CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-524

STATISTICAL REVIEW(S)

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:	21-524 / N000
Drug Name:	Chlorascrub™ (3.15% (w/v) Chlorhexidine gluconate with 70% (v/v) Isopropyl alcohol) Swabstick, Maxi Swabstick, Swab
Indication(s):	Patient preoperative and preinjection skin preparation
Applicant:	Les Enterprises SoluMed Inc.
Date(s):	Letter Date: July 26, 2004
	Stamp Date: August 5, 2004
	PDUFA Goal Date: June 5, 2005
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	B. Sue Bell, Ph.D.
Concurring Reviewers:	Daphne Lin, Ph.D.
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Keywords: NDA review, combination drug

Table of Contents

LIST OF TABLES

Appears This Way
On Original

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

As a preoperative skin preparation, Chlorascrub™ solution demonstrated efficacy first at the abdominal site by meeting the 2 $\log_{10}$ reduction in bacterial counts criterion at 10 minutes and a decrease in counts from baseline at 6 hours as specified in the 1994 Tentative final Monograph (TFM) in studies SLM-SC-03 and SLM-SC-04 and second at the groin site by meeting the 3 $\log_{10}$ reduction in bacterial counts criterion at 10 minutes and a decrease in counts from baseline at 6 hours in studies SLM-SC-03 and SLM-SC-08. At the groin site, the comparator product Hibiclens failed to meet the 3 $\log_{10}$ reduction in bacterial counts criterion at 10 minutes but the active vehicle product isopropyl alcohol that is also approved for this indication just met the criterion.

As a preinjection site preparation, Chlorascrub™ solution demonstrated efficacy at the forearm site by meeting the 1 $\log_{10}$ reduction in bacterial counts criterion at 30 seconds.

Table 3 summarizes the results for the three pivitol studies across treatment arms, treatment sites and sampling times providing sample sizes and 95% confidence intervals in addition to the mean $\log_{10}$ reduction statistics.

1.2 Brief Overview of Clinical Studies

There were three confirmatory studies included in this submission that were designed to demonstrate the efficacy in order to meet the criteria in the 1994 TFM. All three studies included three treatment arms for test product (Chlorascrub™), active vehicle (70% v/v IPA), and comparator product (Hibiclens). Studies SLM-SC-03 and SLM-SC-04 included product applications to the forearm, abdomen, and groin using Chlorascrub™ Swabsticks, Maxi Swabsticks or Swabs that contained from 1.0 mL (Swabs) to 5.1 mL (Maxi Swabsticks) of solution. Study SLM-SC-08 included only product application to the groin after it was learned that study SLM-SC-04 had failed to meet the criteria of a 3 $\log_{10}$ reduction in bacterial counts at 10 minutes because the lab treated an area larger than intended for the applicator.

A total of 574 subjects enrolled in eight trials were evaluated for safety. This included 256 subjects enrolled in the three pivotal efficacy trials, 241 patients enrolled in two safety trials, and 77 subjects enrolled in three pilot trials designed to evaluate the efficacy trial protocols.

1.3 Statistical Issues and Findings

The 1994 Tentative Final Monograph (TFM) guided the design of the three pivotal studies. To be granted an indication for use as a preoperative skin preparation, the TFM requires that the test product produce an average of a 2 $\log_{10}$ reduction in bacterial count

on the abdomen and a 3 $\log_{10}$ reduction in bacterial count on the groin at 10 minutes and that the bacterial count not return to baseline by 6 hours.

Study SLM-SC-04 failed to meet the TFM criteria for the groin at 10 minutes because an inappropriate applicator was used for the size of the area treated resulting in too little test product being applied. There were inconsistencies in this application between the protocol, the study report provided by the lab, and the summary provided by the Sponsor. However, the Sponsor's explanation of what went wrong is consistent with the results and study SLM-SC-08 conducted on the groin produced results meeting the TFM criteria.

For an indication of preinjection site preparation, Chlorascrub™ achieved mean $\log_{10}$ reductions in bacterial counts on the forearm of 2.70 and 1.96 at 30 seconds exceeding the requirement for a 1.0 $\log_{10}$ reduction in bacterial count.

