CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-623

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-623
Name of drug:	S-Caine patch (lidocaine and tetracaine topical patch) 70 mg
Indication:	[redacted]
Applicant:	ZARS, Inc.
Dates:	Letter 12/17/04; PDUFA 06/23/05
Review priority:	S
Biometrics division:	Division of Biometrics II (HFD 715)
Statistical reviewer:	Joan Buenconsejo
Statistics team leader:	Thomas Permutt, Ph.D.
Biometrics division director:	S. Edward Nevius, Ph.D.
Medical division:	HFD 170
Clinical team:	Howard Josefberg, M.D.
Project manager:	Allison Meyer

Keywords: NDA review, clinical studies, analysis of variance, Cochran-Mantel-Haenszel, responder analysis

Table of Contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Based on the evidence presented from study SC-55-04, the heating component contributed to the efficacy of the S-Caine Patch.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Three clinical studies were conducted by ZARS to confirm the claim that the heating component of the S-Caine Patch contributes to product efficacy.

The first proposed study, SC-53-04, was designed as a pilot study to obtain preliminary information on the variability and magnitude of heat, application time, and stimulus intensity on the efficacy According to the applicant, the results from this pilot study were intended to be used for designing the second study.

The second proposed study, SC-54-04, was designed to be a pivotal study that would use a randomized, double-blind methodology to compare an S-Caine patch with heat to an S-Caine patch without heat for induction of local anesthesia prior to a vascular access procedure. The Agency on May 4, 2004 agreed that data obtained from these trials would, if positive, be adequate to demonstrate the role of the heating component in product efficacy.

Based on the results from the pilot study SC-53-04, a total of 250 subjects were randomized, 1:1 and received either an S-Caine Patch with heat or a "no heat" S-Caine Patch on the left or right antecubital surface. Following the 20-minute application period, a 16-gauge, 1-inch catheter was inserted into the antecubital vein. Following the vascular access procedure, efficacy evaluation was performed. The primary measure of efficacy was the subject's evaluation of pain intensity using the VAS score. The secondary measure of efficacy variable was the subject's overall impression of the local anesthetic.

In study SC-54-04, there was no statistically significant difference between the subjects receiving the heated S-Caine Patch and subjects receiving the unheated S-Caine patch (using either the mean VAS score or the geometric mean VAS score), although the mean VAS score was slightly lower in the heated group. Similarly, there was no difference between the treatment groups in the proportion of subjects who had adequate anesthesia, as well as in the proportion of subjects who would use it again.

According to the applicant,t hey discovered a flaw in the preparation of the "no heat" patches that invalidated the results of SC-54-04. Specifically, an investigation was undertaken by the applicant, and it was discovered that the "no heat" patches were, unexpectedly, generating heat. Therefore, an additional definitive study (SC-55-04) that used the same study design as SC-54-04 was conducted. In contrast, the "no heat" patches in this new study (SC-55-04) had their heating element completely removed to ensure that the patches had no capability of generating heat.

In study SC-55-04, the mean VAS scores were statistically significantly lower for subjects receiving the heated S-Caine patch than for subjects receiving the unheated S-Caine patch. Similarly, statistically significantly more subjects who received the heated S-Caine patch reported adequate anesthesia compared with those who received the unheated patches. Furthermore, statistically significantly more subjects who received the heated S-Caine patch reported that they would use the product again compared with those who received the unheated patch.

1.3 STATISTICAL ISSUES AND FINDINGS

No statistical issues were identified after reviewing these clinical studies that can not be addressed by post-hoc analyses.

2 INTRODUCTION

2.1 OVERVIEW

This is a review of the clinical data from three clinical studies conducted by ZARS to document the contribution of heat to the efficacy of the S-Caine Patch. This is part of ZARS' complete response to the February 4, 2004 approvable letter, which the Agency stated that ZARS failed to demonstrate the contribution of the heating component to the efficacy of the S-Caine Patch. At that time, the Agency proposed revised language in the product labeling underscoring that ZARS failed to demonstrate the contribution of the heating component to product efficacy. Currently the applicant, ZARS, is asserting that the heating component of the S-Caine Patch contributes to product efficacy. Note that this is the only efficacy issue remaining from the original NDA.

2.2 DATA SOURCES

This statistical review is based on data submitted in Studies SC-53-04, SC-54-04 and SC-55-04.

The electronic submission of this NDA can be found on the internal network drive at \\Cdsesub1\n21623\N_000\2004-12-17 .

The electronic datasets for all the studies are under \\Cdsesub1\n21623\N_000\2004-12-17 .

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 BACKGROUND

This statistical review focuses on the three clinical studies (SC-53-04, SC-54-04, and SC-55-04) conducted to investigate the contribution of the heating component to the efficacy of the S-Caine Patch.

The first proposed study, SC-53-04, was designed as a pilot study to obtain preliminary information on the variability and magnitude of heat, application time, and stimulus intensity on the efficacy According to the applicant, the results from this pilot study were intended to be used for designing the second study. The second proposed study, SC-54-04, was designed to be a pivotal study that would use a randomized, double-blind methodology to compare an S-Caine patch with heat to an S-Caine patch without heat for induction of local anesthesia prior to a vascular access procedure. The Agency on May 4, 2004 agreed that data obtained from these trials would, if positive, be adequate to demonstrate the role of the heating component in product efficacy.

ZARS conducted both studies but, according to them, discovered a flaw in the preparation of the "no heat" patches that invalidated the results of SC-54-04. Specifically, an investigation was undertaken by the applicant, and it was discovered that the "no heat" patches were, unexpectedly, generating heat. An additional definitive study (SC-55-04) that used the same study design as SC-54-04 was conducted. However, in the SC-55-04 study, the "no heat" patches had their heating element completely removed to ensure that the patches had no capability of generating heat.

3.1.2 SUMMARY OF STUDY METHODOLOGY AND RESULTS

3.1.2.1 STUDY SC-53-04

Study SC-53-04 was a multicenter, parallel pilot study designed to obtain preliminary information on the variability and magnitude of the effect of heat, application time (20 minutes versus 30 minutes application time), and stimulus intensity (16- versus 18-gauge catheter) on the efficacy of the S-Caine Patch. Eighty-six subjects were randomized to 1 of 8 treatment groups with respect to heated vs. "no heat" patches, the application time (20 vs. 30 minutes) and the size of the catheter used to obtain vascular access (16- vs. 18-gauge). The study patch was applied for the assigned treatment time (20 or 30 minutes). Following the removal of the study patch, a 16- or 18-gauge, 1-inch catheter was to be inserted into the antecubital vein and a flash of blood was to be obtained. Efficacy evaluations were performed following the procedure. The subject and the investigator were blinded to the treatment allocation, but the sponsor and the pharmacist (who applied and removed the patch) were not blinded. Note that only the pharmacist was unblinded in Study SC-54-04 and Study SC-55-04.

During the first day of enrollment, sponsor representatives and the unblinded pharmacist noted that the "no heat" patches, were, in fact, heating. Heat was detected qualitatively with a perception of heat when a hand was placed over the patch. Study enrollment was temporarily stopped following the discovery that the "no heat" patches were producing noticeable heat. Eight subjects had received the "no heat" patches prior to stopping enrollment on day 1. Data from these subjects were excluded from the efficacy analysis in the study by the applicant. To remedy the situation, ZARS instructed the unblinded pharmacist at each study site to perform additional *ad hoc* deactivation procedure on the remaining patches randomized to be "no heat" patches.

Number of subjects in each treatment group (ITT, and evaluable, as well as subjects who had protocol deviation) are presented (Table 1). A total of 88 subjects were randomized to eight treatment groups. All subjects met eligibility criteria, and all subjects completed the study. However, eight subjects who were assigned to receive unheated S-Caine patch (treatment groups 5 to 8) on Day 1 were excluded because it was discovered that the patches had produced some heat. Thus the efficacy population (evaluable) consisted of data from 80 subjects. Meanwhile, the most common protocol deviation was that the study patch was applied longer than the required application time (4 out of 7 subjects).

Demographic and baseline characteristics of subjects in the randomized and evaluable populations are summarized in Table 2. The characteristics of subjects were not different between the randomized and the evaluable population. The majority of subjects were Caucasian. There were also higher proportion of male subjects, and the mean age of subjects was 41 years. Skin Type III (burns moderately/tans gradually) and IV (burns minimally/always tans) were the most common skin types.

Table 1: No. of subjects by treatment group

Treatment Group	Description	Randomized	Evaluable	Protocol Deviations
1	Patch with Heat 16-gauge 20 minutes	10	10	1
2	Patch with Heat 18-gauge 20 minutes	9	9	0
3	Patch with Heat 16-gauge 30 minutes	13	13	1
4	Patch with Heat 18-gauge 30 minutes	11	11	2
5	Patch no Heat 16-gauge 20 minutes	10	8	1
6	Patch no Heat 18-gauge 20 minutes	12	11	1
7	Patch no Heat 16-gauge 30 minutes	11	8	0
8	Patch no Heat 18-gauge 30 minutes	12	10	0

Table 2: Subject Characteristics (Study SC-53-04) – All Subjects Enrolled (N=88) and All Evaluable Subjects (N=80)

	Randomized N=88	Evaluable N=80
Gender, N (%)		
Female	41 (47%)	37 (46%)
Male	47 (53%)	43 (54%)
Age		
Mean ± SD, y	41 ± 14	41 ± 14
Race, N		
Asian	23 (26%)	23 (29%)
Black	3 (3%)	3 (4%)
Caucasian	54 (61%)	46(58%)
Hispanic	5 (6%)	5 (6%)
Other	3 (3%)	3 (4%)
Height		
Mean ± SD, in	67 ± 4	67 ± 4
Weight		
Mean ± SD, lbs	174 ± 45	176 ± 46
Skin Type, N		
I	5 (6%)	3 (4%)
II	15 (17%)	14 (18%)
III	30 (34%0	25 (31%0
IV	25 (28%)	25 (31%)
V	13 (15%)	13 (16%)
VI	0 (0%)	0 (0%)

Subjects used a 100-mm Visual Analog Scale (VAS) to rate the pain they had experienced during the vascular access procedure. Descriptive statistics for VAS scores for each treatment groups are summarized in Table 3. Because the study was designed to estimate the variability among treatment groups rather than to compare treatment groups, no inferential statistics were reported by the Applicant. It appears that the mean VAS score among those excluded from the study are slightly lower than the mean VAS score among those in the evaluable population. Exclusion of subjects also appears to affect the percentage of subjects who had adequate anesthesia and percentage of subjects who would use the patch again. Nonetheless, it appears that the mean VAS score among subjects who received the heated patch is less than the mean VAS score among those subjects who received the unheated patch, except on subjects who received no heat, 30 minute application, and 18-gauge needle. Furthermore, it appears that needle size played no part in the difference in mean VAS score between subjects receiving the unheated and the heated patch at 20 minute application time. However, the needle size at 30 minute application may influence the difference. It seems that subjects with 16-gauge needle have higher mean VAS scores compared to subjects with 18-gauge needle across the treatment group. Furthermore, subjects receiving 18-gauge needle and the unheated patch appear to have less pain compared to subjects receiving 18-gauge needle and the heated patch.

The mean VAS scores appear to correlate very well with subjects' overall assessment of anesthetic. Again, there is a big difference in patient satisfactions (% subjects who had adequate anesthesia and % subjects who would use again) between the heated and unheated patch, particularly among subjects with 20 minute application time. However, it seems that at 30 minute application time,t here is no evidence of difference in patient satisfaction between the heated and unheated patch regardless of needle size. Note however that because the sample size is very small, these results are not definitive.

A clearer presentation of possible differences between heated and unheated, between 20 minute application and 30 minute application, between 16- and 18-gauge needle, and between male and female, are presented in Table 4. Quantitatively as expected, subjects receiving no heat patch have higher mean VAS score compared to subjects receiving heated patch. Furthermore, subjects with 16-gauge needle have higher mean VAS score compared to subjects with 18-gauge needle. Subjects receiving 20 minute application appears to also have a higher VAS score than those receiving 30 minute application. Meanwhile, it appears that there is no gender difference, although female subjects had a higher mean VAS score compared to male subjects.

Similarly, subjects' overall assessment of anesthesia appeared to be in favor of the heated patch, as well as to the 18-gauge needle. There is slightly higher favorability in patient satisfaction among subjects receiving the 30-minute application. It also appears that female subjects had a slightly better satisfaction with the patch compared to male subjects.

Table 3: Visual Analog Scale (VAS) Scores by treatment group (Study SC-53-04) – All Subjects Enrolled (N=88) and All Evaluable Subjects (N=80)

		Treatment Group							
	Total	Heat 20 min 16-g	Heat 20 min 18-g	Heat 30 min 16-g	Heat 30 min 18-g	No Heat 20 min 16-g	No Heat 20 min 18-g	No Heat 30 min 16-g	No Heat 30 min 18-g
All Patients	**88**	**10**	**9**	**13**	**11**	**10**	**12**	**11**	**12**
VAS									
Mean	17.9	17.0	10.2	16.7	13.8	30.4	23.8	22.5	8.7
STD	20.2	18.5	14.6	16.0	16.8	17.4	29.9	24.9	14.2
Median	10.5	9.0	4.0	14.0	9.0	24.0	14.0	12.0	3.0
Range	(0 – 97)	(0 – 63)	(1 – 40)	(0 – 52)	(0 – 53)	(11 – 65)	(0 – 97)	(2 – 81)	(0 – 51)
Geometric	10.1	11.2	6.1	11.0	7.8	27.4	10.3	14.1	5.0
% Adequate	74%	80%	100%	62%	91%	30%	67%	73%	92%
% Again	70%	80%	89%	54%	100%	20%	67%	64%	92%
Evaluable Patients	**80**	**10**	**9**	**13**	**11**	**8**	**11**	**8**	**10**
VAS									
Mean	18.7	17.0	10.2	16.7	13.8	34.0	24.0	28.9	10.1
STD	20.9	18.5	14.6	16.0	16.8	17.5	31.3	26.7	15.3
Median	10.5	9.0	4.0	14.0	9.0	32.5	11.0	23.0	5.0
Range	0 – 97	0 – 63	1 – 40	0 – 52	0 – 53	15 – 65	0 – 97	5 – 81	0 – 51
Geometric Mean	10.5	11.2	6.1	11.0	7.8	31.2	9.6	20.3	5.8
% Adequate	73%	80%	100%	62%	91%	13%	73%	63%	90%
% Again	70%	80%	89%	54%	100%	13%	73%	50%	90%

Table 4: Visual Analog Scale Scores by Variables of Presence/Absence of Heat, Application Time, Needle Size, and Gender (Study SC-53-04) – All Subjects Enrolled (N=88) and All Evaluable Subjects (N=80)

		Patch		Minutes Application		Needle Gauge		Gender	
	Total	With Heat	No Heat	20	30	16	18	Female	Male
All Patients	**88**	**41**	**47**	**41**	**47**	**44**	**44**	**41**	**47**
VAS									
Mean	17.9	14.7	20.9	20.8	15.3	21.3	14.4	16.6	19.0
STD	20.2	16.1	23.3	22.1	18.3	19.5	20.6	22.6	18.1
Median	10.5	8.0	12.0	15.0	8.0	15.0	5.0	8.0	14.0
Range	0 – 97	0 – 63	0 – 97	0 – 97	0 – 81	0 – 81	0 – 97	0 – 97	0 – 67
Geometric Mean	10.1	8.9	11.4	11.9	8.8	14.4	7.1	8.1	12.3
% Adequate	74%	81%	67%	68	79	61	86	76	72
% Again	70%	79%	62%	63	77	55	86	71	70
Evaluable Patients	**80**	**37**	**43**	**38**	**42**	**39**	**41**	**37**	**43**
VAS									
Mean	18.7	14.7	23.5	21.0	16.7	22.8	14.9	17.4	19.9
STD	20.9	16.1	24.7	22.9	18.9	20.1	21.1	23.5	18.5
Median	10.5	8.0	15.0	13.0	9.5	16.0	6.0	8.0	15.0
Range	0 – 97	0 – 63	0 – 97	0 – 97	0 – 81	0 – 81	0 – 97	0 – 97	0 – 67
Geometric Mean	10.5	8.9	12.7	11.5	9.7	15.5	7.3	8.3	12.9
% Adequate	73%	81%	62%	68	76	56	88	76	70
% Again	70%	79%	59%	66	74	51	88	70	70

Additional analysis was performed to assess the mean VAS score between subjects receiving the heated patch and subjects receiving the unheated patch. The higher the mean VAS scores, the greater the pain the subjects had scored. It appears that a higher proportion of subjects receiving unheated patch had more pain compared to subjects receiving heated patch (Figure 1 and Figure 2).

Figure 1: Patient's Pain Profile (Study SC-53-04) – All Subjects Randomized

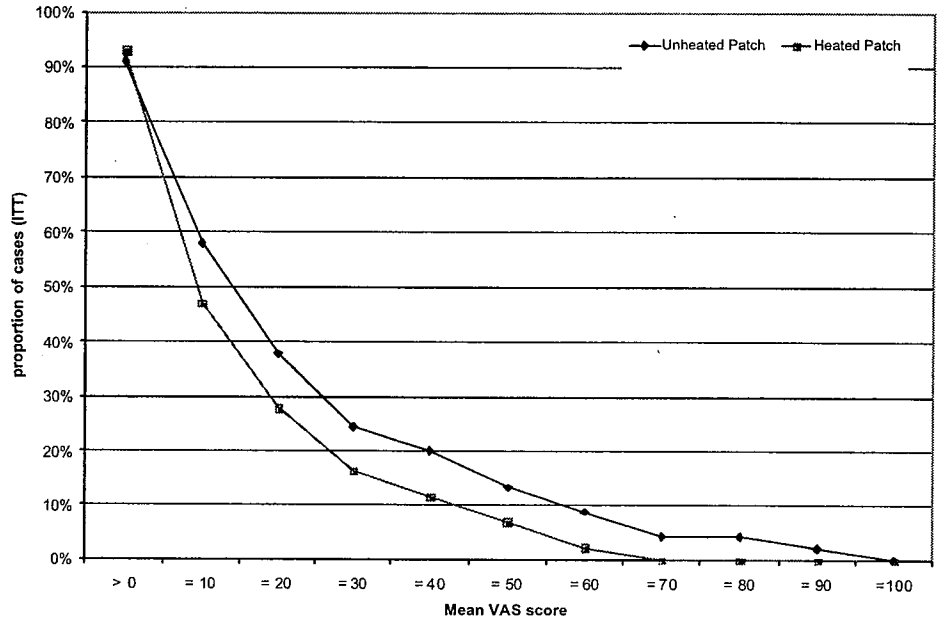
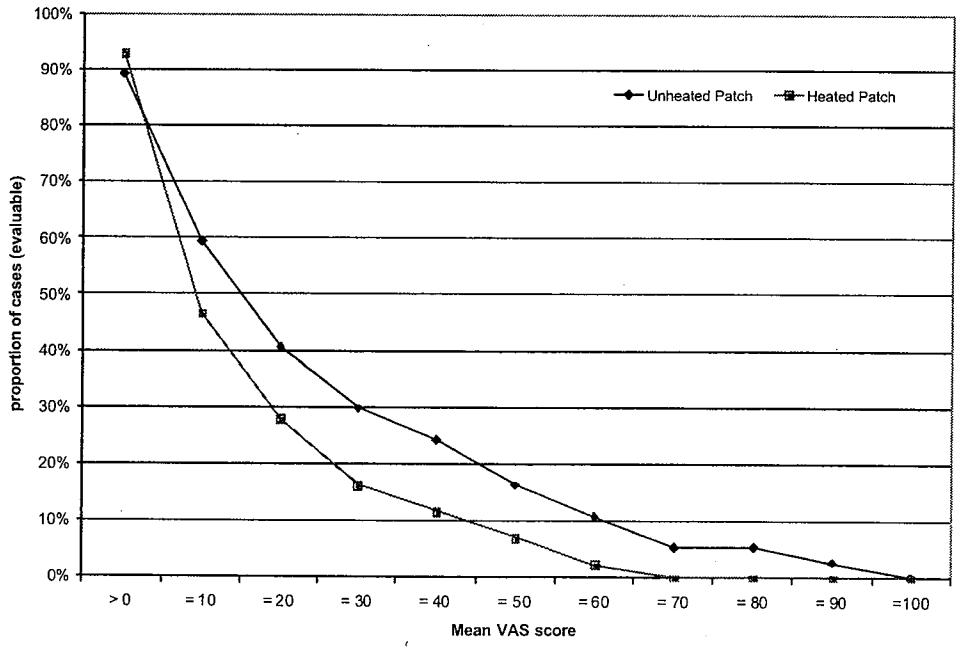


Figure 2: Patient's Pain Profile (Study SC-53-04) – All Evaluable Subjects



3.1.2.2 STUDY SC-54-04

Study SC-54-04 was a parallel, randomized, double-blind, multicenter study designed to compare the effectiveness of an S-Caine Patch with heat to an S-Caine Patch without heat ("no heat" patches) in providing local anesthesia prior to a vascular access procedure in healthy adult volunteers.

The estimated standard deviation and the estimated magnitude of the effect from data in Study SC-53-04 were used to aid in the design of this study. Sample size was determined based on the pilot study (SC-53-04) with parallel treatments. According to the applicant, the preliminary analysis of log transformed VAS scores had a root mean squared error of 1.2 and observed differences for 16 gauge needle (deactivated minus with heat) of 0.6 (30 minute application) and 1.0 (20 minute application). With 123 subjects per treatment group, there would be 95% power when the standard deviation equals 1.2 and the difference between heat and no heat is 0.55 on the log transformed scale. An amendment was made prior to any subjects' enrolling in the study. This amendment increased the sample size from 200 to 250 subjects and reduced the S-Caine Patch application time from 30 to 20 minutes.

Before I proceed to the statistical methods and results, I would like to comment about the sample size calculation. Recall from the analysis of pilot Study SC-53-04, that it appears that needle size in subjects receiving 30 minute application may influence the difference in pain score between subjects receiving heated patch and subjects receiving unheated patch. There is no clear reason why applicant chose 16-gauge needle and changed application time from 30 minutes to 20 minutes. Furthermore, there is no justification as to why log-transformed VAS scores are used instead of the regular VAS scores. There was also no justification provided in the pilot study why VAS scores were log-transformed. Recalculating the sample size using the untransformed mean VAS scores from the pilot study (16-gauge needle with 20 minute application), a sample size of 250 subjects is more than sufficient to provide at least 90% power. Therefore, sample size of 250 should not affect the interpretability of the results.

A total of 250 subjects were randomized to one of two treatment groups; 122 subjects received the heated S-Caine Patch and 128 subjects received the unheated S-Caine Patch. The study patch was applied to the subject's right antecubital surface for 20 minutes. Following the removal of the study patch, a 16-gauge, 1-inch catheter was inserted into the antecubital vein. Subject's evaluation of pain intensity using the VAS score was obtained, followed by subject's overall impression of the local anesthetic (i.e. secondary outcome measures). Note that the subject, the investigator, and the sponsor were blinded. Only the pharmacist is unblinded in the study.

According to the applicant, all subjects in both treatment groups met eligibility criteria for the study, and all subjects completed the study. Based on my count, there were 17 subjects who had some protocol violations, five of which were due to their patch being applied for 21 minutes instead of the required 20-minute application.

Demographic and baseline characteristics of subjects in the randomized populations are summarized in Table 5. Similar to the Pilot Study (SC-53-04), the majority of subjects were Caucasian. There were also higher proportion of male subjects, and the mean age of subjects was 38 years. Skin Type III (burns moderately/tans gradually) and IV (burns minimally/always tans) were the most common skin types.

Table 5: Demographic and Baseline Characteristics – Study SC-54-04

		Treatment Group	
	Total	Heated	Unheated
N	250	122	128
Gender, N (%)			
Female	128 (51)	63 (52)	65 (51)
Male	122 (49)	59 (48)	63 (49)
Age			
Mean ± SD, y	38 ± 15	39 ± 16	37 ± 14
Race, N			
Asian	52 (21)	25 (20)	27 (21)
Black	21 (8)	10 (8)	11 (9)
Caucasian	106 (42)	52 (43)	54 (42)
Hispanic	29 (12)	13 (11)	16 (12)
Other	42 (17)	22 (18)	20 (16)
Height			
Mean ± SD, in	66 ± 4	67 ± 4	66 ± 5
Weight			
Mean ± SD, lbs	179 ± 52	178 ± 54	180 ± 51
Skin Type, N			
I	8 (3)	4 (3)	4 (3)
II	30 (12)	19 (16)	11 (9)
III	90 (36)	44 (36)	46 (36)
IV	61 (24)	28 (23)	33 (26)
V	45 (18)	20 (16)	25 (20)
VI	16 (6)	7 (6)	9 (7)

Subjects used a 100-mm Visual Analog Scale (VAS) to rate the pain they had experienced during the vascular access procedure. Descriptive statistics for VAS scores for each treatment groups are summarized in Table 6. There was no statistically significant difference for the mean VAS scores between the subjects receiving the heated S-Caine Patch and subjects receiving the unheated S-Caine patch ($p=0.4700$), although the mean VAS score was slightly lower in the heated group. Similarly, there was no difference between the treatment groups in the proportion of subjects who had adequate anesthesia ($p=0.209$), nor in the proportion of subjects who would use it again ($p=0.391$).

