Safety and Efficacy of CANKERS AWAY™ Medication for the Treatment of Canker Sores (Aphthous Ulcers)

A Multicenter, Placebo Controlled, Randomized and Double-Blind Study

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BACKGROUND

Canker sores, otherwise known as aphthous ulcers or recurrent aphthous stomatitis, are perhaps the most common soft tissue lesions seen by a dentist. Aphthous stomatitis is characterized by one or more usually small, painful ulcers inside the mouth and lips. The typical life cycle of a lesion starts with a tingling at the site of the future ulcer (prodrome stage), and soon after, a red macule appears. This is followed by the breakdown of the epithelium (ulceration). The ulcer has a characteristic crater-like center filled with yellowish material composed of coagulated tissue fluids, oral bacteria and white blood cells. Recurrent attacks are common, with 2-3 ulcers typically occurring during each attack. Ten to 15 ulcers have been noted in some individuals. Recurrence rates vary from one lesion 2 to 3 times per year, to an uninterrupted succession of multiple lesions.[1] Aphthous ulcers may affect patients of any age although the most common age range is from 10 to 50 years, with females being affected more often than males. It is estimated that approximately 20-30% of the population suffers from aphthous ulcers at some point in their lives.[2,3]

The etiology of canker sores is unknown, but stress and local trauma are usually the predominant precipitating factors.[1] Other putative causes include allergies, nutritional deficiencies, and hormonal variations. Canker sores do not appear to be caused by viruses or bacteria, although an allergy to a type of bacterium commonly found in the mouth may trigger them in some people. There is research suggesting that canker sores may be caused by an autoimmune etiology.[2] A computer search on aphthous ulcers from 1966 to present lists over 200 research studies, many of which investigated immunological factors. Although aphthous ulcers often resemble recurrent intraoral herpetic ulcers (RIHU), aphthous ulcers occur on the unattached and movable mucosa (lips, tongue, buccal mucosa, mucobuccal fold, floor of mouth, soft palate), whereas IRHU occur primarily on the immovable mucosa (hard palate, attached gingiva).[1]

Most patients suffering from an aphthous ulcer use over the counter medications as their first, and often only, line of therapy. These products include anesthetic mouth rinses, analgesic ointments and coating agents. Some prescription treatments include tetracycline mouth rinses, topical corticosteroids, systemic steroids, and even laser treatment has been attempted. However, there is widespread disappointment in their effectiveness. There are no curative measures reported to date.[4]

OBJECTIVES

The purpose of this study was to evaluate the safety and efficacy of Cankers Away preparation to reduce the pain of canker sores, and secondarily, to assess its effect on healing.

METHODS

The present study was a prospective, randomized, placebo controlled and double-blind evaluation in which patients with active canker sores were enrolled. The study was conducted at four investigational sites which included the private practice of three dentists and one dermatologist.

A brief medical history was taken for each patient followed by an oral exam. As many as three sores could be evaluated and treated per patient. Baseline evaluations were recorded by the investigator for sore location, size and depth, color, presence of crusting or infection, duration and stage. Patients scored their baseline pain on an ordinal scale.

The test agent was applied to the lesion with a saturated cotton swab for 30 seconds. After approximately 4 minutes, the patient was questioned as to his/her relief of pain. Fifteen minutes later, a second evaluation of pain was made, followed by a second application of the test agent. A third assessment of pain was made immediately following the second application. Information concerning adverse reactions was elicited by questioning the patient as to whether they experienced any problems due to the use of the test agent. All responses were recorded on case report forms.

The patient was then given the study sample and instructed to use the material twice a day for the next two days. The next day the patient returned to the office for an evaluation of pain, healing and adverse events, followed by a final evaluation at Day 3 (or 4). If the patient failed to return for either of the last two evaluations, a telephone interview was attempted, and if successful, used in the data analysis.

Only patients with active canker sores were enrolled in the study. The treatment regimen for this study covered a three day period and was designed to determine the amount of pain relief on Day 1, 2 and 3, with special emphasis on Day 1.

Blinding to the investigators and patients was assured by packaging both the Cankers Away and placebo test samples in identical bottles. The color and consistency of both liquids were identical. The only identifying marking on the bottles was a unique and random code number. No communication was permitted between the sponsor and the investigators, or the clinical monitor, regarding the code assignments. Each of the four investigators was originally assigned to 20 patients, and each received 10 Cankers Away bottles and 10 placebo bottles. During the initial office visit, the investigator pulled one of the study bottles at random and treated the patient accordingly. The investigator recorded the code number on the case report form. Upon completion of the study and data entry for the statistical report, the code was unsealed and entered into the database.

