# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-586**

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | 21-586/Amendment [redacted] |
| **Drug Name:** | DuraPrep Surgical Solution |
| **Indication(s):** | Use as a patient preoperative skin preparation |
| **Applicant:** | 3M Health Care Inc. |
| **Date(s):** | Stamp Date March 28, 2006<br>PDUFA Goal Date September 29, 2006 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | Biometrics 4 |
| **Statistical Reviewer:** | Stan Lin |
| **Concurring Reviewers:** | Mo Huque |
| **Medical Division:** | Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products |
| **Clinical Team:** | Debbie Lumpkin<br>Colleen Rogers |
| **Project Manager:** | Laura Shay |

**Keywords:** Preoperative Skin Preparation, Active Control

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

With the issues mentioned in section 5.1, primarily for lacking of a negative control in the study, and which are not amenable to statistical correction or adjustment, and also the lack of useful supportive data, it is difficult to provide an overall conclusion from a statistical stand point. Those issues aside, and if the data from the study is the only concern, then it is likely that it showed a mean of 3 $\log_{10}$ reduction in microbial count for the groin area. However, the study results are difficult to interpret.

## 1.2 Brief Overview of Clinical Studies

The DuraPrep NDA #21-586 was submitted in October, 2003. In August 2004, an NDA approvable letter was issued requesting that an additional study be performed to demonstrate that DuraPrep solution achieves a mean of 3 $\log_{10}$ reduction in skin flora on the groin at 10 minutes post application. Study 12MS 10214 was conducted to "Assess the Antimicrobial Effectiveness of 3M DuraPrep Surgical Solution Against Resident Human Skin Flora on the Groin Region," in response to the request.

## 1.3 Statistical Issues and Findings

The current efficacy study only randomized two treatments within subjects and with no negative control. This can severely negatively influence the conduct of the study. Even though an analysis of the data from the "evaluable" subjects show a mean of 3 $\log_{10}$ bacterial reduction, the experimental design and conduct of the study as well as the á priori expectation of the study make it very vulnerable to bias, and results difficult to interpret.

# 2. INTRODUCTION

## 2.1 Overview

An Approvable Letter for NDA #21-586 for DuraPrep Surgical Solution was issued in August, 2004. The Approvable Letter stated that the primary deficiency of NDA 21-586, "is that the data provided failed to demonstrate that DuraPrep Surgical Solution achieves the expected mean of three $\log_{10}$ reduction of bacterial counts in the groin at ten minutes after application." This amendment provides the results for a new study,. 12MS 10214, "Study to Assess the Antimicrobial Effectiveness of 3M DuraPrep Surgical Solution Against Resident Human Skin Flora on the Groin Region."

Section 9.3.1) were notified and invited to participate in the Treatment Phase of the study. Those subjects who qualified for the study continued to follow instructions until completion of the scheduled Treatment Day. Subjects were not allowed to shower or bathe the test areas for 48 hours prior to Screening and Treatment Days. The Treatment Phase was scheduled no sooner than 72 hours and no later than 7 days from the screening baseline collection time.

After screening, a total of 66 subjects were evaluable for efficacy and 62 subjects completed the study. Study completion was defined as having data from a treatment pair available at the 10 minute and 6 hour time points. Following the baseline sample collection, randomly assigned contra lateral test areas were prepped with DuraPrep solution or Hibiclens cleanser. Microbial samples were collected at +10 minutes (± 30 sec.), +6 hours (± 30 min.) and +24 hours (± 60 min.) post-preparation from the groin. Post-preparation timing began upon completion of investigational material application.

### 3.1.4 Study Endpoints

Antimicrobial effects as measured in $\log_{10}$-reduction.

### 3.1.5 Analysis Populations

A total of 107 subjects were assigned screening numbers for the study 102 subjects were screened for microbial counts, 81 subjects were randomized and 80 received study treatment. Of the 81 randomized subjects, 80 (98.8%) were evaluable for safety and 66 (81.5%) were evaluable for efficacy. A total of 62 (76.5%) subjects completed the study and 19 (23.5%) subjects did not complete the study. Fourteen (17.3%) subjects did not complete the study because treatment day baseline criteria were not met. Of the remaining 5 subjects who did not complete the study, 4 subjects had site contamination at one or more of the sampling sites and 1 subject was excluded prior to treatment due to acne on the treatment site. According to the study report, only subjects who met the minimum baseline inclusion criteria on the Screening and Treatment Days of the study on both sides of the body were considered evaluable for efficacy. In the event of missing efficacy data at some but not all time points, paired data from the available time points were included in the analysis. If data from a treatment pair were not available, the data from a single treatment were not included in the analysis, since the design of the study was paired. Sixty-six (66) subjects resulted in data evaluable for efficacy.

### 3.1.6 Statistical Methodologies

The effectiveness criteria are for a 3-log reduction in bacteria 10 minutes after product application. Log reductions were calculated by subtracting the post-treatment log counts from the average of the Screening Day and Treatment Day baseline log-transformed bacterial counts. Results are then summarized by treatment group.

### 3.1.7 Efficacy Results

The sponsor's results for the $\log_{10}$ reduction data at the 10-minute sampling time are summarized in table 1 at the end of this document. Included are baseline average count and average reductions from baseline, in $\log_{10}$ units. It can be seen from the table that for both the test and control Hibiclens products, the point estimates for the reductions are at least 3. It can be shown that the confidence intervals also lie to the right of 3.

*Comment: In total, 80 subjects were enrolled and actively participated in the study—their CFU reduction numbers were collected, at least partially for most. The sponsor's analysis included data from 66 subjects for the 10-minute evaluation, excluded data from 15 subjects who either had at least one-sided of groin area baseline $\log_{10}$ value not reaching 5, or who did not have a paired data (DuraPrep and Hibiclens) available at the time point of interest. Strictly speaking, it may be reasonable to expect in real world applications that not every skin-prep application will start from a baseline of at least 5. For example, if it is good to reduce a 5 to 1.5 (a 3.5 log reduction,) i.e., resultant 1.5 or lower is good skin-prep result, then to reduce someone with 4.5 at baseline to 1.5 (which is only a 3 log reduction), or to 1 (a 3.5 log reduction,) would still be meaningful reduction even though the baseline did not quite reach 5.00. Similarly, for a product not being able to achieve a reduction to 1 or 1.5 no matter what the starting value is, (for example starting with a 5 or a 4,) would still not be good enough. Arguing this way, the analysis could have included all enrolled subjects, i.e., an intent-to-treat approach. This reviewer made such an analysis that included all 80 subjects and on 10-minute reduction data. The results are not significantly different from those of the sponsor's on 66 subjects.*

*Comment: It is interesting to note that the sponsor had stated: "It is **NOT** appropriate to require a 3-log reduction when the criterion is based on test methodology different from current methodology, which requires neutralizer in the sampling solution." (-Meeting minutes, Oct. 2004.) The sponsor's statement presumably was an attempt to explain why the prior two studies had failed. And yet, in this current study, with neutralizer, the results do meet the criterion on both testing products, even with at least 14 patients not meeting test day baseline requirements.*

*Comment: Regardless of the just mentioned, it can be also mentioned that from a purely scientific point of view, the design of the current study disallows for an unbiased answer to the question posed originally. This is because the study was a two-treatment study with no negative control, conducted all at one laboratory. Even if one counts this as a positive study, the "single-center" confounding of its results means that had the same study conducted at the laboratories which gave two separate negative results before, (i.e., not showing a 3 log reduction) the positive result of the current study may not be replicated. Or, the current positive results may not be translated to other laboratories, or other surgical site around the country. It is also obvious to point out that, without study blinding and with the given expectation that both treatments need to "win" to pass regulatory hurdles, the experimenter's incentive might be just to record "good" values for both treatments.*

*Done correctly, the current study should have been conducted at one of the two original laboratories. That way, it could help to show that chance might have played a role in the failed*

*study and that if the studies were done more rigorously at those same laboratories, a positive study can result.*

### 3.2 Evaluation of Safety

Please refer to the clinical review of the reviewing Medical Officer, Dr. Steven Osborne, Office of Nonprescription Products.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This was a clinical use simulation study, in that healthy adult subjects were recruited to evaluate the surgical scrub efficacy of the test product. No special or subgroup analysis were performed or requested.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The current efficacy study only randomizes two treatments within subjects and with no negative control. This can severely negatively influence the conduct of the study. Even though an analysis of the data from the "evaluable" subjects show a mean of 3 $\log_{10}$ bacterial reduction, the experimental design and conduct of the study as well as the á priori expectation of the study make it very vulnerable to bias, and results difficult to interpret.

### 5.2 Conclusions and Recommendations

With the issues mentioned in section 5.1, which are not amenable to statistical correction or adjustment, and also the lack of useful supportive data, it is difficult to provide an overall conclusion from a statistical stand point. Those issues aside, and if the data from the study is the only concern, then it is likely that it showed a mean of 3 $\log_{10}$ reduction in microbial count for the groin area. However, the study results are difficult to interpret.

