CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The goal of this application is an indication as a topical local anesthetic for use on normal intact skin for local dermal anesthesia. S-caine is a cream that forms a "pliable peel on the skin when exposed to air." In the clinical studies included in this application, the product was applied for 20-30 minutes for dermal procedures the applicant considered minor, and 60 minutes for dermal procedures considered major.

The applicant completed four prospectively planned, randomized, double-blind, placebo-controlled Phase 3 studies in adults to assess efficacy. In each study, patients were undergoing a different dermal procedure: dermal filler injections on the face, non-ablative facial laser resurfacing, pulsed dye laser therapy, or laser-assisted tattoo removal.

The primary efficacy endpoint was the patient's pain intensity. In all 4 adult studies there was a statistically significant difference in favor of S-caine Peel versus placebo. Four secondary endpoints (two patient and two investigator assessments) also showed support of efficacy. For these endpoints, in all 4 adult studies, S-caine Peel showed a statistically significant difference versus placebo.

This application had been submitted previously (11/03) and had received a Non-approvable action due to data integrity and study ethics concerns. At that time, the Division requested the sponsor redo the efficacy studies in adults and also investigate the efficacy in the children under 12 years of age. A single placebo-controlled study in children ages 5-17 was performed for this current resubmission. In that study, there was not a significant statistical difference between the placebo and S-caine Peel treatment groups. A subgroup analysis of children ages 5-11 showed no support for the efficacy of S-caine Peel in this pediatric population.

In summary, the prospectively planned analyses for the primary efficacy endpoint in adults showed a statistically significant difference in favor of S-caine Peel versus placebo. The secondary endpoints provide supportive evidence of efficacy. However, there was not evidence of efficacy in pediatric patients ages 17 and under. Based on these analyses, there is consistent and sufficient evidence to support the efficacy of S-caine Peel for adults but not for children.

1.2 Brief Overview of Clinical Studies

Table 1 provides brief descriptions of the designs for the clinical studies to assess efficacy. The applicant completed four Phase 3 studies in adults which were prospectively planned to meet the Division's efficacy requirements. In all 4 studies in adults, the single primary efficacy endpoint was patient's pain intensity. Secondary endpoints included patient assessment of adequate pain relief, along with investigator's assessments of pain intensity and adequate relief.

In addition, a single pediatric study was performed to assess efficacy in children ages 5-17.

The efficacy endpoints were similar to the adult studies. The questionnaire for the children to assess pain intensity was different, and was designed and validated to measure pain in children. The investigator's assessments were the same.

All 5 studies were randomized, double-blind, placebo-controlled studies. Three used paired applications of the studies drugs to different areas of skin, while the other two studies used parallel treatment groups. All were prospectively planned to assess the efficacy of S-caine Peel versus placebo.

Table 1: Clinical Trials

Study (# of centers)	Design	Treatment groups (N)	Duration of treatment
SCP-40-05 (3 sites; US)	Randomized, Double-blind, Placebo-control, Paired	Concurrent placebo (n=70)	30 minute application, followed by dermal filler injection on the face
SCP-41-05 (4 sites; US)	Randomized, Double-blind, Placebo-control, Paired	Concurrent placebo (n=54)	30 minute application, followed by non-ablative facial laser resurfacing
SCP-42-05 (5 sites; US)	Randomized, Double-blind, Placebo-control, Parallel Arm	Placebo (n=42 S-caine Peel; n=38 placebo)	20 minute application, followed by pulsed dye laser therapy
SCP-43-05 (3 sites; US)	Randomized, Double-blind, Placebo-control, Paired	Concurrent placebo (n=63)	60 minute application, followed by laser-assisted tattoo removal
SCP-46-05 (3 sites; US) Pediatric study	Randomized, Double-blind, Placebo-control, Parallel Arm	Placebo (n=41 S-caine Peel; n=40 placebo)	30 minute application, followed by a vascular access procedure

1.3 Statistical Issues and Findings

In all 5 studies, the statistical analyses planned in the protocol were appropriate for the study

design and endpoints. There were no changes from the protocols to the analyses presented in the application.

In the 4 studies for use in adults for various dermal procedures, there was statistically significant evidence in favor of S-caine Peel versus placebo for the primary and secondary endpoints. These consistent results support the use of S-caine Peel in adults.

The single study in children did not show statistically significant differences for S-caine Peel versus placebo. It did not provide sufficient evidence to support the use in children.