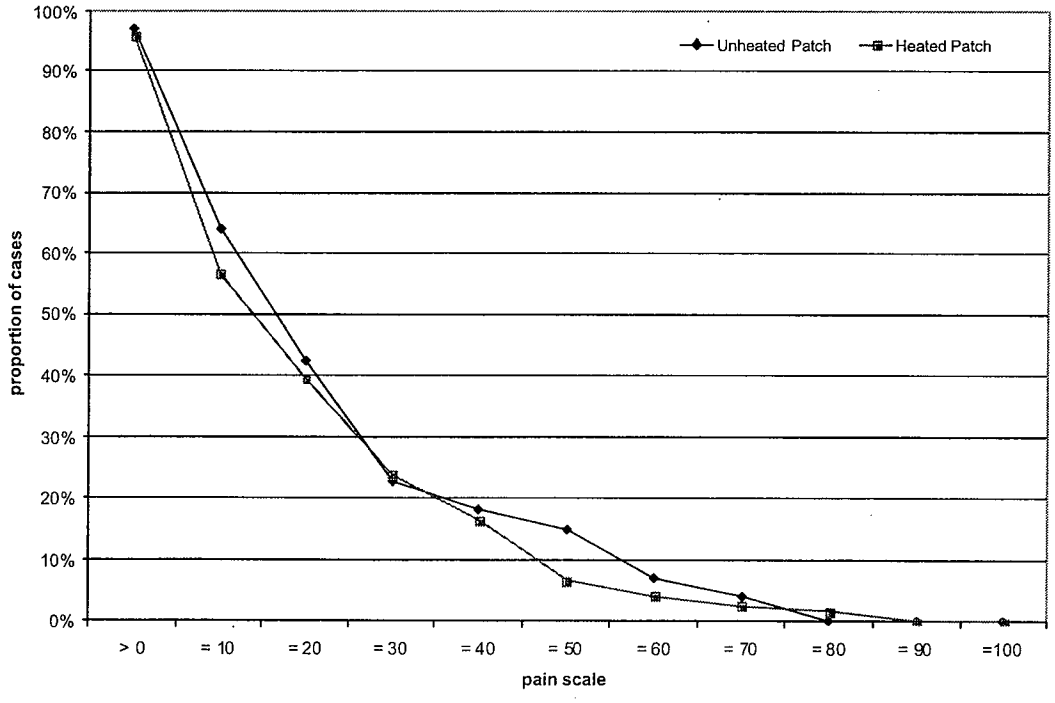
Table 6: Visual Analog Scale Scores by Treatment Group (Study SC-54-04) – All Subjects who were evaluable for Efficacy

	Total	Treatment Group		P-value
		Heated S-Caine Patch	Unheated S-Caine Patch	
	N=250	N=122	N=128	
VAS				
Mean	20.3	19.4	21.2	0.4700[1]
STD	19.3	18.8	19.8	
Median	14.0	13.0	14.0	
Range	0 – 85	0 – 85	0 – 77	
Geometric Mean	13.3	12.5	14.1	0.379
% Adequate	179 (72%)	92 (75%)	87 (68%)	0.209[2]
% Again	184 (74%)	93 (76%)	91 (71%)	0.391[2]

[1] using two-sample t-test
[2] using Fishers exact test

Additional analysis was performed to assess the mean VAS score between subjects receiving the heated patch and subjects receiving the unheated patch. The higher the mean VAS scores, the greater the pain the subjects had scored. It appears that there is no difference in mean pain score between subjects receiving unheated patch and subjects receiving heated patch (Figure 3).

Figure 3: Patient's Pain Profile (Study SC-54-04)



According to the applicant, the most likely reason that this study did not demonstrate a difference between the heated and unheated S-Caine patch is attributable to the fact that the "no heat" patches were generating a significant amount of heat. Based on two *in vitro* studies conducted to evaluate the deactivation procedure that was used for the unheated patches, the "no heat" patches were found to be generating heat after 14 days of storage. The temperature profile of the "no heat" patches at release testing (0 days of storage) showed no significant heating while results from the first *in vitro* study demonstrated that the temperature profile of "no heat" patches studied after 56 days of storage had significant heating. The second *in vitro* study demonstrated that "no heat" patch temperatures began to rise after 3 days of storage and increased continuously after 7 and 14 days of storage. Given that approximately 14 days elapsed between the SC-54-04 deactivation procedure and the application of study patches to subjects in Study SC-54-04, the results from this study indicate that the "no heat" patches would have heated significantly during the clinical study.

3.1.2.3 STUDY SC-55-04

Similar to Study SC-54-04, Study SC-55-04 was a parallel, randomized, double-blind, multicenter study designed to compare the effectiveness of an S-Caine Patch with heat to an S-Caine Patch without heat ("no heat" patches) in providing local anesthesia prior to a vascular access procedure in healthy adult volunteers. However in this trial, the heating component of the patch was completely removed from the "no heat" patches to eliminate any possibility of heat generation during patch application.

Similar to SC-54-04, a total of 250 subjects were randomized, 1:1, to receive either the heated (N=124) or unheated S-Caine (N=126) Patch. The study patch was applied to the subject's right antecubital surface for 20 minutes. Following the removal of the study patch, a 16-gauge, 1-inch catheter was inserted into the antecubital vein. Subject's evaluation of pain intensity using the VAS score was obtained, followed by subject's overall impression of the local anesthetic (i.e. secondary outcome measures). Note that the subject, the investigator, and the sponsor were blinded. Only the pharmacist is unblinded in the study.

According to the applicant, all subjects in both treatment groups met eligibility criteria for the study, and all subjects completed the study.

Demographic and baseline characteristics of subjects in the randomized population are summarized in Table 7. Similar to the Pilot Study (SC-53-04) and Study SC-54-04, the majority of subjects were Caucasian. However, there were more female subjects in this study compared to the two previous studies, and the mean age of subjects was much lower (i.e. 34 years). Skin Type III (burns moderately/tans gradually) and IV (burns minimally/always tans) were still the most common skin types.

Table 7: Demographic and Baseline Characteristics – Study SC-55-04

		Treatment Group	
	Total	Heated	Unheated
N	250	124	126
Gender, N(%)			
Female	136 (54)	67 (54)	69 (55)
Male	114 (46)	57 (46)	57 (45)
Age			
Mean ± SD, y	34.3 ± 13.4	35.1 ± 13.4	33.5 ± 13.4
Race, N			
Asian	56 (22)	23 (19)	33 (26)
Black	8 (3)	6 (5)	2 (2)
Caucasian	127 (51)	61 (49)	66 (52)
Hispanic	27 (11)	19 (15)	8 (6)
Other	32 (13)	15 (12)	17 (13)
Height			
Mean ± SD, in	66.6 ± 4.0	66.6 ± 4.1	66.5 ± 3.9
Weight			
Mean ± SD, lbs	169.7 ± 46.5	171.8 ± 49.9	167.5 ± 42.9
Skin Type, N			
I	9 (4)	5 (4)	4 (3)
II	47 (19)	26 (21)	21 (17)
III	99 (40)	46 (37)	53 (42)
IV	66 (26)	30 (24)	36 (29)
V	27 (11)	16 (13)	11 (9)
VI	2 (1)	1 (1)	1 (1)

Subjects used a 100-mm Visual Analog Scale (VAS) to rate the pain they had experienced during the vascular access procedure. Descriptive statistics for VAS scores for each treatment groups are summarized in Table 8. The mean VAS scores were significantly lower for subjects receiving the heated S-Caine patch than for subjects receiving the unheated S-Caine patch (p=0.0183). In context, the ratio of heated to unheated means was 77%, or the heat reduced the pain score by 23%. Similarly, significantly more subjects who received the heated S-Caine patch reported adequate anesthesia compared to those who received the unheated patches (71% vs. 53%, p=0.004). Furthermore, significantly more subjects who received the heated S-Caine patch reported that they would use the product again compared to those who received the unheated patch (71% vs. 55%, p=0.009).

Table 8: Visual Analog Scale Scores by Treatment Group (Study SC-55-04) – All Subjects who were evaluable for Efficacy

	Total	Treatment Group		P-value
		Heated S-Caine Patch	Unheated S-Caine Patch	
	N=250	N=124	N=126	
VAS				
Mean	25.4	22.1	28.7	0.0183[1]
STD	22.0	20.7	22.8	
Median	20.0	16.5	22.0	
Range	0 – 97	0 – 97	0 – 95	
Geometric Mean	17.1	14.2	20.5	0.0065[1]
% Adequate	62%	71%	53%	0.004[2]
% Again	63%	71%	55%	0.009[2]

[1] using two-sample t-test
[2] using Fisher's exact test

Exploratory analysis was done to compare centers, to evaluate consistency among centers, and to compare treatments within each center for the subjects' rating of pain intensity using the VAS, as well as using the subject's overall assessment of the adequacy of anesthetic and percentage of subjects who would use the product again. For the continuous outcome (i.e. geometric mean VAS score), a two-way analysis of variance with fixed terms for center, treatment, and center by treatment, including unadjusted p-values from pairwise least square (LS) means to compare centers and to compare treatments with each center was conducted by the applicant. For categorical variables, the following tests were performed by the applicant: a Fisher Exact test for each center to compare treatments, a Cochran-Mantel-Haenszel test stratified on center to compare treatments, a Fisher Exact test on combined treatments to compare centers, and a logistic regression with terms for treatment, center, and treatment by center. The p-values were not adjusted for multiplicity.

Although descriptive statistics by center could provide potential information about the treatment groups (e.g. magnitude and direction of the difference), I do not see any benefits in conducting/providing unadjusted p-values from pairwise least square (LS) means to compare centers and to compare treatments with each center. Not only does the data lack power to detect treatment difference within each subgroups, multiplicity is also a problem.

Nonetheless, descriptive statistics by center and treatment and a two-way analysis of variance (with fixed terms for center and treatment) are presented (Table 9). As shown in the table, VAS scores were significantly lower for subjects receiving the heated S-Caine patch than for subjects receiving the unheated S-Caine patch ($p=0.0178$) even when center is adjusted for. There is also significant interaction between treatment groups and center ($p=0.0442$). Again, there is no clear justification by the applicant why log-transformed VAS data was used in the analysis.

Comparing mean VAS scores between treatment groups by center, mean VAS scores at Center 4 appears to shift in direction, having a higher mean VAS score in the heated group compared to the unheated group.

Stratifying by centers and applying Cochran-Mantel-Haenszel test, significantly more subjects who received the heated S-Caine patch reported adequate anesthesia compared with those who received the unheated patches (p=0.003). Furthermore, significantly more subjects who received the heated S-Caine patch reported that they would use the product again compared with those who received the unheated patch (p=0.008). Both tests showed no heterogeneity across different centers using the Breslow-Day test of heterogeneity.

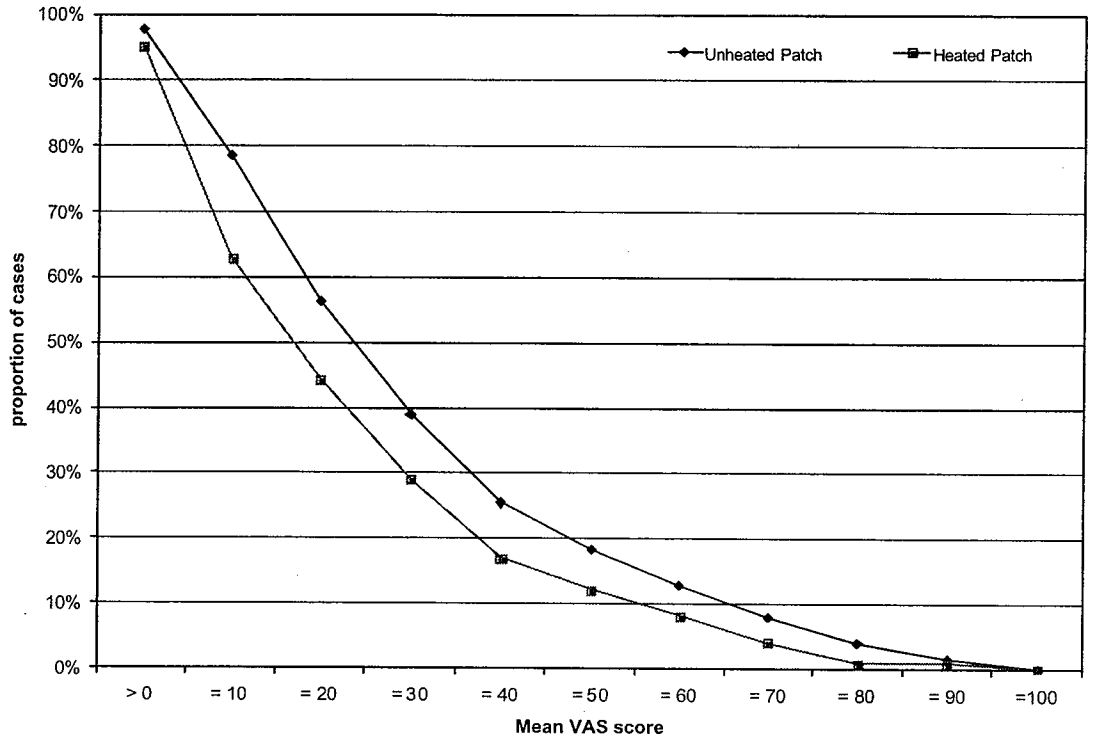
Table 9: Exploratory Analysis of VAS scores by Treatment and Center (Study SC-55-04)

	Center 1			Center 2			Center 3			Center 4		
	Total	Heated	No Heat	Total	Heated	No Heat	Total	Heated	No Heat	Total	Heated	No Heat
All Patients	60	30	30	60	30	30	70	34	36	60	30	30
VAS												
Mean	27.4	25.3	29.6	25.8	18.5	33.1	22.7	16.4	28.6	26.1	28.9	23.3
STD	22.9	23.4	22.6	23.2	17.9	25.7	17.9	13.6	19.6	24.3	25.2	23.4
Median	22.5	16.5	25.5	18.5	13.5	27.5	19.0	14.5	25.5	18.5	28.5	16.5
Range	0 – 90	0 – 77	1 – 90	0 – 85	0 – 71	1 – 85	0 – 68	0 – 60	0 – 68	0 – 97	1 – 97	0 – 95
Geometric	18.6	15.6	22.2	16.9	12.1	23.6	16.4	11.9	22.0	16.7	18.5	15.0
P-value (Mean)	0.0178[a]	0.0211[b]										
P-value (geometric)	0.0066[a]	0.008[b]										
% Adequate	37 (62)	21 (70)	16 (53)	38 (63)	23 (77)	15 (50)	51 (73)	22 (61)	29 (85)	29 (48)	15 (50)	14 (47)
P-value	0.003											
Breslow-Day	0.4049											
% Again	38 (63)	23 (38)	15 (50)	39 (65)	21 (70)	18 (60)	46 (66)	26 (76)	20 (56)	34 (57)	18 (60)	16 (53)
P-value	0.008											
Breslow-Day	0.5954											

[a] ANOVA with center and treatment
[b] ANOVA with center, treatment, and interaction

Additional analysis was performed to assess the mean VAS score between subjects receiving the heated patch and subjects receiving the unheated patch. The higher the mean VAS scores, the greater the pain the subjects had scored. It appears that significantly higher proportion of subjects who received the heated S-Caine patch reported lower VAS score compared with those who received the unheated patches (Figure 4).

Figure 4: Patient's Pain Profile (Study SC-55-04)



3.2 EVALUATION OF SAFETY

Dr. Josefberg will provide a safety evaluation based on these new clinical studies in his review.

4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

Because the clinical studies reviewed covered only the efficacy of the heating component of the S-Caine Patch and not the efficacy of the actual drug (i.e. S-Caine Patch), subgroup analysis was not conducted.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The three clinical studies conducted were straightforward in terms of the statistical methods used and the results from analyses of the datasets. Although statistical issues were identified after reviewing the three clinical studies, these issues were not critical and were easily addressed by post-hoc analyses. Example of these issues is on the choice of primary efficacy variable (i.e. using transformed VAS pain score instead of untransformed VAS pain score). There was no clear justification on the use of transformed VAS scores. However, there is evidence, from post-hoc analysis, that the results were consistent when mean of the untransformed VAS scores were used as primary efficacy variable. For the purpose of interpretability, I think that the means of the untransformed VAS scores should be used in the label, unless a clear justification why this is not true is provided. Another example is the comparison of treatment groups by each center. Although descriptive statistics by center could provide potential information about the treatment groups (e.g. magnitude and direction of the difference), I do not see any benefits in conducting/providing unadjusted p-values from pairwise least square (LS) means to compare centers and to compare treatments with each center. Not only does the data lack power to detect treatment difference within each subgroups, multiplicity is also a problem.

Another issue that comes to mind is the choice of 20 minute application using 16-gauge, 1-inch catheter. There is no clear justification as to why the applicant chose this combination. There is no evidence that it was based on the results from the pilot study.

In terms of study results and conclusion, I agree with the applicant that in Study SC54-04, there was no statistically significant difference between the subjects receiving the heated S-Caine Patch and subjects receiving the unheated S-Caine patch (using either the mean VAS score or the geometric mean VAS score), although the mean VAS score was slightly lower in the heated group. Similarly, there was no difference between the treatment groups in the proportion of subjects who had adequate anesthesia, as well as in the proportion of subjects who would use it again. Although the applicant pointed out a possible flaw in the preparation of the "no heat" patches that potentially may have influenced the results in this study, I am not totally convinced that this reason alone would have biased the results tremendously. Therefore in consultation with Dr. Josefberg, I conducted additional analyses based on pooling data from Study SC-54-04 and Study SC-55-04. Although this pooled study may not provide us with answers as to what happened with the "no heat" patches in Study SC-54-04, a significant finding from this pooled study could at least give us supportive evidence that the heating component contributed to the efficacy of the S-Caine Patch.

The following results are the collective evidence from the pooled analyses.

Demographic and baseline characteristics of subjects in the randomized population are summarized in Table 10. The majority of subjects were Caucasian. There were more female subjects, and the mean age of subjects was 38 years. Skin Type III (burns moderately/tans gradually) and IV (burns minimally/always tans) were still the most common skin types.

Table 10: Demographic and Baseline Characteristics – Pooled Study

		Treatment Group	
	Total	Heated	Unheated
N	500	246	254
Gender, N (%)			
Female	264 (53)	130 (53)	134 (53)
Male	236 (47)	116 (47)	120 (47)
Age			
Mean ± SD, y	38 ± 15	39 ± 16	37 ± 14
Race, N			
Asian	108 (22)	48 (20)	60 (24)
Black	29 (6)	16 (7)	13 (5)
Caucasian	233 (47)	113 (46)	120 (47)
Hispanic	56 (11)	32 (13)	24 (9)
Other	74 (15)	37 (15)	37 (15)
Height			
Mean ± SD, in	66 ± 4	67 ± 4	66 ± 4
Weight			
Mean ± SD, lbs	179 ± 52	178 ± 54	180 ± 51
Skin Type, N			
I	17 (3)	9 (4)	8 (3)
II	77 (15)	45 (18)	32 (13)
III	189 (38)	90 (37)	99 (39)
IV	127 (25)	58 (24)	69 (27)
V	72 (14)	36 (15)	36 (14)
VI	18 (4)	8 (3)	10 (4)

Subjects used a 100-mm Visual Analog Scale (VAS) to rate the pain they had experienced during the vascular access procedure. Descriptive statistics for VAS scores for each treatment groups are summarized in Table 11. The mean VAS scores were significantly lower for subjects receiving the heated S-Caine patch than for subjects receiving the unheated S-Caine patch (unadjusted p=0.0269; adjusted p=0.0259). In context, the ratio of heated to unheated means was 84% or the heat reduced the pain score by 16%. Similarly, significantly more subjects who received the heated S-Caine patch reported adequate anesthesia compared to those who received the unheated patches (73% vs. 61%, unadjusted p=0.0032; adjusted p=0.0027). Furthermore, significantly more subjects who received the heated S-Caine patch reported that they would use the product again compared to those who received the unheated patch (74% vs. 63%, unadjusted p=0.0125; adjusted p=0.0101).

Table 11: Visual Analog Scale Scores by Treatment Group (Pooled Study) – All Subjects who were evaluable for Efficacy

	Total	Treatment Group: Heated S-Caine Patch	Treatment Group: Unheated S-Caine Patch	Unadjusted P-value	Adjusted[3] P-value
	N=500	N=246	N=254		
VAS					
Mean	22.9	20.8	24.9	0.0269[1]	0.0259[1]
STD	20.8	19.8	21.6		
Median	17.0	14.5	19.0		
Range	(0 – 97)	(0 – 97)	(0 – 95)		
Geometric Mean	15.1	13.3	17.0	0.0123[1]	0.0118[1]
% Adequate	334 (67)	180 (73%)	154 (61%)	0.0032[2]	0.0027[2]
% Again	341 (68%)	181 (74%)	160 (63%)	0.0125[2]	0.0101[2]

[1] using two-sample t-test
[2] using Fisher's exact test or Cochran-Mantel Haenszel test stratified on study
[3] adjusting for study

Exploratory analysis was done to compare centers, to evaluate consistency among centers, and to compare treatments within each center for the subjects' rating of pain intensity using the VAS, as well as using the subject's overall assessment of the adequacy of anesthetic and percentage of subjects who would use the product again. For the continuous outcome (i.e. mean VAS score and geometric mean VAS score), a two-way analysis of variance with fixed terms for center, treatment, and center by treatment, as well as adjusting for study were conducted. For categorical variables, Cochran-Mantel-Haenszel test stratified on center to compare treatments and logistic regressions with terms for treatment, center, and treatment by center, as well as adjusting for study were also conducted. The p-values were not adjusted for multiplicity.

Descriptive statistics by center and treatment and results of analysis of variance are presented (Table 12). As shown in the table, VAS scores were significantly lower for subjects receiving the heated S-Caine patch than for subjects receiving the unheated S-Caine patch when center was adjusted for ($p=0.0279$), as well as when study was adjusted for ($p=0.0254$). There was no significant interaction between treatment groups and center ($p=0.3393$).

Comparing mean VAS scores between treatment groups by center, mean VAS scores at Center 4 appears to shift in direction, having a higher mean VAS score in the heated group compared to the unheated group.

Stratifying by centers and applying Cochran-Mantel-Haenszel test, significantly more subjects who received the heated S-Caine patch reported adequate anesthesia compared with those who received the unheated patches (adjusted for center, $p=0.0028$; adjusted for center and study, $p=0.0024$). Furthermore, significantly more subjects who received the heated S-Caine patch reported that they would use the product again compared with those who received the unheated patch (adjusted for center, $p=0.0110$; adjusted for center and study, $p=0.0101$). All tests reported no heterogeneity across different centers/study using the Breslow-Day test of heterogeneity.

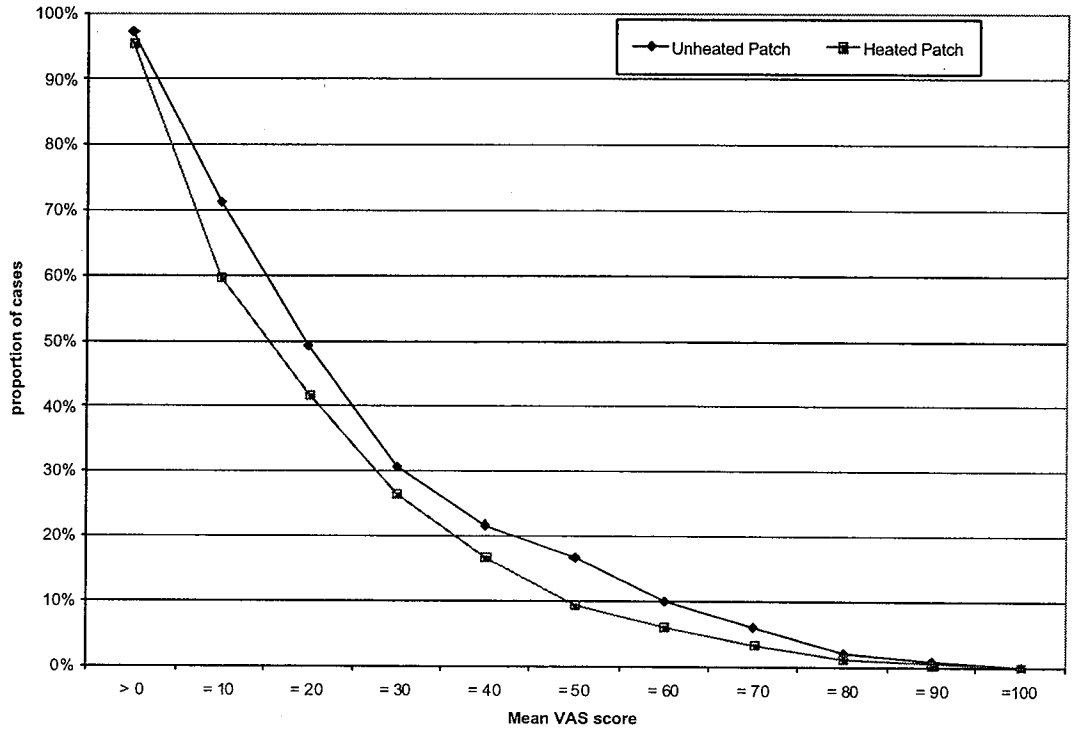
Table 12: Exploratory Analysis of VAS scores by Treatment and Center (Pooled Study)

	Center 1			Center 2			Center 3			Center 4		
	Total	Heated	No Heat	Total	Heated	No Heat	Total	Heated	No Heat	Total	Heated	No Heat
All Patients	120	59	61	130	64	66	130	63	67	120	60	60
VAS												
Mean	23.3	21.3	25.2	23.1	19.2	27.0	23.7	20.8	26.4	21.2	22.0	20.5
STD	21.3	21.1	21.5	21.0	18.3	22.7	19.5	18.3	20.3	21.7	22.0	21.7
Median	16.5	12.0	22.0	18.0	13.0	20.5	19.0	18.0	22.0	14.0	14.5	13.5
Range	0 – 90	0 – 85	0 – 90	0 – 85	0 – 71	1 – 85	0 – 84	0 – 84	0 – 68	0 – 97	0 – 97	0 – 95
Geometric	15.1	13.3	17.0	15.6	12.5	19.4	16.4	14.5	18.6	12.6	12.7	12.4
P-value (Mean)	0.0279[a]	0.0325[b]	0.0254[c]									
P-value (geometric)	0.0129[a]	0.0148[b]	0.0117[c]									
% Adequate	81 (68)	43 (73)	38 (62)	89 (68)	49 (77)	40 (61)	91 (70)	51 (81)	40 (60)	73 (61)	37 (62)	36 (60)
P-value	0.0028[a]	0.0024[c]										
Breslow-Day	0.3213	0.6385										
% Again	82 (68)	46 (78)	36 (59)	90 (69)	48 (75)	42 (64)	91 (70)	48 (76)	43 (64)	78 (65)	39 (65)	39 (65)
P-value	0.0110[a]	0.0102[c]										
Breslow-Day	0.4353	0.6406										

[a] ANOVA with center and treatment
[b] ANOVA with center, treatment, and center*treatment
[c] ANOVA with center, treatment, and study

Additional analysis was performed to assess the mean VAS score between subjects receiving the heated patch and subjects receiving the unheated patch. The higher the mean VAS scores, the greater the pain the subjects had scored. It appears that significantly higher proportion of subjects who received the heated S-Caine patch reported lower VAS score compared with those who received the unheated patches (Figure 5).