Primary Reviewer: Stan Lin

Concurring Reviewer(s): Mo Huque



cc:
HFD-560/Debbie Lumpkins
HFD-560/Colleen Rogers
HFD-560/Daiva Shetty
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# Table 1

**Summary of Log Reduction of Bacterial Counts (CFU/cm2) DuraPrep Solution versus Hibiclens Cleanser (Efficacy-Evaluable Population)**

**Protocol Number 05-010214**

| | Treatment Group | | Paired Difference P-value | |
|---|---|---|---|---|
| | **Hibiclens (N = 66)** | **DuraPrep Solution (N = 66)** | | |
| Baseline Value | | | | |
| n | 66 | 66 | 66 | 0.0825 |
| Mean (SD) | 5.37 (0.262) | 5.42 (0.317) | 0.04 (0.205) | |
| Median | 5.30 | 5.32 | 0.01 | |
| Min – Max | 5.04-6.16 | 5.05-6.34 | -0.36-0.77 | |
| 95% CI | | | (-0.01, 0.09) | |
| Log Reduction **10 Minutes** | | | | |
| n | 66 | 66 | 66 | 0.4716 |
| Mean (SD) | 3.41 (0.967) | 3.32 (0.927) | -0.09 (1.053) | |
| Median | 3.31 | 3.14 | -0.24 | |
| Min – Max | -1.13-5.35 | 1.49-5.77 | -1.98-6.07 | |
| 95% CI | | | (-0.35, 0.17) | |
| Log Reduction **6 hours** | | | | |
| n | 62 | 62 | 62 | 0.0499 |
| Mean (SD) | 2.81 (0.698) | 2.65 (0.815) | -0.16 (0.624) | |
| Median | 2.66 | 2.39 | -0.28 | |
| Min - Max | 1.69-4.89 | 1.18-4.41 | -2.05-1.37 | |
| 95% CI | | | (-0.32, -0.00) | |

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/s/
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Stan Lin
7/28/2006 12:11:54 PM
BIOMETRICS

Slight changes to exe summary, and page 6

Mohammad Huque
7/28/2006 12:21:42 PM
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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:** | 21,586 / N000 |
| **Drug Name:** | DuraPrep Surgical Solution® [Iodophor (0.7% available Iodine) and Isopropyl alcohol (74% w/w) solution] |
| **Indication(s):** | Use as a patient preoperative skin preparation |
| **Applicant:** | 3M Health Care Inc. |
| **Date(s):** | Submitted: October 24, 2003<br>Received: October 27, 2003 |
| **Review Status:** | Standard review |
| **Biometrics Division:** | Division of Biometrics III (HFD-725) |
| **Statistical Reviewer:** | Scott Komo, Dr.P.H. |
| **Concurring Reviewers:** | Daphne Lin, Ph.D. |
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| **Project Manager:** | Maureen Dillon Parker |

**Keywords:** NDA review, combination drug

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# 1. EXECUTIVE SUMMARY

## 1.1. CONCLUSIONS AND RECOMMENDATIONS

DuraPrep solution was able to demonstrate efficacy as a preoperative skin preparation at the abdominal site by meeting the 2-log 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 both of their studies. However, neither study met the 3-log reduction at 10 minutes criterion for the groin site that is also specified in the TFM. Although in one study, there was a significant difference in reduction of counts favoring DuraPrep over Hibiclens, the approved active comparator.

Because DuraPrep solution contains 2 active ingredients, iodine and isopropyl alcohol (IPA), the Agency considered the product a combination product. However, an agreement was reached where only the contribution of iodine needed to be demonstrated. The Sponsor was able to demonstrate the contribution of iodine to the product in two studies.

## 1.2. BRIEF OVERVIEW OF CLINICAL STUDIES

There were five pivotal studies included in this submission. Studies 8304 and 8918 were designed to demonstrate the efficacy in order to meet the criteria in the 1994 TFM. Studies 8197 and 9302 were designed to demonstrate the contribution of iodine ($I_2$) in DuraPrep. These studies were necessary because DuraPrep was considered a combination drug. Note, by agreement, the Sponsor did not have to demonstrate the contribution of the alcohol component in these studies. Study 8198 was designed to demonstrate the durability and persistence of the antimicrobial activity of DuraPrep film (DuraPrep solution once it is dry) following a wash with autologous blood and saline.

## 1.3. STATISTICAL ISSUES AND FINDINGS

In the two studies designed to show the efficacy of DuraPrep against resident skin flora as outlined in the TFM, both DuraPrep and the approved comparator, Hibiclens, were able to meet the criteria for the abdomen site both in the 2-log reduction at 10 minutes and the reduction in bacterial counts at 6 hours. However, in both studies, neither DuraPrep nor Hibiclens was able to meet the 3-log reduction at 10 minutes criterion for the groin site. For both treatments, the bacterial counts at 6 hours post-treatment did not exceed the baseline counts at the groin site in either study. In Study 8304, the mean log reduction at 10 minutes at the groin site was 2.76 for DuraPrep compared to 2.93 for Hibiclens. In the other study, Study 8918, at the groin site, using a paired t-test, there was a statistically significant difference in reduction in counts at 10 minutes favoring DuraPrep (DuraPrep mean log counts= 2.37; Hibiclens mean log counts=1.94; p=0.0030); no significant difference in reduction in counts at 6 hours (DuraPrep mean log counts=2.29; Hibiclens mean log counts=2.31; p=0.8566); and a statistically significantly difference at 24 hours favoring Hibiclens (DuraPrep mean log counts=2.13; Hibiclens

mean log counts=2.69; p=0.0061). An issue is that both treatments did not meet the criterion of a 3-log reduction at the groin site at 10 minutes in either study. The fact that Hibiclens, the approved comparator, fell short of meeting the TFM criterion by more than 1 unit on a $\log_{10}$ based scale raises some questions about the study. Furthermore, the percentage of subjects who achieved the 3-log reduction in counts is very low (see Table 1). In Study LIMS 8918, only 18.3% of the DuraPrep subjects and 14.9% of the Hibiclens subjects achieved the 3-log reduction in counts at the groin site. In addition, for Study LIMS 8304, the percentage of subjects who achieved the 3-log reduction at the groin site is almost 15% lower in the DuraPrep subjects than for the Hibiclens subjects (Hibiclens=51.3% vs. DuraPrep=35.7%). However, the clinical significance of the test article not meeting the 3-log reduction criterion at the groin site is unknown because reduction in log bacterial counts is an unvalidated surrogate marker.

**Table 1: Percentage of subjects who meet the TFM threshold at 10 minutes -- (Studies 8304 and 8918)**

| | %Subjects meeting the TFM threshold at 10 minutes (#Evaluable Subjects) | |
|---|---|---|
| Study | Abdomen Site (2-log reduction) | Groin Site (3-log reduction) |
| LIMS 8304 | | |
| Hibiclens | 45.16 (31) | 51.28 (39) |
| DuraPrep w/o $I_2$ | 70.00 (30) | 25.81 (31) |
| DuraPrep | 67.21 (61) | 35.71 (70) |
| LIMS 8918 | | |
| Hibiclens | 55.88 (34) | 14.89 (47) |
| Betadine combination | 81.82 (11) | 23.08 (13) |
| DuraPrep | 64.44 (45) | 18.33 (60) |

In studies 8197 and 9302, the Sponsor was able to demonstrate the contribution of iodine to the test article. An agreement reached earlier between the Sponsor and the Agency precluded the Sponsor from having to demonstrate the contribution of the other component, isopropyl alcohol.

In Study 8198, the Sponsor was able to demonstrate the activity of DuraPrep against a bacterial challenge on prepped skin, following a blood and saline wash used to simulate surgery.

# 2. INTRODUCTION

## 2.1. OVERVIEW

### 2.1.1. CLASS AND INDICATION

DuraPrep solution is intended as a pre-operative skin preparation. It is a topical antimicrobial product consisting of two active ingredients, an iodophor (0.7% available iodine) and isopropyl alcohol (IPA) (74% w/w). Isopropyl alcohol is a short chain alcohol. The iodophor active ingredient, iodine acrylate copolymer solution, contains a [redacted] copolymer, which remains dissolved in the IPA until the solution is applied dermally. The copolymer consists of [redacted] The active ingredients in DuraPrep solution (iodine and IPA) are well-established and effective as broad-spectrum antimicrobials. DuraPrep solution has a wide spectrum of activity against gram-positive bacteria, gram-negative bacteria, and yeasts. DuraPrep solution is bactericidal on contact and has a persistent antimicrobial effect.

### 2.1.2. HISTORY OF DRUG DEVELOPMENT

DuraPrep solution was introduced into the US market in 1988 as an over-the-counter (OTC) drug product under the 1978 TFM for Health Care Antiseptic Drug Products. In 1994, a second TFM was published that was more specific in its allowable active ingredient description (povidone-iodine rather than iodophor). 3M met with the Agency in December 1994 to discuss the chemistry of DuraPrep solution and the implications of the 1994 TFM, at which time the Agency indicated that the DuraPrep solution chemistry was not covered under the scope of the new TFM. The Agency further determined that DuraPrep solution would be allowed to stay on the market while 3M worked toward New Drug Application (NDA) submission.

Based on the 25 October 1995 pre-Investigational New Drug (IND) meeting, it was determined that an NDA would be submitted for DuraPrep solution for the indication of patient pre-operative skin preparation. Because DuraPrep solution contains 2 active ingredients, iodine and IPA, the Agency considers the product a combination product. As such, the contribution of each active ingredient would need to be demonstrated. Further, the Agency stated that human absorption data would not be required for NDA approval; however, the Agency requested that 3M submit the report for the 3M French Absorption study (SRFE 1621) as part of the NDA. The IND 49-411, for the investigation of DuraPrep solution, was filed on 8 December 1995 and went into effect on 14 January 1996. Frequent and open communications with the Agency from the time of IND submission throughout the course of the clinical development plan have resulted in 5 face-to-face meetings, approximately 14 teleconferences, and 53 submissions to the IND and have provided 3M guidance and insight to resolve difficult issues and continue

moving forward toward finalization of an agreeable clinical test plan. Key agreements and/or understandings resulting from these meetings are summarized in this section.