2. Introduction

2.1 Overview

This statistical review covers four Phase 3 studies in adults (SCP-0-05, SCP-41-05, SCP-42-05, SCP-43-05), and one Pediatric study (SCP-46-05). These are referred to as studies 40, 41, 42, 43, and 46. In all the studies S-caine Peel was compared to placebo. Studies 40, 41, and 42 involved a minor dermatologic procedure and used a 20-30 minute application. Study 43 involved a major dermatologic procedure and used a 60 minute application. Study 46 involved a venous vascular access procedure in children ages 5-17 and used a 30 minute application.

2.2 Data Sources

All data was supplied by the applicant to the electronic data room (edr) in SAS transport format. All necessary documentation, formats, and links were provided as well.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Study SCP-40-05 (conducted 6/05 to 9/05)

Design

Study 40 was a randomized, double-blind, placebo-controlled study using paired application. The primary objective was to assess the efficacy of S-caine Peel for induction of local dermal anesthesia for dermal filler injection in adults. This was considered a minor dermal procedure and used a 30-minute application. During screening, two similar areas on the face were identified for treatment and designated as top/right or bottom/left. Patients were randomized to receive S-caine Peel on one area and a blinded placebo treatment on the other area.

The primary efficacy variable was pain intensity, measured on a 0-100 VAS scale where 0 = no pain and 100 = the worst pain you can imagine. This was recorded immediately following completion of the dermal filler injections in each treatment area. Secondary efficacy variables include patient's evaluation of adequate pain relief (yes/no) and would the patient use this study drug again if given the option (yes/no). Investigator evaluations included assessment of patient's pain intensity (0=no pain; 1=slight pain; 2=moderate pain; 3=severe pain) and evaluation of adequate anesthesia (yes/no). For all endpoints, paired tests were used to compare S-caine Peel to placebo.

This was a multicenter study, with 3 sites, all in the U.S. Site 1 enrolled 14 (20%), site 2 enrolled 21 (30%) and site 3 enrolled 35 (50%) of the patients. Patients were randomized within each site.

Patient Disposition

A total of 70 patients were randomized and completed the study. There were no discontinuations. This was the planned sample size for this study, based on the single primary efficacy endpoint.

Baseline Demographics

The patients enrolled in this study were predominantly female and Caucasian. Demographic characteristics are described in Table 2 below. The patient demographics were similar across all 3 sites.

Table 2: Study 40 - Patient Demographics for All Randomized Patients

	Total (n=70)
Age	
Mean (SD)	50.5 (8.9)
Median	50.0
Range	27, 70
Gender	
Female	67 (96%)
Male	3 (4%)
Race	
Caucasian	66 (94%)
Black	1 (1%)
Hispanic	1 (1%)
Other	2 (3%)
Skin Type	
I Always burns easily, rarely tans	5 (7%)
II Always burns easily, tans minimally	12 (17%)
III Burns moderately, tans gradually	31 (44%)
IV Burns minimally, always tans well	14 (20%)
V Rarely burns, tans profoundly	7 (10%)
VI Never burns, deeply pigmented	1 (1%)

Efficacy Results

The primary efficacy variable is patient's pain intensity, measured using a 0-100 mm VAS scale immediately following the dermal injection procedure. The scale anchors were 0=no pain and 100= the worst pain you can imagine. A lower score represents less pain, and is more favorable. All patients received both S-caine Peel and placebo treatments on different areas of the face, so the comparison is a paired t-test. As shown in Table 3, there was a statistically significant difference in favor of S-caine Peel versus placebo ($p<0.0001$).

There are 4 secondary variables of interest, two assessed by the patient and two assessed by the investigator. The patients endpoints are: Did the study drug provide adequate pain relief for the procedure (yes/no)? and Would you have topical anesthesia administered using this study drug again (yes/no)? Investigators assessed the patient's pain intensity using a 4-point scale (0=no pain; 1=slight pain; 2=moderate pain; 3=severe pain) and assessed if the drug provided adequate anesthesia (yes/no). For these categorical variables, a McNemar test was used to compare S-caine Peel to placebo. For all 4 endpoints, the results indicate a statistically significant difference in favor of S-caine Peel versus placebo. These results are shown in Table 3.

The efficacy results were compared for the 3 sites. For all 5 endpoints, the results were similar across the sites.

The results from study 40 indicate that S-caine Peel is effective for local anesthesia for facial dermal filler injection in adults.

