CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210872Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 210872
Drug Name:	ZuraPrep solution (isopropyl alcohol 70% v/v) 10.5 mL
Indication(s):	Patient preoperative skin preparation solution for use in presurgical settings as an antiseptic/antimicrobial agent to reduce bacteria that potentially can cause skin infection
Applicant:	Zurex Pharma, Inc.
Date(s):	Received: 06/29/2018
Review Priority:	Standard
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Keywords: Responder rate, Average Treatment Effect, Log_{10} reduction, Confidence interval

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1 EXECUTIVE SUMMARY

This document is a statistical review of two pivotal studies ZX-ZP-0073 and ZX-ZP-0074 submitted by the applicant to support marketing of ZuraPrep[1] solution (isopropyl alcohol 70% v/v) 10.5 mL for patient preoperative skin preparation. The two pivotal studies were randomized, vehicle and active controlled, evaluator blinded, single center studies in healthy volunteers, who received 2 of 3 possible study products on the abdomen and 2 of 3 possible study products on the groin. The three products were ZuraPrep 10.5 mL (test product), ChloraPrep 10.5 mL (active control) and ZuraPrep 10.5 mL vehicle. Bacterial counts were measured at baseline, 30 seconds, 10 minutes and 6 hours post-treatment application. Prior to trial initiation, the FDA and the sponsor agreed upon the study design and analysis procedures which aligned with the December 2017 FDA Final Rule on the Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over the Counter Human Use.

The primary study objectives were assessed at 10 minutes post-treatment to show:

- A 70% responder rate of the test product (lower bound of the two-sided 95% confidence interval (CI) of percent responders greater than or equal to 70%). A responder is defined as a subject with a 2 $\log_{10}$ Colony Forming Units (CFU) / cm^2 bacterial reduction when treated on the abdomen, and, a 3 $\log_{10}$ CFU / cm^2 bacterial count reduction from baseline in the groin region.
- Statistical superiority to the vehicle by a margin of 1.2 (in $\log_{10}$ CFU / cm^2) and non-inferiority to the active control by a margin of 0.5 (in $\log_{10}$ CFU / cm^2), when comparing the average treatment effect.

Secondary study objectives for the test product were to show:

- A 70% responder rate of the test product at 30 seconds and 6 hours post application. At 30 seconds, a responder is defined as done at 10 minutes. At 6 hours a responder is a subject with bacterial counts (in $\log_{10}$ CFU / cm^2) below baseline. This definition was for both groin and abdomen regions.
- Statistical superiority to the vehicle by a margin of 1.2 units and non-inferiority to the active control by a margin of 0.5 units, when comparing the average treatment effect on the 30 second bacterial counts.

To support the efficacy of preoperative skin preparation products, it is expected that data for both abdominal and groin regions from two adequate and well-controlled studies conducted at independent laboratories show substantial evidence of efficacy. From a statistical standpoint, there is sufficient evidence that ZuraPrep 10.5 mL is effective and adds benefits beyond those of the ZuraPrep vehicle. Specifically, both studies ZX-ZP-0073 and ZX-ZP-0074 demonstrated that:

- ZuraPrep 10.5 mL had a responder rate greater than 70% at 10 minutes in both body regions; (see Figures 7 and 8); and

[1] ZuraPrep was the proprietary name proposed in the original submission and this may not be reflective of the final FDA approved proprietary name for this product.

- ZuraPrep 10.5 mL is statistically superior (based on average treatment effects) to both the vehicle and non-inferior to the active control at 10 minutes in both body regions (see Figures 9 and 10) which satisfies the effectiveness criteria defined in the 2017 Final Rule.

The sponsor also demonstrated persistent antimicrobial properties for the test product; but only in the groin region in both studies. Persistent antimicrobial properties, as defined in the December 2017 Final Rule, is demonstrated by a 100% responder rate at 6 hours. This criterion was met for the groin region in both studies. However, for the abdomen region, the responder rate at 6 hours was 99.4% in ZX-ZP-0073 and 99.1% in ZX-ZP-0074.

2 INTRODUCTION

2.1 Overview

The sponsor submitted two Phase 3 clinical trials to support the safety and efficacy of the antiseptic ZuraPrep (isopropyl alcohol 70% solution, 10.5 mL applicator) for the indication of patient pre-operative skin preparation. The design of the two randomized, evaluator blinded, pivotal clinical trials (ZX-ZP-0073 and ZX-ZP-0074) were reviewed under IND 117045[2]. Following implementation of the recommendations from the agency regarding the study design, the study protocol was agreed upon.

The two trials were similar in design with two primary objectives. The first objective was to demonstrate non-inferiority of ZuraPrep to the active control (NI margin = 0.5) and superiority of ZuraPrep to the vehicle control with a margin of 1.2 on the Average Treatment Effect (ATE). The ATE was estimated from a linear regression of posttreatment bacterial count (at 10 minutes) on treatment and the baseline count. The second co-primary objective was to demonstrate that the lower-bound of the 95% confidence interval was greater than 70% for the responder rate at 10 minutes. The trials are summarized in Table 1 below. The review of efficacy is based upon trials ZX-ZP-0073 and ZX-ZP-0074.

Table 1. Summary of Pivotal Efficacy Studies

Trial ID	Enrollment	Drug Products	Sample Size - Abdomen Region	Sample Size – Groin Region	Duration
ZX-ZP-0074	August 3, 2016 – August 3, 2017	ZuraPrep	324	343	14 day washout before screening day, followed by treatment day with less than 24 hours exposure to product
		ChloraPrep	320	352	
		ZuraPrep vehicle	68	74	
ZX-ZP-0073	July 27, 2016 – April 12, 2017	ZuraPrep	342	330	
		ChloraPrep	340	326	
		ZuraPrep vehicle	69	68	

[2] The protocol was reviewed at the IND stage by FDA statistical reviewers from the Division of Biometrics VII (see statistical review from Dr. Yueqin Zhao, submitted to DARRTS on June 16, 2017).

2.2 Data Sources

The sponsor submitted electronic documents and datasets for both ZX-ZP-0073 and ZX-ZP-0074. These datasets include baseline characteristics, disposition, and study endpoints for all subjects randomized. Clinical study reports (CSRs) of each individual trial were made available.

The following file folders available within the CDER Electronic Document Room (EDR) were used in this review:

- Clinical Study Reports for ZX-ZP-0073 and ZX-ZP-0074, submitted on 06/29/2018: \\CDSESUB1\evsprod\NDA210872\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\Preop-Skin-Prep\5351-stud-rep-contr
- Integrated Summary of Efficacy, submitted on 06/29/2018: \\CDSESUB1\evsprod\NDA210872\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\Preop-Skin-Prep\5353-rep-analys-data-more-one-stud\ise
- Multi-Module submitted on 09/27/2018 in response to FDA information request: \\CDSESUB1\evsprod\NDA210872\0003\m1\us
- Datasets used for the analyses, submitted on 06/29/18: \\CDSESUB1\evsprod\NDA210872\0001\m5\datasets , and clinical datasets submitted on 09/27/2018 in response to FDA information request: \\CDSESUB1\evsprod\NDA210872\0003\m5\datasets
- Multi-Module submitted on 10/24/2018 in response to FDA information request: \\CDSESUB1\evsprod\NDA210872\0005\m1\us

Note that some of the documents and datasets referred above are different from the ones submitted in the original submission on 06/29/2018 because of information requests and amendments sent during the review of this NDA; details are provided in Section 3.1.

The format, content, and documentation of the data submitted in support of this application was adequate to conduct our statistical review of the antimicrobial efficacy of ZuraPrep for the indication of preoperative skin preparation.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor and the investigator were responsible for ensuring proper study conduct with regard to protocol adherence and validity of the data recorded on the Case Report Forms (CRFs). The investigator gave the Zurex Pharma study monitor direct access to source documents that supported data on the CRFs and made available such records to authorized Zurex Pharma quality assurance, IRB and regulatory personnel for inspection and/or copying. Note that the source documents are defined as any original documents, data, and records where data are first recorded (e.g. CRF, questionnaire, consent form, laboratory notes).

The Zurex Pharma study monitor assessed the progress of the study by performing the following oversight:

- Periodic on-site review
- Telephone communications and e-mail
- Review of CRFs and source documents

During the review of the analysis data sets provided in the original submission for Trial ZX-ZP-0074, the reviewer identified issues with the dataset submitted by the sponsor. Specifically, sample counts produced by the reviewer's analysis did not match those reported by the sponsor. In response, dated August 22, 2018, the sponsor submitted amendments to the NDA on September 27, 2018 and October 24, 2018, where they reported errors in the analysis datasets originally submitted for study ZX-ZP-0074. For ZX-ZP-0074., four groin regions and two abdomen regions should have been excluded as treatment day baseline failures but were not. Of the four groin regions that should have been excluded as treatment day baseline failures, three were treated with the active control ChloraPrep and one received ZuraPrep. Both abdomen regions that should have been excluded were treated with ZuraPrep.

The sponsor reported 49 individual instances of protocol deviations reported for ZX-ZP-0074. Of these, four resulted in samples being lost or not collected at 10 minutes (1 sample lost at groin region) and 6 hours (1 sample lost at groin region and 2 samples not performed at abdomen region) post application. For responder rate analysis, these samples were classified as non-responders. Other protocol deviations for ZX-ZP-0074 did not impact interpretations of findings pertaining to primary or secondary endpoints. The sponsor also reported 11 individual instances of protocol deviations for ZX-ZP-0073; none of these impacted the interpretation of study findings pertaining to primary or secondary endpoints.

Blinding and unblinding procedures were well documented. The investigational products were not blinded from the investigator or other study staff performing the investigational product application or bacterial sample collections. The staff member(s) performing bacterial enumeration was blinded from the identification of treatment assignment. Each sample was plated in duplicate and manually (visually) counted. The study personnel performing the bacterial enumeration were not involved in the investigational product application or the collection of samples. Three individual instances of protocol deviations in study ZX-ZP-0074 were reported to be related to unblinding. These instances involved a non-blinded technician performing bacterial enumeration due to unknown reasons. The non-blinded technician did not perform testing procedures in two of these instances and the data from the third instance were not used in the study as the subject failed the treatment day baseline counts.

The sponsors' submission included the original study protocol with all subsequent amendments which described the analysis plan and any changes. This application and subsequent amendments were sent in electronic format. The submission was well organized and easy to navigate.