On 13 March 1996, a teleconference was held to discuss test methods and sampling plans. At this teleconference, the Agency stated that based on formulation issues, the use of a DuraPrep solution control formulated without alcohol would not be required.

On 28 July 1998, The Agency indicated that the pivotal clinical trials would need to be conducted at 2 independent test laboratories. Further, with respect to subject screening and enrollment in the pivotal clinical trials, 3M was advised that per the TFM, the screening and treatment day baseline values should be averaged, and that both values must be above the required baseline value.

At the End of Phase II meeting, the Agency agreed that if no difference in efficacy was detected between Duraprep and the vehicle control in the standard preop studies, then two Bacterial Challenge Studies would be needed to demonstrate efficacy. These studies would need to be conducted at two independent laboratories.

An End-of-Phase II Meeting was held on 6 November 2000 to review key Agency agreements reached to date, and to review and discuss chemistry and clinical plan issues. With respect to the clinical plan, the Agency concurred that the requirement for the clinical investigation of DuraPrep solution in the pediatric population would be waived based on the inclusion of a contraindication for use in children less than 2 months of age. (This contraindication has been incorporated and is reflected in current product labeling.) The Agency also requested that 3M conduct 1 additional pilot and neutralization validation study in support of use of the MSS prior to initiating pivotal clinical trials. (These studies were completed and submitted to the IND on 7 August 2001, and reviewed with the Agency via teleconference on 20 December 2001.)

A teleconference was held on 4 October 2001 to discuss the DuraPrep solution applicator design and product labeling (with strengthened warnings and directions for use) as a more appropriate alternative to a contraindication for use with electrocautery. The Agency agreed with the strengthened product labeling, and suggested that it be implemented. The Agency also requested additional studies, including a DuraPrep solution vapor dissipation study, a dry time study, and a drape adhesion study to better clarify the risk of flammability.

A teleconference was held on April 11, 2002 to review and discuss the final draft pivotal study protocols, and review the draft Target Product Information, as requested by the Agency. The Agency found all study protocols acceptable, but requested that another complexed iodine (such as Betadine) be added to the Bacterial Challenge test protocols. (Based on the successful outcome of this teleconference, 3M initiated pivotal clinical trials on 22 April 2002.)

On 12 June 2003, a teleconference was held to discuss the results of LIMS 8304 and LIMS 8918, "Pivotal Studies to Assess the Antimicrobial Effectiveness of 3M DuraPrep Solution Against Resident and Human Skin Flora on Abdomen and Groin Regions". At that meeting, with regard to issue of conducting another study to meet the log reduction criteria specified in the TFM, (since 8918 did not achieve a 3-log reduction in the groin), the Agency concluded that repeating the study was not necessary based on the preliminary look at the data provided by 3M. The Agency, however, recommended that the data be submitted in the NDA along with a rationale as to why the Agency should find it acceptable. The Agency clarified that this does not mean that the application will be approved, but that they have concluded that repeating the study would not be beneficial. The Agency further stated that at this time they do not have any additional statistical requests. However, the Agency will consider alternate analyses once the NDA is submitted.

On 21 August 2003, a meeting was held with the Agency at which 3M presented the DuraPrep solution Benefits and Risks Conclusions. Information presented demonstrated that the benefits of using DuraPrep solution, which include fast and persistent antimicrobial efficacy, as well as enhanced incise drape adhesion, infection rate-reduction benefits, reduced application time, and improved user compliance, far exceed the risk of flammability-related events. The Agency concurred with this conclusion, and stated that a contraindication for use with electrocautery would not be required, but that the Agency would continue to work with 3M toward ways to lower the incidence of flammability.

## 2.2. DATA SOURCES

**Table 2: Pivotal Studies included in the submission**

| Study | Design | Sample Size Abdomen/Groin | Electronic Archive |
|---|---|---|---|
| LIMS 8304 | • Treatment arms<br>o DuraPrep solution<br>o DuraPrep w/o $I_2$ and Hibiclens cleanser<br>• Randomized<br>• Partially blinded<br>• Paired comparison | 83/74 randomized<br><br>61/70 evaluable | \\cdsesub1\n21586\N_000\2003-10-24\clinstat\efficacy\lims8304.pdf |
| LIMS 8918 | • Treatment arms<br>o DuraPrep solution<br>o Hibiclens cleanser<br>o Betadine combination<br>• Randomized<br>• Partially blinded<br>• Paired comparison | 58/69 randomized<br><br>45/60 evaluable | \\cdsesub1\n21586\N_000\2003-10-24\clinstat\efficacy\lims8918.pdf |
| LIMS 8197 | • Treatment arms<br>o DuraPrep solution<br>o DuraPrep w/o $I_2$<br>o Betadine combination<br>o Untreated recovery control<br>• Randomized<br>• Partially blinded<br>• Paired comparison | 31 randomized<br>24 evaluable | \\cdsesub1\n21586\N_000\2003-10-24\clinstat\efficacy\lims8197.pdf |
| LIMS 9302 | • Treatment arms<br>o DuraPrep solution<br>o DuraPrep w/o $I_2$<br>o Betadine combination<br>o Untreated recovery control<br>• Randomized<br>• Partially blinded<br>• Paired comparison | 28 randomized<br>24 evaluable | \\cdsesub1\n21586\N_000\2003-10-24\clinstat\efficacy\lims9302.pdf |
| LIMS 8198 | • Treatment arms<br>o DuraPrep solution<br>o Betadine combination<br>• Randomized<br>• Partially blinded<br>• Paired comparison | 16 randomized<br>12 evaluable | \\cdsesub1\n21586\N_000\2003-10-24\clinstat\efficacy\lims8198.pdf |

# 3. STATISTICAL EVALUATION

## 3.1. EVALUATION OF EFFICACY

### 3.1.1. STUDY DESIGN AND ENDPOINTS

The primary objective of the clinical program for DuraPrep solution was to establish antimicrobial effectiveness according to the Tentative Final Monograph (TFM) criteria. However, the test methods specified in the TFM are generally applicable to water-soluble formulations. A unique aspect of DuraPrep solution is that it dries to a water-insoluble film that resists being washed away during surgery. This necessitated a series of test-method development studies to identify and validate appropriate modifications to the test methods. Based on these studies, modifications to the TFM methods were identified and found acceptable by the Agency for use in the pivotal efficacy studies of DuraPrep solution. In addition, the results of these development studies were not able to demonstrate the contribution of iodine in DuraPrep solution. Therefore, a bacterial challenge method, where bacteria are placed on top of the dried DuraPrep film, was developed to show the contribution of iodine.

The efficacy studies for DuraPrep solution examined its antimicrobial activity relative to the efficacy of DuraPrep w/o $I_2$ (DuraPrep polymer vehicle without added iodine/iodide), Hibiclens cleanser, and Betadine combination (Betadine Surgical Scrub and Betadine Solution) in healthy human subjects. Activity against resident bacterial flora on the abdomen and/or groin was evaluated in the pivotal studies, LIMS 8304 and LIMS 8918, which were designed based on methods specified in the TFM. The contribution of iodine to the antimicrobial efficacy of DuraPrep solution was examined in LIMS 8197 and LIMS 9302 using a bacterial challenge method in which bacteria were applied to the surface of dried prepped skin. Activity against a bacterial challenge on prepped skin, following a blood and saline wash to simulate surgery, was evaluated in LIMS 8198.

**STUDY LIMS 8304**

This was a randomized, partially blinded, paired-comparison study in which each subject received DuraPrep solution and either Hibiclens cleanser or DuraPrep w/o $I_2$. 83 subjects were randomized and received study treatment on the abdomen site, and 74 subjects were randomized and received study treatment on the groin site

Microbial samples were collected at 2 minutes (±30 seconds), 10 minutes (±1 min), 6 hours (±15 min), and 24 hours (±30 min) post-preparation (abdomen) and at 10 minutes (±1 min), 6 hours (±15 min), and 24 hours (±30 min) post-preparation (groin). Post-preparation timing began upon completion of the investigational material application.

Log reductions were calculated by subtracting the post-treatment log-transformed bacterial counts from the average of the Screening Day and baseline Treatment Day log-transformed bacterial counts.

Primary Objective:
The primary objective was to satisfy the criteria in the TFM, which requires a 2-log reduction of bacterial counts on the abdomen and a 3-log reduction on the groin at 10 minutes. At both sites, the bacterial counts must not return to baseline within 6 hours. In addition, the other objective was to demonstrate the contribution of iodine to the formulation. DuraPrep solution w/o $I_2$ was included to evaluate the contribution of iodine to the antimicrobial activity of DuraPrep solution. Hibiclens cleanser was included as a comparison product.

Secondary Objective
The secondary objective was to compare the activity of DuraPrep solution with that of Hibiclens cleanser.

Primary Efficacy Endpoint:
Log reduction of resident skin flora on abdominal sites and groin sites at 10 minutes, 6 hours, and 24 hours following the application of the investigational material. In addition, log reduction of resident skin flora was also measured at 2 minutes for the abdomen site.

