

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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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 MEMORANDUM

NDA#	208,288
SDN#	045
Drug Name	3M SoluPrep Film-Forming Sterile Surgical Solution
Indication	Patients preoperative skin preparation
Applicant	3M Health Care Business
Dates	Received date: March 3, 2017 Review completion: August 4, 2017 PDUFA: September 3, 2017
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Project Manager	Celia Peacock

1. BACKGROUND

The sponsor, 3M Health Care Business is seeking approval for marketing of SoluPrep™ film-forming sterile surgical solution (2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol, hereafter SoluPrep). A Complete Response (CR) letter was issued in May 6, 2016 for the original submission (July 6, 2015)¹. This is a resubmission that addresses the comments listed in the CR letter.

One of reasons for the CR was that the sponsor failed to show effectiveness of SoluPrep in the groin area in one of two clinical simulation studies. Therefore, the CR letter required the sponsor to conduct another clinical simulation study at the groin area. The sponsor requested a formal dispute resolution arguing that there was no need to conduct a new clinical simulation study. The sponsor's request was granted by agency². As a result, there is no new clinical simulation study for review in this resubmission.

This statistical memorandum focus' is on the sponsor's label statement in section 14 clinical studies. Our recommendation on labeling is based on preplanned analyses and new analyses of the data in the original submission. The new analyses follow effectiveness criteria outlined in the upcoming 2018 Final Rule for healthcare professional topical antiseptics. Thus, we propose to include results of both analyses of responder and average treatment effect in labeling. Note that the two clinical simulation studies in the original submission were reviewed by former statistical reviewer, Dr. Mushfiqur Rashid.³

2. REVIEWER'S REANALYSIS BY NEW EFFECTIVENESS CRITERIA

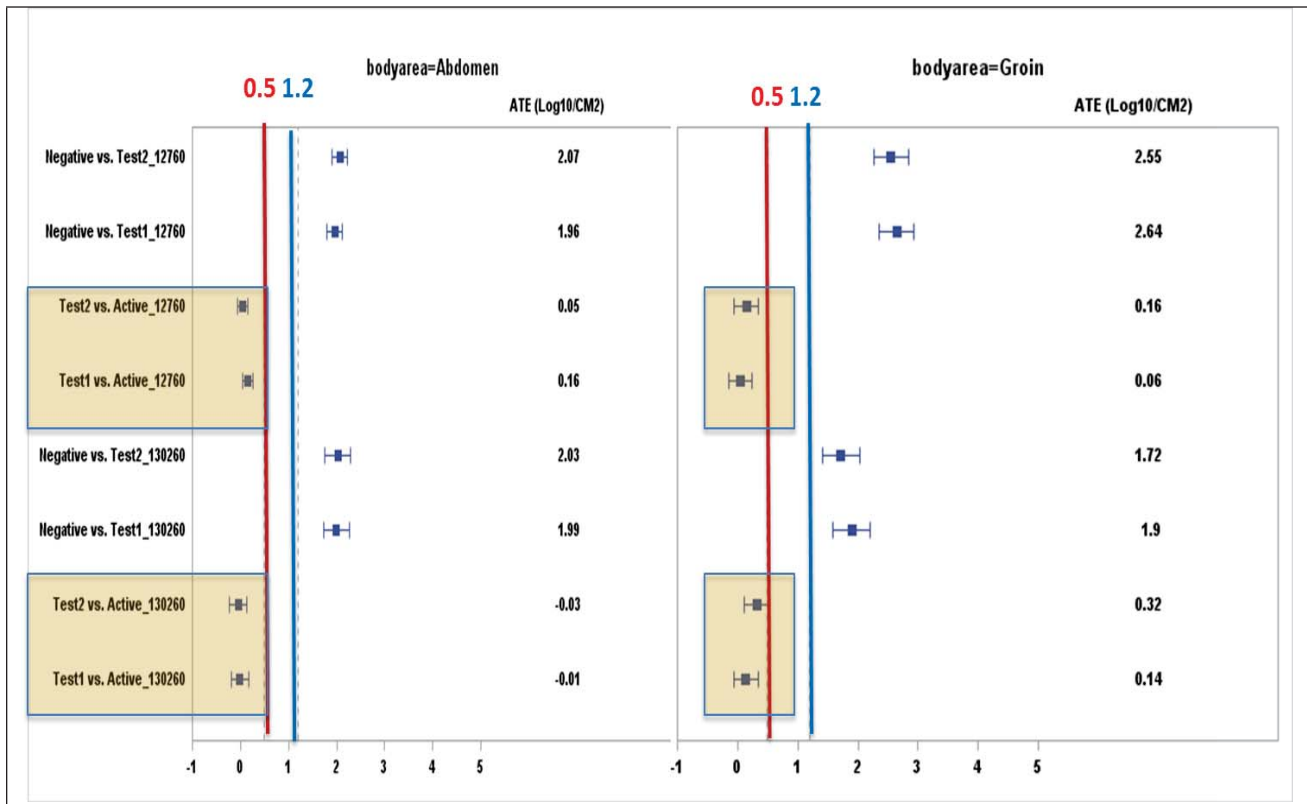
The effectiveness criteria in the 2015 Tentative Final Monograph (TFM) are based on responder rate in each treatment arm, where the responder rate is the proportion of those subjects with a change from baseline bacterial count exceeding an specific threshold; $2 \log_{10}/\text{cm}^2$ for abdomen at 30 seconds; $3 \log_{10}/\text{cm}^2$ for groin at 30 seconds. Then, a test product is considered effective only if the responder rate significantly exceeds 70%.

The new effectiveness criteria in 2018 Final rule is based on average treatment effect (ATE), which is estimated by linear regression of bacterial count at 10 mins (or 30 seconds) in $\log_{10}$ scale on the effect of treatment arm and bacterial count at baseline in $\log_{10}$ scale. There are two criteria required to show effectiveness of test product: non-inferiority to active control and superiority to negative control. For the non-inferiority criterion, ATE is defined as contrast of treatment effect of test product minus the treatment effect of the active control in the linear regression. Then, upper bound of 95% confidence interval of the ATE should be less than 0.5. On the other hand, ATE is defined as the contrast of treatment effect of negative control minus

the treatment effect of the test drug for the superiority criterion, and lower bound of 95% confidence interval of the ATE should be greater than 1.2.

We re-analyzed data submitted in the original submission and applied the new criteria. As shown in Figure 1, SoluPrep is shown to be effectiveness at both body areas in two studies by the new criteria.

Figure 1: The average treatment effect of SoluPrep to Active Control (ChloroPrep) and Negative Control (saline) from two pivotal studies (EM-05-012760 and EM-05-013260).



Footnote: Test1 and Test 2 in the study 130260 are SoluPrep 10.5 ml clear with and without HEDTA (Hydroxyethyl Ethylenediaminetriacetic Acid). Test1 and Test2 in the study 12760 are SoluPrep tinted 10.5ml and 26 ml, respectively. Active and Negative refer to active control (ChloroPrep) and negative control (saline).

3. TARGET PRODUCT INFORMATION LABEL

We recommend following revision to the sponsor's proposed labeling statement (in italic).

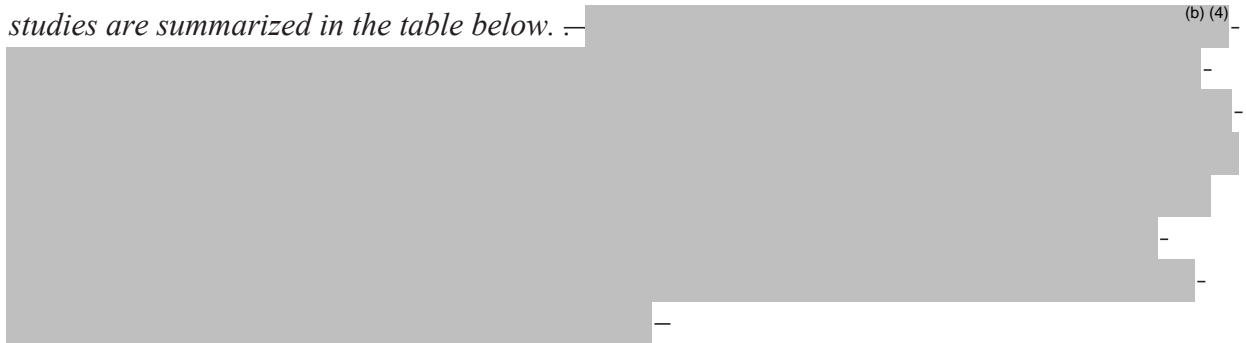
14 Clinical Studies

Pivotal Studies:

Three pivotal studies were conducted to evaluate the safety and antimicrobial efficacy of 3M CHG/IPA Prep on the abdominal and inguinal regions. One of these studies was discontinued prematurely due to technical and data quality issues; thus, efficacy data were not evaluable.

In the pivotal studies, efficacy was assessed from analyses of bacterial counts of cultures obtained from test sites on the abdominal and inguinal regions. The results from two pivotal studies are summarized in the table below. —

(b) (4)

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Study EM-05012760

	3M CHG/IPA Prep, 10.5ml,tinted	3M CHG/IPA Prep, 26ml,tinted	Saline
<i>Abdominal Region</i>			
<i>N</i>	205	201	62
<i>Responder rate*, % (95% CI)</i>	81.5 (76.1, 86.8)	87.1 (82.4, 91.7)	0
<i>Bacterial Count Reduction Mean (SD)**</i>	2.66 (0.71)	2.74 (0.64)	0.64 (0.49)
<i>Difference in Mean Compared to Saline***</i>	1.96 (1.8, 2.12)	2.07 (1.91, 2.23)	
<i>Inguinal Region</i>			
<i>N</i>	204	203	59
<i>Responder rate*, % (95% CI)</i>	82.4 (77.1, 87.6)	79.8 (74.3, 85.3)	6.8 (0.4, 13.2)
<i>Bacterial Count Reduction Mean (SD)**</i>	3.98 (1.03)	3.89 (0.93)	1.34 (1.10)
<i>Difference in Mean Compared to Saline</i>	2.64 (2.35, 2.93)	2.55 (2.27, 2.94)	

*Responder defined as a subject with 2-log₁₀/cm² (abdominal region) and 3-log₁₀/cm² (inguinal region) bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours

** log₁₀/cm² scale

*** This is the average treatment effect of test drug compared to saline. It is estimated from a linear regression of final bacterial count on treatment and baseline bacterial count

