

Name of Company: ZARS, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use only)</i>
Name of Finished Product: S-Caine™ Peel (lidocaine 7% and tetracaine 7% cream)		
Name of Active Ingredients: lidocaine 7% and tetracaine 7%		
Title of Study: : A Randomized, Double-Blind, Placebo Controlled, Paired Study Evaluating S-Caine™ Peel (Lidocaine 7% and Tetracaine 7% Cream) for Induction of local dermal anesthesia for Laser-Assisted Tattoo Removal in Adults.		
Investigators and Study Centers: Aesthetic Surgery and Dermatology Private Practice, New York City, NY 10021, USA Laser and Skin Surgery Center of New York, 317 East 34 th Street, New York, New York 10016, USA Gateway Aesthetic Institute and Laser Center 15W. South Temple Suite 400 Salt Lake City, Utah 84101, USA		
Publication (reference): None		
Study Start Date: June 15, 2005 Study Completion Date: September 26, 2005		Phase of Development: 3
Objectives: The primary objective of this study was to evaluate the efficacy of S-Caine Peel when applied for 60 minutes for induction of local dermal anesthesia before Laser-assisted tattoo removal in adults. The secondary objective was to monitor the nature and frequency of adverse events (AEs) associated with the application of S-Caine Peel.		
Methodology: This was a multicenter (3 study sites), randomized, double-blind, placebo controlled, paired study to evaluate the efficacy of S-Caine Peel in providing local dermal anesthesia for laser-assisted tattoo removal in approximately 60 adults. Patients had a screening visit that included: obtaining written consent, evaluating eligibility criteria, obtaining a medical history, a brief physical examination and a urine pregnancy test (for women of childbearing potential). The screening visit could occur on the same day as the procedure visit. At the procedure visit, patients who met the eligibility criteria were randomized to receive a 60-minute (± 2 minutes) application of S-Caine Peel on either the top/right treatment area or bottom/left treatment area and to receive a concurrent 60-minute (± 2 minutes) application of the placebo on the alternate treatment area. The treatment areas were defined as 2 similar anatomical locations that had similar tattoo characteristics. Study drug was applied first to the top/right treatment area, then concurrently to the bottom/left treatment area. Similarly, the study drug was removed first from the top/right treatment area and then was removed from the bottom/left treatment area. Following the removal of the study drugs, the investigator evaluated the skin at each study drug treatment area for erythema, edema, blanching and other skin reactions. The top/right treatment area was evaluated first followed by evaluation of the bottom/left treatment area. After the skin evaluations, the laser procedure was done on the top/right treatment area, followed by the patient and investigator efficacy evaluations for the top/right treatment area. The laser procedure was then done on the bottom/left treatment area, followed by the patient and investigator efficacy evaluations for the bottom/left treatment area. The laser procedure for each treatment area was initially limited to between 10-25 pulses, and the same number of laser pulses and same laser settings were used on both treatment areas. After the laser procedures and efficacy evaluations were completed, the patient received a handout and a verbal explanation of potential delayed skin reactions. The patient was then dismissed from the study center. For the post-procedure follow-up, the patient was contacted between 20-72 hours after study drug application to assess the drug application sites for AEs, including any signs of delayed skin reaction.		
Number of Patients (Planned and Analyzed): Approximately 60 adult patients were planned to be enrolled at 3 study centers. Sixty-three patients enrolled and received treatment with S-Caine Peel and placebo and 62 patients completed the study; 63 were analyzed for safety and 62 were analyzed for efficacy. One patient discontinued the study by withdrawing consent after study drug application but before the laser procedure (reason discontinued was categorized as "other").		
Diagnosis and Main Criteria for Inclusion: Adult patients who were 18 years of age or older and had elected to undergo laser-assisted tattoo removal were eligible to participate in the study. Patients were excluded if they had known allergies, sensitivities or contraindications to lidocaine, tetracaine or other local anesthetics of the amide or ester type or to any components of the test materials		
Test product, dose and mode of administration, batch number: S-Caine Peel, composed of a 1:1 (w:w) eutectic mixture of 7% lidocaine, and 7% tetracaine, was applied topically. The		

