indicated to undergo a vascular access procedure

Patients undergoing PICC line placement were not eligible.

Proper informed consent from the parent’s child/guardian was required before conducting any procedure.

#### Study procedures

Patients meeting criteria for study participation were to be randomized to placebo or S-Caine. A separate randomization was to be generated for each center and age group (5-11 years, and 12-17 years). Patients were to then be educated on the use of the Colored Analog Scale.<sup>15</sup>

Study drug would be placed on either the patient’s left or right antecubital surface, covering an area of 10 cm<sup>2</sup>. Drug was to be applied for 30 minutes, and the investigator was to examine the site for skin reactions immediately thereafter. A qualified staff member (e.g. phlebotomist, nurse) would then perform the venous vascular procedure, recording the type of procedure and the gauge of the needle used.

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<sup>15</sup> The Colored Analog Scale (CAS) is a 14.5 cm triangular shape varying in width and hue from 1cm wide and light pink at the bottom, to 3 cm wide and deep red hue at the top. A plastic marker slides along the length of the scale to provide a pain rating continuum from no pain (bottom of the scale) to the most pain (top of the scale). On the other side of the scale is a corresponding 0-10 scale.

After completion of the procedure, the investigator (or designee) was to evaluate the procedural pain intensity and adequacy of analgesia, and then the patient would rate his/her pain. Follow-up with the patient was to occur between 20 and 72 hours post procedure.

#### Statistical analysis

##### *Primary efficacy parameter*

The primary efficacy variable was the patient's pain intensity, as measured by the CAS score. The CAS measured pain from a range of 0 (no pain) to 10 (worst pain). The primary efficacy analysis would compare the pain scores for the S-Caine and placebo patients.

##### *Secondary efficacy parameters*

The secondary efficacy variables were:

- Investigator's rating of post-procedural pain intensity – categorical scale
  - 0 = no pain; 1 = slight pain; 3 = moderate pain; 4 = severe pain
- Investigator's overall impression of study drug effectiveness
  - Did the study drug provide adequate anesthesia for the procedure (yes/no)

#### **Applicant's Study Results**

##### Enrollment

The first patient was enrolled on June 21, 2005, and the last patient completed study procedures on October 4, 2005.

##### **Enrollment – Study SCP-46-05**

<b>Center/PI/Site #</b>	<b># patients</b>
Jacobi Medical Center, Bronx NY; Dr. Wiznia; Site #1	42
Children's Hospital, Boston MA; Dr. Sethna; Site #2	33
Children's National Medical Center, Washington DC; Dr. Verghese; Site #3	6

##### Subject disposition

Eighty-one patients enrolled, with 41 randomized to S-Caine and 40 to placebo. One patient (patient #1204, placebo) withdrew from the study after drug application – she did not undergo the blood draw due to fear.

##### Protocol deviations

The following deviations were noted:

##### **Summary of protocol deviations – Study SCP-46-05**

<b>Deviation</b>	<b># patients</b>
One or more vital signs were not collected in a manner specified by the protocol	41
Post-procedure follow-up was conducted outside of the 20-72 hour window	6
Written informed consent was not properly completed	5
Study coordinator performed the skin evaluations	5
Patient was randomized out of sequence	2
Study drug was not applied for 30 minutes	2 <sup>a</sup>

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N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

Patient (and not he guardian) was given the handout regarding potential delayed reactions. In each case, the guardian did not read English.	2
Post-procedure follow-up was conducted with the patient, rather than the child	2
Patient was assigned to receive drug for age category 5-11 years, but was 12 years old	1

<sup>a</sup> Study drug was applied for 35 minutes (patient 2203) and for 25 minutes (patient 1224)  
(Adapted from Applicant's Table 10.2, CSR for Study SCP-46-05; Vol. 14, p. 8-3681)

REVIEWER COMMENT: The deviations likely to impact the study results include:

- Performance of the skin evaluations by the study coordinator – if the study coordinator were unskilled in these assessments, information about the dermal effects of S-Caine could be limited. However, because the skin evaluation process was relatively straight-forward, and because only a few patients were involved, this deviation is not likely to have seriously impacted the safety results

Demographics and Medical History

Overall, most (60%) of the enrolled patients were between 12 and 17 years. The mean age for the S-Caine and placebo groups was 12 years. Over half of the enrollees were male, with slightly more males in the S-Caine group than the placebo group. There was racial heterogeneity, as well as diversity in skin types.

The most common indication for treatment was a blood draw (93% of patients), followed by initiation of an IV line (7%),

**Demographics, Safety Population (n = 81) – Study SCP-46-05**

Parameter	Category or Statistic	S-Caine	Placebo
Age group, N (%)	5-11 years	17 (41%)	16 (40%)
	12-17 years	24 (59%)	24 (60%)
Age (year)	N	41	40
	Mean ± SD	11.9 ± 3.7	11.9 ± 3.2
Gender, N (%)	Female	17 (41%)	20 (50%)
	Male	24 (59%)	20 (50%)
Race, N (%)	Black	12 (29%)	14 (35%)
	Caucasian	12 (29%)	15 (38%)
	Hispanic	1 (2%)	10 (25%)
	Asian	0	1 (3%)
	Other	3 (7%)	0
Skin Type, N (%)	I	0	3 (8%)
	II	2 (5%)	2 (5%)
	III	5 (12%)	4 (10%)
	IV	11 (27%)	10 (25%)
	V	16 (39%)	16 (13%)
	VI	7 (17%)	8 (20%)
Vascular access procedure, N (%)	Blood draw	38 (93%)	37 (93%)*
	I.V. Start	3 (7%)	3 (8%)

\* Patient No. 1204 did not undergo the procedure, but data regarding the procedure she was intended to undergo are included

(Adapted from Applicant's Tables 11.1 and 11.3, CSR for Study SCP-46-05, Vol. 14, p. 8-3683; p. 8-3685)

Applicant's efficacy results

*Primary efficacy variable*

The mean pain intensity score, as reported using the Colored Analog Scale (CAS), was 1.77 for the S-Caine group, and 2.03 for the placebo group. These scores were not statistically different. The lack of a significant difference between groups was found among all the treatment centers.

**Applicant's primary efficacy analysis – Study SCP-46-05**

Parameter	Statistic	S-Caine	Placebo	p-value (paired t test)
CAS for pain intensity	N	41	39	0.64
	Mean ± SD	1.77 ± 2.46	2.03 ± 2.34	
	Median	0.75	1.5	
	Min, Max	0.00, 9.50	0.00, 8.50	

(Adapted from Applicant's Table 11.4, CSR for Study SCP-46-05, Vol. 14, p. 8-3686)

ZARS did not conduct any sub-group analyses, including an analysis by age category (e.g. 5-11 years, 12-17 years).

*Secondary efficacy variables*

The results of the secondary efficacy analyses showed no considerable differences (be it numeric or statistical) between the S-Caine and placebo groups. This was true even when the data were analyzed by the individual treatment centers.

**Applicant's secondary efficacy analysis – Study SCP-46-05**

Parameter	Statistic	S-Caine	Placebo	p-value
Investigator's rating of pain intensity	N (%)	23 (56%)	24 (62%)	0.56
		11 (27%)	11 (28%)	
		6 (15%)	2 (5%)	
		1 (2%)	2 (5%)	
Investigator's rating of drug adequacy	N (%)	28 (68%)	28 (72%)	0.81

(Adapted from Applicant's Table 11.5, CSR for Study SCP-46-05, Vol. 14, p. 8-3687)

REVIEWER'S CONCLUSION: The Applicant's analysis show that S-Caine is no more efficacious than placebo in reducing the pain associated with minor vascular access procedures such as blood draws and I.V. insertions.

### **11.7 Appendix 7: Study SCP-44-05 – Duration of effect, NDA resubmission**

“A randomized, double-blind, paired, placebo controlled study evaluating the duration of anesthetic effect produced by S-Caine (lidocaine 7% and tetracaine 7% cream) when applied for 30 and 60 minutes.”

#### Objectives

- To evaluate the duration of anesthetic effect produced by S-Caine (S-Caine)
- To evaluate the nature and frequency of AEs associated with S-Caine use

#### Study design

This was a phase 3, randomized, double-blind, paired, placebo controlled study conducted at a single US-based center.

Approximately 40 adult subjects were to be enrolled. Each subject would serve as his/her own control, with application of both the S-Caine and placebo patches. Subjects would be randomized to application for either 30 or 60 minutes.

Eligibility criteria were the same as for Study SCP-40-05 (see Appendix 2), except that were subjects healthy volunteers, and subjects were excluded if they had taken any analgesic medication during the 24 hours before the procedure.

#### Study procedures

Subjects were to be randomized in a non-blinded manner to one of two application time groups: 30 minutes or 60 minutes. Two treatment areas covering 200 cm<sup>2</sup> at the anterior surfaces of the right and left thigh would be identified and outlined with a marker. Both S-Caine and placebo would be applied simultaneously to the areas, in a double-blind, randomized manner.

At the end of the 30/60 minute application period, study drug was to be removed, starting with the right side. The treatment areas were to immediately be evaluated for erythema, edema, blanching, or other adverse reactions, again beginning with the right side.

Following skin evaluation, the investigator would administer 5 pinpricks to the treated area using a 21-gauge needle and the subject would indicate the number of pinpricks that elicited pain. Pinprick testing was to be done at the right and then the left thigh, without repetition at a previously tested area. Pinprick testing would occur at 30 minute intervals, until 13 hours post drug application. Pinprick testing was to be conducted by the same individual.

After completion of the procedure and efficacy assessments, the subjects would be instructed regarding potential delayed skin reactions and to contact the study center should they experience an AE. The study center was to contact the subjects via telephone between 20 and 72 hours after drug application to assess for AEs.

### Statistical analysis

#### *Efficacy*

The primary efficacy variable was the duration of anesthesia, described using descriptive statistics.

*Onset of anesthesia* = First time that the subject reports  $\leq 2$  painful pinpricks for two consecutive time points

*End of anesthesia* = First time that the subject reports  $\geq 3$  painful pinpricks for two consecutive time points

*Duration of anesthesia* = Difference between onset and end of anesthesia

A secondary efficacy analysis was descriptive statistics for the number of painful pinpricks at each time point by treatment.

#### *Safety*

AEs were to be summarized descriptively by treatment and application time group.