Study EM-05-013260

	3M CHG/IPA Prep, 10.5ml, clear	3M CHG/IPA Prep,10.5ml with HEDTA	Saline
<i>Abdominal Region</i>			
<i>N</i>	196	202	59
<i>Responder rate*, % (95% CI)</i>	81.1 (75.6, 86.6)	81.7 (76.3, 87.0)	8.5 NA
<i>Bacterial Count Reduction Mean (SD)**</i>	2.78 (0.94)	2.73 (1.00)	0.76 (0.81)
<i>Difference in Mean Compared to Saline</i>	1.99 (1.73, 2.26)	2.03 (1.76,2.29)	
<i>Inguinal Region</i>			
<i>N</i>	208	209	61
<i>Responder rate*, % (95% CI)</i>	38.9 (32.3, 45.6)	46.9 (40.1, 53.7)	1.6 (NA)
<i>Bacterial Count Reduction Mean (SD)**</i>	2.84 (1.19)	2.99 (1.13)	1.01 (0.67)
<i>Difference in Mean Compared to Saline***</i>	1.9 (1.59, 2.2)	1.72 (1.42, 2.03)	

*Responder defined as a subject with 2-log₁₀/cm² (abdominal region) and 3-log₁₀/cm² (inguinal region) bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours

** log₁₀/cm² scale

**** This is the average treatment effect of test drug compared to saline. It is estimated from a linear regression of final bacterial count on treatment and baseline bacterial count*

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(b) (4)

4. REFERENCES

1. Complete Response Letter

<http://darrts.fda.gov:9602/darrts/viewCommunication.do?fromPage=appHistoryDirect&communicationId=3927975&fromHistoryPage=true&appPk=214654>

2. Dispute Appeal Resolution

<http://darrts.fda.gov:9602/darrts/viewCommunication.do?fromPage=appHistoryDirect&communicationId=3999368&fromHistoryPage=true&appPk=214654>

3. Statistical Review by Dr. Dr. Mushfiqur Rashid

<http://darrts.fda.gov:9602/darrts/viewCommunication.do?fromPage=appHistoryDirect&communicationId=3914870&fromHistoryPage=true&appPk=214654>

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/s/

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08/24/2017

RIMA IZEM
08/24/2017



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/BLA #: 208288

Drug Name: 3M SoluPrep Film-Forming Sterile Surgical Solution

Indication(s): Patient preoperative skin preparation, for preparation of the skin prior to surgery, and helps reduce bacteria that potentially can cause skin infection

Applicant: 3M Health Care Business

Date(s): July 6, 2015

Review Priority: Standard

Biometrics Division: Division of Biometrics IV

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Keywords: Responder rate, Log₁₀ reduction, Confidence interval, Fisher Exact test, Normal approximation

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1 EXECUTIVE SUMMARY

Introduction:

The Applicant has submitted two pivotal studies (EM-05-012760 - Abdomen/Groin Study and EM-05-013260 - Abdomen/Groin Study) which evaluated the antimicrobial efficacy and safety of 3M CHG/IPA Prep for patient preoperative skin preparation. Both studies were randomized, controlled, third-party blind, single center studies in healthy volunteers, who received 2 of 4 possible study products on the abdomen and/or 2 of 4 possible study products on the groin. The four products in Study EM-05-012760 were 3M CHG/IPA Prep 10.5 mL (tinted), 3M CHG/IPA Prep 26 mL (tinted), ChloraPrep[®] (positive control) and saline (negative control) whereas the four products in Study EM-05-013260 were 3M CHG/IPA Prep 10.5 mL (clear), 3M CHG/IPA 10.5 (clear) with hydroxyethyl ethylenediaminetriacetic acid (HEDTA), ChloraPrep[®] (positive control) and saline (negative control). A currently marketed alcohol-based CHG solution, ChloraPrep[®] Patient Preoperative Skin Preparation (ChloraPrep[®]), was used as an active control, and sterile 0.9% saline was used as a negative control. The purpose of the active control is to validate the study conduct to assure that the expected results are produced.

The primary objective of the two studies was to evaluate the antimicrobial efficacy of 3M CHG/IPA Prep:

- 1) 10.5 mL (tinted) and 26 mL (tinted) in study EM-05-012760 for preoperative skin preparation
- 2) 10.5 mL (clear) and 10.5 mL (clear) HEDTA in study EM-05-013260 for preoperative skin preparation.

The primary endpoint of each pivotal study was to achieve antimicrobial efficacy defined as having the lower bound of the 95% CI of percent responders greater than or equal to 70%. On the abdomen, a responder was defined as a subject with a 2 log₁₀/cm² bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours. On the inguinal region, a responder was a subject with a 3 log₁₀/cm² bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours.

Superiority of each drug product to the negative control in responder rate was tested separately using the Fisher's exact test. There were 2 comparisons of experimental products to the negative control. A Hochberg step-up procedure was used to adjust for the 2 comparisons. If both-p-values were less than or equal to 0.05, both products were considered superior to the negative control. If the p-value for 1 product exceeded 0.05, the other was required to be less than 0.025 to be considered superior to the negative control.

Likewise, responder rate confidence intervals (CIs) were produced for the two experimental products. A Hochberg step-up approach was utilized in this situation as well. If the lower bound of the 95% CI for the responder rate was greater than or equal to 70% for both products, both products met the acceptance criteria. However, if the lower bound of the 95% CI for the

responder rate for an experimental product was less than 70%, then the lower bound of the 97.5% CI for responder rate for the other experimental product must have been greater than or equal to 70% for that product to meet the acceptance criteria.

According to FDA Tentative Final Monograph (Federal Register, Volume 59, No. 116, June 1994, Proposed Rules), secondary efficacy criteria were a mean 2-log reduction from baseline in bacteria on an abdominal test site and a mean 3-log reduction on an inguinal test site within 10 minutes after product use, and the bacterial cell count for each test site was not to exceed the baseline count at 6 hours after product use. The secondary efficacy criteria of mean reduction from baseline in bacterial count were to support the primary analyses.

Safety endpoints were incidence of adverse events (AEs) reported during the study and the assessment of irritation ratings.

Assessments:

Based on the review of the efficacy data submitted, this reviewer has the following assessments:

- In Study EM-05-012760 for both the abdominal and inguinal regions, the primary efficacy endpoint of achieving $\geq 70\%$ for the lower bound of the 95% CI for the responder rate was met by two drug products (3M CHG/IPA Prep 10.5 mL, 3M CHG/IPA Prep 26 mL) and active control (ChloraPrep[®]). For the abdominal region, the responder rates were 81.5%, 87.1%, and 89.9% for 3M CHG/IPA Prep 10.5 mL, 3M CHG/IPA Prep 26 mL, and ChloraPrep[®], respectively. For the inguinal region, the responder rates were 82.4%, 79.8%, and 84.0% for 3M CHG/IPA Prep 10.5 mL, 3M CHG/IPA Prep 26 mL, and ChloraPrep[®], respectively. For both body regions, both drug products and the active control demonstrated significantly greater responder rates (p -value <0.001) than the negative control (saline). Note that p -values satisfied multiplicity adjustments criteria (Hochberg's procedure) proposed by the Applicant.
- In Study EM-05-013260 for the abdominal region only, the primary efficacy endpoint of achieving $\geq 70\%$ for the lower bound of the 95% CI for the responder rate was met by the two drug products (3M CHG/IPA Prep and 3M CHG/IPA Prep with HEDTA) and active control (ChloraPrep[®]). For the abdominal region, the responder rates were 81.1%, 81.7%, and 83.2% for 3M CHG/IPA Prep, 3M CHG/IPA Prep with HEDTA, and ChloraPrep[®], respectively. For the inguinal region, the primary efficacy endpoint of achieving $\geq 70\%$ for the lower bound of the 95% CI for the responder rate was not met by 3M CHG/IPA Prep, 3M CHG/IPA Prep with HEDTA, and ChloraPrep[®]. The responder rates were 38.9%, 46.9%, and 53.0% for 3M CHG/IPA Prep, 3M CHG/IPA Prep with HEDTA, and ChloraPrep[®], respectively. For both body regions, both drug products and the active control demonstrated significantly greater responder rates (p -value <0.001) than the negative control (saline).
- Study EM-05-012760 satisfied secondary endpoint criteria for mean log reductions at 10 minutes. However, in Study EM-05-013260 neither drug product (3M CHG/IPA Prep and 3M CHG/IPA Prep with HEDTA) nor the control product satisfied the secondary

endpoint criteria of mean log reductions at 10 minutes for inguinal region. However, the mean log reduction criteria came close to the recommended 3 log₁₀ reduction in the inguinal site: 3M CHG/IPA Prep 10.5 mL (2.87), 3M CHG/IPA Prep with HEDTA 10.5 mL (2.99) and ChloroPrep® (3.17).

In summary, in Study EM-05-012760 for both the abdominal and inguinal regions and in Study EM-05-013260 for the abdominal region only, the primary efficacy endpoint of achieving ≥70% for the lower bound of the 95% CI for responder rate was met by all active study products. In Study EM-05-013260 for inguinal region only, the primary efficacy endpoint of achieving ≥70% for the lower bound of the 95% CI for responder rate was not met by the two drug products or the *active control* product.

The Applicant's safety evaluation from these two studies indicates that the product was safe and well tolerated. See Medical Officer Teresa Podruchny's review in DARRTS for details.

Conclusions:

In this submission, for the two drug products, we have replicative evidence of efficacy for the abdomen site and there is no replicable evidence for the inguinal site. Also the active control did not meet primary efficacy criterion in the failed inguinal region study. However, in the failed inguinal region study (Study EM-05-013260), the mean log reduction criteria (secondary endpoint) comes close to the recommended 3 log₁₀ reduction in the inguinal site: 3M CHG/IPA Prep 10.5 mL (2.87), 3M CHG/IPA Prep with HEDTA 10.5 mL (2.99) and ChloroPrep® (3.17). Thus there is marginal evidence of the antimicrobial efficacy of the two products for the inguinal site for patient preoperative skin preparation.

In order to support the efficacy of preoperative skin preparation products, it is expected that efficacy data for both abdominal and inguinal regions from two adequate and well-controlled studies conducted at independent laboratories satisfy the efficacy criteria. This application did not meet those criteria. Instead there are two independent studies at abdominal sites and one study at inguinal sites showing evidence of efficacy with both the primary responder analysis as well as a mean log reduction analysis. In the second inguinal site study the active control also failed the primary endpoint analyses, pointing to the possibility that it was a problem with the study. Additionally, though the test products did not meet the secondary endpoint of mean 3 log₁₀ reduction, the test arm with the to-be-marketed formulation came extremely close at 2.99.