Reviewer Comments:

- *For pivotal study ZX-ZP-0073, the reviewer was able to reproduce the analyses for the co-primary endpoints and secondary endpoints from datasets ZP0073f1.xpt and ZP0073f2.xpt that the sponsor originally provided.*

- *For pivotal study ZX-ZP-0074, the reviewer was not able to reproduce the analyses for the co-primary endpoints and secondary endpoints using the datasets in the original submission. However, following an information request and subsequent amendments submitted by the sponsor, the reviewer was able to reproduce the primary and secondary analyses using the subsequently submitted datasets ZP0074f1.xpt and ZP0074f2.xpt.*

3.2 Evaluation of Efficacy

The review of efficacy is based on two pivotal studies, ZX-ZP-0073 and ZX-ZP-0074. The sites for ZX-ZP-0073 and ZX-ZP-0074 were MicroBioTest, Inc. (MBT) in Sterling, Virginia and BioScience Laboratories, Inc. (BSLI) in Bozeman, Montana, respectively.

3.2.1 Study Design and Endpoints

Studies ZX-ZP-0073 and ZX-ZP-0074 were randomized, vehicle and active controlled, third party blind (staff performing bacterial enumeration), single center trials performed and designed according to the procedures outlined in the 1994 Food and Drug Administration Tentative Final Monograph (TFM) for Effectiveness Testing on the Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use (1994 TFM), the 2015 FDA Proposed Rule to the 1994 TFM (2015 Amendment to TFM), and ASTM International methodology standards. The study procedures were also consistent with the December 2017 FDA Final Rule on the Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over the Counter Human Use.

Both trials enrolled healthy volunteers of at least 18 years of age with no dermatological conditions or known history of sensitivity to natural rubber latex, adhesive skin products, isopropyl alcohol, chlorhexidine gluconate, or other investigational product ingredients. Additional study design elements are presented below for ZX-ZP-0073 and ZX-ZP-0074. Note that unless specified, the description holds for both studies. For details about the treatment application procedures, we refer to Dr. Anita Kumar's clinical microbiology review.

Study Schedule

Each study consisted of 3 phases: a pre-treatment phase (14-day washout to allow for the removal of any antimicrobial agents from the subject's skin), a screening phase, and a treatment phase (scheduled at least 72 hours after screening baseline collection).

Baseline Criteria

Baseline bacterial count in Colony Forming Units (CFU) were assessed on screening day and on treatment day. Both the screening day criteria and treatment day criteria were baseline counts of at least 1.0×10^3 CFU/cm^2 per abdominal region and/or 1.0×10^5 CFU/cm^2 per groin region.

Randomization and Replacements

Subjects were randomized after screening eligibility was determined to receive two of the three investigational products (one product for the right side, one product for the left side). In study ZX-ZP-0073, subjects received the same treatments on both abdomen and groin regions on each side of the body. In study ZX-ZP-0074, the two treatments received on the left and right sides could differ across anatomical regions. Following application of products, each treatment site was further sub-divided into four areas of the same dimension for post-application sampling of skin flora at baseline, 30 seconds, 10 minutes and 6 hours. The randomization schedule used to assign investigational products for the treatment of subjects on the groin and abdomen was a nondeterministic block design that ensured that subjects were balanced with respect to treatments, left/right body side, and sampling time/sampling area. The treatment assignments were balanced such that the number of readings per anatomical region met the sample size requirements.

The sponsor summarized the randomization plan as follows:

"

1. Define a treatment block size that is balanced with respect to treatments, left/right body side, and sampling time/sampling area
2. Randomize the block.
3. Treat the block. Count the treatment day baseline successes per treatment and body area.
4. Total the number of the treatment day baseline successes per treatment and body area to date. If any of treatment day baseline success totals are less than the minimum desired group size for each treatment and body area, treat another block of subjects.
5. Repeat steps 2 through 4 as needed. If the number of successful treatments for a body area is reached, stop treating that body area. For example, if block 10 has sufficient total successes for the abdomen but not for the groin, treat blocks 11 and later on the groin only.

This plan means there are no replacement subjects – treatments continue until the minimum numbers are met. There are no re-used treatments, creating a non-deterministic randomization design."

Blinding

With regards to blinding procedure, the sponsor notes the following:

"The study materials will not be blinded from the Investigator or other study staff performing the study material application or bacterial sample collections. The staff member(s) performing bacterial enumeration will be blinded from the identification of treatment assignment. The study staff performing the bacterial enumeration will not be involved in the study material application or the collection of samples. The Raw Data Sheet sections of the case report form will be maintained separately (from the pages within the case report form which include study treatment identifications) during the conduct phase of the study. The study staff performing the bacterial enumeration will record counts directly onto the Raw Data Sheet pages of the case report form without accessing the subject study documentation folder containing the other case report form

pages. The Raw Data Sheets will be compiled with the entire case report form after all data recording has been completed. The CRF will serve as the source document."

Endpoints

Co-primary endpoints were assessed in each trial to establish the benefit of ZuraPrep for each body region, the abdominal and groin regions. The first co-primary endpoint is responder rates at 10 minutes post-treatment for each of abdominal and groin regions. At 10 minutes, a responder on the abdomen is defined as having at least a 2 $\log_{10}$ / cm^2 bacterial reduction compared to baseline; a responder on the groin region is defined as having at least a 3 $\log_{10}$ / cm^2 bacterial reduction compared to baseline.

The second co-primary endpoint is the average treatment effect (ATE) at 10 minutes post-application using the $\log_{10}$ scale for all counts for each of the abdominal and groin regions. The ATE was estimated from a linear regression of posttreatment bacterial count on treatment and the baseline count. The ATE co-primary endpoints are prescribed in the December 2017 Final Rule. In anticipation of this rule, these endpoints were added as an amendment to the study protocol per the FDA's advice letter on July 10, 2017.

Secondary responder rate endpoints are responder rates at 30 seconds and 6 hours post-treatment for the abdominal and groin regions. At 30 seconds, a responder is defined as done at 10 minutes. At 6 hours, a responder is defined as having counts below baseline for the groin and abdomen region.

A secondary ATE endpoint was ATE at 30 seconds, estimated using the same linear regression model as for the primary endpoint.

Additional secondary endpoints assessed in this review are reduction in bacterial counts ($\log_{10}$ scale) at 30 seconds, 10 minutes and 6 hours, and mean bacterial counts ($\log_{10}$ scale) at baseline and all post-application time points.

3.2.2 Statistical Methodologies

The statistical methodologies described in this section were pre-specified in the reviewed study protocol unless otherwise noted.

Sample Size

For the active treatments, ZuraPrep and the active control (ChloraPrep), assuming a minimum 77.8% responder rate and a two-sided Type I error rate of 0.05, the sponsor estimated the sample size to be 267 for 80% power. The assumed responder rate was based on results from pilot study ZX-ZP-0068, where 28 of 36 body regions treated with ChloraPrep achieved the required reduction in bacterial colony forming units at 10 minutes. The sponsor chose this rate as this was the lowest responder rate for active treatments that did pass the goal of 70% in pilot studies. For the inactive control, the sponsor calculated the required sample size based on two different endpoints. The first estimate was based on the number necessary to show a difference between

the inactive control and an active treatment in responder rate proportions at 10 minutes with at least 80% power. The second estimate was based on the number necessary to show a difference between the inactive control and an active treatment with respect to the secondary endpoint of reduction in bacterial counts (log_{10} scale) at 6 hours with at least 80% power. For the first estimate, based on pilot studies, the inactive control was assumed to achieve a responder rate of at most 20.0% (3/15). Further, assuming a 77.8% responder rate for active treatments as above and a two-sided Type I error rate of 0.05, the required sample size was determined to be 14[3]. For the second estimate based on differences at 6 hours, the sponsor assumed that the differences in reduction in bacterial counts (log_{10} scale) between the active treatments and vehicle control were at least 0.566 and the standard deviation was at most 1.273. This lead to an estimated sample size of 39.7 (rounded up to 40) for obtaining at least 80% power. Since the second estimate was larger, the sponsor concluded that it should be used for the study.

Using the above calculations and design considerations, the sponsor justified the sample size to be used in the study as follows:

> "In order to be more conservative and provide for an equal block design, a sample size of 320 for the active treatment groups and 64 for the inactive control group was chosen. 32 each of the inactive control group get paired with each of the active treatment groups, leaving 320 – 32 = 288 each of the active treatment groups to be compared to each other. The overall study size for this design would be ((320 * 2) + 64) / 2 = 352 subjects without treatment day baseline failures."

It is worth noting that sample size calculations were not based on the ATE endpoints. These endpoints were added as an amendment to the study protocol per the FDA's advice letter on July 10, 2017, making the study consistent with the December 2017 Final Rule.

Main Efficacy Analysis:

For both ZX-ZP-0073 and ZX-ZP-0074, the efficacy analysis was performed on a modified intent to treat (mITT) population which included all subjects passing the treatment day baseline bacterial count requirement and having a bacterial count result at any one of the three sample times: 30 seconds, 10 minutes or 6 hours.

- Responder Rate Analysis and Criteria for Evaluation

The sponsor calculated responder rates and associated 95% confidence intervals (CIs) for each body region and time point. The CIs for all responder rates are based on Fisher exact tests. The primary efficacy objective was to demonstrate that the lower bound of the 95% confidence interval for the responder rate at 10 minutes to be ≥70% for each body region. Secondary efficacy objectives were to demonstrate that the 30-second and 6-hour lower bounds of the 95% confidence intervals for the responder rates to be ≥70% for each body region.

- Average Treatment Effect Analysis and Criteria for Evaluation

As noted above, the ATE at 10 minutes (primary goal) and 30 seconds (secondary goal) was estimated from a linear regression of posttreatment bacterial count on the treatment and the

[3] Two-group continuity corrected chi-squared test of equal proportions.

baseline count, where counts were measured on the $\log_{10}$ scale. The objective was to demonstrate:

1. ZuraPrep was non-inferior to the active control (ChloraPrep) with a 0.5 margin (i.e. the upper bound of the 95% confidence interval of the difference in ATE values ≤ 0.5) at each body region, and
2. ZuraPrep was superior to the inactive control (ZuraPrep without isopropyl alcohol) by a margin of 1.2 (i.e., lower bound of the 95% confidence interval of the difference in ATE values ≥ 1.2) at each body region.

- Adjustment for Multiplicity

The protocol-specified primary efficacy endpoints for each of the Phase 3 trials were co-primary and did not require multiple comparison adjustments. There were no unplanned interim analyses of efficacy data.

Sensitivity Analysis

As noted earlier, the sponsor calculated ATEs through a linear regression of post treatment bacterial count on treatment and baseline bacterial count. This analysis assumes statistical independence of all the observations used in the analysis for each body region. However, statistical independence of observations could be questioned as the study involves multiple observations from the same subject. For example, a subject may be randomized to receive ZuraPrep on the left side and ChloraPrep on the right side. For the ATE analysis at each body region this subject contributes an observation for ZuraPrep and one for ChloraPrep. Since both of these observations are analyzed in the same linear regression analysis, any possible correlation between these two observations must be taken into account. Thus, the DB7 reviewer also conducted a sensitivity analyses for the ATE analyses at each body region using subject-specific random effects to account for correlation between observations from different sampling sites (right and left side of body) within each subject.