For an indication of preoperative skin preparation, Chlorascrub™ achieved mean $\log_{10}$ reductions in bacterial counts of 2.86 and 2.22 at 10 minutes on the abdomen exceeding the requirement for a 2.0 $\log_{10}$ reduction in bacterial count. Chlorascrub™ achieved mean $\log_{10}$ reductions in bacterial counts of 3.36 and 3.86 at 10 minutes on the groin exceeding the requirement for a 3.0 $\log_{10}$ reduction in bacterial count.

Hibiclens, the comparator product, failed to meet the requirement for a 3.0 $\log_{10}$ reduction in bacterial count at 10 minutes on the groin; but IPA that was included as the active vehicle and is also approved for this indication just met the requirement providing some assurance of assay sensitivity.

Because the chlorhexidine gluconate (CHG) is a longer acting component and the IPA is faster acting, there is no difference in the reduction in bacterial counts at 30 seconds or at 10 minutes. At a meeting with the Sponsor held March 22, 2002, the Division stated that the contribution of CHG is acceptable if shown in at least one study and at some time point. The combination product Chlorascrub™ was shown to be superior to its active vehicle IPA at 6 hours and at 24 hours on the groin site in study SLM-SC-08 and at 24 hours on the abdomen site in study SLM-SC-03.

2. Introduction

2.1 Overview

2.1.1 Class and Indication

NDA 21-524 was submitted to support the application for approval of Chlorascrub™ as a topical antimicrobial for the uses of skin antiseptic, skin preparation prior to surgery, and skin preparation prior to injection ——— . Chlorascrub™ combines two active ingredients, 3.15% (w/v) chlorhexidine gluconate and 70% (v/v) isopropyl alcohol. Swabstick and Maxi Swabstick are intended for use as both patient preoperative skin preparations and patient preinjection skin preparations, while the Swab is intended for use for patient preinjection skin preparation only. Under IND 59,446, three phase 3 confirmatory studies were conducted to evaluate the antimicrobial efficacy of Chlorascrub™ in comparison to product vehicle and a reference product, two safety/dermal studies were conducted to evaluate the human skin irritation and sensitization potential of Chlorascrub™. The design of the pivotal trials was based on the 1994 Tentative Final Monograph (TFM).

2.1.2 History of Drug Development

Please refer to the clinical review for a more complete summary of the regulatory activity concerning this product. An Pre-IND submission was made on August 12, 1998 with IND 59,446 being submitted December 5, 1999. ———

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NDA 21-524 was submitted July 26, 2004.

2.2 Data Sources

Table 1: Pivotal Studies included in the submission

Study	Design	Sample Size	Electronic Archive
SLM-SC-03 — Study # 020509-103)	Treatment Arms • Chlorascrub™ (3.15% CHG with 70% IPA) • Active Vehicle (70% IPA) • Hibiclens (4% CHG) Randomized Partially blinded Paired comparison	Planned to treat and analyze 40 treatment sites for each drug on each of the abdomen, groin, and forearm.	\\cdsesub1\N21524\N_000\2004-11-05\CRT\Data for Efficacy Studies\SC03 Efficacy File Definitions.pdf
SLM-SC-04 — Study # 01-108607-11)	Treatment Arms • Chlorascrub™ (3.15% CHG with 70% IPA) • Active Vehicle (70% IPA) • Hibiclens (4% CHG) Randomized Partially blinded Paired comparison	Planned to treat and analyze 40 treatment sites for each drug on the abdomen and groin and 30 treatment sites for each drug on the forearm.	\\cdsesub1\N21524\N_000\2004-11-05\CRT\Data for Efficacy Studies\SC04 Efficacy File Definitions.pdf
SLM-SC-08 — Study # 521-102)	Treatment Arms • Chlorascrub™ (3.15% CHG with 70% IPA) • Active Vehicle (70% IPA) • Hibiclens (4% CHG) Randomized Partially blinded Paired comparison	Planned to treat and analyze 40 treatment sites for each drug on the groin.	\\cdsesub1\N21524\N_000\2004-11-05\CRT\Data for Efficacy Studies\SC08 Efficacy File Definitions.pdf

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The primary objective of the clinical program for Chlorascrub™ is to establish antimicrobial effectiveness according to the Tentative Final Monograph (TFM) criteria for preoperative skin preparation and for preinjection skin preparation. This statistical review will provide highlights of the protocols but for a more complete discussion, please refer to the clinical review.