2 INTRODUCTION

2.1 Overview

The antimicrobial efficacy of 3M CHG/IPA Prep configurations was examined in the 2 pivotal studies (Study EM-05-012760 and Study EM-05-013260). These two studies included the tinted preparation in 10.5-mL and 26-mL applicators and the colorless preparation in 10.5-mL applicators, all without (hydroxyethyl)ethylenediaminetriacetic acid (HEDTA), and the colorless preparation in 10.5-mL applicators with HEDTA [REDACTED] (b) (4)

[REDACTED] Note that the 3M™ CHG/IPA Prep with HEDTA is the proposed to-be-marketed formulation. Study EM-05- 013260 served as a bridge between the products with and without HEDTA.

Note also the purpose for the positive control is to validate the study conduct to assure that the expected results are produced.

The following table provides the description of the two pivotal phase 3 trials:

Table 1: Description of Efficacy Studies

Number of Study Sites	Study Start/End Dates and Actual/Planned Randomized	Study and Control Drugs: Dose, Route, and Regimen	Study Objectives	Number of Subjects by Arm: Entered/Completed	Duration of Study; Duration of Exposure	Diagnosis Inclusion Criteria
MicroBioTest (Sterling, VA) EM-05-012760	01 Oct 2013/ 16 Jun 2014 Abdomen: 406/330 Groin: 391/330	Test= 3M CHG/IPA Prep (10.5 mL and 26 mL, both tinted); Controls= ChloroPrep® (26 mL tinted) and saline (20 mL)	To evaluate antimicrobial efficacy and safety of 3M CHG/IPA Prep	Abdomen: 406/406 Groin: 391/391	4 weeks (minimum 14-day Pre-treatment Phase, 1-day Screening phase, 1-day Treatment Phase); 6 to 7 hours	Healthy subjects with no skin condition on test areas and with screening bacterial counts ≥ 3.0 $\log_{10}/\text{cm}^2$ (abdomen) and/or ≥ 5.0 $\log_{10}/\text{cm}^2$ (groin)
EM-05-013260 BioScience Laboratories (Bozeman, MT)	27 Jun 2014/ 12 Mar 2015 Abdomen: 569/330 Groin: 404/330	Test= 3M CHG/IPA Prep (10.5 mL colorless) and 3M CHG/IPA Prep with HEDTA (10.5 mL colorless); Controls= ChloroPrep® (10.5 mL clear) and saline (20 mL)	To evaluate antimicrobial efficacy and safety of 3M CHG/IPA Prep	Abdomen: 569/568 Groin: 404/403	4 weeks (minimum 14-day Pre-treatment Phase, 1-day Screening phase, 1-day Treatment Phase); 6 to 7 hours	Healthy subjects with no skin condition on test areas and with screening bacterial counts ≥ 2.5 $\log_{10}/\text{cm}^2$ (abdomen) and/or ≥ 5.0 $\log_{10}/\text{cm}^2$ (groin)

Note: Extracted from Table 1 of Applicant's Clinical Summary, Module 2.7, page 13

The two studies had identical protocols except they differed in test products and screening criteria for the abdominal region. In study EM-05-013260, subjects were required to meet a screening day baseline count of $\geq 2.5 \log_{10}$ per cm^2 bilaterally on the abdominal region where as in Study EM-05-012760, subjects were required to meet a screening day baseline count of $\geq 3.0 \log_{10}$ per cm^2 bilaterally on the abdominal region.

It is to be noted here that there was another pivotal study (Study EM-05-012759) that was the first of the two initially designed pivotal studies. As this study was discontinued prematurely due to technical and data quality issues, no efficacy analyses were conducted, but the safety data were analyzed by the Applicant. As a result, efficacy data from the discontinued study will not be discussed in this review.

2.2 Data Sources

The Applicant has reported that raw colony counts from each of the dilutions were recorded on the appropriate data collection sheet for each subject at each collection time point. Screening Day calculations of colony-forming unit (CFU)/mL and CFU/ cm^2 of skin were reviewed by the Investigator and/or designee, and automatically performed on the electronic case report form (eCRF) upon entry of raw data into the Clindex[®] software to determine subject eligibility for treatment.

The primary efficacy data (including demographic data) and the baseline characteristics datasets were provided in the file ADSL.xpt (data for efficacy endpoint: one record per subject) under the network drive:

<\\cdsesub1\EVSPROD\NDA208288\0000\m5\datasets\EM-05012760\analysis\ADSL\datasets>
for Study EM-05012760

and

<\\cdsesub1\EVSPROD\NDA208288\0000\m5\dataset\EM-05-013260\analysis\ADSL\datasets>
for Study EM-05-013260.

The treatment group was denoted by TRTSEQP (planned treatment sequence at time of assessment). The data for primary efficacy with responder (1) or non-responder (0) were in column ALRESPNFN (Abdomen left responder flag number), ARRESPNFN (Abdomen right responder flag number), GLRESPNFN (Groin left responder flag number) and GRRESPNFN (Groin Right responder flag number) at 10 minute post dose (MBTPT=10 MINUTE POSTDOSE).

The secondary efficacy data were provided, in the file ADMB.xpt (contains many rows per subject but includes the actual continuous values of the micro count) under the network drive:

<\\cdsesub1\EVSPROD\NDA208288\0000\m5\datasets\EM-05012760\analysis\admb\datasets>
for study EM-05012760

and

<\\cdsesub1\EVSPROD\NDA208288\0000\m5\dataset\EM-05-013260\analysis\admb\datasets>
for studyEM-05-013260.

The treatment group was denoted by TRTP (planned treatment). The data for $\log_{10}$ in microbiological count from baseline (MBTESTCD='LOG10REC') at 10 minutes (MBTPT=10 Minute POSTDOSE) and the data for $\log_{10}$ reduction in microbiological count from baseline $\log_{10}$ reduction (MBTTESTCD='LOG10RED') at 6 hours (MBTPT=6 HR POSTDOSE) are provided under the variable 'AVAL' with MBLOC for ABDOMEN (MBLOC='ABDOMEN LEFT' or MBLOC='ABDOMEN RIGHT') and MBLOC for GROIN (MBLOC='GROIN LEFT' or MBLOC='GROIN RIGHT').

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Applicant has stated that the data for EM-05-012760 and EM-05-013260 were collected using an electronic case report form (eCRF). The Applicant has further stated the following:

3M, as Applicant of this study, was responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of the data recorded. The 3M study monitor assessed the progress of the study by performing the following oversight:

- Periodic on-site review
- Ongoing review of electronic documentation via Clindex®
- Communication via telephone and e-mail
- Review of source documents

Data were entered either directly into the eCRF or onto a data collection sheet (DCS) then transferred into the eCRF; wherever the data were entered first was considered the source document. The Investigator or designee gave the 3M study monitor direct access to source documents that supported data on the eCRFs and made available such records to authorized 3M quality assurance, IRB and regulatory personnel for inspection and/or copying.

The quality and integrity of the submission are acceptable. The submission uses the electronic common technical document (eCTD) format. The submission is well organized and easy to navigate. Submitted Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets meet the Clinical Data Interchange Standards Consortium (CDISC) standards. It is possible to reproduce the primary endpoint and the secondary endpoints from both the SDTM and ADaM datasets that the Applicant provided.

3.2 Evaluation of Efficacy

The efficacy review is based on two pivotal studies, EM-05-012760 and EM-05-013260. EM-05-012760 was performed at MicroBioTest, Inc. (MBT) in Sterling, Virginia and EM-05-013260 was performed at Bioscience Laboratories (BSL), Inc. in Bozeman, Montana.

3.2.1 Study Design and Endpoints

Studies EM-05-012760 and EM-05-013260 were randomized, controlled, third-party blind (statistician and study staff performing bacterial enumeration), single center studies in healthy volunteers, who received 2 of 4 possible study products on the abdomen and/or 2 of 4 possible study products on the groin.

The Applicant reported:

The study products could not be blinded from the investigator or study staff performing the product application, sample collection, and skin assessment due to the obvious differences in applicator design and other physical characteristics. However, the study staff performing the bacterial enumeration was not be involved in the study product application or the collection of samples and, therefore, was blinded to the study products. The statistician performing the analysis was also to be blinded and was not provided the coded treatment designations until the study had been completed. The blind was broken after data lock.

In both studies, healthy male and female volunteers, 18 years of age or older, who had no dermatological conditions or known history of sensitivity to acrylate-, CHG-, or alcohol-containing products, medical tapes, or natural rubber latex, and who had Screening Day baseline counts meeting specified criteria were enrolled into this study.

Both studies consisted of 3 phases: the Pretreatment Phase (washout), the Screening Phase, and the Treatment Phase. Healthy subjects who met the inclusion/exclusion criteria were entered into a minimum 14-day Pretreatment Phase to allow for the removal of any antimicrobial agents from the subject's skin.

The Applicant has mentioned:

A sufficient number of subjects who met the inclusion criteria were enrolled into the Treatment Phase such that approximately 660 abdominal and 660 inguinal regions (randomized between left and right sides) were evaluable for efficacy at study completion. On Treatment Day, subjects were assigned a subject number and were randomized into 1 of the 6 treatment groups shown in Table 2 for each body region for which they met the inclusion criteria.

Table 2: Description of 6 treatment groups

Study	Treatment Group	Left and Right treatment
EM-05-012760 ^a	1	3M CHG/IPA (test product 1) and 3M CHG/IPA (test product 2)
	2	3M CHG/IPA (test product 1) and ChloroPrep [®]
	3	3M CHG/IPA (test product 2) and ChloroPrep [®]
	4	3M CHG/IPA (test product 1) and Saline
	5	3M CHG/IPA (test product 2) and Saline
	6	ChloroPrep [®] and Saline
EM-05-013260 ^b	1	3M CHG/IPA Prep and 3M CHG/IPA Prep with HEDTA
	2	3M CHG/IPA Prep and ChloroPrep [®]
	3	3M CHG/IPA Prep with HEDTA and ChloroPrep [®]
	4	3M CHG/IPA Prep and saline
	5	3M CHG/IPA Prep with HEDTA and saline
	6	ChloroPrep [®] and saline

Note: a: Extracted from Table 2, page 20 of Applicant’s Final Clinical Study Report (study EM-05-012760)

b: Extracted from Table 2, page 23 of Applicant’s Final Clinical Study Report (study EM-05-013260)

The applicant has mentioned:

The left and right test areas on each subject’s abdominal and inguinal regions were assigned according to a computer-generated randomization schedule to receive 1 of 4 study products. Randomization was balanced between left and right sides, resulting in 6 different combinations of treatments, or treatment groups for each of the two regions, the abdominal and inguinal regions.