Study Population

This study included 80 patients. Half the patient population received Cankers Away (test group), and the other half, placebo (control group). Each patient could be treated for up to 3 lesions, all of which were always assigned to the same treatment but evaluated separately.

Any person presenting with a canker sore was considered for inclusion in the study. Potential patients responded to advertisements and were initially screened by the sponsor over the telephone to ensure they currently had a painful canker sore. Subjects who had a canker sore that was unresponsive to prior treatment with available agents were allowed to enroll as long as they discontinued any concomitant treatment. The investigators were required to make a clinical diagnosis, and thereafter made all final decisions with respect to patient inclusion.

Each patient's written informed consent was obtained before enrollment in the study. The study was conducted in the United States according to Good Clinical Practice (GCP) guidelines.

Clinical Procedures

A schedule of assessments is listed in **Table 1**. Baseline readings were taken on Day 1. A total of 5 post-treatment pain assessments were made by the patient over the course of the study; three on Day 1, one on Day 2 and one on Day 3 (or 4). Healing was assessed by the patient on Day 3 (or 4). Adverse events were assessed by the patient at each application, and a specific query on adverse events was included in each study visit. At the end of the final visit (on Day 3 or 4), 4 post-treatment global evaluation questions were asked to assess the patients' opinion regarding healing, adverse reaction, any unpleasantness due to the treatment and whether they would use the treatment substance again.

Monitoring of the study was conducted by the sponsor following GCP guidelines. The monitor made periodic visits to the study sites to assure the accuracy and completeness of records, documentation of patients lost to follow-up, and that the obligations of the investigators were being fulfilled.

Efficacy Assessment

Pain was the primary outcome measure. At each evaluation, pain was assessed by the

patient using the following grading scale:

Pain Level	Symptoms
0	None
1	Slight
2	Fairly painful, discomfort lasting less than 3 minutes
3	Very painful, discomfort lasting more than 3 minutes, or impeding food intake
4	Severe pain, allowing only liquid intake

Patient assessment of healing was used as a secondary outcome measure and was recorded at the final evaluation in the form of the following question:"Was healing improved in this trial compared to the outcome of previous canker sores or treatments?"

Statistical Methods

All statistical analysis was done using SAS software (Cary, NC). Data on demographics were evaluated on a per patient basis, while evaluations of efficacy were made separately on individual lesions. Data were displayed in tabular form using SAS PROC FREQ and PROC UNIVARIATE. Differences in distribution between treatment groups were tested by Chi square analysis or one way analysis of variance (ANOVA). Correlations between continuous variables were calculated by PROC CORR.

Analysis of efficacy data was performed using ANOVA of ranked data (PROC GLM), using PROC MEANS to generate the mean scores and standard errors of the mean (SEM). Where appropriate, comparisons of categorical scores were made using Chi square analysis. Pain scores were expressed as raw scores and as changes from baseline. In the latter, positive scores represented improvements, while negative scores represented worsening of the lesion.

Lesion diameters were converted to areas as follows. When a single dimension was given, the lesion was assumed to be circular, and the formula $A = \pi r^2$ was used to calculate the area. When two dimensions were given, the lesion was assumed to be rectangular, and the product of the two dimensions was used to calculate the area. In all cases, $p \leq 0.05$ was considered to be statistically significant.

Analysis of Efficacy

The first goal of the study was to determine the effect of Cankers Away on the attenuation of the pain of canker sores, both on a short term basis (Day 1), as well as on a longer term basis (Day 2 and Day 3 or 4). Effectiveness was determined by the patients' evaluation of pain at each assessment over the course of the study. The treatment was considered effective if there was a significant reduction in pain in the test group as compared to the control group. Assessment of efficacy was performed on both the intent to treat as well as the evaluable population.

The secondary goal was to evaluate the effect of Cankers Away on healing.