Table 3: Study 40 – Efficacy Results for All Randomized Patients

Efficacy Variable:		S-caine Peel	Placebo	Difference	p-value
Primary: Patient's pain intensity VAS 0-100	N Mean (SD) Median Min, Max	70 24 (18) 22 1, 79	70 37 (24) 33 1, 91	 -13 (23)	 <0.0001 *
Secondary - Patient Assessments	N	70	70		
Adequate pain relief?	Yes No	46 (66%) 24 (34%)	30 (43%) 40 (57%)	23%	0.0052 **
Would use study drug again?	Yes No	47 (67%) 23 (33%)	33 (47%) 37 (53%)	20%	0.0094 **
Secondary - Investigator Assessments	N	70	70		
Assessment of pain	No pain Slight pain Mod. Pain Severe pain	25 (36%) 33 (47%) 12 (17%) 0 (0%)	11 (16%) 26 (37%) 30 (43%) 3 (4%)	20% 10% -26% -4%	<0.0001 **
Adequate anesthesia?	Yes No	55 (79%) 15 (21%)	36 (51%) 34 (49%)	28%	0.0013 **

* Paired t-test
** McNemar test

Study SCP-41-05 (conducted 6/05 to 9/05)

Design

Study 41 was a randomized, double-blind, placebo-controlled study using paired application. The primary objective was to assess the efficacy of S-caine Peel for providing local dermal anesthesia for non-ablative facial laser resurfacing in adults. This was considered a minor dermal procedure and used a 30-minute application. Patients were randomized to receive S-caine Peel on either the left or right side of the face, and a blinded placebo treatment on the opposite side.

The primary efficacy variable was pain intensity, measured on a 0-100 VAS scale where 0 = no pain and 100 = the worst pain you can imagine. This was recorded immediately following completion of the laser procedure in each treatment area. Secondary efficacy variables include patient's evaluation of adequate pain relief (yes/no) and would the patient use this study drug again if given the option (yes/no). Investigator evaluations included assessment of patient's pain intensity (0=no pain; 1=slight pain; 2=moderate pain; 3=severe pain) and evaluation of adequate anesthesia (yes/no). For all endpoints, paired tests were used to compare S-caine Peel to placebo.

This was a multicenter study, with 4 sites, all in the U.S. Of the 54 patients enrolled, site 1 enrolled 6 (11%), site 2 enrolled 16 (30%), site 3 enrolled 19 (35%), and site 4 enrolled 13 (24%) of the patients. Patients were randomized within each site.

Patient Disposition

A total of 54 patients were randomized and completed the study. There were no discontinuations. The applicant planned for a sample size of 50 patients, based on the single primary endpoint.

The laser procedure was stopped prematurely due to pain on the S-caine treated area for 1 patient and on the placebo treated area for 4 patients. In all cases efficacy measures were assessed prior to use of any rescue medication for pain.

Baseline Demographics

The patients enrolled in this study were predominantly female and Caucasian. Demographic characteristics are described in Table 4 below. The patient demographics were similar across all 4 sites.

Table 4: Study 41 - Patient Demographics for All Randomized Patients

	Total (n=54)
Age	
Mean (SD)	42.3 (14.1)
Median	45.5
Range	18, 75
Gender	
Female	42 (78%)
Male	12 (22%)
Race	
Caucasian	51 (94%)
Asian	1 (1%)
Black	1 (1%)
Hispanic	1 (1%)
Skin Type	
I Always burns easily, rarely tans	5 (9%)
II Always burns easily, tans minimally	24 (44%)
III Burns moderately, tans gradually	14 (26%)
IV Burns minimally, always tans well	10 (19%)
V Rarely burns, tans profoundly	0 (0%)
VI Never burns, deeply pigmented	1 (2%)

Efficacy Results

The primary efficacy variable is patient's pain intensity, measured using a 0-100 mm VAS scale immediately following the laser procedure. The scale anchors were 0=no pain and 100= the worst pain you can imagine. A lower score represents less pain, and is more favorable. All patients received both S-caine Peel one side of the face and placebo on the other side, so the comparison is a paired t-test. As shown in Table 5, there was a statistically significant difference in favor of S-caine Peel versus placebo ($p<0.0001$).

There are 4 secondary variables of interest, two assessed by the patient and two assessed by the investigator. The patients endpoints are: Did the study drug provide adequate pain relief for the procedure (yes/no)? and Would you have topical anesthesia administered using this study drug again (yes/no)? Investigators assessed the patient's pain intensity using a 4-point scale (0=no pain; 1=slight pain; 2=moderate pain; 3=severe pain) and assessed if the drug provided adequate anesthesia (yes/no). For these categorical variables, a McNemar test was used to compare S-caine Peel to placebo. For all 4 endpoints, the results indicate a statistically significant difference in favor of S-caine Peel versus placebo, as shown in Table 5.