The applicant describes the sampling and prepping procedures as follows:

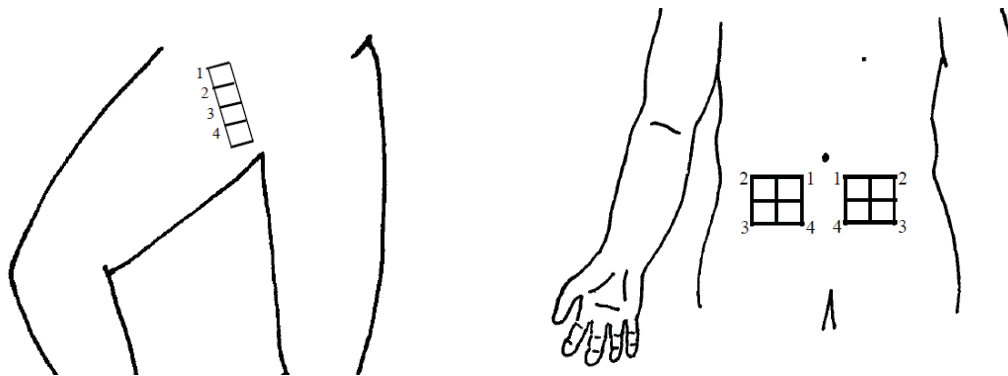
After completing the treatment inclusion/exclusion criteria form and visually inspecting the skin test areas, a sterile template to mark 4 sampling sites (for baseline pre-prep, 10-minute post-prep, 6-hour post-prep and unused) within each abdominal test area. Baseline samples were collected using a cup scrub technique from the right and left test areas per the sampling randomization schedule; for the abdominal region, sampling was randomized to Sites 1, 3, and 4 (Site 2 was always the unused site). Similarly, the inguinal test areas were marked and baseline samples were collected per the sampling randomization schedule; for the inguinal region, sampling was randomized to Sites 2, 3, and 4 (Site 1 was always the unused site). See Figure 1 below for test site diagrams.

Following baseline sample collection, contralateral abdominal and inguinal test areas were prepped with 1 of the 4 study products according to the treatment randomization code assigned to each subject. The duration of each prep procedure was recorded on the appropriate form. Post-prep timing began after study product application, including the 3-minute drying time.

Microbial samples were collected using a cup scrub technique at 10 minutes post-prep from each test area. After the 10-minute samples were collected, a sterile non-occlusive dressing was secured over the remaining sample sites to allow subjects restricted mobility and to protect the sites from contamination between sampling times. Subjects were allowed to leave the study site as long as they returned within 6 hours for the next sample collection and met the compliance

criteria upon their return. After the 6-hour post-prep collection, residual study products were removed from the skin with alcohol wipes.

Figure 1. Test Site Diagrams



Note: Extracted from page 42, Applicant's Protocol, study EM-05-012760

In both studies, the planned study duration for each subject was up to 4 weeks (a minimum 14-day Pretreatment Phase, 1-day Screening Phase, and 1-day Treatment Phase). Exposure to study treatment was approximately 6-7 hours for each subject.

A schedule of study procedure is presented in Table 3.

Table 3: Schedule of Study Procedures

Study Procedure	14-Day Pretreatment Phase	Screening Phase	Treatment Day			
			Baseline	Skin Prep	Post-prep: 10 minutes ± 30 seconds	Post-prep: 6 hours ± 30 minutes
Informed consent	X					
Inclusion/exclusion criteria	X	X	X			
Demographics			X			
Assign screening number	X					
Dispense personal hygiene kit	X					
Perform clipping (if necessary)	X ^a	X ^a				
Perform visual skin assessment		X	X			
Assign subject number			X			
Skin irritation rating			X		X	X
Apply study products				X		
Collect microbial samples		X	X		X	X
Protocol compliance, verification ^b						X

^aIf clipping was needed, subjects were to return to the study site 72 hours prior to their scheduled Screening Day and Treatment Day.

^bVerification was to confirm that subjects complied with the study instructions during the 6 hours post-prep.

Note: Extracted from Table 4, page 28 of Final Clinical Study Report, Study EM-05-012760

Efficacy Endpoints:

Primary:

As defined by the Applicant, the primary efficacy variable was the lower bound of the 95% confidence interval for responder rate. This must be greater than or equal to 70.0%.

A responder was defined as having bilateral locations which meet the Treatment Day microbial baseline requirements for which the 10-minute $\log_{10}$ CFU/cm² reduction from baseline is 2.00 or greater for the abdominal region, or 3.00 or greater for the inguinal region, and whose skin flora do not return to baseline at the 6-hour sample collection time (has a $\log_{10}$ CFU/cm² reduction from baseline greater than 0).

Secondary endpoints:

Individually for abdomen and inguinal regions:

- $\log_{10}$ /cm² baseline skin flora
- $\log_{10}$ /cm² recovery of skin flora at 10 minutes and 6 hours following application of the study materials
- $\log_{10}$ /cm² reduction of skin flora, relative to Treatment Day baseline $\log_{10}$ / cm², at 10 minutes and 6 hours following application of the study materials.

Safety endpoints

The principal measure of safety was the incidence of adverse events reported during the study and a summary of the skin irritation rating scores. A skin irritation rating of 3 post-treatment in any category represents significant irritation and qualifies as an Adverse Event.

3.2.2 Statistical Methodologies

According to the Applicant, raw data of bacterial counts (CFU/mL) were converted to $\log_{10}$ /cm². The counts of less than one $\log_{10}$ /cm² were treated as $\log_{10}(1)$ /cm² 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 Treatment Day baseline log recovery.

Sample size estimation:

The Applicant has reported that one sample size calculation applies to both investigational products. It is expected that there will be no significant difference in performance between the investigational products. The Applicant's sample size determination is below:

It has been the experience of 3M that it is more difficult to pass the 10-minute $\log_{10}$ reduction criteria on the inguinal region than on the abdominal region. Therefore, the sample size was calculated based on the inguinal region. The same sample size will be used for the abdominal region.

The $\log_{10}$ microbial reductions for the investigational product and for ChloroPrep® at 10 minutes sampling time were estimated in a study conducted in Romania as 3.98 and 3.87, respectively, with a standard error of 0.15. An estimate of $\log_{10}$ microbial reduction for the negative control (saline) was obtained from studies conducted by an outside laboratory. This estimate was 1.35 (on the abdomen) with a standard error of 0.083. An assumption was made that a reduction of 2.35 would occur for the inguinal region.

Sample size was determined through simulation using R2.1.8.0, Excel 2007 and SAS® 9.2, Proc Means. One thousand means, representing 1000 studies, were generated using the above means and standard errors and an assumption of normal distribution. Individual $\log_{10}$ reduction samples were generated from the study mean using a standard deviation of 1.0 and the assumption of normal distribution. Percent responders were calculated for each treatment for each study. The lower bound of the 95% confidence interval for percent responders was then calculated for each study using the normal approximation to the binomial distribution. The differences in percent responders between the active treatments and the negative control were also calculated by study using the normal approximation to the binomial distribution. With a sample size of 200 observations per active treatment and 60 observations for the negative control (330 total subjects), the following results were obtained:

- The investigational product had a lower bound of the 95% confidence interval for responder percentage >70%, 95.1% of the time.
- ChloroPrep® had a lower bound of the 95% confidence interval for responder percentage >70%, 81.7% of the time.
- The investigational product was superior to the negative control 100% of the time.
- ChloroPrep® was superior to the negative control 100% of the time.

In both studies, the Applicant recruited and screened more subjects than randomized. In addition, the Applicant anticipated that there would be many subjects who would not pass the microbial criteria and even subjects who would pass but might not attend the Treatment Day visit.

Primary Efficacy Analyses:

On the abdomen, a responder was defined as a subject with a 2 $\log_{10}/\text{cm}^2$ bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours. On the inguinal region, a responder was a subject with a 3 $\log_{10}/\text{cm}^2$ bacterial reduction at 10 minutes and for whom the skin flora did not return to baseline at 6 hours.

Percent responders will be calculated for the investigational products, the marketed active control product, and the negative control product.

The following steps to demonstrate the efficacy of the investigational products were followed individually for the abdominal and inguinal regions:

- Two-sided 95% confidence intervals (CIs) for responder rates used the normal approximation to the binomial. No CI for responder rate for the negative control was produced.
- Superiority of each active product to the negative control was to be tested separately using either Fisher's exact test or a chi-squared test.
- There were two comparisons of experimental products to the negative control. A Hochberg step-up procedure was used to adjust for the two comparisons. If both-values were less than or equal to 0.05, both products were considered superior to the negative control. If the p-value for one product exceeded 0.05, the other was required to be less than 0.025 to be considered superior to the negative control.
- Likewise, responder rate CIs were produced for the two experimental products. A Hochberg step-up approach was utilized in this situation as well. If the lower bound of the 95% CI for responder rate was greater than or equal to 70% for both products, both products met the acceptance criteria. However, if the lower bound of the 95% CI for responder rate for an experimental product was less than 70%, then the lower bound of the 97.5% CI for responder rate for the other experimental product must have been greater than or equal to 70% for that product to meet the acceptance criteria.

Additionally, the results were assessed according to FDA Tentative Final Monograph (Federal Register, Volume 59, No. 116, June 1994, Proposed Rules). Secondary efficacy criteria were a mean 2-log reduction from baseline in bacteria on an abdominal test site and a mean 3-log reduction on an inguinal test site within 10 minutes after product use, and the bacterial cell count for each test site was not to exceed the baseline count at 6 hours after product use. The secondary efficacy criteria of mean reduction from baseline in bacterial count were to support the primary analyses.

Analysis Populations:

There were 4 subject populations defined for the study analyses:

- All available subjects (AAS) population: All subjects who consented for the study, including screening visit failures, were termed the AAS population.
- Safety population/ Intent-to-treat (ITT) population: All subjects who were randomized and received at least 1 study treatment in the study. The ITT population was to be used for disposition, demographics, protocol deviation, and safety tables, and all listings except the disposition listing.

- Modified ITT (mITT) population: The mITT data set was used as the primary efficacy population. All subjects who met baseline requirements on at least 1 side of the abdominal region on Treatment Day were included in the mITT analysis for that side of the abdominal region, and all subjects who met baseline requirements on at least 1 side of the inguinal region were included in the mITT analysis for that side of the inguinal region. The exclusion of subjects who did not meet baseline requirements made this data set a modified ITT data set. A treatment side of a subject was excluded from the mITT population when the baseline $\log_{10}$ CFU/cm² was outside the range of 3.00 to 5.50 for the abdomen and the range of 5.00 to 7.50 for the inguinal region.
- Per-protocol (PP) population: The PP population was used as a secondary efficacy population. A treatment side was excluded from the PP population when one of the following deviations occurred:
 - A laboratory accident resulted in no bacterial count data at 10 minutes.
 - A laboratory accident resulted in no bacterial count data at 6 hours, and the 10 minute $\log_{10}$ reduction was 2.00 or greater on the abdomen or 3.00 or greater on the groin.
 - A treatment side had a compromised dressing at 6 hours.
 - A subject was not compliant to study requirements during the time between the 10-minute and 6-hour sample collection.