Reviewer Comments:

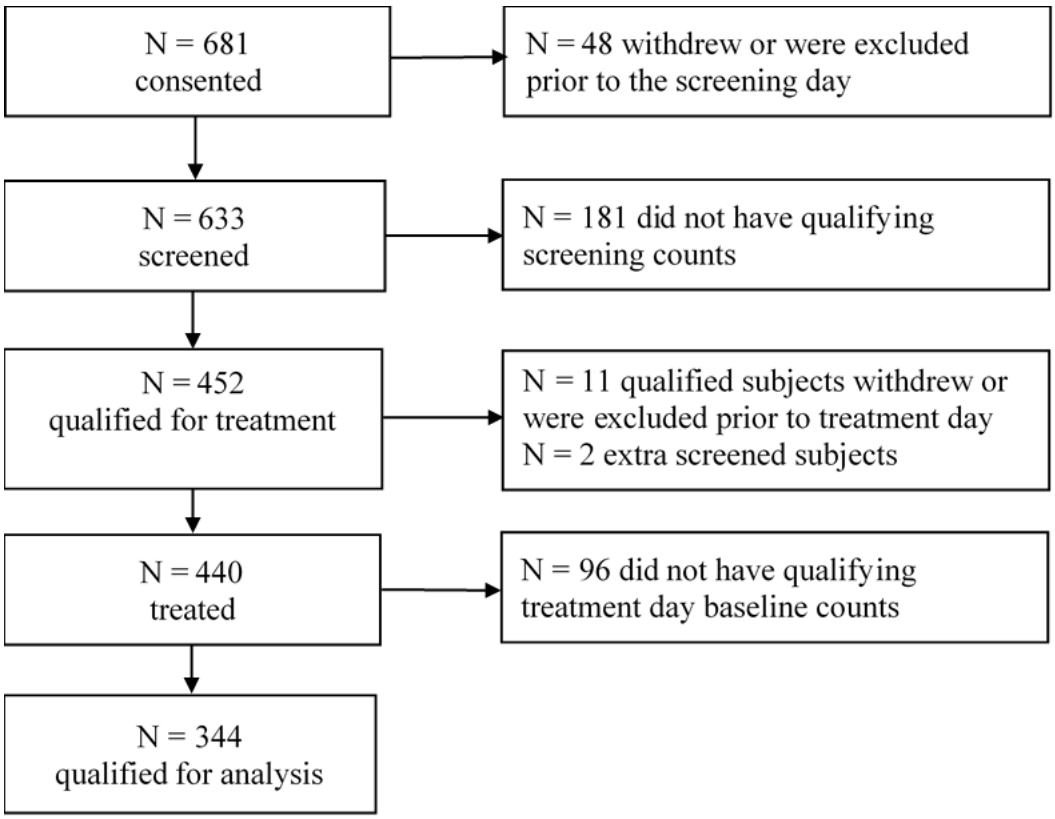
- *The DB7 reviewer was not able to replicate the sponsor's ATE analysis results using the datasets in the original submission for both ZX-ZP-0073 and ZX-ZP-0074. The DB7 reviewer was unable to reproduce the sample size numbers in the mITT sample for study ZX-ZP-0074 using analysis datasets 'ZP0074f1.xpt' and 'ZP0074f2.xpt'. Further, the DB7 reviewer found that the sponsor's reported analyses in Study ZX-ZP-0073 CSR Table 9 and Table 10, and Study ZX-ZP-0074 CSR Table 12 and Table 21 for the ATE efficacy endpoints were different from the planned analysis detailed in the protocol in both ZX-ZP-0073 and ZX-ZP-0074. Specifically, in ZX-ZP-0073, the data were analyzed using a two-way random effects ANOVA, with sample time and treatment as two fixed effects factors and subject as a random effect. In ZX-ZP-0074, the data were analyzed using a linear regression analysis for each pairwise comparison adjusting for baseline values. The protocol for both studies stated that the ATE goals of non-inferiority and superiority will be assessed using a linear regression analysis with baseline as a continuous covariate, and, treatment as a categorical covariate.*

- *The above issues resulted in an information request from the FDA on August 22, 2018. In response, the sponsor submitted amendments on September 27, 2018 which included new analysis datasets 'ZP0074f1.xpt' and 'ZP0074f2.xpt'. These updated datasets were used in the DB7 reviewer's analysis presented in the next section. Additionally, the sponsor submitted an amendment on October 24, 2018 which contained the results from the ATE analysis performed as specified in the protocol. These are considered as the results of the sponsor's analysis for the ATE efficacy endpoints.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In ZX-ZP-0073, a total of 681 subjects were consented and 633 subjects were screened. Among the screened subjects, 452 passed screening day baseline criteria and 440 were randomized and treated. Among the randomized subjects, 344 passed treatment baseline criteria and were included in the main analyses. For a disposition flowchart, see Figure 1.

Figure 1. Flow Chart of Subject Disposition for Study ZX-ZP-0073

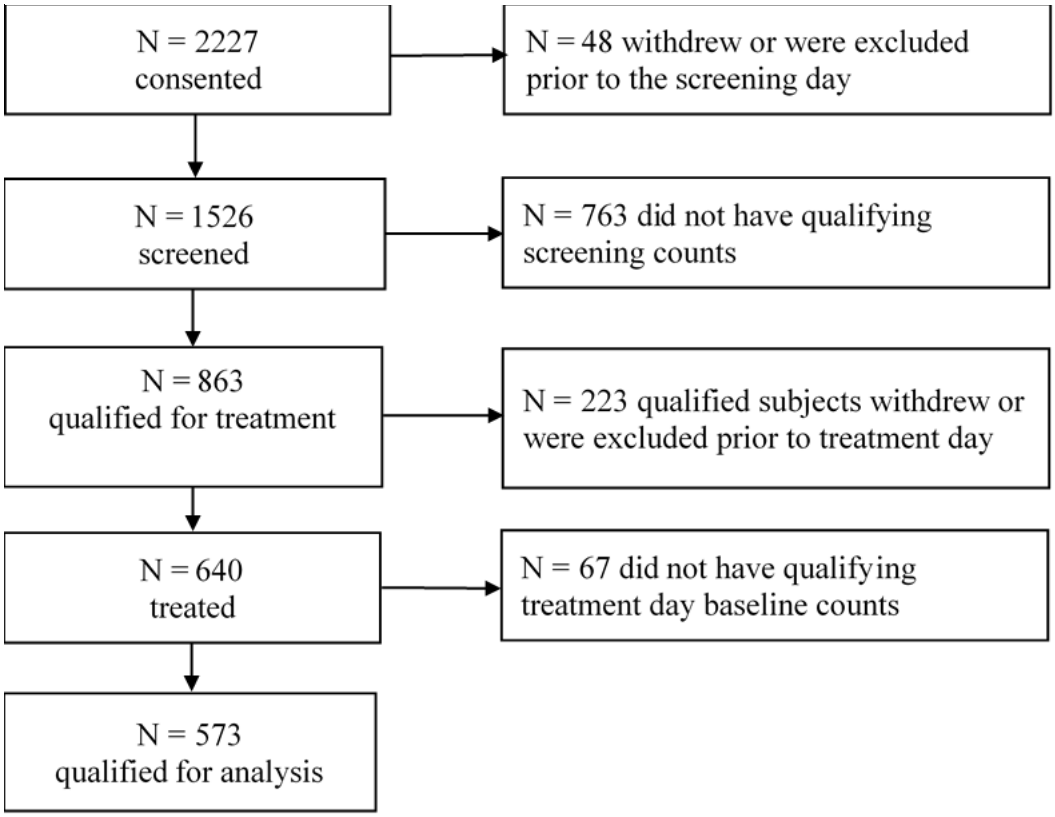


Source: Integrated Summary of Efficacy
Reviewer verified the sample size for subjects randomizd and qualified for analysis in ZP0073f1.xpt.

In ZX-ZP-0074, a total of 2227 subjects were consented and 1526 subjects were screened. Among the screened subjects, 863 passed screening day baseline criteria and 640 were randomized and treated. Of these 640, 416 subjects were treated on both abdomen and groin regions, 155 subjects were treated only on the abdomen region and 69 subjects were treated only

on the groin region. Among these randomized and treated subjects, 573 passed treatment baseline criteria and were included in main analyses. For a disposition flowchart, see Figure 2.

Figure 2. Flow Chart of Subject Disposition for Study ZX-ZP-0074



Source: Integrated Summary of Efficacy
Reviewer verified the sample size for subjects randomized and qualified for analysis in ZP0074f1.xpt.

Sample Size by Treatment Arm and Body Region

The mITT population counts were verified using the data provided by examining the breakdown of randomized subjects by the treatment pair each subject was randomized to receive and the number of subjects who were excluded after randomization at each body region and treatment arm. Tables are presented in the Appendix.

Demographic Characteristics

Table 2 summarizes demographic characteristics in each study, by body region, for the mITT population. Within each study and body region, the distributions of age, sex, and race were similar between the three treatment arms. Note that across trials, differences in demographic characteristics were apparent with study ZX-ZP-0073 enrolling more females and fewer Caucasians than study ZX-ZP-0074. It is also worth noting that race and ethnicity were reported separately in ZX-ZP-0074, but combined into one variable for study ZX-ZP-0073.