The results were compared across the 4 sites. For the three patient reported outcomes, the results were consistent across the 4 sites, with the treatment effect being in favor of S-caine Peel. For the two investigator endpoints, in Sites 1-3, a similar pattern of results in favor of

S-caine Peel were observed. However, in Site 4 the placebo treatment was assessed as being equal to the S-caine Peel group on the investigator o utcomes. Since the overall results were highly significant, the Site 4 results do not impact the conclusions from this study.

The results from study 41 indicate that S-caine Peel is effective for local anesthesia for non-ablative facial laser resurfacing in adults.

Table 5: Study 41 – Efficacy Results for All Randomized Patients

Efficacy Variable:		S-caine Peel	Placebo	Difference	p-value
Primary: Patient's pain intensity VAS 0-100	N Mean (SD) Median Min, Max	54 21 (19) 16 0, 71	54 38 (24) 36 1, 89	-17 (28)	<0.0001 *
Secondary - Patient Assessments	N	54	54		
Adequate pain relief?	Yes No	45 (83%) 9 (17%)	20 (37%) 34 (63%)	25%	<0.0001 **
Would use study drug again?	Yes No	45 (83%) 9 (17%)	21 (39%) 33 (61%)	24%	<0.0001 **
Secondary - Investigator Assessments	N	54	54		
Assessment of pain	No pain Slight pain Mod. Pain Severe pain	25 (46%) 22 (41%) 6 (11%) 1 (2%)	17 (31%) 15 (28%) 16 (30%) 6 (11%)	8% 7% -10% -5%	0.0005 **
Adequate anesthesia?	Yes No	47 (87%) 7 (13%)	30 (56%) 24 (44%)	17%	<0.0001 **

* Paired t-test
** McNemar test

Study SCP-42-05 (conducted 6/05 to 10/05)

Design

Study 42 was a randomized, double-blind, placebo-controlled, parallel arm study. The primary objective was to evaluate the efficacy of S-caine Peel for induction of local dermal anesthesia before pulse dye laser (PDL) therapy in adults. This was considered a minor dermal procedure and used a 20-minute application. All patients were undergoing PDL therapy for vascular lesions on the face. Patients were randomly assigned to receive either S-caine Peel or a blinded placebo.

The efficacy assessments were based on the initial 25-125 laser pulses of the PDL procedure. The procedure was stopped for all efficacy outcomes to be completed by the patient and investigator. If necessary, the PDL procedure would then be continued.

The primary efficacy variable was pain intensity, measured on a 0-100 VAS scale where 0 = no pain and 100 = the worst pain you can imagine. Secondary efficacy variables include patient's evaluation of adequate pain relief (yes/no) and would the patient use this study drug again if given the option (yes/no). Investigator evaluations included assessment of patient's pain intensity (0=no pain; 1=slight pain; 2=moderate pain; 3=severe pain) and evaluation of adequate anesthesia (yes/no). For the continuous variable (VAS), a 2-sample t-test was used to compare S-caine to placebo. For the categorical variables, the Fisher or Wilcoxon exact tests were used for the comparisons.

This was a multicenter study, with 5 sites, all in the U.S. Table 6 shows the enrollment by site. Patients were randomized within each site.

Table 6: Study 42 – Enrollment by Site

Site	S-caine (N=42)	Placebo (N=38)	Enrolled (N=80)
1	5	4	9 (11%)
2	1	0	1 (1%)
3	3	2	5 (6%)
4	13	12	25 (31%)
5	20	20	40 (50%)

Patient Disposition

Of the 80 subjects randomized, 79 completed the study. In the protocol, the planned sample size was 40 patients per treatment arm, for a total of 80.

The single discontinuation was in the placebo group. The patient received treatment but did not undergo the laser procedure.

Baseline Demographics

The patients in this study were predominantly female and Caucasian. Demographic characteristics are described in Table 7.

The sites were dissimilar on two of the demographic variables. Site 4 had more males (64%) than females (36%), while the other sites had more females (73%) than males (27%). More patients at Site 5 had higher skin type rankings than at the other sites. Of the patients at Site 5, only 8% had skin type I or II, while the other sites had 78% of patients with skin type I or II. These differences between the sites did not shown any differences in treatment effect across the sites.