Table 1. SUMMARY SCHEDULE OF CLINICAL PROCEDURES AND ASSESSMENTS

CLINICAL PROCEDURES AND ASSESSMENTS	CASE REPORT FORM PAGE	VISITS		
		1st	2nd	3rd
		DAYS		
		1	2	3 or 4
Demographic Information	Patient Information (page 1)	X		
General Medical History		X		
Baseline Data (Canker sore assessment: Description, Stage and Pain Score)	Oral Exam (page 2)	X		
Treatment (application of test agent 2x/day)		X	X	X (day 3)
Pain Assessment	Treatment (page 3)	XXX	X	X
Healing Assessment			X	X
Adverse Event Assessment		X	X	X
Post-Treatment Global Evaluation Questions: 1. Was healing improved in this trial compared to the outcome of previouscanker sores or treatments? 2. Any adverse reaction or irritation? 3. Was there any unpleasantness? 4. Would patient use this treatment substance again?	Post-Treatment (page 3)			X

Table 2. PATIENT AND LESION ENROLLMENT BY TREATMENT POPULATION

Population	Treatment	Visit	1		2		3	
		Days	1		2		3 or 4	
		Objectives of Visit	BASELINE DATA (Demographics, Medical History, Oral Exam) TREATMENT EVALUATION (Pain and Adverse Event assessment)		EVALUATION (Pain and Adverse Event assessment) (2nd day of treatment)		EVALUATION (Pain, Healing & Adverse Event assessment) (3rd day of treatment) (on Day 3)	
			Patients	Lesions	Patients	Lesions	Patients	Lesions
Intent-to-Treat	Cankers Away		40	62	39	61	38	59
	Placebo		39*	50**	37	48	35	47
	Total		79	112	76	109	73	106
Evaluable	Cankers Away		40	62	37	55	27	34
	Placebo		39*	50**	37	48	28	37
	Total		79	112	74	103	55	71

*40 patients were enrolled at baseline, but one patient (#328) was subsequently withdrawn from the analysis due to a misdiagnosis.
**51 lesions were enrolled at baseline, but only 50 were treated due to patient #328 being withdrawn from the study.

Patients were questioned as to whether there was an improvement in healing compared to their experience with previous sores or treatments. Cankers Away was considered to have a beneficial effect on healing if there was a significant improvement in healing noted by the test group in comparison to the control group.

Safety Assessment

At each visit, patients were evaluated and questioned regarding current or between-treatment adverse experience due to the study product. All adverse events were recorded on the case report form. The investigator was not asked to specifically characterize adverse events with respect to their relationship to the study treatment. Assessment of safety was performed on the intent-to-treat population.

RESULTS

Eighty patients enrolled in the study. One control patient was entered and completed visit 1, but was diagnosed as not having a canker sore and was subsequently withdrawn from the analysis. Twenty patients violated the protocol, twelve of whom received Cankers Away and eight received placebo treatment. All violations consisted of failures to return for follow-up visits within the time range prescribed in the protocol. None of the violations occurred during the first visit, one was on the second visit only, two were on both visits 2 and 3, and the remaining violations were on the third visit only. The number of patients and lesions enrolled in each treatment group of the evaluable and intent-to-treat population are shown in **Table 2.**

The evaluable patient population excluded any patient visit which fell outside the per-protocol time limit, (i.e., they came in on Day 5 instead of Day 3 or 4), including patients who were prematurely dropped from the study. Visits 2 and 3, therefore, have fewer patients than visit 1 **(Table 2).** Data collected via telephone interview was included in the evaluable population. The intent-to-treat population consisted of all patients who enrolled and completed the study, including data that was not "per-protocol" because the patient did not return at an appropriate time for a follow-up visit **(Table 2).** Except where noted, data was analyzed for the intent-to-treat population. A total of 6 patients dropped out of the study prematurely. Two from the Cankers Away group and four from the placebo group. Two of the placebo and one Cankers Away patient dropped out on Day 2, and two placebo and one Cankers Away patient dropped out on Day 3. These patients are excluded from both the intent-to-treat and the evaluable populations, but are only excluded from the time they disappear. Reasons for patient drop-out are listed in **Table 3.**

Table 3. PATIENTS PREMATURELY DROPPED FROM THE STUDY.