Figure 5: Patient's Pain Profile (Pooled Study)



5.2 CONCLUSIONS AND RECOMMENDATIONS

Based on the evidence presented from study SC-55-04, the heating component contributed to the efficacy of the S-Caine Patch.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joan Buenconsejo
4/26/05 10:10:12 AM
BIOMETRICS

Thomas Permutt
4/26/05 03:14:39 PM
BIOMETRICS
concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review—IND Protocol

CLINICAL STUDIES

NDA:	21-623
Name of drug:	S-Caine Patch (lidocaine 70 mg and tetracaine 70 mg)
Applicant:	Zars
Indication:	[redacted]
Documents reviewed:	meeting package
Project manager:	Lisa Malandro
Dates:	received 2 April 2004, meeting 3 May 2004
Statistical reviewer:	Thomas Permutt (team leader)
Biometrics division director:	S. Edward Nevius, Ph.D.

Keywords: IND review, clinical studies

1 SUMMARY

The subject submission is a briefing package for a meeting held 3 May 2004 to discuss the applicant's plan to address deficiencies in NDA 21-623 noted in our action letter 4 February 2004. The product is a patch containing the local anesthetics lidocaine and tetracaine and also incorporating a chemical heating element thought to enhance the effects of the drugs. We noted, "The S-Caine heating element has not been demonstrated to contribute to product efficacy." We required either evidence of the contribution or labeling stating the absence of such evidence.

The meeting package contains a protocol for a double-blind, parallel-group study comparing the test article to a nonheating patch. The protocol appears generally to address satisfactorily the issue of the contribution of the heating element, and we said so at the meeting. Some technical aspects of the protocol did not warrant taking meeting time for discussion, and we promised comments in writing.

2 COMMENTS

1. The primary analysis proposed is a comparison of the means of the logarithms of pain reported by subjects on a visual analog scale (VAS). We think the means of the untransformed VAS scores would be more readily interpretable.

2. The primary analysis is a simple t-test, but a model with center effects is described as "exploratory." It is probably advantageous for the primary analysis in multicenter trials to incorporate center effects.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Permutt
6/22/04 03:27:19 PM
BIOMETRICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

STABILITY STUDIES

NDA:	21-623
Name of drug:	S-Caine (lidocaine 70 mg and tetracaine 70 mg) patch
Applicant:	Zars
Indication:	[redacted]
Document reviewed:	electronic data at \\CDSESUB1\N21623\N_000\2003-08-01\SASFDA2.xpt
Project manager:	Lisa Malandro
Chemistry reviewer:	Ravi Harapanhalli, Ph.D.
Dates:	letter 31 March 2003; user fee goal (10 months) 4 February 2004
Statistical reviewer:	Thomas Permutt

S-Caine patch is a mixture of the local anesthetics lidocaine and tetracaine, intended to be applied to the skin to produce local anesthesia. The rationale for the mixture is physicochemical rather than medical: the mixture has a lower melting point than either of the components, allowing the formulation of a liquid-in-liquid emulsion. The patch also incorporates a chemical heating element which may enhance the migration of drug into the skin.

No report on stability appears to have been submitted except for the referenced data set itself. It contains data at 25C/60%RH for 18 months with vertical storage. There are also 12 months of data under higher temperatures, as well as some studies of horizontal storage, cold storage and freeze-thaw cycles. The requested expiration dating is for [redacted] which can potentially be supported only by extrapolation of the 18 months of room-temperature data, on which I therefore focus here, in consultation with Dr. Harapanhalli.

Many of the observations for impurities are represented by a missing value code. I take this to mean that none of the impurity was detected, rather than that the test was not performed. This is not documented, however, and should be confirmed with the applicant.

Only seven individual determinations were outside the specifications at any time. Table 1 shows these seven observations along with replicate determinations of the same batch at the same time. In all cases the mean of the replicates was well within the specifications.

To evaluate the possible extrapolation of expiration dating to [redacted], I fit the customary linear regression model. That is, the value was modeled as a linear function of time in each batch by ordinary least squares. Batches were pooled with respect to slope and intercept if neither the slopes nor the intercepts were significantly different at level 0.25. A common slope and separate intercepts were fit if the intercepts but not the slopes were significantly different for the three batches.

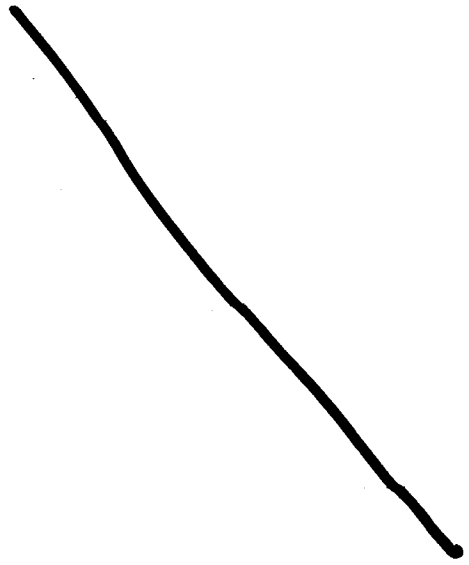
All the parameters but one would support a tentative extrapolation to [redacted] The assay for tetracaine, however, approaches the lower limit of 90 percent of the label claim by 18 months. The lower confidence bound crosses the specification just before [redacted]

Accordingly, I recommend that the requested expiration dating of [redacted] not be granted. Dating to 18 months at room temperature is supported by real-time data. Extrapolation to [redacted] may be tentatively permitted, to be confirmed by real-time data when available. Longer dating may also be granted later on accrual of favorable data.

The figures show the observations, the specifications and the 95-percent confidence intervals for the regression lines for parameters identified by Dr. Harapanhalli as being of particular interest.

Table 1. Determinations out of specifications, and replicates of same.

Obs	TEMP_HUM	ORIENTAT	batch	time	parm	lo	hi	value
1	25/60	vertical						
2	25/60	vertical						
3	25/60	vertical						
4	25/60	vertical						
5	25/60	vertical						
6	25/60	vertical						
7	25/60	vertical						
8	25/60	vertical						
9	25/60	vertical						
10	25/60	vertical						
11	25/60	vertical						
12	25/60	vertical						
13	25/60	vertical						
14	25/60	vertical						
15	25/60	vertical						
16	25/60	vertical						
17	25/60	vertical						
18	25/60	vertical						
19	25/60	vertical						
20	25/60	vertical						
21	25/60	vertical						
22	25/60	vertical						
23	25/60	vertical						
24	25/60	vertical						
25	25/60	vertical						
26	25/60	vertical						
27	25/60	vertical						
28	25/60	vertical						
29	25/60	vertical						
30	25/60	vertical						
31	25/60	vertical						
32	25/60	vertical						
33	25/60	vertical						



Appears This Way
On Original

16 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Statistical- 6

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Permutt
1/16/04 12:51:36 PM
BIOMETRICS

Karl Lin
1/16/04 01:20:36 PM
BIOMETRICS
Concur with review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-623
Drug Name:	S-Caine patch (lidocaine 70 mg and tetracaine 70 mg)
Indication(s):	[redacted]
Applicant:	ZARS, Inc.
Date(s):	Vol 1, 1.48-1.63, dated March 31, 2003 Addendum dated August 1, 2003
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Milton C. Fan, Ph.D. (HFD-715)
Concurring Reviewers:	Thomas Permutt, Ph.D. (HFD-715)
Medical Division:	Anesthetic, Critical Care, and Addition Drug Products (HFD-170)
Clinical Team:	Howard Josefberg, M.D. (HFD-170)
Project Manager:	Lisa Malandro (HFD-170)

Keywords: clinical study, crossover study, VAS

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

1.1.1 Pediatric Studies

The sponsor has submitted two controlled efficacy study (SC-20-01, SC-21-01) in support of the proposed claim.

For the primary endpoint, patient's evaluation of pain, younger children (used photographic scale) in S-Caine treated group had statistically significantly lower pain score than those in placebo treated group, as observed in both studies. But, for older children (used numerical scale), both of studies revealed that the treatment difference was not statistically significant.

For the secondary endpoints, Study SC-20-01 indicated that the treatment difference was statistically significant in investigator's evaluation of patient's pain and independent observer's evaluation of patient's pain, but was not statistically significant in investigator's overall impression of the local anesthetic.

Contrary to finding from study SC-20-01, Study SC-21-01 revealed that the treatment difference was statistically significant in investigator's overall impression of the local anesthetic, but was not statistically significant in both investigator's evaluation of patient's pain and independent witness' evaluation of patient's pain. However, this reviewer found that overall statistically significant results in investigator's overall impression of the local anesthetic was driven by the result from Center 6, dominated by younger children.

It might need an additional large efficacy study to show the efficacy for older children and to resolve the inconsistent results for secondary endpoints, as observed from Studies SC-20-01 and SC-21-01.

1.1.2. Vascular Access Procedures in Adult Patients

The sponsor has submitted two randomized, placebo-controlled, cross-over studies (Study SC-11-1 and Study SC-24-1) for adults in support of the proposed claim.

The placement of the active and placebo treatments was randomized to either the subject's right or left antecubital surface. The sponsor did not address the statistical issues of pooling site (right arm and left arm). If treatment by placement site interaction exists, then the result of cross-over study is very difficult to interpret. To maintain blinding during the trial is challenging for the cross-over study. Particularly, when the endpoint is subjective measurement, it is difficult to control potential biases resulted from a cross-over study.

The sponsor failed to perform the test for a difference between residual effects.

For Study SC-11-1, it was found that there is no difference in mean VAS scores measured at between right arm and left arm for S-Caine treated group. However, for placebo treated group the difference in mean VAS scores measured at right arm and left arm was large; mean and median of VAS scores measured at left arm were three times those measured at right arm.

This reviewer performed Mann-Whitney-Wilcoxon test for a difference between residual effects when the response variable is quantitative but not necessary normally distributed. The results of Mann-Whitney Wilcoxon test showed the difference between two treatments' residual effect was statistically significant at significance level of 0.10.

This reviewer performed Mann-Whitney-Wilcoxon test for the direct effects using measurements obtained from the right arm. The resulting for testing the hypothesis of equal direct effects showed that the treatment difference in favor of S-Caine was statistically significant at the 0.01 level. However, the treatment difference, about 7.0 mm in mean and 8.0 in median, might not be clinical meaningful.

For Study SC-24-1, it was found that there is no difference in mean VAS scores measured at between right arm and left arm for placebo treated group for both Center 1 and Center 2. However, for S-Caine treated group mean of VAS scores measured at right arm for Center 1 was larger than that for Center 2. The reverse was true for left arm. The median of VAS scores measured at right arm was about two times that measured at left arm for Center 1. The reverse was true for Center 2.

This reviewer performed Mann-Whitney-Wilcoxon test for a difference between residual effects when the response variable is quantitative but not necessary normally distributed. The results of Mann-Whitney Wilcoxon test showed that the difference between two treatments' residual effect is not statistically significant at significant level of 0.10.

This reviewer performed Mann-Whitney-Wilcoxon test for the direct effects for Center 1 and Center 2. The results for testing the hypothesis of equal direct effects for Center 1 and Center 2 showed that the treatment difference was statistically significant at the 0.05 level and 0.01 level, for Center 1 and for Center 2, respectively.

For secondary efficacy variables, results from this study across centers were inconsistent. The overall statistical significance was driven by high statistical significant results from Center 2.

There were inconsistent results for secondary endpoints across centers for Studies SC-24-01.

It might need an additional large multi-center parallel efficacy study to show the effectiveness of S-Caine patch.

1.1.3. Minor Dermatologic Procedure in Adult Patients

The sponsor has submitted one controlled efficacy study (SC-22-01) for geriatric patients and one study (SC-23-01) for adult patients in support of the proposed claim.

For geriatric patient, Study SC-22-01 indicated that treatment difference was not statistically significant in primary endpoint, patient VAS score, and in all secondary endpoints, additional patient pain evaluation and investigator's evaluation of patient's pain, independent observer's evaluation of patient pain and investigator's overall impression of the local anesthetic from Intent-to-Treat analysis.

For adult patient, Study SC-23-01 revealed that treatment difference in favor of S-Caine was statistically significant for primary endpoint, patient VAS core and all secondary endpoints, patient's overall impression, investigator's evaluation of patient's pain, independent witness' evaluation of patient's pain, and investigator's overall impression. This reviewer found that patient VAS score with S-Caine was statistically significantly lower than placebo across centers.

1.2 Brief Overview of Clinical Studies

1.2.1 Pediatric Studies

The sponsor has submitted two controlled efficacy study (SC-20-01, SC-21-01) in support of the proposed claim.

1.2.1.1 Study SC-20-01

This study was a multi-center (2 sites), randomized, double-blind, placebo-control study to evaluate the S-Caine patch for indication of local anesthesia for vascular access procedures in pediatric patients. In addition, Quantitative Sensory Testing (QST) was performed on certain patients to assess thermal sensation and vibratory sensation.

The objectives of this study were to compare the clinical effectiveness of an S-Caine patch to a placebo patch in providing clinically useful local anesthesia for vascular access procedures in pediatric patients and to access and compare thermal and vibratory sensations (age 7-17 years) following applications of both the S-Caine patch and EMLA Anesthetic Disc as measured by Quantitative Sensory Testing (QST).

In this statistical evaluation, QST evaluation would not be addressed.

All patients aged 3-17 underwent a vascular access procedures were randomized, 2:1, active: placebo into one to two treatment groups (1) active S-Caine patch or (2) placebo S-Caine patch.

The S-Caine patch (active or placebo) was placed directly over the designated treatment area for 20 minutes prior to the vascular access procedures. Immediately following removal of the patch, the investigator performed the "Evaluation of Skin Reactions" evaluating erythema and edema. The vascular access procedures would then be performed. Upon completion of the vascular access procedure, the patient assessed the amount of pain associated with the procedure using the Oucher Self Assessment Pain Scale. The pain evaluation should be completed upon the first attempt to gain IV access. The investigator also evaluated the degree of anesthesia the patch provided by completing a Post-Procedure Pain Assessment (0=no pain, 1=slight pain, 2=moderate pain, and 3=severe pain) and by stating (yes) if the patch provided adequate

anesthesia for the procedure. In addition, an independent observer scored his/her perception of the patient's pain by completing the Post-Procedure Pain Assessment.

The Oucher is a poster-like instrument used to measure pain intensity in children ages 3-17. The Oucher consists of two scales: a 0-100 numerical scale for older children and a six picture photographic for younger children.

The primary efficacy endpoint was patient pain as determined by the Oucher Pain Scale, a patient self-assessment pain tool widely validated in pediatric patients.

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

Oucher pain scales and assessment scales for efficacy and evaluation of skin reactions were compared between treatment groups stratified by study center using Mantel-Haenszel summary chi-square tests. Oucher scale results were further stratified by the scale used.

From a previous study, the percent of placebo patients with no pain was no greater than 30 percent. The effectiveness of an S-Caine patch is expected to be in excess of 70 percent for patients with no pain. Using a two-sided significance level of five percent and a power of 80 percent, 36 active and 18 placebo patients per group are needed. This study was initially designed for two centers, each center with thirty total patients for a total 40 active and 20 placebo patients.

A total of 65 patients entered the study and were randomized to treatment; 43 to the S-Caine patch group and 22 to the placebo group.

1.2.1.2 Study SC-21-01

This was a multi-center (6 sites), randomized, double-blind, clinical study to compare the effectiveness of the S-Caine patch to the EMLA anesthetic disc in providing clinically useful local anesthesia for minor dermatological procedures (curettage or shave biopsy) or for injection of subcutaneous lidocaine in pediatric patients.

The objective of this study was to compare the clinical effectiveness of an S-Caine Patch to an EMLA anesthetic disc in providing clinically useful local anesthesia in pediatric patients aged 7-17 undergoing curettage or shave biopsy procedure or subcutaneous injection of lidocaine.

Patients, ages 3-17 was separated by age into two groups: (1) patients ages 3-6 and (2) patients ages 7-17. In each group, patients were randomized (1:1) into one of two treatment groups: (1) active S-Caine patch or (2) EMLA anesthetic disc. In this study, the S-Caine patch was applied for 30 minutes and the EMLA anesthetic disc was applied for 60 minutes.

The group of patents ages 3-6 received either the S-Caine patch or the EMLA anesthetic disc prior to the administration of a lidocaine injection. The group of patients ages 7-17 received either the S-Caine patch or the EMLA anesthetic disc prior to minor dermatological procedure (curettage or shave biopsy).

Each patient assessed the amount of pain associated with the procedure by completing the Oucher Self Assessment Pain Scale. For patient ages 7-17, the Oucher pain assessment was completed after the minor dermatological procedure was performed. If the patient required a rescue lidocaine injection during the minor dermatological procedure, patient should assessed the amount of pain experienced prior to the administration of the rescue injection. For patient ages 3-6, the Oucher pain assessment was completed immediately after the lidocaine injection had been administered. The investigator evaluated the degree of anesthesia the topical anesthetic provided by completing a pain assessment scale and by stating if the topical anesthetic provided adequate anesthesia for the procedure. An independent observer also scored his/her perception of the patient's pain utilizing the Post-Procedure Pain Assessment Scale.

The primary efficacy endpoint for the study was patient pain as determined by the Oucher Pain Scale.

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

Oucher pain scales and assessment scales for efficacy and evaluation of skin reactions were compared between treatment groups stratified by study center using Mantel-Haenszel summary chi-square tests. Oucher scale results were further stratified by the scale used.

From a previous study, the percent of patients receiving S-Caine patch who had no pain was 67%, compared to 10% of placebo patients. This study was designed for 80 total patients, 40 at each of two centers, with 20 patients receiving each treatment per center. The sample size will detect a difference in responses as much as 33% between EMLA and S-Caine, using a two-sided significance level of 5% and a power of 80%.

Six amendments were made to the protocol. The major changes to the protocol were to modify the design of study from a double-blind study comparing the S-Caine patch to EMLA to a double-blind placebo controlled study and to modify statistical procedure and sample size determination as a result of the design changes to the study.

A total of 88 patients were randomized: 41 to the S-Caine patch group and 47 to the placebo group. All patients completed the study.

1.2.2 Vascular Access Procedures in Adult Patients

1.2.2.1 SC-11-01

This was a randomized, double-blind, placebo-controlled, cross-over study to evaluate the effectiveness of the S-Caine patch in providing clinical useful local anesthesia for vascular access procedures in adult subjects.

The objective of this study was to compare the clinical effectiveness of an S-Caine patch to a placebo patch in providing clinically useful local anesthesia for vascular access procedures in adult subjects.

Each subject, ages 18 years and older, received one active and one placebo S-Caine patch on either antecubital surface (one patch on the subject's left antecubital surface and one patch on the subject's right antecubital surface). The placement of the active and placebo treatments was randomized, 1:1, to either the subject's right or left antecubital surface. The S-Caine patch (active or placebo) was placed directly over the designated treatment area for 20 minutes prior to vascular access procedure.

Immediately following removal of the patches, the investigator performed the "Evaluation of Skin Reactions" evaluating erythema and edema. Vascular access then was obtained in the subject's antecubital vein in the right arm. The subject's right antecubital surface should always be treated first.

Upon completion of the vascular access procedure in this arm, the subject assessed the amount of pain associated with the procedure using the Visual Analogue Scale (VAS Scale). The pain evaluation should be completed upon the first attempt to gain vascular access. The investigators also evaluated the degree of anesthesia the patch provided by completing a Post-Procedure Pain Assessment and by stating if the patch provided adequate anesthesia for the procedure. An independent observer also scored his/her perception of the patient's pain utilizing the Post-Procedure Pain Assessment Scale.

Following completion of the vascular access procedure in the right arm and subsequent pain evaluations, the investigator performed the vascular access procedure in the left arm. The same procedure and pain evaluations were performed for the procedure in this arm as they were for the right arm.

The primary efficacy endpoint was subject pain as determined by: (1) Visual Analogue Pain Scale (VAS Scale) and (2) investigator's evaluation of patient pain employing a uniform scale for such analysis.

VAS was compared using ANOVA for a crossover design or Wilcoxon signed rank test. Procedure duration, evaluation of skin reaction and pain assessment scales were compared between treatments using Wilcoxon signed rank tests.

Based on a previous study, active treatment eliminated pain when placebo did not in 80% of the cases, while placebo was better in only 10%. To detect a sign test preference of 80% vs. 20% in favor of active treatment, 19 patients are needed. Calculations were made assuming 80% power and a two-sided significance level of 5%.

A total of 21 subjects received both S-Caine and placebo treatment. One protocol deviation occurred during the study. The randomization was reversed for Subject 108. The S-Caine patch was applied to the left arm instead of the right arm. The statistical analysis was performed on how the patches were actually administered and not according to the randomization.

1.2.2.2 Study SC-24-01

This was a randomized, double-blind, placebo-controlled, cross-over study to evaluate the effectiveness of a twenty minute S-Caine patch application in providing clinical useful local anesthesia for vascular access procedures in adult subjects.

The objective of this study was to compare the clinical effectiveness of an S-Caine patch to a placebo patch in providing clinically useful local anesthesia for vascular access procedures in adult subjects.

Each subject, ages 18 years and older, simultaneously received both an active and on placebo S-Caine patch application for twenty minutes. The application sites were randomized (1:1) between the right and left antecubital surfaces. Each subject underwent venipuncture in both the right and let antecubital veins.

Immediately following the patch treatments, the investigator performed the "Evaluation of Skin Reactions" evaluating erythema, edema, and eschar formation. The subject was asked to look away from the insertion sites and an angiocatheter was inserted into the antecubital veins.

Upon completion of each vascular access procedure, the subject assessed the amount of pain associated with each procedure by completing the Visual Analogue Scale (VAS Scale). The pain evaluation should be completed upon the first attempt to gain IV access. The investigators also evaluated the degree of anesthesia the patch provided by completing a Post-Procedure Pain Assessment and by stating if the patch provided adequate anesthesia for the procedure.

The primary efficacy endpoint was subject pain as determined by: (1) Visual Analogue Pain Scale (VAS Scale) and (2) investigator's evaluation of patient pain employing a standardized scale.

Visual analog results were compared using paired t-tests or Wilcoxon signed rank test. Efficacy assessment scale results and evaluation of skin reaction results were analyzed using Wilcoxon signed rank tests and sign tests.

The sample size of 40 patients between two centers is sufficient to detect a paired difference between treatments of 15 points on the VAS (SD=25 point) or a sign test preference of 80% vs. 20% in favor of active treatment, both with 80% power and a two-sided significance level of 5%.

Two amendments were made to the protocol. The major changes of amendments were to add the independent observer efficacy evaluation and to add the requirement for study subjects to return to the site between 24-48 hours after the study drug application.

In addition to the amendments made the protocol, an additional 20 subjects were enrolled in the study because the first 20 subjects enrolled at one site received study treatment for 30 minutes instead of 20 minutes. Approval was obtained by the IRB prior to enrolling the additional 20 subjects.

Forty subjects were to simultaneously receive an S-Caine Patch and placebo patch 20 minutes prior to the start of a vascular access procedure. ——— site (Center 2) erroneously applied the patch for 30 minutes for the first 20 subjects, so an additional 20 subjects were enrolled utilizing the correct 20-minute application.

Efficacy was based only on subjects who received the 20-minute applications. None of subjects in ——— site were included in the efficacy evaluation and an additional 20 subjects were included in the efficacy evaluation.

Subject No. 24228 only had the S-Caine-patch applied due to a defective placebo patch.

1.2.3 Minor Dermatologic Procedure in Adult Patients

1.2.3.1 SC-22-01

This was a randomized, double-blind, placebo-controlled study to evaluate the effectiveness of an S-Caine patch in providing clinical useful local anesthesia for minor dermatological procedures in patients seventy years of age and above.

The objective of this study was to compare the clinical effectiveness of an S-Caine patch to a placebo patch in providing clinically useful local anesthesia for minor dermatological procedures in geriatric patients (70 years and older).

Each patient, ages 70 years and older, was randomized (2:1, active: placebo) to receive either active or placebo S-Caine patch, 30 minutes prior to the scheduled shave biopsy or excision procedure.