Table 2. Demographic Characteristics of treated subjects (by treatment group and body area)							
		Abdomen			Groin		
		ZuraPrep	ChloraPrep	Vehicle	ZuraPrep	ChloraPrep	Vehicle
ZX-ZP-0073							
Sample Size		N = 342	N = 340	N = 69	N = 330	N = 326	N = 68
Age	Mean (SD)	38.1 (15.4)	38.0 (15.2)	39.5 (15.1)	37.9 (15.2)	37.7 (15.1)	39.6 (15.3)
Sex (%)	Female	40.6	41.5	39.1	36.1	37.1	38.2
	Male	59.4	58.5	60.9	63.9	62.9	61.8
Race (%)	Asian	27.5	26.8	27.5	27.0	26.1	25.0
	Black	19.6	21.2	21.7	17.3	19.0	22.1
	Caucasian	38.6	37.9	43.5	39.4	39.0	45.6
	Hispanic	10.8	10.3	5.8	12.1	11.4	5.9
	Other	3.5	3.8	1.5	4.2	4.6	1.5
ZX-ZP-0074							
Sample Size		N = 324	N = 320	N = 68	N = 343	N = 352	N = 74
Age	Mean (SD)	38.2 (17.4)	38.3 (17.1)	38.6 (17.0)	34.9 (16.6)	34.9 (16.5)	33.1 (14.9)
Sex (%)	Female	24.7	26.9	30.9	14.0	13.1	8.1
	Male	75.3	73.1	69.1	86.0	86.9	91.9
Race (%)	African American	0.9	1.3	0.0	1.5	1.7	2.7
	Asian	0.9	0.3	2.9	1.5	1.4	1.4
	Caucasian	89.5	89.7	89.7	89.2	88.1	87.8
	Native American	2.5	2.8	2.9	3.2	3.7	2.7
	Not disclosed	4.3	4.4	4.4	3.8	4.3	4.1
	Other	1.9	1.6	0.0	0.9	0.9	1.4
Ethnicity	Latino	3.7	4.1	1.5	2.9	2.8	2.7
	Non-Latino	88.9	88.1	92.7	91.8	91.8	89.2
	Not disclosed	7.4	7.8	5.9	5.3	5.4	8.1

Source: Reviewer Table, derived from ZP0073dm.xpt, ZP0074dm.xp

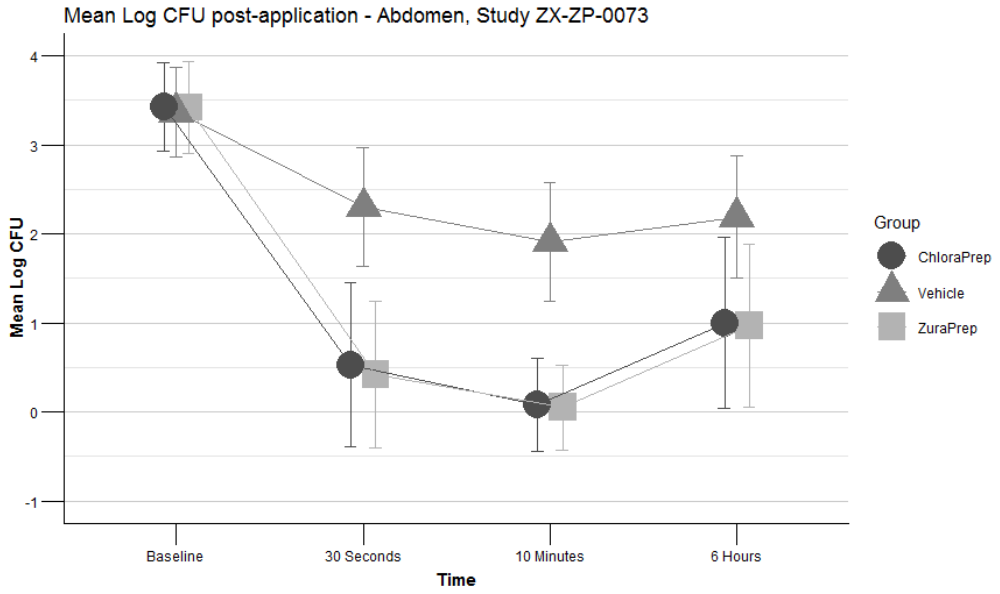
3.2.4 Results and Conclusions

Descriptive Analysis of Mean Bacterial Counts Over Time

The following section briefly describesthe analysis of mean bacterial counts (log_{10} scale) at baseline, at 30 seconds, 10 minutes and 6 hours post application.

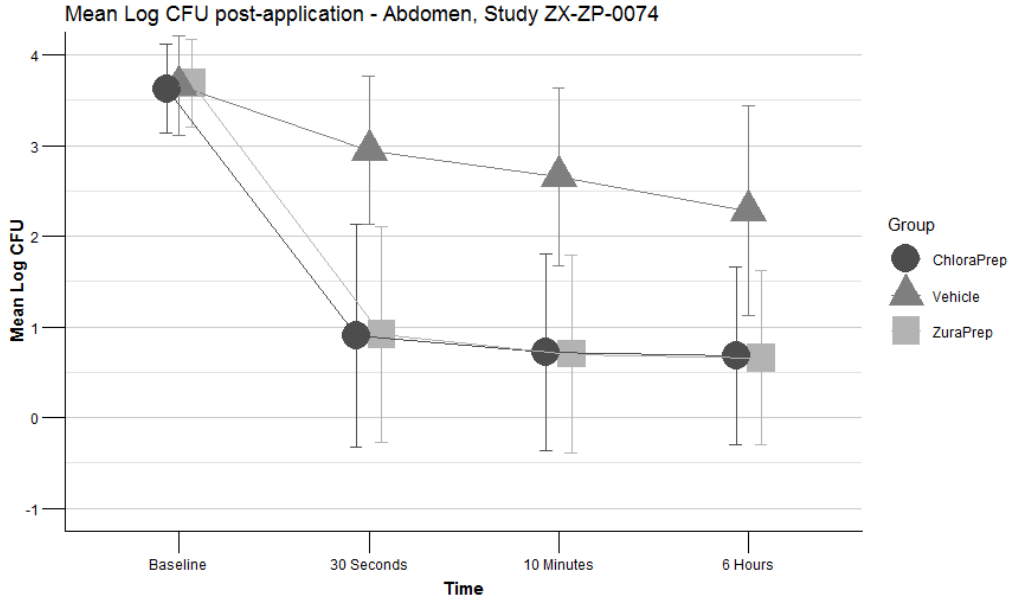
The mean bacterial counts at each time point, in each body region, for each study are visually represented in Figures 3 to 6 below. Importantly, it is seen that the there are no differences in mean bacterial counts at baseline across the different treatment arms. The mean bacterial counts at baseline are also seen to be similar across the two pivotal studies for each body region. Of the three post-application time points, the reduction in bacterial count is most at 10 minutes for both active treatments in the groin region for both studies and in the abdomen region for study ZX-ZP-0073. In study ZX-ZP-0074, the reduction from baseline bacterial count in the abdomen region for both active treatments were slightly higher at 6 hours than at 10 minutes. Detailed tables containing mean bacterial count values at each time point and the standard deviations are provided in the Appendix.

Figure 3. Mean Bacterial Count (log10 scale) – Abdomen Region, ZX-ZP-0073 (mITT)



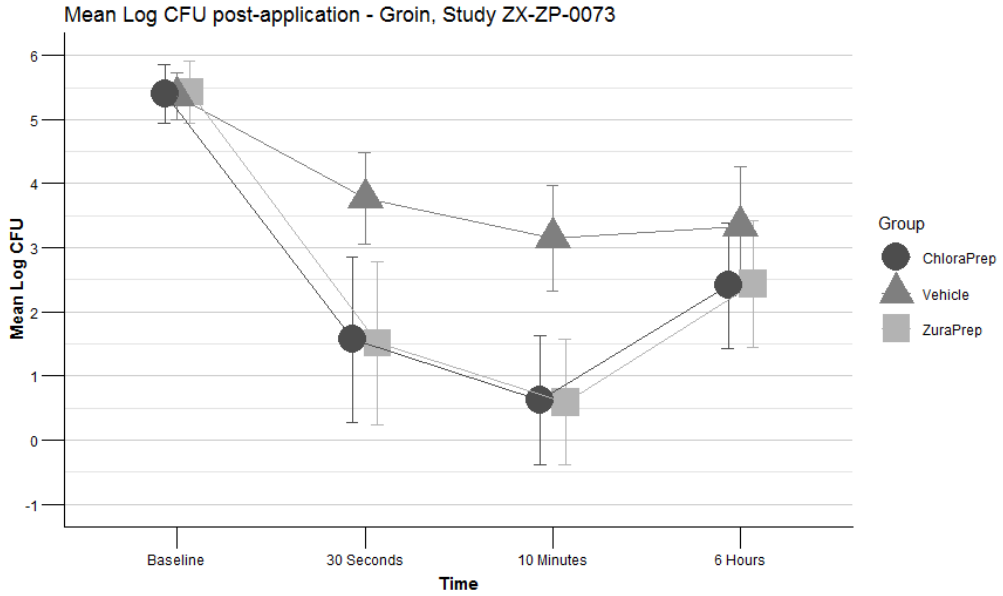
Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

Figure 4. Mean Bacterial Count (log10 scale) – Abdomen Region, ZX-ZP-0074 (mITT)



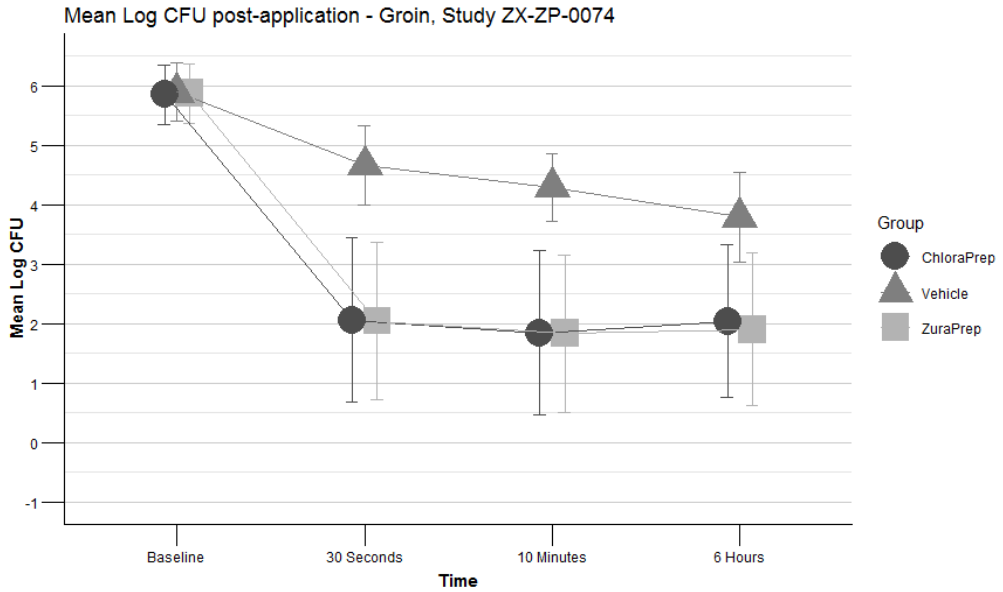
Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

Figure 5. Mean Bacterial Count (log10 scale) – Groin Region, ZX-ZP-0073 (mITT)



Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

Figure 6. Mean Bacterial Count (log10 scale) – Abdomen Region, ZX-ZP-0073 (mITT)



Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

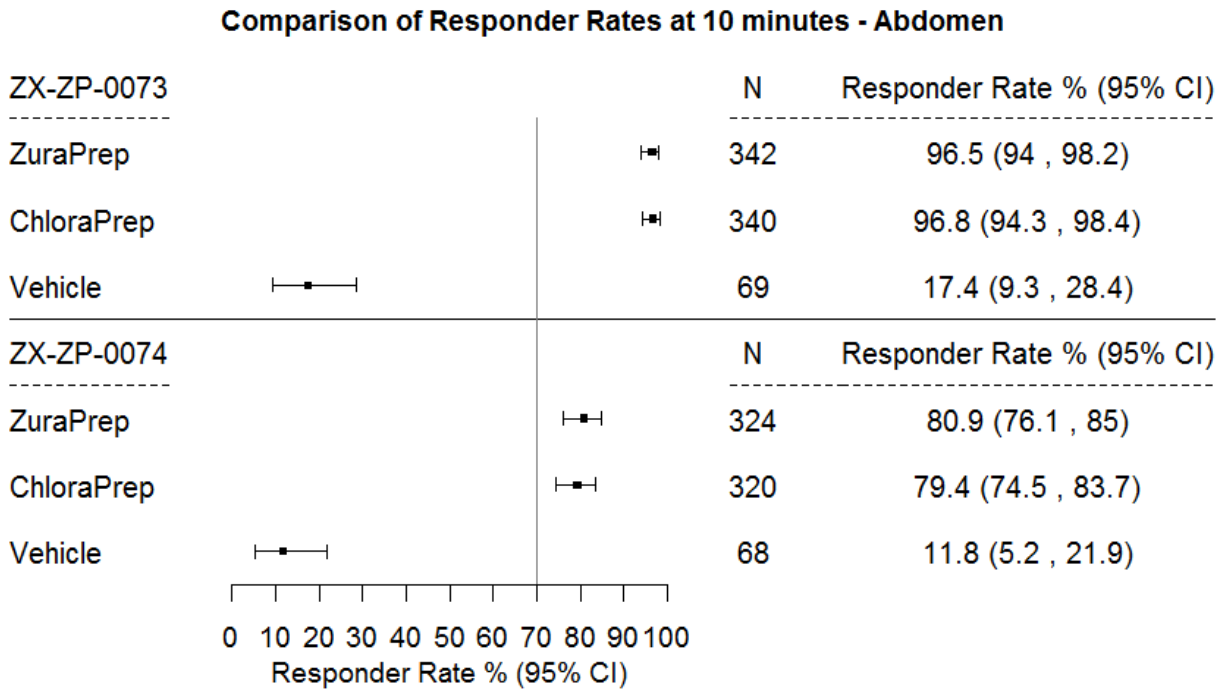
Tables detailing the mean reduction in bacterial count values at each time point along with corresponding confidence intervals are provided in the Appendix.

Primary Endpoints

- Responder Rate Analysis at 10 Minutes

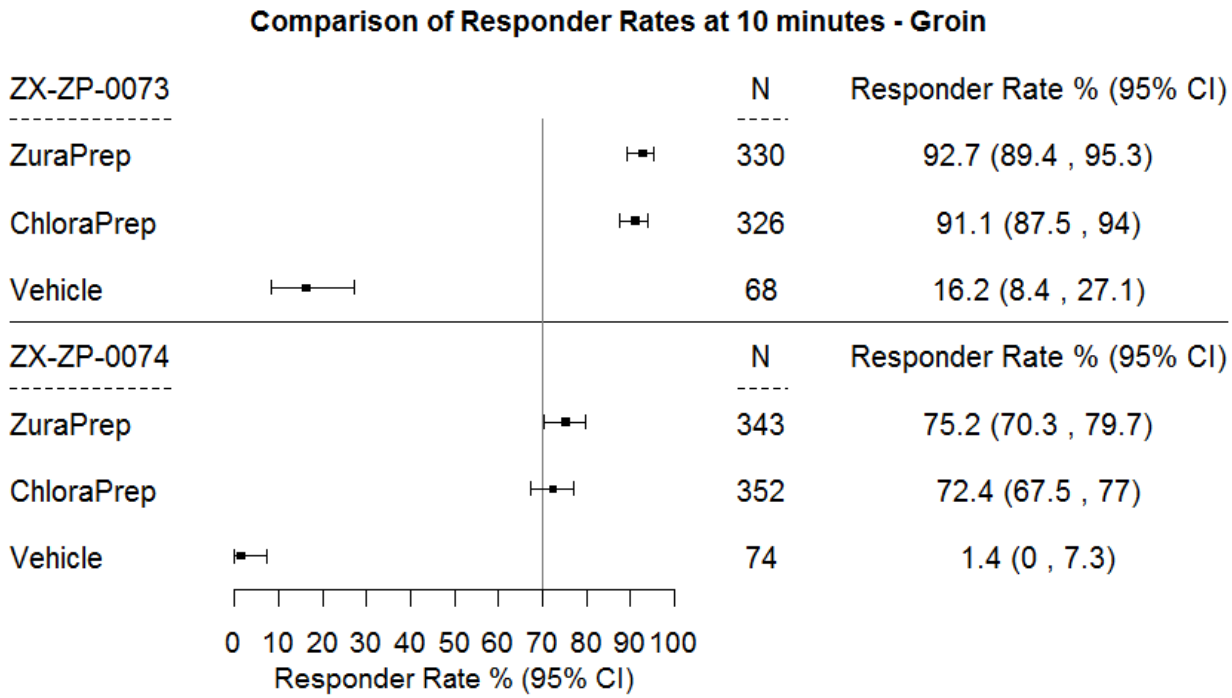
A summary of the efficacy results for each body region is presented in the forest plots in Figure 7 (abdomen) and 8 (groin) below. The efficacy goals with respect to responder rate were met in both studies at 10 minutes post-application at the abdomen region as lower bounds of the 95% confidence intervals were above 70% for the investigational product ZuraPrep and the active control ChloraPrep. At the groin region, the efficacy goals were met for both ZuraPrep and ChloraPrep in study ZX-ZP-0073; but, only for ZuraPrep in study ZX-ZP-0074. The estimated mean responder rate at the groin region in study ZX-ZP-0074 for ChloraPrep was however still above the 70% threshold.

Figure 7. Responder Rate Analysis at 10 Minutes Post-application – Abdomen Region (mITT)



Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

Figure 8. Responder Rate Analysis at 10 Minutes Post-application – Groin Region (mITT)

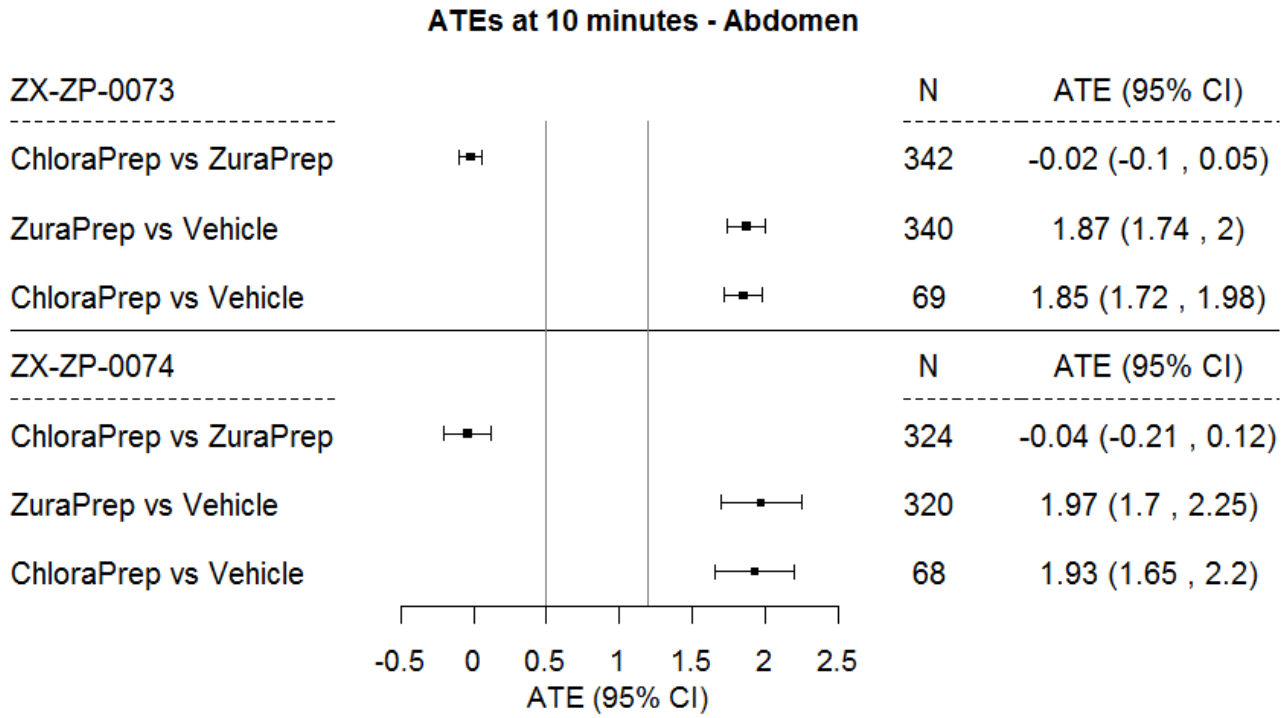


Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

- ATE Analysis at 10 minutes

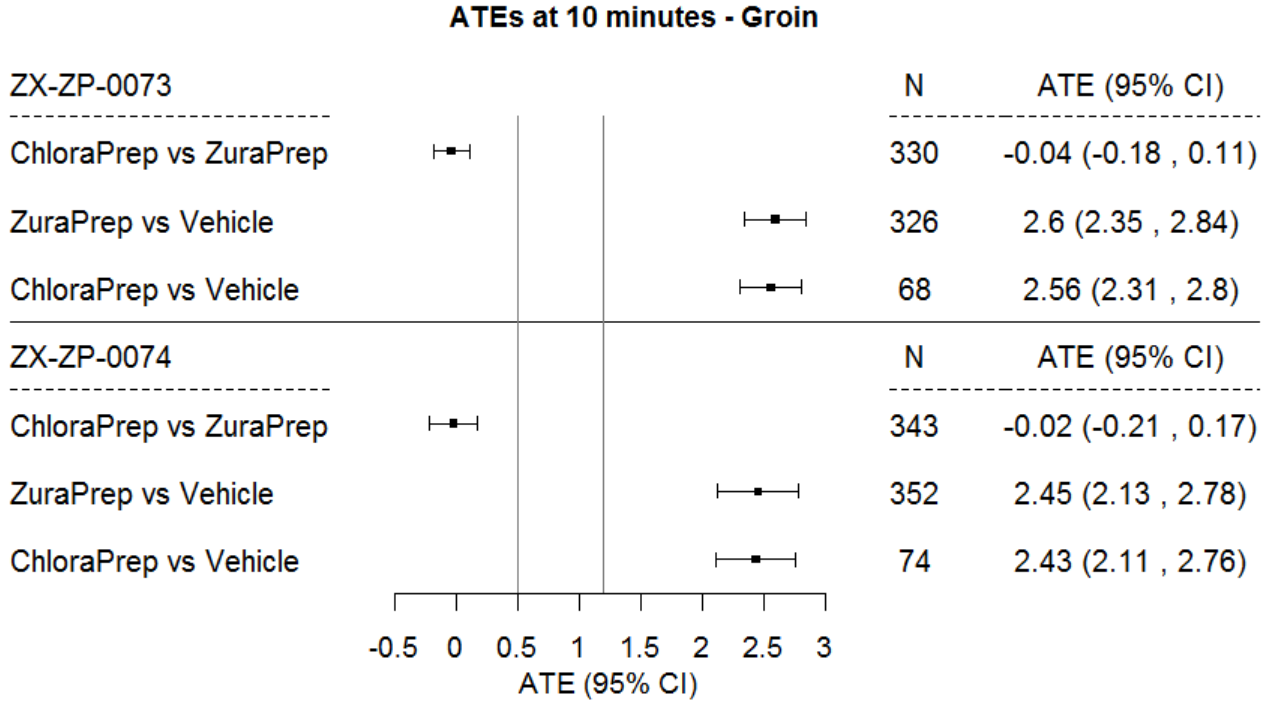
A summary of the ATE analysis results for each body region is presented in the forest plots in Figure 9 (abdomen) and 10 (groin) below. The efficacy goals with respect to ATE were met in both studies at 10 minutes post-application as ZuraPrep was found to be non-inferior to ChloraPrep by a margin of 0.5 (upper bound of 95% confidence interval < 0.5) and superior to ZuraPrep Vehicle by a margin of 1.2 (lower bound of 95% confidence interval > 1.2).