### **Applicant's Study Results**

#### Enrollment

The study was conducted at a single site in the US (Radiant Research, CA). A total of 40 subjects were enrolled and treated with study drug.

#### Protocol deviations

Altogether, 83 protocol deviations were reported among all 40 treated patients. The types of deviations are shown in the table below:

#### **Summary of protocol deviations – Study SCP-44-05**

<b>Deviation</b>	<b>N subjects</b>
The randomization application time was not followed	36
Multiple technicians performed pinprick tests	30
Screening ID and not the randomization ID was entered on the CRF	All subjects
Subject was contacted > 72 h after study drug application	10
Pinprick tests for the 30- and 60- time points were performed > 5 minutes of the scheduled time	4
Pinprick tests for the 90- 780 time points were performed > 5 minutes of the scheduled time	2
Study drug applied to the subject's left thigh first, then right	1

(Source: Applicant's Table 10.2, CSR for Study SCP-44-05, Vol. 12, p. 8-30901)

The most significant deviation is the lack of adherence of the study investigator to the sponsor-provided randomization schedule for study drug application. Instead of randomly assigning subjects to the application periods, the investigator assigned the first 20 subjects to a 30-minute application, and the next 16 subjects to a 60-minute

application. When the investigator recognized the error, the final 4 subjects were correctly assigned application times based on the randomization schedule.

The lack of adherence to the randomization schedule impacted the statistical analysis and therefore could have affected the efficacy outcome. However, the Applicant revised the statistical analysis plan and analyzed the data based on the actual application time groups, rather than on the randomized application time groups.

Another notable “deviation” was the use of multiple technicians to perform the pinprick tests, instead of the same individual conducting the testing throughout the study. However, the investigator requested and received approval to assign one primary pinprick technician for every 4 subjects, and the change was effected prior to any subject enrollment. Therefore, this deviation is really a protocol amendment, and not a deviation.

The other deviations either occurred in too few patients to have had a considerable impact on study outcome (i.e. delayed/early pinpricks testing) or were unlikely change the efficacy results (i.e. contact of subjects > 72 hours post application).

Subject disposition

Thirty-nine of the 40 treated subjects completed the study.

One subject (Subject No. 032) discontinued the study due to burning pain at the left application site.

Demographics

The median age was 41 years, and 60% of the subjects were female. About half of the subjects were Caucasian (53%), 28% were Hispanic, and 20% were black. The most common skin types were Type II (28%) and Type III (30%). Overall, the two application groups (30 and 60 minutes) had similar demographic characteristics, even though the subjects were not randomized to application time.

**Demographics, Safety population (n = 40) – Study SCP-44-05**

Parameter	Category or Statistic	S-Caine	Placebo	Total
Age (year)	N	22	18	40
	Mean ± SD	40.1 ± 14.7	41.6 ± 14.4	40.8 ± 14.4
Gender, N (%)	Female	13 (59)	11 (61)	24 (60)
	Male	9 (41)	7 (39)	16 (40)
Race, N (%)	Black	5 (23)	3 (17)	8 (20)
	Caucasian	11 (50)	10 (56)	21 (53)
	Hispanic	6 (27)	5 (28)	11 (28)
Skin Type, N (%)	I	2 (9)	4 (22)	6 (15)
	II	8 (36)	3 (17)	11 (28)
	III	5 (23)	7 (39)	12 (30)
	IV	1 (5)	1 (6)	2 (5)
	V	3 (14)	1 (6)	4 (10)
	VI	3 (14)	2 (11)	5 (13)

(Adapted from Applicant’s Table 11.1, CSR for Study SCP-44-05, Vol. 12, p. 8-3093)

### Applicant's efficacy results

#### *Primary efficacy endpoint – Mean duration of anesthesia*

Duration of anesthesia was defined as the difference between the onset of anesthesia (the first time that the # painful pinpricks was  $\leq 2$  for two consecutive time points) and the end of anesthesia ((the first time that the # painful pinpricks was  $\geq 3$  for two consecutive time points).

The mean duration of anesthesia for the S-Caine group (i.e. combined 30- and 60-minute applications) was 565 minutes, compared to 99 minutes for the combined placebo group. This difference reached statistical significance ( $p < 0.0001$ ).

#### *Secondary efficacy endpoints*

The Sponsor conducted several efficacy analyses, without adjustment for multiplicity. The results are summarized in the tables below.

##### *a) Mean duration of anesthesia*

###### a. 30-minute application

The mean duration of anesthesia for the 30-minute S-Caine group was 551 minutes (95% CI 459, 643), which was considerably greater than the mean duration for the 30-minute placebo application of 158 minutes (95% CI 51, 265).

###### b. 60-minute application

Similarly, the mean duration for the 60-minute Flexixaine group was longer than that of the 60-minute placebo group: 582 minutes (95% CI 498, 665) vs. 27 minutes (95% CI 3, 51).

###### c. 30- vs. 60-minute S-Caine application

Comparison of the mean duration of anesthesia for the 30- and 60-minute S-Caine groups showed no statistically significant difference ( $p = 0.62$ )

COMMENT: The Applicant noted that because 55% ( $n = 22$ ) of S-Caine subjects and 6% ( $n = 6$ ) of placebo subjects still had anesthesia (i.e.  $\leq 2$  painful pinpricks) at the end of the 780 minute evaluation period, these applications were censored for duration of anesthesia. Therefore, the CIs may underestimate the actual duration of anesthesia, and the width of the CI is probably smaller than it would be if there were no censored data.

##### *b) Median duration of anesthesia*

The median duration of anesthesia was 660 minutes for the combined 30- and 60-minute S-Caine groups, and 0 minutes for the combined placebo applications ( $p < 0.0001$ ). Similar median anesthesia durations were observed for the 30- and 60 minute S-Caine group, with no statistically significant difference observed between them.

Summary of Applicant's duration of anesthesia results, full analysis population\* (n = 40) – Study SCP-44-05

Table 11.4 Anesthesia Summary, Full Analysis Population (N=40)

Parameter	Statistic/ Category	30 min Application S-Caine	30 min Application Placebo	30 min Application P value	60 min Application S-Caine	60 min Application Placebo	60 min Application P value	Total S-Caine	Total Placebo	Total P value
Did Subject Have Anesthesia? *n(%)	Yes	22 (100%)	12 (55%)	0.0020 <sup>a</sup>	18 (100%)	5 (28%)	0.0002 <sup>a</sup>	40 (100%)	17 (43%)	<.0001 <sup>a</sup>
	No	0	10 (45%)		0	13 (72%)		0	23 (58%)	1.00 <sup>b</sup>
Onset of Anesthesia (min)*	N	22	12		18	5		40	17	0.37 <sup>d</sup>
	Mean±SD	87±41	193±223	0.0897 <sup>c</sup>	100±47	354±227	0.0443 <sup>c</sup>	93±44	240±230	0.0082 <sup>c</sup>
	95% CI <sup>e</sup>	69, 106	51, 334		77, 123	72, 636		79, 107	122, 358	
	Median	90.0	45.0		90.0	390.0		90.0	210.0	
	Min,Max	30,180	30,660		60,240	90,690		30,240	30,690	
End of Anesthesia (min)	N	22	12		18	5		40	17	0.45 <sup>d</sup>
	Mean±SD	638±199	483±290	0.10 <sup>e</sup>	682±153	450±209	0.20 <sup>f</sup>	658±179	473±263	0.0297 <sup>e</sup>
	95% CI <sup>e</sup>	550, 727	298, 667		606, 758	191, 709		600, 715	338, 608	
	Median	765.0	465.0		780.0	450.0		780.0	450.0	
	Min,Max	120,780	90,780		330,780	210,780		120,780	90,780	
Duration of Anesthesia (min)*	N	22	22		18	18		40	40	0.62 <sup>d</sup>
	Mean±SD	551±208	158±241	<.0001 <sup>c</sup>	582±168	27±48	<.0001 <sup>c</sup>	565±189	99±191	<.0001 <sup>c</sup>
	95% CI <sup>e</sup>	459, 643	51, 265		498, 665	3, 51		504, 625	38, 160	
	Median	660.0	60.0		675.0	0.0		660.0	0.0	
	Min,Max	60,750	0,750		270,720	0,150		60,750	0,750	
Did subject still have anesthesia at 780 min? * n(%)	Yes	11 (50%)	5 (23%)	0.0703 <sup>a</sup>	11 (61%)	1 (6%)	0.0063 <sup>a</sup>	22 (55%)	6 (15%)	0.0004 <sup>a</sup>
	No	11 (50%)	17 (77%)		7 (39%)	17 (94%)		18 (45%)	34 (85%)	0.54 <sup>b</sup>

<sup>a</sup> McNemar test, compare S-Caine vs. Placebo

<sup>b</sup> Fisher exact test, compare S-Caine 30 min vs. S-Caine 60 min

<sup>c</sup> Paired t test, compare S-Caine vs. Placebo

<sup>d</sup> Two sample t-test, compare S-Caine 30 min vs. S-Caine 60 min

<sup>e</sup> From one-sample t test

<sup>f</sup> If no anesthesia, onset set to missing, duration to 0, end to missing

\* Full analysis population = all subjects who had study drugs applied and had ≥ 1 subsequent efficacy evaluation  
 (Source: Applicant's Table 11.4, CSR for Study SCP-44-05, Vol. 12, p. 8-3086)

c) *Onset of anesthesia*

The mean onset of anesthesia for the combined S-Caine applications was 93 minutes, compared to 240 minutes for the placebo group. The difference was statistically significant ( $p = 0.008$ ). The mean times for onset of anesthesia for the 30-minute S-Caine and placebo applications were 87 and 193 minutes, respectively. Mean onset of anesthesia for the 60-minute application was 100 minutes, vs. 354 minutes for the 60-minute placebo application. There was no statistically significant difference in anesthesia onset times between the 30- and 60-minute S-Caine groups.