Immediately following the patch treatments, the investigator performed the "Evaluation of Skin Reactions" evaluating erythema, edema, and eschar formation. The investigator then began the minor dermatological procedure. At any time during the procedure, the investigator might perform a rescue lidocaine injection if the patients was not receiving adequate anesthesia.

Upon completion of the minor dermatological procedure, the patient assessed the amount of pain associated with each procedure by completing the Visual Analogue Scale (VAS Scale). If the patient received a rescue injection, the patient would assess the amount of pain he/she experienced during the procedure, prior to the rescue injection. The investigators also evaluated

the degree of anesthesia the patch provided by completing a Post-Procedure Pain Assessment and by stating if the patch provided adequate anesthesia for the procedure. An independent observer also scores his/her perception of the patient's pain utilizing the Post-Procedure Pain Assessment Scale.

The primary efficacy endpoint was patient pain as determined by: (1) Visual Analogue Pain Scale (VAS Scale) and (2) investigator's evaluation of patient pain employing a standardized scale.

Demographic and background variables were summarized using descriptive statistics and compared between treatment groups using t-tests for continuous variables, Mann Whitney tests for ordered categorical data and Fisher's exact test for dichotomous responses.

Visual analog pain scales results were compared between treatments using t-tests or Mann Whitney tests. Assessment scales for efficacy and evaluation of skin reactions were compared between groups using Mann Whitney tests. Dichotomous results were compared using Fisher's exact tests.

Based on a previous study, a treatment difference between active and placebo of approximately 15 units was seen with a standard deviation of 15 in VSA. Using a two-sided significance level of 5% and a power of 80%, 26 active patients and 13 placebo patients are needed (2:1 randomization). The study was designed for a total of 50 patients.

Four amendments were made to the protocol.

Amendments 1 and 2 were implemented prior any patients enrolling in study. The major changes were to reduce the age criteria for study enrollment from 70 years to 65 years and to increase the sample size from 50 to 75 so that efficacy differences among different types of procedures could be explored.

Amendment 3 was implemented approximately 1 month after the study had commenced. The major change was to increase the number of investigational sites to 4 and to increase the sample size from 75 to 80 patients.

A total of 79 patients were randomized: 54 to the S-Caine group and 25 to the placebo group. All patients completed the study.

One of the 4 centers, Center 3 did not follow the assigned randomization schedule, but chose patches at random from the pool of patches.

1.2.3.2 SC-23-01

This was a multi-center (2 sites), randomized, double-blind, placebo-controlled study to evaluate the effectiveness of an S-Caine patch in providing clinical useful local anesthesia for minor dermatological procedures in adult patients.

The objective of this study was to compare the clinical effectiveness of an S-Caine patch to a placebo patch in providing clinically useful local anesthesia for minor dermatological procedures in adult patients.

Each patient, ages 18 years and older, was randomized (1:1, active: placebo) to receive either active or placebo S-Caine patch, 30 minutes prior to the scheduled shave biopsy or excision procedure. Treatment groups were further stratified by procedure, 2:1, shave biopsy; excision procedure.

Immediately following the patch treatments, the investigator performed the "Evaluation of Skin Reactions" evaluating erythema, edema, and eschar formation. The investigator then began the minor dermatological procedure. At any time during the procedure, the investigator might perform a rescue lidocaine injection if the patients was not receiving adequate anesthesia.

Upon completion of the minor dermatological procedure, the patient assessed the amount of pain associated with each procedure by completing the Visual Analogue Scale (VAS Scale). If the patient received a rescue injection, the patient would assess the amount of pain he/she experienced during the procedure, prior to the rescue injection. The investigators also evaluated the degree of anesthesia the patch provided by completing a Post-Procedure Pain Assessment and by stating if the patch provided adequate anesthesia for the procedure. An independent observer also scores his/her perception of the patient's pain utilizing the Post-Procedure Pain Assessment Scale.

The primary efficacy endpoint was patient pain as determined by: (1) Visual Analogue Pain Scale (VAS Scale) and (2) investigator's evaluation of patient pain employing a standardized scale.

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

Visual analog pain scales results were compared between treatments using ANOVA with the factors: site, treatment, procedure and associated interaction. Assessment scales for efficacy and evaluation of skin reactions were compared between groups stratified by study site and procedure type using Mantel-Haenszel summary chi-square tests for ordered or dichotomous data.

Based on a previous study, a treatment difference between active and placebo of approximately 15 units was seen with a standard deviation of 15 in VSA. Using a two-sided significance level of 5% and a power of 80%, 17 patients per group are needed. The study was designed for two centers (30 patients each) for a total of 60 patients.

Two amendments were made to the protocol. The main changes in the first amendment were to increase the number of patients in each group from 30 to 45, for a total of 90 patients and to

eliminate the plan to stratify the patients by procedure. The main changes in the second amendment were to add an additional study site, for a total of 3 study sites (30 patients each).

A total of 94 patients were randomized: 45 to the S-Caine group and 45 to the placebo group. All patients completed the study.

1.3 Statistical Issues and Findings

1.3.1 Pediatric Studies

The sponsor has submitted two controlled efficacy study (SC-20-01, SC-21-01) in support of the proposed claim.

For the primary endpoint, patient's evaluation of pain, younger children (used photographic scale) in S-Caine treated group had statistically significantly lower pain score than those in placebo treated group, as observed in both studies. But, for older children (used numerical scale), both of studies revealed that the treatment difference was not statistically significant.

For the secondary endpoints, Study SC-20-01 indicated that the treatment difference was statistically significant in investigator's evaluation of patient's pain and independent observer's evaluation of patient's pain, but was not statistically significant in investigator's overall impression of the local anesthetic.

Contrary to finding from study SC-20-01, Study SC-21-01 revealed that the treatment difference was statistically significant in investigator's overall impression of the local anesthetic, but was not statistically significant in both investigator's evaluation of patient's pain and independent witness' evaluation of patient's pain.

There were inconsistent results for secondary endpoints across studies.

1.3.2. Vascular Access Procedures in Adult Patients

The sponsor has submitted two randomized, placebo-controlled, cross-over studies (Study SC-11-1 and Study SC-24-1) for adults in support of the proposed claim.

The placement of the active and placebo treatments was randomized to either the subject's right or left antecubital surface. The sponsor did not address the statistical issues of pooling site (right arm and left arm). If treatment by placement site interaction exists, then the result of cross-over study is very difficult to interpret. To maintain blinding during the trial is challenging for the cross-over study. Particularly, when the endpoint is subjective measurement, it is difficult to control potential biases resulted from a cross-over study.

The sponsor failed to perform the test for a difference between residual effects.

For Study SC-11-1, it was found that there was no difference of mean VAS scores measured at between right arm and left arm for S-Caine treated group. However, for placebo treated group

the difference in mean VAS scores measured at right arm and left arm was large; median and mean of VAS scores measured at left arm were three times those measured at right arm.

This reviewer performed Mann-Whitney-Wilcoxon test for a difference between residual effects when the response variable is quantitative but not necessary normally distributed. The results of Mann-Whitney Wilcoxon test showed the difference between two treatments' residual effect was statistically significant at significance level of 0.10.

This reviewer performed Mann-Whitney-Wilcoxon test for the direct effects using measurements obtained from the right arm. The resulting for testing the hypothesis of equal direct effects showed the treatment difference in favor of S-Caine was statistically significant at the 0.01 level. However, the treatment difference, about 7.0 mm in mean and 8.0 in median might not be clinical meaningful.

For Study SC-24-1, it was found that there was no difference in mean of VAS scores measured at between right arm and left arm for placebo treated group for both Center 1 and Center 2. However, for S-Caine treated group the mean of VAS scores measured at right arm for Center 1 was larger than that for Center 2. The reverse was true for left arm. The median of VAS scores measured at right arm were about two times that measured at left arm for Center 1. The reverse was true for Center 2.

This reviewer performed Mann-Whitney-Wilcoxon test for a difference between residual effects when the response variable is quantitative but not necessary normally distributed. The results of Mann-Whitney Wilcoxon test showed that the difference between two treatments' residual effect was not statistically significant at significant level of 0.10.

This reviewer performed Mann-Whitney-Wilcoxon test for the direct effects for Center 1 and Center 2. The results for testing the hypothesis of equal direct effects for Center 1 and Center 2 showed that the treatment difference was statistically significant at the 0.05 level and 0.01 level, for Center 1 and for Center 2, respectively.

For secondary efficacy variables, results from this study across centers are inconsistent. The overall statistical significance was driven by high statistical significant results from Center 2.

There were inconsistent results for secondary endpoints across centers for Studies SC-24-01.

1.3.3. Minor Dermatologic Procedure in Adult Patients

The sponsor has submitted one controlled efficacy study (SC-22-01) for geriatric patients and one study (SC-23-01) for adult patients in support of the proposed claim.

For geriatric patient, Study SC-22-01 indicated that treatment difference was not statistically significant in primary endpoint, patient VAS score, and in all secondary endpoints, additional patient pain evaluation and investigator's evaluation of patient's pain, independent observer's evaluation of patient pain and investigator's overall impression of the local anesthetic from Intent-to-Treat analysis.

For adult patient, Study SC-23-01 showed that treatment difference in favor of S-Caine was statistically significant for primary endpoint, patient VAS core and all secondary endpoints, patient's overall impression, investigator's evaluation of patient's pain, independent witness' evaluation of patient's pain, and investigator's overall impression. This reviewer found that patient's VAS score with S-Caine was statistically significantly lower than placebo across centers.

This study SC-23-01 was the sole study to show effectiveness of S-Caine patch.

2. INTRODUCTION

2.1 Overview

In the current NDA, the sponsor seeks approval of the S-Caine Patch for the indication of a

2.2 Data Sources

The sponsor has submitted six pivotal studies for the claim. These studies include:

Pediatric Studies

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

Study SC-21-01: A Randomized, Double-blind, Placebo Controlled Clinical Study Evaluating the S-Caine Patch for Induction of Local Anesthesia for Lidocaine Injection in Pediatric Patients

Vascular Access Procedures in Adult Patients

Study SC-11-01: A Randomized, Double-blind, Placebo Controlled Cross-Over Clinical Study Evaluating the S-Caine Patch for Induction of Local Anesthesia of the Skin Prior to Vascular Access Procedures in Adult Subjects

Study SC-24-01: A Randomized, Double-blind, Placebo Controlled Cross-Over Clinical Study Evaluating the S-Caine Patch for Induction of Local Anesthesia Prior to Vascular Access Procedures in Adult Subjects

Minor Dermatologic Procedures in Adult Patients

Study SC-22-01: A Randomized, Double-blind, Placebo Controlled Clinical Study Evaluating the S-Caine Patch for Induction of Local Anesthesia Prior to Minor Dermatologic Procedures in Geriatric Patients

Study SC-23-01: A Randomized, Double-blind, Placebo Controlled Clinical Study Evaluating the S-Caine Patch for Induction of Local Anesthesia for Minor Dermatologic Procedures in Adult Patients

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Pediatric Studies

3.1.1.1 Study SC-20-01

3.1.1.1.1. Study Design

This study was a multi-center (2 sites), randomized, double-blind, placebo-control study to evaluate the S-Caine patch for indication of local anesthesia for vascular access procedures in pediatric patients. In addition, Quantitative Sensory Testing (QST) was performed on certain patients to assess thermal sensation and vibratory sensation.

The objectives of this study were to compare the clinical effectiveness of an S-Caine patch to a placebo patch in providing clinically useful local anesthesia for vascular access procedures in pediatric patients and to access and compare thermal and vibratory sensations (age 7-17 years) following applications of both the S-Caine patch and EMLA Anesthetic Disc as measured by Quantitative Sensory Testing (QST).

In this statistical evaluation, QST evaluation would not be addressed.

All patients aged 3-17 underwent a vascular access procedures were randomized, 2:1, active: placebo into one to two treatment groups (1) active S-Caine patch or (2) placebo S-Caine patch.

The S-Caine patch (active or placebo) was placed directly over the designated treatment area for 20 minutes prior to the vascular access procedures. Immediately following removal of the patch, the investigator performed the "Evaluation of Skin Reactions" evaluating erythema and edema. The vascular access procedures would then be performed. Upon completion of the vascular access procedure, the patient assessed the amount of pain associated with the procedure using the Oucher Self Assessment Pain Scale. The pain evaluation should be completed upon the first attempt to gain IV access. The investigator also evaluated the degree of anesthesia the patch provided by completing a Post-Procedure Pain Assessment (0=no pain, 1=slight pain, 2=moderate pain, and 3=severe pain) and by stating (yes) if the patch provided adequate anesthesia for the procedure. In addition, an independent observer scored his/her perception of the patient's pain by completing the Post-Procedure Pain Assessment.

The Oucher is a poster-like instrument used to measure pain intensity in children ages 3-17. The Oucher consists of two scales: a 0-100 numerical scale for older children and a six picture photographic for younger children.

The primary efficacy endpoint was patient pain as determined by the Oucher Pain Scale, a patient self-assessment pain tool widely validated in pediatric patients.

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

Oucher pain scales and assessment scales for efficacy and evaluation of skin reactions were compared between treatment groups stratified by study center using Mantel-Haenszel summary chi-square tests. Oucher scale results were further stratified by the scale used.

From a previous study, the percent of placebo patients with no pain was no greater than 30 percent. The effectiveness of an S-Caine patch is expected to be in excess of 70 percent for patients with no pain. Using a two-sided significance level of five percent and a power of 80 percent, 36 active and 18 placebo patients per group are needed. This study was initially designed for two centers, each center with thirty total patients for a total 40 active and 20 placebo patients.

3.1.1.1.2 Sponsor's Analysis

A total of 65 patients entered the study and were randomized to treatment; 43 to the S-Caine patch group and 22 to the placebo group.

One patient (No. 20215) was assigned to receive placebo but withdrew consent prior to undergoing any study procedures. One patient (No. 20201) who received treatment with the S-Caine patch, was uncooperative and refused to undergo the procedure following patch treatment. Following application of the study patch the study staff determined that 2 patient (No. 20237 and No. 20231) did not require vascular access procedure: Patient 20237 who received the S-Caine patch and patient 20231 who received the placebo patch.

Data from 41 of 43 patients in the S-Caine patch group and 20 of 21 patients in the placebo group were included in the efficacy analyses. Three patients (2 in the S-Caine patch: 20201 and 20237 and one in the placebo: 20231) were excluded from the efficacy analyses because they did not undergo the vascular access procedure and no efficacy evaluations were performed.

3.1.1.1.2.1 Treatment Group Comparability

A summary of the number of patients by demographic and baseline characteristics and minor dermatological procedure by treatment group is given in Attached Table 1.

As seen from Attached Table 1, the treatment groups appeared similar with regard to all demographic and baseline characteristics and minor dermatological procedure except skin type. There were significant center differences for race, skin type, procedure type, needle gauge, and procedure duration.

3.1.1.1.2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy endpoint was patient's evaluation of pain following the vascular access procedure using the Oucher Pain Scale. The patient used the numerical scale (0-100, 11 point categorical scale) or the photographic scale (0-100, 6-point categorical scale with numbers associated with pictures).

The results of Oucher scores by treatment group for patients who used the photographic version of the scale, generally children who were 6 or 7 years old or less, are listed below.

Photographic Scale
Study SC-20-1

		S-Caine			Placebo		
Center	N	Mean	Median	N	Mean	Median	P-value
Center 1	11	16.4	0.0	6	56.7	60.0	
Center 2	14	17.1	0.0	5	68.0	80.0	
Total	25	16.8	0.0	11	61.8	80.0	<0.001

Compiled by this reviewer from Table 14.2.1, Vol.53.
p-value was obtained by Mann-Whitney test.
Mean was computed by this reviewer.

The results of Oucher scores by treatment group for patients who used the numeric version of the scale are listed below.

Numerical Scale
Study SC-20-1

		S-Caine			Placebo		
Center	N	Mean	Median	N	Mean	Median	P-value
Center 1	9	20.0	10.0	4	40.0	40.0	
Center 2	7	16.4	0.0	5	44.0	50.0	
Total	16	18.4	7.5	9	42.2	50.0	0.159

Compiled by this reviewer from Table 14.2.1, Vol.53.
p-value was obtained by Mann-Whitney test.
Mean was computed by this reviewer

As seen from tables above, S-Caine patch was significant more effective than placebo patch in younger children (i.e., those used the photographic version of the Oucher Scale). But, the results were not statistically significant for older patients (i.e., those used the numerical version of the Oucher Scale).

3.1.1.1.2.3 Sponsor's Analysis of Secondary Efficacy Variable

3.1.1.1.2.3.1 Investigator's Evaluation of Patient's Pain

The investigator assessed the amount of pain they felt the patient had experienced during the vascular access procedure. The results of investigator's assessments are summarized below.

Investigator's Evaluation of Patient's Pain
Study SC-20-01

Center	Pain Rating	S-Caine	Placebo	p-value
Center 1	No Pain	15 (75.0%)	2 (20.0%)	
	Slight Pain	3 (15.0%)	6 (60.0%)	
	Moderate Pain	2 (10.0%)	2 (20.0%)	
Center 2	No Pain	16 (76.2%)	2 (20.0%)	
	Slight Pain	2 (9.5%)	5 (50.0%)	
	Moderate Pain	3 (14.3%)	3 (30.0%)	
Total	No Pain	31 (75.6%)	4 (20.0%)	
	Slight Pain	5 (12.2%)	11 (55.0%)	
	Moderate Pain	5 (12.2%)	5 (25.0%)	0.001

Complied by this reviewer from Table 14.2.2. Vol. 53
P-value was obtained by Mantel-Haenszel summary chi-square.

As seen from the table above, there was significant treatment difference in favor of S-Caine patch in terms of investigator's evaluation of patient's pain.

3.1.1.1.2.3.2 Investigator's Overall Impression of the Local Anesthetic

The investigator was asked whether the local anesthetic provided adequate anesthesia for the procedure.

The results of adequate anesthesia provided are summarized below.

Adequate Anesthesia Provided
Primary Per-Protocol Analysis
Study SC-20-01

Center	S-Caine	Placebo	p-value
Center 1	16/20 (80.0%)	8/10 (80.0%)	
Center 2	17/21 (81.0%)	6/10 (60.0%)	
Total	33/41 (80.5%)	14/20 (70.0%)	0.556

Compiled by this reviewer from Table 14.2.2. Vol. 53.
P-value was obtained by Mantel-Haenszel summary chi-square.

As seen from the table above, there was no treatment difference in terms of adequate anesthesia provided.

3.1.1.1.2.3.3 Independent Observer's Evaluation of Patient's Pain

The independent observer also assessed the amount of pain they felt the patient had experienced during the vascular access procedure. The results of independent observer's assessments are summarized below.

Independent Observer's Evaluation of Patient's Pain
Study SC-20-01

Center	Pain Rating	S-Caine	Placebo	p-value
Center 1	No Pain	15 (75.0%)	2 (20.0%)	
	Slight Pain	3 (15.0%)	5 (50.0%)	
	Moderate Pain	2 (10.0%)	2 (20.0%)	
	Severe Pain		1 (10%)	
Center 2	No Pain	16 (76.2%)	1 (10.0%)	
	Slight Pain	3 (14.3%)	6 (60.0%)	
	Moderate Pain	2 (9.5%)	3 (30.0%)	
Total	No Pain	31 (75.6%)	3 (15.0%)	
	Slight Pain	6 (14.6%)	11 (55.0%)	
	Moderate Pain	4 (9.8%)	5 (25.0%)	
	Severe Pain		1 (5.0%)	<0.0001

Complied by this reviewer from Table 14.2.2. Vol. 53
P-value was obtained by Mantel-Haenszel summary chi-square.

As seen from the table above, there was significant treatment difference in favor of S-Caine patch in terms of independent observer's evaluation of patient's pain.

3.1.1.1.3 Reviewer's Comments and Evaluation

3.1.1.1.3.1 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

The patient used the numerical scale (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100) or the photographic scale (0, 20, 40, 60, 70, 80, 100) for Oucher Pain Scale for patient's evaluation of pain following the vascular access procedure. The sponsor used Mann-Whitney test to compare S-Caine patch vs. placebo.

In this study the scale of measurement is integer scores and is not continuous. The more appropriate method of analyzing data with integer scores is to use Cochran-Mantel-Haenszel test stratified by center. Furthermore, the observed numerical scales used in this study were 0, 5, 10, 20, 30, 40, 50, 70, 80, and 100. The observed scales were not equal spaced. This reviewer re-analyzed patient's evaluation of pain using Cochran-Mantel-Haenszel method stratified by center using table scores for photographic scale and using modified ridit scores for numerical scale. The results gave the similar results as those given by the sponsor. But, p values were 0.0009 and 0.2545 for photographic scale and numeric scale, respectively.

3.1.1.1.3.2 Reviewer's Analysis of Analysis of Primary Efficacy Variable Adjusted for Skin Type

There was baseline imbalance in skin types (p=0.017). The reviewer performed a post-hoc covariance analysis for patient's evaluation of pain for patients who used the photographic scale using the Cochran-Mantel-Haenszel test stratified by skin type. The resulting p-value was 0.0577, much larger than that without adjusting for skin type (p<0.001).

3.1.1.2 Study SC-21-01

3.1.1.2.1 Study Design

This was a multi-center (6 sites), randomized, double-blind, clinical study to compare the effectiveness of the S-Caine patch to the EMLA anesthetic disc in providing clinically useful local anesthesia for minor dermatological procedures (curettage or shave biopsy) or for injection of subcutaneous lidocaine in pediatric patients.

The objective of this study was to compare the clinical effectiveness of an S-Caine Patch to an EMLA anesthetic disc in providing clinically useful local anesthesia in pediatric patients aged 7-17 undergoing curettage or shave biopsy procedure or subcutaneous injection of lidocaine.

Patients, ages 3-17 was separated by age into two groups: (1) patients ages 3-6 and (2) patients ages 7-17. In each group, patients were randomized (1:1) into one of two treatment groups: (1) active S-Caine patch or (2) EMLA anesthetic disc. In this study, the S-Caine patch was applied for 30 minutes and the EMLA anesthetic disc was applied for 60 minutes.

The group of patents ages 3-6 received either the S-Caine patch or the EMLA anesthetic disc prior to the administration of a lidocaine injection. The group of patients ages 7-17 received either the S-Caine patch or the EMLA anesthetic disc prior to minor dermatological procedure (curettage or shave biopsy).

Each patient assessed the amount of pain associated with the procedure by completing the Oucher Self Assessment Pain Scale. For patient ages 7-17, the Oucher pain assessment was completed after the minor dermatological procedure was performed. If the patient required a rescue lidocaine injection during the minor dermatological procedure, patient should assessed the amount of pain experienced prior to the administration of the rescue injection. For patient ages 3-6, the Oucher pain assessment was completed immediately after the lidocaine injection had been administered. The investigator evaluated the degree of anesthesia the topical anesthetic provided by completing a pain assessment scale and by stating if the topical anesthetic provided adequate anesthesia for the procedure. An independent observer also scored his/her perception of the patient's pain utilizing the Post-Procedure Pain Assessment Scale.

The primary efficacy endpoint for the study was patient pain as determined by the Oucher Pain Scale.

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

Oucher pain scales and assessment scales for efficacy and evaluation of skin reactions were compared between treatment groups stratified by study center using Mantel-Haenszel summary chi-square tests. Oucher scale results were further stratified by the scale used.

From a previous study, the percent of patients receiving S-Caine patch who had no pain was 67%, compared to 10% of placebo patients. This study was designed for 80 total patients, 40 at each of two centers, with 20 patients receiving each treatment per center. The sample size will detect a difference in responses as much as 33% between EMLA and S-Caine, using a two-sided significance level of 5% and a power of 80%.

Six amendments were made to the protocol. The major changes to the protocol were to modify the design of study from a double-blind study comparing the S-Caine patch to EMLA to a double-blind placebo controlled study and to modify statistical procedure and sample size determination as a result of the design changes to the study.

3.1.1.2.2 Sponsor's Analysis

A total of 88 patients were randomized: 41 to the S-Caine patch group and 47 to the placebo group. All patients completed the study.

3.1.1.2.2.1 Treatment Comparability

A summary of the number of patients by demographic and baseline characteristics and minor dermatological procedure by treatment group is given in Attached Table 2.

As seen from Attached Table 2, the treatment groups appeared similar with regard to all demographic and baseline characteristics and minor dermatological procedure. There were significant center differences for age, race, height, weight, and time to injection.

3.1.1.2.2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy endpoint was patient's evaluation of pain following the vascular access procedure using the Oucher Pain Scale. The patient used the numerical scale (0-100, 11 point categorical scale) or the photographic scale (0-100, 6-point categorical scale with numbers associated with pictures).

The results of Oucher scores by treatment group for patients who used the photographic version of the scale, generally children who were 6 or 7 years old or less, are listed below.

Photographic Scale
Study SC-21-01

	S-Caine			Placebo		
N	Mean	Median	N	Mean	Median	P-value
21	23.8	0.0	22	58.2	70	0.005

Compiled by this reviewer from Table 14.2.1, Vol.54.
p-value was obtained by Mann-Whitney test.
Mean was computed by this reviewer

The results of Oucher scores by treatment group for patients who used the numeric version of the scale are listed below.

Numerical Scale
Study SC-21-01

	S-Caine			Placebo		
N	Mean	Median	N	Mean	Median	P-value
20	18.0	10.0	25	20.0	10.0	0.322

Compiled by this reviewer from Table 14.2.1, Vol.54.
p-value was obtained by Mann-Whitney test.
Mean was computed by this reviewer

As seen from tables above, the results of the patient's Oucher Scale indicated that the S-Caine patch was significantly more effective than placebo in the younger patients (i.e., those who used the photographic scale), but not in the older patients (i.e., those who used the numeric scale).