Table 7: Study 42 - Patient Demographics for All Randomized Patients

	S-caine (n=42)	Placebo (n=38)
Age		
Mean	46.8	50.8
(SD)	(14.5)	(14.2)
Median	47.5	50.5
Range	21, 78	20, 81
Gender		
Female	27 (64%)	22 (58%)
Male	15 (36%)	16 (42%)
Race		
Caucasian	40 (95%)	38 (100%)
Asian	1 (2%)	0 (0%)
Hispanic	1 (2%)	0 (0%)
Skin Type		
I Always burns easily, rarely tans	0 (0%)	1 (0%)
II Always burns easily, tans minimally	17 (40%)	16 (40%)
III Burns moderately, tans gradually	17 (40%)	12 (40%)
IV Burns minimally, always tans well	5 (12%)	8 (12%)
V Rarely burns, tans profoundly	3 (7%)	1 (7%)
VI Never burns, deeply pigmented	0 (0%)	0 (0%)

Efficacy Results

The primary efficacy variable is patient's pain intensity, measured using a 0-100 mm VAS scale immediately following the initial 25-125 laser pulse of the procedure. The scale anchors were 0=no pain and 100= the worst pain you can imagine. A lower score represents less pain, and is more favorable. As shown in Table 8, there was a statistically significant difference in favor of S-caine Peel versus placebo (p=0.0008).

There are 4 secondary variables of interest, two assessed by the patient and two assessed by the investigator. The patients endpoints are: Did the study drug provide adequate pain relief for the procedure (yes/no)? and Would you have topical anesthesia administered using this study drug again (yes/no)? Investigators assessed the patient's pain intensity using a 4-point scale (0=no pain; 1=slight pain; 2=moderate pain; 3=severe pain) and assessed if the drug provided adequate anesthesia (yes/no). For the yes/no questions, Fisher's exact test was used for comparison, and for the 4-point scale Wilcoxon's exact test was used. For all 4 endpoints, the results indicate a statistically significant difference in favor of S-caine Peel versus placebo, as shown in Table 8.

For comparisons between sites, the three sites with small enrollments (sites 1, 2, and 3) were combined. This was not discussed in the protocol. There is no indication that the decision was based on anything except sample size, and the combined site has a total of 15 patients, less than either of the sites with higher enrollment (Site 4 = 25; Site 5 = 40). Comparisons across the sites showed similar treatment effects for the 5 efficacy variables.

The results from study 42 indicate that S-caine Peel is effective for local anesthesia for pulse laser dye therapy in adults.

Table 8: Study 42 – Efficacy Results for All Randomized Patients

Efficacy Variable:		S-caine Peel	Placebo	Difference	p-value
Primary: Patient's pain intensity VAS 0-100	N Mean (SD) Median Min, Max	42 16 (20) 11 0, 84	37 31 (17) 30 4, 81	 -15 (18)	0.0008 *
Secondary - Patient Assessments	N	42	37		
Adequate pain relief?	Yes No	38 (90%) 4 (10%)	22 (59%) 15 (41%)	31%	0.0016 **
Would use study drug again?	Yes No	38 (90%) 4 (10%)	24 (65%) 13 (35%)	25%	0.0069 **
Secondary - Investigator Assessments	N	42	37		
Assessment of pain	No pain Slight pain Mod. Pain Severe pain	28 (67%) 13 (31%) 1 (2%) 0 (0%)	8 (22%) 22 (59%) 7 (19%) 0 (0%)	45% -28% -17%	<0.0001 ***
Adequate anesthesia?	Yes No	39 (93%) 3 (7%)	24 (65%) 13 (35%)	28%	0.0040 **

* Two sample t-test
** Fisher exact test
*** Wilcoxon exact test

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Study SCP-43-05 (conducted 6/05 to 9/05)

Design

Study 43 was a randomized, double-blind, placebo-controlled study using paired application. The primary objective was to assess the efficacy of S-caine Peel when applied for 60 minutes for induction of local dermal anesthesia prior to laser-assisted tattoo removal in adults. This was considered a major dermal procedure.

The area for tattoo removal was divided into top/right and bottom/left treatment areas, each with similar anatomical locations and tattoo characteristics. Patients were randomized to receive S-caine Peel on either the top/right or bottom/left treatment area, and a blinded placebo on the opposite area. For each treatment area, the initial laser procedure of 10-25 pulses was assessed for efficacy. After the limited 10-25 pulses, the procedure was stopped for all the efficacy assessments on one area. Next the initial 10-25 laser pulses were done on the other area then stopped to complete the efficacy assessments. After all efficacy assessments were completed, the laser procedure continued for the tattoo removal.