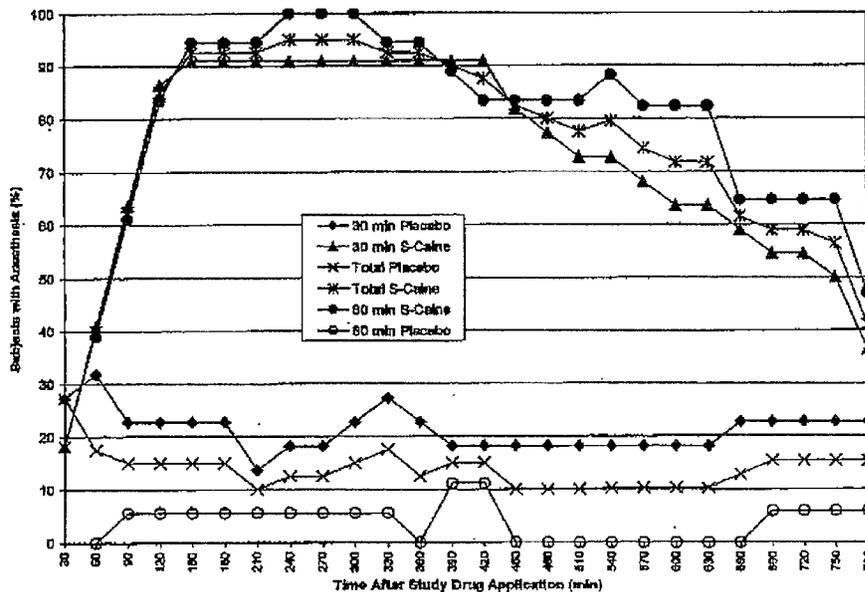
d) *End of anesthesia*

For the combined S-Caine applications, the mean end of anesthesia was 658 minutes, and 473 minutes for the combined placebo applications ( $p = 0.03$ ). End of anesthesia times were statistically similar for the 30- and 60-minute S-Caine groups (638 and 682 minutes, respectively ( $p = 0.45$ )).

As described above, of the combined 30- and 60-minute applications, 55% of S-Caine subjects compared to 23% of placebo subjects still had anesthesia at the end of the study (780 minutes) ( $p = 0.0004$ ). Fifty percent of the 30-minute S-Caine subjects and 61% of the 60-minute S-Caine subjects had persistent anesthesia, and the difference was not statistically significant ( $p = 0.54$ ).

The figure below graphs the percentages of patients with anesthesia at all study time points, including the 780-minute (study end) time point. The S-Caine applications (both individual and combined) consistently had greater anesthesia than did the placebo applications, over the entire duration of the study.

Percentage of subjects with anesthesia by time and treatment – Study SCP-44-05



(Applicant's Figure 11.2, CSR for Study SCP-44-05, Vol. 12, p. 8-3103)

REVIEWER COMMENTS AND ADDITIONAL ANALYSIS

As explained in Section 5.1, the Applicant’s measure for assessing drug effect really evaluated duration of analgesia (i.e. decreased pain sensation), as opposed to anesthesia (total absence of sensation). *Therefore, the Applicant determined times of onset, end, and duration of an analgesic effect for the 30- and 60-minute S-Caine applications.*

ZARS’ efficacy analyses show that both the 30- and 60-minute S-Caine applications resulted in a longer mean duration of analgesia compared to the placebo applications (9.4 hours vs. 1.7 hours). Furthermore, there were no significant numerical or statistical differences in the mean onset, end, and duration of analgesia between the 30- and 60-minute S-Caine applications.

To determine whether the 30- and 60-minute S-Caine applications varied with respect to the degree of analgesia, I calculated the number of patients who reported absolutely no painful sensation (zero painful pinpricks) at key study time points. I considered zero painful pinpricks to be indicative of a complete analgesic effect.

**Reviewer’s analysis of frequency of zero painful pinpricks (i.e. complete analgesia) at selected study time points – Study SCP-44-05**

Time point (post-drug application)	N (%)			
	S-Caine application		Placebo application	
	30 min N = 22	60 min N = 18	30 min N = 22	60 min N = 18
30 min	3 (14%)	0 (0%)	0 (0%)	0 (0%)
120 min (2 h)	12 (54%)	9 (50%)	2 (9%)	1 (6%)
390 min (6.5 h)	15 (68%)	14 (78%)	2 (9%)	0 (0%)
480 min (8 h)	13 (59%)	10 (56%)	1 (4%)	0 (0%)
780 min (13 h) – Study end	4 (18%)	3 (17%)	3 (14%)	0 (0%)

The analysis shows that considerably more S-Caine than placebo patients groups reported zero painful pinpricks (complete analgesia), at each of the selected time points. This was true for both the 30- and 60-minute applications. Additionally, the proportions of patients who had no painful pinpricks were similar for both the 30- and 60-minute S-Caine groups, indicating no difference in analgesic effect between the two applications. The data show that by 2 hours post-dose, at least half of S-Caine-treated patients did not have pain upon pinprick testing.

Almost 20% of both S-Caine 30- and 60-minute patients reported a complete analgesic effect at 13 hours post-dose. In comparison, 14% of the 30-minute placebo patients and 0% of the 60-minute placebo patients reported complete analgesia at study end.

Overall, the data from this study lend further support for the efficacy of S-Caine as a topical analgesic. However, the study does not completely characterize the duration of analgesic effect, since a considerable number of patients reported either partial analgesia ( $\leq 2$  painful pinpricks) or complete analgesia (zero painful pinpricks) at the end of the 13 hour evaluation period.

**11.8 Appendix 8: Study SCP-45-05 – Safety in adults, NDA resubmission**

“An open-label safety study to evaluate the use of S-Caine (lidocaine 7% and tetracaine 7%) in adult patients undergoing a minor or major dermatological procedure.”

Objectives: To evaluate

- The safety of a single administration of S-Caine before a minor/major dermal procedure
- To evaluate the adequacy of anesthesia provided

Study design

This was an open label, single dose trial conducted at 8 sites in the U.S.

Study population and procedures:

Approximately 370 adult patients were to be enrolled. A single dose of S-Caine would be applied to the treatment site for 20-30 minutes (for minor dermal procedures) or 60 minutes (for major procedures). The amount applied would be determined by the size of the treatment area:

Surface area of treatment site (cm <sup>2</sup> )	Length of S-Caine for 1mm thickness (cm)	Weight of S-Caine dispensed (g)
5	1.5	0.5
10	3	1
20	6	3
40	12	5
80	24	11
100	30	13
150	46	20
200	61	26
250	76	33
300	91	40
350	106	46
400	121	53

Eligibility criteria were the same as for Study SCP-40-05 (see Appendix 2).

Minor dermal procedures could be vascular access, collagen injections, pulsed-dye laser therapy, laser-assisted hair removal, and non-ablative laser facial resurfacing.

Permitted major dermal procedures were laser leg vein ablation and laser-assisted tattoo removal.

Study procedures

A dermal treatment area measuring between 5 and 400 cm<sup>2</sup> was to be identified on each eligible subject. S-Caine was to be applied to the area, with the amount dispensed determined by the size of the area. Drug application time would vary by procedure category (minor vs. major).

Clinical Review NDA resubmission  
N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

Immediately following removal of the Peel, investigators were to first perform the standard skin evaluation for erythema, blanching, and edema, and then perform the study procedure. Both subjects and investigators would rate the adequacy of the drug effect (“did this drug provide adequate pain relief for the procedure? (yes/no)” and “did the study drug provide adequate anesthesia for the procedure? (yes/no),” respectively).

Patients were to be discharged with instructions to call the center regarding any reactions at the Peel application site. Follow-up would occur via telephone between 20-72 hours after drug application.

#### Statistical analysis

##### *Safety measures*

- Adverse events
- Skin evaluations (erythema, edema, and blanching – see Appendix 2)

##### *Efficacy measures*

- Patient impression of drug adequacy:  
“Did study drug provide adequate pain relief for the procedure?” (yes/no)
- Investigator impression of drug adequacy  
“Did study drug provide adequate anesthesia for the procedure?” (yes/no)

Both subjects and investigators would be blinded to the other’s evaluation.

#### Protocol amendments

##### *Amendment – August 4, 2005*

The sample size was increased to 410 subjects to achieve the targeted enrollment for patients 65+ years (i.e. to ensure adequate representation of this specific age group).

### **Applicant’s Study Results**

#### Enrollment

The study began on May 2, 1005 and ended on September 28, 2005. Ten U.S. sites participated in the trial.

#### Subject disposition

Altogether, 408 patients were enrolled, 2 of whom withdrew due to an adverse event:

##### **Withdrawals due to adverse events – Study SCP-45-05**

Patient	S-Caine dose/duration	Adverse Event leading to discontinuation
3013 70 yo M	15 minutes 15 cm <sup>2</sup> ; Approx 3 g	Dizziness, diaphoresis, hypotension after 15 minute drug application. Pt reported diarrhea & dehydration prior to procedure
4011 27 yo F	20 minutes 27 cm <sup>2</sup> ; Approx 3 g	Edema at the treatment site (lip area) after drug removal

Protocol deviations

The protocol deviations are listed in the table that follows. No deviation was either serious enough or occurred frequently enough to have adversely affected interpretation of the study results.

**Summary of protocol deviations – Study SCP-45-05**

Deviation	No. Patients
Temperature taken tympanically and not orally	156
Post procedure follow-up conducted outside of 20-72 h window	13
Drug application area outside of the pre-specified range of 5-400 cm <sup>2</sup>	12 <sup>a</sup>
Drug applied outside of the protocol-specified time	10 <sup>b</sup>
Inadequate completion of the Informed Consent form	8
Two different dermal procedures were performed	4
Patient handout not given at the procedure visit	3
S-Caine not applied as directed	1
Blood pressure not taken as part of physical exam	1
Skin evaluation not performed immediately; instead performed 5 min after drug removal	1
Patient did not complete evaluation of adequacy of pain relief	1
Skin evaluation performed after dermal procedure had started	1

<sup>a</sup> The application areas that deviated from the protocol ranged from 1-4 cm<sup>2</sup>

<sup>b</sup> Two patients had an application time of 60 minutes for a minor dermal procedure; 7 patients had application times of 31-40 minutes for a minor dermal procedure; 1 patient had an application time of 62 minutes for a major dermal procedure.

Demographics and Medical History

Sixty nine percent of the patients were female and the mean patient age was 48 years. There was good racial representation, with 73% Caucasian, 19% Hispanic, and 6% Black patients. The predominant skin types were III (35%), II (25%), and IV (24%). The sample’s medical conditions were typical of a population that includes both healthy people and people with a chronic medical condition.