COMMENT: *For change from baseline, this review uses the average of the screening day baseline and the test day baseline for consistency with other recent statistical reviews for the same indications. The clinical review reports change from baseline using the test day baseline. This reviewer reviewed results based on both approaches for baseline and found little difference in estimates and no difference in conclusions.*

The three pivotal efficacy studies for Chlorscrub examined its antimicrobial activity relative to the efficacy of Isopropyl Alcohol (IPA) that is the Chlorascrub™ vehicle without added Chlorhexidine Gluconate (CHG) and to the efficacy of Hibiclens clenser in healthy human subjects. Activity against resident bacterial flora on the forearm, abdomen and/or groin was evaluated in the pivotal studies, SLM-SC-03, SLM-SC-04, and on the groin in study SLM-SC-08. The study designs were based on methods specified in the TFM. Table 2 presents the applicators and body sites actually used for each study.

Table 2: Areas and Applicators used in Studies SLM-SC-03, SLM-SC-04, and SLM-SC-08 – Sponsor reported in volume 1, section 3, pages 168-169.

	Area Borders in inches	Applicator
Forearm		
SLM-SC-03 (Study No. 020509-103)	2.5 X 2.5	Swab
SLM-SC-04 (Study No. 01-108607-11)	2.5 X 2.5	Swab
Abdomen		
SLM-SC-03 (Study No. 020509-103)	4 X 4	Maxi Swabstick
SLM-SC-04 (Study No. 01-108607-11)	7 X 7	Swabstick
Groin		
SLM-SC-03 (Study No. 020509-103)[1]	3 X 5	Swabstick
SLM-SC-04 (Study No. 01-108607-11)[1]	7 X 7	Maxi Swabstick
SLM-SC-08 (Study No. 521-102)	3 X 7.5	Maxi Swabstick

[1]Reported by Sponsor in volume 1, section 3, pages 168-169.

COMMENT: *Contrary to above table, study report for SLM-SC-03 (Volume 26, page 42) reported that a 4x4 area on the groin was treated with a Swabstick and a 7x7 area on the abdomen was treated with a Maxi Swabstick and study report for SLM-SC-04 (Volume 26, page 71) reported that a 4x4 area on the abdomen was treated with a Swabstick and a 7x7 area on the groin was treated with a Maxi Swabstick. Nevertheless, the area and applicator for Study SLM-SC-08 is consistently reported and provides*

confirmatory evidence of the combination product being superior to the active vehicle at 6 hours and at 24 hours and that the test product meets the TFM log_{10} reduction requirement at 10 minutes.

Study SLM-SC-03

The protocol 020509-103.01 prepared by [redacted] dated July 12, 2002 was to evaluate and compare the immediate and persistent antimicrobial activity of one test product (Chlorascrub™ composed of 3.15% CHG with 70% IPA), the active vehicle (70% IPA), and a reference product (Hibiclens®) used as a patient skin antimicrobial preparation prior to an injection, as well as a preoperative antimicrobial skin preparation. Three Chlorascrub™ product configurations were studied by using the swab on the forearm on a 2.5 by 2.5 inches area, a Maxi swabstick on the abdomen on a 4 by 4 inches area, and swabstick on the groin on a 7 by 7 inches area.

COMMENT: *See Table 2 and related comment regarding inconsistencies in the protocol and the submission with respect to the size of the areas and the applicators used for each body site.*

The plan was to enroll a minimum of 85 human subjects for the inguinal portion and a minimum of 60 human subjects for the forearm and abdominal portions using bilateral product applications. Forearm evaluation was at 30 seconds and approximately 24 hours after skin prepping. The abdominal site and groin site evaluations were at 30 seconds ± 10 seconds, 10 minutes ± 30 seconds, 6 hours ± 15 minutes, and 24 hours ± 30 minutes post-skin-prepping. Monitoring of adverse events and observation of skin irritation on the abdomen and the groin were before and approximately 10 minutes, 6 hours, and 24 hours after drug application.