The primary efficacy variable was pain intensity, measured on a 0-100 VAS scale where 0 = no pain and 100 = the worst pain you can imagine. This was recorded immediately following completion of the laser procedure in each treatment area. Secondary efficacy variables include patient's evaluation of adequate pain relief (yes/no) and would the patient use this study drug again if given the option (yes/no). Investigator evaluations included assessment of patient's pain intensity (0=no pain; 1=slight pain; 2=moderate pain; 3=severe pain) and evaluation of adequate anesthesia (yes/no). For all endpoints, paired tests were used to compare S-caine Peel to placebo.

This was a multicenter study, with 4 sites, all in the U.S. One site (#3) was discontinued before any patients were enrolled. Of the 63 patients enrolled, site 1 enrolled 26 (41 %), site 2 enrolled 4 (6%), and site 4 enrolled 133 (52%) of the patients. Patients were randomized within each site.

Patient Disposition

A total of 63 patients were randomized and 62 completed the study. The applicant's planned sample size was 60 patients, based on the single primary endpoint.

The only discontinuation had Other listed as the reason. That patient withdrew consent after application of the study drug but prior to the start of the laser-assisted tattoo removal procedure. Of patients who started the laser procedure, none stopped prior to completing the initial 10-25 pulses for the efficacy assessments on each treatment area.

Baseline Demographics

The patients enrolled in this study were predominantly female and Caucasian. Demographic characteristics are described in Table 9 below. The patient demographics were similar across all 3 sites which enrolled patients.

Table 9: Study 43 - Patient Demographics for All Randomized Patients

	Total (n=63)
Age	
Mean (SD)	33.0 (11.2)
Median	30.0
Range	20, 67
Gender	
Female	47 (75%)
Male	16 (25%)
Race	
Caucasian	47 (75%)
Asian	3 (5%)
Black	1 (2%)
Hispanic	9 (14%)
Other	3 (5%)
Skin Type	
I Always burns easily, rarely tans	2 (3%)
II Always burns easily, tans minimally	9 (14%)
III Burns moderately, tans gradually	25 (40%)
IV Burns minimally, always tans well	26 (41%)
V Rarely burns, tans profoundly	1 (2%)
VI Never burns, deeply pigmented	0 (0%)

Efficacy Results

The primary efficacy variable is patient's pain intensity, measured using a 0-100 mm VAS scale immediately following the initial 10-25 pulse laser procedure. The scale anchors were 0=no pain and 100= the worst pain you can imagine. A lower score represents less pain, and is more favorable. All patients received both S-caine Peel one section of the tattoo removal area and placebo on the other section, so the comparison is a paired t-test. As shown in Table 10, there was a statistically significant difference in favor of S-caine Peel versus placebo ($p<0.0001$).

There are 4 secondary variables of interest, two assessed by the patient and two assessed by the investigator. The patients endpoints are: Did the study drug provide adequate pain relief for the procedure (yes/no)? and Would you have topical anesthesia administered using this study drug again (yes/no)? Investigators assessed the patient's pain intensity using a 4-point scale (0=no pain; 1=slight pain; 2=moderate pain; 3=severe pain) and assessed if the drug provided adequate anesthesia (yes/no). For these categorical variables, a McNemar test was used to compare S-caine Peel to placebo. For all 4 secondary endpoints, the results indicate a statistically significant difference in favor of S-caine Peel versus placebo, as shown in Table 10.

The results were compared across the 3 sites which enrolled patients. For all 5 endpoints, the

results were similar, in favor of S-caine Peel versus placebo, across the sites .

The results from study 43 indicate that S-caine Peel is effective for local anesthesia for pulsed dye laser tattoo removal in adults.

Table 10: Study 43 – Efficacy Results for All Randomized Patients

Efficacy Variable:		S-caine Peel	Placebo	Difference	p-value
Primary: Patient's pain intensity VAS 0-100	N Mean (SD) Median Min, Max	62 39 (25) 32 2, 88	62 59 (22) 62 0, 98	 -20 (28)	<0.0001 *
Secondary - Patient Assessments	N	62	62		
Adequate pain relief?	Yes No	33 (53%) 29 (47%)	11 (18%) 51 (82%)	24%	<0.0001 **
Would use study drug again?	Yes No	34 (55%) 28 (45%)	8 (13%) 54 (87%)	26%	<0.0001 **
Secondary - Investigator Assessments	N	62	62		
Assessment of pain	No pain Slight pain Mod. Pain Severe pain	8 (13%) 25 (40%) 21 (34%) 8 (13%)	3 (5%) 8 (13%) 28 (45%) 23 (37%)	8% 17% -7% -18%	<0.0001 **
Adequate anesthesia?	Yes No	33 (53%) 29 (47%)	10 (16%) 52 (84%)	23%	<0.0001 **