The majority of patients (n=389, 96%) underwent a minor dermatological procedure. The remaining 18 patients (4%) underwent a major procedure. The types of superficial dermatological procedures were lesion removal (57%), injection (15%), dermatologic laser procedure (14%), and vascular access (14%).

Applicant’s Safety Results

*Exposure*

The median/mean application time was ~ 27 minutes. The median and mean application areas were 10 cm<sup>2</sup> and 44 cm<sup>2</sup>, respectively. The chest/back was the most common site of application (29% of patients), followed by the face/scalp (22%), neck (13%), and arm (11%). Drug was also applied to the extremities (hand, leg, foot).

*Adverse events*

Altogether, 96 patients (24%) spontaneously reported at least one AE. There were no deaths or SAEs. Dermatological AEs were the most commonly reported class of events. Other relatively frequent AEs coded that are usually coded under the COSTART terms of “BODY” and “HEMIC AND LYMPHATIC” were reported, however these generally

described an event at the treatment/procedure area. The AEs occurring in at least 1% of patients are listed below

**Adverse events – Study SCP-45-05**

Body System	S-Caine (N, %)
Number of Patients	408 (100%)
Patients with $\geq$ 1 AE	96 (24%)
BODY	23 (6%)
Pain	22 (5%)
HEMIC AND LYMPHATIC	5 (1%)
Echymosis	5 (1%)
SKIN	82 (20%)
Edema	6 (1%)
Erythema	10 (2%)
Petechial rash	8 (2%)
Postoperative wound	53 (13%)

REVIEWER COMMENT: 'Postoperative wound' was the most frequent AE. This reflects an outcome of the dermal procedure, and not treatment with S-Caine. Pain was the next most common AE, but it could have been related to the dermal procedure and not treatment with S-Caine. A petechial rash was described in 2% of patients that could possibly have been due to study drug, and not the dermal procedure.

*Skin AEs (per the Skin Evaluation after drug removal)*

Erythema was observed with the greatest frequency upon skin evaluation (34% of patients). Most areas of erythema were slight to well-defined. Blanching was the next most commonly observed reaction, occurring in 16% of patients and was generally slight with indistinct outline. Edema was the least frequent of the three specific reactions, observed in 5% of patients. There were only 2 cases of moderate-severe edema.

*Efficacy*

Altogether, 69% (n=279) of the patients reported that S-Caine provided adequate pain relief. For 71% (n=290) of patients, investigators stated that the drug provided adequate anesthesia.

REVIEWER'S CONCLUSIONS

S-Caine is generally well-tolerated in patients undergoing a superficial dermal procedure and, for most patients, adequately decreases the pain associated with the procedure.

### **11.9 Appendix 9: Study SCP-47-05 – Safety in pediatrics, NDA resubmission**

“An open-label safety study to evaluate the use of S-Caine (lidocaine 7% and tetracaine 7% cream) in pediatric patients undergoing a minor or major dermal procedure.”

Objectives: To evaluate

- The safety of a single administration of S-Caine over intact skin before a major/minor procedure
- The adequacy of anesthesia provided

Study design

This was a single dose, open-label safety study to be conducted at approximately 5 U.S. sites.

Study population and procedures:

The trial was to enroll about 80 pediatric patients. S-Caine would be applied for 20-30 minutes (minor dermal procedures) or 60 minutes (major dermal procedures), with the amount of drug determined by the size of the area for the dermal procedure.

Eligibility criteria were the same as for Study SCP-40-05 (See Appendix 2), except that patients were included if they:

- Were aged 0 – 17 years, inclusive
- Required a minor or major dermal procedure

Study procedures

Study procedures were the same as for Study SCP-40-05.

Statistical analysis

Safety and efficacy measures were the same as for Study SCP-45-05, except that patients were not asked to rate the adequacy of S-Caine anesthesia.

Protocol amendments

*Key amendments – April 22 and August 3, 2005*

The protocol specified the targeted number of patients per age category, with limitation of enrollment of specific age groups, to ensure adequate representation of the various groups.

### **Applicant's Study Results**

Enrollment

The study started on May 18 and ended on October 4, 2005.

Subject disposition

There were 83 patients who enrolled in the study and were dosed with S-Caine. One patient did not complete the follow-up visit. This was a 2-day old girl who was

Clinical Review NDA resubmission  
N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

administered a 20-minute application of S-Caine prior to a phenylketonuria (PKU) heel stick.

No patients were known to have discontinued due to an adverse event.

#### Protocol deviations

The table below shows the types of protocol violations that were noted. None is likely to have negatively impacted the results of the study.

#### **Protocol deviations – Study SCP-47-05**

<b>Deviation</b>	<b>No. Patients</b>
Informed consent was not properly completed	7
Post-procedure follow-up obtained outside of the 20-72 hour window	3
S-Caine applied outside of the specified 20-30 minute window	1*
Blood pressure not taken as part of the physical exam	1

\* Patient received S-Caine for 13 minutes

#### Demographics and Medical History

The majority of enrolled patients were aged 2-11 years. The mean age of enrollees was 5 years. Most patients were female (70%) and Hispanic patients comprised the largest racial category (46%), followed by Caucasians (35%) and Blacks (14%). Skin types IV and II were the most frequent (36% and 35%, respectively).

About one third of patients (35%) underwent a lesion removal procedure, 20% were given an injection, and 10% (each) underwent a vascular access and dermatologic laser procedures. The remaining 25% of patients underwent a heel stick for PKU testing (n=6) or another type of dermal procedure (n = 15).

#### Applicant's Safety Results

##### *Exposure*

Of the 83 treated patients, 1 received a 13-minute application of S-Caine and the others received a 20-30 minute application. Older patients tended to be exposed for 30 minutes, and younger ones for 20 minutes. The arm, hand, and leg were the most common sites of application (30%, 22%, and 17% of patients, respectively). The median and mean application areas were 8 cm<sup>2</sup> and 16 cm<sup>2</sup>.

##### *Adverse events*

Fourteen patients (17%) had an adverse event. There were deaths or SAEs. There were two systemic events: fever (4%, n=3) and nervousness (1%, n=1). Most AEs were dermal in nature. AEs occurring in at least 1% of patients are listed below:

#### **Adverse events – Study SCP-47-05**

<b>Body System</b>	<b>S-Caine (N, %)</b>
Number of Patients	83 (100%)

Clinical Review NDA resubmission  
 N 21-717, S-Caine (lidocaine and tetracaine 7%/7% cream)

Patients with $\geq 1$ AE	14 (17%)
BODY	4 (5%)
Fever	3 (4%)
Pain	1 (1%)
HEMIC AND LYMPHATIC	2 (2%)
Echymosis	1 (1%)
Purpura	1 (1%)
NERVOUS SYSTEM	1 (1%)
Nervousness	1 (1%)
SKIN	11 (13%)
Edema	4 (5%)
Erythema	2 (2%)
Postoperative wound	6 (7%)
Pruritis	2(2%)

(Source: Applicant's Table 12.4, Study SCP-47-05 CSR, p. 8-4208)

REVIEWER COMMENT: 'Postoperative wound' likely reflects the outcome of the dermal procedure (e.g. lesion removal), and not treatment with S-Caine. The 'HEMIC AND LYMPHATIC' AEs of echymosis and purpura and the 'BODY' AE of pain were not systemic reactions, but rather local reactions at the treatment site.

*Skin AEs (per the Skin Evaluation after drug removal)*

Upon evaluation of the skin using pre-specified criteria, erythema was the most common observed skin reaction (29% of patients), followed by blanching (13%) and edema (6%). There were no moderate-severe cases of erythema or edema. None of the patients had extreme blanching, however 1 (1%) had marked blanching.

*Efficacy*

Investigators reported that S-Caine provided adequate anesthesia for 67% of the patients. One treated patient discontinued lesion removal due to intolerance of pain and was given rescue medication. No other patients were treated with rescue medication.

REVIEWER'S CONCLUSIONS

S-Caine is generally well-tolerated in pediatric patients undergoing superficial dermal procedures.

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MEDICAL OFFICER



## FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS  
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410

### Medical Team Leader Memo

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NDA #	21-717
Related IND #	—
Drug Name	S-Caine Peel
Sponsor	ZARS, Inc.
Proposed Indication	“As a topical anesthetic for local dermal analgesia”
Type of Submission	New Drug Application
Date of Submission	04APR2004
Date of Receipt (CDR)	08APR2004
Review Date	14SEP2004
Primary Reviewer:	Howard Josefberg, MD
Secondary Reviewer	Nancy Chang, MD
Project Manager	Pratibha Rana

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## 1 Background

S-Caine Peel is a eutectic mixture of lidocaine 7% and tetracaine 7% in a cream that forms a pliable peel on the skin when exposed to air. It is intended to provide topical anesthesia for cutaneous procedures.

An NDA for a related product, S-Caine Patch (N21-623) was submitted 4/4/03 and the NDA was found to be approvable primarily due to CMC deficiencies. S-Caine Patch is also a topical local anesthetic product utilizing a eutectic mixture of 70 mg lidocaine and 70 mg of tetracaine contained in a patch with an integrated heating element. Clinical review of this application found that safety and efficacy in adults was demonstrated; however, results in pediatric patients did not consistently demonstrate statistically significant differences between active and placebo treatments, most likely due to underpowering of these studies. In addition, data were not provided to support safety and efficacy in pediatric patients less than 4 months of age, and data describing results of a study of cumulative irritation and sensitization potential were not adequate to permit full review. By prior agreement with the sponsor, because of the similarity in the composition of these products, the cumulative irritation and sensitization study utilizing the S-Caine Patch could be used to support the safety of the S-Caine Peel, and a separate irritation/sensitization study would

not be required using the S-Caine Peel. Similarly, data from the S-Caine Patch NDA demonstrating that lidocaine and tetracaine each contribute to the effects of the drug may be applied to satisfy the Combination Rule for the S-Caine Peel NDA.

Topical lidocaine products have already been approved in concentrations up to 5% and injectable lidocaine products approved in concentrations up to 10%. Tetracaine has been used extensively in clinical practice for decades as an injectable local anesthetic and as a component of various topical anesthetic products; however, it has never been approved by FDA.