3.1.1.2.2.3 Sponsor's Analysis of Secondary Efficacy Variable

3.1.1.2.2.3.1 Investigator's Evaluation of Patient's Pain

The investigator assessed the amount of pain they felt the patient had experienced during the lidocaine injection. The results of investigator's assessments are summarized below.

Investigator's Evaluation of Patient's Pain
Study SC-21-01

Pain Rating	S-Caine	Placebo	p-value
No Pain	18 (43.9%)	17 (36.2%)	
Slight Pain	14 (34.1%)	12 (25.5%)	
Moderate Pain	6 (14.6%)	15 (31.9%)	
Severe Pain	3 (7.3%)	3 (6.4%)	0.401

Complied by this reviewer from Table 14.2.2. Vol. 54
P-value was obtained by Mantel-Haenszel summary chi-square, stratified by center..

As seen from the table above, there was no treatment difference in terms of investigator's evaluation of patient's pain.

3.1.1.2.2.3.2 Investigator's Overall Impression of Local Anesthetic

The investigator was asked whether the local anesthetic provided adequate anesthesia for the procedure.

The results of adequate anesthesia provided are summarized below.

Adequate Anesthesia Provided
Study SC-21-01

Oucher Scale	S-Caine	Placebo	p-value
Photographic	17/21 (81.0%)	6/22 (27.3%)	0.00067[a]
Numeric	15/20 (75.0%)	18/25 (72.0%)	1.000[a]
Total	32/41 (78.0%)	24/47 (51.1%)	0.028[b]

Complied by this reviewer from Table 14.2.2 and A7 pages 54-370-371. Vol. 54
[a]p-value was obtained by Fisher's exact test.
[b]P-value was obtained by Mantel-Haenszel summary chi-square, stratified by center..

As seen from the table above, the S-Caine patch was significantly more effective than placebo in the younger patients (i.e., those who used the photographic scale), but not in the older patients (i.e., those who used the numeric scale). Overall, the S-Caine patch was significant more effective than placebo in terms of investigator's overall impression of the local anesthetic.

3.1.1.2.2.3.3 Independent Witness' Evaluation of Patient's Pain

An independent witness also assessed the amount of pain they felt the patient had experienced during the lidocaine injection. The results of independent witness assessments are summarized below.

Independent Witness' Evaluation of Patient's Pain
Study SC-21-01

Pain Rating	S-Caine	Placebo	p-value
No Pain	19 (46.3%)	16 (34.0%)	
Slight Pain	14 (34.1%)	14 (29.8%)	
Moderate Pain	5 (12.2%)	14 (29.8%)	
Severe Pain	3 (7.3%)	3 (6.4%)	0.269

Complied by this reviewer from Table 14.2.2. Vol. 54
P-value was obtained by Mantel-Haenszel summary chi-square, stratified by center.

As seen from the table above, there was no treatment difference in terms of independent witness's evaluation of patient's pain.

3.1.1.2.3 Reviewer's Comments and Evaluation

3.1.1.2.3.1 Reviewer's Comments on Sponsor's Sample Size

The sample size was determined by the assumption that the percent of patients receiving S-Caine who had no pain was 67%, compared to 10% of placebo patients. As observed from the results of this study the percents of patients who had no pain were about 45% and 35% for S-Caine patch and placebo, respectively. The assumed percent of patients who had no pain was too low for placebo and too high for S-Cain patch. The sample size turned out to be inadequate.

3.1.1.2.3.2 Review's Comments on Sponsor's Analysis of Primary Efficacy Variable

Attached Table 3 summarizes results of analysis of photographic scale and numerical scale by center.

The patient used the numerical scale (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100) or the photographic scale (0, 20, 40, 60, 70, 80, 100) for Oucher Pain Scale for patient's evaluation of pain following the vascular access procedure. The sponsor used Mann-Whitney test to compare S-Caine patch vs. placebo.

In this study the scale of measurement is integer scores and is not continuous. The more appropriate method of analyzing data with integer scores is to use Cochran-Mantel-Haenszel test stratified by center. This reviewer re-analyzed patient's evaluation of pain using Cochran-Mantel-Haenszel method adjusted for center. The results gave the similar results as those given by the sponsor. But, p values were 0.010 and 0.7614 for photographic scale and numeric scale, respectively.

3.1.1.2.3.3 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Variable

Results of analysis of investigator's evaluation of patient's pain by center and independent witness' evaluation of patient's pain are given in Attached Tables 4 and 5, respectively.

The results from both investigator's evaluation and independent witness' evaluation of patient's pain indicated that there was no treatment difference.

The statistically significant results of the S-Caine patch in terms of investigator's overall impression of the local anesthetic was driven by the highly statistically significant results for the younger patients (i.e., those who used the photographic scale).

This reviewer re-analyzed data for investigator's overall impression of the local anesthetic by center. The results are given below.

Adequate Anesthesia Provided
Study SC-21-01

Center	S-Caine	Placebo	p-value
Center 1	7/7 (100.0%)	6/7 (85.7%)	1.0000[a]
Center 2	0/1 (0.0%)	1/4 (25.0%)	1.0000[a]
Center 3	7/8 (87.5%)	6/8 (75.0%)	1.0000[a]
Center 4	6/6 (100.0%)	4/6 (66.7%)	0.4545[a]
Center 5	3/7 (42.9%)	4/8 (50.0%)	1.0000[a]
Center 6	9/12 (75.0%)	3/14 (21.4%)	0.0162[a]
Total	32/41 (78.0%)	24/47 (51.1%)	0.0146[b]

Compiled by this reviewer from Table 14.2.2. Vol. 54.
[a]P-value was obtained by Fisher's exact test.
[b]P-value was obtained by Mantel-Haenszel summary chi-square, stratified center.

As seen from the table above, this overall statistical significant result was also driven by the result for Center 6. Center 6 was dominated by younger patients (i.e. those who used the photographic scale). In Center 6 among 26 patients there were 22 patients aged 6 years old or less. If Center 6 were excluded, p-value adjusted for center would be 0.3331.

3.1.2 Vascular Access Procedures in Adult Patients

3.1.2.1 SC-11-01

3.1.2.1.1 Study Design

This was a randomized, double-blind, placebo-controlled, cross-over study to evaluate the effectiveness of the S-Caine patch in providing clinical useful local anesthesia for vascular access procedures in adult subjects.

The objective of this study was to compare the clinical effectiveness of an S-Caine patch to a placebo patch in providing clinically useful local anesthesia for vascular access procedures in adult subjects.

Each subject, ages 18 years and older, received one active and one placebo S-Caine patch on either antecubital surface (one patch on the subject's left antecubital surface and one patch on the subject's right antecubital surface). The placement of the active and placebo treatments was randomized, 1:1, to either the subject's right or left antecubital surface. The S-Caine patch (active or placebo) was placed directly over the designated treatment area for 20 minutes prior to vascular access procedure.

Immediately following removal of the patches, the investigator performed the "Evaluation of Skin Reactions" evaluating erythema and edema. Vascular access then was obtained in the subject's antecubital vein in the right arm. The subject's right antecubital surface should always be treated first.

Upon completion of the vascular access procedure in this arm, the subject assessed the amount of pain associated with the procedure using the Visual Analogue Scale (VAS Scale). The pain evaluation should be completed upon the first attempt to gain vascular access. The investigators also evaluated the degree of anesthesia the patch provided by completing a Post-Procedure Pain Assessment and by stating if the patch provided adequate anesthesia for the procedure. An independent observer also scored his/her perception of the patient's pain utilizing the Post-Procedure Pain Assessment Scale.

Following completion of the vascular access procedure in the right arm and subsequent pain evaluations, the investigator performed the vascular access procedure in the left arm. The same procedure and pain evaluations were performed for the procedure in this arm as they were for the right arm.

The primary efficacy endpoint was subject pain as determined by: (1) Visual Analogue Pain Scale (VAS Scale) and (2) investigator's evaluation of patient pain employing a uniform scale for such analysis.

VAS was compared using ANOVA for a crossover design or Wilcoxon signed rank test. Procedure duration, evaluation of skin reaction and pain assessment scales were compared between treatments using Wilcoxon signed rank tests.

Based on a previous study, active treatment eliminated pain when placebo did not in 80% of the cases, while placebo was better in only 10%. To detect a sign test preference of 80% vs. 20% in favor of active treatment, 19 patients are needed. Calculations were made assuming 80% power and a two-sided significance level of 5%.

3.1.2.1.2 Sponsor's Analysis

A total of 21 subjects received both S-Caine and placebo treatment. One protocol deviation occurred during the study. The randomization was reversed for Subject 108. The S-Caine patch was applied to the left arm instead of the right arm. The statistical analysis was performed on how the patches were actually administered and not according to the randomization.

3.1.2.1.2.1 Treatment Group Comparability

Demographic and baseline characteristics of subjects are summarized in Attached Table 6.

As seen from Attached Table 6, there were no statistically significant difference between treatment order groups for any demographic variable and procedure duration..

3.1.2.1.2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy variable was the subject's evaluation of pain following each vascular access procedure. Subject used a 100-mm VAS to rate the pain they had experienced during each procedure. The results of subjects' VAS scores by treatment are summarized below.

Subject's VAS Scores
Study SC-11-01

S-Caine		Placebo		
N	Median (mm)	N	Median (mm)	P-value
21	1	21	9	0.004

Compiled by this reviewer from Table 14.2.1, Vol.53.
p-value was obtained by Wilcoxon Signed Rank test.

3.1.2.1.2.3 Sponsor's Analysis of Secondary Efficacy Variable

3.1.2.1.2.3.1 Subject's Overall Impression of the Local Anesthetic

Subjects were asked whether the local anesthetic eliminated pain during the procedure and they would use the patch again for anesthesia. The results of eliminating pain and "would use again" are summarized below.

Eliminating Pain
Study SC-11-01

S-Caine	Placebo	p-value
17/21 (81%)	5/21 (24%)	0.003

Compiled by this reviewer from Table 14.2.1, Vol.53.
p-value was obtained by McNemar Chi-square test.

Would Use Again
Study SC-11-01

S-Caine	Placebo	p-value
16/21 (76%)	3/21 (14%)	<0.001

Compiled by this reviewer from Table 14.2.1, Vol.53.
p-value was obtained by McNemar Chi-square test.

As seen from tables above, the difference between treatments was statistically significant in terms of eliminating pain and "would use again."

3.1.2.1.2.3.2 Investigator's Evaluation of Subject's Pain

The investigator assessed the amount of pain they felt the subject had experienced during each vascular access procedure. The results of investigator's assessments are summarized below.

Investigator's Evaluation of Patient's Pain
Study SC-11-01

	Pain Rating	S-Caine	Placebo	p-value
	No Pain	19 (90.5%)	5 (23.8%)	
	Slight Pain	2 (9.5%)	14 (66.6%)	
	Moderate Pain	0 (0.0%)	2 (9.5%)	
	Severe Pain	0 (0.0%)	0 (0.0%)	0.001

Complied by this reviewer from Table 14.2.3. Vol 53
P-value was obtained by Wilcoxon signed rank test.

As seen from tables above, the difference between treatments was statistically significant in terms of investigator's evaluation of patient's pain

3.1.2.1.2.3.3 Investigator's Overall Impression of the Local Anesthetic

The investigator was asked whether the local anesthetic provided adequate anesthesia for the procedure. The results of adequate anesthesia provided are summarized below.

Adequate Anesthesia
Study SC-11-01

S-Caine	Placebo	p-value
19/21 (90%)	5/21 (24%)	<0.001

Compiled by this reviewer from Table 14.2.3, Vol.53.
p-value was obtained by McNemar Chi-square test.

As seen from tables above, the difference between treatments was statistically significant in terms of investigator's overall impression of the local anesthetic.

3.1.2.1.2.3.4 Independent Observer's Evaluation of Subject's Pain

The independent observer also assessed the amount of pain they felt the subject had experienced during each vascular access procedure. The results of independent observer's assessments are summarized below.

Independent Observer's Evaluation of Patient's Pain
Study SC-11-01

	Pain Rating	S-Caine	Placebo	p-value
	No Pain	18 (85.7%)	6 (28.6%)	
	Slight Pain	3 (14.3%)	12 (57.1%)	
	Moderate Pain	0 (0.0%)	3 (14.3%)	
	Severe Pain	0 (0.0%)	0 (0.0%)	0.003

Complied by this reviewer from Table 14.2.2. Vol 53
P-value was obtained by Wilcoxon signed rank test.

As seen from tables above, the difference between treatments was statistically significant in terms of independent observer's evaluation of patient's pain.

3.1.2.1.3 Reviewer's Evaluation

3.1.2.1.3.1 Reviewer's Comments on Sponsor's Study Design

This study was designed as a single center, double-blind, placebo-controlled, and cross-over study. The placement of the active and placebo treatments was randomized to either the subject's right or left antecubital surface. The sponsor did not address the statistical issues of pooling site (right arm and left arm). If treatment by site interaction exists, then result of cross-over study is very difficult to interpret. To maintain blinding during the trial is challenging for the cross-over study. Particularly, the endpoint is subjective measurement.

3.1.2.1.3.2 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

The results of subject's VAS scores by site and treatment are summarized below.

Subject's VAS Scores
Study SC-11-01

		Right Arm			Left Arm	
Treatment	No.	Mean(mm)	Median(mm)	No.	Mean(mm)	Median(mm)
Placebo	12	10.17	8.0	9	32.89	25.0
S-Caine	9	3.33	0.0	12	3.25	2.0

Complied by this reviewer.

As seen from table above, there is no difference of mean VAS scores measured at right arm and left arm for S-Caine group. However, for placebo the difference in mean VAS scores measured at right arm and left arm is large; median and median of VAS scores measured at left arm were three times those measured at right arm. The difference between residual effects needs to be tested.

As suggested by Koch (1972) "The Use of Non-Parametric Methods in the Statistical Analysis of Two-period Change Over Design" Biometrics, 28, 577-584, this reviewer performed Mann-Whitney-Wilcoxon test for a difference between residual effects when the response variable is quantitative but not necessary normally distributed.

The ranks of sums and ranks of differences are given in Attached Table 7.

The resulting test statistics is $\chi^2 = 2.91$. So, the difference between two treatments' residual effect was statistically significant at significant level of 0.10. If a significant difference is found between the residual effects, the direct effects may be compared by applying Mann-Whitney-Wilcoxon test to the measurements obtained in Period 1 only.

According to the protocol the right arm was treated first. This reviewer performed Mann-Whitney-Wilcoxon test for the direct effects using measurements obtained from the right arm. The resulting for testing the hypothesis of equal direct effects was $\chi^2 = 8.065$ with 1 degree of freedom, which is statistically significant at the 0.01 level. However, the treatment difference, about 7.0 mm in mean and 8.0 in median, might not be clinical meaningful.

3.1.2.1.3.3 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Variable

This sponsor used McNemar Chi-square test to evaluate subject's and investigator's overall impressions of local anesthetic. The design aspect was ignored in the sponsor's analysis. It is assumed in McNemar's test that there is no period effect (site effect in this study). Jones and Kenward (1989) stated that McNemar's test is not considered wholly suitable for cross-over trials. Some statistical methods (e.g. Mainland-Gart test and Prescott's test given in Jones and Kenward (1989) "Design and Analysis of Cross-Over Trial") for cross-over design for binary response variable will be more appropriate to be used.

Furthermore, this reviewer performed re-analysis of secondary efficacy variables (adequate anesthesia, eliminating pain, and would use again) using measurements obtained from the right arm by Fishser's exact test for the direct effects. The results are given below.

Reviewer's Re-analysis of Secondary Efficacy Endpoints
Based on Right Arm's Measurement
Study Sc-11-01

Endpoint	S-caine	Placebo	p-value
Investigator's Overall Impression Adequate Anesthesia	8/9 (89%)	4/12 (33%)	0.0244
Subject's Overall Impression Eliminating Pain	8/9 (89%)	3/12 (25%)	0.0056
Would Use Again	8/9 (89%)	2/12 (17%)	0.0019

Compiled by this reviewer.

As seen from table above, results from reviewer's re-analysis based on data from right arm were similar to those obtained by the sponsor using McNemar Chi-square test in terms of statistical significance.

The reviewer performed re-analysis of investigator's evaluation of subject's pain and independent observer's evaluation of subject's pain using Cochran-Mantel-Haenszel method using modified scores based on data from right arm. The results are given below.

Reviewer's Re-Analysis of Investigator's Evaluation of Patient's Pain based on Right Arm's Data
Study SC-11-01

Pain Rating	S-Caine	Placebo	p-value
No Pain	8 (89%)	4 (33%)	0.0129
Slight Pain	1 (11%)	7 (58%)	
Moderate Pain	0 (0.0%)	1 (8.3%)	

Complied by this reviewer.

Reviewer's Re-Analysis of Independent Observer's Evaluation of Patient's Pain based on Right Arm's Data
Study SC-11-01

Pain Rating	S-Caine	Placebo	p-value
No Pain	8 (89%)	4 (33%)	0.0129
Slight Pain	1 (11%)	7 (58%)	
Moderate Pain	0 (0.0%)	1 (8.3%)	

Compiled by this reviewer.

As seen from tables above, results from reviewer's re-analysis based on data from right arm were similar to those obtained by the sponsor using Wilcoxon signed ranked test in terms of statistical significance.

3.1.2.2 Study SC-24-01

3.1.2.2.1 Study Design

This was a randomized, double-blind, placebo-controlled, cross-over study to evaluate the effectiveness of a twenty minute S-Caine patch application in providing clinical useful local anesthesia for vascular access procedures in adult subjects.

The objective of this study was to compare the clinical effectiveness of an S-Caine patch to a placebo patch in providing clinically useful local anesthesia for vascular access procedures in adult subjects.

Each subject, ages 18 years and older, simultaneously received both an active and on placebo S-Caine patch application for twenty minutes. The application sites were randomized (1:1) between the right and left antecubital surfaces. Each subject underwent venipuncture in both the right and let antecubital veins.

Immediately following the patch treatments, the investigator performed the "Evaluation of Skin Reactions" evaluating erythema, edema, and eschar formation. The subject was asked to look away from the insertion sites and an angiocatheter was inserted into the antecubital veins.

Upon completion of each vascular access procedure, the subject assessed the amount of pain associated with each procedure by completing the Visual Analogue Scale (VAS Scale). The pain

evaluation should be completed upon the first attempt to gain IV access. The investigators also evaluated the degree of anesthesia the patch provided by completing a Post-Procedure Pain Assessment and by stating if the patch provided adequate anesthesia for the procedure.

The primary efficacy endpoint was subject pain as determined by: (1) Visual Analogue Pain Scale (VAS Scale) and (2) investigator's evaluation of patient pain employing a standardized scale.

Visual analog results were compared using paired t-tests or Wilcoxon signed rank test. Efficacy assessment scale results and evaluation of skin reaction results were analyzed using Wilcoxon signed rank tests and sign tests.

The sample size of 40 patients between two centers is sufficient to detect a paired difference between treatments of 15 points on the VAS (SD=25 point) or a sign test preference of 80% vs. 20% in favor of active treatment, both with 80% power and a two-sided significance level of 5%.

Two amendments were made to the protocol. The major changes of amendments were to add the independent observer efficacy evaluation and to add the requirement for study subjects to return to the site between 24-48 hours after the study drug application.

In addition to the amendments made the protocol, an additional 20 subjects were enrolled in the study because the first 20 subjects enrolled at one site received study treatment for 30 minutes instead of 20 minutes. Approval was obtained by the IRB prior to enrolling the additional 20 subjects.

3.1.2.2.2 Sponsor's Analysis

Forty subjects were to simultaneously received an S-Caine Patch and placebo patch 20 minutes prior to the start of a vascular access procedure. ——— ; site (Center 2) erroneously applied the patch for 30 minutes for the first 20 subjects, so an additional 20 subjects were enrolled utilizing the correct 20-minute application.

Efficacy was based only on subjects who received the 20-minute applications. None of subjects in ——— ; site were included in the efficacy evaluation and an additional 20 subjects were included in the efficacy evaluation.

Subject No. 24228 only had the S-Caine-patch applied due to a defective placebo patch.

3.1.2.2.2.1 Treatment Group Comparability

Demographic and baseline characteristics of subjects are summarized in Attached Table 8.

As seen from Attached Table 8, there were no statistically significant difference between treatment order groups for any demographic variable and procedure duration..

3.1.2.2.2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy variable was the subject's evaluation of pain following each vascular access procedure. Subjects used a 100-mm VAS to rate the pain they had experienced during each procedure. The results of subjects' VAS scores by treatment is summarized below.

Subject's VAS Scores
Study SC-24-01

	S-Caine			Placebo			
Center	N	Mean(mm)	Median (mm)	N	Mean(mm)	Median (mm)	P-value
Center 1	20	11.8	4.0	20	24.4	21.5	
Center 2	20	12.3	9.5	19	34.5	34.0	
Total	40	12.1	5.0	39	29.3	28.0	<0.001

Compiled by this reviewer from Table 14.2.1, Vol.57.
p-value was obtained by Wilcoxon Signed Rank test.

3.1.2.2.2.3 Sponsor's Analysis of Secondary Efficacy Variable

3.1.2.2.2.3.1 Subject's Overall Impression of the Local Anesthetic

Subjects were asked whether the local anesthetic eliminated pain during the procedure and they would use the patch again for anesthesia. The results of adequate pain relief and "would use again" are summarized below.

Adequate Pain Relief
Study SC-24-01

Center	S-Caine	Placebo	p-value
Center 1	14/20 (70.0%)	8/20 (40.0%)	
Center 2	15/20 (75.0%)	4/19 (21.1%)	
Total	29/40 (72.5%)	12/39 (30.8%)	0.002

Compiled by this reviewer from Table 14.2.1, Vol.57.
p-value was obtained by McNemar Chi-square test.

Would Use Again
Study SC-24-01

Center	S-Caine	Placebo	p-value
Center 1	12/20 (60.0%)	10/20 (50.0%)	
Center 2	16/20 (80.0%)	3/19 (15.8%)	
Total	28/40 (70.0%)	13/39 (33.3%)	0.006

Compiled by this reviewer from Table 14.2.1, Vol.57.
p-value was obtained by McNemar Chi-square test.

As seen from tables above, the difference between treatments was statistically significant in terms of eliminating pain and "would use again."

3.1.2.2.2.3.2 Investigator's Evaluation of Subject's Pain

The investigator assessed the amount of pain they felt the subject had experienced during each vascular access procedure. The results of investigator's assessments are summarized below.

Investigator's Evaluation of Patient's Pain
Study SC-24-01

Center	Pain Rating	S-Caine	Placebo	p-value
Center1	No pain	13 (65.0%)	11 (55.0%)	
	Slight Pain	5 (25.0%)	9 (45.0%)	
	Moderate Pain	2 (10.0%)	0 (0.0%)	
Center 2	No Pain	12 (60.0%)	2 (10.5%)	
	Slight Pain	7 (35.0%)	12 (63.2%)	
	Moderate Pain	1 (5.0%)	5 (26.3%)	
Total	No Pain	25 (62.5%)	13 (33.3%)	
	Slight Pain	12 (30.0%)	21 (53.8%)	
	Moderate Pain	3 (7.5%)	5 (12.8%)	0.021

Complied by this reviewer from Table 14.2.2. Vol 57
P-value was obtained by Wilcoxon signed rank test.

As seen from tables above, the difference between treatments was statistically significant in terms of investigator's evaluation of patient's pain

3.1.2.2.2.3.3 Investigator's Overall Impression

The investigator was asked whether the local anesthetic provided adequate anesthesia for the procedure. The results of adequate anesthesia provided are summarized below.

Adequate Anesthesia
Study SC-24-01

Center	S-Caine	Placebo	p-value
Center 1	12/20 (60.0%)	7/20 (35.0%)	
Center 2	12/20 (60.0%)	2/19 (10.5%)	
Total	24/40 (60.0%)	9/39 (23.1)	0.004

Compiled by this reviewer from Table 14.2.2, Vol.57.
p-value was obtained by McNemar Chi-square test.

As seen from tables above, the difference between treatments was statistically significant in terms of investigator's overall impression of the local anesthetic.

3.1.2.2.2.3.4 Independent Observer's Evaluation of Subject's Pain

The independent observer also assessed the amount of pain they felt the subject had experienced during each vascular access procedure. The results of independent observer's assessments are summarized below.

Independent Observer's Evaluation of Patient's Pain
Study SC-24-01

Center	Pain Rating	S-Caine	Placebo	p-value
Center1	No pain	14 (70.0%)	11 (55.0%)	
	Slight Pain	5 (25.0%)	9 (45.0%)	
	Moderate Pain	1 (5.0%)	0 (0.0%)	
Center 2	No Pain	13 (65.0%)	4 (21.1%)	
	Slight Pain	6 (30.0%)	9 (47.4%)	
	Moderate Pain	1 (5.0%)	6 (31.6%)	
Total	No Pain	27 (67.5%)	15 (38.5%)	
	Slight Pain	11 (27.5%)	18 (46.2%)	
	Moderate Pain	2 (5.0%)	6 (15.4%)	0.015

Complied by this reviewer from Table 14.2.2. Vol 57
P-value was obtained by Wilcoxon signed rank test.

As seen from tables above, the difference between treatments was statistically significant in terms of independent observer's evaluation of patient's pain.

3.1.2.2.3 Reviewer's Evaluation

3.1.2.2.3.1 Reviewer's Comments on Sponsor's Study Design

This study was designed as a multi-center, double-blind, placebo-controlled, and cross-over study. The placement of the active and placebo treatments was randomized to either the subject's right or left antecubital surface. The sponsor did not address the statistical issues of pooling site (right arm and left arm). If treatment by site interaction exists, then result of cross-over study is very difficult to interprete. To maintain blinding during the trial is challenging for the cross-over study. Particularly, when the endpoint is subjective measurement, it is difficulty to control potential biases resulted from a cross-over study.