Study Design: randomized, active control, parallel group, open-label, phase 3, and clinical trial. A computer generated randomization schedule randomly assigned the right and left forearms, abdomen, and groin treatment sites for each subject within each group. The technicians responsible for plating and data collection were blinded as to product assignment. During the 14 day pre-test period, subjects avoided the use of medicated soaps, lotions, shampoos, deodorants, avoided bathing in chlorinated pools and/or hot tubs, and avoided use of UV tanning beds. Subjects used a personal hygiene kit provided by the study for the course of the study. Subjects did not shave within 5 days or bathe or shower within 48 hours of the test period. A screening period followed the pre-test period for 7 days during which time subjects were sampled at the forearm, abdomen, and groin on both sides. Subjects were eligible for one or more anatomical sites based on baseline criteria of ≥ 2.0 log_{10}/cm^2 for the forearm, ≥ 2.5 log_{10}/cm^2 for the abdomen, and ≥ 4.5 log_{10}/cm^2 for the groin. The 3 products were assigned randomly to the subjects, such that one of the test materials was applied to one side and another to the other side. The 7 day period following the screening period constitutes the test week. Prior to sampling on Test Day One, subjects were questioned regarding adherence to the protocol and were examined physically at the sampling sites. Irritation was scored immediately before samples were taken at baseline and post-prepping samples.

Enrollment: Healthy human subjects at least 18 years of age but not more than 70 were to be recruited to ensure that 40 treatment sites for each drug available for analysis. Exclusion criteria included allergies or sensitivities to CHG or alcohols, pregnant or nursing females, an active skin rash or break in the skin at the testing site regions, contact dermatitis, participation in a clinical trial within the past 30 days, use of any systemic or topical antibiotic medications, steroids, or other product known to affect the normal microbial flora of the skin, insulin-dependent diabetes or use of any medications that may interfere with the study, compromised immunity or HIV positive, mitral valve prolapse, or an unwillingness to fulfill the requirements of the Protocol.

Primary Efficacy Endpoint: Effective antimicrobial activity will be defined as a 1.0 $\log_{10}$ or greater decrease in the mean number of CFU per square centimeter of skin on the forearm, as a 2.0 $\log_{10}$ or greater decrease in the mean number of CFU per square centimeter of skin on the abdomen, and as a 3.0 $\log_{10}$ or greater decrease in the mean number of CFU per square centimeter of skin on the inguina. In addition, the mean number of CFU per square centimeter of skin must remain below the mean number of CFU per square centimeter of skin at baseline for 24 hours after drug application.

COMMENT: *TFM requires bacterial counts below baseline for 6 hours after product use.*

Study SLM-SC-04

The protocol for SLM-SC-04 (a.k.a. [redacted] Study No. 01-108607) prepared by [redacted] was intended to be the same as for Study SLM-SC-03 except that the instructions reversed the size of the areas on the abdomen and the groin. See Table 2 for a comparison of areas prepared and application methods used by site. Because the swabstick was used on an area larger than it was intended on the groin, this study failed to meet the 3 $\log_{10}/cm^2$ reduction criteria for the groin.

Study SLM-SC-08

Study SLM-SC-08 provides data on the groin site to replace the groin site data from study SLM-SC-04 that was inadequate (see volume 1, section 3, page 168-169). The protocol for SLM-SC-08 (a.k.a. [redacted] Study No, 521-102) was the same as the protocol for Study SLM-SC-03 except that it was limited to a study of a 3 by 7.5 inch area of the groin site prepared using the Maxi swabstick.

3.1.2 Summary of Efficacy

Chlorascrub™ meets the efficacy standard set by the Tentative Final Monograph (TFM). Table 3 summarizes the results for the three confirmatory studies.

Using the forearm site to demonstrate skin antisepsis prior to injection [redacted], the requirement for a 1 $\log_{10}$ reduction in the bacterial count at 30 seconds was met by the test product Chlorascrub™, by the active vehicle product isopropyl alcohol (IPA), and by the comparator product Hibiclens.