Figure 9. ATE Analysis at 10 Minutes Post-application – Abdomen Region (mITT)



Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

Figure 10. ATE Analysis at 10 Minutes Post-application – Groin Region (mITT)



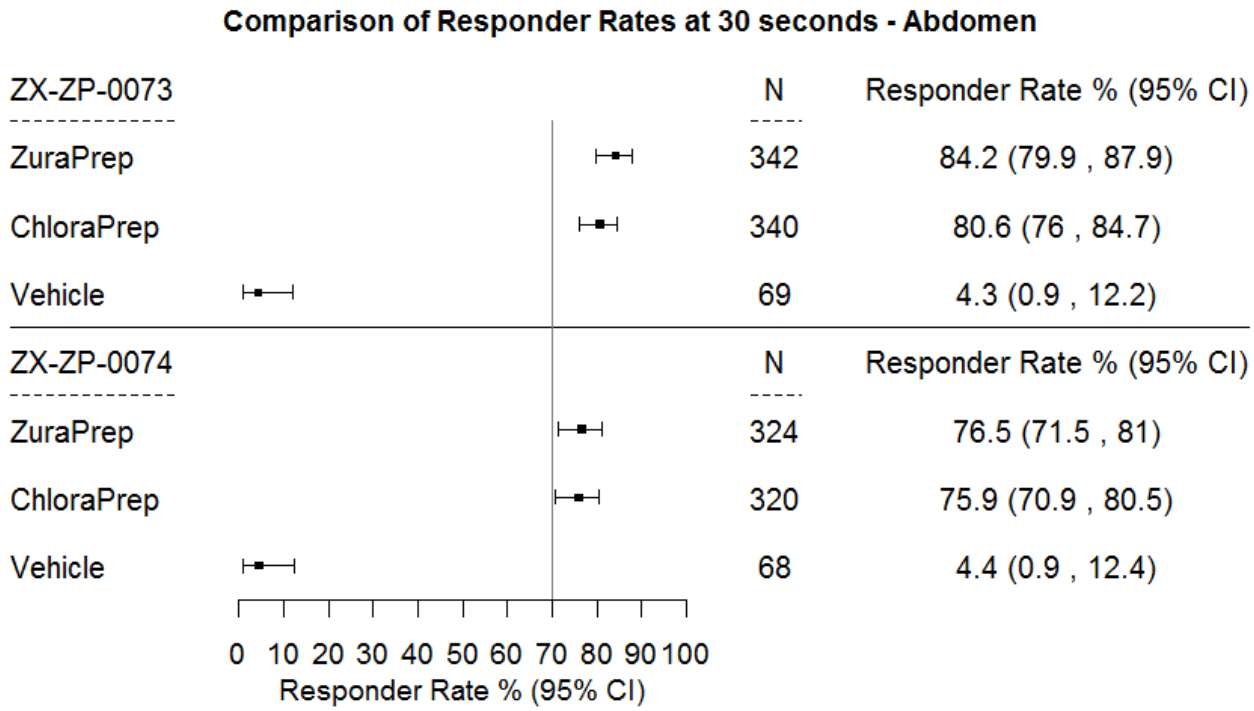
Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

Secondary Endpoints

- Responder Rate Analysis at 30 seconds

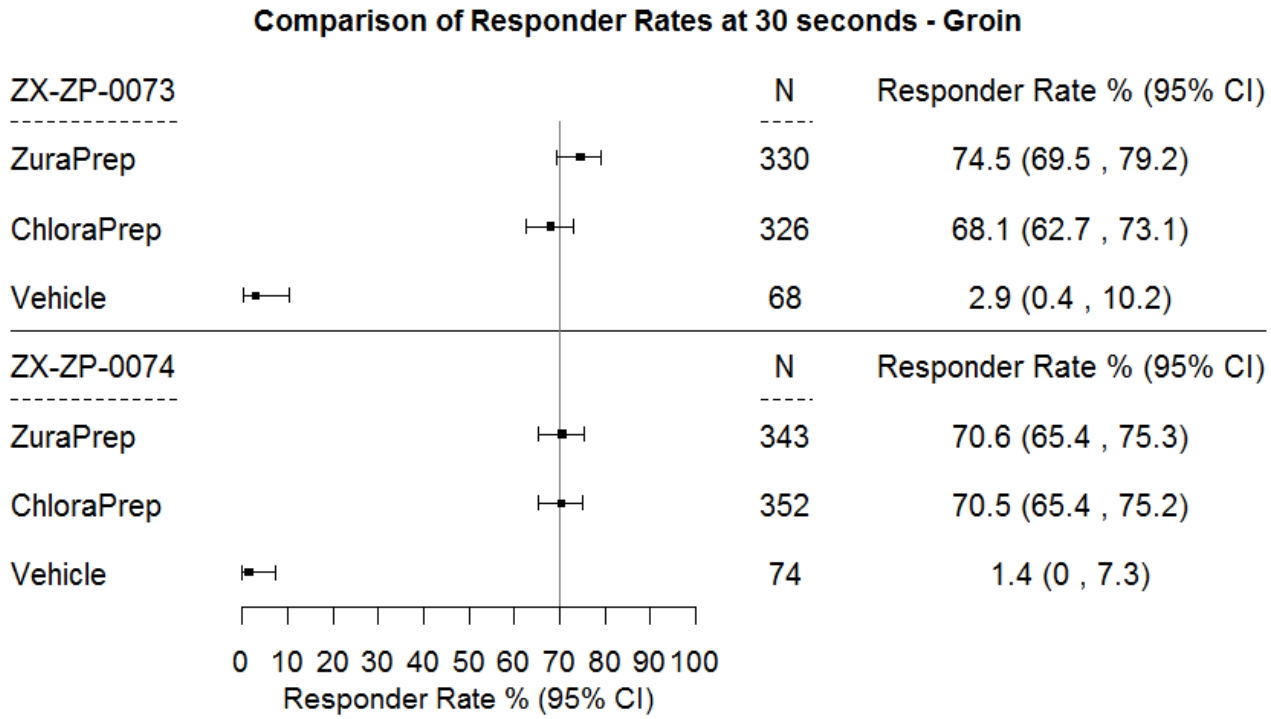
A summary of the efficacy results at 30 seconds for each body region is presented in the forest plots in Figure 11 (abdomen) and 12 (groin) below. The efficacy goals with respect to responder rate were met for both products in both studies in the abdomen region. For the groin region, the 95% confidence intervals included the 70% threshold for both products in both studies.

Figure 11. Responder Rate Analysis at 30 Seconds Post-application – Abdomen Region (mITT)



Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

Figure 12. Responder Rate Analysis at 30 Seconds Post-application – Groin Region (mITT)