Investigator	Patient #	Treatment	Dropout Time	Reasons
Zuckerman	213	Placebo	Day 3	Patient could not be reached
Zeidman	306	Placebo	Day 3	Patient could not be reached
Zeidman	316	Cankers Away	Day 2	Scheduled to take bar exam and could not take time for visit
Zeidman	331	Placebo	Day 2	Patient felt he got placebo and went to another doctor for treatment.
Lo Pinto	403	Placebo	Day 2	Could not get baby sitter for final visit
Lo Pinto	405	Cankers Away	Day 3	Patient out of town week of last visit

Seventy seven of the 79 patients enrolled in the study were chronic canker sore sufferers (**Table 4**). Fifty nine patients (75%) reported a recurrence rate of every other month or more often. Nine of these patients (12%) were constant sufferers who were never without a canker sore. Sixteen patients

(21%) reported a recurrence rate of 2-5 sores per year. Two patients reported having canker sores "often", and 2 did not respond to the question, "How often do the canker sores occur?".

Table 4.
CANKER SORE RECURRENCE RATE TOTAL NUMBER OF PATIENTS= 79

Recurrence Rate	Total # of Patients
Constant, always have a sore in mouth	9
1 sore per week	2
Every 2-4 weeks	16
1 sore per month	18
Every other month	14
2-5 Sores per year	16

Two patients responded that they got canker sores "often", and therefore did not fit into a specific category.
Two patients did not respond to the question "How often do the canker sores occur?"

The demographic data and baseline characteristics of the patients pooled from all investigator sites are summarized in **Tables 5 and 6.** In both the intent-to-treat and evaluable populations there were no statistically significant differences between the groups at baseline. Forty patients were randomized to receive Cankers Away and 40 to placebo treatment. One placebo patient was withdrawn from the study because the investigator could not confirm the diagnosis of an aphthous ulcer. There were no statistically significant differences between the treatment groups in gender, age, height, or weight. At baseline, a total of 113 lesions were entered, 62 in the Cankers Away group and 51 in the placebo group. Only 5-6% of the lesions in both groups were in the prodrome stage; the remaining lesions were almost evenly divided between early, peak and resolving stages, with no significant difference in the distribution of scores between the two treatment groups. The mean pain scale (2.0 ± 0.1 vs. 2.0 ± 0.1) and duration of the lesions (4.2 ± 0.4 vs. 4.2 ± 0.3 days) were nearly identical. Although there were fewer lesions with crusting in the Cankers Away group (27% vs. 31%), these differences were nonsignificant. Significantly more of the Cankers Away lesions were judged to be infected than placebo lesions (18% vs. 4%, $p<0.025$), and their mean crater depth was less (0.61 ± 0.06 vs. 0.88 ± 0.10 mm, $p<0.05$) as was their mean area (7.9 ± 1.1 vs. 12.1 ± 1.9 mm2, $p<0.05$).

Correlation analyses were performed between lesion depth, area, and baseline pain. In all cases these correlations were weak ($r<.4$) indicating that lesion size and appearance did not significantly influence pain. The distribution of patients and number of lesions differed per investigator (Tables 5 & 6). Both Fenig and Zuckerman had 20 patients, while Zeidman had 29 and Lo Pinto had 10. Fenig had 34 sores, Zuckerman had 36, Zeidman had 32 and Lo Pinto had 11.

Primary Efficacy Variable: Pain

When examining the raw pain scores (**Tables 7a & 7b**), on Day 1, mean scores show that there was less pain associated with the Cankers Away treated lesions than those treated with placebo, but this difference was not significant. By the next day, however, and at the final assessment on Day 3 (or 4), the Cankers Away pain scores were approximately half that of the placebos, a difference which was statistically significant ($p = 0.0126$ on Day 2 and $p = 0.0047$ on Day 3 (or 4) for the evaluable population). The differences between treatment and control were nearly identical when comparing the evaluable population and the intent-to-treat population.

An even stronger pattern of pain reduction emerged when changes from baseline scores were examined (Tables 8a & 8b). Although there was some difference seen 4 minutes after application of the test substances on Day 1, 15 minutes

Table 5. PATIENT BASELINE DEMOGRAPHICS

	Cankers Away	Placebo	Total
Number of Patients	40	40*	80
Fenig	10	10	20
Zuckerman	13	7	20
Zeidman	11	19*	30*
Lo Pinto	6	4	10
Gender			
Female	23 (58%)	21 (54%)	44 (56%)
Male	17 (42%)	18 (46%)	35 (44%)
Age			
Mean ± SEM	38 ± 2	42 ± 3	40 ± 2
Min - Max	22 - 64	20 - 89	20 - 89
25th - 75th percentile	27 - 49	28 - 55	27 - 50
Height (inch)			
Mean ± SEM	67.2 ± 0.5	66.8 ± 0.6	66.9 ± 0.4
Min - Max	61.0 - 75.0	60.0 - 80.0	60.0 - 80.0
25th - 75th percentile	64.8 - 69.0	64.0 - 69.5	64.5 - 69.0
Weight (pound)			
Mean ± SEM	143 ± 4	148 ± 6	146 ± 4
Min - Max	110 - 200	102 - 270	102 - 270
25th - 75th percentile	123 - 165	122 - 175	122 - 166

*One patient was later withdrawn from the study due to a misdiagnosis.