## **2 Summary of Efficacy**

The sponsor has conducted 11 clinical studies with efficacy endpoints using their final formulation, 7 in adults, 1 in geriatric patients, and 3 in pediatric patients. See Table 1 below, which was taken and modified from Dr. Josefberg's review.

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**Table 1: Studies Reviewed for Efficacy Findings**

Study	Procedure Type	Population (n) <sup>1</sup>	Design	Site	Duration <sup>2</sup> (minutes)
“Minor”	Dermal Procedures				
20-02	Pulsed Dye Laser Therapy	Adult (30/30)	parallel	face	20
22-02	Laser-Assisted Hair Removal	Adult (50/50)	W-S <sup>3</sup>	face, arm/underarm, bikini area	30
25-02	“Vascular Access”	Adult (55/55)	W-S <sup>3</sup>	antecub	30
26-02	Collagen Injection (Face)	Adult (52/52)	W-S <sup>3</sup>	face	30
27-02	Pulsed Dye Laser Therapy (vs. EMLA 60 min)	Peds 1-3 yrs (40/40)	parallel	face/neck	30
28-02	“Vascular Access”	Peds 3-17 yrs (40/43)	parallel	antecub	30
29-02	Pre-Lidocaine Injection	Peds 3-17 yrs (45/48)	parallel	limbs, trunk, head/neck	30
32-02	Non-Ablative Facial Laser Resurfacing	Adults (41/41)	W-S <sup>3</sup>	face	30
33-02	“Vascular Access”	Geriatric (55/55)	W-S <sup>3</sup>	antecub	30
“Major”	Dermal Procedures				
21-02	Laser-Assisted Tattoo Removal	Adult (30/30)	W-S <sup>3</sup>	?	60
23-02	Laser Ablation of Leg Veins	Adult (60/60)	W-S <sup>3</sup>	leg	60
	Anesthetic Endpoints				
34-03	Duration of Anesthetic Effect	Adult (41/41)	W-S	forearms	30, 60

<sup>1</sup> number of exposures to S-Caine/Placebo. In the within-subject control studies, S-Caine and Placebo treatments were both applied to each subject.

<sup>2</sup>duration of S-Caine peel application

<sup>3</sup>within-subject placebo control

The selected durations of application for S-Caine Peel were based on the results of Phase 2 trials where application duration times varied from 15 minutes to 90 minutes across a limited number of dermal procedures. These studies were generally consistent with an increase in analgesic efficacy with increasing application times up to 90 minutes. The application times selected for study in the pivotal trials generally reflected an attempt to select an effective dosing duration for which further increases in dosing duration were not associated with large incremental analgesic benefits.

## 2.1 Adult Trials

### 2.1.1 "Pivotal" Efficacy Trials

The 7 adult within-subject studies (22-02, 25-02, 26-02, 32-02, 33-02, 21-02, 23-02) were nearly identical in design and also had very similar results. All of these studies were conducted as randomized, double-blind, placebo-controlled studies where the placebo was identical to S-Caine Peel except that it did not contain any local anesthetic (ie lidocaine or tetracaine). Subjects were adults 18 years of age and older, except in study 33-02, which only recruited subjects 65 and older. Subjects were excluded for active atopic

dermatitis, prescription analgesic use within 24 hours, or damaged skin at the treatment site. Each subject received concurrent treatment with both the active and placebo peels. Active or placebo peels were randomly applied either to different areas of the same procedure site (e.g. for laser-assisted hair removal), or to similar but separate treatment sites (e.g. left or right antecubital fossa for vascular access procedures). Duration of peel application was prespecified to be 60 minutes or 30 minutes, for procedures designated by the sponsor as "major" or "minor", respectively. After application, the peel was removed from both treatment and placebo areas, and the investigator would sequentially treat one area, perform efficacy evaluations for that area, and then treat the second area and repeat efficacy evaluations for that area. The primary efficacy variable for each study was the subject's evaluation of pain caused by the procedure on a 100 mm VAS scale. Secondary efficacy endpoints included evaluation of the adequacy of pain relief (yes/no) by the subject and investigator. In addition, the subject was asked if they would choose the drug again, and the investigator and independent observer assessed the amount of pain experienced by the subject using a 4-point categorical scale.

Study 20-02 differed from the within-subject studies primarily in that it utilized a parallel group placebo controlled design. Subjects scheduled to undergo pulsed dye laser treatment of vascular lesions on the face (i.e. port wine stains, hemangiomas, spider angiomas, telangiectasias) were randomized 1:1 to receive a single 20-minute application of S-Caine peel or placebo peel. The placebo peel was the same as for the within-subject studies (i.e. S-Caine peel without local anesthetics). The primary and secondary efficacy measures were the same as for the within-subject studies.

**Table 2: Efficacy results for Adult efficacy studies**

Study	Procedure	Median VAS (mm)		p-value	Secondaries
		S-Caine Peel	Placebo		
20-02 <sup>^</sup>	Pulsed Dye Laser Therapy Face	15	33	<0.001	*
22-02	Laser-Assisted Hair Removal				
25-02	"Vascular Access" <sup>#</sup>				
26-02	Collagen Injection (Face)	16	35.5	<0.001 <sup>b</sup>	*
32-02	Non-Ablative Facial Laser Resurfacing	29.5	58.5	<0.001 <sup>a</sup>	*
33-02	"Vascular Access" <sup>#</sup> (Geriatric)				
21-02	Laser-Assisted Tattoo Removal	38	68	0.001	*
23-02	Laser Ablation of Leg Veins				

<sup>#</sup>In "vascular access" procedure studies, investigators obtained a "flash" of blood in antecubital veins without venous cannulation.

<sup>^</sup>Study 20-02 was a parallel-group control study. All of the other adult pivotal studies were within-subject control studies.

<sup>a</sup>Repeated measures ANOVA with grouping factors of randomization group and center and the repeated measure of treatment

<sup>b</sup>Wilcoxon signed rank test

\* secondary endpoint results were all consistent with an analgesic effect of S-Caine and significant differences were found between S-Caine Peel and placebo groups

\*\*non-significant differences between S-Caine Peel and placebo groups were found, but all differences were "in the right direction", consistent with an analgesic effect of S-Caine

### Summary of efficacy in adults

The differences in median VAS scores between S-Caine and placebo groups (the primary endpoint for these trials) were generally modest but significant. The secondary endpoints also supported an analgesic effect of S-Caine peel in the context of the tested procedures. Because most of the studies were within-subject controlled studies with simultaneous application of S-Caine and placebo, the absolute differences are likely to have been magnified because the subjects were aware that one site was active drug and the other was placebo. Similarly, the differences between placebo and active groups with respect to the secondary outcome measures are likely to have been similarly affected. This idea is supported by analyses in some trials that showed that the VAS score difference varied significantly depending on the order of application and testing for S-Caine vs placebo. Therefore, the usual standards for assessing the clinical relevance of absolute VAS score differences should not be applied in the context of the within-subject trials, and instead, these trials should be viewed as trials to determine whether or not subjects could perceive a difference between test drug and placebo. Nevertheless, in aggregate, the results of the adult trials, 7 within-subject and 1 parallel group, demonstrate that patients can perceive a difference between placebo and active treatments and that S-Caine Peel exerts an analgesic effect in the context of the superficial cutaneous procedures that were studied.

### 2.1.2 Study 34-03 Duration of Anesthetic Effect

This was a randomized, multicenter double-blind placebo controlled study that used pinprick testing to determine the duration of anesthetic effect of S-Caine peel. Forty adult volunteers were randomized 1:1 to receive 30 or 60 minute concurrent applications of S-Caine and placebo peel on separate forearms. Subjects were asked to indicate the number of pinpricks that elicited pain following 10 pinpricks with a 21-gauge needle. Pinprick testing was performed prior to application, immediately after the peel application period, and then at 30-minute intervals until 8 hours after study drug removal. Although telephone follow-up at 24-48 hours was conducted for adverse events, patients were not followed past 8 hours for anesthetic effect.

On average, decreased sensation to pinprick was evident at the time of peel removal, and the maximum anesthetic effect (mean peak effect: <1/10 pinpricks reported as painful) was achieved at approximately 120 minutes after peel removal. At the 8-hour time point, only 16 of 24 subjects had sufficient recovery of sensation to report pain with at least 5 of 10 pinpricks. While mean pinprick scores were slightly lower immediately after a 60-minute application compared to a 30-minute application (6.2 vs. 8.6), the time course of return to sensation was not appreciably different within the limitation of this study.

These data are sufficient to demonstrate that S-Caine Peel produces a decrease in sensation (anesthesia) to the site of application and that this anesthetic effect likely mediates the analgesic effect demonstrated in clinical trials. However, it is insufficient to characterize the time course of anesthesia produced by S-Caine Peel.

## 2.2 Pediatric Trials

### 2.2.1 Placebo-Controlled Studies (28-02 and 29-02)

Trials 28-02 and 29-02 were both randomized, parallel, double-blind, placebo-controlled studies utilizing 30-minute applications of active or placebo peel in pediatric subjects 3-17 years of age. Subjects were randomized 1:1 to receive active or placebo peel prior to antecubital blood draw or IV insertion (study 28-

02) or prior to a medically indicated lidocaine injection (study 29-02). The primary efficacy measure for these studies was an Oucher Self-Assessment Pain Scale. A numeric Oucher Scale using numerical values of 1-100 in increments of 10 was generally used in patients 7-17 years of age. A photographic Oucher Scale (6-point categorical scale utilizing children's faces in various degrees of distress) was generally used in patients 3-6 years of age. The investigator determined the scale to be used based on the patient's ability to perform certain cognitive tasks. A few subjects did use a scale that did not correlate with their chronological age; however, the results of cognitive testing were not documented in these studies.

Other outcome measures included investigator assessment of patient anxiety following peel removal and prior to the procedure, investigator and independent observer assessments of pain, and investigator evaluation of adequacy of anesthesia.

Table 3: Pediatric Primary Efficacy Results, ages 3-17

Study		# subjects S-Caine/placebo	Median Oucher Score <sup>1</sup>		p-value <sup>2</sup>
			S- Caine Peel	Placebo	
<b>28-02</b>	<b>venous access</b>				
	numeric	22/21	0	10	0.003
	photo	18/22	0	10	0.560
<b>29-02</b>	<b>lidocaine injection</b>				
	numeric	19/25			
	photo	26/23			

<sup>1</sup>Numeric Oucher Scale was scored from 0-100 in increments of 10. Photographic Oucher was scored from 0 to 100 in increments of 20.