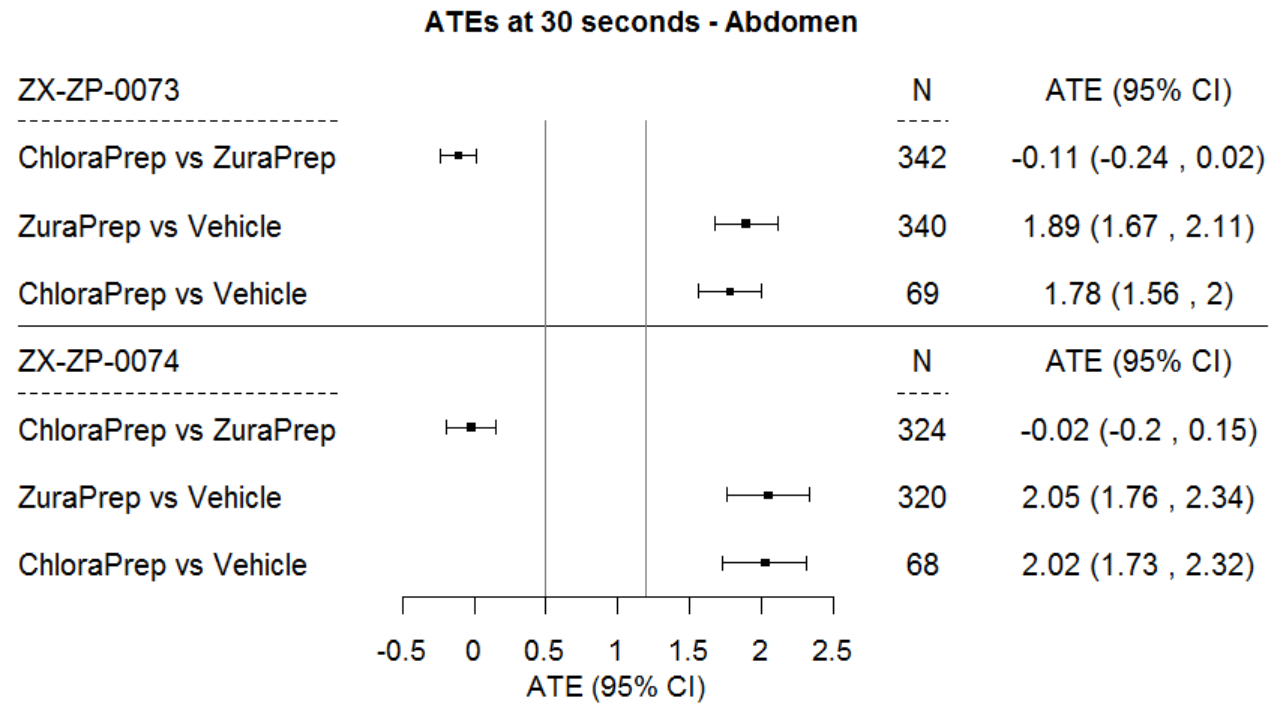


Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

- ATE Analysis at 30 seconds

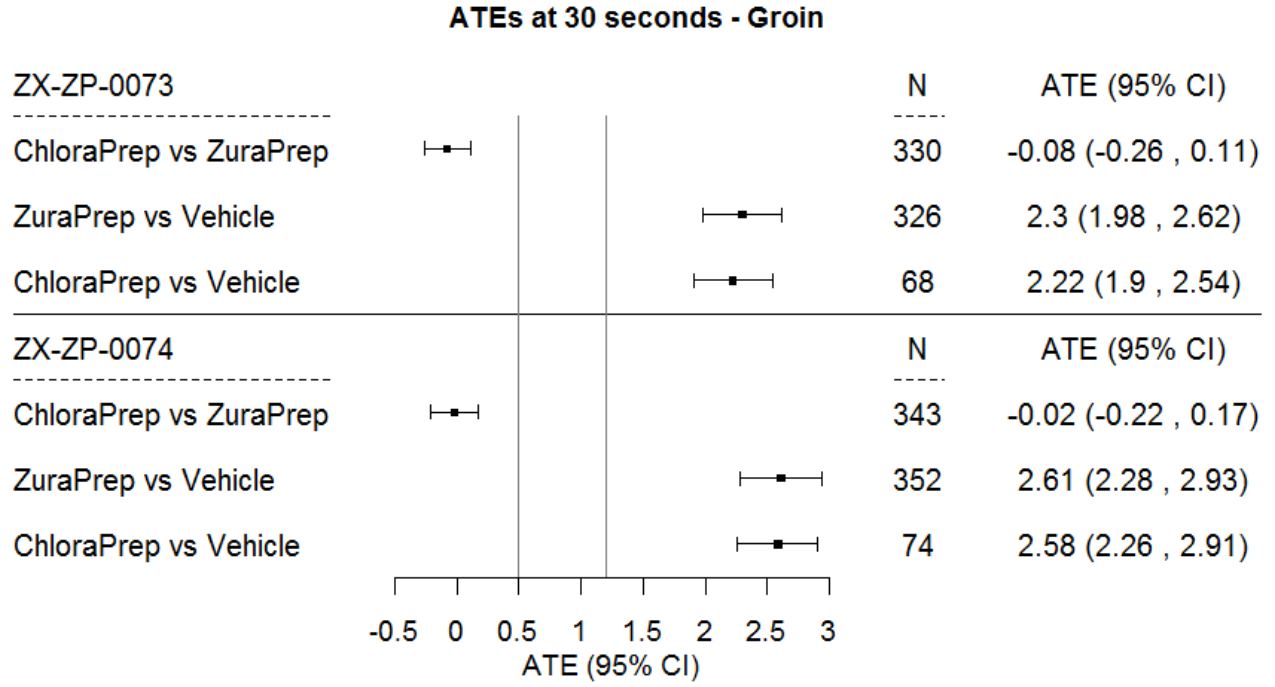
The ATE analysis results for each body region are presented in the forest plots in Figure 13 (abdomen) and 14 (groin) below. All efficacy objectives were met with respect to ATE at 30 seconds as well.

Figure 13. ATE Analysis at 30 Seconds Post-application – Abdomen Region (mITT)



Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

Figure 144. ATE Analysis at 30 Seconds Post-application – Groin Region (mITT)



Source: Reviewer Figure derived from ZP0073f1.xpt, ZP0073f2.xpt, ZP0074f1.xpt, ZP0074f2.xpt

- Responder Rate Analysis at 6 hours

The lower bound of the 95% confidence interval for the 6-hour responder rate exceeded 70% for the abdomen and groin in all treatment groups for studies ZX-ZP-0074 and ZX-ZP-0073. Responder rates with 95% confidence intervals at 6 hours post application are presented for each study in Table 3 below. The sponsor was only able to demonstrate persistent antimicrobial activity for ZuraPrep 10.5 mL, defined in the 2017 Final Rule as responder rate of 100% at 6 hours, in the groin region for both studies. In the abdomen region the responder rate at 6 hours

Table 3. Responder Rate With 95% Confidence Interval at 6 Hours Post-Application

Study	Abdomen			Groin		
	Vehicle Rate (%) (95% CI)	ZuraPrep Rate (%) (95% CI)	ChloraPrep Rate (%) (95% CI)	Vehicle Rate (%) (95% CI)	ZuraPrep Rate (%) (95% CI)	ChloraPrep Rate (%) (95% CI)
ZX-ZP-0074	N = 324	N = 320	N = 68	N = 343	N = 352	N = 74
	86.8 (76.4, 93.8)	99.1 (97.3, 99.8)	99.1 (97.3, 99.8)	100.0 (96.0, 100.0)	100.0 (99.1, 100.0)	99.4 (98.0, 99.9)
ZX-ZP-0073	N = 342	N = 340	N = 69	N = 330	N = 326	N = 68
	97.1 (89.9, 99.7)	99.4 (97.9, 99.9)	100.0 (98.9, 100.0)	100.0 (94.7, 100.0)	100.0 (98.9, 100.0)	100.0 (98.9, 100.0)

Abbreviations: CI = confidence interval;

was 99.4% and 99.1% in study ZX-ZP-0073 and ZX-ZP-0074, respectively.

Source: ZX-ZP-0073 CSR Table 5; Study ZX-ZP-0074 CSR Table 18 and Table 20; Reproduced by Reviewer.

Sensitivity Analysis

Given that the two pivotal studies used a study design that includes multiple measurements from the same subject the ATE analysis was conducted using a regression model with a subject-specific random intercept to account for any possible correlation between two measurements from the same subject. Like the primary analysis, the sensitivity analysis was conducted using the datasets submitted by the sponsor and using the mITT population. The analysis led to similar conclusions as the primary analysis. Specifically, in an analysis adjusting for subject-specific correlation, the efficacy goals with respect to ATE were met in both studies at 30 seconds and 10 minutes post-application as ZuraPrep was found to be non-inferior to ChloraPrep by a margin of 0.5 and superior to vehicle by a margin of 1.2. The results are detailed in Tables 4 and 5 below.

Table 4. Study ZX-ZP-0073 Non-Inferiority and Superiority – Sensitivity analysis			
Body Area	**Treatments**	**30 Seconds**	**10 Minutes**
		ATE Difference (95% CI)	**ATE Difference (95% CI)**
Groin	Non-inferiority (ChloraPrep vs ZuraPrep)	-0.06 (-0.19 to 0.06)	-0.03 (-0.14 to 0.07)
	Superiority – ZuraPrep vs Vehicle	2.39 (2.12 to 2.66)	2.55 (2.33 to 2.78)
	Superiority – ChloraPrep vs Vehicle	2.33 (2.05 to 2.60)	2.52 (2.30 to 2.74)
Abdomen	Non-inferiority - ChloraPrep vs ZuraPrep	-0.10 (-0.19 to -0.01)	-0.01 (-0.07 to 0.04)
	Superiority – ZuraPrep vs Vehicle	1.85 (1.65 to 2.05)	1.86 (1.74 to 1.98)
	Superiority – ChloraPrep vs Vehicle	1.75 (1.55 to 1.95)	1.84 (1.72 to 1.96)
ATE = average treatment effect; CI = confidence interval.			

Source: Reviewer Table derived from ZP0073f1.xpt, ZP0073f2.xpt

Table 5. Study ZX-ZP-0074 Non-Inferiority and Superiority – Sensitivity analysis			
Body Area	**Treatments**	**30 Seconds**	**10 Minutes**
		ATE Difference (95% CI)	**ATE Difference (95% CI)**
Groin	Non-inferiority (ChloraPrep vs ZuraPrep)	-0.03 (-0.18 to 0.13)	-0.06 (-0.22 to 0.09)
	Superiority – ZuraPrep vs Vehicle	2.61 (2.26 to 2.95)	2.58 (2.24 to 2.92)
	Superiority – ChloraPrep vs Vehicle	2.58 (2.24 to 2.93)	2.52 (2.18 to 2.86)
Abdomen	Non-inferiority - ChloraPrep vs ZuraPrep	-0.02 (-0.14 to -0.18)	-0.04 (-0.20 to 0.12)
	Superiority – ZuraPrep vs Vehicle	2.04 (1.70 to 2.37)	1.92 (1.58 to 2.25)
	Superiority – ChloraPrep vs Vehicle	2.06 (1.73 to 2.39)	1.87 (1.54 to 2.21)
ATE = average treatment effect; CI = confidence interval.			

Source: Reviewer Table derived from ZP0074f1.xpt, ZP0074f2.xpt

3.3 Evaluation of Safety

All treated subjects were evaluated for safety. The main measures of safety were skin irritation scores and incidence of reported adverse events. No skin irritation and no adverse event were observed for any subject in Study ZX-ZP-0073. Minimal skin irritation and treatment-emergent adverse events for six subjects were reported for study ZX-ZP-0074. With a small number of adverse events, statistical comparisons are inconclusive, and the data are better assessed qualitatively. Thus, for further evaluation of safety, we refer to the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

For preoperative skin preparation simulation studies, the Division of Nonprescription Drug Products does not require subgroup analyses since the clinical simulation studies are conducted on healthy volunteers who are not treated for sickness. However, the sponsor reported the number of non-responders at 10 minutes by age (divided into three categories), race (categorized as Caucasian and other) and sex. The reviewer examined the distribution of non-responders by sex and race. The proportions of non-responders to the total for these demographic characteristics seemed relatively constant across the two treatment groups at t 10 minutes after application in both groin and abdomen regions in both pivotal studies (see Table 6 below).