3.1.2.2.3.2 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

The results of subject's VAS scores by site, treatment and center are summarized below.

Subject's VAS Scores
Study SC-24-01

Center	Treatment	Right Arm No.	Right Arm Mean(mm)	Right Arm Median(mm)	Left Arm No.	Left Arm Mean(mm)	Left Arm Median(mm)
Center 1	Placebo	10	24.3	19.5	10	24.5	24.50
	S-Caine	10	16.7	4.5	10	6.9	2.5
Center 2	Placebo	9	34.7	34.0	10	34.3	24.0
	S-Caine	10	11.2	5.5	10	13.3	12.0

Complied by this reviewer.

As seen from table above, there is no difference in mean VAS scores measured at right arm and left arm for placebo treated group for both Center 1 and Center 2. However, for S-Caine treated group mean VAS scores measured at right arm for Center 1 was larger than that for Center 2. The reverse was true for left arm. The median of VAS scores measured at right arm were about two times those measured at left arm for Center 1. The reverse was true for Center 2. The difference between residual effects needs to be tested.

As suggested by Koch (1972) "The Use of Non-Parametric Methods in the Statistical Analysis of Two-period Change Over Design" Biometrics, 28, 577-584, this reviewer performed Mann-Whitney-Wilcoxon test for a difference between residual effects when the response variable is quantitative but not necessary normally distributed.

The subject No. 24228 only the S-Caine patch applied. In this reviewer's analysis, the VAS score for placebo for subject No. 24338 was assumed to be "0" (best case approach).

The ranks of sums and ranks of difference are given in Attached Table 9.

The resulting test statistics are $\chi^2 = 1.041$ and 0.023, for Center 1 and Center 2, respectively. So, the difference between two treatments' residual effect is not statistically significant at significant level of 0.10.

This reviewer performed Mann-Whitney-Wilcoxon test for the direct effects for Center 1 and Center 2. The resulting for testing the hypothesis of equal direct effects for Center 1 is $\chi^2 = 4.013$ with 1 degree of freedom, which is statistically significant at the 0.05 level. For Center 2 testing statistics is $\chi^2=7.406$ with 1 degree of freedom, which is statistically significant at the 0.01 level.

3.1.2.2.3.3 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Variable

This sponsor used McNemar Chi-square test to evaluate subject's and investigator's overall impressions of local anesthetic. The design aspect was ignored in the sponsor's analysis. It is assumed in McNemar's test that there is no period effect (site effect in this study). Jones and Kenward (1989) stated that McNemar's test is not considered wholly suitable for cross-over trials. Some statistical methods (e.g. Mainland-Gart test and Prescott's test given in Jones and

Kenward (1989) "Design and Analysis of Cross-Over Trial") for cross-over design for binary response variable will be more appropriate to be used.

Furthermore, this reviewer performed re-analysis of secondary efficacy variables, adequate anesthesia, eliminating pain, and would use again, using Fishser's exact test for the direct effects. In this reviewer's analysis, the response of secondary endpoints for placebo for subject No. 24338 was assumed to be "success" (best case approach). The results are given below.

Reviewer's Re-analysis of Secondary Efficacy Endpoints
Study SC-24-01

	Center 1			Center 2		
Endpoint	S-Caine	Placebo	p-value	S-Caine	Placebo	p-value
Investigator's Overall Impression Adequate Anesthesia	12/20 (60%)	7/20 (35%)	0.2049	12/20 (60%)	3/20 (15%)	0.0079
Subject's Overall Impression Adequate Pain Relief	14/20 (70%)	8/20 (40%)	0.1110	16/20 (80%)	5/20 (25%)	0.0012
Would Use Again	12/20 (60%)	10/20 (50%)	0.7512	16/20 (80%)	4/20 (20%)	0.0004

Compiled by this reviewer.

P-values for total were 0.0030, 0.0003 and 0.0033 for adequate anesthesia, adequate pain relief, and would use again, respectively. These p-values resulting from this reviewer's re-analysis were similar to those obtained by the sponsor using McNemar Chi-square test in terms of statistical significance. However, as seen from table above, results from this study across centers were inconsistent. The overall statistical significance was driven by high statistical significant results from Center 2.

The reviewer performed re-analysis of investigator's evaluation of subject's pain and independent observer's evaluation of subject's pain using Cochran-Mantel-Haenszel method using modified scores based on data from right arm. The results are given below.

Reviewer's Re-Analysis of Investigator's Evaluation of Patient's Pain
Study SC-24-01

	Center 1			Center 2		
Pain Rating	S-Caine	Placebo	p-value	S-Caine	Placebo	p-value
No Pain	13 (65%)	11 (55%)	0.7297	12 (60%)	3 (15%)	0.0027
Slight Pain	5 (25%)	9 (45%)		7 (35%)	12 (60%)	
Moderate Pain	2 (10%)			1 (5%)	5 (25%)	

Complied by this reviewer.

Reviewer's Re-Analysis of Independent Observer's Evaluation of Patient's Pain
Study SC-24-01

	Center 1				Center 2	
Pain Rating	S-Caine	Placebo	p-value	S-Caine	Placebo	p-value
No Pain	14 (70%)	11 (55%)	0.4141	13 (65%)	5 (25%)	0.0061
Slight Pain	5 (25%)	9 (45%)		6 (30%)	9 (45%)	
Moderate Pain	1 (5%)			1 (5%)	6 (30%)	

Complied by this reviewer.

P-values for total were 0.0197 and 0.0113 for investigator's evaluation of patient's pain, and independent observer's evaluation of patient's pain, respectively. These p-values resulting from this reviewer's re-analysis were similar to those obtained by the sponsor using Wilcoxon signed rank test in terms of statistical significance. However, as seen from table above, the overall statistical significance was driven by results from Center 2.

3.1.3 Minor Dermatologic Procedure in Adult Patients

3.1.3.1 SC-22-01

3.1.3.1.1 Study Design

This was a randomized, double-blind, placebo-controlled study to evaluate the effectiveness of an S-Caine patch in providing clinical useful local anesthesia for minor dermatological procedures in patients seventy years of age and above.

The objective of this study was to compare the clinical effectiveness of an S-Caine patch to a placebo patch in providing clinically useful local anesthesia for minor dermatological procedures in geriatric patients (70 years and older).

Each patient, ages 70 years and older, was randomized (2:1, active: placebo) to receive either active or placebo S-Caine patch, 30 minutes prior to the scheduled shave biopsy or excision procedure.

Immediately following the patch treatments, the investigator performed the "Evaluation of Skin Reactions" evaluating erythema, edema, and eschar formation. The investigator then began the minor dermatological procedure. At any time during the procedure, the investigator might perform a rescue lidocaine injection if the patients was not receiving adequate anesthesia.

Upon completion of the minor dermatological procedure, the patient assessed the amount of pain associated with each procedure by completing the Visual Analogue Scale (VAS Scale). If the patient received a rescue injection, the patient would assess the amount of pain he/she experienced during the procedure, prior to the rescue injection. The investigators also evaluated the degree of anesthesia the patch provided by completing a Post-Procedure Pain Assessment and by stating if the patch provided adequate anesthesia for the procedure. An independent

observer also scores his/her perception of the patient's pain utilizing the Post-Procedure Pain Assessment Scale.

The primary efficacy endpoint was patient pain as determined by: (1) Visual Analogue Pain Scale (VAS Scale) and (2) investigator's evaluation of patient pain employing a standardized scale.

Demographic and background variables were summarized using descriptive statistics and compared between treatment groups using t-tests for continuous variables, Mann Whitney tests for ordered categorical data and Fisher's exact test for dichotomous responses.

Visual analog pain scales results were compared between treatments using t-tests or Mann Whitney tests. Assessment scales for efficacy and evaluation of skin reactions were compared between groups using Mann Whitney tests. Dichotomous results were compared using Fisher's exact tests.

Based on a previous study, a treatment difference between active and placebo of approximately 15 units was seen with a standard deviation of 15 in VSA. Using a two-sided significance level of 5% and a power of 80%, 26 active patients and 13 placebo patients are needed (2:1 randomization). The study was designed for a total of 50 patients.

Four amendments were made to the protocol.

Amendments 1 and 2 were implemented prior any patients enrolling in study. The major changes were to reduce the age criteria for study enrollment from 70 years to 65 years and to increase the sample size from 50 to 75 so that efficacy differences among different types of procedures could be explored.

Amendment 3 was implemented approximately 1 month after the study had commenced. The major change was to increase the number of investigational sites to 4 and to increase the sample size from 75 to 80 patients.

3.1.3.1.2 Sponsor's Analysis

A total of 79 patients were randomized: 54 to the S-Caine group and 25 to the placebo group. All patients completed the study.

One of the 4 centers, Center 3 did not follow the assigned randomization schedule, but chose patches at random from the pool of patches.

Two "per-protocol" efficacy populations were evaluated.

The first per-protocol efficacy population excluded patients on whom cauterization procedure was performed following shave biopsy and who evaluated pain the aggregate (4 in S-Caine group; 22301, 22302, 22303, 22303, and 22304) and exclude patients on whom cryotherapy

procedure was performed (1 in placebo group: 22402). Cryotherapy was not a protocol-approved procedure.

The second per-protocol efficacy population excluded patients that were excluded in the first per-protocol efficacy analysis and patients who were enrolled at Study Center #3 (14 in S-Caine group and 6 in placebo group). This study center did not follow the assigned randomization schedule, but chose patches at random from the pool of patches.

The sponsor considered the first per-protocol efficacy population as the primary efficacy population.

3.1.3.1.2.1 Treatment Group Comparability

A summary of the number of patients by demographic and baseline characteristics and minor dermatological procedure by treatment group is given in Attached Table 10.

As seen from Attached Table 10, the treatment groups appeared similar with regard to all demographic and baseline characteristics and minor dermatological procedure. There were significant center difference for height, weight, skin type, procedure, procedure duration, and procedure depth.

3.1.3.1.2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy variable was the patient's VAS scores, a 100-mm VAS to rate the pain patient had experienced during the procedure. The results for primary per-protocol are summarized below.

Patient VAS Score by Center
Primary Per-Protocol Analysis
Study SC-22-01

		S-Caine			Placebo		
Center	N	Mean	Median	N	Mean	Median	P-value
Center 1	10	14.9	4.0	5	29.6	29.0	
Center 2	10	13.5	4.0	4	16.3	19.0	
Center 3	10	35.2	20.5	6	25.5	20.5	
Center 4	20	16.6	10.5	9	26.1	29.0	
Total	50	19.3	9.50	24	25.0	22.5	0.041

Compiled by this reviewer from Table 14.2.1, Vol.55.
p-value was obtained by Mann-Whitney test.

The sponsor also performed the second per-protocol and Intent-to-Treat analyses. The second per-protocol efficacy analysis excluded patients that were excluded in the primary per-protocol efficacy analysis and patients who were enrolled at Study Center #3. For the second per-protocol analysis, median scores for this efficacy subsets were 7.0 in the S-Caine and 24.5 in the placebo group (p=0.020, Mann-Whitney test).

For Intent-to-Treat Analysis including all patients, the median scores were 11.0 in the S-Caine group and 21.0 in the placebo group (p=0.089, Mann-Whitney test).

The results for patient VAS scores by procedure are listed below.

Patient VAS Score by Procedure Type
Primary Per-Protocol Analysis
Study SC-22-01

	S-Caine		Placebo		
Procedure	N	Median	N	Median	P-value
Shave Biopsy	17	13.0	9	21.0	0.877
Excision	32	7.0	15	25.0	0.020

Copied by this reviewer from Table 11.4, Vol.55
p-value was obtained by Mann-Whitney test.

As seen from the above, median VAS scores with S-Caine were significantly lower than placebo for excision.

3.1.3.1.2.3 Sponsor's Analysis of Secondary Efficacy Variable

3.1.3.1.2.3.1 Additional Patient Pain Evaluation

Patients were asked whether the local anesthetic eliminated pain during the procedure and they would use the patch again for anesthesia. The results of adequate pain relief and "would use patch again for anesthesia" are summarized below.

Adequate Pain Relief
Primary Per-Protocol Analysis
Study SC-22-01

Center	S-Caine	Placebo	p-value
Center 1	8/10 (80.0%)	3/5 (60.0%)	
Center 2	8/10 (80.0%)	4/4 (100.0%)	
Center 3	5/10 (50.0%)	5/6 (83.3%)	
Center 4	7/20 (35.0%)	3/9 (33.3%)	
Total	28/50 (56.0%)	15/24 (62.5%)	0.767

Compiled by this reviewer from Table 14.2.1. Vol. 55.
P-value was obtained by Mantel-Haenszel summary chi-square.

Would Use Patch Again for Anesthesia
Primary Per-Protocol Analysis
Study SC-22-01

Center	S-Caine	Placebo	p-value
Center 1	8/10 (80.0%)	3/5 (60.0%)	
Center 2	9/10 (90.0%)	4/4 (100.0%)	
Center 3	4/10 (40.0%)	5/6 (83.3%)	
Center 4	7/20 (35.0%)	3/9 (33.3%)	
Total	28/50 (56.0%)	15/24 (62.5%)	0.726

Compiled by this reviewer from Table 14.2.1. Vol. 55.
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.1.2.3.2 Investigator' s Evaluation of Patient's Pain

The investigators assessed the amount of pain they felt the patient had experienced during the minor dermatological procedure. The results of these assessments are summarized below.

Investigator's Evaluation of Patient's Pain
Primary Per-Protocol Analysis
Study SC-22-01

Center	Pain Rating	S-Caine	Placebo	p-value
Center 1	No Pain	2 (20.0%)	0 (0.0%)	
	Slight Pain	5 (50.0%)	2 (40.0%)	
	Moderate Pain	3 (30.0%)	3 (60.0%)	
Center 2	No Pain	4 (40.0%)	1 (25.0%)	
	Slight Pain	3 (30.0%)	3 (75.0%)	
	Moderate Pain	3 (30.0%)	0 (0.0%)	
Center 3	No Pain	6 (60.0%)	5 (83.3%)	
	Slight Pain	1 (10.0%)	0 (0.0%)	
	Moderate Pain	3 (30.0%)	1 (16.7%)	
Center 4	No Pain	5 (25.0%)	1 (11.1%)	
	Slight Pain	14 (70.0%)	7 (77.8%)	
	Moderate Pain	1 (5.0%)	1 (11.1%)	
Total	No Pain	17 (34.0%)	7 (29.2%)	0.696
	Slight Pain	23 (46.0%)	12 (50.0%)	
	Moderate Pain	10 (20.0%)	5 (10.0%)	

Complied by this reviewer from Table 14.2.3. Vol. 55
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.1.2.3.3 Investigator's Overall Impression of the Local Anesthetic

The investigator was asked whether the local anesthetic provided adequate anesthesia for the procedure.

The results of adequate anesthesia provided are summarized below.

Adequate Anesthesia Provided
Primary Per-Protocol Analysis
Study SC-22-01

Center	S-Caine	Placebo	p-value
Center 1	7/10 (70.0%)	3/5 (60.0%)	
Center 2	7/10 (70.0%)	3/4 (75.0%)	
Center 3	6/10 (60.0%)	5/6 (83.3%)	
Center 4	7/20 (35.0%)	2/9 (22.2%)	
Total	27/50 (54.0%)	13/24 (54.2%)	0.838

Compiled by this reviewer from Table 14.2.3. Vol. 55.
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.1.2.3.4 Independent Observer Evaluation of Patient Pain

An independent witness also evaluated patient pain caused by the minor dermatological procedure. The results of these assessments are summarized below.

Independent Witness' Evaluation of Patient's Pain
Primary Per-Protocol Analysis
Study SC-22-01

Center	Pain Rating	S-Caine	Placebo	p-value
Center 1	No Pain	3 (30.0%)	0 (0.0%)	
	Slight Pain	4 (40.0%)	2 (40.0%)	
	Moderate Pain	3 (30.0%)	3 (60.0%)	
Center 2	No Pain	4 (40.0%)	1 (25.0%)	
	Slight Pain	3 (30.0%)	3 (75.0%)	
	Moderate Pain	3 (30.0%)	0 (0.0%)	
Center 3	No Pain	5 (50.0%)	4 (66.7%)	
	Slight Pain	2 (20.0%)	1 (16.7%)	
	Moderate Pain	3 (30.0)	1 (16.7%)	
Center 4	No Pain	6 (30.0%)	1 (11.1%)	
	Slight Pain	14 (70.0%)	7 (77.8%)	
	Moderate Pain	0 (0.0%)	1 (11.1%)	
Total	No Pain	18 (36.0%)	6 (25.0%)	0.416
	Slight Pain	23 (46.0%)	13 (54.2%)	
	Moderate Pain	9 (18.0%)	5 (20.8%)	

Complied by this reviewer from Table 14.2.3. Vol. 55.
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.1.2.3.5 Rescue Medication

At any time during the procedure, the investigator could administer a rescue lidocaine injection if he/she determined that the patient wasn't received adequate anesthesia.

There was a significant difference among centers for rescue administration but there was no difference between the treatment groups. For all patients enrolled (n=79), 35% (19/54) of patients in the S-Caine group was administered a rescue medication compared with 28% (7/25) of patients in the placebo group (p=0.561, Mantel-Haenszel summary chi-square).

3.1.3.1.3 Reviewer's Comments and Evaluation

3.1.3.1.3.1 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Variable

The sponsor's results for primary per-protocol are biased in favor of S-Caine. In the primary per-protocol analysis, four patients in S-Caine group (22301, 22302, 22303 and 22304) and one patient in placebo (22402) were excluded. These four S-Caine subjects were in Center 3 with VAS scores of 88, 44, 52, and 11, respectively. The one placebo subject was in Center 4 with VAS score of 16. Excluding three S-Caine subjects with high VAS scores (88, 44, and 52), one

S-Caine subject with average VAS score (11) and one placebo subject with low VAS score (16), the p-value was reduced from 0.089 from ITT analysis to 0.041 from primary per-protocol analysis. This analysis is data driven and should be considered as a post-hoc analysis.

3.1.3.1.3.1.1 Intent-to-Treat Analysis of Patient's VAS Score by Center

The reviewer performed the Wilcoxon test for patient VAS scores by center. The results are given below.

Patient VAS Score by Center
Intent-to-Treat Analysis
Study SC-22-01

		S-Caine			Placebo		
Center	N	Mean	Median	N	Mean	Median	P-value
Center 1	10	14.9	4.0	5	29.6	29.0	0.1477
Center 2	10	13.5	4.0	4	16.3	19.0	0.4892
Center 3	14	39.1	37.0	6	25.5	20.5	0.6237
Center 4	20	16.6	10.5	10	25.1	22.5	0.1094
Total	54	21.5	11.0	25	24.7	21.0	0.0944

Tabulated by this reviewer from efficacy data
p-value was obtained by Wilcoxon test.

As seen from table above, from ITT analysis the treatment difference was not statistically significant across centers and for total. Furthermore, placebo group had numerical lower VAS scores than S-Caine group in Center 3.

3.1.3.1.3.2 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Variable

The sponsor's results of analyses of secondary efficacy variables based on primary per-protocol population might be biased in favor of S-Caine. This reviewer re-analyzed the secondary variables based on ITT population. The results are given below.

3.1.3.1.3.2.1 Additional Patient Pain Evaluation

Adequate Pain Relief
Intent-to-Treat Analysis
Study SC-22-01

Center	S-Caine	Placebo	p-value
Center 1	8/10 (80.0%)	3/5 (60.0%)	
Center 2	8/10 (80.0%)	4/4 (100.0%)	
Center 3	8/14 (57.1%)	5/6 (83.3%)	
Center 4	7/20 (35.0%)	3/10 (30.0%)	
Total	31/54 (57.4%)	15/25 (60.0%)	0.7239

Tabulated by this reviewer from efficacy data.
P-value was obtained by Mantel-Haenszel summary chi-square.

Would Use Patch Again for Anesthesia
Intent-to-Treat Analysis
Study SC-22-01

Center	S-Caine	Placebo	p-value
Center 1	8/10 (80.0%)	3/5 (60.0%)	
Center 2	9/10 (90.0%)	4/4 (100.0%)	
Center 3	7/14 (50.0%)	5/6 (83.3%)	
Center 4	7/20 (35.0%)	4/10 (40.0%)	
Total	31/54 (57.4%)	16/25 (64.0%)	0.4738

Tabulated by this reviewer from efficacy data.
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.1.3.2.2 Investigator's Evaluation of Patient's Pain

Investigator's Evaluation of Patient's Pain
Intent-to-Treat Analysis
Study SC-22-01

Center	Pain Rating	S-Caine	Placebo	p-value
Center 1	No Pain	2 (20.0%)	0 (0.0%)	
	Slight Pain	5 (50.0%)	2 (40.0%)	
	Moderate Pain	3 (30.0%)	3 (60.0%)	
Center 2	No Pain	4 (40.0%)	1 (25.0%)	
	Slight Pain	3 (30.0%)	3 (75.0%)	
	Moderate Pain	3 (30.0%)	0 (0.0%)	
Center 3	No Pain	7 (50.0%)	5 (83.3%)	
	Slight Pain	3 (21.4%)	0 (0.0%)	
	Moderate Pain	4 (28.6%)	1 (16.7%)	
Center 4	No Pain	5 (25.0%)	1 (10.0%)	
	Slight Pain	14 (70.0%)	8 (80.0%)	
	Moderate Pain	1 (5.0%)	1 (10.0%)	
Total	No Pain	18 (33.3%)	7 (28.0%)	0.6298
	Slight Pain	25 (46.3%)	13 (52.0%)	
	Moderate Pain	11 (20.4%)	5 (20.0%)	

Tabulated by this reviewer from efficacy data.
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.1.3.2.3 Investigator's Overall Impression of the Local Anesthetic

Adequate Anesthesia Provided
Intent-to-Treat Analysis
Study SC-22-01

Center	S-Caine	Placebo	p-value
Center 1	7/10 (70.0%)	3/5 (60.0%)	
Center 2	7/10 (70.0%)	3/4 (75.0%)	
Center 3	9/14 (64.3%)	5/6 (83.3%)	
Center 4	7/20 (35.0%)	2/10 (20.0%)	
Total	30/54 (55.6%)	13/25 (52.0%)	0.8412

Tabulated by this reviewer from efficacy data.
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.1.3.2.4 Independent Observer Evaluation of Patient's Pain

Independent Witness' Evaluation of Patient's Pain
Intent-to-Treat Analysis
Study SC-22-01

Center	Pain Rating	S-Caine	Placebo	p-value
Center 1	No Pain	3 (30.0%)	0 (0.0%)	
	Slight Pain	4 (40.0%)	2 (40.0%)	
	Moderate Pain	3 (30.0%)	3 (60.0%)	
Center 2	No Pain	4 (40.0%)	1 (25.0%)	
	Slight Pain	3 (30.0%)	3 (75.0%)	
	Moderate Pain	3 (30.0%)	0 (0.0%)	
Center 3	No Pain	6 (42.9%)	4 (66.7%)	
	Slight Pain	4 (28.6%)	1 (16.7%)	
	Moderate Pain	3 (21.4%)	1 (16.7%)	
	Severe Pain	1 (7.1%)	0 (0.0%)	
Center 4	No Pain	6 (30.0%)	1 (10.0%)	
	Slight Pain	14 (70.0%)	8 (80.0%)	
	Moderate Pain	0 (0.0%)	1 (10.0%)	
Total	No Pain	19 (35.2%)	6 (24.0%)	0.3593
	Slight Pain	25 (46.3%)	14 (56.0%)	
	Moderate Pain	9 (16.7%)	5 (20.0%)	
	Severe Pain	1 (1.9%)	0 (0.0%)	

Complied by this reviewer from Table 14.2.3. Vol. 55.
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.2 SC-23-01

3.1.3.2.1 Study Design

This was a multi-center (2 sites), randomized, double-blind, placebo-controlled study to evaluate the effectiveness of an S-Caine patch in providing clinical useful local anesthesia for minor dermatological procedures in adult patients.

The objective of this study was to compare the clinical effectiveness of an S-Caine patch to a placebo patch in providing clinically useful local anesthesia for minor dermatological procedures in adult patients.

Each patient, ages 18 years and older, was randomized (1:1, active: placebo) to receive either active or placebo S-Caine patch, 30 minutes prior to the scheduled shave biopsy or excision procedure. Treatment groups were further stratified by procedure, 2:1, shave biopsy; excision procedure.

Immediately following the patch treatments, the investigator performed the "Evaluation of Skin Reactions" evaluating erythema, edema, and eschar formation. The investigator then began the minor dermatological procedure. At any time during the procedure, the investigator might perform a rescue lidocaine injection if the patients was not receiving adequate anesthesia.

Upon completion of the minor dermatological procedure, the patient assessed the amount of pain associated with each procedure by completing the Visual Analogue Scale (VAS Scale). If the patient received a rescue injection, the patient would assess the amount of pain he/she experienced during the procedure, prior to the rescue injection. The investigators also evaluated the degree of anesthesia the patch provided by completing a Post-Procedure Pain Assessment and by stating if the patch provided adequate anesthesia for the procedure. An independent observer also scores his/her perception of the patient's pain utilizing the Post-Procedure Pain Assessment Scale.

The primary efficacy endpoint was patient pain as determined by: (1) Visual Analogue Pain Scale (VAS Scale) and (2) investigator's evaluation of patient pain employing a standardized scale.