<sup>2</sup>Mann-Whitney test

Table 4: Pediatric Secondary Efficacy Results, ages 3-17

	S-Caine	Placebo	p-value <sup>a</sup>
<b>Study 28-02 venous access</b>	n = 40	n = 43	
Investigator: No Pain (% subjects)	75	44	0.002
Independent Observer: No Pain	75	58	0.133
Investigator: Adequate Anesthesia	75	44	0.008
<b>Study 29-02 lidocaine injection</b>	n = 45	n = 48	
Investigator: No Pain			
Independent Observer: No Pain			
Investigator: Adequate Anesthesia			

<sup>a</sup> Mantel-Haenszel chi-square test

Study 27-02 was not designed to make a determination of efficacy. Furthermore, because there were no meaningful differences between S-Caine and EMLA arms in this study, and it was not at all clear that even EMLA was effective in this setting, this study does not contribute to the assessment of efficacy in general or in this age group in particular.

Of note, efficacy data for pediatric use of S-Caine Patch were also somewhat inconsistent and inconclusive on review of that NDA.

### **3 Safety**

A total of 619 pediatric and adult subjects received the final S-Caine Peel formulation, and an additional 736 received a developmental formulation that differed from the final formulation only in the inactive ingredients and/or manufacturing process. The safety database for the S-Caine Patch, which also contains a eutectic mixture of 1:1 lidocaine and tetracaine is relevant to the S-Caine Peel, and indeed, some components of that application have been allowed to be applied to the present NDA application: namely, the fixed combination rule and the requirement for a cumulative local irritation/sensitization study.

One study, SCP-05-00, included 10 subjects who received 4 concurrent applications of S-Caine Peel Developmental Formulation A for 15, 30, 45, and 60 minutes. These were the only subjects in the safety database who received multiple exposures, and plasma samples were not obtained in these subjects. There were no studies of repeat exposures to the same site. The majority of subjects (443/619) received a 30-minute exposure of S-Caine Peel. 134 subjects received a 60-minute exposure, and 12 subjects were exposed for 120 minutes. At least 55 subjects ages 65 years of age or older were exposed to S-Caine Peel.

Assessments for local adverse events occurred immediately after removal of S-Caine Peel (and before the dermal procedure), as well as immediately after the dermal procedure. Follow-up for delayed adverse events occurred by telephone contact 24-48 hours after completion of the procedure. Immediately after peel removal, only moderate to severe cases of erythema and edema were recorded as adverse events. During Phase 2 trials (developmental formulations), only events that were not expected outcomes of the dermal procedure were recorded as adverse events. However, during Phase 3 trials (final formulation), all adverse events, whether expected or unexpected, were recorded as adverse events. Thus, the apparent incidence of adverse events appears higher with the final formulation as compared to the developmental formulations.

#### **3.1 Systemic Adverse Events**

All 15 reported systemic adverse events were from trials utilizing the final formulation of S-Caine Peel, and only one AE (headache) was reported as severe. These 15 events occurred in 9 subjects, 6 of which were pediatric patients who received 30-minute applications (of which 2 received placebo). The other 3 subjects who experienced systemic adverse events were adults enrolled in the PK trial 30-02.

There were no serious adverse events or withdrawals due to adverse events in the safety database.

Table 6 Systemic Adverse Events, controlled trials

Body System	COSTART	Final	Placebo*
<hr/>			
Number of Subjects		539	985
<hr/>			
Peds studies 28-02, 29-02			
30-minute applications			
BODY	Headache	1**	0
DIG	Vomiting	1	2
RES	Hyperventilation	1	0
RES	Pharyngitis	1	0
PK study 30-02			
BODY	Headache	2	NA
DIG	Vomiting	1	NA
NER	Dizziness	2	NA
CV	Syncope	1	NA

\* Number of placebo subjects reported here is for all controlled trials, including developmental formulations. NA is listed in the placebo column for the PK study because this study enrolled no placebo subjects

\*\*Single subject who reported 4 headaches ranging from mild to severe is reported here only once.

### 3.2 Local (Dermal) Adverse Events



### **3.3 Continuing or Delayed Adverse Events**

### **3.4 PK**

In adults, systemic exposure to lidocaine increased with increasing surface area of application and with increasing application times up to 400 cm<sup>2</sup> and 120 minutes. The effect of varying the thickness of application was not studied. Systemic levels achieved in elderly subjects were somewhat lower and associated with a somewhat lower C<sub>max</sub> compared to other adult subjects. The highest single C<sub>max</sub> was 217 ng/mL, with T<sub>max</sub> ranging from approximately 2-8 hours.

Although tetracaine levels were not measurable in any adults, tetracaine levels were detectable in 8/33 pediatric subjects despite lower maximum durations and surface areas of exposure. All pediatric exposures were for 30 minutes only, and maximum surface areas of exposure were 10, 30, 50 and 80 cm<sup>2</sup> for age groups premature, 0-2 yrs, 3-6 yrs, and 7-12 years, respectively. Highest levels of lidocaine in pediatric subjects were 55, 71, and 84 ng/mL, all of which were reported in premature infants (and two of which were discounted by the sponsor as outliers). Highest levels of tetracaine were 15, 56, and 93 ng/mL, again with two values discounted as outliers. T<sub>max</sub> for lidocaine in pediatric subjects was 3-7 hours, and T<sub>max</sub> was 1 hour or less for tetracaine.

Despite a much lower surface area of exposure, systemic exposures were greatest in the premature infants compared to the other age groups, and with comparable surface area exposures, systemic exposure was generally greater in the younger age groups compared to the older age groups. Variability in systemic levels and the presence of "outliers" with relatively high systemic levels also generally increased with decreasing age.

Systemic exposure to drug was not demonstrated to "plateau" with exposures of up to 120 minutes and with surface area applications of up to 400 cm<sup>2</sup> in adults. Thus, it must be assumed that longer duration exposures or larger surface area applications are likely to result in greater systemic exposures.

### **3.5 Summary of Safety**

While this product does not appear to have been associated with any major safety concerns, the following limitations should be kept in mind when interpreting the safety results.

### 3.5.1 Limitations of safety database and potential safety concerns

Placebo in all trials was S-Caine peel absent local anesthetic (i.e. lidocaine and tetracaine). Therefore, comparison of adverse events between S-Caine and placebo groups can only distinguish events that may have been caused by the local anesthetics. Adverse events, particularly local adverse events that may have been caused by the inactive ingredients, can not be distinguished from "background". In addition, "final formulation" placebo data are not separated out in these analyses and therefore the placebo data presented include two different sets of criteria for the reporting of adverse events.

Routine examination of skin occurred only immediately after peel removal and immediately after the dermal procedure. Delayed local reactions and effects of S-Caine on healing or effectiveness of repair could not be captured well with the studies as designed. Follow-up after the procedure consisted only of a telephone contact and reporting of events would have been further obscured by the fact that some local skin reaction is expected after most of the procedures tested.

Safety data in younger pediatric patients is limited. A total of 9 pediatric subjects less than 3 years of age were studied in PK trials: 3 premature and 6 who were 0-2 years of age. Controlled trials enrolled 15 pediatric subjects 1 month – 1 year of age, and 7 subjects at 1 year of age. All pediatric exposures were for 30 minutes only and the surface areas of exposure were much less than for adults.

Repeat and multiple exposure data are not available for the final S-Caine Peel formulation. A single trial of 10 subjects entailed simultaneous exposures to a developmental peel, but no PK data were obtained. Cumulative irritation and sensitization study using S-Caine Patch is still incomplete for full review.

Extent of exposure and uniformity of application (and methods for assuring uniformity) of the S-Caine Peel are not well documented in the clinical trials, and data are not available to assess the effects of varying thickness of application or of application of an occlusive dressing to the peel. Special applicators were provided in some studies to aid in achieving a thin 1-mm uniform layer of cream; however, these applicators will not be marketed with the product.

Duration of effect is not well characterized, as the trial designed to examine this question did not follow subjects to resolution of anesthetic effect.

Use of S-Caine Peel in certain anatomic sites such as near mucous membranes and around the eye have not been adequately studied for safety.

Systemic exposure to local anesthetics appears to be much greater in pediatric subjects, particularly in younger age groups.

Prolonged exposure to S-Caine Peel and application to large surface areas may increase risk of local and systemic reactions.

## 4 Ethics and Data Integrity Issues

Following preliminary review of this NDA, DSI was consulted to inspect the study site for study 28-02 when it was found that over half of the enrollment consisted of pediatric subjects from a single site who did not require an IV access procedure. This was done in violation of the protocol.

In addition, DSI was consulted to inspect the sponsor, ZARS, upon discovery of a potential data integrity issue: two columns of efficacy data appeared to have been transposed from the S-Caine Peel column to the placebo column in study 33-02 (Geriatric venous access).

At the time that this memo was completed, a formal written report from DSI is still pending. However, I will summarize my understanding of their current findings based on a teleconference on 9/8/04 with DSI reviewers from headquarters and the DSI field inspector.

DSI inspected one site for study 28-02 that enrolled healthy children who did not require a vascular access procedure. In the course of inspecting ZARS itself, DSI conducted a detailed review of both sites for study 33-02, and a more superficial review of data from other sites and studies.

#### Findings from study 28-02

43 pediatric subjects were enrolled at the inspected site, all under protocol violation (i.e. none required a vascular access procedure). This was done without submitting a formal amendment to the protocol to FDA or to the IRB. Although the medical monitor visited this site three times during the conduct of the study, the violation was not detected or reported until the study was completed.

Medical monitors were not appropriately trained.

Although the investigator is at fault for enrolling subjects under a protocol violation and in violation of ethical principles, ZARS was responsible for the medical monitoring and the inappropriate training of medical monitors for this study (and possibly others). Because the study site is a CRO that is known for recruitment for healthy volunteer studies, the fact of ZARS having contracted with this CRO for this particular study may also bring into question ZARS' involvement and knowledge of this ethical violation.

The PI for this site also was a PI in study 31-02 (PK) for S-Caine Peel as well as one study for the S-Caine Patch NDA.

#### Findings from inspection of ZARS

No QA processes were in place following data lock.