Procedures for Accounting for Missing, Unused, and Spurious Data:

The Applicant stated,

Missing Treatment Day baseline data were to be given a value of “0” and be handled as a treatment side that did not meet the Treatment Day baseline requirement. This treatment side was not included in either the modified intent-to-treat population or the per-protocol population. For missing microbial data in the mITT population at either 10 minutes or 6 hours (but the treatment side had a Treatment Day baseline that met the requirements for inclusion), the treatment side had the $\log_{10}$ reduction imputed as “0” for either 10 minutes or 6 hours, as appropriate. This imputation made the treatment side a non-responder. When this imputation occurred, the treatment side was coded to be excluded from the per-protocol population. On Treatment Day, when a plate at the lowest dilution (highest concentration of bacteria) had no observed colonies, a value of “1” was used, consistent with standard microbiology.

Of note, the Applicant did not provide the amount of missing data in the study report.

3.2.3 Patient Disposition and Demographic Characteristics

Study EM-05-012760

Subject Disposition by Study Product:

The Applicant's summary of the subject disposition for Study EM-05-012760 is as follows:

A total of 510 subjects provided informed consent; of these, 489 (95.9%) subjects had screening data for microbial counts for both abdominal and inguinal regions. For the abdominal region, 67 (13.7%) subjects did not pass the microbial criteria and 16 (3.3%) subjects passed but did not attend the Treatment Day visit; thus, 406 (79.6%) subjects were randomized to 6 treatment groups for the abdominal region. For the inguinal region, 86 (17.6%) subjects did not pass the microbial criteria and 12 (2.5%) subjects passed but did not attend the Treatment Day visit thus 391 (76.7%) subjects were randomized to 6 treatment groups for the inguinal region.

Table 4 provides the subject disposition for Study EM-05-012760 by 4 treatment regimens.

Table 4: Subject disposition for Study EM-05-012760

Disposition, n (%)	3M CHG/IPA Prep10.5 mL	3M CHG/IPA Prep, 26 mL	ChloroPrep®	Saline
Abdominal Region				
Randomized sides	246 (100.0)	245 (100.0)	247 (100.0)	74 (100.0)
mITT population	205 (83.3)	201 (82.0)	198 (80.2)	62 (83.8)
PP population	204 (82.9)	201 (82.0)	197 (79.8)	62 (83.8)
Completed study	246 (100.0)	245 (100.0)	247 (100.0)	74 (100.0)
Inguinal Region				
Randomized sides	238 (100.0)	238 (100.0)	236 (100.0)	70 (100.0)
mITT population	204 (85.7)	203 (85.3)	200 (84.7)	59 (84.3)
PP population	203 (85.3)	202 (84.9)	199 (84.3)	59 (84.3)
Completed study	238 (100.0)	238 (100.0)	236 (100.0)	70 (100.0)
Discontinued early from study	0	0	0	0

Note: Extracted from Table 6, page 42, Applicant's Final Clinical Study Report, study EM-05-012760

There were minimal exclusions from the per protocol population in this study due to protocol violation, including missing data (2 removed from the per protocol population for the abdominal region and 3 removed for the inguinal region). There were only 3 subjects with imputed zero log reductions.

The Applicant reported that:

On the abdominal region, 246 subjects received 3M CHG/IPA Prep 10.5 mL, 245 subjects received 3M CHG/IPA Prep 26 mL, 247 subjects received ChloroPrep®, and 74 subjects received saline.

On the inguinal region, 238 subjects received 3M CHG/IPA Prep 10.5 mL, 238 subjects received 3M CHG/IPA Prep 26 mL, 236 subjects received ChloroPrep®, and 70 subjects received saline. All subjects who were randomized received their treatments and completed the study.

Demographic Characteristics

The applicant provided demographic summary by 6 randomized treatment groups instead of four treatment regimens. This reviewer agrees with the Applicant’s demographic summary by 6 randomized treatment groups instead of four treatment regimens since each subject received two different treatments in the two (left and right) sides of each region. Table 5 provides subject demographics for the ITT/Safety population summarized by body region and 6 randomized treatment groups. It can be seen from Table 5 that for both body regions, demographics were similar across treatment groups. Overall, the mean age was 36 years, there were approximately 50% women and 50% men, and the main races/ethnicities were approximately 38% white, 32% Asian, 17% black, and 12% Hispanic/Latino.

Table 5: Subject Demographics (ITT/Safety Population, Study EM-05-012760):

Characteristic	3M CHG/IPA Prep, 10.5 mL, and 3M CHG/IPA Prep, 26 mL	3M CHG/IPA Prep, 10.5 mL, and ChloroPrep	3M CHG/IPA Prep, 26 mL, and ChloroPrep	3M CHG/IPA Prep, 10.5 mL, and Saline	3M CHG/IPA Prep, 26 mL, and Saline	ChloroPrep and Saline	Total
Abdominal Region							
Randomized N	110	111	111	25	24	25	406
Age (years)							
N	110	111	111	25	24	25	406
Mean (SD)	36.5 (14.49)	35.4 (14.93)	36.9 (14.35)	33.4 (13.94)	34.8 (14.46)	33.9 (12.85)	35.9 (14.4)
Median	30.5	31	32	28	30.5	29	31
Min-Max	18-72	18-80	18-73	18-68	20-72	18-58	18-80
Sex [n (%)]							
Male	57 (51.8)	57 (51.4)	53 (47.7)	14 (56.0)	11 (45.8)	10 (40.0)	202 (49.8)
Female	53 (48.2)	54 (48.6)	58 (52.3)	11 (44.0)	13 (54.2)	15 (60.0)	204 (50.2)
Race/Ethnicity [n (%)]							
American Indian or Alaska native	1 (0.9)	1 (0.9)	0	0	1 (4.2)	0	3 (0.7)
Asian	35 (31.8)	33 (29.7)	36 (32.4)	7 (28.0)	6 (25.0)	12 (48.0)	129 (31.8)
Black or African American	22 (20.0)	16 (14.4)	21 (18.9)	5 (20.0)	2 (8.3)	3 (12.0)	69 (17.0)
Hispanic/Latino	13 (11.8)	14 (12.6)	11 (9.9)	1 (4.0)	5 (20.8)	3 (12.0)	47 (11.6)
Native Hawaiian or other Pacific islander	1 (0.9)	0	0	0	0	0	1 (0.2)
White	38 (34.5)	46 (41.4)	40 (36.0)	12 (48.0)	10 (41.7)	7 (28.0)	153 (37.7)
Other	0	2 (1.8)	3 (2.7)	0	0	0	5 (1.2)
Inguinal Region							
Randomized N	108	107	106	23	24	23	391
Age (years)							
N	108	107	106	23	24	23	391
Mean (SD)	35.5 (14.79)	37.8 (14.74)	34.2 (13.8)	33.4 (11.72)	40.5 (14.64)	37.7 (17.74)	36.1 (14.56)

Table 5(continued)

Characteristic	3M CHG/IPA Prep, 10.5 mL, and 3M CHG/IPA Prep, 26 mL	3M CHG/IPA Prep, 10.5 mL, and ChloroPrep	3M CHG/IPA Prep, 26 mL, and ChloroPrep	3M CHG/IPA Prep, 10.5 mL, and Saline	3M CHG/IPA Prep, 26 mL, and Saline	ChloroPrep and Saline	Total
Median	30	37	30	29	41.5	29	31
Min-Max	18-80	18-72	18-71	18-59	18-73	18-69	18-80
Sex [n (%)]							
Male	64 (59.3)	58 (54.2)	54 (50.9)	11 (47.8)	10 (41.7)	11 (47.8)	208 (53.2)
Female	44 (40.7)	49 (45.8)	52 (49.1)	12 (52.2)	14 (58.3)	12 (52.2)	183 (46.8)
Race/Ethnicity [n (%)]							
American Indian or Alaska native	0	1 (0.9)	1 (0.9)	1 (4.3)	0	0	3 (0.8)
Asian	36 (33.3)	34 (31.8)	32 (30.2)	7 (30.4)	6 (25.0)	11 (47.8)	126 (32.2)
Black or African American	17 (15.7)	17 (15.9)	18 (17.0)	4 (17.4)	3 (12.5)	5 (21.7)	64 (16.4)
Hispanic/Latino	10 (9.3)	10 (9.3)	18 (17.0)	3 (13.0)	4 (16.7)	1 (4.3)	46 (11.8)
Native Hawaiian or other Pacific islander	1 (0.9)	1 (0.9)	0	0	0	0	2 (0.5)
White	42 (38.9)	44 (41.1)	36 (34.0)	8 (34.8)	11 (45.8)	6 (26.1)	147 (37.6)
Other	3 (2.8)	1 (0.9)	1 (0.9)	0	0	0	5 (1.3)

Note: Extracted from Table 7, page 45, Applicant's Final Clinical Study Report (study EM-05-012760)

Study EM-05-013260

Subject Disposition by Study Product:

According to the Applicant, in study EM-05-013260:

A total of 1035 subjects provided informed consent for the abdominal region; of these, 823 (79.5%) subjects had screening data for microbial counts. For the abdominal region, subjects not treated included 233 (28.3%) subjects who did not pass the microbial criteria, 3 (0.4%) subjects who did not meet inclusion/exclusion criteria on Treatment Day, and 18 (2.2%) subjects who passed the microbial criteria, but did not attend the Treatment Day visit; 1 (0.1%) subject did not pass the microbial criteria, but was randomized and treated. Thus, 569 (55.0%) subjects were randomized to 6 treatment groups for the abdominal region.

A total of 715 subjects provided informed consent for the inguinal region; of these, 579 (81.0%) subjects had screening data for microbial counts. For the inguinal region, subjects not treated included 138 (23.9%) subjects who did not pass the microbial criteria, 4 (0.7%) subjects who did not meet inclusion/exclusion criteria on Treatment Day, and 33 (5.7%) subjects who passed the microbial criteria, but did not attend the Treatment Day visit; 1 (0.2%) subject did not meet inclusion/exclusion criteria on Treatment Day, but was randomized and treated. Thus, 404 (56.5%) subjects were randomized to 6 treatment groups for the inguinal region.