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

Visual analog pain scales results were compared between treatments using ANOVA with the factors: site, treatment, procedure and associated interaction. Assessment scales for efficacy and evaluation of skin reactions were compared between groups stratified by study site and procedure type using Mantel-Haenszel summary chi-square tests for ordered or dichotomous data.
Based on a previous study, a treatment difference between active and placebo of approximately 15 units was seen with a standard deviation of 15 in VSA. Using a two-sided significance level of 5% and a power of 80%, 17 patients per group are needed. The study was designed for two centers (30 patients each) for a total of 60 patients.

Two amendments were made to the protocol. The main changes in the first amendment were to increase the number of patients in each group from 30 to 45, for a total of 90 patients and to eliminate the plan to stratify the patients by procedure. The main changes in the second amendment were to add an additional study site, for a total of 3 study sites (30 patients each).

3.1.3.2.2 Sponsor's Analysis

A total of 94 patients were randomized: 45 to the S-Caine group and 45 to the placebo group. All patients completed the study.

3.1.3.2.2.1 Treatment Group Comparability

A summary of the number of patients by demographic and baseline characteristics and minor dermatological procedure by treatment group is given in Attached Table 11.

As seen from Attached Table 11, the treatment groups appeared similar with regard to all demographic and baseline characteristics and minor dermatological procedure. There were significant differences among centers for race and age, but treatment groups were comparable among centers.

3.1.3.2.2.2 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy variable was the patient's VAS scores, a 100-mm VAS to rate the pain patient had experienced during the procedure. The results are summarized below.

Patient VAS Score by Center
Study SC-23-01

	S-Caine		Placebo		
Center	N	Median	N	Median	P-value
Center 1	16	2.5	18	20.0	
Center 2	14	11.0	16	36.5	
Center 3	15	5.0	15	58.0	
Total	45	5.0	49	31.0	<0.001

Compiled by this reviewer from Table 14.2.1, Vol.56.
p-value was obtained by Mann-Whitney test.

As seen from the table above, median VAS scores with S-Caine were significantly lower than placebo.

The results for patient VAS scores by procedure are listed below.

Patient VAS Score by Procedure Type
Study SC-23-01

	S-Caine		Placebo		
Procedure	N	Median	N	Median	P-value
Shave Biopsy	4	3.5	7	58.0	0.089
Excision	18	6.0	22	33.0	0.017
Curettage	5	1.0	5	12.0	0.341
Electrodessication	11	3.0	8	32.5	0.028
Skin Tag	3	2.0	4	40.5	
Keloid Injection	2	23.5	2	4.5	
Cryotherapy	2	4.0	1	75.0	

Copied by this reviewer from Table 11.4 Vol. 56.
p-value was obtained by Mann-Whitney test.

As seen from the table above, median VAS scores with S-Caine were significantly lower than placebo for excision and for electrodessication. Treatment differences for shave biopsy and curettage were consistent with results for other procedures but were not statistically significant, likely due to small number of patients undergoing this study of procedure.

3.1.3.2.2.3 Sponsor's Analysis of Secondary Efficacy Variable

This reviewer considered patient's overall impression, investigator's evaluation of patient's pain, investigator's overall impression, and independent witness's evaluation of patient's pain were secondary efficacy variables.

3.1.3.2.2.3.1 Patient's Overall Impression

Patients were asked whether the local anesthetic eliminated pain during the procedure and they would use the patch again for anesthesia. The results of adequate pain relief and "would use patch again for anesthesia" are summarized below.

Adequate Pain Relief
Study SC-23-01

Center	S-Caine	Placebo	p-value
Center 1	14/16 (87.5%)	6/18 (33.3%)	
Center 2	9/14 (64.3%)	8/16 (50.0%)	
Center 3	10/15 (66.7%)	4/15 (26.7%)	
Total	33/45 (73.3%)	18/49 (36.7%)	<0.001

Compiled by this reviewer from Table 14.2.1. Vol. 56.
P-value was obtained by Mantel-Haenszel summary chi-square.

Would Use Patch Again for Anesthesia
Study SC-23-01

Center	S-Caine	Placebo	p-value
Center 1	11/16 (68.8%)	8/18 (44.4%)	
Center 2	13/14 (92.9%)	14/16 (87.5%)	
Center 3	10/15 (66.7%)	4/15 (26.7%)	
Total	34/45 (75.6%)	26/49 (53.1%)	0.023

Compiled by this reviewer from Table 14.2.1. Vol. 56.
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.2.2.3.2 Investigator's Evaluation of Patient's Pain

The investigators assessed the amount of pain they felt the patient had experienced during the minor dermatological procedure. The results of these assessments are summarized below.

Investigator's Evaluation of Patient's Pain
Study SC-23-01

Center	Pain Rating	S-Caine	Placebo	p-value
Center 1	No Pain	10 (62.5)	2 (11.1%)	
	Slight Pain	5 (31.3%)	10 (55.6%)	
	Severe Pain	1 (6.3%)	6 (33.3%)	
Center 2	No Pain	5 (35.7%)	2 (12.5%)	
	Slight Pain	5 (35.7%)	5 (31.3%)	
	Moderate Pain	4 (28.6%)	9 (56.3%)	
	Severe Pain	0 (0.0%)	0 (0.0%)	
Center 3	No Pain	8 (53.3%)	1 (6.7%)	
	Slight Pain	2 (13.3%)	4 (26.7%)	
	Moderate Pain	4 (26.7%)	10 (66.7%)	
	Severe Pain	1 (6.7%)	0 (0.0%)	
Total	No Pain	23 (51.1%)	5 (10.2%)	<0.001
	Slight Pain	12 (26.7%)	19 (38.8%)	
	Moderate Pain	9 (20.0%)	25 (51.0%)	
	Severe Pain	1 (2.2%)	0 (0.0%)	

Complied by this reviewer from Table 14.2.4. Vol. 56
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.2.2.3.3 Investigator's Overall Impression

The investigator was asked whether the local anesthetic provided adequate anesthesia for the procedure.

The results of adequate anesthesia provided are summarized below.

Adequate Anesthesia Provided
Study SC-23-01

Center	S-Caine	Placebo	p-value
Center 1	13/16 (81.3%)	6/18 (33.3%)	
Center 2	9/14 (64.3%)	8/16 (50.0%)	
Center 3	10/15 (66.7%)	5/15 (33.3%)	
Total	32/45 (71.1%)	19/49 (38.8%)	0.004

Compiled by this reviewer from Table 14.2.1. Vol. 56.
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.2.2.3.4 Independent Witness' Evaluation of Patient's Pain

An independent witness also evaluated patient pain caused by the minor dermatological procedure. The results of these assessments are summarized below.

Independent Witness' Evaluation of Patient's Pain
Study SC-23-01

Center	Pain Rating	S-Caine	Placebo	p-value
Center 1	No Pain	11 (68.8%)	2 (11.1%)	
	Slight Pain	5 (31.3%)	7 (38.9%)	
	Severe Pain	0 (0.0%)	9 (50.0%)	
Center 2	No Pain	6 (42.9%)	2 (12.5%)	
	Slight Pain	4 (28.6%)	5 (31.3%)	
	Moderate Pain	3 (21.4%)	9 (56.3%)	
	Severe Pain	1 (7.1%)	0 (0.0%)	
Center 3	No Pain	7 (46.7%)	1 (6.7%)	
	Slight Pain	3 (20.0%)	5 (33.3%)	
	Moderate Pain	4 (26.7%)	9 (60.0%)	
	Severe Pain	1 (6.7%)	0 (0.0%)	
Total	No Pain	24 (53.3%)	5 (10.2%)	<0.001
	Slight Pain	12 (26.7%)	17 (34.7%)	
	Moderate Pain	7 (15.6%)	27 (55.1%)	
	Severe Pain	2 (4.4%)	0 (0.0%)	

Complied by this reviewer from Table 14.2.4. Vol. 56.
P-value was obtained by Mantel-Haenszel summary chi-square.

3.1.3.2.2.3.5 Rescue Medication

At any time during the procedure, the investigator could administer a rescue lidocaine injection if he/she determined that the patient wasn't received adequate anesthesia.

There was a significant difference between the treatment groups. 22% of patients in the S-Caine group was administered a rescue medication compared with 49% of patients in the placebo group

(p=0.0008, Mantel-Haenszel summary chi-square). This further supported the efficacy of S-Caine over placebo.

3.1.3.2.3 Reviewer's Comments and Evaluation

3.1.3.2.3.1 Reviewer's Evaluation on Sponsor's Analysis of Primary Efficacy Variable

This reviewer performed Wilcoxon test for primary efficacy variable by center. The results are summarized below.

Patient VAS Score by Center
Study SC-23-01

		S-Caine			Placebo		
Center	N	Mean	Median	N	Mean	Median	P-value
Center 1	16	5.5	2.5	18	20.6	20.0	0.0018
Center 2	14	20.3	11.0	16	37.1	36.5	0.0603
Center 3	15	24.7	5.0	15	54.5	58.0	0.0170
Total	45	16.4	5.0	49	36.4	31.0	<0.0001

Compiled by this reviewer from Table 14.2.1, Vol.56.
p-value was obtained by this reviewer using Wilcoxon test.

As seen from the table above, patient VAS scores with S-Caine were statistically significantly lower than placebo across centers.

3.2 Evaluation of Safety

3.2.1 Pediatric Study

Study SC-20-01 indicated that patients who received S-Caine patch had slightly more erythema than patients who received placebo, but the difference was not statistically significant (51% vs. 43%, p=0.216).

Study SC-21-01 showed patients who received S-Caine patch treatment had significantly more erythema (46% vs. 23%; p=0.006) than patients who received placebo treatment. All 9 occurrences of edema were in the S-Caine patch group (p=0.003).

3.2.2 Vascular Access Procedures in Adult Patients

Study SC-11-01 indicated that the S-Caine treatment sites had significantly more erythema than placebo treatment sites (29% vs. 0%; p=0.031). Six patients had very slight erythema with S-Caine treatment.

However, Study SC-24-01 revealed there were no apparent differences in terms of adverse events between S-Caine and placebo treatment in the study.

3.2.3 Minor Dermatologic Procedure in Adult Patients

Study SC-22-01 indicated that patients in the S-Caine group experienced slightly more erythema and edema than patients in the placebo group (22% vs. 16%, p=0.105 for erythema and 11% vs. 0%, p=0.074 for edema).

Study SC-23-01 also indicated that patients in the S-Caine group experienced slightly more erythema and edema than patients in the placebo group (44% vs. 33%, p=0.056 for erythema and 9% vs. 2%, p=0.273 for edema).

3.2.4 Integrity Safety Analysis

Summary of incidences of erythema and edema by study is given below. This reviewer performed Breslow-Day to test whether the incidences of erythema and edema could be pooled from six studies. It was found that only the incidences of erythema across studies could be pooled (Breslow-Day p=0.2948). The incidences of edema across studies could not be pooled (Beslow-Day p<0.0001). This reviewer also performed a treatment comparison in terms of incidences of erythema across studies using Chochran-Mantel-Haenszel. The results revealed that patients in the S-Caine group experienced statistically significantly more erythema than patients in the placebo group.

Incidences of Erythema and Edema by Study

Study	S-Cain	Erythem Placebo	p-value	S-Caine	Edema Placebo	p-value
SC-20-01	22/43 (51%)	9/21 (43%)	0.216	0 (0%)	2/21 (10%)	0.190
SC-21-01	19/41 (46%)	11/47 (23%)	0.006	9/41 (22%)	0/47 (0%)	0.003
SC-11-01	6/21 (29%)	0/21 (0%)	0.031	0/21 (0%)	0/21 (0%)	
SC-24-01	2/60 (3%)	0/60 (0%)				
SC-22-01	12/54 (22%)	4/25 (16%)	0.105	6/54 (11%)	0/25 (0%)	0.074
SC-23-01	20/45 (44%)	16/49 (33%)	0.056	4 /45 (9%)	1/49 (2%)	0.273
Total	82/264 (32%)	40/223 (18%)	0.0014	19/264 (7%)	3/223 (1%)	

Compiled by this reviewer.
P-value for total is obtained using Cochran-Mante-Haenszell method adjusted for study.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

No conclusion on race can be drawn due to lack of representation of Black and other race. No conclusion on gender and age can be drawn due to limited sample size.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Pediatric Studies

The sponsor has submitted two controlled efficacy study (SC-20-01, SC-21-01) in support of the proposed claim.

For the primary endpoint, patient's evaluation of pain, younger children (used photographic scale) in S-Caine treated group had statistically significantly lower pain score than those in placebo group, as observed in both studies. But, for older children (used numerical scale), both of studies revealed that the treatment difference was not statistically significant.

For the secondary endpoints, Study SC-20-01 indicated that the treatment difference was statistically significant in investigator' evaluation of patient's pain and independent observer's evaluation of patient's pain, but was not statistically significant in investigator's overall impression of the local anesthetic.

Contrary to finding from study SC-20-01, Study SC-21-01 revealed that the treatment difference was statistically significant in investigator's overall impression of the local anesthetic, but was not statistically significant in both investigator's evaluation of patient's pain and independent witness' evaluation of patient's pain.

There were inconsistent results for secondary endpoints across studies.

5.1.2. Vascular Access Procedures in Adult Patients

The sponsor has submitted two randomized, placebo-controlled, cross-over studies (Study SC-11-1 and Study SC-24-1) for adults in support of the proposed claim.

The placement of the active and placebo treatments was randomized to either the subject's right or left antecubital surface. The sponsor did not address the statistical issues of pooling site (right arm and left arm). If treatment by placement site interaction exists, then result of cross-over study is very difficult to interprete. To maintain blinding during the trial is challenging for the cross-over study. Particularly, when the endpoint is subjective measurement, it is difficulty to control potential biases resulted from a cross-over study.

The sponsor failed to perform the test for a difference between residual effects.

For Study SC-11-1, it was found that there is no difference of mean VAS scores measured at between right arm and left arm for S-Caine group. However, for placebo the difference in mean

VAS scores measured at right arm and left arm is large; median and median of VAS scores measured at left arm were three times those measured at right arm.

This reviewer performed Mann-Whitney-Wilcoxon test for a difference between residual effects when the response variable is quantitative but not necessary normally distributed. The results of Mann-Whitney Wilcoxon test showed the difference between two treatments' residual effect was statistically significant at significance level of 0.10.

This reviewer performed Mann-Whitney-Wilcoxon test for the direct effects using measurements obtained from the right arm (to be conservative). The resulting for testing the hypothesis of equal direct effects showed the treatment difference in favor of S-Caine is statistically significant at the 0.01 level. However, the treatment difference, about 7.0 mm in mean and 8.0 in median might not be clinical meaningful.

For Study SC-24-1, it was found that there is no difference of mean VAS scores measured at between right arm and left arm for placebo treated group for both Center 1 and Center 2. However, for S-Caine treated group the difference in mean VAS scores measured at right arm for Center 1 is larger that for Center 2. The reverse is true for right arm. The median of VAS scores measured at right arm were about two times those measured at left arm for Center 1. The reverse was true for Center 2.

This reviewer performed Mann-Whitney-Wilcoxon test for a difference between residual effects when the response variable is quantitative but not necessary normally distributed. The results of Mann-Whitney Wilcoxon test showed that the difference between two treatments' residual effect is not statistically significant at significant level of 0.10.

This reviewer performed Mann-Whitney-Wilcoxon test for the direct effects for Center 1 and Center 2. The results for testing the hypothesis of equal direct effects for Center 1 and Center 2 showed that the treatment difference was statistically significant at the 0.05 level and 0.01 level, for Center and for Center 2, respectively.

For secondary efficacy variables, results from this study across centers are inconsistent. The overall statistical significance was driven by high statistical significant results from Center 2.

There were inconsistent results for secondary endpoints across centers for Studies SC-24-01.

5.1.3. Minor Dermatologic Procedure in Adult Patients

The sponsor has submitted one controlled efficacy study (SC-22-01) for geriatric patients and one study (SC-23-01) for adult patients in support of the proposed claim.

For geriatric patient, Study SC-22-01 indicated that treatment difference was not statistically significant in primary endpoint, patient VAS score, and in all secondary endpoints, additional patient pain evaluation and investigator's evaluation of patient's pain, independent observer's evaluation of patient pain and investigator's overall impression of the local anesthetic from Intent-to-Treat analysis.

For adult patient, Study SC-23-01 revealed showed that treatment difference in favor of S-Caine was statistically significant for primary endpoint, patient VAS core and all secondary endpoints, patient's overall impression, investigator's evaluation of patient's pain, independent witness' evaluation of patient's pain, and investigator's overall impression. This reviewer found that patient's VAS score with S-Caine was statistically significantly lower than placebo across centers.

This study SC-23-01 is the sole study to show effectiveness of S-Caine patch.

5.2 Conclusions and Recommendations

5.2.1. Pediatric Studies

The sponsor has submitted two controlled efficacy study (SC-20-01, SC-21-01) in support of the proposed claim.

For the primary endpoint, patient's evaluation of pain, younger children (used photographic scale) in S-Caine treated group had statistically significantly lower pain score than those in placebo treated group, as observed in both studies. But, for older children (used numerical scale), both of studies revealed that the treatment difference was not statistically significant.

For the secondary endpoints, Study SC-20-01 indicated that the treatment difference was statistically significant in investigator' evaluation of patient's pain and independent observer's evaluation of patient's pain, but was not statistically significant in investigator's overall impression of the local anesthetic.

Contrary to finding from study SC-20-01, Study SC-21-01 revealed that the treatment difference was statistically significant in investigator's overall impression of the local anesthetic, but was not statistically significant in both investigator's evaluation of patient's pain and independent witness' evaluation of patient's pain. However, this reviewer found that overall statistically significant results in investigator's overall impression of the local anesthetic was driven by the result from Center 6, dominated by younger children.

It might need an additional large efficacy study to show the efficacy for older children and to resolve the inconsistent results for secondary endpoints, as observed from Studies SC-20-01 and SC-21-01.

5.2.2. Vascular Access Procedures in Adult Patients

The sponsor has submitted two randomized, placebo-controlled, cross-over studies (Study SC-11-1 and Study SC-24-1) for adults in support of the proposed claim.

The placement of the active and placebo treatments was randomized to either the subject's right or left antecubital surface. The sponsor did not address the statistical issues of pooling site (right arm and left arm). If treatment by placement site interaction exists, then result of cross-over

study is very difficult to interpret. To maintain blinding during the trial is challenging for the cross-over study. Particularly, when the endpoint is subjective measurement, it is difficult to control potential biases resulted from a cross-over study.

For Study SC-11-1, it was found that there was no difference of mean VAS scores measured at between right arm and left arm for S-Caine treated group. However, for placebo treated group the difference in mean VAS scores measured at right arm and left arm is large; mean and median of VAS scores measured at left arm were three times those measured at right arm.

This reviewer performed Mann-Whitney-Wilcoxon test for a difference between residual effects when the response variable is quantitative but not necessary normally distributed. The results of Mann-Whitney Wilcoxon test showed the difference between two treatments' residual effect was statistically significant at significance level of 0.10.

This reviewer performed Mann-Whitney-Wilcoxon test for the direct effects using measurements obtained from the right arm (to be conservative). The resulting for testing the hypothesis of equal direct effects showed the treatment difference in favor of S-Caine was statistically significant at the 0.01 level. However, the treatment difference, about 7.0 mm in mean and 8.0 mm in median might not be clinical meaningful.

For Study SC-24-1, it was found that there was no difference of mean VAS scores measured at between right arm and left arm for placebo treated group for both Center 1 and Center 2. However, for S-Caine treated group mean VAS scores measured at right arm for Center 1 was larger than that for Center 2. The reverse was true for left arm. The median of VAS scores measured at right arm were about two times those measured at left arm for Center 1. The reverse was true for Center 2.

This reviewer performed Mann-Whitney-Wilcoxon test for a difference between residual effects when the response variable is quantitative but not necessary normally distributed. The results of Mann-Whitney Wilcoxon test showed that the difference between two treatments' residual effect is not statistically significant at significant level of 0.10.

This reviewer performed Mann-Whitney-Wilcoxon test for the direct effects for Center 1 and Center 2. The results for testing the hypothesis of equal direct effects for Center 1 and Center 2 showed that the treatment difference was statistically significant at the 0.05 level and 0.01 level, for Center and for Center 2, respectively.

For secondary efficacy variables, results from this study across centers are inconsistent. The overall statistical significance was driven by high statistical significant results from Center 2.

It is very difficult to control biases due to crossover design. Fleiss, J.L. (1986) stated that Biometric and Epidemiological Methodology Advisory Committee to the U.S. Food and Drug Administration recommended in June of 1977 that, in effect, the crossover design be avoided in comparative clinical studies except in the rarest instances.

It might need an additional large multi-center parallel efficacy study to show the effectiveness of S-Caine patch.

5.2.3. Minor Dermatologic Procedure in Adult Patients

The sponsor has submitted one controlled efficacy study (SC-22-01) for geriatric patients and one study (SC-23-01) for adult patients in support of the proposed claim.

For geriatric patient, Study SC-22-01 indicated that treatment difference was not statistically significant in primary endpoint, patient VAS score, and in all secondary endpoints, additional patient pain evaluation and investigator's evaluation of patient's pain, independent observer's evaluation of patient pain and investigator's overall impression of the local anesthetic from Intent-to-Treat analysis.

For adult patient, Study SC-23-01 revealed showed that treatment difference in favor of S-Caine was statistically significant for primary endpoint, patient VAS core and all secondary endpoints, patient's overall impression, investigator's evaluation of patient's pain, independent witness' evaluation of patient's pain, and investigator's overall impression. This reviewer found that patient VAS score with S-Caine was statistically significantly lower than placebo across centers.

6. ATTACHMENT

Table 1 Demographic and Baseline Characteristics by Treatment Group --- CS-20-01

Characteristic	S-Caine (n=43)	Placebo (n=21)	p-value
Gender			0.716[a]
Male	28 (65%)	12 (57%)	
Female	15 (35%)	9 (43%)	
Race			0.365[c]
Caucasian	25 (58%)	15 (71%)	
Black	14 (33%)	4 (19%)	
Hispanic	4 (9%)	2 (10%)	
Age (yr)			
Mean (SD)	8.0 (4.6)	7.7 (4.4)	0.781[b]
Height (inches)			
Mean (SD)	50.5 (10.8)	48.6 (10.9)	0.498[b]
Weight (lbs)			
Mean (SD)	78.1 (51.7)	65.5 (37.1)	0.293[b]
Skin Type			0.017[a]
(I) Always Burns/Rarely Tans	1 (2%)	2 (10%)	
(II) Always Burns/Tans Minimally	3 (7%)	4 (19%)	
(III) Burns Moderately/Tans Gradually	10(23%)	7 (33%)	
(IV) Burns Minimally/Always Tans	13 (30%)	4 (19%)	
(V) Rarely Burns/Tans Profoundly	6 (14%)	1 (5%)	
(VI) Never Burns/Deeply Pigmented	10 (23%)	3 (14%)	
Pre-Procedure Behavior			0.596[a]
Calm	21 (49%)	9 (43%)	
Slightly Frightened	14 (32%)	7 (33%)	
Frightened	8 (19%)	5 (24%)	
Procedure			0.696[d]
Blood Draw	16 (35%)	7 (33%)	
IV Access	26 (60%)	14 (67%)	
None Specified	1 (5%)	0 (0%)	
IV Catheter Gauge			0.361[e]
18 Gauge	1 (2%)	0 (0%)	
20 Gauge	5 (12%)	3 (15%)	
21 Gauge	14 (33%)	4 (20%)	
22 Gauge	20 (46%)	10 (50%)	
23 Gauge	2 (5%)	3 (15%)	

Table 1 Demographic and Baseline Characteristics by Treatment Group --- CS-20-01 (Continued)

Characteristic	S-Caine (n=43)	Placebo (n=21)	p-value
Location of Procedure			
Right Antecubital Vein	20 (46%)	8 (38%)	
Left Antecubital Vein	13 (32%)	7 (33%)	
Right Hand	1 (2%)	1 (5%)	
Left Hand	9 (21%)	5 (24%)	
Procedure Duration (min)	(N=41)	(N=20)	0.638 [a]
< 1	29 (71%)	13 (65%)	
1-1.9	9 (22%)	5 (25%)	
2+	3 (7%)	2 (10%)	

Copied from Table 11.1 and Table 11.3.
[a]Mantel-Haenszel summary chi-square, stratified by center.
[b]Two-way ANOVA with factors: treatment group, center, and treatment by center.
[c]Mantel-Haenzel summary chi-square (Caucasian vs. Other), stratified by center.
[d]Fisher's exact test, Center 2 only.
[e]Pearson Chi-Square, Center 2 only.