Analysis Populations:

Only subjects who met the minimum baseline inclusion criteria on the Screening and Treatment Days of the study on both sides of the body were considered evaluable for efficacy for that region. In the event of missing efficacy data at some but not all time points, paired data from the available time points were included in the analysis. Since the design of the study was paired, if data from a treatment pair were not available, the data from a single treatment were not included in the analysis. Sixty-one abdomen subjects and 70 groin subjects were evaluable for efficacy

**STUDY LIMS 8918**

LIMS 8918 was a randomized, partially blinded, paired-comparison study in which each subject received DuraPrep solution and either Hibiclens cleanser or Betadine® Surgical Scrub and Betadine® Solution (hereafter called Betadine combination). Antimicrobial effectiveness was evaluated by measuring the log reduction of resident skin flora (on abdomen sites and on groin sites) following investigational material application.

Healthy subjects were entered into a 14-day Pretreatment Phase during which standardized, non-antimicrobial soaps, shampoos, and deodorants were used. Following the Pretreatment Phase, each subject was required to visit the test facility on an arranged day for collection of screening baseline samples from the abdomen and groin regions. A visual skin assessment of each test area was performed and the screening baseline samples were collected using the cup scrub technique. Screening baseline samples were taken from each of the 2 contralateral test areas within each body region using MSS. Subjects whose screening baseline samples met the minimum values for inclusion in the study were notified and invited to participate in the Treatment Phase of the study.

Following the baseline sample collection, randomly assigned contralateral test areas were prepped with DuraPrep solution and either Hibiclens cleanser or Betadine combination.

Microbial samples were collected at 2 minutes (±30 seconds), 10 minutes (±1 minute), 6 hours (±15 minutes), and 24 hours (±30 minutes) post-preparation (abdomen) and at 10 minutes (±1 minute), 6 hours (±15 minutes), and 24 hours (±30 minutes) post-preparation (groin).

Post-preparation timing began upon completion of investigational material application. Microbial samples were collected using the cup scrub technique. DuraPrep solution-treated and Betadine® combination-treated sites were sampled with MSS. Hibiclens cleanser-treated sites were sampled with SSS. Bacterial counts were performed by individuals who were blinded to the identities of the test product associated with each sample.

Log reductions were calculated by subtracting the post-treatment log-transformed bacterial counts from the average of the Screening Day and Treatment Day baseline log-transformed bacterial counts. The primary objective was to satisfy the criteria in the TFM, which requires a 2-log reduction of bacterial counts on the abdomen and a 3-log reduction on the groin at 10 minutes, and in both cases the bacterial counts must not return to the baseline level within 6 hours.

The primary measure of efficacy for this study was the log reduction of a bacterial challenge applied to the prepped surface of the skin. The log reductions were evaluated at bacterial inoculation times immediately after the preparations were dry and at 2 hours and 6 hours following treatment (DuraPrep solution, DuraPrep w/o $I_2$, and Betadine combination) and bacterial residence times of 5 and 30 minutes at each of these inoculation time points.

**STUDY LIMS 8197**

This was a randomized, partially blinded, paired-comparison study designed to evaluate the contribution of iodine to the antimicrobial activity of DuraPrep solution. Antimicrobial effectiveness was evaluated by measuring the log reduction of a bacterial challenge with 4 different challenge organisms (*Staphylococcus aureus*, *Serratia marcescens*, *Enterococcus faecalis*, and *Escherichia coli*). Log reduction of organisms recovered from the antiseptic-treated test sites (calculated from corresponding untreated control sites) was determined at 3 post-preparation time points and 2 organism residence times. Log reductions of the bacterial challenge achieved with DuraPrep film were compared with those achieved with DuraPrep without iodine ($I_2$). Betadine® Surgical Scrub and Betadine® Solution (Betadine combination) were tested for information only.

There were 4 test areas (DuraPrep solution, DuraPrep w/o $I_2$, Betadine combination, and an untreated recovery control) on each subject's back. Furthermore, each test area contained 6 individual test sites (3 inoculation times and 2 bacterial residence times On

the Treatment Day, each subject was prepared for 4 test areas on the back, 1 for each treatment).

Healthy subjects were entered into a minimum 7-day Pretreatment Phase during which standardized, non-antimicrobial soaps, shampoos, and deodorants were used. Following the Pretreatment Phase, subjects meeting all inclusion and no exclusion criteria were randomized to treatment and bacterial strain on the Treatment Day. After randomization, on the Treatment Day, each subject's back was prepared. When the preparations were dry, individual sites within each test area were inoculated with 50 µL (approximately 108 colony forming units ([CFU]/mL) of the challenge organism. After inoculation, the test organism remained *in situ* for 5 or 30 minutes prior to sample collection. The organisms were recovered using a modified cup scrub technique. The inoculation of individual sites within each test area and recovery of organisms were repeated in the same manner at approximately 2 hours and 6 hours post-preparation. After sample collection, the inoculated sites were disinfected with 70% isopropyl alcohol. Bacterial counts were performed by individuals who were blinded to the identity of the test product associated with each sample. Four to 8 days following treatment, subjects returned for a dermatological evaluation of the test sites. At this visit, a qualified individual visually examined the test area of the skin to ensure that there was no infection present. The maximum planned duration of the study was 16 days.

**STUDY LIMS 9302**

This was a randomized, partially blinded, paired-comparison study designed to evaluate the contribution of iodine to the antimicrobial activity of DuraPrep solution. Antimicrobial effectiveness was evaluated by measuring the log reduction of a bacterial challenge with 4 different challenge organisms (*Staphylococcus aureus*, *Serratia marcescens*, *Enterococcus faecalis*, *and Escherichia coli*). Log reduction of organisms recovered from the antiseptic-treated test sites (calculated from corresponding untreated control sites) was determined at 3 post-preparation time points and 2 organism residence times. Log reductions of the bacterial challenge achieved with DuraPrep film were compared with those achieved with DuraPrep without iodine. Betadine® Surgical Scrub and Betadine® Solution (Betadine combination) was tested for information only. Healthy subjects were entered into a Pretreatment Phase of at least 7 days during which standardized, non-antimicrobial soaps, shampoos, and deodorants were used. Following the Pretreatment Phase, subjects meeting all inclusion and no exclusion criteria were assigned treatment numbers and randomized to treatment and bacterial strain on Treatment Day. On the 1-day Treatment Day, each subject was prepared for 4 test areas on the back, 1 for each treatment (DuraPrep solution, DuraPrep w/o $I_2$, Betadine combination, and an untreated recovery control). Each test area contained 6 individual test sites (3 inoculation times and 2 bacterial residence times). When the preparations were dry, individual sites within each test area were inoculated with 50 µL (approximately 108 colony forming units [CFU]/mL) of the challenge organism. After inoculation, the test organism remained *in situ* for 5 or 30 minutes prior to sample collection. The organisms were recovered using a modified cup scrub technique. The

inoculation of individual sites within each test area and recovery of organisms was repeated in the same manner at approximately 2 hours and 6 hours after preparation. After sample collection, the inoculated sites were disinfected with 70% isopropyl alcohol. Bacterial counts were performed by individuals who were blinded to the identity of the test product associated with each sample.

Four to 8 days following treatment, subjects returned for a dermatological evaluation of the test sites. At this visit, a qualified individual visually examined the test area of the skin to ensure that there was no infection present. The maximum planned duration of the study was 16 days.

**STUDY LIMS 8198**

This was a randomized, partially blinded, paired-comparison study to evaluate the durability and persistence of the antimicrobial activity of DuraPrep film and Betadine combination following a wash with autologous blood and saline. Antimicrobial effectiveness was evaluated by measuring the log reduction of a bacterial challenge with *S. aureus* after a wash-off procedure simulating surgery. The log reduction of organisms recovered from the antiseptic-treated test sites (compared with corresponding untreated control sites) was determined at 2 post-preparation time points and 2 organism residence times. Log reductions of the bacterial challenge achieved with DuraPrep film were compared with those achieved with Betadine combination. Healthy subjects were entered into a 7-day Pretreatment Phase during which standardized, non-antimicrobial soaps, shampoos, and deodorants were used. Following the Pretreatment Phase, subjects meeting all inclusion and no exclusion criteria were assigned treatment numbers and randomized to treatment on the Treatment Day. On the 1-day Treatment Day, each subject was prepared for 3 test areas on the back, one for each treatment (DuraPrep solution, Betadine combination, and an untreated control). Each test area contained 4 individual test sites (2 inoculation times and 2 bacterial residence times). Ten minutes after treatment (when the preparations were expected to be dry), test areas were washed with autologous blood and saline to simulate exposure to fluids during surgery. Individual sites within each test area were inoculated with the challenge organism approximately 15 minutes post-preparation (including completion of the blood and saline wash). After inoculation, the test organism remained in situ for 5 or 30 minutes prior to sample collection. The organisms were recovered using a modified cup scrub technique. The inoculation of individual sites within each test area and recovery of organisms was repeated in the same manner at approximately 6 hours post-preparation. Enumeration of bacterial counts was performed by individuals who were blinded to the identities of the test product associated with each sample.

### 3.1.2. PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A summary of the demographic and baseline characteristics for Studies 8304 and 8918 are contained in Table 3 for Studies 8304 and 8918 and Table 4 for Studies 8197, 9302, and 8198.