Table 6. Proportion of Nonresponders at 10 Minutes by Sex, Race (mITT)

Study	Groin				Abdomen			
	Sex		Race		Sex		Race	
	Female	Male	Caucasian	Other	Female	Male	Caucasian	Other
ZX-ZP-0073								
ZuraPrep	1.4% (2/139)	4.9% (10/203)	2.3% (3/132)	4.3% (9/210)	5.0% (6/119)	8.5% (18/211)	8.5% (11/130)	6.5% (13/200)
ChloraPrep	0% (0/141)	5.5% (11/199)	3.9% (5/129)	2.8% (6/211)	8.3% (10/121)	9.3% (19/205)	7.1% (9/127)	10.1% (20/199)
ZX-ZP-0074								
ZuraPrep	16.3% (13/80)	20.1% (49/244)	20.3% (59/290)	8.8% (3/34)	39.6% (19/48)	22.4% (66/295)	23.9% (73/306)	32.4% (12/37)
ChloraPrep	16.3% (14/86)	22.2% (52/234)	20.2% (58/287)	21.6% (8/37)	45.7% (21/46)	24.8% (76/306)	27.7% (86/310)	26.2% (11/42)

Source: Study ZX-ZP-0073 CSR Appendix 16.2.4 and Appendix 16.2.7; Study ZX-ZP-0074 CSR Appendix 16.2.4 and Appendix 16.2.6. Reproduced by Reviewer

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

To evaluate the safety and efficacy of ZuraPrep, the sponsor conducted two randomized, evaluator-blinded, active and vehicle-controlled clinical trials: ZX-ZP-0073 and ZX-ZP-0074. The design, endpoints and planned analyses of these two trials were agreed upon. Co-primary endpoints were used to establish the efficacy of ZuraPrep: responder rate and average treatment effect of the change from baseline in bacterial counts – both evaluated at 10 minutes and in two body regions, abdomen and groin.

Results based on responder rates demonstrated that ZuraPrep and ChloraPrep met the study objective target of 70% at 10 minutes in pivotal study ZX-ZP-0073, with the ZuraPrep treatment arm having responder rates of 96.5% (95% CI, [94.0 , 98.2]) and 92.7% (95% CI, [89.4 , 95.3]), respectively, in the abdomen and the groin. ZuraPrep also met the study objective target of 70% at 10 minutes in the other pivotal study ZX-ZP-0074 with responder rates of 80.9% (95% CI, [76.9 , 85.0]) and 75.3% (95% CI, [70.2 , 79.7]), respectively, in the abdomen and the groin. In this study ChloraPrep met the target in the groin region and had a mean value above 70% target in the abdomen region. Results based on average treatment effect met study objectives as they demonstrated that ZuraPrep 10.5 mL is statistically superior to the vehicle and non-inferior to ChloraPrep 10.5 mL at 10 minutes and 30 seconds, in both body regions and studies. ChloraPrep 10.5 mL was also statistically superior to the vehicle in both pivotal studies at both body regions at 10 minutes and 30 seconds.

5.2 Conclusions and Recommendations

From a statistical standpoint, there is sufficient evidence that ZuraPrep 10.5 mL is effective and adds benefits beyond the vehicle. Specifically, both ZX-ZP-0073 and ZX-ZP-0074 show that:

- Responder rates of ZuraPrep 10.5 mL were greater than 70% at 10 minutes for both body regions;
- ZuraPrep is statistically superior to the vehicle and non-inferior to the ChloraPrep at 10 minutes and 30 seconds, for both body regions based on average treatment effects, the effectiveness criteria outlined in the 2017 Final Rule; and
- ZuraPrep 10.5 mL showed persistent antimicrobial properties in the groin region at 6 hours.

The validity of the studies was confirmed as ChloraPrep 10.5 mL, an approved product, met the 70% responder rate criteria and was found to be statistically superior to the vehicle control in ATE analysis at 10 minutes post-application.

Both pivotal studies failed to demonstrate persistent antimicrobial properties in the abdomen.

6 APPENDIX

Sample Size by Treatment Arm and Body Region

Tables 1 and 2 below provide a breakdown of randomized subjects by the treatment pair each subject was randomized to receive and the number of subjects who were excluded after randomization at each body region and treatment arm. This analysis verified the mITT population counts using the data provided by the sponsor.

Appendix Table 1. Sample Size by Treatment Pair Randomized in ZX-ZP-0073

Randomized Treatment Pair	Number of subjects at baseline	Failed Treatment Day baseline – both (right and left) sites	Failed Treatment Day – ZuraPrep site only	Failed Treatment Day – ChloraPrep site only	Failed Treatment Day – Vehicle site only
Abdomen					
ZuraPrep / ChloraPrep	360	53	0	2	--
Vehicle / ZuraPrep	40	4	1	--	1
Vehicle /ChloraPrep	40	5	--	0	1
Groin					
Zura / ChloraPrep	360	65	0	2	--
Vehicle / ZuraPrep	40	5	0	--	0
Vehicle /ChloraPrep	40	7	--	0	0

Source: Reviewer Table, derived from ZP0073f1.xpt, ZP0073f2.xpt

Appendix Table 2. Sample Size by Treatment Pair Randomized in ZX-ZP-0074

Randomized Treatment Pair	Number of subjects at baseline	Failed Treatment Day baseline – both (right and left) sites	Failed Treatment Day – ZuraPrep site only	Failed Treatment Day – ChloraPrep site only	Failed Treatment Day – Vehicle site only
Abdomen					
ZuraPrep / ChloraPrep	468	115	63	69	--
Vehicle / ZuraPrep	51	12	5	--	5
Vehicle /ChloraPrep	53	14	--	3	5

Groin					
Zura / ChloraPrep	397	61	29	20	--
Vehicle / ZuraPrep	44	3	5	--	3
Vehicle /ChloraPrep	44	6	--	2	2

Source: Reviewer Table, derived from ZP0074f1.xpt, ZP0074f2.xpt

Mean Bacterial Count (log_{10} scale) Descriptive Statistics

Tables 3 and 4 below provide mean bacterial count values and the corresponding standard deviations at 30 seconds, 10 minutes and 6 hours post-application.

Appendix Table 3. Mean Log_{10} CFU/cm^2 values with Standard Deviation (SD) – ZX-ZP-0073

Body Area		N	Baseline		30 Seconds		10 Minutes		6 Hours	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Abdomen	ChloraPrep	340	3.4	0.5	0.5	0.9	0.1	0.5	1.0	1.0
	Vehicle	69	3.4	0.5	2.3	0.7	1.9	0.7	2.2	0.7
	ZuraPrep	342	3.4	0.5	0.4	0.8	0.1	0.5	1.0	0.9
Groin	ChloraPrep	326	5.4	0.4	1.6	1.3	0.6	1.0	2.4	1.0
	Vehicle	68	5.4	0.4	3.8	0.7	3.1	0.8	3.3	0.9
	Zuraprep	330	5.4	0.5	1.5	1.3	0.6	1.0	2.4	1.0

Source: Reviewer Table derived from ZP0073f1.xpt, ZP0073f2.xpt

Appendix Table 4. Mean Log_{10} CFU/cm^2 values with Standard Deviation (SD) – ZX-ZP-0074

Body Area		N	Baseline		30 Seconds		10 Minutes		6 Hours	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Abdomen	ChloraPrep	320	3.6	0.5	0.9	1.2	0.7	1.1	0.7	1.0
	Vehicle	68	3.7	0.5	2.9	0.8	2.7	1.0	2.3	1.2
	ZuraPrep	324	3.7	0.5	0.9	1.2	0.7	1.1	0.7	1.0
Groin	ChloraPrep	352	5.8	0.5	2.1	1.4	1.8	1.4	2.0	1.3
	Vehicle	74	5.9	0.5	4.7	0.7	4.3	0.6	3.8	0.8
	Zuraprep	343	5.9	0.5	2.0	1.3	1.8	1.3	1.9	1.3

Source: Reviewer Table derived from ZP0074f1.xpt, ZP0074f2.xpt

Reduction in Bacterial Count (log_{10} scale) Descriptive Analysis

Complementing Figures 3 through 6 in the main body of the review, Tables 5, 6 and 7 below describe results of the analysis of bacterial count reduction from baseline at 30 seconds, 10 minutes and 6 hours post-application.

Appendix Table 5. Reduction in Bacterial Count (Mean log_{10} Values) with 95% Confidence Interval at 30 Seconds Post-Application

Study	Abdomen			Groin		
	Vehicle Mean (95% CI)	ZuraPrep Mean (95% CI)	ChloraPrep Mean (95% CI)	Vehicle Mean (95% CI)	ZuraPrep Mean (95% CI)	ChloraPrep Mean (95% CI)
ZX-ZP-0074	0.71 (0.56, 0.86)	2.77 (2.64, 2.89)	2.73 (2.60, 2.86)	1.23 (1.07, 1.39)	3.82 (3.68, 3.97)	3.79 (3.64, 3.94)
ZX-ZP-0073	1.07 (0.84, 1.30)	2.99 (2.87, 3.10)	2.89 (2.78, 3.00)	1.59 (1.35, 1.82)	3.91 (3.80, 4.03)	3.83 (3.71, 3.94)

Abbreviations: CI = confidence interval;

Source: ZX-ZP-0073 CSR Table 6; Study ZX-ZP-0074 CSR Table 8 and Table 10; Reproduced by Reviewer.

Appendix Table 6. Reduction in Bacterial Count (Mean log_{10} Values) with 95% Confidence Interval at 10 Minutes Post-Application

Study	Abdomen			Groin		
	Vehicle Mean (95% CI)	ZuraPrep Mean (95% CI)	ChloraPrep Mean (95% CI)	Vehicle Mean (95% CI)	ZuraPrep Mean (95% CI)	ChloraPrep Mean (95% CI)
ZX-ZP-0074	1.00 (0.78, 1.21)	2.99 (2.87, 3.11)	2.91 (2.79, 3.03)	1.60 (1.44, 1.76)	4.04 (3.90, 4.18)	4.01 (3.86, 4.16)
ZX-ZP-0073	1.47 (1.30, 1.65)	3.35 (3.27, 3.44)	3.34 (3.26, 3.43)	2.23 (2.05, 2.41)	4.83 (4.74, 4.91)	4.78 (4.69, 4.87)

Abbreviations: CI = confidence interval;

Source: ZX-ZP-0073 CSR Table 6; Study ZX-ZP-0074 CSR Table 13 and Table 15; Reproduced by Reviewer.

Appendix Table 7. Reduction in Bacterial Count (Mean log_{10} Values) with 95% Confidence Interval at 6 Hours Post-Application						
Study	Abdomen			Groin		
	Vehicle Mean (95% CI)	ZuraPrep Mean (95% CI)	ChloraPrep Mean (95% CI)	Vehicle Mean (95% CI)	ZuraPrep Mean (95% CI)	ChloraPrep Mean (95% CI)
ZX-ZP-0074	1.37 (1.10, 1.64)	3.03 (2.91, 3.14)	2.96 (2.85, 3.06)	2.10 (1.91, 2.28)	3.96 (3.83, 4.10)	3.81 (3.67, 3.95)
ZX-ZP-0073	1.17 (0.96, 1.38)	2.45 (2.34, 2.55)	2.42 (2.32, 2.53)	2.03 (1.82, 2.24)	3.00 (2.90, 3.11)	2.99 (2.88, 3.09)
Abbreviations: CI = confidence interval;						

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