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S-Caine Peel was applied at approximately 1 mm in thickness and remained on the treatment area for 60 minutes (±2 minutes). The lot number for S-Caine Peel used in this study was PE-2080		
Duration of Treatment: Patients received a 60-minute concurrent application of S-Caine Peel and placebo.		
Reference Therapy, Dose and mode of Administration, Batch Number: The placebo contained inactive ingredients instead of the active ingredients and was applied topically for 60 minutes (±2 minutes). The placebo was indistinguishable in appearance and texture to the active drug product. The lot number for the placebo formulation used in this study was PE-2084.		
Criteria for Evaluation: Efficacy Variable: The primary efficacy variable was the patient's evaluation of procedural pain intensity using the Visual Analog Scale (VAS). Secondary efficacy variables were the patient's evaluations of: 1) Did this study drug provide adequate pain relief for the procedure? (yes/no); and 2) Would you have topical anesthesia administered using this study drug again if given the option? (yes/no); and the investigator's evaluations of: 3) The patient's procedural pain intensity using a 4-point categorical scale; and 4) Did the study drug provide adequate anesthesia for the procedure? (yes/no). Safety: Safety and tolerability were evaluated based on the frequency of adverse events and on the evaluation of skin reactions. Skin reactions were evaluated after study drug removal using a 5-point categorical scale for erythema (no erythema through severe erythema to slight eschar formation), edema (no edema through severe edema) and blanching (no blanching through extreme blanching with a distinct outline of the treated site). The patient was given a handout and instructed to report onset of any delayed skin reaction following treatment, Patients were contacted 20-72 hours after application of the study drugs to assess the drug application sites for any delayed skin reactions or other adverse events.		
Statistical Methods: Demographic and other baseline data were summarized descriptively. The primary analysis of efficacy was a paired t-test of VAS scores to compare treatments. The secondary analysis of efficacy was an exact McNemar test of secondary efficacy variables. Exploratory analysis of demographic and other baseline data included descriptive statistics by center, Exploratory analysis of efficacy variables included descriptive statistics by center and treatment. Exploratory analysis of the VAS scores was an ANOVA (terms for center, sequence, center by sequence, patient within center by sequence, treatment, period, center by treatment, and center by period). Pairwise comparisons of centers and comparison of treatments within each center were done using least squares means. Exploratory analysis of the secondary efficacy variables compared treatments within each center using an exact McNemar test. Safety data were summarized descriptively by treatment. All statistical tests were two-sided, using a 0.05 level of significance. Missing data were treated as missing for all analyses. There was no adjustment for multiplicity. The full analysis population (patients who had study drug applied and had at least one subsequent efficacy measurement) was used for all efficacy analyses, The safety population (patients who had study drug applied and had at least one subsequent safety assessment) was used for safety, demographics and other baseline data analyses.		
Summary –Conclusions Efficacy Results: S-Caine Peel was effective in providing clinically useful topical anesthesia for laser-assisted tattoo removal in adults. Patient-reported mean VAS pain intensity scores were significantly lower for S-Caine Peel applications than for placebo applications (39.1 vs. 58.6, P<0.0001, paired t test). More patients reported adequate procedural pain relief for S-Caine Peel compared to placebo (53% vs. 18%, P<0.0001, McNemar test). In addition, more patients would have S-Caine Peel administered again for topical anesthesia if given the option, compared to placebo (55% vs. 13%, P<0.0001, McNemar test). Patients were rated by the investigator as having less procedural pain with S-Caine Peel compared to placebo (P<0.0001, McNemar test) and more patients were rated by the investigator as having no pain or slight pain with S-Caine Peel compared to placebo (53% vs. 18%). A greater number of patients were assessed by the investigator as having adequate anesthesia with S-Caine Peel application compared to placebo application (53% vs. 16%, P<0.0001, McNernar test). Safety Results: A concurrent 60-minute application of S-Caine Peel and placebo was well tolerated in this study. During the course of the study (including the 20-72 hour follow-up) a total of 54 patients had adverse events. None of the patients had a serious adverse event. Almost all adverse events were local to the S-Caine Peel treatment area or placebo treatment area; only one patient had an adverse event that was not specific to a		

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treatment area. Most adverse events were considered by the investigator to not be related or unlikely related to study treatment and were generally consistent with what would be expected from laser tattoo removal procedures. Adverse events that were considered at least possibly related to study treatment included erythema (n=5 patients at S-Caine Peel and n=4 patients at placebo treatment area) and pain (n=1 patients at S-Caine Peel and n=1 patient at placebo treatment area). All adverse events were considered by the investigator to be mild or moderate in severity with the exception of 1 patient that experienced adverse events (erythema) at both the S-Caine Peel treatment area and the placebo treatment area that were considered by the investigator to be severe in severity. Skin adverse events were common and occurred in an equal percentage of patients at the S-Caine Peel treatment area and at the placebo treatment area. These included erythema (81% of patients for both S-Caine Peel and placebo treatment areas), edema (57%), petechial rash (scabbing) (38%), vesiculobullous rash (blistering) (19%), skin discoloration (8%), pruritus (3%), and rash (2%). Other adverse events included pain (11% of patients for both S-Caine Peel and placebo treatment areas) and ecchymosis (6% of patients for S-Caine Peel treatment area and 5% for placebo treatment area). At the skin evaluations, erythema was more commonly reported in the S-Caine Peel treatment areas (43% of patients) compared to placebo treatment areas (24%). Edema (one patient each for placebo and S-Caine Peel treatment areas) and blanching (2 patients at each treatment area, placebo and S-Caine Peel) were rare. No moderate or severe erythema, edema or blanching was reported at the evaluation of skin reactions. Conclusion: A 60-minute administration of S-Caine Peel was effective in providing dermal anesthesia for tattoo removal. Patient-reported pain intensity VAS scores were significantly lower for S-Caine Peel vs. placebo applications ($P < 0.0001$, paired t test). All patient and investigator efficacy evaluations significantly and consistently favored S-Caine Peel treatment over placebo treatment (all P values < 0.0001, McNemar test), S-Caine Peel was safe and well tolerated in patients. Most adverse events were considered by the investigator to not be related or unlikely related to study treatment. Adverse events that were considered at least possibly related to study treatment included erythema and pain and these adverse events occurred at both the S-Caine Peel and placebo treatment area. Mild erythema and edema occurred more frequently at S-Caine Peel than placebo application sites.		
Date of report: December 14, 2005		