**STUDY LIMS 8304**

83 subjects were randomized and received study treatment on the abdomen site, and 74 subjects were randomized and received study treatment on the groin site. Thirty-five of these subjects were randomized for treatment on both the abdomen and the groin. A total of 2 (2.4%) subjects in the abdomen group and 13 (17.6%) subjects in the groin group did not complete the study (the 2 abdomen subjects were also groin subjects). These 2 subjects (Subject 001A/001G and Subject 002A/002G) and 2 additional groin subjects (Subjects 003G and 004G) did not complete the study because the wrong sampling solution was used. Six (8.1%) groin subjects did not complete the study due to contamination of the test site. Of the remaining 3 groin subjects who did not complete the study, 1 subject (Subject 029G) did so due to personal reasons, 1 subject (Subject 006G) had the product applied to the wrong side (noncompliant with the randomization scheme), and 1 subject's (Subject 052G) 6-hour sample was not taken. Once the error was noted, the technician did not finish the sampling.

**STUDY LIMS 8918**

58 subjects were randomized and received study treatment on the abdomen site, and 69 subjects were randomized and received study treatment on the groin site. Twenty-seven of these subjects qualified for treatment on both the abdomen and the groin. A total of 4 (6.9%) subjects in the abdomen group and 22 (31.9%) subjects in the groin group did not complete the study. Contamination of 1 or more of the test sites was the most common reason for non-completion of the study (3 [5.2%] abdomen subjects and 20 [29.0%] groin subjects did not complete the study due to site contamination). One groin subject did not complete the study (Subject 006G) due to experiencing an AE. One (1.7%) abdomen subject (Subject 122A) and 1 (1.4%) groin subject (Subject 023G) did not complete the study because of a laboratory accident (these laboratory accidents were protocol deviations). For Subject 122A the wrong sampling solution was used. For Subject 023G, baseline samples were not collected prior to treatment.

**Table 3: Demographic and Other Baseline Characteristics — Studies LIMS 8304 and 8918: (All Randomized Subjects) — Sponsor's Table 4**

| Demographic Characteristic | Study 8304 | | Study 8918 | |
|---|---|---|---|---|
| | Abdomen Subjects (N=83) | Groin Subjects (N=74) | Abdomen Subjects (N=58) | Groin Subjects (N=69) |
| Age (years) | | | | |
| Mean (SD) | 34.2 (13.69) | 34.6 (14.06) | 52.9 (12.70) | 57.4 (10.96) |
| Median | 30.0 | 30.0 | 53.5 | 59.0 |
| Range | 18 - 68 | 19 - 74 | 23 - 73 | 23 - 73 |
| Gender (n [%]) | | | | |
| Male | 65 (78.3) | 45 (60.8) | 25 (43.1) | 23 (33.3) |
| Female | 18 (21.7) | 29 (39.2) | 33 (56.9) | 46 (66.7) |
| Race (n [%]) | | | | |
| Caucasian | 78 (94.0) | 71 (95.9) | 45 (77.6) | 61 (88.4) |
| Black | 1 (1.2) | 0 | 13 (22.4) | 7 (10.1) |
| Asian | 0 (0) | 1 (1.4) | 0 (0) | 0 (0) |
| Hispanic | 2 (2.4) | 0 (0) | 0 (0) | 0 (0) |
| Native American | 1 (1.2) | 1 (1.4) | 0 (0) | 1 (1.4) |
| Other | 1 (1.2) | 1 (1.4) | 0 (0) | 0 (0) |
| Height (inches) | | | | |
| Mean (SD) | 69.7 (3.92) | 68.0 (4.83) | 67.1 (3.96) | 66.1 (3.88) |
| Median | 70.0 | 68.0 | 66.5 | 66.0 |
| Range | 57 - 77 | 57 - 76 | 59 - 74 | 59 - 74 |
| Weight (pounds) | | | | |
| Mean (SD) | 184.7 (39.14) | 170.7 (35.91) | 187.0 (34.02) | 178.8 (33.41) |
| Median | 180.0 | 165.0 | 182.5 | 180.0 |
| Range | 110 - 325 | 105 - 300 | 120 - 270 | 106 - 270 |

**STUDY LIMS 8197**

Thirty-one subjects were randomized and received treatment in the study. All 31 subjects were evaluable for efficacy. Of these subjects, 24 (77.4%) completed the study. Seven (22.6%) subjects did not complete the study because of protocol deviations

**STUDY LIMS 9302**

Twenty-eight subjects were randomized and received treatment in the study. Of these, 24 (85.7%) subjects were evaluable for efficacy and completed the study. Four (14.3%).6%) subjects did not complete the study because of protocol deviations

**STUDY LIMS 8198**

A total of 21 subjects entered the study; 16 were randomized and received study treatment. A total of 4 subjects did not complete the study. Three subjects did not complete the study due to contamination of 1 or more of the test sites. Two of these subjects did not have valid assessments at any time point because the site used non-sterile gauze; these 2 subjects were not considered evaluable for efficacy. One of these subjects (Subject #001) did not have a valid bacterial count at 15 minutes post-preparation

(DuraPrep solution) with a 30-minute inoculation time because the inoculum did not stay on the test site resulting in contamination. One subject (Subject #002) was recorded by the study site as having not completed the study and was replaced because several of the bacterial residence times were outside the allowable range. However, this subject technically did complete the study and had data for all time points, and all data from this subject were included in the efficacy analysis.

**Table 4: Demographic and Other Baseline Characteristics — Studies LIMS 8197, 9302, and 8198 (Sponsor's Table 5): (All Randomized Subjects)**

| Demographic Characteristic | Study 8197 (n=31) | Study 9302 (n=28) | Study 8198 (n=16) |
|---|---|---|---|
| Age (years) | | | |
| Mean (SD) | 23.9 (6.32) | 57.2 (9.91) | 43.6 (16.71) |
| Median | 22.0 | 58.0 | 44.0 |
| Min-Max | 18 – 43 | 24 - 70 | 20 - 68 |
| Gender (n [%]) | | | |
| Male | 28 (90.3) | 6 (21.4) | 7 (43.8) |
| Female | 3 (9.7) | 22 (78.6) | 9 (56.3) |
| Race (n [%]) | | | |
| Caucasian | 31 (100.0) | 27 (96.4) | 15 (93.8) |
| Black | 0 | 1 (3.6) | 0 |
| Asian | 0 | 0 | 1 (6.3) |
| Hispanic | 0 | 0 | 0 |
| Native American | 0 | 0 | 0 |
| Other | 0 | 0 | 0 |
| Height (inches) | | | |
| Mean (SD) | 71.7 (3.07) | 65.4 (2.92) | 68.0 (4.07) |
| Median | 72.0 | 65.5 | 68.0 |
| Min-Max | 64 – 76 | 58 - 72 | 63 - 76 |
| Weight (pounds) | | | |
| Mean (SD) | 198.0 (34.65) | 167.9 (27.10) | 175.1 (36.90) |
| Median | 185.0 | 164.0 | 170.0 |
| Min-Max | 155 – 310 | 132 - 250 | 115 - 260 |

### 3.1.3. STATISTICAL METHODOLOGIES

Raw data (CFU/mL) were converted to $\log_{10}$ CFU/cm$^2$. Counts of less than 1 CFU/cm$^2$ were treated as 1 CFU/cm$^2$, such that the log transformations were 0. Data were analyzed separately for the abdomen and the groin regions. Log reductions were calculated by subtracting the post-treatment log recovery from the average of the Screening and Treatment Day baseline log recovery.

**STUDY LIMS 8304 AND LIMS 8918**

The first primary objective was assessed by calculating the mean log reduction on the abdomen and the groin for DuraPrep solution-treated sites. If a 2-log reduction on the abdomen and a 3-log reduction on the groin were achieved within 10 minutes, and if counts did not return to baseline within 6 hours, the criteria of the TFM were met. In

addition, the 95% confidence limits around log reductions were provided for all time points. The second primary objective was assessed by comparing the difference in log reductions between DuraPrep solution and DuraPrep w/o $I_2$. The primary comparison was at 24 hours. A paired t-test was conducted at $p<0.05$ (2-tailed). The contribution of iodine was demonstrated if the log reduction for DuraPrep solution was significantly greater than the log reduction for DuraPrep w/o $I_2$, on either the abdomen or groin test area.

The secondary objectives were assessed as follows: (1) A paired t-test on the difference between baseline and the 24-hour post-preparation counts was conducted ($p<0.05$; 2-tail) for the DuraPrep solution-treated sites. If the 24-hour post-preparation counts were significantly below the baseline counts, the objective of demonstrating 24-hour efficacy was met. (2) The comparison of log reduction of DuraPrep solution to that of Hibiclens cleanser was assessed using a paired t-test conducted at $p<0.05$ (2-tailed).

Descriptive statistics were provided by treatment for each body site and each post-preparation sampling time point. All data from subjects evaluable for efficacy were included in the primary analysis, except for laboratory accidents resulting in contaminated or unusable samples. In the event of missing data at some but not all time points, paired data from the available time points were included in the analysis. Since the study design was paired, if data from a treatment pair were not available, the data from the single side were not included in the analysis.

**STUDIES LIMS 8197 AND LIMS 9302**

Statistical significance of the difference in log reduction between DuraPrep solution and DuraPrep w/o $I_2$ was assessed at each time point using a paired t-test. The primary analysis was across organisms at the 6-hour post-preparation time point, with a 30-minute organism residence time. Success was defined as a significantly greater log reduction for DuraPrep solution-treated sites compared with DuraPrep w/o $I_2$-treated sites. Significance was assessed at $\alpha = 0.05$ (2-sided). In addition, the 95% confidence limits on the paired difference between treatments were calculated for each organism at each time point. A nonparametric analysis (Wilcoxon signed rank test) was also conducted to verify the results. Data for the Betadine-treated sites were summarized using descriptive statistics only.