Table 2 Demographic and Baseline Characteristics by Treatment Group --- CS-21-01

Characteristic	S-Caine (n=41)	Placebo (n=47)	p-value
Gender			1.000[a]
Male	21 (51%)	26 (55%)	
Female	20 (49%)	21 (45%)	
Race			0.731[c]
Caucasian	21 (51%)	27 (57%)	
Black	3 (7%)	2 (4%)	
Hispanic	17 (41%)	18 (38%)	
Age (yr)			
Mean (SD)	8.9 (4.1)	8.2 (4.4)	0.215[b]
Height (inches)			
Mean (SD)	54.6 (10.9)	51.7 (10.9)	0.098[b]
Weight (lbs)			
Mean (SD)	86.1 (44.0)	81.4 (55.3)	0.514[b]
Skin Type			0.860[a]
(I) Always Burns/Rarely Tans	1 (2%)	2 (4%)	
(II) Always Burns/Tans Minimally	6 (15%)	6 (13%)	
(III) Burns Moderately/Tans Gradually	14 (34%)	18 (38%)	
(IV) Burns Minimally/Always Tans	16 (39%)	14 (30%)	
(V) Rarely Burns/Tans Profoundly	2 (5%)	6 (13%)	
(VI) Never Burns/Deeply Pigmented	2 (5%)	1 (2%)	
Pre-Procedure Behavior			0.141[a]
Calm	22 (54%)	21(45%)	
Slightly Frightened	4 (10%)	9 (19%)	
Frightened	1 (2%)	3 (6%)	
Not Evaluated	14 (34%)	14 (30%)	
Needle Gauge			
20 Gauge	3 (7%)	2 (4%)	
30 Gauge	38 (93%)	45 (96%)	
Location of Procedure			
Head/Neck	4 (10%)	9 (19%)	
Back	11 (27%)	10 (21%)	
Chest/Abdomen	6 (15%)	1 (2%)	
Arm/Shoulder	13 (32%)	16 (34%)	
Hip/Leg	7 (17%)	11 (23%)	

Table 2 Demographic and Baseline Characteristics by Treatment Group --- CS-21-01 (Continued)

Characteristic	S-Caine (n=41)	Placebo (n=47)	p-value
Time Patch Removal to Injection (min)			
Mean (SD)	2.8 (2.8)	3.0 (4.3)	0.323[d]
Injection Dose (mL)			
0.05	12 (29%)	14 (30%)	
0.1-0.9	12 (29%)	14 (30%)	
1.0-1.2	17 (41%)	18 (38%)	
4.0		1 (2%)	

Copied from Table 11.1 and Table 11.3.
[a]Mantel-Haenszel summary chi-square, stratified by center.
[b]Two-way ANOVA with factors: treatment group, center, and treatment by center.
[c]Mantel-Haenzel summary chi-square (Caucasian vs. Other), stratified by center.
[d]Two-way ANOVA with square root transformation.

Table 3 Photographic Scale and Numerical Scale by Center --- Study SC-21-1

Photographic Scale
Study SC-21-1

	S-Caine			Placebo			
Center	N	Mean	Median	N	Mean	Median	P-value
Center 1	3	6.7	0.0	2	80.0	80.0	
Center 2	0			1	40.0	40.0	
Center 3	2	10.0	10.0	3	66.7	100.0	
Center 4	3	33.3	0.0	2	60.0	60.0	
Center 5	2	60.0	60.0	3	60.0	80.0	
Center 6	11	21.8	0.0	11	52.7	40.0	
Total	21	23.8	0.0	22	58.2	70.0	0.005

Compiled by this reviewer from Table 14.2.1, Vol.53.
p-value was obtained by Mann-Whitney test.

Numerical Scale
Study SC-21-1

	S-Caine			Placebo			
Center	N	Mean	Median	N	Mean	Median	P-value
Center 1	4	0.0	0.0	5	16.0	10.0	
Center 2	1	80.0	80.0	3	36.7	30.0	
Center 3	6	13.3	10.0	5	10.0	10.0	
Center 4	3	13.3	10.0	4	17.5	15.0	
Center 5	5	20.0	10.0	5	22.0	10.0	
Center 6	1	60.0	60.0	3	26.7	30.0	
Total	20	18.0	10.0	25	20.0	10.0	0.322

Compiled by this reviewer from Table 14.2.1, Vol.53.
p-value was obtained by Mann-Whitney test.

Table 4 Investigator's Evaluation of Patient's Pain by Center --- Study SC-21-1

Investigator's Evaluation of Patient's Pain
Study SC-21-1

Center	Pain Rating	S-Caine	Placebo	p-value
Center 1	No Pain	5 (71.4%)	6 (85.7%)	
	Slight Pain	2 (28.6%)	0 (0.0%)	
	Moderate Pain	0 (0.0%)	1 (14.3%)	
Center 2	No Pain	0 (0.0%)	0 (0.0%)	
	Slight Pain	0 (0.0%)	2 (50.0%)	
	Moderate Pain	0 (0.0%)	2 (50.0%)	
	Severe Pain	1 (100%)		
Center 3	No Pain	2 (25.0%)	4 (50.0%)	
	Slight Pain	5 (62.5%)	2 (25.0%)	
	Moderate Pain	1 (12.5%)	2 (25.0%)	
Center 4	No Pain	2 (33.3%)	2 (33.3%)	
	Slight Pain	3 (50.0%)	3 (50.0%)	
	Moderate Pain	1 (16.7%)	1 (16.7%)	
Center 5	No Pain	3 (42.9%)	3 (37.5%)	
	Slight Pain	1 (14.3%)	3 (37.5%)	
	Moderate Pain	3 (42.9%)	2 (25.0%)	
Center 6	No Pain	6 (50.0%)	2 (14.3%)	
	Slight Pain	3 (25.0%)	2 (14.3%)	
	Moderate Pain	1 (8.3%)	7 (50.0%)	
	Severe Pain	2 (16.7%)	3 (21.4%)	
Total	No Pain	18 (43.9%)	17 (36.2%)	
	Slight Pain	14 (34.1%)	12 (25.5%)	
	Moderate Pain	6 (14.6%)	15 (31.9%)	
	Severe Pain	3 (7.3%)	3 (6.4%)	0.40137

Complied by this reviewer from Table 14.2.2. Vol. 53
P-value was obtained by Mantel-Haenszel summary chi-square.

Table 5 Independent Witness' Evaluation of Patient's Pain by Center -- Study SC-21-1

Independent Witness' Evaluation of Patient's Pain
Study SC-21-1

Center	Pain Rating	S-Caine	Placebo	p-value
Center 1	No Pain	5 (71.4%)	4 (57.1%)	
	Slight Pain	2 (28.6%)	2 (28.6%)	
	Moderate Pain	0 (0.0%)	1 (14.3%)	
Center 2	No Pain	0 (0.0%)	0 (0.0%)	
	Slight Pain	0 (0.0%)	2 (50.0%)	
	Moderate Pain	0 (0.0%)	2 (50.0%)	
	Severe Pain	1 (100%)		
Center 3	No Pain	2 (25.0%)	4 (50.0%)	
	Slight Pain	5 (62.5%)	3 (37.5%)	
	Moderate Pain	1 (12.5%)	1 (12.5%)	
Center 4	No Pain	3 (50.0%)	2 (33.3%)	
	Slight Pain	2 (33.3%)	3 (50.0%)	
	Moderate Pain	1 (16.7%)	1 (16.7%)	
Center 5	No Pain	3 (42.9%)	4 (50.0%)	
	Slight Pain	2 (28.6%)	2 (25.0%)	
	Moderate Pain	2 (28.6%)	2 (25.0%)	
Center 6	No Pain	6 (50.0%)	2 (14.3%)	
	Slight Pain	3 (25.0%)	2 (14.3%)	
	Moderate Pain	1 (8.3%)	7 (50.0%)	
	Severe Pain	2 (16.7%)	3 (21.4%)	
Total	No Pain	19 (46.3%)	16 (34.0%)	
	Slight Pain	14 (34.1%)	14 (29.8%)	
	Moderate Pain	5 (12.2%)	14 (29.8%)	
	Severe Pain	3 (7.3%)	3 (6.4%)	0.26885

Complied by this reviewer from Table 14.2.2. Vol. 53
P-value was obtained by Mantel-Haenszel summary chi-square.

Table 6 Demographic and Baseline Characteristics by Treatment Group --- CS-11-01

Characteristic	S-Caine in Left Arm (n=12)	S-Caine in Right Arm (n=9)	p-value
Gender			0.367 [a]
Male	6 (50%)	2 (22%)	
Female	6 (50%)	7 (78%)	
Race			1.000
Caucasian	12 (100%)	9 (100%)	
Age (yr)			
Mean (SD)	34.9 (9.8)	36.8 (13.1)	0.713 [b]
Height (inches)			
Mean (SD)	67.8 (6.3)	68.4 (2.6)	0.787 [b]
Weight (lbs)			
Mean (SD)	167.0 (50.3)	174.1 (39.7)	0.731 [b]
Skin Type			1.000 [c]
(I) Always Burns/Rarely Tans	1 (8%)	0 (0%)	
(II) Always Burns/Tans Minimally	2 (17%)	2 (22%)	
(III) Burns Moderately/Tans Gradually	2 (17%)	2 (22%)	
(IV) Burns Minimally/Always Tans	4 (33%)	3 (33%)	
(V) Rarely Burns/Tans Profoundly	3 (25%)	2 (22%)	
(VI) Never Burns/Deeply Pigmented	0 (0%)	0 (0%)	
Procedure Duration (min)			0.763 [c]
3 Minutes	3 (25%)	2 (22%)	
4 Minutes	4 (33%)	2 (22%)	
5 Minutes	4 (33%)	5 (55%)	
10 Minutes	1 (8%)	0 (0%)	

Copied from Table 11.1 and Table 11.4.
[a]Fisher's Exact test (two-tail)
[b]Two-Sample t-test
[c]Mann-Whitney U Statistic.

Table 7 Ranks of Sums and Ranks of Differences of VAS Scores by Treatment Site Group --- CS-11-01

---------- Treatment Site Group=S-Caine-Left Arm ----------

Obs	ptn	S-caine	Placebo	sum	diff	rsum	rdiff
1	103	0	18	18	18	11.0	18.0
2	104	19	7	26	-12	14.5	7.0
3	106	2	2	4	0	2.5	11.0
4	107	5	5	10	0	8.5	11.0
5	108	2	2	4	0	2.5	11.0
6	109	5	24	29	19	18.0	19.5
7	110	0	5	5	5	4.0	14.0
8	115	1	9	10	8	8.5	16.0
9	116	3	9	12	6	10.0	15.0
10	117	2	5	7	3	5.5	13.0
11	120	0	9	9	9	7.0	17.0
12	121	0	27	27	27	16.0	21.0
Mean		3.23	10.17	13.41	6.92	9.0	7.44

---------- Treat Site Group=S-Caine-Right Arm ----------

Obs	ptn	S-caine	Placebo	sum	diff	rsum	rdiff
13	101	4	22	26	-18	14.5	6.0
14	102	4	59	63	-55	20.0	3.0
15	105	0	95	95	-95	21.0	1.0
16	111	0	28	28	-28	17.0	4.0
17	112	0	56	56	-56	19.0	2.0
18	113	0	1	1	-1	1.0	9.0
19	114	22	3	25	19	12.5	19.5
20	118	0	25	25	-25	12.5	5.0
21	119	0	7	7	-7	5.5	8.0
Mean		3.33	32.89	36.22	-25.53	13.67	6.39

Table 8 Demographic and Baseline Characteristics by Treatment Group --- CS-24-01

Characteristic	S-Caine in Left Arm (n=20)	S-Caine in Right Arm (n=20)	
Gender			0.7440[a]
Male	7 (35%)	8 (40%)	
Female	13 (65%)	12 (60%)	
Race			0.8145 [a]
Caucasian	10 (50%)	8 (40%)	
Black	6 (30%)	7 (35%)	
Other	4 (20%)	5 (25%)	
Age (yr)			
Mean (SD)	33.4 (9.9)	37.6 (11.2)	0.2112 [b]
Height (inches)			
Mean (SD)	67.7 (5.7)	66.3 (4.4)	0.3884 [b]
Weight (lbs)			
Mean (SD)	172.3 (47.3)	164.4 (43.0)	0.5838 [b]
Skin Type			0.5037 [a]
(I) Always Burns/Rarely Tans	0 (0%)	0 (0%)	
(II) Always Burns/Tans Minimally	2 (10%)	3 (15%)	
(III) Burns Moderately/Tans Gradually	8 (40%)	4 (20%)	
(IV) Burns Minimally/Always Tans	1 (5%)	4 (20%)	
(V) Rarely Burns/Tans Profoundly	5 (25%)	5 (25%)	
(VI) Never Burns/Deeply Pigmented	4 (20%)	4 (20%)	
Procedure Duration (min)			0.7828 [a]
<1 Minutes	10 (50%)	10 (50%)	
3 Minutes	0 (0%)	1 (5%)	
4 Minutes	2 (10%)	1 (5%)	
5 Minutes	1 (5%)	2 (10%)	
6-12 Minutes	7 (35%)	6 (30%)	

Compiled by this reviewer.
[a]Pearson chi-square
[b]Two-Sample t-test

Table 9 Ranks of Sums and Ranks of Differences of VAS Scores by Treatment Site Group --- CS-24-01

---------- Cennter=1 group=S-Caine-Left Arm ----------

Obs	ptn	S-caine	Placebo	sum	diff	rsum	rdiff
1	103	0	20	20	20	4.0	15.0
2	104	34	2	36	-32	12.5	4.0
3	105	14	10	24	-4	6.0	11.0
4	106	3	66	69	63	19.0	19.0
5	111	5	1	6	-5	1.0	10.0
6	112	2	19	21	17	5.0	13.0
7	113	1	37	38	36	14.0	17.0
8	115	8	2	10	-6	2.0	8.5
9	117	0	53	53	53	17.0	18.0
10	118	2	33	35	31	11.0	16.0
Mean		6.9	24.3	31.2	17.3	9.15	13.15

---------- Center=1 group=S-Caine-Right Arm ----------

Obs	ptn	S-caine	Placebo	sum	diff	rsum	rdiff
11	101	22	11	33	11	10.0	12.0
12	102	2	50	52	-48	16.0	1.0
13	107	4	42	46	-38	15.0	2.5
14	108	8	46	54	-38	18.0	2.5
15	109	95	2	97	93	20.0	20.0
16	110	5	23	28	-18	8.5	7.0
17	114	22	4	26	18	7.0	14.0
18	116	2	26	28	-24	8.5	6.0
19	119	3	9	12	-6	3.0	8.5
20	120	4	32	36	-28	12.5	5.0
Mean		16.7	24.50	41.2	-7.8	11.85	7.85

Table 9 Ranks of Sums and Ranks of Differences of VAS Scores by Treatment Site Group --- CS-24-01 (Continued)

---------- Center=2 group=S-Caine-Left Arm ----------

Obs	ptn	S-caine	Placebo	sum	diff	rsum	rdiff
1	222	18	30	48	12	11.5	14
2	223	14	34	48	20	11.5	15
3	227	17	54	71	37	17.5	18
4	228	19	0	19	-19	4.0	6
5	231	0	54	54	54	15.0	20
6	232	0	46	46	46	10.0	19
7	233	49	47	96	-2	19.0	10
8	235	6	34	40	28	8.5	16
9	237	0	2	2	2	1.0	12
10	239	10	11	21	1	5.0	11
Mean		13.3	31.2	44.5	17.9	10.3	14.1

---------- Center=2 group=S-Caine-Right Arm ----------

Obs	ptn	S-caine	Placebo	sum	diff	rsum	rdiff
11	221	9	16	25	-7	6.0	8.0
12	224	51	20	71	31	17.5	17.0
13	225	1	50	51	-49	13.0	2.0
14	226	2	28	30	-26	7.0	4.5
15	229	0	3	3	-3	2.0	9.0
16	230	13	39	52	-26	14.0	4.5
17	234	0	15	15	-15	3.0	7.0
18	236	22	18	40	4	8.5	13.0
19	238	2	96	98	-94	20.0	1.0
20	240	12	58	70	-46	16.0	3.0
Mean		11.2	34.3	45.5	-23.1	10.7	6.9

Table 10 Demographic and Baseline Characteristics by Treatment Group --- CS-22-01

Characteristic	S-Caine (n=54)	Placebo (n=25)	p-value
Gender			0.671[a]
Male	30 (56%)	16 (64%)	
Female	24 (44%)	9 (36%)	
Race			1.000
Caucasian	54 (100%)	25 (100%)	
Age (yr)			
Mean (SD)	74.6 (6.9)	73.3 (6.7)	0.769[b]
Height (inches)			
Mean (SD)	66.4 (4.2)	66.4 (4.0)	0.955[b]
Weight (lbs)			
Mean (SD)	177 (40)	173 (33)	0.390[a]
Skin Type			0.464[a]
(I) Always Burns/Rarely Tans	13 (24%)	4 (16%)	
(II) Always Burns/Tans Minimally	18 (33%)	7 (28%)	
(III) Burns Moderately/Tans Gradually	17(31%)	12 (48%)	
(IV) Burns Minimally/Always Tans	5 (9%)	2 (8%)	
(V) Rarely Burns/Tans Profoundly	1 (2%)	0 (0%)	
(VI) Never Burns/Deeply Pigmented	0 (0%)	0 (0%)	
Procedure			0.842[a]
Shave Biopsy	22 (41%)	9 (36%)	
Excision	32 (59%)	15 (60%)	
Cryotherapy	0 (0%)	1 (4%)	
Procedure Depth (mm)			
Mean (SD)	1.5 (0.6%)	1.5 (0.6)	0.930[b]
Location of Procedure			
Neck/Head	11 (20%)	6 (24%)	
Back	10 (19%)	3 (12%)	
Chest/Abdomen	6 (11%)	6 (24%)	
Arm/Shoulder	17 (31%)	2 (8%)	
Hip/Leg	9 (17%)	8 (32%)	
Penis	1 (2%)	0 (0%)	
Procedure Duration (min)			
Mean (SD)	1.5 (1.0)	1.6 (1.0)	0.695[b]

Copied from Table 11.1 and Table 11.3.
[a]Mantel-Haenszel summary chi-square, stratified by center.
[b]Two-way ANOVA with factors: treatment group, center, and treatment by center.

Table 11 Demographic and Baseline Characteristics by Treatment Group --- CS-23-01

Characteristic	S-Caine (n=45)	Placebo (n=49)	p-value
Gender			0.889[a]
Male	14 (31%)	15 (31%)	
Female	31 (69%)	34 (69%)	
Race			0.890[c]
Caucasian	26 (58%)	28 (57%)	
Black	4 (9%)	6 (12%)	
Hispanic	15 (33%)	15 (31%)	
Age (yr)			
Mean (SD)	39.6 (13.4)	41.4 (13.8)	0.455[b]
Height (inches)			
Mean (SD)	65.9 (3.5)	65.8 (4.0)	0.974[b]
Weight (lbs)			
Mean (SD)	171.2 (37.5)	171.3 (41.6)	0.981[b]
Skin Type			0.206[a]
(I) Always Burns/Rarely Tans	6 (13%)	3 (6%)	
(II) Always Burns/Tans Minimally	12 (27%)	9 (18%)	
(III) Burns Moderately/Tans Gradually	11(24%)	16 (33%)	
(IV) Burns Minimally/Always Tans	11 (24%)	13 (27%)	
(V) Rarely Burns/Tans Profoundly	3 (7%)	7 (14%)	
(VI) Never Burns/Deeply Pigmented	2 (4%)	1 (2%)	
Procedure			0.920[d]
Shave Biopsy	4 (9%)	7 (14%)	
Excision	18 (40%)	22 (45%)	
Curetage	5 (11%)	5 (10%)	
Electrodessication	11 (24%)	8 (16%)	
Skin Tag	3 (7%)	4 (8%)	
Keloid Injection	2 (4%)	2 (4%)	
Cryotherapy	2 (4%)	1 (2%)	
Procedure Depth (mm)			
Mean (SD)	1.5 (0.7%)	1.6 (0.8)	0.381[b]
Location of Procedure			
Neck/Head	9 (20%)	15 (31%)	
Back	10 (22%)	6 (12%)	
Chest/Abdomen	10 (22%)	6 (12%)	
Arm/Shoulder	11 (24%)	20 (41%)	
Leg	5 (11%)	2 (4%)	
Procedure Duration (min)			
Mean (SD)	2.3 (1.5)	2.7 (2.4)	0.412[b]

Copied from Table 11.1 and Table 11.3.[a]Mantel-Haenszel summary chi-square, stratified by center.
[b]Two-way ANOVA with factors: treatment group, center, and treatment by center.
.[c]Mantel-Haenszel summary chi-square (Caucasin vs. other), stratified by center. [d]Pearson Chi-square.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Milton Fan
1/16/04 03:52:30 PM
BIOMETRICS

please sign it off

Thomas Permutt
1/20/04 08:28:29 AM
BIOMETRICS
See my secondary review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

SECONDARY REVIEW—CLINICAL STUDIES

NDA:	21-623
Name of drug:	S-Caine (lidocaine 70 mg and tetracaine 70 mg) patch
Applicant:	Zars
Indication:	[redacted]
Document reviewed:	primary review by Milton Fan, Ph.D.
Project manager:	Lisa Malandro
Clinical reviewer:	Howard Josefberg, M.D.
Dates:	letter 31 March 2003; user fee goal (10 months) 4 February 2004
Statistical reviewer:	Thomas Permutt

1 INTRODUCTION

This is a secondary review to the primary statistical review by Milton Fan, Ph.D. While I commend Dr. Fan for his thorough review of the data in this application, I do not concur with his conclusions and recommendations. Dr. Fan recommends additional studies in pediatric patients and in adults undergoing venipuncture, but I do not think they are necessary. I believe the application as it stands contains substantial evidence that the drug is effective for local dermal anesthesia.

The differences between Dr. Fan's opinion and mine seem to stem mainly from different views in two areas. We appear to disagree, first, about the merits of two cross-over studies in adults undergoing venipuncture and, second, in our approach to the problem of collective evidence in the application as a whole.

2 CROSS-OVER STUDIES

The two studies in adults undergoing venipuncture reviewed by Dr. Fan (SC-11-01 and SC-24-01) were of similar design. Subjects had a patch placed on each arm at about the same time, one S-Caine and one placebo patch, with the allocation of treatments to the right or left arm being random. They then had venipuncture in the antecubital fossae of both arms, and they reported the pain associated with each puncture.

The word *cross-over* applied to such a study, though well accepted, merits some attention because this is not quite the kind of study to which it most strictly applies. In a classic cross-over study patients receive one treatment for a while and then *cross over* to another. The principal difficulty in the interpretation of such studies concerns the possibility of a carry-over (or, as Dr. Fan calls it, residual) effect. If patients are cured of a disease by the first treatment, good outcomes may be observed while they are on a subsequent, inferior treatment. These good outcomes may be falsely attributed to the second treatment, which then appears to be better than the first. The temporal sequence is critical to the issue of carry-over.

In the studies in question, a mathematically similar "carry-over" effect can still be defined (and, to a limited extent, estimated), but the interpretation is so different as to be bizarre. If the placebo patch were better than the S-Caine patch, but if it worked principally by anesthetizing the right arm when applied to the left, this beneficial effect of the placebo patch would be falsely attributed to the S-Caine patch that was applied to the right arm.

I think the within-subject (cross-over) design is a good one in this setting. By comparing each subject's experience with S-Caine to his or her own experience with placebo, variation between patients, which can be expected to be wide, is controlled for. I think the possibility of carry-over can and should be discounted a priori, rather than tested for statistically by Dr. Fan's methods. His methods of carrying out this testing are appropriate, assuming it needs to be done, but they are nevertheless not very reliable, as such studies are not designed to detect such effects.

In any case, Dr. Fan offers an alternative way of looking at these studies. Any randomized, cross-over study contains within it a randomized, parallel-group study. Some patients are allocated at random to receive one treatment first, and others receive the other treatment first. If the data from subsequent treatments are ignored, these can be considered parallel treatment arms. This analysis, as Dr. Fan says, is conservative: I think it is unreasonably conservative in this case, and if it had failed I would attach little importance to it. It succeeded, though. There is, as Dr. Fan suggests, a little awkwardness in defining the "first" treatment: again, this is because this is not a classic, temporal, cross-over study. However, calling the right arm the first treatment, there are significant differences in both studies between patients treated with S-Caine in the right arm and patients treated with placebo in the right arm. Such a "direct" effect (in Dr. Fan's terminology) could not be tainted by a residual (carry-over) effect even if there were one.

3 COLLECTIVE EVIDENCE

Dr. Fan considers evidence of efficacy separately for the three kinds of studies (pediatric patients, venipuncture in adults, and dermatologic procedures in adults and geriatric patients), even under the heading, "Collective Evidence." In pediatric patients he recommends further study because the analysis was stratified by age and statistically significant effects were found in only one of the two age strata, and also because of discordances in some secondary analyses. In adult patients he recommends an additional study with a parallel-group design.

The proposed indication, however, is [redacted] The application is submitted under section 505(b)(2) and refers to a listed drug with a very similar indication. Arguably each of the six studies furnishes some "evidence that the drug will have the effect that it purports or is represented to have," local dermal anesthesia. Incontrovertibly, at least some of the six studies do, including the younger strata of the pediatric studies as well as the adult dermatologic study.

How finely to separate different uses of a drug, in estimating "the effect" it may have, is a difficult question, and largely one of clinical judgment. Still, there are statistical aspects of it, which Dr. Fan leaves unaddressed. The data from these six studies (or eight strata) are not consistent with the hypothesis of no effect in any study or stratum. Nor is there the slightest reason to suspect beneficial effects in some studies or strata and harmful effects in others: at worst, some of the strata show little effect at all, and some suggest an effect in the right direction without being statistically significant individually. The only tenable hypothesis, given the data, is that the drug at least sometimes has a beneficial effect and that it has a beneficial effect on average. This is generally all that is known even about a drug in which all trials are successful, and so it can hardly be said to fall short of the usual standard for approval.

This leaves, however, the important question of the conditions of use for which the drug should be recommended. This is a matter of the risks and benefits in different uses, and, again, principally one of clinical judgment. It should be borne in mind, however, that this drug may be most useful in the very populations where it is most difficult to show its effect:

young children, and patients about to undergo relatively painful procedures. Young children may not be able to report pain accurately, and patients in more painful procedures may not be willing to undergo controlled trials. I would suggest, therefore, that it might be better to be silent on the question of exactly what procedures and populations the drug is best suited to, than to try to limit its use to populations like those successfully studied, as long as the benefits are believed to outweigh the risks in a broader population.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Permutt
1/9/04 05:45:18 PM
BIOMETRICS