To demonstrate skin antisepsis prior to surgery, the TFM requires that at 10 minutes following application there is at least a 2 $\log_{10}$ reduction in the bacterial count on the abdomen and a 3 $\log_{10}$ reduction in the bacterial count on the groin. In addition, the bacterial count must stay below baseline for at least 6 hours. All treatment arms in all studies met the 6 hour criteria and, in fact, continue to stay well below baseline for 24 hours. For the abdomen site, all three test arms in both studies SLM-SC-03 and SLM-SC-04 met the TFM requirement for a 2 $\log_{10}$ reduction in bacterial count by 10 minutes. For the groin site, study SLM-SC-04 failed to meet the TFM requirement for a 3 $\log_{10}$ reduction. As discussed above, the Sponsor attributed this failure to a larger than planned area being treated with the swabstick. The Division agreed that the Sponsor could repeat the study in only the groin site. In study SLM-SC-08 all three test arms met the TFM requirement for a 3 $\log_{10}$ reduction in bacterial count.

COMMENT: *In Study SLM-SC-03, Hibiclens did not meet the 3 $\log_{10}$ reduction in bacterial count while IPA just met the requirement. Because IPA is both the active vehicle product and a valid comparator product, it can reasonably replace Hibiclens for the purpose of assay sensitivity in this study.*

Table 3: Summary of Log_{10} Reduction of Bacterial Counts (CFU/cm^2) for Chlorascrub™ vs. Isopropyl Alcohol vs. Hibiclens by Sampling Site, by Sampling Time and by Study – Forearm for support of Preinjection Site Preparation and Abdomen and Groin for support of Preoperative Skin Preparation.

Sampling Site Sampling Time Study	Chlorascrub™ (Test Product)		Isopropyl Alcohol (Active Vehicle Product)		Hibiclens (Comparator Product)	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
Forearm Site						
Log_{10} Reduction[1] at:						
30 Seconds						
SLM-SC-03	41	2.70 (2.35,3.05)	41	2.69 (2.38,3.00)	38	2.75 (2.43,3.07)
SLM-SC-04	41	1.96 (1.65,2.26)	38	1.93 (1.57,2.30)	41	1.88 (1.54,2.22)
24 Hours						
SLM-SC-03	41	2.55 (2.17,2.93)	41	2.37 (2.02,2.72)	38	2.41 (1.99,2.83)
SLM-SC-04	41	2.04 (1.71,2.38)	37	1.78 (1.39,2.16)	37	2.13 (1.82,2.43)
Abdomen Site						
Log_{10} Reduction[1] at:						
10 Minutes						
SLM-SC-03	40	2.86 (2.53,3.19)	42	2.57 (2.24,2.89)	40	2.11 (1.70,2.53)
SLM-SC-04	46	2.22 (1.90,2.54)	45	2.18 (1.88,2.47)	41	2.06 (1.84,2.29)
6 Hours						
SLM-SC-03	40	2.83 (2.54,3.12)	42	2.51 (2.17,2.85)	40	2.58 (2.23,2.94)
SLM-SC-04	46	2.38 (2.08,2.68)	45	2.44 (2.16,2.72)	41	2.39 (2.14,2.63)
24 Hours						
SLM-SC-03	40	3.09 (2.91,3.28)	42	2.49 (2.20,2.79)	40	2.50 (2.11,2.89)
SLM-SC-04	46	2.51 (2.29,2.74)	44	2.14 (1.81,2.48)	40	2.13 (1.76,2.50)
Groin Site						
Log_{10} Reduction[1] at:						
10 Minutes						
SLM-SC-03	41	3.36 (2.99,3.73)	39	3.04 (2.70,3.37)	39	2.48 (2.08,2.88)
SLM-SC-04[2]	48	2.20 (1.90,2.50)	49	2.21 (1.87,2.54)	49	1.32 (0.98,1.66)
SLM-SC-08	41	3.86 (3.56,4.16)	41	3.59 (3.29,3.89)	41	2.95 (2.63,3.27)
6 Hours						
SLM-SC-03	42	3.05 (2.72,3.37)	39	2.67 (2.33,3.01)	40	2.71 (2.45,2.97)
SLM-SC-04[2]	49	2.68 (2.30,3.05)	46	2.40 (1.99, 2.82)	50	1.91 (1.64,2.17)
SLM-SC-08	41	4.10 (3.77,4.43)	41	2.89 (2.64,3.14)	41	3.40 (3.10,3.69)
24 Hours						
SLM-SC-03	40	3.50 (3.09,3.92)	37	1.75 (1.33,2.16)	38	2.81 (2.40,3.22)
SLM-SC-04[2]	45	3.20 (2.88,3.51)	43	1.85 (1.48,2.22)	40	2.35 (1.96,2.75)
SLM-SC-08	41	4.33 (3.99,4.67)	41	2.68 (2.42,2.93)	41	3.74 (3.42,4.06)

CI = confidence interval.