* Paired t-test
** McNemar test

Study SCP-46-05 (conducted 6/05 to 10/05)

Design

Study 46 was a randomized, double-blind, placebo-contr olled, parallel arms study in children ages 5-17. The primary objective of the study was to evaluate the efficacy of S-caine Peel in providing local derm al anesthesia before a venous vascular access procedure. A 30-minute application was used. Patients were randomized to receive either S-caine Peel or blinded placebo.

Efficacy was based on the first attempt to gain vascular access. If the first attempt not successful, the procedure was stopped to complete the efficacy assessments. Further attempts at vascular access would then be continued.

Because the patients were children, the measurement tool for the primary efficacy endpoint used a Colored Analog Scale (CAS) rather than the VAS used in the studies of adults. The primary efficacy variable was pain intensity, measured on a 0-10 CAS scale where 0 = no pain and 10 = the most pain. For this variable, a 2-sample t-test was used to compare S-caine to placebo.

The two secondary endpoints were the investigator's evaluation assessment of patient's pain intensity (0=no pain; 1=slight pain; 2=moderate pain; 3=severe pain) and evaluation of adequate anesthesia (yes/no). For these categorical variables, the Fisher or Wilcoxon exact tests were used for the comparisons.

This was a multicenter study, with 3 sites, all in the U.S. Table 11 shows the enrollment by site. Patients were randomized within each site.

Table 11: Study 46 – Enrollment by Site

Site	S-caine (N=41)	Placebo (N=40)	Enrolled (N=81)
1	21	21	42 (52%)
2	17	16	33 (41%)
3	3	3	6 (7%)

Patient Disposition

Of the 81 subjects randomized, 80 completed the study. In the protocol, the planned sample size was 40 patients per treatment arm, for a total of 80.

The single discontinuation was in the placebo group. The patient received treatment but did not undergo the venous access procedure.

Baseline Demographics

The treatment groups were well balanced across the demographic characteristics, listed in Table 12. The two age subgroups, 5-11 and 12-17, are of interest to the Medical Officer for

looking at the efficacy results.

The 3 sites were compared on the demographic variables, with one notable difference. Site 3 enrolled 6 patients, all in the 12-17 age group. In Sites 1 and 2, 44% of patients were in the 5-11 age group and 56% were in the 12-17 age group. Since Site 3 had much smaller enrollment, this imbalance did not impact the efficacy results.

Table 12: Study 46 - Patient Demographics for All Randomized Patients

	S-caine (n=41)	Placebo (n=40)
Age		
Mean	11.9	11.9
(SD)	(3.7)	(3.2)
Median	13.0	12.5
Range	5, 17	5, 17
Age group		
5-11 years	17 (41%)	16 (40%)
12-17 years	24 (59%)	24 (60%)
Gender		
Female	17 (41%)	20 (50%)
Male	24 (59%)	20 (50%)
Race		
Caucasian	12 (29%)	15 (38%)
Asian	0 (0%)	1 (3%)
Black	19 (46%)	14 (35%)
Hispanic	7 (17%)	10 (25%)
Other	3 (7%)	0 (0%)
Skin Type		
I Always burns easily, rarely tans	0 (0%)	3 (8%)
II Always burns easily, tans minimally	2 (5%)	2 (5%)
III Burns moderately, tans gradually	5 (12%)	4 (10%)
IV Burns minimally, always tans well	11 (27%)	10 (25%)
V Rarely burns, tans profoundly	16 (39%)	13 (33%)
VI Never burns, deeply pigmented	7 (17%)	8 (20%)

Efficacy Results

The primary efficacy variable is patient's pain intensity, measured using a 0-10 CAS scale immediately following the first attempt of the venous access procedure. The scale anchors were 0=no pain and 10 0=the most pain. A lower score represents less pain, and is more favorable. As shown in Table 13, there was not sufficient evidence of a difference between S-caine Peel versus placebo (p=0.64).