**STUDY LIMS 8198**

The paired difference in log reduction between the test products was calculated for each subject. Statistical significance of the difference in log reduction between treatments was assessed at each time period using a paired t-test. The primary analysis was on the 6-hour post-preparation time point, with a 30-minute organism residence time. Success was defined as a significantly greater log reduction for DuraPrep solution-treated sites compared with Betadine combination-treated sites. Significance was assessed at $\alpha = 0.05$ (2-sided). A nonparametric analysis (Wilcoxon signed rank test) was also conducted to verify the results. In addition, the 95% confidence limits on the paired difference

between treatments were calculated. The level of color remaining for each preparation after the blood and saline wash was compared using the nonparametric Wilcoxon signed rank test.

### 3.1.4. RESULTS AND CONCLUSIONS

**STUDY LIMS 8304**

The results are the DuraPrep subjects are displayed in Table 5. For the group where DuraPrep solution was applied to the abdominal site, a mean 2.65-log reduction of bacterial counts was achieved at 10 minutes, and at 6 hours the mean log reduction was 2.49, thereby satisfying both the TFM criteria of a 2-log reduction at 10 minutes and a reduction in counts from baseline at 6 hours. The secondary objective was to demonstrate the 24-hour efficacy of DuraPrep solution. At 24 hours, the log reduction of bacterial counts was 1.95, a statistically significant reduction from baseline ($p<0.0001$).

For the group where DuraPrep solution was applied to the groin site, a mean log reduction of 2.76 was achieved at 10 minutes, and at 6 hours.the mean log reduction was 2.86. The Sponsor claims that they met the 3-log reduction criterion by rounding. I do not agree with the use of rounding as the TFM criterion is usually interpreted as greater than or equal to. However, the Sponsor was able to meet the other TFM criteria of a reduction in counts from baseline at 6 hours by demonstrating a statistically significant ($p<0.0001$) reduction in bacterial counts from baseline at all time points. The 24-hour efficacy of DuraPrep solution was also confirmed at the groin site since there was a mean log reduction of 2.36 at 24 hours, a statistically significant reduction from baseline ($p<0.0001$).

**Table 5: Summary of Log Reduction of Bacterial Counts (CFU/cm$^2$) For DuraPrep Treated Sites in the Efficacy Evaluable Population – Study LIMS 8304: (Sponsor's Table 2.7.3.2)**

| Sampling Time | Abdomen | | Groin | |
|---|---|---|---|---|
| | DuraPrep Solution (N=61) | p-value[1] | DuraPrep Solution (N=70) | p-value[1] |
| Baseline Value[2] | | | | |
| Mean (SD) | 3.83 (0.613) | N/A | 6.40 (0.476) | N/A |
| Log Reduction[3] at: | | | | |
| 2 Minutes | | | | |
| Mean (SD) | 2.57 (1.357) | <0.0001 | ND | |
| 95% CI | (2.22, 2.92) | | | |
| 10 Minutes | | | | |
| Mean (SD) | 2.65 (1.371) | <0.0001 | 2.76 (1.110) | <0.0001 |
| 95% CI | (2.30, 3.00) | | (2.50, 3.03) | |
| 6 Hours | | | | |
| Mean (SD) | 2.49 (1.512) | <0.0001 | 2.86 (1.359) | <0.0001 |
| 95% CI | (2.10, 2.88) | | (2.52, 3.19) | |
| 24 Hours | | | | |
| Mean (SD) | 1.95 (1.740) | < 0.0001 | 2.36 (1.385) | < 0.0001 |
| 95% CI | (1.50, 2.39) | | (2.02, 2.69) | |

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval; ND = not done; N/A = not applicable.

[1] Based on paired t-test (1-tailed) on the log reduction (difference between baseline and the post-preparation log counts).

[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.

[3] Log Reduction = average of Screening and baseline Treatment Day log transformed bacterial counts minus post-treatment log-transformed bacterial counts.

The contribution of iodine to the bactericidal activity of DuraPrep solution was assessed by comparing the log reduction of bacterial counts achieved with DuraPrep solution with the log reduction of bacterial counts achieved with DuraPrep w/o $I_2$. The primary comparison was at 24 hours. At 24 hours, the log reduction of resident bacterial flora for DuraPrep solution was not statistically significantly different from the log reduction for DuraPrep w/o $I_2$ on either the abdomen ($p = 0.8817$) or the groin ($p = 0.9742$). The results of these comparisons for the abdomen and groin sites are shown in Table 6.

**Table 6: Summary of Log Reduction of Bacterial Counts (CFU/cm$^2$) for DuraPrep Sites vs. DuraPrep w/o $I_2$ Tested Sites – Abdomen and Groin Subjects (EFF Population) – Study LIMS 8304: Sponsor's tables 2.7.3.3 and 2.7.3.4**

| Sampling Time | Treatment Group: DuraPrep w/o $I_2$ | Treatment Group: DuraPrep Solution | Paired Difference | p-value[1] |
|---|---|---|---|---|
| Abdomen Site | (N = 30) | (N = 30) | | |
| Baseline Value[2] | | | | |
| Mean (SD) | 3.72 (0.558) | 3.82 (0.549) | 0.10 (0.403) | 0.1929 |
| 95% CI | | | (-0.05, 0.25) | |
| Log Reduction[3] at: | | | | |
| 2 Minutes | | | | |
| Mean (SD) | 2.44 (1.315) | 2.70 (1.347) | 0.27 (1.360) | 0.2939 |
| 95% CI | | | (-0.24, 0.77) | |
| 10 Minutes | | | | |
| Mean (SD) | 2.53 (1.233) | 2.83 (1.291) | 0.30 (1.345) | 0.2352 |
| 95% CI | | | (-0.20, 0.80) | |
| 6 Hours | | | | |
| Mean (SD) | 2.19 (1.604) | 2.64 (1.513) | 0.45 (1.314) | 0.0688 |
| 95% CI | | | (-0.04, 0.94) | |
| 24 Hours | | | | |
| Mean (SD) | 2.16 (1.592) | 2.20 (1.804) | 0.04 (1.581) | 0.8817 |
| 95% CI | | | (-0.55, 0.63) | |
| Groin Site | (N=31) | (N=31) | | |
| Baseline Value[2] | | | | |
| Mean (SD) | 6.38 (0.550) | 6.41 (0.472) | 0.03 (0.292) | 0.5508 |
| 95% CI | | | (-0.08, 0.14) | |
| Log Reduction[3] at: | | | | |
| 10 Minutes | | | | |
| Mean (SD) | 2.58 (0.935) | 2.53 (0.839) | -0.06 (1.109) | 0.7837 |
| 95% CI | | | (-0.46, 0.35) | |
| 6 Hours | | | | |
| Mean (SD) | 2.72 (1.396) | 2.97 (1.381) | 0.25 (1.525) | 0.3772 |
| 95% CI | | | (-0.32, 0.82) | |
| 24 Hours | | | | |
| Mean (SD) | 2.26 (1.068) | 2.27 (1.478) | 0.01 (1.176) | 0.9742 |
| 95% CI | | | (-0.43, 0.45) | |

SD = standard deviation; CI = confidence interval.

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and DuraPrep w/o $I_2$ post-preparation log counts.

[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.

[3] Log Reduction = average of Screening and baseline Treatment Day log-transformed bacterial counts minus post-treatment log transformed bacterial counts.

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

Generally, for both the abdomen and the groin sites, there were no statistically significant ($p<0.05$) differences in the log reduction between DuraPrep solution and Hibiclens as shown in Table 7. The one exception occurred at the 6-hour time point for the groin where Hibiclens had a significantly greater reduction in log counts than DuraPrep solution ($p=0.0115$).

**Table 7: Summary Log Reduction of Bacterial Counts (CFU/cm2) for DuraPrep Sites vs. Hibiclens for Abdomen and Groin Subjects – Study LIMS 8304: Sponsor's tables 2.7.3.5 and 2.7.3.6**

| Sampling Time | Treatment Group: Hibiclens Cleanser | Treatment Group: DuraPrep Solution | Paired Difference | p-value[1] |
|---|---|---|---|---|
| Abdomen Site | (N = 31) | (N = 31) | | |
| Baseline Value[2] | | | | |
| Mean (SD) | 3.83 (0.491) | 3.84 (0.678) | 0.00 (0.488) | 0.9665 |
| 95% CI | | | (-0.18, 0.18) | |
| Log Reduction[3] at: | | | | |
| 2 Minutes | | | | |
| Mean (SD) | 2.52 (1.595) | 2.45 (1.377) | -0.07 (1.499) | 0.7916 |
| 95% CI | | | (-0.62, 0.48) | |
| 10 Minutes | | | | |
| Mean (SD) | 1.83 (1.647) | 2.48 (1.444) | 0.65 (1.872) | 0.0616 |
| 95% CI | | | (-0.03, 1.34) | |
| 6 Hours | | | | |
| Mean (SD) | 2.02 (1.522) | 2.34 (1.520) | 0.32 (1.657) | 0.2960 |
| 95% CI | | | (-0.29, 0.92) | |
| 24 Hours | | | | |
| Mean (SD) | 2.01 (1.456) | 1.70 (1.669) | -0.31 (1.281) | 0.1887 |
| 95% CI | | | (-0.78, 0.16) | |
| Groin Site | (N=39) | (N=39) | | |
| Baseline Value[2] | | | | |
| Mean (SD) | 6.39 (0.478) | 6.40 (0.486) | 0.01 (0.332) | 0.8893 |
| 95% CI | | | (-0.10, 0.11) | |
| Log Reduction[3] at: | | | | |
| 10 Minutes | | | | |
| Mean (SD) | 2.93 (1.168) | 2.95 (1.265) | 0.03 (1.137) | 0.8843 |
| 95% CI | | | (-0.34, 0.40) | |
| 6 Hours | | | | |
| Mean (SD) | 3.36 (1.087) | 2.70 (1.318) | -0.66 (1.477) | 0.0115 |
| 95% CI | | | (-1.16, -0.16) | |
| 24 Hours | | | | |
| Mean (SD) | 2.92 (1.222) | 2.51 (1.411) | -0.42 (1.490) | 0.1251 |
| 95% CI | | | (-0.95, 0.12) | |

SD = standard deviation; CI = confidence interval.