Table 6 provides subject disposition for study EM-05-013260 (conducted at Bio-Sciences Laboratories).

Table 6: Subject disposition for Study EM-05-013260

Disposition, n (%)	3M CHG/IPA Prep	3M CHG/IPA Prep with HEDTA	ChloraPrep®	Saline
Abdominal Region				
Randomized sides	343	344	347	104
mITT population	196 (57.1)	202 (58.7)	196 (56.5)	59 (56.7)
PP population	191 (55.7)	197 (57.3)	191 (55.0)	59 (56.7)
Completed study	343 (100.0)	343 (99.7)	346 (99.7)	104(100%)
Discontinued early from study	0	1 (0.3)	1 (0.3)	0
Inguinal Region				
Randomized sides	242	244	248	74
mITT population	208 (86.0)	209 (85.7)	219 (88.3)	61 (82.4)
PP population	204 (84.3)	199 (81.6)	213 (85.9)	56 (75.7)
Completed study	241 (99.6)	244 (100.0)	248 (100.0)	73 (98.6)
Discontinued early from study	1 (1.4)	0	0	1 (1.4)

Note: Extracted from Table 6, page 50, Applicant’s Final Clinical Study Report, study EM-05-013260

There were slightly more exclusions from the per protocol population in this study due to protocol violation, including missing data (15 removed from the per protocol population for the abdominal region and 25 removed for the inguinal region) compared to Study EM-050012760. There were only 3 subjects with imputed zero log reductions.

It can be seen from Table 6:

On the abdominal region, 343 subjects were randomized to receive 3M CHG/IPA Prep, 344 subjects were randomized to receive 3M CHG/IPA Prep with HEDTA, 347 subjects were randomized to receive ChloraPrep®, and 104 subjects were randomized to receive saline. On the inguinal region, 242 subjects were randomized to receive 3M CHG/IPA Prep, 244 subjects were randomized to receive 3M CHG/IPA Prep with HEDTA, 248 subjects were randomized to receive ChloraPrep®, and 74 subjects were randomized to receive saline.

Subject Demographics

There are no noticeable imbalances between treatment groups with respect to demographic characteristics in Study EM-05-013260. Subject demographics for the ITT/Safety population are summarized by body region and 6 randomized treatment groups by 6 in Table 7. It can be seen from Table 7:

That for both body regions, demographics were similar across treatment groups. Overall, the mean age was 31 years. For the abdominal region (569 subjects), there were approximately 71% men and 29% women, and the main races/ethnicities were approximately 91% white, 4% Hispanic/Latino, 2% Asian, 1% black, 1% American Indian or Alaska native, 1% other, and <1% native Hawaiian or other Pacific islander. For the inguinal region (404 subjects), there were approximately 74% men and 26% women, and the main races/ethnicities were approximately 91% white, 4% Hispanic/Latino, 3% Asian, 2% other, 1% American Indian or Alaska native, <1% black, and <1% native Hawaiian or other Pacific islander.

Table 7: Subject Demographics (ITT/Safety Population, EM-05-013260)

Characteristic	3M CHG/IPA Prep and 3M CHG/IPA Prep with HEDTA	3M CHG/IPA Prep and ChloraPrep	3M CHG/IPA Prep with HEDTA and ChloraPrep	3M CHG/IPA Prep and Saline	3M CHG/IPA Prep with HEDTA and Saline	ChloraPrep and Saline	Total
Abdominal Region							
Randomized N	154	156	155	33	35	36	569
Age (years)							
N	154	156	155	33	35	36	569
Mean (SD)	29.9 (13.69)	31.7 (15.9)	31.6 (15.85)	29.8 (14.97)	27.1 (12.73)	31.5 (13.87)	30.8 (14.94)
Median	23	24	24	23	21	26	23
Min-Max	18-74	18-79	18-80	18-64	18-65	18-66	18-80
Sex [n (%)]							
Male	112 (72.7)	115 (73.7)	106 (68.4)	24 (72.7)	27 (77.1)	21 (58.3)	405 (71.2)
Female	42 (27.3)	41 (26.3)	49 (31.6)	9 (27.3)	8 (22.9)	15 (41.7)	164 (28.8)
Race/Ethnicity [n (%)]							
American Indian or Alaska native	3 (1.9)	1 (0.6)	2 (1.3)	1 (3.0)	1 (2.9)	0	8 (1.4)
Asian	3 (1.9)	5 (3.2)	4 (2.6)	0	1 (2.9)	0	13 (2.3)
Black or African American	1 (0.6)	5 (3.2)	1 (0.6)	0	0	1 (2.8)	8 (1.4)
Hispanic/Latino	2 (1.3)	8 (5.1)	6 (3.9)	3 (9.1)	1 (2.9)	1 (2.8)	21 (3.7)
Native Hawaiian or other Pacific islander	2 (1.3)	1 (0.6)	0	0	0	0	3 (0.5)
White	142 (92.2)	137 (87.8)	145 (93.5)	29 (87.9)	33 (94.3)	34 (94.4)	520 (91.4)
Other	3 (1.9)	3 (1.9)	0	1 (3.0)	0	0	7 (1.2)
Inguinal Region							
Randomized N	106	111	113	25	25	24	404
Age (years)							
N	106	111	113	25	25	24	404
Mean (SD)	30.1 (15.21)	30.5 (13.75)	32.3 (15.4)	31.3 (15.84)	29.5 (12.49)	25.5 (10.19)	30.6 (14.51)

Characteristic	3M CHG/IPA Prep and 3M CHG/IPA Prep with HEDTA	3M CHG/IPA Prep and ChloroPrep	3M CHG/IPA Prep with HEDTA and ChloroPrep	3M CHG/IPA Prep and Saline	3M CHG/IPA Prep with HEDTA and Saline	ChloroPrep and Saline	Total
Abdominal Region							
Randomized N	154	156	155	33	35	36	569
Age (years)							
N	154	156	155	33	35	36	569
Mean (SD)	29.9 (13.69)	31.7 (15.9)	31.6 (15.85)	29.8 (14.97)	27.1 (12.73)	31.5 (13.87)	30.8 (14.94)
Median	23	24	24	23	21	26	23
Min-Max	18-74	18-79	18-80	18-64	18-65	18-66	18-80
Sex [n (%)]							
Male	112 (72.7)	115 (73.7)	106 (68.4)	24 (72.7)	27 (77.1)	21 (58.3)	405 (71.2)
Female	42 (27.3)	41 (26.3)	49 (31.6)	9 (27.3)	8 (22.9)	15 (41.7)	164 (28.8)
Race/Ethnicity [n (%)]							
American Indian or Alaska native	3 (1.9)	1 (0.6)	2 (1.3)	1 (3.0)	1 (2.9)	0	8 (1.4)
Asian	3 (1.9)	5 (3.2)	4 (2.6)	0	1 (2.9)	0	13 (2.3)
Black or African American	1 (0.6)	5 (3.2)	1 (0.6)	0	0	1 (2.8)	8 (1.4)
Hispanic/Latino	2 (1.3)	8 (5.1)	6 (3.9)	3 (9.1)	1 (2.9)	1 (2.8)	21 (3.7)
Native Hawaiian or other Pacific islander	2 (1.3)	1 (0.6)	0	0	0	0	3 (0.5)
White	142 (92.2)	137 (87.8)	145 (93.5)	29 (87.9)	33 (94.3)	34 (94.4)	520 (91.4)
Other	3 (1.9)	3 (1.9)	0	1 (3.0)	0	0	7 (1.2)
Inguinal Region							
Randomized N	106	111	113	25	25	24	404
Age (years)							
N	106	111	113	25	25	24	404
Mean (SD)	30.1 (15.21)	30.5 (13.75)	32.3 (15.4)	31.3 (15.84)	29.5 (12.49)	25.5 (10.19)	30.6 (14.51)

Note: Extracted from Table 7, page 54, Applicant's Final Clinical Study Report, study EM-05-013260

3.2.4 Results and Conclusions

The primary evaluation of the efficacy of 3M CHG/IPA Prep is based on data from two phase 3 studies for preoperative skin preparation. The reviewer’s primary analysis was consistent with the Applicant’s analysis. We summarize the primary efficacy analyses of Study EM-05-012760 and Study EM-05-013260 in the Tables 8 and 10 below.

Study EM-05-012760

Primary analyses:

The primary efficacy analysis is summarized in the following table.

Table 8: Responders Rate (mITT Population, Study EM-05-012760)

	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep, 26 mL	ChloraPrep®	Saline
Abdominal Region				
N	205	201	198	62
Responder ^a , n (%)	167 (81.5)	175 (87.1)	178 (89.9)	0
95% CI for rate ^b	76.1%, 86.8%	82.4%, 91.7%	85.7%, 94.1%	NA
P-value relative to negative control ^c	<0.001	<0.001	<0.001	NA
Inguinal Region				
N	204	203	200	59
Responder ^a , n (%)	168 (82.4)	162 (79.8)	168 (84.0)	4 (6.8)
95% CI for rate ^b	77.1%, 87.6%	74.3%, 85.3%	78.9%, 89.1%	0.4%, 13.2%
P-value relative to negative control ^c	<0.001	<0.001	<0.001	NA

a: A responder for a treatment was defined as having a side that met the Treatment Day microbial baseline requirements for which the 10-minute log₁₀ count/cm² reduction from baseline was 2.00 or greater for the abdominal region or 3.00 or greater for the inguinal region and whose skin flora did not return to baseline at the 6-hour sample collection time.

b: The 95% CI for responder rate was calculated based on the normal approximation to the binomial distribution.

c P-value was calculated using Fisher’s exact test.

Note: Extracted from Table 8, page 48, Applicant’s Final Clinical Study Report, study EM-05-012760

In the mITT population, it is seen from Table 8 that the primary efficacy endpoint of achieving ≥70% for the lower bound of the 95% CI for responder rate was met by the two drug products and the active control (3M CHG/IPA Prep 10.5 mL, 3M CHG/IPA Prep 26 mL, and ChloraPrep®) in the abdominal and inguinal regions.

For both body regions, all active products demonstrated significantly greater responder rates (p-value<0.001) than the negative control (saline). Note that p-values satisfied multiplicity adjustments criteria (Hochberg's procedure) proposed by the Applicant.

Statistical Reviewer's Comments:

Hochberg's step-up procedure was used to adjust for the inclusion of 2 investigational products. However, all p-values of the active products compared to the negative control were less than 0.05, and all lower bounds of the 95% CI for all active products were $\geq 70\%$, so no adjustment steps were necessary.