[1] Log_{10} Reduction = average of Screening and Treatment Day baseline log_{10}-transformed bacterial counts minus post-treatment log_{10}-transformed bacterial counts.

[2] Data included for completeness. Study SLM-SC-08 was conducted on the groin site after problems identified with application used in Study SLM-SC-04 (volume 1, section 3 page 169).

Note: Only subjects with data available from a treatment pair for a given sampling time point are included in this summary table.

Table 4 presents the percentage of subjects who meet the TFM requirements by body site, by treatment arm, and by study. A subject was a success if on the forearm there was at least a 1 $\log_{10}$ reduction in the bacterial count at 30 seconds, if on the abdomen there was at least a 2 $\log_{10}$ reduction, and if on the groin there was at least a 3 $\log_{10}$ reduction.

Table 4: Percentage of subjects who meet the TFM threshold at 30 seconds for preinjection site preparation and at 10 minutes for preoperative site preparation -- (Studies SLM-SC-03, SLM-SC-04, and SLM-SC-08)

	%Subjects meeting the TFM threshold (# success/# evaluable)		
	Preinjection Site Preparation	Preoperative Site Preparation	
	Forearm Site (1 $\log_{10}$ reduction at 30 seconds)[1]	Abdomen Site (2 $\log_{10}$ reduction at 10 minutes)[1]	Groin Site (3 $\log_{10}$ reduction at 10 minutes)[1]
SLM-SC-03 (— Study No. 020509-103)			
Chlorascrub™ (Test Product)	92.7% (38/41)	82.5% (33/40)	53.7% (22/41)
Isopropyl Alcohol (Active Vehicle)	92.7% (38/41)	78.6% (33/42)	41.0% (16/39)
Hibiclens (Comparator Product)	94.7% (36/38)	55.0% (22/40)	30.8% (12/39)
SLM-SC-04 (— Study No. 01-108607-11)			
Chlorascrub™ (Test Product)	87.8% (36/41)	65.2% (30/46)	
Isopropyl Alcohol (Active Vehicle)	86.8% (33/38)	68.9% (31/45)	
Hibiclens (Comparator Product)	75.6% (31/41)	70.7% (29/41)	
SLM-SC-08 (— Study No. 521-102)			
Chlorascrub™ (Test Product)			80.5% (33/41)
Isopropyl Alcohol (Active Vehicle)			75.6% (31/41)
Hibiclens (Comparator Product)			43.9% (18/41)

1Baseline is the average of the screen day and test day baselines.

3.2 Evaluation of Safety

The sponsor evaluated safety based on the occurrence of adverse events. No statistical analyses were performed.

There were no major safety issues identified and there were no deaths. Refer to the clinical review for more details on safety studies performed for 14-day cumulative irritation patch test and repeated insult patch test for evaluation of sensitization.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The sponsor did not submit any analyses that examined any gender, race or age differences for the pivotal trials. Because of the small sample sizes in the pivotal trials, no meaningful results can be obtained from these analyses. Table 5 provides summary statistics of age, gender, and race for the subjects included in each study.

Table 5: Demographic and Other Baseline Characteristics — Studies SLM-SC-03 by ——, SLM-SC-04 by —, and SLM-SC-08 by —— (All Randomized Subjects)

Demographic Characteristic	SLM-SC-03	SLM-SC-04	SLM-SC-08
Age (years)			
	(N=205)	(N=118)	(N=81)
Mean (SD)	28.7 (12.5)	51.7 (13.2)	37.5 (11.2)
Median	23.0	54.0	37.0
Range	18 - 69	20 - 69	18 - 63
Gender (n [%])			
Male	145 (69.0)	32 (27.1)	29 (35.8)
Female	60 (28.6)	86 (72.9)	52 (64.2)
Race (n [%])			
Caucasian	195 (92.9)	103 (87.3)	54 (66.7)
Black	1 (0.5)	15 (12.7)	8 (9.9)
Asian	0 (0)	0 (0)	14 (17.3)
Hispanic	2 (1.0)	0 (0)	5 (6.2)
Native American	5 (2.4)	0 (0)	0 (0)
Other	2 (1.0)	0 (0)	0 (0)