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and Hibiclens cleanser post-preparation log counts.

[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.

[3] Log Reduction = average of Screening and baseline Treatment Day log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.

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

In conclusion, the results of this study demonstrate that DuraPrep solution satisfies the criteria defined in the TFM for demonstrating antimicrobial activity on the abdomen site. On the abdomen, there was a greater than 2-log reduction of bacterial counts by 10 minutes that did not return to baseline by 6 hours. At the groin site, the reduction of bacterial counts at 10 minutes (2.76-log reduction) did not meet the criterion defined in the TFM (3-log reduction); at 6 hours post-preparation the log reduction of bacterial counts was 2.86; indicating bacterial counts remained below baseline.

The contribution of iodine to the bactericidal activity of DuraPrep solution was not demonstrated using the methods outlined in this study. There were no statistically significant differences between DuraPrep solution and DuraPrep w/o $I_2$ in the log reduction of resident bacterial flora at any time point on either the abdomen or the groin.

**STUDY LIMS 8918**

The results for the DuraPrep arm are displayed in Table 8. For the group where DuraPrep solution was applied to the abdominal site, a 2.35-log reduction of bacterial counts was achieved at 10 minutes, and at 6 hours the mean log reduction was 2.31, thereby satisfying and exceeding the 2-log reduction criterion of the TFM. At all time points, the changes from baseline were statistically significant ($p<0.0001$). A secondary objective was to demonstrate the 24-hour efficacy of DuraPrep solution. At 24 hours, the mean log reduction of bacterial counts was 1.27, a statistically significant reduction from baseline ($p<0.0001$).

For the group where DuraPrep solution was applied to the groin site, a mean log reduction of 2.23 was achieved at 10 minutes, and at 6 hours the mean log reduction was 2.27. This reduction is much lower than the 3-log reduction criterion of the TFM. At all time points, the changes from baseline were statistically significant ($p<0.0001$). The 24-hour efficacy of DuraPrep solution was also confirmed at the groin site since there was a mean log reduction of 2.19 at 24 hours, a statistically significant reduction from baseline ($p<0.0001$). Based on the above data, this study did not meet the 3-log criterion for the groin site. After seeing the above results, the Sponsor proposed to demonstrate efficacy by comparing its antimicrobial activity to Hibiclens. These results are shown in Table 9.

Table 8: Summary of Log Reduction of Bacterial Counts (CFU/cm2) for DuraPrep Sites - Abdomen and Groin (EFF) – Study LIMS 8918: Sponsor's table 2.7.3.7

| Sampling Time | Abdomen | | Groin | |
|---|---|---|---|---|
| | DuraPrep Solution (N = 45) | p-value[1] | DuraPrep Solution (N = 60) | p-value[1] |
| Baseline Value [2] | | | | |
| Mean (SD) | 3.53 (0.415) | N/A | 5.83 (0.487) | N/A |
| Log Reduction[3] at: | | | | |
| 2 Minutes | | | | |
| Mean (SD) | 2.38 (1.268) | <0.0001 | ND | |
| 95% CI | (2.00, 2.76) | | | |
| 10 Minutes | | | | |
| Mean (SD) | 2.35 (1.251) | <0.0001 | 2.23 (1.059) | <0.0001 |
| 95% CI | (1.98, 2.73) | | (1.96, 2.50) | |
| 6 Hours | | | | |
| Mean (SD) | 2.31 (1.196) | <0.0001 | 2.27 (0.972) | <0.0001 |
| 95% CI | (1.95, 2.66) | | (2.02, 2.53) | |
| 24 Hours | | | | |
| Mean (SD) | 1.27 (1.233) | <0.0001 | 2.19 (0.879) | <0.0001 |
| 95% CI | (0.90, 1.64) | | (1.95, 2.43) | |

SD = standard deviation; CI = confidence interval; ND = not done; N/A = not applicable.
[1] Based on paired t-test (1-tailed) on the log reduction (difference between baseline and the post-preparation log counts at a given sampling time point).
[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.
[3] Log Reduction = average of Screening and baseline Treatment Day log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.

Generally, for both the abdomen and the groin at most time points, the difference in the log reduction between DuraPrep solution and Hibiclens cleanser was not statistically significant ($p<0.05$). However, DuraPrep solution was significantly more effective than Hibiclens cleanser on the abdomen at 6 hours ($p=0.0221$) and on the groin at 10 minutes ($p=0.0030$), as shown in Table 9. On the groin at 24 hours, Hibiclens cleanser was significantly more effective than DuraPrep solution ($p=0.0061$). At the rest of the time points on both the abdomen and the groin, the differences in the log reduction between the DuraPrep solution group and the Hibiclens cleanser group were not statistically significant ($p=0.2132$).

In the small number of subjects studied in the DuraPrep solution versus Betadine combination group, both preparations met the TFM requirement of a 2-log reduction on the abdomen. Neither preparation met the TFM requirement of a 3-log reduction on the groin.

**Table 9: Summary of Log Reduction of Bacterial Counts (CFU/cm$^2$) for DuraPrep Sites vs. Hibiclens sites - Abdomen and Groin (EFF) – Study LIMS 8918: Sponsor's table 2.7.3.8**

| Sampling Time | Treatment Group: Hibiclens Cleanser | Treatment Group: DuraPrep Solution | Paired Difference | p-value[1] |
|---|---|---|---|---|
| Abdomen Site | (N = 34) | (N = 34) | | |
| Baseline Value[2] | | | | |
| Mean (SD) | 3.51 (0.329) | 3.52 (0.433) | 0.01 (0.358) | 0.8193 |
| 95% CI | | | (-0.11, 0.14) | |
| Log Reduction[3] at: | | | | |
| 2 Minutes | | | | |
| Mean (SD) | 2.16 (1.229) | 2.42 (1.294) | 0.26 (1.415) | 0.3064 |
| 95% CI | | | (-0.25, 0.76) | |
| 10 Minutes | | | | |
| Mean (SD) | 2.15 (1.302) | 2.47 (1.146) | 0.32 (1.581) | 0.2433 |
| 95% CI | | | (-0.23, 0.87) | |
| 6 Hours | | | | |
| Mean (SD) | 1.75 (1.149) | 2.31 (1.266) | 0.56 (1.329) | 0.0221 |
| 95% CI | | | (0.09, 1.03) | |
| 24 Hours | | | | |
| Mean (SD) | 1.78 (0.883) | 1.57 (1.154) | -0.21 (0.940) | 0.2132 |
| 95% CI | | | (-0.55, 0.13) | |
| Groin Site | (N=47) | (N=47) | | |
| Baseline Value[2] | | | | |
| Mean (SD) | 5.89 (0.480) | 5.82 (0.511) | -0.07 (0.387) | 0.2481 |
| 95% CI | | | (-0.18, 0.05) | |
| Log Reduction[3] at: | | | | |
| 10 Minutes | | | | |
| Mean (SD) | 1.94 (0.964) | 2.37 (1.085) | 0.43 (0.940) | 0.0030 |
| 95% CI | | | (0.15, 0.71) | |
| 6 Hours | | | | |
| Mean (SD) | 2.31 (0.947) | 2.29 (0.971) | -0.02 (0.743) | 0.8566 |
| 95% CI | | | (-0.25, 0.21) | |
| 24 Hours | | | | |
| Mean (SD) | 2.69 (0.882) | 2.13 (0.796) | -0.56 (1.077) | 0.0061 |
| 95% CI | | | (-0.95, -0.17) | |

SD = standard deviation; CI = confidence interval.

[1] Based on paired t-test (2-tailed) on difference between DuraPrep solution and Hibiclens cleanser post-preparation log counts.

[2] Baseline = average of Screening and Treatment Day baseline log-transformed bacterial counts.

[3] Log Reduction = average of Screening and Treatment Day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.

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

In conclusion, the antimicrobial effectiveness of DuraPrep solution meets the criteria defined in the TFM for sites on the abdomen since a greater than 2-log reduction of resident bacterial counts was achieved by 10 minutes post-preparation and counts did not return to baseline values by 6 or 24 hours post-preparation. For the groin site, a mean log reduction of 2.23 was achieved at 10 minutes. This is much less than the 3-log reduction criterion defined in the TFM. Neither of the control products, Hibiclens cleanser or Betadine combination, met the 3-log criterion on the groin. At all time points, the changes from baseline for DuraPrep solution were statistically significant ($p<0.0001$), indicating that bacterial counts remained below baseline.