Secondary analyses:

Table 9 provides the summary statistics of log-transformed bacterial (skin flora) counts at each time point and reduction from baseline to each follow-up time point by study product and body region for the mITT population.

Table 9: Summary Statistics of Log-transformed Bacterial (Skin Flora) Endpoints (mITT Population, Study EM-05-012760)

Time Point	Endpoint	Statistics	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep, 26 mL	ChloraPrep	Saline
Abdominal Region						
Baseline	Log ₁₀ /cm ² Skin Flora	N	205	201	198	62
		Mean (SD)	3.35 (0.427)	3.31 (0.370)	3.31 (0.391)	3.26 (0.342)
		Median	3.15	3.14	3.16	3.15
		Min-Max	3.01 - 5.32	3.02 - 4.74	3.01 - 5.21	3.01 - 4.96
10 Minutes	Log ₁₀ Recovery	N	205	201	198	62
		Mean (SD)	0.69 (0.604)	0.57 (0.575)	0.53 (0.499)	2.63 (0.582)
		Median	0.37	0.20	0.20	2.65
	Log ₁₀ Reduction	Min-Max	0.20 - 3.33	0.20 - 2.91	0.20 - 2.65	1.49 - 4.52
		N	205	201	198	62
		Mean (SD)	2.66 (0.705)	2.74 (0.644)	2.79 (0.565)	0.64 (0.487)
6 Hours	Log ₁₀ Recovery	Median	2.84	2.86	2.85	0.51
		Min-Max	0.91 - 5.12	0.23 - 4.54	1.16 - 4.54	-0.38 - 1.55
		N	205	201	198	62
	Log ₁₀ Reduction	Mean (SD)	1.87 (0.804)	1.66 (0.804)	1.54 (0.807)	2.80 (0.726)
		Median	1.89	1.72	1.62	2.78
		Min-Max	0.20 - 3.61	0.20 - 3.74	0.20 - 3.51	1.04 - 4.63
Log ₁₀ Reduction	N	205	201	198	62	
	Mean (SD)	1.48 (0.866)	1.64 (0.864)	1.77 (0.899)	0.46 (0.651)	
	Median	1.42	1.55	1.71	0.41	
Min-Max	-0.17 - 4.18	-0.37 - 3.97	-0.28 - 4.62	-0.86 - 2.06		
Inguinal Region						
Baseline	Log ₁₀ /cm ² Skin Flora	N	204	203	200	59
		Mean (SD)	5.44 (0.490)	5.42 (0.469)	5.44 (0.479)	5.39 (0.447)
		Median	5.22	5.21	5.22	5.14
		Min-Max	5.01 - 6.93	5.01 - 6.90	5.00 - 6.83	5.00 - 6.57
10 Minutes	Log ₁₀ Recovery	N	204	203	200	59
		Mean (SD)	1.47 (1.119)	1.53 (1.039)	1.40 (1.089)	4.06 (1.211)
		Median	1.45	1.50	1.44	4.19
		Min-Max	0.20 - 4.88	0.20 - 4.56	0.20 - 4.28	0.20 - 6.54

Time Point	Endpoint	Statistics	3M CHG/IPA Prep, 10.5 mL	3M CHG/IPA Prep, 26 mL	ChloraPrep	Saline
	Log ₁₀ Reduction	N	204	203	200	59
		Mean (SD)	3.98 (1.034)	3.89 (0.929)	4.03 (0.965)	1.34 (1.095)
		Median	4.09	3.82	4.03	1.23
		Min-Max	0.51 - 6.60	1.55 - 6.17	1.30 - 5.90	-0.66 - 4.85
6 Hours	Log ₁₀ Recovery	N	204	203	200	59
		Mean (SD)	3.20 (1.037)	3.07 (1.032)	2.80 (1.007)	4.31 (0.941)
		Median	3.35	3.23	2.98	4.49
	Log ₁₀ Reduction	Min-Max	0.20 - 5.10	0.20 - 5.59	0.20 - 4.91	1.39 - 5.62
		N	204	203	200	59
		Mean (SD)	2.24 (1.103)	2.35 (1.046)	2.63 (1.047)	1.08 (0.834)
Median	2.16	2.20	2.48	0.99		
Min-Max	0.09 - 6.43	-0.42 - 5.30	0.38 - 6.08	-0.22 - 4.05		

Note: Extracted from Table 9, page 50, Applicant's Final Clinical Study Report, study EM-05-012760

Both drug products and the active control met mean log reduction criteria: 2 log₁₀ and 3 log₁₀ reductions in bacterial counts at 10 minutes for abdominal and inguinal test sites. Both drug products and the active control showed a sustained reduction below the baseline bacterial counts at 6 hours for abdominal and inguinal regions, respectively. Thus Study EM-05-012760 satisfied secondary efficacy criteria for mean log reductions. Note that in all treatment arms for both sites, 6 hour recovery values are higher than 10 minute recovery values.

Study EM-05-013260

The primary efficacy analysis is summarized in the following table.

Table 10: Responder Rate (mITT Population, study EM-05-013260)

	3M CHG/IPA Prep	3M CHG/IPA Prep with HEDTA	ChloraPrep®	Saline
Abdominal Region				
N	196	202	196	59
Responder ^a , n (%)	159 (81.1)	165 (81.7)	163 (83.2)	5 (8.5)
95% CI for rate ^b	(75.6, 86.6)	(76.3, 87.0)	(77.9, 88.4)	NA
P-value relative to negative control ^c	<0.001	<0.001	<0.001	NA
Inguinal Region				
N	208	209	219	61
Responder ^a , n (%)	81 (38.9)	98 (46.9)	116 (53.0)	1 (1.6)
95% CI for rate ^b	(32.3, 45.6)	(40.1, 53.7)	(46.4, 59.6)	NA
P-value relative to negative control ^c	<0.001	<0.001	<0.001	NA

a: A responder for a treatment was defined as having a site that met the Treatment Day microbial baseline requirements for which the 10-minute log₁₀ count/cm² reduction from baseline was 2.00 or greater for the abdominal region or 3.00 or greater for the inguinal region and whose skin flora did not return to baseline at the 6-hour sample collection time.

b: The 95% CI for responder rate was calculated based on the normal approximation to the binomial distribution.

c: P-value was calculated using Fisher's exact test.

Note: Extracted from Table 8, page 57, Applicant's Final Clinical Study Report, study EM-05-013260

In Study EM-05-013260 for the abdominal region only, the primary efficacy endpoint of achieving $\geq 70\%$ for the lower bound of the 95% CI for responder rate was met by the two test products and the active product. For the inguinal region mITT population, the lower bound of the 95% CI for responder rate did not meet the criterion of $\geq 70\%$ for the two drug products or the active control product. For both abdominal and inguinal regions, responder rates for the two drug products and the control product were higher and statistically significantly different compared to the saline control ($p < 0.001$). Note that p-values satisfied multiplicity adjustments criteria (Hochberg's procedure) proposed by the Applicant.

Secondary analyses:

Table 11 provides the summary statistics of log-transformed bacterial (skin flora) counts at each time point and reduction from baseline to each follow-up time point by study product and body region for the mITT population.

Table 11: Summary Statistics of Log-transformed Bacterial (Skin Flora) Endpoints (mITT Population, Study EM-05-013260)

Time Point	Endpoint	Statistics	3M CHG/IPA Prep	3M CHG/IPA Prep with HEDTA	ChloraPrep	Saline		
Abdominal Region								
Baseline	Log ₁₀ /cm ² Skin Flora	N	196	202	196	59		
		Mean (SD)	3.63 (0.460)	3.61 (0.479)	3.64 (0.487)	3.64 (0.533)		
		Median	3.51	3.48	3.54	3.47		
		Min-Max	3.00 - 5.26	3.00 - 5.13	3.01 - 5.39	3.00 - 5.00		
10 Minutes	Log ₁₀ Recovery	N	196	201	196	59		
		Mean (SD)	0.85 (0.947)	0.88 (0.984)	0.90 (0.938)	2.88 (0.703)		
		Median	0.42	0.42	0.54	2.93		
	Log ₁₀ Reduction	Min-Max	0.24 - 4.55	0.24 - 4.22	0.24 - 4.92	1.43 - 4.57		
		N	196	202	196	59		
		Mean (SD)	2.78 (0.935)	2.73 (1.002)	2.75 (0.973)	0.76 (0.814)		
6 Hours	Log ₁₀ Recovery	Median	2.96	2.94	2.90	0.72		
		Min-Max	-0.95 - 4.44	-0.22 - 4.89	-0.71 - 5.15	-0.82 - 2.54		
		N	196	201	196	59		
	Log ₁₀ Reduction	Mean (SD)	0.80 (0.840)	0.74 (0.789)	0.81 (0.935)	2.65 (0.886)		
		Median	0.33	0.24	0.42	2.58		
		Min-Max	0.24 - 3.43	0.24 - 3.37	0.24 - 4.30	0.42 - 4.99		
Inguinal Region	Log ₁₀ /cm ² Skin Flora	N	208	209	219	61		
		Mean (SD)	6.23 (0.604)	6.21 (0.563)	6.27 (0.618)	6.09 (0.626)		
		Median	6.28	6.33	6.34	6.16		
	10 Minutes	Log ₁₀ Recovery	Min-Max	5.00 - 7.49	5.08 - 7.37	5.00 - 7.47	5.00 - 7.45	
			N	208	208	218	60	
			Mean (SD)	3.39 (1.096)	3.21 (1.042)	3.08 (1.137)	5.08 (0.676)	
Log ₁₀ Reduction		Median	3.61	3.36	3.26	5.28		
		Min-Max	0.24 - 5.61	0.24 - 5.72	0.24 - 4.90	2.55 - 6.21		
		N	196	202	196	59		
	Log ₁₀ Reduction	Mean (SD)	2.83 (0.851)	2.86 (0.899)	2.83 (0.971)	1.00 (0.970)		
		Median	2.95	2.99	2.98	0.86		
		Min-Max	-0.03 - 4.59	0.00 - 4.69	-0.67 - 4.81	-0.88 - 3.56		
		Log ₁₀ Reduction	N	208	209	219	61	
			Mean (SD)	2.84 (1.191)	2.99 (1.125)	3.17 (1.243)	1.01 (0.668)	
			Median	2.74	2.93	3.13	1.04	
		6 Hours	Log ₁₀ Recovery	Min-Max	-0.25 - 6.70	0.00 - 6.15	0.00 - 6.36	-0.87 - 3.30
				N	208	209	219	60
				Mean (SD)	2.76 (1.202)	2.73 (1.220)	2.58 (1.182)	4.85 (0.749)
			Log ₁₀ Reduction	Median	2.95	3.03	2.76	4.83
				Min-Max	0.24 - 5.44	0.24 - 5.13	0.24 - 5.17	2.59 - 6.50
				N	208	209	219	61
		Log ₁₀ Reduction	Mean (SD)	3.46 (1.312)	3.49 (1.329)	3.69 (1.286)	1.23 (0.732)	
			Median	3.44	3.29	3.57	1.23	
			Min-Max	0.35 - 6.84	0.14 - 6.49	0.61 - 6.77	-0.13 - 3.03	

Note: Extracted from Table 10, page 61, Applicant's Final Clinical Study Report, study EM-05-013260

For the abdominal site, both drug products and the active control met the mean log reduction criteria: 2 log₁₀ reductions in bacterial counts at 10 minutes. However, neither drug product met the mean 3 log₁₀ reductions in bacterial counts at 10 minutes for inguinal site. The active control met the mean log reduction criteria for the inguinal site: 3 log₁₀ reductions in bacterial counts at 10 minutes. Though, neither drug product made the 3 log₁₀ reductions criteria for the inguinal site, the test arm with HEDTA, the to-be-marketed formulation was very close at 2.99. Both drug products and the active control showed a sustained reduction below the baseline bacterial counts at 6 hours for abdominal and inguinal test. In all treatment arms for both sites, 6 hour recovery values are lower than 10 minute recovery values.