There are 2 secondary variables of interest. These are the investigator's assessment of

patient's pain intensity using a 4-point scale (0=no pain; 1=s light pain; 2=moderate pain; 3=severe pain) and if the drug provided adequate anesthesia (yes/no). For the 4-point scale the Wilcoxon's exact test was used for comparison and for the yes/no question Fisher's exact test was used for comparison. For both endpoints, there is not sufficient evidence to show a difference between S-caine Peel versus placebo, as shown in Table 13.

The Medical Officer requested the efficacy results by age subgroups: 5-11 years old and 12-17 years old. These are shown in Table 14. There is no notable age effect on the efficacy outcomes, and this does not provide any evidence to support efficacy of S-caine Peel for use in children.

Comparisons across the sites showed similar treatment effects for the 3 efficacy variables.

The results from study 46 indicate that S-caine Peel has not been shown to be effective for local anesthesia for a venous vascular access procedure in children.

Table 13: Study 46 – Efficacy Results for All Randomized Patients

Efficacy Variable:		S-caine Peel	Placebo	Difference	p-value
Primary: Patient's pain intensity CAS 0-10	N Mean (SD) Median Min, Max	41 1.8 (2.5) 0.8 0, 9.5	39 2.0 (2.3) 1.5 0, 8.5	 -0.3 (2.4)	 0.64 *
Secondary - Investigator Assessments	N	41	39		
Assessment of pain	No pain Slight pain Mod. Pain Severe pain	23 (56%) 11 (27%) 6 (15%) 1 (2%)	24 (62%) 11 (28%) 2 (5%) 2 (5%)	-1% 4% -3%	0.56 ***
Adequate anesthesia?	Yes No	28 (68%) 13 (32%)	28 (72%) 11 (28%)	-4%	0.81 **

* Two sample t-test
** Fisher exact test
*** Wilcoxon exact test

Table 14: Study 46 – Subgroup Analysis by Age Group

Efficacy Variable:		Age 5-11		Age 12-17	
		S-Caine	Placebo	S-Caine	Placebo
Primary: Patient's pain intensity CAS 0-10	N Mean (SD) Median Min, Max	17 1.8 (2.6) 0.3 0, 9.5	16 1.4 (1.8) 0.3 0, 5	24 1.8 (2.4) 0.9 0, 8	23 2.4 (2.6) 1.8 0, 8.5
Secondary - Investigator Assessments	N	17	16	24	23
Assessment of pain	No pain Slight pain Mod. Pain Severe pain	11 (65%) 3 (18%) 2 (12%) 1 (6%)	13 (81%) 2 (13%) 1 (6%) 0	12 (50%) 8 (33%) 4 (17%) 0	11 (48%) 9 (39%) 1 (4%) 2 (9%)
Adequate anesthesia?	Yes No	12 (71%) 5 (29%)	14 (88%) 2 (13%)	16 (67%) 8 (33%)	14 (61%) 9 (39%)

3.2 Evaluation of Safety

The Medical Officer did not request any safety analyses, and no safety issues were identified during the review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

Subgroup analyses for gender and race were conducted for each study. There were no notable differences in treatment effects for these characteristics in any of the studies.

4.2 Other Special/Subgroup Populations

The primary concern about age was whether the applicant provided information to support the use of S-caine Peel in children. Study 46 was planned to address this issue. It did not show sufficient evidence to support use for local anesthesia for a venous vascular access procedure in children.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

There were no statistical issues presented by the 5 clinical studies in this application. The 4 studies of S-caine Peel for use in adults for a variety of dermal procedures all show statistically significant difference in favor of S-caine Peel versus placebo. This was true for the single primary and four secondary endpoints.

The single study planned to show efficacy for use in children, study 46, did not provide sufficient evidence to support that indication. Neither the primary nor secondary variables showed evidence of efficacy for S-caine Peel in children for a venous vascular access procedure.

The label proposed by the applicant does raise one statistical issue. In the clinical trials section, the applicant states that '
." In the Pediatric Use section the proposed language is that '
However, study 46 was prospectively designed with the primary goal of assessing efficacy, and it was not able to show a difference versus placebo. If study 46 had show a statistically significant results, the applicant would likely have proposed presenting the results in the label. Since the study failed, I think the two statements above are misleading, and that instead the failed study should be mentioned.

5.2 Conclusions and Recommendations

The studies in this application provide sufficient evidence to support the indication of S-caine Peel for local dermal anesthesia in adults undergoing dermal procedures such as dermal filler injections, non-ablative facial laser resurfacing, pulsed dye laser therapy, or laser-assisted

tattoo removal.

There is not sufficient evidence to support use in children for a venous vascular access procedure.

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