Generally, for both the abdomen and the groin at most time points, the difference in the log reduction between DuraPrep solution and Hibiclens cleanser was not statistically significant. At the 6-hour time point on the abdomen and the 10-minute time point on the groin, DuraPrep solution was significantly more effective than Hibiclens cleanser ($p=0.0221$ and $p=0.0030$, respectively), whereas at the 24-hour time point on the groin Hibiclens cleanser was significantly more effective than DuraPrep solution ($p=0.0061$). Using these results, the Sponsor's premise is that in this study, DuraPrep has similar antimicrobial activity as the approved comparator, Hibiclens, and in fact was superior at the 10-minute testing used in the TFM criterion and therefore has demonstrated efficacy.

**STUDY LIMS 8197**

The log reductions of the bacterial counts following treatment with DuraPrep solution or DuraPrep w/o $I_2$ were calculated by subtracting the treatment log count from that of the appropriate untreated control. The primary analysis was conducted on the 6 -hour, post-preparation time point with a 30-minute bacterial residence time. At the primary analysis time point (6 hours post-preparation, 30-minute residence time), the mean log reduction of the bacterial challenge was significantly greater for DuraPrep film (2.96) than for DuraPrep w/o $I_2$ film (-0.18; $p<0.0001$, based on a paired t-test). At all time points, the log reduction for DuraPrep film was greater than for DuraPrep w/o $I_2$ film. All of these differences were statistically significant ($p=0.0003$, based on paired t-tests).

At the primary analysis time point (6-hours post-preparation, 30-minute residence time), based on a paired t-test, the mean log reduction of the bacterial challenge was significantly greater for DuraPrep film than for DuraPrep w/o $I_2$ film ($p=0.0009$) for each of the bacterial organisms (*S. aureus*, p-value<0.0001; *S. marcescens*, p-value<0.0007; *E. coli*, p-value=0.0009) tested except *E. faecalis* (p-value= 0.1823). These findings were confirmed with the non-parametric signed rank test.

**STUDY LIMS 9302**

The log reductions of bacterial counts following treatment with DuraPrep solution or DuraPrep w/o $I_2$ are summarized across organisms were calculated by subtracting the treatment log count from that of the appropriate untreated control. The primary analysis

was conducted on the 6-hour, post-preparation time point with a 30-minute bacterial residence time. At the primary analysis time point (6-hours post-preparation, 30-minute residence time), the mean log reduction of the bacterial challenge was significantly greater on DuraPrep film (3.77) than on DuraPrep w/o $I_2$ film (0.05) ($p<0.0001$, based on a paired t-test). At all time points, the log reduction on DuraPrep film was greater than on DuraPrep w/o $I_2$ film. Except for the initial time point, all the differences were statistically significant ($p \leq 0.0185$, based on a paired t-test). The initial time point was significant based on the non-parametric signed-rank test.

At the primary analysis time point (6-hours post-preparation, 30-minute residence time), based on a paired t-test, the mean log reduction of the bacterial challenge was significantly greater on DuraPrep film than on DuraPrep w/o $I_2$ film for all 4 bacterial organisms (*S. aureus*, p-value= 0.0034; *S. marcescens*, p-value= 0.0033; *E. faecalis*, p-value= 0.0007; and E. coli, p-value <0.0001). This was confirmed with the non-parametric signed rank test. The paired difference was the greatest with *E. coli* (4.86) and the least with *E. faecalis* (2.32). The paired difference was the greatest with *E. coli* (4.86) and the least with *E. faecalis* (2.32).

**STUDY LIMS 8198**

Log reductions for a treated sample were calculated by subtracting the recovery log count taken from the treated sample from that of the appropriate untreated recovery control. The primary analysis was done for the 6-hour, post-preparation time point with a 30-minute bacterial residence time. At the primary analysis time point (6 hours post-preparation, 30-minute residence time), the log reduction of the bacterial challenge was statistically significantly greater on DuraPrep film (mean log reduction = 4.191) than on Betadine combination (mean log reduction = 2.667) ($p = 0.0098$, based on a paired t-test). There was also a greater log reduction of the bacterial challenge on DuraPrep film than on Betadine combination at 6 hours post-preparation, 5-minute residence time, and at 15 minutes post-preparation, 30-minute residence time, and lower log reduction at the 15-minute post-preparation, 5-minute residence time but the differences at these time points were not statistically significant. The persistence of the antimicrobial activity of DuraPrep film was confirmed. For DuraPrep film, the log reductions of the bacterial challenge for a 5-minute residence time were 1.731 and 2.586 for 15 minutes and 6 hours post-preparation, respectively (Table 6). For a 30-minute residence time, the log reductions of the bacterial challenge were 3.749 and 4.191 for 15 minutes and 6 hours post-preparation, respectively. The antimicrobial activity of Betadine combination against the bacterial challenge was slightly less at 6 hours post-preparation compared with 15 minutes post-preparation for both a 5-minute residence time (2.839 at 15 minutes and 2.366 at 6 hours) and a 30-minute residence time (3.326 at 15 minutes and 2.667 at 6 hours).

The level of color remaining for each preparation was visually assessed by the study coordinator prior to and just following the blood and saline wash and at 6 hours following the application of the preparation. Prior to the blood and saline wash, the color

of the Betadine combination and the DuraPrep solution preparations were clearly visible on all 16 subjects. Both immediately following the blood and saline wash and at 6 hours following the application of the preparations, the color on 100% of the DuraPrep-treated sites still remained clearly visible. The color of the Betadine combination-treated sites was less evident; none of the sites had clearly visible color at either time point, approximately 75% of the Betadine combination-treated sites had no visible color and approximately 25% had only slightly visible color at both time points following the wash. The difference in the visual assessment of the color of the DuraPrep solution and the Betadine combination preparations was statistically significant both immediately following the blood and saline wash ($p<0.0001$) and at 6 hours following the preparation ($p=0.0001$).

## 3.2. EVALUATION OF SAFETY

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

### STUDY LIMS 8304

DuraPrep solution, DuraPrep w/o $I_2$, and Hibiclens cleanser were well tolerated by the study population. No adverse events (AE's) were reported or observed during this study.

### STUDY LIMS 8918

DuraPrep solution, Hibiclens cleanser, and Betadine combination were well tolerated by the study population. Only 1 subject (#518) experienced an AE (verbatim term: pain in groin region upon removal of tape); this event was mild in intensity and was not considered to be related to study treatment.

### STUDY LIMS 8197

No AE's were reported in this study.

### STUDY LIMS 9302

One subject experienced an AE during this study. Subject 109 had 1 red papule over the left scapular area at the site of application of DuraPrep solution. This was observed 4 days after treatment and removal of the test materials (at the dermatological evaluation visit). The event was mild in intensity, no action was taken, and the subject recovered within 5 days from the onset of the event. The investigator considered the event to be not related to treatment with DuraPrep solution but instead was due to the application of the microorganism

### STUDY LIMS 8198

No AE's were reported in this study.

# 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.

## 4.2. OTHER SPECIAL/SUBGROUP POPULATIONS

No other subgroup analyses were performed.

# 5. SUMMARY AND CONCLUSIONS

## 5.1. STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In both studies LIMS 8304 and 8918, the TFM criteria at the abdomen site was met. However, neither study met the TFM criteria at the groin site. In Study 8304, the Sponsor asserts that both DuraPrep and Hibiclens met the TFM criterion of a 3-log reduction for the groin site at 10 minutes by rounding up the mean log reductions of 2.76 and 2.93 respectively. I do not agree with their use of rounding up. The log reduction criterion is usually interpreted as greater than or equal to. Their method involves rounding $\log_{10}$ transformed counts so the actual amount of rounding on the untransformed scale is magnified. However, because reduction in log bacterial counts is an unvalidated surrogate marker, it is unknown what the clinical difference between the observed mean log reduction of 2.76 at the groin site and the 3-log reduction in the TFM.

In Study 8918, for the subjects who received both DuraPrep and Hibiclens, at the groin site, using a paired t-test, there was a statistically significant difference in reduction in counts at 10 minutes favoring DuraPrep (DuraPrep mean log counts= 2.37; Hibiclens mean log counts=1.94; p=0.0030); no significant difference in reduction in counts at 6 hours (DuraPrep mean log counts=2.29; Hibiclens mean log counts=2.31; p=0.8566); and a statistically significantly difference at 24 hours favoring Hibiclens (DuraPrep mean log counts=2.13; Hibiclens mean log counts=2.69; p=0.0061). An issue is that both treatments did not meet the criterion of a 3-log reduction at the groin site at 10 minutes. The fact that Hibiclens, the approved comparator, fell short of meeting the TFM criterion by more than 1 unit on a $\log_{10}$ based scale raises some questions about the study. Furthermore, the percentage of subjects who achieved the 3-log reduction in counts is very low (see Table 1). In Study LIMS 8918, only 18.3% of the DuraPrep subjects and 14.9% of the Hibiclens subjects achieved the 3-log reduction in counts at the groin site. In addition, for Study LIMS 8304, the percentage of subjects who achieved the 3-log reduction at the groin site is almost 15% lower in the DuraPrep subjects than for the Hibiclens subjects (51.3% vs. 35.7%).

In studies 8197 and 9302, the Sponsor was able to demonstrate the contribution of iodine to the test article. An agreement reached earlier between the Sponsor and the Agency

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