4.2 Other Special/Subgroup Populations

No subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The 1994 Tentative Final Monograph (TFM) guided the design of the three pivotal studies. To be granted an indication for use as a preoperative skin preparation, the TFM requires that the test product produce an average of a 2 $\log_{10}$ reduction in bacterial count on the abdomen and a 3 $\log_{10}$ reduction in bacterial count on the groin at 10 minutes and that the bacterial count not return to baseline by 6 hours.

Study SLM-SC-04 failed to meet the TFM criteria for the groin at 10 minutes because an inappropriate applicator was used for the size of the area treated resulting in too little test product being applied. There were inconsistencies in this application between the protocol, the study report provided by the lab, and the summary provided by the Sponsor. However, the Sponsor's explanation of what went wrong is consistent with the results and study SLM-SC-08 conducted on the groin produced results meeting the TFM criteria.

For an indication of preinjection site preparation, Chlorascrub™ achieved mean $\log_{10}$ reductions in bacterial counts on the forearm of 2.70 and 1.96 at 30 seconds exceeding the requirement for a 1.0 $\log_{10}$ reduction in bacterial count.

For an indication of preoperative skin preparation, Chlorascrub™ achieved mean $\log_{10}$ reductions in bacterial counts of 2.86 and 2.22 at 10 minutes on the abdomen exceeding the requirement for a 2.0 $\log_{10}$ reduction in bacterial count. Chlorascrub™ achieved mean $\log_{10}$ reductions in bacterial counts of 3.36 and 3.86 at 10 minutes on the groin exceeding the requirement for a 3.0 $\log_{10}$ reduction in bacterial count.

Hibiclens, the comparator product, failed to meet the requirement for a 3.0 $\log_{10}$ reduction in bacterial count at 10 minutes on the groin; but IPA that was included as the active vehicle and is also approved for this indication just met the requirement providing some assurance of assay sensitivity.

Because the chlorhexidine gluconate (CHG) is a longer acting component and the IPA is faster acting, there is no difference in the reduction in bacterial counts at 30 seconds or at 10 minutes. At a meeting with the Sponsor held on March 22, 2002, the Division stated that the contribution of CHG is acceptable if shown in at least one study and at some time point. The combination product Chlorascrub™ was shown to be superior to its active vehicle IPA at 6 hours and at 24 hours on the groin site in study SLM-SC-08 and at 24 hours on the abdomen site in study SLM-SC-03.

5.2 Conclusions and Recommendations

As a preoperative skin preparation, Chlorascrub™ solution demonstrated efficacy first at the abdominal site by meeting the 2 $\log_{10}$ reduction in bacterial counts criterion at 10 minutes and a decrease in counts from baseline at 6 hours as specified in the 1994 Tentative final Monograph (TFM) in studies SLM-SC-03 and SLM-SC-04 and second at

the groin site by meeting the 3 $\log_{10}$ reduction in bacterial counts criterion at 10 minutes and a decrease in counts from baseline at 6 hours in studies SLM-SC-03 and SLM-SC-08. At the groin site, the comparator product Hibiclens failed to meet the 3 $\log_{10}$ reduction in bacterial counts criterion at 10 minutes but the active vehicle product isopropyl alcohol that is also approved for this indication just met the criterion.

As a preinjection site preparation, Chlorascrub™ solution demonstrated efficacy at the forearm site by meeting the 1 $\log_{10}$ reduction in bacterial counts criterion at 30 seconds.

SIGNATURES/DISTRIBUTION LIST

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Date: April 25, 2005

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HFD-520/David Bostwick
HFD-520/Jean Mulinde
HFD-520/Janice Soreth
HFD-560/Tia Frazier
HFD-725/B. Sue Bell
HFD-725/Daphne Lin
HFD-725/Mo Huque
HFD-700/Chuck Anello

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/s/

Sue Bell
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Daphne Lin
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