Discrepancies in some cases were found between CRF, CRT, and final study reports.

Drug accountability issues: e.g. labels for study products were produced that could not be accounted for.

Analysis of data after data lock: The particular issue of the transposed data columns in study 33-02 was examined. Apparently, the sponsor examined the results of the first analysis, found that the placebo was apparently more effective than S-Caine Peel and made a decision that the S-Caine and Placebo had been incorrectly assigned. They supported this decision by the fact that S-Caine tubes were generally slightly heavier than placebo tubes, and that the documented weights associated with one column, which was subsequently re-assigned to the S-Caine column, were slightly more than in the other column. However, the source of the error was not documented, and except for the presumptive evidence of identity based on tube weights, there is no primary documentation to definitively determine which treatment was administered in each instance. ZARS' explanation for this event (that the tubes had probably been mislabeled at the plant) less than reassuring. Any mislabeling would have been done by the ZARS central location, and this brings into question the identity of drug that was applied to every subject across all the ZARS studies. The lack of documentation to ascertain the identity of each tube in the face of possible mislabeling is very concerning. Other incidents involving questionable data analysis and reporting practices after data lock were also discovered.

Upon further review of the NDA, Dr. Josefberg has also identified additional issues related to data integrity and questionable data analysis practices and these are discussed further in his review.

## 5 Conclusions

Review of the data submitted to the NDA leads to the conclusion that S-Caine Peel has been demonstrated to be reasonably safe and effective in adults. Questions remain about appropriate uses of this product in pediatrics for which benefit would clearly outweigh risk.

Following their inspection of ZARS, which included detailed inspection of 3 study sites, the DSI inspector discovered serious problems at all 3 sites, leading DSI to conclude that the problems identified should be assumed to be systemic throughout all of the studies sponsored by ZARS. Fundamental issues related to medical monitoring, the inability to definitively identify the treatment given in each circumstance and to questionable data analysis and reporting practices call into question the integrity of the data presented in this application. Based on these findings DSI plans to recommend non-approval of this application and rejection of all of the data submitted.

## 6 Recommendations

I recommend non-approval of S-Caine Peel due to data integrity and ethics issues identified on DSI inspection.

### Further Recommendations

Should further internal deliberations determine that the data should be accepted despite the preliminary recommendations from DSI, I would recommend the following:

1. 

2.

4. 

5.

6.

If a non-approvable is issued, the sponsor should address recommendations for further studies contained in items 2-6 in any future submission.

The previous NDA submission by ZARS for S-Caine Patch will need to be reconsidered in light of the data integrity issues discovered in the course of this review.

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X § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

## MEMORANDUM

Date: September 11, 2004

From: Sara F. Goldkind, M.D., M.A.  
Bioethicist, Office of Pediatric Therapeutics, OC

Through: Dianne Murphy, M.D.  
Director, Office Pediatric Therapeutics, OC

To: Nancy Chang, M.D.  
Team Leader, Division of Anesthetic, Critical Care, and Addiction Drug  
Products (HFD-170), CDER

Subject: Consultation on S-Caine Peel  
NDA 21-717

NB This consultation is being completed in a very short time-frame to accommodate the review division's NDA action date of 9/15/04.

**Date of Consultation:**

September 8, 2004

**Materials Reviewed**

1. Pertinent sections of Protocol Number SCP-28-02: A Randomized, Double-Blind, Placebo controlled Study Evaluating The S-Caine Peel (Lidocaine 7% and Tetracaine 7% Cream) For Induction of Local Dermal Anesthesia for Vascular Access procedures in Pediatric Patients
2. Pertinent sections of Nancy Chang's Secondary Review of S-Caine Peel, 8/27/04
3. T-Con with Nancy Chang, 9/9/04
4. T-Con with Carolann Currier, Reviewer Division of Scientific Investigation, 9/9/04
5. T-Con with DACCADP (HFD-170), DSI, and Ginger Sykes the field inspector, 9/9/04

### **Background**

March 2004 the review division noticed that there were discrepancies between paper and electronic submissions of the data. Additionally, the review division realized that one investigator for Protocol #28-02 enrolled all 43 pediatric patients into the study under a protocol violation without submitting a modification of the protocol to the IRB of record for approval prior to recruitment and enrollment. The protocol states explicitly in section 9.3.1 *Inclusion Criteria* that study eligibility required a vascular access for medical purposes.<sup>1</sup> The investigator in question randomly recruited children from a database of children who did need neither an intravenous catheter nor blood draws.

The review division alerted DSI of this violation. The sponsor, Zars, Inc., and the DSI field inspector went to the investigator's site to monitor and inspect respectively.

### **Question**

Can the data from the pediatric study #28-02 be used in support of the NDA application for this product?

### **Response**

**The data acquired under the protocol violation should not be used in consideration of the NDA application for S-Caine Peel for the following reasons: 1) the investigator disregarded multiple human subject protection mechanisms, and; 2) the investigator disregarded ethical principles in general related to human research and in specific related to pediatric research.**

1. Institutional Review Board (IRB) oversight is one such protection.
  - a. Failure to submit a significant protocol modification, that is the inclusion of children for whom vascular access was **not** a necessity of medical care, violates 21 CFR 56 *Institutional Review Boards*. Delineated functions include, ensuring that changes in approved research may not be initiated without further IRB review and approval.<sup>2</sup>
  - b. Failure to submit this protocol modification means the IRB could not review the changes in accordance with 21 CFR 50, Subpart D *Additional Safeguards for Children in Clinical Investigations*.
  - c. Failure to submit the protocol modifications for IRB reconsideration results in a diminution of IRB to evaluate important criteria for approval, namely, equity of subject selection.<sup>3</sup>
2. The process of informed consent-of which parental permission and assent are derivative-is another protection for research subjects. This process demands that pertinent information (required by the subject to make a reasonable and informed decision) will be provided by the investigator. At a minimum, the informed

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<sup>1</sup> A Randomized, Double-Blind, Placebo controlled Study Evaluating The S-Caine Peel (Lidocaine 7% and Tetracaine 7% Cream) For Induction of Local Dermal Anesthesia for Vascular Access procedures in Pediatric Patients, Protocol Number SCP-28-02, NDA 21-717, page 16.

<sup>2</sup> 21 CFR 56.108 (a)(4).

<sup>3</sup> 21 CFR 56.111 (a)(3).

consent process warrants integrity to the protocol inclusion criteria (must reflect what the protocol actually proposed to do).

3. The informed consent process is a reflection of the ethical principle of autonomy and even more basically of respect for persons. This principle was codified in The Nuremberg Code of 1947, The Belmont Report of 1979, and the Declaration of Helsinki 2000 Revision, and the Code of Federal Regulations 21 CFR 50 Subpart B *Informed Consent of Human Subjects*. Lack of an appropriate informed consent process violates the enumerated ethical documents and regulations.
4. The inclusion of healthy children for whom no vascular access was warranted medically is a gross violation of ethical consensus regarding pediatric research.
  - a. The Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee (11/15/99) issued a consensus statement that *in general, pediatric studies should be conducted in subjects who may benefit from participation in the trial.*<sup>4</sup> The protocol modifications deviated from FDA advisory committee recommendations.
  - b. The National Commission for Protection of Human Subjects of Biomedical and Behavioral Research, states that *procedures should be used for diagnostic or treatment purposes whenever possible.*<sup>5</sup> The investigator's protocol modifications do not satisfy this recommendation. Parenthetically, it is important to note that the recommendations of this Commission are the basis of the present Code of Federal Regulations.
  - c. E11 Clinical Investigation of Medicinal Products in the Pediatric Population<sup>6</sup> offers guidelines regarding the ethical conduct of research in the pediatric population, and suggestions for the minimization of "distress" which are not reflected in the protocol modification.

### **Additional Analysis**

The conclusion to disregard data collected under problematic circumstances, includes these considerations:

1. Risk to future study subjects: the research could be easily replicated in an ethical manner, without incurring undue risk or burden on the patient population requiring vascular access for medical care. The most frequent adverse events were local erythema and edema.<sup>7</sup>
2. Risk to children exposed to the product through off-label use: PK data indicates that for a given surface area there is proportionally more absorption of the drug as age decreases. Therefore, it seems that the maximum dose for children would need to be adjusted downward from the adult dose. Nancy Chang concluded that

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<sup>4</sup> FDA Office of Pediatric Therapeutics website.

<sup>5</sup> Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Research Involving Children, DHEW Publication No. (OS) 77-0004, U.S. Government Printing Office, Washington, D.C., Recommendation 2.

<sup>6</sup> Guidance for Industry, E11 Clinical Investigations of Medicinal Products in the Pediatric Population, ICH, December 2000, 12-4.

<sup>7</sup> Nancy Chang, Medical Team Leader Memo, Secondary Review of S-Caine Peel, 8/27/04, Section 3 Safety.

the “risk of off-label use would probably be small if this information is included in the label.”<sup>8</sup> The review division is currently considering the label. Given this safety inclusion, which can be based upon other ethically obtained PK data, it again seems unnecessary to use unethically derived data to protect children from future exposure to this product.

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<sup>8</sup> T-Con with Carolann Currier, Reviewer Division of Scientific Investigation, 9/9/04 and T-Con with DACCADP (HFD-170), DSI, and Ginger Sykes the field inspector, 9/9/04

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Checking the document in DFS for Sara Goldkind

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 30, 2004

FROM: Gerard G. Nahum, MD  
Pregnancy Labeling Team, OND, HFD-020

THROUGH: Sandra Kweder, MD  
Deputy Director, OND, HFD-020

TO: Bob Rappaport  
DHHS/ FDA/ CDER/ OND/ ODE II/ DACADP, HFD-170  
Division of Anesthetic, Critical Care, and Addiction Drug  
Products, NDA 21-717

SUBJECT: S-Caine Peel (lidocaine 7% and tetracaine 7% cream)  
Pregnancy and Nursing Mothers Section Labeling

Consult received: August 16, 2004  
Due date: August 31, 2004

**I. EXECUTIVE SUMMARY**

The Division of Anesthetic, Critical Care, and Addiction Drug Products has requested that the Pregnancy Labeling Team (PLT) review both the Use in Pregnancy and Nursing Mothers sections of the proposed Package Insert for TetraPeel (AKA S-caine Peel). The proposed labeling that was reviewed was submitted as an Addendum to Nonannotated Package Insert by ZARS, Inc. in 03/04.