Table 6. CANKER SORE BASELINE CHARACTERISTICS

	Cankers Away	Placebo	Total
Number of Canker Sores	62	51*	113
Fenig	19	15	34
Zuckerman	24	12	36
Zeidman	12	20*	32*
Lo Pinto	7	4	11
Canker Sore Stage			
Prodrome	3 (5%)	3 (6%)	6 (5%)
Early	24 (39%)	15 (29%)	39 (35%)
Ulcer At Its Height	17 (27%)	18 (35%)	35 (31%)
Resolving	18 (29%)	15 (30%)	33 (29%)
Pain Scale			
Mean ± SEM	2.00 ± 0.12	1.97 ± 0.13	1.98 ± 0.09
Min - Max	0.00 - 4.00	0.00 - 3.50	0.00 - 4.00
25th -75 percentile	1.00 - 3.00	1.00 - 3.00	1.00 - 3.00
Approximate Area (mm2)			
Mean ± SEM **	7.9 ± 1.1	12.1 ± 1.9	9.8 ± 1.1
Min - Max	0.8 - 50.2	0.2 - 72.0	0.2 - 72.0
25th -75 percentile	1.8 - 12.3	3.1 - 19.6	1.8 - 12.6
Crusting			
Yes	17 (27%)	16 (31%)	33 (29%)
No	45 (73%)	35 (69%)	80 (71%)
**Infected ** **			
Yes	11 (18%)	2 (4%)	13 (12%)
No	50 (82%)	47 (96%)	97 (88%)
Missing	1	2	3
Duration			
Mean ± SEM	4.15 ± 0.44	4.17 ± 0.33	4.16 ± 0.28
Min - Max	1.00 - 21.00	0.25 - 10.00	0.25 - 21.00
25th -75 percentile	2.00 - 5.00	3.00 - 7.00	2.00 - 5.00

*One patient was later withdrawn from the study due to a misdiagnosis.
** P-value < 0.05 between treatment groups

later the improvement in Cankers Away treated scores was approximately twice that of the placebo (p = 0.0115). This statistical significance disappeared when the test substance was reapplied, but it reappeared at the final two assessments (p = 0.0025 on Day 2, and p = 0.0046 on Day 3 (or 4) for the evaluable population). The loss of statistically significant pain relief when measured immediately (as opposed to waiting the 4 minutes) after application may be related to a temporary stinging reported by some patients when product was applied to their lesions. The results were nearly identical when comparing the evaluable and the intent-to-treat population.

To determine whether there were any statistical interactions among the investigators, a two way analysis of variance was performed analyzing the change in pain by treatment and investigator **(Table 9).** The two way ANOVA confirmed the pattern of statistical superiority of Cankers Away at 15 minutes after the first application, and at Days 2 and 3-4. Although there were investigator differences at the first two evaluation times and at Day 3-4, this difference affected both treatment groups equivalently, and generated no statistical interactions except for the evaluation immediately after the second application on Day 1. This can be explained by differences in measurement techniques of the investigators; Fenig, Lo Pinto, and Zuckerman recorded pain levels immediately after the re-application of test substance, while Zeidman waited 2-3 minutes to evaluate pain. Since approximately one third of the Cankers Away patients reported a stinging sensation upon application (see below), Zeidman's patients were given more time for the stinging to subside.

The study evaluated canker sores at various stages of disease. A two way ANOVA was performed to look at the effect of lesion stage and treatment on pain scores **(Table 10).** There were no statistically significant interactions between lesion stage and treatment at any evaluation time, and the pattern of significance due to treatment was unchanged when corrected for lesion stage.

Secondary Efficacy Variable: Healing

Table 11 gives the patients' answers from the post-treatment questionnaire. Significantly more Cankers Away patients than those treated with placebo felt that healing was improved compared to previous canker sores or treatments (65% vs. 38%, p = 0.025). A greater number of Cankers Away than placebo patients were willing to use the treatment substance again, however, the difference was not significant (73% vs. 53%).