3.3 Evaluation of Safety

In this submission, the Applicant provided safety data from two completed pivotal studies (Study EM-05-012760 and Study EM-05-013260), one discontinued pivotal study (Study EM-05-012759) and one safety challenge study (EM-05-012853- multiple applications over extended periods of time) designed to assess exaggerated application conditions of the test product.

The Applicant has mentioned:

- No AEs were reported in Studies EM-05-012760 and EM-05-012759.
- In Study EM-05-013260, a total of 5/569 (0.9%) subjects experience TEAEs after treatment on the abdominal region and 4/404 (1.0%) subjects experienced TEAEs after treatment on the inguinal region. All TEAEs involved the skin. One subject reported moderate skin irritation on both sides of the abdominal and inguinal regions (specifically, dryness and itching on both abdominal sides, and itching on both inguinal sides); all 4 moderate events of skin irritation were considered probably related to the study products on each side (3M CHG/IPA Prep and 3M CHG/IPA Prep with HEDTA). All other TEAEs were considered mild. After treatment on the abdominal region, mild events included an unexpected skin abrasion (1 subject, not related), burning sensation (2 subjects, probably related to ChloroPrep® and 3M CHG/IPA Prep, respectively), and allergic reaction (1 subject, probably related to 3M CHG/IPA Prep with HEDTA). After treatment on the inguinal region, mild events included skin abrasion (1 subject, not related), warmth/heat sensation (1 subject, possibly related to 3M CHG/IPA Prep), and burning sensation (1 subject, probably related to 3M CHG/IPA Prep with HEDTA).

The Applicant reported that there were no deaths, SAEs, or discontinuations due to AEs in any of the pivotal studies.

Note that Study EM-05-012853 was designed to assess exaggerated application conditions of the test product and the reviewer of this was deferred to the prescription review division by the Medical Officer Teresa Podruchny.

The medical officer has mentioned in her review, “My review did not lead to safety findings that would preclude approval unless the different formulations/formulation redesigns used in the development program prohibit support of the safety data that resulted from studies that did not use the final to-be-marketed formulation”. This reviewer agrees with the medical reviewer’s findings. See Medical Officer’s review in DARRTS for further details.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

For preoperative skin preparation simulation studies, the DNDP does not require subgroup analyses since the clinical simulation studies are conducted on healthy volunteers who are not treated for sickness. This reviewer agrees with the DNDP's standing on the subgroup analyses.

4.2 Other Special/Subgroup Populations

There were no subgroup analyses conducted in this submission.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During the review, this reviewer observed that:

- In Study EM-05-012760 for both the abdominal and inguinal regions and in Study EM-05-013260 for the abdominal region only, the primary efficacy endpoint of achieving $\geq 70\%$ for the lower bound of the 95% CI for responder rate was met by all active study products. In Study EM-05-013260 for inguinal region only, the primary efficacy endpoint of achieving $\geq 70\%$ for the lower bound of the 95% CI for responder rate was not met by two drug products or the *active control* product.
- Study EM-05-012760, conducted at MBT, satisfied secondary efficacy criteria for mean log reductions at 10 minutes and 6 hours for both the abdominal and inguinal regions. Study EM-05-013260, conducted at BSL, neither test product satisfied the secondary efficacy criteria for inguinal region; however, both test products did satisfy the secondary efficacy criteria for abdominal region. Thus, there are differences in efficacy results between the two clinical laboratories for the inguinal region. It should be noted here that mean log reduction criteria (secondary endpoint) for the failed groin study the HEDTA version (proposed marketed product) was 2.99 which is close to the recommended 3 $\log_{10}$ reduction in the inguinal site.

In Study EM-05-012760 and Study EM-05-013260, both drug products and the active control demonstrated significantly greater responder rates (p -value <0.001) than the negative control (saline) for both body regions. Note that p -values satisfied multiplicity adjustments criteria (Hochberg's procedure) proposed by the Applicant.

The review team explored possible reasons for the failed results of the inguinal site in Study EM-05-13260 but was unable to determine any. According to the Applicant, it was observed in the past that at the inguinal site, one laboratory (e.g., MBT) consistently reported meeting both the primary and secondary efficacy criteria while the other laboratory (e.g., BSL) does not provide reproducible findings. The Applicant reported that the reasons for differences in efficacy in the

inguinal area, between the two laboratories, are not clear.

We did note another difference between the results of the two studies that might have been due to the different laboratories. The 6 hours recovery values were higher than the 10 minute recovery values in all study arms at both the abdomen and inguinal sites in study EM-05-120760 (the MBT study conducted in Sterling, VA) while in study EM-05-13760 (the BSL study conducted in Bozeman, MT) the 6 hour recovery values were lower compared to the 10 minute values for all study arms at both body sites. This, however, could possibly be related to the location of the site and not due to the study conduct.

5.2 Collective Evidence

The following table contains the main findings of efficacy from Study EM-05-012760 and Study EM-05-013260. It provides responder rates and mean log reductions at 10 minutes.

Table 12: Responder Rate and Mean log reduction (mITT Population, Study EM-05-012760 and Study EM-05-013260) at 10 minutes

	Study EM-05-012760				Study EM-05--130260			
	Tinted 3M CHG/IPA Prep, 10.5 mL	Tinted 3M CHG/IPA Prep, 26 mL	Tinted ChloroPrep, 26 mL	Saline 20 mL	Clear 3M CHG/IPA Prep, 10.5 mL	Clear 3M CHG/IPA Prep with HEDTA, 10.5 mL	Tinted Chloro Prep 10.5 mL	Saline 20 mL
Abdominal Region								
N	205	201	198	62	196	202	196	59
Responder (%)	167 (81.5)	175 (87.1)	178 (89.9)	NA0	159 (81.1)	165 (81.7)	163 (83.2)	5 (8.5)
95% CI for responder rate	76.1, 86.8	82.4, 91.7	85.7,94.1	NA	75.6,86.6	76.3,87.0	77.9, 88.4	NA
Mean log reduction (SD)	2.66 (0.71)	2.74 (0.64)	2.79 (0.57)	0.64 (0.49)	2.78 (0.935)	2.73 (1.002)	2.75 (0.973)	0.76 (0.814)
95% CI for mean log reduction	2.56, 2.77	2.65, 2.83	2.71, 2.87	0.52, 0.76	2.65, 2.91	2.59, 2.89	2.61, 2.89	0.55, 0.97
Inguinal Region								
N	204	203	200	59	208	209	219	61
Responder (%)	168 (82.4)	162 (79.8)	168 (84.0)	4 (6.8)	81 (38.9)	98 (46.9)	116 (53.0)	1 (1.6)
95% CI for responder rate	77.1, 87.6	74.3, 85.3	78.9, 89.1	0.4, 13.2	32.3,65.6	40.1,53.7	46.4, 59.6	NA
Mean log reduction (SD)	3.98 (1.03)	3.89 (0.93)	4.03 (0.97)	1.34 (1.1)	2.84 (1.19)	2.99 (1.13)	3.17 (1.24)	1.01 (0.67)
95% CI for mean log reduction	3.84, 4.12	3.76,4.01	3.90, 4.16	1.06,1.62	2.68, 3.00	2.84, 3 .14	3.00, 3.33	0.84, 1.18

Note: The 95% CI for responder rate was calculated based on the normal approximation to the binomial distribution.

Note: Extracted from Table 18, page 72, Module 2

In Study EM-05-012760 for both the abdominal and inguinal regions and in Study EM-05-013260 for the abdominal region only, the primary efficacy endpoint of achieving $\geq 70\%$ for the lower bound of the 95% CI for responder rate was met by the two drug products and the control product. In Study EM-05-013260 for inguinal region only, the primary efficacy endpoint of achieving $\geq 70\%$ for the lower bound of the 95% CI for responder rate was not met by any of the drug products or the active control.

For each study, the mean log reduction in bacterial (skin flora) count at 10 minutes is presented by study product and body region in Table 12. In both studies, all active products achieved mean log reductions of approximately 2.7 on the abdominal region at 10 minutes post-prep. In Study EM-05-012760, all active products achieved mean log reductions of approximately 3.9 on the inguinal region at 10 minutes post-prep. In Study EM-05-013260, mean log reductions were 2.84, 2.99, and 3.17 for 3M CHG/IPA Prep, 3M CHG/IPA Prep with HEDTA, and ChloroPrep, respectively, on the inguinal region at 10 minutes post-prep. Note that in both studies on both body regions, all active products maintained mean bacterial counts below baseline for 6 hours.

5.3 Conclusions and Recommendations

In order to support the efficacy of preoperative skin preparation products, it is expected that efficacy data for both abdominal and inguinal regions from two adequate and well-controlled studies conducted at independent laboratories satisfy the efficacy criteria. This application did not meet those criteria. Instead there are two independent studies at abdominal sites and one study at inguinal sites showing evidence of efficacy with both the primary responder analysis as well as a mean log reduction analysis. In the second inguinal site study, the active control also failed the primary endpoint analyses, pointing to the possibility that it was a problem with the study. Additionally, though the test products did not meet the secondary endpoint of mean 3 $\log_{10}$ reduction, the test arm with the to-be-marketed formulation came extremely close at 2.99.

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/s/

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04/08/2016

KAREN M HIGGINS
04/08/2016
I concur.