TetraPeel is a new topical product that is designed for use as a local skin anaesthetic and is composed of 7% lidocaine and 7% tetracaine in a cream base. It is unique in that it is a combination product that uses both a relatively short acting (lidocaine) and long-acting (tetracaine) local anaesthetic in concert to achieve its topical anaesthetic effects.

There is a long usage history of lidocaine as both a local anaesthetic and as an agent for epidural/ spinal analgesia and anaesthesia during pregnancy. There is also a substantial, but lesser, history of tetracaine use during pregnancy, primarily for spinal/ epidural analgesia and anaesthesia for both control of discomfort during labor and for cesarean section. Based on this human usage experience, as well as on the data from case-control studies that have previously examined the possible teratogenic effects of local anaesthetic use in pregnancy, the PLT has made recommendations to modify the wording of the labeling that has been submitted by the sponsor for TetraPeel.

## **II. BACKGROUND**

The Division of Anesthetic, Critical Care, and Addiction Drug Products has asked the PLT to review both the Use in Pregnancy and Nursing Mothers sections of the proposed Package Insert that was submitted for TetraPeel as an Addendum to Nonannotated Package Insert by ZARS, Inc. in 03/04 (AKA S-caine Peel). TetraPeel is a new topical product that is designed for use as a local skin anaesthetic and is composed of 7% lidocaine and 7% tetracaine in a cream base (NDA 21-717).

It is assumed by the PLT that the animal data provided in the proposed label by ZARS, Inc. concerning the teratogenic and behavioral effects in animals is correct, complete, and properly interpreted. No further review of the animal data included in the proposed label by ZARS, Inc. has been made by the PLT, although relevant supplementary animal data from the literature has been proposed for inclusion in the label.<sup>6-8</sup> The PLT assumes that the information from these three references will be further assessed by the Pharmacology/ Toxicology review team for inclusion in the animal data section of the label. The sections of the current proposed labeling by ZARS, Inc. that are relevant to use during pregnancy and lactation and that have been drawn upon by the PLT in making its recommendations include those entitled "Pharmacokinetics", "Individualization of Dose", "Precautions", "Use in Pregnancy", "Teratogenic Effects", "Labor and Delivery", "Nursing Mothers", "Overdosage", and "Dosage and Administration".

## **III. LITERATURE REVIEWED**

The Addendum to Nonannotated Package Insert for TetraPeel (AKA S-caine Peel) that has been provided by ZARS, Inc. as the revised 03/04 proposed product labeling, and the entries for lidocaine and for tetracaine in TERIS (the Teratogen Information System), REPROTOX, and Shepard's Catalog of Teratogenic Agents have been reviewed, in addition to the individual peer-reviewed articles cited in section IV.

## **IV. RECOMMENDATIONS/ CONCLUSIONS**

Based on the information provided by ZARS, Inc. and a review of the available literature pertaining to the human experience concerning the use of both lidocaine and tetracaine during pregnancy, the PLT recommends:

- (1) that the sponsor clarify the milk:plasma information in the Nursing Mothers section. What is the source of the information and study specifics for defining the milk:plasma ratio as 0.4 in the label (i.e., the sample size, dose and route of lidocaine administration, timing of sampling relative to drug administration, whether the milk:plasma ratio was determined from single time point samples or derived from milk and plasma AUCs, etc.)? Although it is not referenced by the sponsor, it is suspected that the information reported by ZARS, Inc. may be a direct recapitulation of previously published data by Zeisler *et al* that pertains to a single patient who received a 720 mg IV lidocaine bolus with breast milk and lidocaine levels obtained 5-7 hours later (Zeisler JA, Gaarder TD, DeMesquita SA. Lidocaine excretion in breast milk. Drug Intell Clin Pharm 1986;20:691-3), and

- (2) there should be labeling modifications for the Pregnancy and Lactation sections of the Package Insert as shown below. References are included for completeness, but it is not the PLT's expectation that these would all necessarily be included in the product labeling:

**Use in Pregnancy:**

**Teratogenic Effects: Pregnancy Category B.**

**Labor and Delivery:** Neither lidocaine nor tetracaine is contraindicated in labor and delivery. In humans, the use of lidocaine for labor conduction analgesia has not been associated with an increased incidence of adverse fetal effects either during delivery or during the neonatal period.<sup>9-14</sup> Tetracaine has also been used as a conduction anaesthetic for cesarean section without apparent adverse effects on offspring.<sup>15,16</sup> Should TetraPeel be used concomitantly with other products containing lidocaine and/or tetracaine, total doses contributed by all formulations must be considered.

**Nursing Mothers:** Lidocaine is excreted into human milk and it is not known if tetracaine is excreted into human milk. Therefore, caution should be exercised when TetraPeel is administered to a nursing mother since the milk:plasma ratio of lidocaine is 0.4 and is not determined for tetracaine. In a prior report, when lidocaine was used as an epidural anaesthetic for cesarean section in 27 women, a milk:plasma ratio of 1.07 ±0.82 was found by using AUC values.<sup>17</sup> Following single dose administration of 20 mg of lidocaine for a dental procedure, the point value milk:plasma ratio was similarly reported as 1.1 five to six hours after injection.<sup>18</sup> Thus, the estimated maximum total daily dose of lidocaine delivered to the infant via breast milk would be approximately 36 µg/kg. Based on these data and the low concentrations of lidocaine and tetracaine found in the plasma after topical administration of TetraPeel in recommended doses, the small amount of these primary compounds and their metabolites that would be ingested orally by a suckling infant is unlikely to cause adverse effects (see CLINICAL PHARMACOLOGY – Pharmacokinetics).<sup>17-19</sup>

1. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Publishing Sciences Group, Inc. John Wright, Ed. Littleton, Massachusetts, 1977.

2. Sakuma S, Oka T, Okuno A, Yoshioka H, Shimizu T, Ogawa H. Placental transfer of lidocaine and elimination from newborns following obstetrical epidural and pudendal anesthesia. *Pediatr Pharmacol* 1985;5(2):107-15.
3. Kuhnert BR, Philipson EH, Pimental R, Kuhnert PM, Zuspan KJ, Syracuse CD. Lidocaine disposition in mother, fetus, and neonate after spinal anesthesia. *Anesth Analg* 1986;65(2):139-44.
4. Guay J, Gaudreault P, Boulanger A, Tang A, Lortie L, Dupuis C. Lidocaine hydrocarbonate and lidocaine hydrochloride for cesarean section: Transplacental passage and neonatal effects. *Acta Anaesthesiol Scand* 1992;36(7):722-7.
5. Banzai M, Sato S, Tezuka N, Komiya H, Chimura T, Hiroi M. Placental transfer of lidocaine hydrochloride after prolonged continuous maternal intravenous administration. *Can J Anaesth* 1995;42(4):338-40.
6. Smith RF, Wharton GG, Kurtz SL, Mattran KM, Hollenbeck AR. Behavioral effects of mid-pregnancy administration of lidocaine and mepivacaine in the rat. *Neurobehav Toxicol Teratol* 1986;8(1):61-8.
7. Teiling AK, Mohammed AK, Minor BG, Jarbe TU, Hiltunen AJ, Archer T. Lack of effects of prenatal exposure to lidocaine on development of behavior in rats. *Anesth Analg* 1987;66:533-41.
8. Smith RF, Kurkjian MF, Mattran KM, Kurtz SL. Behavioral effects of prenatal exposure to lidocaine in the rat: Effects of dosage and of gestational age at administration. *Neurotoxicol Teratol* 1989;11(4):395-403.
9. Philipson EH, Kuhnert BR, Syracuse CD. Maternal, fetal, and neonatal lidocaine levels following local perineal infiltration. *Am J Obstet Gynecol* 1984;149(4):403-7.
10. Abboud TK, Afrasiabi A, Sarkis F, Daftarian F, Nagappala S, Noueihed R, Kuhnert BR, Miller F. Continuous infusion epidural analgesia in parturients receiving bupivacaine, chlorprocaine, or lidocaine – maternal, fetal, and neonatal effects. *Anesth Analg* 1984;63(4):421-8.
11. Kileff ME, James FM, Dewan DM, Floyd HM. Neonatal neurobehavioral responses after epidural anesthesia for cesarean section using lidocaine and bupivacaine. *Anesth Analg* 1984;63(4):413-7.
12. Preston PG, Rosen MA, Hughes SC, Glosten B, Ross BK, Daniels D, Shnider SM, Dailey PA. Epidural anesthesia with fentanyl and lidocaine for cesarean section: Maternal effects and neonatal outcome. *Anesthesiology* 1988;68(6):938-43.
13. Kuhnert BR, Harrison MJ, Linn PL, Kuhnert PM. Effects of maternal epidural anesthesia on neonatal behavior. *Anesth Analg* 1984;63(3):301-8.
14. Abboud TK, Sarkis F, Blikian A, Varakian L, Earl S, Henriksen E. *Anesth Analg* 1983;62(5):473-5.
15. Hauch MA, Hartwell BL, Hunt CO, Datta S. Comparative effects of subarachnoid hyperbaric bupivacaine and tetracaine-procaine for cesarean delivery. *Reg Anesth* 1990;15920:81-5.
16. Pan PM, Lin ZF, Lim J, Tung MC, Wei TT. The optimal dose of hyperbaric tetracaine spinal anesthesia for cesarean section. *Ma Zui Xue Za Zhi* 1989;27(4):349-52.
17. Ortega D, Viviand X, Lorec AM, Gamarre M, Martin C, Bruguerolle B. Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. *Acta Anaesthesiol Scand* 1999;43(4):394-7.
18. Lebedevs TH, Wojnar-Horton RE, Yapp P, Roberts MJ, Dusci LJ, Hackett LP, Ilett K. Excretion of lignocaine and its metabolite monoethylglycinexylidide in breast milk following its use in a dental procedure: A case report. *J Clin Periodontol* 1993;20(8):606-8.
19. Dryden RM, Lo MW. Breast milk lidocaine levels in tumescent liposuction. *Plast Reconstr Surg* 2000;105(6):2267-8.

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Gerard G. Nahum, MD  
Medical Officer

Concurrence by:

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Kathleen Uhl, MD  
Medical Team Leader

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