Overall, there were few incidence of adverse reactions, and little difference in the reported adverse reactions between the two treatment groups (Table 11). Two (5%) of the patients receiving Cankers Away reported an adverse reaction, compared with 3 (9%) from the placebo group. One of the Cankers Away lesions had possible bleeding while another reported that the lesion might have gotten worse. Of the placebo group, two lesions got bigger and one was irritated a bit more (**Table 12**). None

of these reactions were serious, and all could have been a consequence of the natural progression of the lesion. Significantly more Cankers Away patients reported unpleasantness associated with the treatment (35% vs. 3%, p = 0.001) (**Table 11**). Of these 13 Cankers Away patients, 7 reported stinging or burning, 3 reported bad taste, and 3 reported both.

DISCUSSION

Efficacy

The data in this study show Cankers Away to be an effective treatment for the alleviation of the pain and soreness of canker sores. A reduction in pain was noted in the Cankers Away group at the 4 minute time point, and pain was significantly improved over placebo at 15 minutes after application and during Days 2 through 4 after treatment. Thus the only time point at which the Cankers Away was not statistically superior was when pain was measured immediately after application (under 5 minutes). Apparently, the perception of stinging made it impossible to measure effectiveness accurately. This is confirmed by the statistically significant increase in the occurrence of stinging in the Cankers Away group as well as the statistically significant investigator interaction, where Zeidman, who waited longer than the others to make an assessment, recorded lower pain scores than the other investigators. Since an additional evaluation was not made after a delay following the second application, it cannot be determined whether the second application eventually would have been found beneficial.

Nevertheless, the relief generated by Cankers Away was evident throughout the course of the study. Both of the evaluation time points after the first day for both raw and improvement scores showed significant improvement over placebo. This data was supported by the findings that more patients who received Cankers Away than those receiving placebo reported improved healing compared to past sores or treatments (p = .025). This is impressive in that the majority of this patient population suffered from chronic recurrent canker sores.

In further examining the response, it was found that the superiority of Cankers Away treatment over placebo remained when different lesion stages were analyzed. It is also impressive that the benefits of Cankers Away over placebo were evident even though significantly more of the lesions treated with Cankers Away were judged to be infected at baseline compared to the placebo.

Rather than a straight saline solution, the placebo used in this study consisted of the inactive ingredients in Cankers Away. One of these, cetylpyridinium chloride, an antimicrobial agent, is found in Kank+A canker sore medication currently on the market. These ingredients may themselves have had a beneficial effect on the lesions, further strengthening the results of this study.

Safety

The safety profile of Cankers Away was excellent. None of the complaints were serious. The unpleasantness associated with the use of Cankers Away related to two factors. The taste was described by various patients as "bitter", "sour", "acid" or "like lemon juice". Application of Cankers Away to a lesion frequently was associated with a transient mild to moderate stinging or burning sensation. As noted in the IND submission, this was anticipated. It is of interest to note that only part of the Cankers Away patient population who reported stinging upon application, ultimately reported this as an unpleasantness in the post-treatment questionnaire. Several patients stated that the unpleasantness was worth the cure; four respondents commented that they were ready to purchase the product immediately.

CONCLUSION

Cankers Away was shown to be a safe and effective treatment for aphthous ulcers. Its efficacy, measured by relief of pain and speed of healing, was significantly better than placebo, and its safety profile was excellent.

Table 7a. PRIMARY EFFICACY RESULTS OF EVALUABLE POPULATION
RAW PAIN SCORES (Mean ± SEM)

	Cankers Away	Placebo	P-value*
Baseline	2.00 ± 0.12	1.97 ± 0.13	NS
Day 1:			
First Application			
Initial Assessment (4 min)	1.50 ± 0.12	1.61 ± 0.14	NS
Second Assessment (15 min)	1.27 ± 0.12	1.57 ± 0.15	NS
Second application			
Initial Assessment (0-3 min)	1.45 ± 0.12	1.52 ± 0.15	NS
Day 2:			
Assessment	0.91 ± 0.12	1.49 ± 0.18	0.0126
Day 3 or 4:			
Assessment	0.63 ± 0.16	1.32 ± 0.20	0.0047

*P-value from the ranks of the data

Table 7b. PRIMARY EFFICACY RESULTS OF INTENT-TO-TREAT POPULATION
RAW PAIN SCORES (Mean ± SEM)

	Cankers Away	Placebo	P-value*
Baseline	2.00 ± 0.12	1.97 ± 0.13	NS
Day 1:			
First Application			
Initial Assessment (4 min)	1.50 ± 0.12	1.61 ± 0.14	NS
Second Assessment (15 min)	1.27 ± 0.12	1.57 ± 0.15	NS
Second application			
Initial Assessment (0-3 min)	1.45 ± 0.12	1.52 ± 0.15	NS
Day 2:			
Assessment	0.90 ± 0.12	1.48 ± 0.17	0.0081
Day 3 or 4:			
Assessment	0.54 ± 0.11	1.15 ± 0.18	0.0037
*P-value from the ranks of the data			

Table 8a. PRIMARY EFFICACY RESULTS OF EVALUABLE POPULATION
IMPROVEMENT IN PAIN SCORES (Mean ± SEM)

	Cankers Away	Placebo	P-value*
Day 1:			
First Application			
Initial Assessment (4 min)	0.50 ± 0.11	0.34 ± 0.07	NS
Second Assessment (15 min)	0.73 ± 0.10	0.38 ± 0.08	0.0115
Second application			
Initial Assessment (0-3 min)	0.55 ± 0.12	0.43 ± 0.09	NS
Day 2:			
Assessment	1.06 ± 0.13	0.46 ± 0.14	0.0025
Day 3 or 4:			
Assessment	1.39 ± 0.18	0.64 ± 0.19	0.0046
*P-value from the ranks of the data			

Table 8b. PRIMARY EFFICACY RESULTS OF INTENT-TO-TREAT POPULATION
IMPROVEMENT IN PAIN SCORES (Mean ± SEM)

	Cankers Away	Placebo	P-value*
Day 1:			
First Application			
Initial Assessment (4 min)	0.50 ± 0.11	0.34 ± 0.07	NS
Second Assessment (15 min)	0.73 ± 0.10	0.38 ± 0.08	0.0115
Second application			
Initial Assessment (0-3 min)	0.55 ± 0.12	0.43 ± 0.09	NS
Day 2:			
Assessment	1.13 ± 0.14	0.45 ± 0.13	0.0011
Day 3 or 4:			
Assessment	1.50 ± 0.15	0.82 ± 0.17	0.0035
*P-value from the ranks of the data			

Table 9. INTERACTION EFFECT OF TREATMENT BY INVESTIGATOR
PRIMARY EFFICACY RESULTS OF INTENT-TO-TREAT POPULATION
IMPROVEMENT IN PAIN SCORES (P-value)*

	Investigator	Treatment	Investigator By Treatment
Day 1:			
Initial Assessment	0.0111	NS	NS
Second Assessment	0.0203	0.0254	NS
Second Application	NS	NS	0.0385
Day 2:			
Assessment	NS	0.0035	NS
Day 3 or 4:			
Assessment	0.0460	0.0012	NS

*P-value from the ranks of the data in 2 way ANOVA.

Table 10.
INTERACTION EFFECT OF TREATMENT BY LESION STAGE
PRIMARY EFFICACY RESULTS OF INTENT-TO-TREAT POPULATION
IMPROVEMENT IN PAIN SCORES

	Lesion Stage	Treatment	Lesion Stage By Treatment
Day 1:			
Initial Assessment	NS	NS	NS
Second Assessment	0.0187	0.0041	NS
Second Application	NS	NS	NS
Day 2:			
Assessment	0.025	0.0041	NS
Day 3 or 4:			
Assessment	NS	0.0150	NS

Table 11. POST-TREATMENT GLOBAL EVALUATION QUESTIONS

	Cankers Away	Placebo	P-Value*
1. Was healing improved in this trial compared to the outcome of previous canker sores or treatments?			
Yes	24 (65%)	13 (38%)	0.025
No	13 (35%)	21 (62%)	
Missing	3	5	
2. Any adverse reaction or irritation?			
Yes	2 (5%)	3 (9%)	NS
No	36 (95%)	32 (91%)	
Missing	2	4	
3. Was there any unpleasantness?			
Yes	13 (35%)	1 (3%)	0.001
No	24 (65%)	34 (97%)	
Missing	3	4	
4. Would patient use this treatment substance again?			
Yes	27 (73%)	18 (53%)	NS
No	10 (27%)	16 (47%)	
Missing	3	5	

*P-value from Chi-Square
** Includes patients dropped from study

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